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Ambulatory monitoring of the cardiovascular system: the role of Pulse Wave Velocity

Josep Solà[1], Stefano F. Rimoldi[2] and Yves Allemann[2]
[1]*CSEM – Centre Suisse d'Electronique et de Microtechnique*
Switzerland
[2]*Swiss Cardiovascular Center Bern, University Hospital*
Switzerland

1. Introduction

Currently the leading cause of mortality in western countries, cardiovascular diseases (CVD) are largely responsible for the ever increasing costs of healthcare systems. During the last decade it was believed that the best trade-off between quality and costs of a healthcare system would pass through the promotion of healthy lifestyles, the early diagnosis of CVD, and the implantation of home-based rehabilitation programs. Hence, the development of novel healthcare structures will irremediably require the availability of techniques allowing the monitoring of patients' health status at their homes. Unfortunately, the ambulatory monitoring of the cardiovascular vital parameters has not evolved as required to reach this aim.

To be exploitable in the long term, ambulatory monitors must of course provide reliable vital information, but even more important, they must be comfortable and inconspicuous: whoever has experimented wearing an ambulatory blood pressure monitor (ABPM) for 24 hours understands what cumbersomeness means. Surprisingly, even if intermittent and obtrusive, ABPM prevails nowadays as the single available method to assess a vascular-related index at home. Hence, a clear demand to biomedical engineers arises: healthcare actors and patients require the development of new monitoring techniques allowing the non-invasive, unobtrusive, automatic and continuous assessment of the cardiac and vascular health status. Concerning cardiac health status, the ambulatory measurement of the electrical and mechanical activities of the heart is already possible by the joint analysis of the electrocardiogram, the phonocardiogram and the impedancecardiogram. But surprisingly, little has been proposed so far for the ambulatory monitoring of vascular-related parameters.

Because several studies have recently highlighted the important role that arterial stiffness plays in the development of CVD, and since central stiffness has been shown to be the best independent predictor of both cardiovascular and all-cause mortality, one might suggest stiffness to be the missing vascular-related parameter in ambulatory cardiovascular

monitoring. However, the only available technique for measuring arterial stiffness non-invasively so far is the so-called Pulse Wave Velocity (PWV). In this chapter we will see that the state of the art in PWV assessment is not compatible with the requirements of ambulatory monitoring. The goal of our work is thus to examine the limitations of the current techniques, and to explore the introduction of new approaches that might allow PWV to be established as the new gold-standard of vascular health in ambulatory monitoring.

This chapter is organized as follows: in Section 2 we introduce the phenomenon of pulse propagation through the arterial tree. In section 3 we provide a large review on the clinical relevance of aortic stiffness and its surrogate, PWV. In Section 4 we perform an updated analysis of the currently existing techniques available for the non-invasive assessment of PWV. Section 5 describes a novel approach to the measurement of PWV based on a non-obtrusive and unsupervised beat-to-beat detection of pressure pulses at the sternum. Finally, Section 6 reviews the historic and current trends on the use of PWV as a non-obtrusive surrogate for arterial blood pressure.

2. The genesis and propagation of pressure pulses in the arterial tree

In cardiovascular research and clinical practice, PWV refers to the velocity of a pressure pulse that propagates through the arterial tree. In particular, we are interested in those pressure pulses generated during left ventricular ejection: at the opening of the aortic valve, the sudden rise of aortic pressure is absorbed by the elastic aorta walls. Subsequently a pulse wave naturally propagates along the aorta exchanging energy between the aortic wall and the aortic blood flow (Figure 1). At each arterial bifurcation, a fraction of the energy is transmitted to the following arteries, while a portion is reflected backwards. Note that one can easily palpate the arrival of arterial pressure pulses at any superficial artery, such as the temporal, carotid or radial artery: already in the year 1500, traditional chinese medicine performed clinical diagnosis by palpating the arrival of pressure pulses at the radial artery (King et al., 2002). But why do clinicians nowadays get interested on the velocity of such pulses, and especially in the aorta? The reason is that the velocity of propagation of aortic pressure pulses depends on the elastic and geometric properties of the aortic wall. We will show later that while arterial stiffness is difficult to measure non-invasively, PWV is nowadays available *in vivo* to clinicians. Hence, the PWV parameter is an easily-accessible potential surrogate for the constitutive properties of the arterial walls.

In order to provide a better understanding of the biomechanics of pulse propagation, we describe here the commonly accepted model of pulse propagation: the Moens-Korteweg equation. For a complete derivation of the model see (Nichols & O'Rouke, 2005). This model assumes an artery to be a straight circular tube with thin elastic walls, and assumes it being filled with an inviscid, homogeneous and incompressible fluid. Under these hypotheses the velocity of a pressure pulse propagating through the arterial wall is predicted to be:

$$PWV^2 = Eh \,/\, d\rho \tag{1}$$

where E stands for the elasticity of the wall (Young's modulus), h for its thickness, D for its diameter and ρ corresponds to the density of the fluid. Even if this model is only a rough

approximation of reality, it provides an intuitive insight on the propagation phenomenon in arteries and, in particular, it predicts that, the stiffer the artery (increased E), the faster a pressure pulse will propagate through it. Therefore, for large elastic arteries such the aorta where the thickness to diameter ratio (h / D) is almost invariable, PWV is expected to carry relevant information related to arterial stiffness.

3. Clinical relevance of Pulse Wave Velocity as a marker of arterial stiffness

We already demonstrated that, from a biomechanical point of view, the velocity of propagation of pressure pulses in large arteries is a surrogate indicator of arterial stiffness. Due to the recent commercialization of semi-automatic devices performing routine measurements of PWV, numerous studies investigating the clinical relevance of arterial stiffness have been conducted during the last decade (Asmar, 1999). In this section we review the most prominent conclusions of these studies. An additional review is given by (Mitchel, 2009).

Cardiovascular disease is the leading cause of morbidity and mortality in western countries and is associated with changes in the arterial structure and function. In particular, arterial stiffening has a central role in the development of such diseases. Nowadays, aortic PWV is considered the gold standard for the assessment of arterial stiffness and is one of the most robust parameters for the prediction of cardiovascular events. Because the structure of the arterial wall differs between the central (elastic) and the peripheral (muscular) arteries, several PWV values are encountered along the arterial tree, with increasing stiffness when moving to the periphery. Because carotid-to-femoral PWV is considered as the standard measurement of aortic arterial stiffness, we will refer to it as simply PWV. In the following we review the most important factors influencing PWV, then we justify the need for a reliable PWV monitoring: on one hand we analyse the pathophysiological consequences of increased arterial stiffness and, on the other hand we highlight the clinical relevance of PWV as an independent marker of cardiovascular risk.

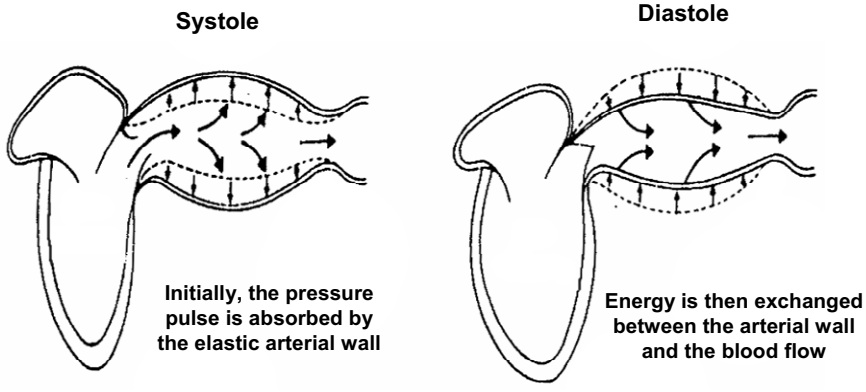


Fig. 1. Genesis of pressure pulses: after the opening of the aortic valve the pulse propagates through the aorta exchanging energy between the aortic wall and the blood flow. Adapted with permission from (Laurent & Cockcroft, 2008).

Fig. 2. The dependency of PWV with age for central elastic arteries (dashed line) and peripheral muscular arteries (continuous line). Adapted from (Avolio et al., 1985).

Major determinants of PWV under normal conditions

Before elucidating the role that PWV plays in the generation and diagnosis of pathological situations, it is necessary to understand which are its determinant factors under normal conditions. It is currently accepted that the four major determinants of PWV are age, blood pressure, gender and heart rate.

Age affects the wall proprieties of central elastic arteries (aorta, carotid, iliac) in a different manner than in muscular arteries (brachial, radial, femoral, popliteal). With increasing age the pulsatile strain breaks the elastic fibers, which are replaced by collagen (Faber & Oller-Hou, 1952). These changes in the arterial structure lead to increased arterial stiffness, and consequently to increased central PWV (Figure 2). On the other hand, there is only little alteration of distensibility of the muscular, *i.e.,* distal, arteries with age (Avolio, 1983; Avolio, 1985; Nichols et al., 2008). This fact supports the use of generalized transfer functions to calculate the central aortic pressure wave from the radial pressure wave in adults of all ages, as will be described in Section 4 (Nichols, 2005).

Arterial blood pressure is also a major determinant of PWV. Increased blood pressure is associated with increased arterial stiffness and vice versa. Ejection of blood into the aorta generates a pressure wave that travels along the whole arterial vascular tree. A reflected wave that travels backwards to the ascending aorta is principally generated in the small peripheral resistance arterioles. With increasing arterial stiffness both the forward and the reflected waves propagate more rapidly along the vessels. Consequently, instead of reaching back the aorta during the diastole, the reflected pulse wave reaches it during the systole. This results in an increase of aortic pressure during systole and reduced pressure during diastole, thus leading to an increase of the so-called Pulsatile Pressure (PP) parameter (Figure 3). Asmar (Asmar et al., 2005) studied large untreated populations of normotensive and hypertensive subjects and found that the two major determinants of PWV were age and systolic blood pressure in both groups. This result confirms the close interdependence between systolic blood pressure and arterial stiffness.

Concerning gender, studies in children revealed no gender difference in PWV, whereas in young and middle age, healthy adult men displayed higher PWV values compared to women (London et al., 1995; Sonesson et al., 1993). Indeed premenopausal women show lower carotid-radial PWV values than age-matched men, but carotid-femoral PWV is found to be similar. Once women become postmenopausal, PWV values become similar to those of age-matched men (London, 1995).

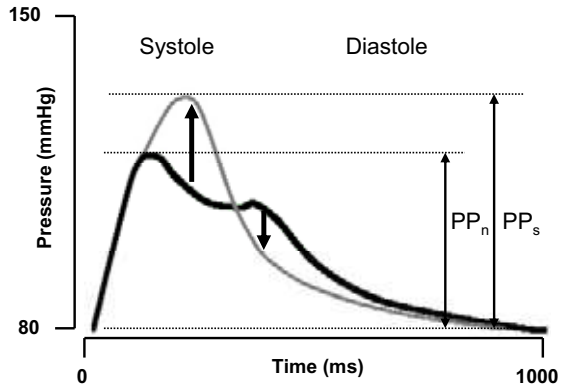


Fig. 3. Consequences of increased arterial stiffness on central blood pressure: increase of systolic and decrease of diastolic central pressures. Pulsatile Pressure is defined as the difference of both pressure amplitudes. PP_n stands for PP under normal conditions and PP_s stands for PP under stiff conditions.

Heart rate is related to PWV through two independent mechanisms. Firstly, heart rate influences PWV because of the frequency-dependant viscoelasticity of the arterial wall: if heart rate increases, the time allowed to the vessels to distend is reduced, resulting in an increased rigidity of the arterial wall. Hence, increasing rate is associated with increasing arterial stiffness. In a recent study, (Benetos et al., 2002) showed that particularly in hypertensive patients increased heart rate was one of the major determinants of accelerated progression of arterial stiffness. Secondly, heart rate is related to PWV through the influence of the sympathetic nervous system: sympathetic activation is associated with increased stiffness of the arteries (Boutouyrie et al., 1994) due to an increase in heart rate, blood pressure and smooth muscle cells tonus.

Why keep arterial stiffness under control?

Up to this point we simply outlined that increased arterial stiffness appears to be normally associated to factors such as aging and blood pressure, among others. As natural as it seems, one might then wonder, why do we need to keep arterial stiffness under controlled (low) values? We will answer this question backwards: what would happen if we did not do so? In other words, we are interested in understanding the pathophysiological consequences of increased arterial stiffness.

Firstly we describe the role of arterial stiffness in the development of endothelial dysfunction. Endothelial dysfunction is the first step in the development of atherosclerosis and plays a central role in the clinical emergence and progression of atherosclerotic vascular disease (Figure 4). The endothelium plays not only an important role in atherogenesis but also in the functional regulation of arterial compliance since endothelial cells release a number of vasoactive mediators such as the vasodilatator nitric oxide (NO) and the vasoconstrictor endothelin. The complex interplay between endothelial function and arterial stiffness leads to a vicious cycle of events, as illustrated in Figure 4 (Dart & Kingwell, 2001).

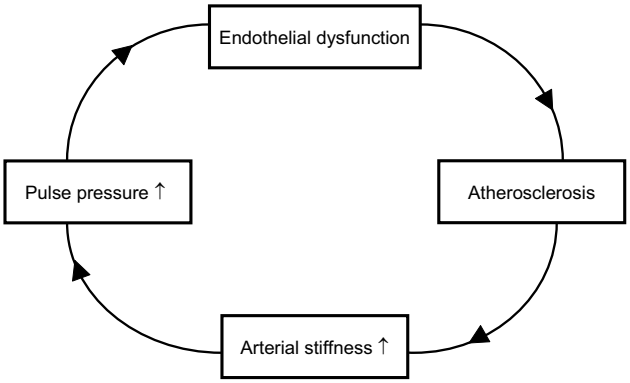


Fig. 4. Vicious circle of events resulting from endothelial dysfunction and augmented arterial stiffness.

Increased arterial stiffness is also an important determinant of myocardium and coronary perfusions. In Figure 3 we already described the mechanism through which increasing arterial stiffness leads to augmented central PP, *i.e.,* the difference between systolic and diastolic aortic pressures. The increase in central systolic pressure is thus associated with an increased afterload, which if persistent, promotes the development of left ventricular (LV) hypertrophy, an independent cardiovascular risk factor (Bouthier et al., 1985; Toprak et al., 2009). Conversely, the decrease in central diastolic pressure compromises myocardial blood supply, particularly in patients with coronary artery stenosis. However, the increased LV-mass induced by the augmented afterload will require an increased oxygen supply. Therefore, a mismatch between oxygen demand and supply may occur, leading to myocardial ischemia, LV diastolic and later systolic dysfunction. The full mechanism is illustrated in Figure 5.

Finally, the widening of central PP induced by increasing arterial stiffness may affect the vascular bed of several end-organs, particularly of brain and kidney. Because both organs are continually and passively perfused at high-volume flow throughout systole and diastole, and because their vascular resistance is very low, pulsations of pressure and flow are directly transmitted to the relatively unprotected vascular bed. By contrast, other organs if exposed to increased PP may protect themselves by vasoconstriction (O'Rourke & Safar, 2005). This unique situation predisposes the brain and kidney to earlier micro- and macrovascular injuries (Laurent et al, 2003; Henskens et al, 2008; Fesler et al., 2007).

Relevance of PWV in clinical conditions

We already described the factors that modify arterial stiffness in normal conditions. We also reviewed the consequences of an increase of arterial stiffness to endothelial function, coronary perfusion and possible damages to heart muscle, brain and kidneys. We are interested in reviewing now the broad uses of PWV as an independent cardiovascular risk factor and its interaction with the others classical risk factors such as arterial hypertension, diabetes mellitus, and dyslipidemia. The independent predictive value of PWV for cardiovascular and all-cause mortality is finally underlined.

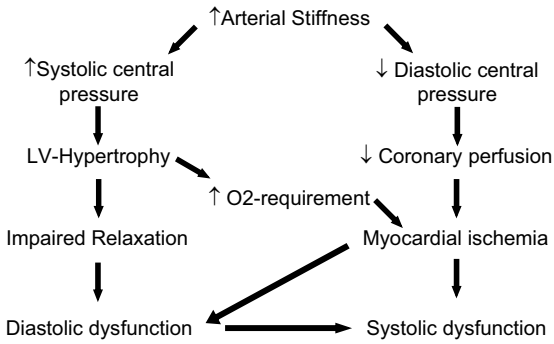


Fig. 5. Effects of increased arterial stiffness on the myocardium and its function.

Structural arterial abnormalities are already observed at an early stage of hypertension. Changes in the structure of the arterial wall, particularly of the matrix and the three-dimensional organization of the smooth muscle cells, have an important impact in determining arterial stiffness. Studies of white-coat hypertension (Glen et al., 1996) and borderline hypertension (Girerd et al, 1989) showed higher values of PWV compared to controls. Moreover, for a similar blood pressure, PWV was higher in patients than in controls, suggesting that the increased PWV was not only due to the elevated blood pressure but also to some structural changes of the arterial wall. As already mentioned, increased arterial stiffness leads to increased central systolic blood pressure, augmented afterload and ultimately left ventricular hypertrophy (Figure 5), which is itself a major cardiovascular risk factor (Bouthier et al., 1985; Lorell et al., 2000). Arterial stiffness and its associated augmented PWV is now recognized as an independent marker of cardiovascular risk (Willum-Hansen et al, 2006; Laurent et al., 2001) especially in hypertensive patients (Mancia et al., 2007).

Diabetes mellitus is one of the major cardiovascular risk factors and has been associated with premature atherosclerosis. There are numerous studies showing that both patients suffering from type 1 diabetes (van Ittersum et al., 2004) and type 2 diabetes (Cruickshank et al., 2002; Schram et al., 2004) have an increased arterial stiffness compared to controls. The increase in arterial stiffening in patients with type 1 and type 2 diabetes mellitus is evident even before clinical micro- and macrovascular complications occur (Giannattasio et al, 1999; Ravikumar et al., 2002), being already present at the stage of impaired glucose tolerance (Henry et al., 2003). Moreover, as in hypertensive patients, increased aortic PWV is identified as an independent predictor of mortality in diabetics (Cruickshank et al., 2002). The increase in arterial stiffness in patients suffering from diabetes mellitus is multifactorial (Creafer et al., 2003) and is associated with structural (Airaksinen et al., 1993) (extracellular matrix), functional (endothelium dysfunction) and metabolic (increased oxidative stress, decreased nitric oxide bioavailability) alterations. The most important mechanism seems to be the glycation of the extracellular matrix with the formation of advanced glycation end-products (AGEs): hyperglycemia favors AGEs formation which is responsible for the altered collagen content of the arterial wall (Airaksinen et al., 1993). A new class of drugs called "AGE breakers" is able to decrease the numbers of collagen cross-links and improve arterial stiffness in both diabetic rats (Wolffenbuttel et al., 1998) and humans (Kass et al., 2001).

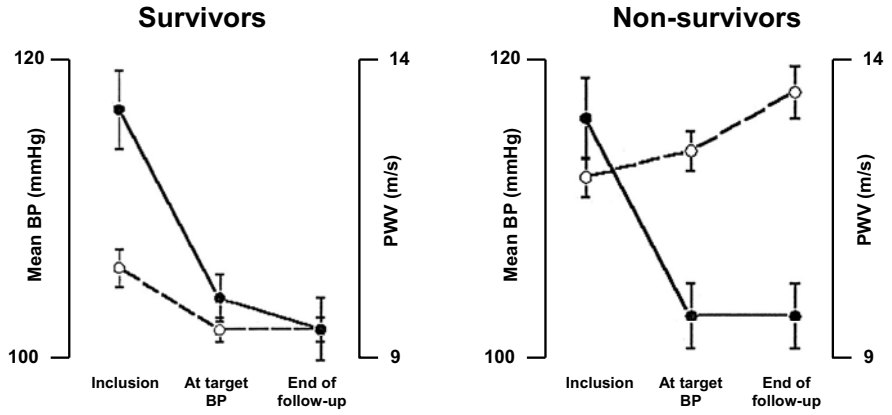


Fig. 6. Changes in mean BP (solid circles) and aortic PWV (open circles) of patients with end-stage renal disease for survivors and non-survivors: despite achievement of target BP non-survivors showed no improvement or even an increase in PWV, demonstrating on the one hand the presence of a pressure-independent component of PWV, and on the other hand, the relevance of PWV as an independent predictor for mortality. Adapted from (Guerin et al., 2001).

The association between lipids and arterial stiffness has been studied since the seventies, but the results are so far controversial. In patients suffering from coronary artery disease (CAD), an association between increased arterial stiffness and higher LDL has been proved (Cameron et al., 1995). On the other hand, in the general population the results regarding the relationship between LDL and arterial stiffness are controversial and some studies have reported a lack of association between total cholesterol and arterial stiffness (Dart et al., 2004).

Acute smoking is associated with increased arterial stiffness in healthy individuals and several patients subgroups, including normotensive, hypertensive and CAD. Studies on the chronic effects of smoking demonstrated contradictory results. However, the largest studies showed that chronic cigarette smoking was associated with increased PWV both in normotensive and hypertensive subjects (Liang et al., 2001; Jatoi et al., 2007).

Arterial hypertension and arterial stiffness induce the same end-organ damages such as coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) and chronic kidney disease (CKD) (Mancia et al., 2002). Many studies showed an association between increased PWV and the severity of CAD (Hirai et al., 1989; Giannattasio et al., 2007), CVD (Laurent et al., 2003; Henskens et al., 2008; Mattace-Raso et al., 2006), PAD (van Popele et al., 2001) and CKD (London et al., 1996; Shinohara et al., 2004).

Beyond its predictive value of morbidity, aortic stiffness appears to be relevant because of its independent predictive value for all-cause and cardiovascular mortality, in patients with arterial hypertension (Laurent et al., 2001), with type-2 diabetes (Cruickshank et al., 2002),

with CKD (Blacher et al., 1999), older age (Mattace-Raso et al, 2006; Meaume et al., 2001; Sutton-Tyrrell et al., 2005) and even in the general population (Willum-Hansen et al., 2006). Figure 6 demonstrates PWV to be a blood-pressure-independent cardiovascular risk factor for patients with end-stage renal disease.

Hence, if it is nowadays accepted (Nilsson et al., 2009) that arterial stiffness and PWV may be regarded as a "global" risk factor reflecting the vascular damage provoked by the different classical risk factors and time, how can we explain its limited use in clinical practice? The main reason seems to be its difficulty to measure. While blood pressure and heart rate are at present easily automatically measured, reliable PWV measurements still require complex recent equipments and, even worse, they require the continuous presence of a skilled well-trained operator.

4. Measuring aortic Pulse Wave Velocity *in vivo*

In the preceding sections we pointed out the need of including a vascular-related parameter into ambulatory monitoring, and we highlighted the clinical relevance of PWV as a surrogate measurement of arterial stiffness. In this section we analyse the strategies and devices that have been so far developed to measure PWV *in vivo*. Although in some cases these techniques rely on rather simplistic physiologic and anatomic approximations, their commercialization has triggered the interest in the diagnostic and prognostic uses of PWV (Boutouyrie et. al., 2009). For the sake of clearness, Table 1 summarizes the different approaches described in this section.

In general, given an arterial segment of length D, we define its PWV as:

$$PWV = D \,/\, PTT \tag{2}$$

where PTT is the so-called Pulse Transit Time, *i.e.,* the time that a pressure pulse will require to travel through the whole segment. Formally PTT is defined as:

$$PTT = PAT_d - PAT_p \tag{3}$$

where PAT_p corresponds to the arrival time of the pressure pulse at the proximal (closer to the heart) extremity of the artery, and PAT_d corresponds to the arrival time of the pressure pulse at its distal (distant to the heart) extremity.

In particular, concerning the aorta, we define PWV as the average velocity of a systolic pressure pulse travelling from the aortic valve (proximal point) to the iliac bifurcation (distal point), as Figure 7 illustrates. Note that this definition concerns the propagation of the pulse through anatomically rather different aortic segments, namely the ascending aorta, the aortic arch and the descending aorta. Accordingly, we re-define aortic PWV as:

$$PWV = (D_{asc} + D_{arch} + D_{desc}) / PTT_a \tag{4}$$

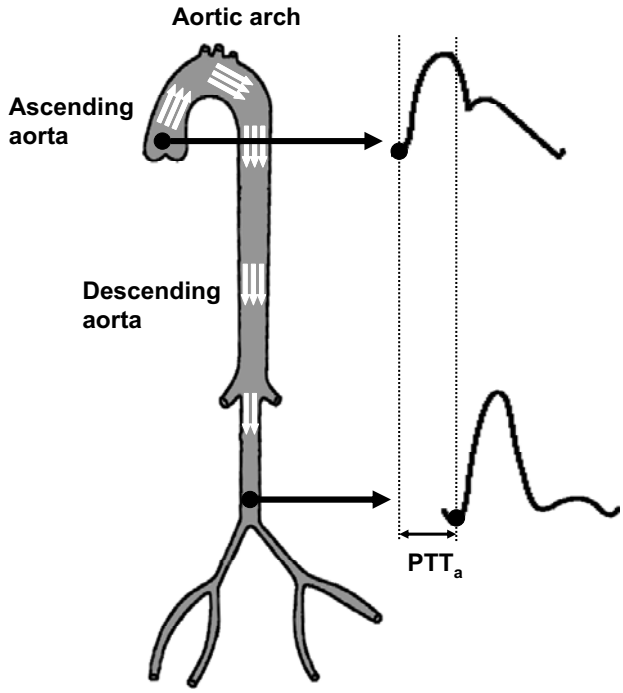


Fig. 7. Aortic PWV is defined as the average velocity of a pressure pulse when travelling from the aortic valve, through the aortic arc until it reaches the iliac bifurcation.

Hence, the *in vivo* determination of aortic PWV is a two-step problem: first one need to detect the arrival times of a pressure pulse at both the ascending aorta and the iliac bifurcation, and secondly one needs to precisely measure the distance travelled by the pulses.

A first group of aortic PWV measurement methods corresponds to those approaches that measure transit times in the aorta in a straight-forward fashion, that is, without relying in any model-based consideration. Because the aorta is not easily accessible by neither optical nor mechanical means, the strategy is to detect the arrival of a pressure pulse at two substitute arterial sites, remaining as close as possible to the aorta (Asmar et al., 1995). Starting from the aorta and moving to the periphery, the first arteries that are accessible are the common carotid arteries (at each side of the neck) and the common femoral arteries (at the upper part of both thighs, near the pelvis). This family of devices assumes thus the carotid-to-femoral transit time to be the best surrogate of the aortic transit time. Currently four commercial automatic devices based on this assumption are available: the Complior (Artech Medical, Paris, France), the Vicorder (Skidmore Medical, Bristol, UK), the SphygmoCor (AtCor Medical, New South Wales, Australia), and the PulsePen (DiaTecne, Milano, Italy). While Complior simultaneously records the arrival of a pressure pulse at the carotid and femoral arteries by means of two pressure sensors (Figure 8), Sphygmocor and PulsePen require performing the two measurements sequentially by means of a single hand-

held tonometer. A simultaneously recorded ECG supports the post-processing of the data obtained from both measurements (Figure 9). It has been suggested that because measurements are not performed on the same systolic pressure pulses, the SphygmoCor might introduce artifactual PTT variability (Rajzer et al., 2008). Unfortunately, there is so far no consensus on whether the transit times obtained by Complior and SphygmoCor display significant differences (Millasseau et al., 2005; Rajzer et al., 2008). Concerning the estimation of the travelled distance D, each manufacturer provides different and inconsistent recommendations on how to derive *D* from superficial morphological measurements with a tape (Rajzer et al., 2008). Regrettably Complior, SphygmoCor and PulsePen require the constant presence of a skilled operator who manually localizes the carotid and femoral arteries and holds the pressure sensors during the examination.

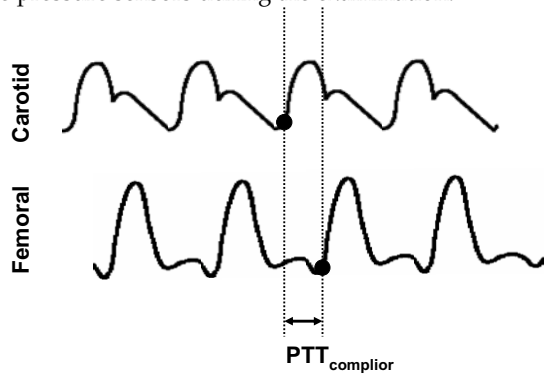


Fig. 8. Pulse transit time (PTT) as measured by Complior. The arrival time of a pressure pulse is simultaneously detected on the carotid and femoral artery. Complior implements as well a correlation-based PTT estimation.

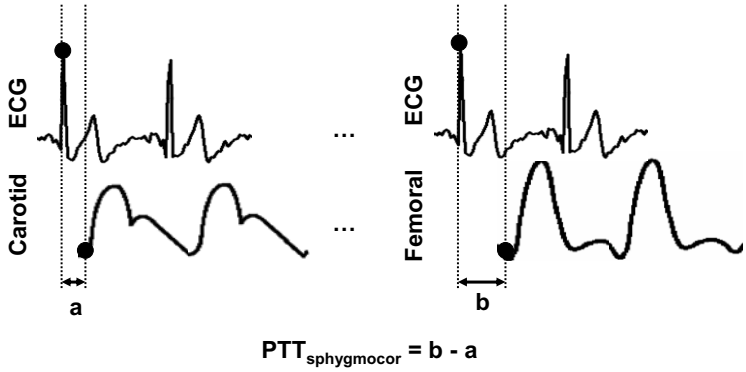


Fig. 9. Pulse transit time (PTT) as measured by SphysgmoCor. The delay between the R-Wave on the ECG and the arrival time of a pressure pulse is sequentially measured on the carotid and the femoral arteries. Both measurements are further combined to obtain a single PTT value.

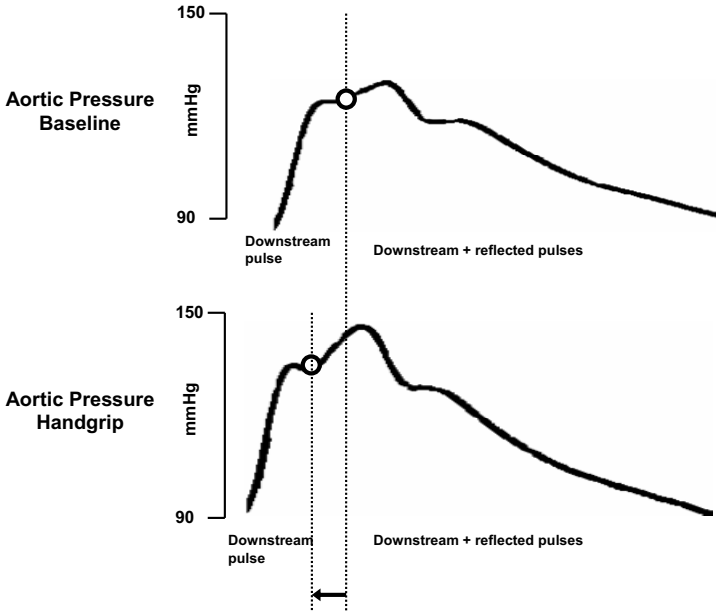


Fig. 10. Time to reflection (Tr) is defined as the arrival time of a pressure pulse that has been reflected in the arterial tree and travels back towards the heart. This example illustrates an important shortening of Tr for a male adult when performing a handgrip effort. During the sustained handgrip, mean arterial pressure is augmented, increasing the stiffness of the aorta and thus aortic PWV. Consequently, the reflected pulse reaches the aortic valve prematurely: Tr is shifted to the left in the bottom pressure pulse.

A second group of devices estimate aortic transit time based on wave reflection theory (Segers et al., 2009). It is generally accepted (Westerhof et al., 2005) that any discontinuity on the arterial tree encountered by a pressure pulse traveling from the heart to the periphery (downstream) will create a reflected wave on the opposite direction (upstream). Main reflection sites in humans are high-resistance arterioles and major arterial branching points. In particular, the iliac bifurcation at the distal extremity of the descending aorta has empirically been shown to be a main source of pulse reflections (Latham et a., 1985). Consequently, a pulse pressure generated at the aortic valve is expected to propagate downstream through the aorta, to reflect at the iliac bifurcation and to propagate upstream towards the heart, reaching its initial point after Tr seconds (Figure 10). Commonly depicted as Time to Reflection, Tr is related to the aortic length (D) and the aortic pulse wave velocity as:

$$Tr = 2\ D/\ PWV \tag{5}$$

Even though the concept of a unique and discrete reflection point in the arterial tree is not widely accepted and is currently the source of fervent discussions (Nichols, 2009), PWV values derived from the time to reflection method have been shown to be at least positively correlated to PWV measured by Complior, r=0.69 (Baulmann et al., 2008) and r=0.36 (Rajzer et al., 2008).

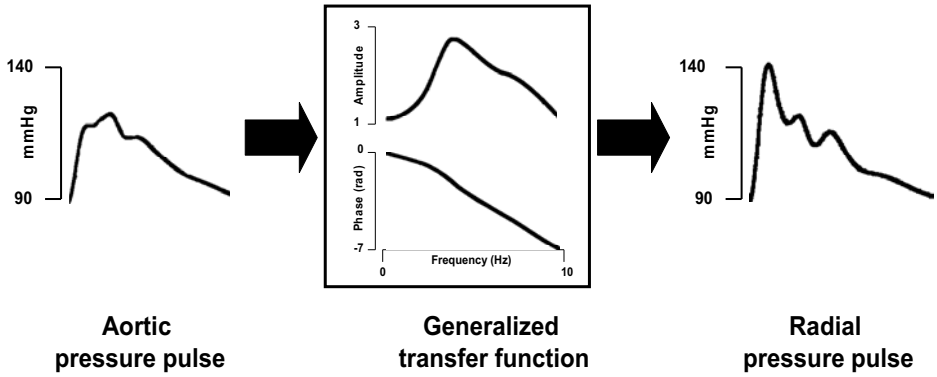


Fig. 11. Example of aortic pressure pulse, radial pressure pulse and the generalized transfer function that relates them. Adapted from (Chen et al., 1997).

Obviously a main issue is how to record aortic pressure pulses non-invasively (Hirata et al., 2006). Two approaches have been proposed so far. A first device, Arteriograph (TensioMed, Budapest, Hungary), records a sequence of pressure pulses at the upper arm by inflating a brachial cuff above systolic pressure, typically 35 mmHg. The brachial pressure waveform is then simply assumed to be a surrogate of the aortic one. Regardless of its manifest lack of methodological formalism, Arteriograph is so far the unique fully automatic and unsupervised commercial available device. Similarly, some recent studies aim at analyzing pressure pulses recorded at the finger to obtain similar results (Millasseau et al., 2006). A second device, SphygmoCor (AtCor Medical, New South Wales, Australia), records pressure pulses at the radial artery by a hand-held tonometer and then estimates an associated aortic pressure pulse by applying a generalized transfer function. In brief, the generalized transfer function approach relies on a series of empirical studies conducted during the 90s in which it was proven that the relationship between aortic and radial pressure pulses is consistent among subjects and unaffected even by aging and drug action (O'Rourke, 2009). Consequently, transfer functions provide a method for universally estimating aortic pressure pulses from radial artery measurements in a non-invasive fashion. Figure 11 illustrates the modulus and phase of the widely accepted aortic-to-radial general transfer function (Chen, et al. 1997). Large population studies (Gallagher et al., 2004) and numerical models of the arterial tree (Karamanoglu et al., 1995) have shown that the generalized transfer function is indeed consistently unchanged for frequencies below 5 Hz.

A third group of approaches comprises those developments based on the R-wave-gated pulse transit time. In brief, this technique exploits the strength of the ECG signal on the human body, and assumes its R-wave to trigger the genesis of pressure pulses in the aorta, at time $T_{R\text{-}wave}$. Then, by detecting the arrival time of a pressure pulse on a distal location (PAT_d) one calculates:

$$PTT_{R\text{-}wave} = PAT_d - T_{R\text{-}wave} \quad (6)$$

Unfortunately the physiological hypothesis relating $PTT_{R\text{-}wave}$ to PWV neglects the effects of cardiac isovolumetric contraction: indeed, after the onset of the ventricle depolarization (R-Wave in the ECG) left ventricles start contracting while the aortic valve remains closed. It is only when the left ventricle pressure exceeds the aortic one, that the aortic valve opens and generates the aortic pressure pulse. The introduced delay is commonly known as Pre-Ejection Period (PEP) and depends on physiological variables such as cardiac preload, central arterial pressure, and cardiac contractibility (Li & Belz, 1993). Hence, $PTT_{R\text{-}wave}$ is to be corrected for the delay introduced by PEP as proposed in (Payne et al., 2006):

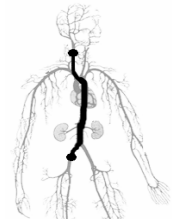
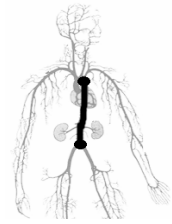
$$PTT'_{R\text{-}wave} = PAT_d - (T_{R\text{-}wave} + PEP) \quad (7)$$

Several strategies to assess PEP non-invasively are nowadays available, mainly based on the joint analysis of the ECG (Berntson et al., 2004) and either an impedance cardiogram or a phono-cardiogram (Lababidi et al., 1970; DeMarzo & Lang, 1996; Ahlström 2008). Nevertheless, even obviating the PEP correction, $PTT_{R\text{-}wave}$ has been shown to be correlated with PWV (r=0.37) (Abassade & Baudouy, 2002) and systolic blood pressure (r=0.64) (Payne et al. 2006). Concerning the distal detection of the pressure pulse arrival time (PAT_d), different approaches have been proposed so far. We describe here the most relevant ones. Novacor (Cedex, France) commercializes an ambulatory method to monitor PWV based on a fully automatic auscultatory approach: the so-called Qkd index. Qkd is defined as the time interval between the R-Wave on the ECG and the second Korotkoff sound detected on an inflated brachial cuff. The device is currently being used to evaluate long-term evolution of systemic sclerosis in large population studies (Constans et al., 2007). A different technology, photo-plethysmography, is probably the approach that has given rise to the largest number of research developments and studies in the field (Naschitz et al., 2005). Being non-obtrusive and cheap, this technology consists in illuminating a human perfused tissue with an infra-red light source and to analyse the changes in absorption due to arterial pulsatility (Allen, 2007). Each time a pressure pulse reaches the illuminated region, the absorption of light is increased due to a redistribution of volumes in the arterial and capillary beds. The analysis of temporal series of light absorption then allows the detection of the arrival of the pressure pulse. Regrettably, to obtain reliable photo-plethysmographic signals is not a simple task and, so far, only those body locations displaying very rich capillary beds have been exploited: namely the finger tips or phalanxes (Smith et al., 1999; Fung et al. 2004; Schwartz, 2004; Muehlsteff et al., 2006, Banet, 2009), the toes (Sharwood-smith et al., 2006; Nitzan et al., 2001) and the ear lobe (Franchi et al, 1996). Undoubtedly, the listed locations correspond to the classical placement of probes for pulse oximetry, or SpO2, in clinical practice (Webster, 1997). It is to be highlighted that recent studies have investigated the feasibility of performing pulse oximetry at innovative regions such as the sternum (Vetter et al., 2009). To reduce the cumbersomeness of measuring ECG has also been the aim of recent researches: a capacitively-coupled ECG mounted on a chair has been recently proposed to monitor $PTT_{R\text{-}wave}$ in computer users (Kim et al., 2006).

Finally, an emerging non-invasive technique remains to be cited, although its implantation in ambulatory monitoring seems nowadays unfeasible: the phase-contrast MR imaging (PCMRI) (Lotz et al., 2002). PCMRI opens the possibility to perform local measurements of PWV for any given segment of the aorta, by simply defining two regions of interest on the

image: a proximal and a distal region. By analysing the evolution of the regional blood flow velocity in each region, one determines the arrival times (PTT_p and PTT_d) of the pressure pulse. Because the distance between both aortic regions (D) can now be precisely measured, this approach is expected to provide highly accurate regional aortic PWV measurements. PCMRI was already introduced in the 90s (Mohiaddin et al., 1989), but the recent advances in MRI capturing rates seem to be encouraging the apparition of new studies (Boese et al., 2000; Gang et al., 2004; Laffon et al., 2004; Giri et al., 2007; Butlin et al., 2008). Fitting in the same category, some studies have been published on the assessment of PAT_d by means of ultrasound Doppler probes (Baguet et al. 2003; Meinders et al., 2001; Jiang et al., 2008).

Note that we have intentionally skipped from our analysis some works that have been performed on the tracking of pressure pulses artificially induced to the arterial wall by mechanical oscillators (Nichols & O'Rourke, 2005). Similarly, we have excluded those works based on the analysis of pressure-diameter and flow-diameter measurements (Westerhof et al., 2005).

Segments of the arterial tree	Method	Measurements of PTT and *D*	AMB	COM
	Carotid to Femoral PTT (simultaneous)	PTT is measured by two pressure sensors placed over the carotid and femoral arteries. *D* is estimated from superficial morphologic measurements.	No	Complior Vicorder
	Carotid to Femoral PTT (sequential)	PTT is measured by a single pressure sensor placed sequentially over the carotid and femoral arteries. ECG is used for synchronization purposes. *D* is estimated from superficial morphologic measurements.	No	SpyhgmoCor PulsePen
	Time to reflection, from brachial pressure pulse	PTT is measured by extracting Tr from the brachial pressure pulse recorded by a brachial obtrusive cuff. *D* is estimated from superficial morphologic measurements.	Yes	Arteriograph
	Time to reflection, from radial pressure pulse (generalized transfer function)	The aortic pressure pulse is estimated by applying a generalized transfer function to a radial pressure pulse recorded by a handheld tonometer. PTT is measured from the associated Tr. D is estimated from superficial morphologic measurements.	No	SphygmoCor

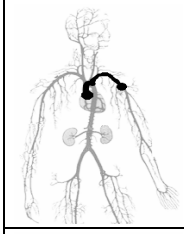
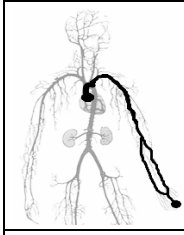
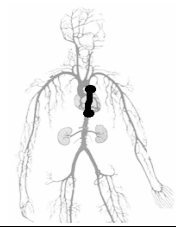
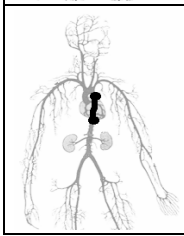
	ECG to brachial pulse transfer time	PTT is approximated as the delay between the R-Wave at the ECG, and the arrival of the pressure pulse at the brachial artery, recorded by a brachial obtrusive cuff. *D* is estimated from superficial morphologic measurements	Yes	NovaCor
	ViSi	PTT is approximated as the delay between the R-Wave at the ECG, and the arrival of the pressure pulse at the digital artery, recorded by photo-plethysmography. *D* is estimated from superficial morphologic measurements	Yes	-
	MR Imaging of aortic blood flow	PTT is measured by detecting the arrival of the pressure pulse at two or more different aortic sites, associated to different regions of interest in the PCMR images. *D* is accurately determined from the images.	No	-
	Sequential Doppler measurements of aortic blood flow	PTT is measured by detecting the arrival of the pressure pulse at two or more different aortic sites, by performing ECG-gated Doppler measurements. *D* is estimated from superficial morphologic measurements	No	-

Table 1. Summary of most relevant approaches to measure aortic PWV. Detailed descriptions are available on the text. PTT stands for Pulse Transit Time, *D* for distance, AMB for ambulatory compatibility, and COMM for commercial devices.

Determination of Pulse Arrival Times

Up to this point we assumed that detecting the arrival time of a pressure pulse at a certain aortic site was an obivous operation. Yet, clinical experience has shown that this is not the case: given a pressure pulse recorded either by tonometry, photo-plethysmography or any other measurement technique, it is not straight-forward to objectively define its Pulse Arrival Time, or PAT (Chiu et al., 1991; Solà et al., 2009). In the past, originally based on the analysis of pressure pulses obtained from cardiac catheterization, PAT was proposed to be estimated by identifying a collection of characteristic points (Chiu et al., 1991). Simply stated, a characteristic point is a typical feature that is expected to be found in any pressure pulse waveform. In particular one is interested in those features describing the position of the wavefront of a pulse. The justification is rather simple: on one hand the wavefront is the most patent representative feature of the arrival time of a pulse (Chiu et al., 1991), and on

the other hand it is expected to be free of deformations created by reflected waves, thus maintaining its identity while propagating through the arterial tree. Conversely, any other feature of the pressure pulse waveform cannot be assigned an identity in a straight-forward manner (Westerhof et al., 2005).

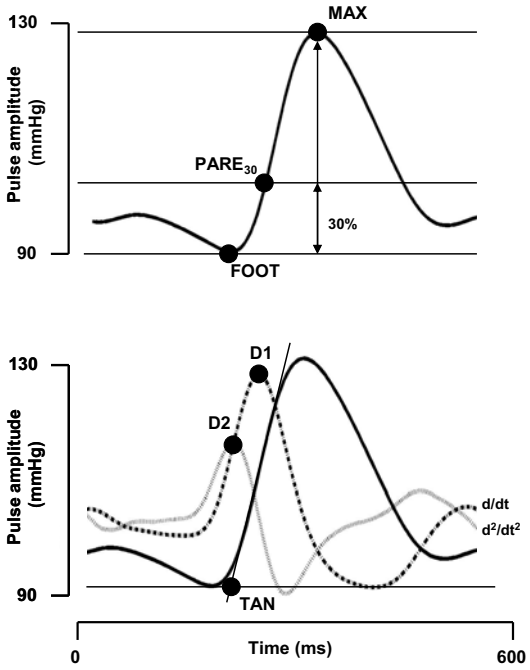


Fig. 12. Characteristic points encountered on a pressure pulse (bold curve) according to state-of-the-art definitions. Time zero corresponds to the R-Wave of a simultaneously recorded ECG.

Hence, the state-of-the-art extraction of characteristic points relies on the morphologic analysis of the wavefront of pressure pulses. The analysis is commonly based on empirically-determined rules, as illustrated in Figure 12. For the sake of completeness, we briefly describe them: the foot of a pressure pulse (FOOT) is defined as the last minimum of the pressure waveform before the beginning of its upstroke. In (Chiu et al., 1991) an iterative threshold-and-slope technique to robustly detect FOOT was proposed. The partial amplitude on the rising edge of the pulse (PARE) is defined as the location at which the pressure pulse reaches a certain percentage of its foot-to-peak amplitude. The maximum of the pressure pulse (MAX) is defined as the time at which the pressure pulse reaches it maximum amplitude. The maximum of the first derivative (D1) is defined as the location of the steepest rise of the pressure pulse. The first derivative is commonly computed using the central difference algorithm in order to reduce noise influences (Mathews & Fink, 2004). The maximum of the second derivative (D2) is defined as the location of the maximum inflection