Assessment of arterial function in pregnancy: recommendations of the International Working Group on Maternal Haemodynamics

Short title: Arterial function

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Short Abstract

There is strong evidence supporting a role of maternal arterial dysfunction in pregnancy-specific disorders such as pre-eclampsia and intra-uterine growth restriction. As more work is focused towards this field, it is important that methods and interpretation of arterial function assessment are utilised appropriately. Here, we summarise techniques and devices commonly used in maternal health studies, with considerations of technical application within pregnant cohorts.

Introduction

Arterial function is recognised as an important 'risk marker' in evaluating cardiovascular disease (CVD). There exist several parameters to assess localised and global arterial function in both clinical and research settings. These are summarised in a consensus report from the European Network for Non-invasive Investigation of Large Arteries[1], however there lacks specific guidance of use in pregnant cohorts. Here, we outline suitable techniques and devices for arterial function assessment in pregnancy and interpretation of results. We also summarise, in brief, key studies of arterial function in normal and adverse outcome pregnancies.

The arterial system

The arterial tree branches from the aorta, terminating in the smallest arterioles, from which capillaries arise. Due to the pulsatile nature of cardiac ejection, blood pressure (and flow) oscillates throughout the arterial tree.

Aortic elasticity plays an important role in buffering oscillatory changes in blood pressure. Additionally, local adjustments to vascular tone in smooth muscle that predominate in smaller arteries and arterioles also help regulate arterial blood flow. Common indices of large artery elasticity and vascular tone regulation include arterial stiffness, arterial wave reflections and endothelial function, as described below.

Arterial stiffness

Large arteries play an important role in buffering cyclical changes in blood pressure (BP), by reducing peak pressure, maintaining diastolic pressure and smoothing blood flow. With arterial stiffening, which occurs with age and pathological processes such as atherosclerosis or genetic predisposition (e.g. with genes involved in the differentiation of vascular smooth muscle cells)[2], there is an overall increase in pulse pressure, resulting in isolated systolic hypertension.. The repeated cyclical stress of a high pulse pressure propagates a vicious cycle of further arterial stiffening through fatigue fracture of the elastic elements within the arterial wall.

Arterial stiffness can be described by the PWV, which indicates the velocity of blood flow in the aorta, which is a large elastin-containing vessel. Augmentation index is taken as a proxy of endothelial function in muscular arteries.

The velocity of the pressure wave is inversely related to vessel elasticity and compliance. As arteries stiffen, transmission velocity, commonly expressed as pulse wave velocity (PWV) increases. PWV also increases as the pressure wave travels from the aorta to the periphery, indicating that vascular compliance is less in the distal parts of the arterial tree.

Aortic PWV (aPWV) is considered the 'gold standard' measurement of arterial stiffness, as the thoracic and abdominal aorta makes the largest contribution to arterial buffering actions, and aPWV is an established independent predictor of outcome[1]. The carotid-femoral pathway is commonly used as a pragmatic representative of the aortic system as it covers the region that exhibits the greatest age-related stiffening[3], and both arteries are superficial and easy to palpate.

Arterial stiffness defined as aPWV is an independent predictor of CV mortality and morbidity in hypertension, type 2 diabetes and end-stage renal failure[1]. In a meta-analysis of over 17,000 participants, aPWV reclassified risk and improved model fit for future cardiovascular events even after accounting for standard risk factors[4]. The 2011 European Society of Hypertension guidelines suggest that in arterial hypertension, PWVcf over 10m/s relates to sub-clinical organ damage and cardiovascular events[5]. There are no reported normal limits for PWV in pregnancy, although <10m/s is within range for healthy non-pregnant women [6]. PWV has been reported to increase significantly with maternal weight and age, but not parity or smoking status[7].

PWV measurement techniques and devices

PWV is calculated by measuring the transit time (Δt) taken for a pressure pulse to travel between 2 set points; in carotid-femoral PWV (PWVcf), from common carotid to the ipsilateral femoral artery. Although direct carotid-femoral measurements are preferred, this may not always be feasible. Several non-invasive devices derive the distance (D) covered by the pulse wave approximated to surface distance between two marked sites. PWV is calculated as PWV= D (meters)/ Δt (seconds). The foot to

foot (with 'foot' of pulse wave defined at the end of diastole) measurement of PWVcf is shown in Figure 1.

Measurement of distance is relatively simple with the use of a ruler or measuring tape, although the site (for example measuring the carotid wave at or above the sternal notch) should always be standardised for all tests within a cohort. In pregnancy, metal callipers rather than tape measure is advised due to the distortion of linear distance measurements from the shape of the pregnant uterus.

To measure time delay between pressure wave forms(Δt), there are a variety of devices utilising either computerized oscillometry[6], applanation tonometry[8], Doppler[9] or mechanotransducers[10]. There is no consensus on which method or device is most valid[11, 12], and most, due to non-invasive features can be suitably applied in pregnancy. Most devices have been validated against invasive testing in non-pregnant cohorts, but not in pregnancy [13-15]. Increment in distending pressure as influenced by mean arterial pressure (MAP) increases PWV and, therefore, MAP levels need to be taken into account when comparing groups. The effect of heart rate is less clear but may be a confounding factor as well[16].

The Complior System® (Colson, France), based on the piezoelectric principle uses skin mechanotransducers to detect simultaneous pressure wave forms which can be visualised in by the operator. Once waveforms of sufficient quality appear, the Δt between the pressure waveforms at both sites is calculated using a correlation algorithm on the initial pulse rise to just after true pulse peak and PWV is calculated

Pressure waves can also be recorded sequentially at different sites, and Δt calculated from a simultaneous ECG recording. SphygmoCor® (ArtCor, Australia), a device with moderate reproducibility[17] uses high-fidelity applanation tonometer to obtain successive proximal and distal pulses a short time apart. Δt is then determined as the time difference of the ECG R-wave in relation to the distal and proximal pulses. As the measurements are a short time apart, changes in heart rate variability have minimal effect on Δt results.

The Arteriograph® (Tensiomed, Hungary) and Vicorder® (Skidmore Medical Limited, United Kingdom) devices uses an oscillometric distension technique to obtain PWV. Vicorder® has not been validated against invasive testing for pulse wave analysis, however it has been validated against SyphygmoCor® and shows good agreement

of aPWV values, though with an inherent bias toward lower Vicorder® aPWV values at higher values of SphygmoCor® aPWV[18]. Arteriograph is based on plethysmography and registers pulsatile pressure changes in an artery. Typically, upper arm blood pressure is first measured using a cuff, which is then inflated at least 35mmHg over the systolic pressure, and brachial artery pressure fluctuations are analysed. The difference in time between the beginning of the first wave and the beginning of the second (reflected wave) is related to a measured distance from the jugulum to the symphysis, resulting in the PWV. With Vicorder, a pad that inflates over several centimetres is placed around patient's neck, and a cuff is around patient's upper right thigh. Both carotid and femoral cuffs are inflated to 65mmHg and the corresponding oscillometric signal from each cuff is obtained in real time. Once the operator is satisfied with waveform quality, the test is terminated and an algorithm of the two waveforms is analysed to produce ∆t.

Arterial wave reflections

Another surrogate measure of arterial stiffness is the arterial pressure waveform, which is a composite of a forward travelling wave generated by left ventricular ejection, and a backward travelling reflected wave arising from sites of impedance mismatch such as arterial taper and major arterial bifurcations. The change in impedance is thought to generate wave reflections (much like the effect of dropping a stone into a small pond, waves hitting the pond edge will be reflected back towards the centre) that summate to form a single effective reflected wave that flows back in the ascending aorta early in the cardiac cycle.

As arterial compliance decreases, the reflected wave superimposes on the pulse pressure at an earlier time adding to the forward wave and augmenting the systolic pressure. This can be quantified through augmentation index (AIx): the ratio of the reflected wave to the pulse pressure, and is usually expressed in percentage (depicted in Figure 2). While PWV reflects aortic stiffness, AIx is to some extent determined by endothelial dysfunction and arterial resistance, and is thought to be a more sensitive early marker of arterial stiffness [19]. Central AIx has shown independent predictive values for all-cause mortality in end stage renal disease

patients, and hypertensive patients[20, 21]. AIx increases linearly with age until 50- 60 years when it plateaus[8, 22].

AIx measurement and devices

AIx should be analysed at the ascending aorta as that most accurately represents the ventricular afterload imposed by central large artery walls. However, it is difficult to obtain direct measurements from central arteries, therefore AIx is commonly estimated either from the radial or the brachial artery waveforms. Using a validated transfer function, an aortic pressure waveform is then calculated. AIx increases with mean arterial pressure (MAP) and is inversely related to heart rate and body height, so these variables should be accounted for when interpreting results. Commonly, AIx is adjusted for a heart rate of 75 beats/min (AIx-75). In pregnancy, maternal racial origin, smoking status, parity, BMI and mean uterine artery PI were not significant predictors of AIx-75[23].

The most widely used approach is to perform tonometry in the upper limb, usually the radial artery, with a high fidelity probe such as the Millar strain gauge transducer (SPT-301, Millar Instruments). The pressure waveform analysis is then inputted into a transfer function[17] (Sphygmocor, AtCor, Australia) to calculate aortic AIx. Alternatively, carotid tonometry can be done. For this, a transfer function is not necessary as the arterial sites are quite close, and the observed waveforms are similar. However carotid tonometry requires more technical expertise and therefore there is more room for operator error, especially in obese patients where the carotid artery may be more difficult to palpate.

While AIx is a relative measurement and can be calculated without calibration, its components: central pulse, heart rate, augmentation and systolic blood pressure are absolute values and require calibration[1].

Oscillometric device such as Vicorder® and Arteriograph® (as described above) can also be used to analyse pressure waveforms. Brachial artery waveforms are obtained using a fluid distension technique via cuff inflation on the upper arm. Similar to tonometry, these waveforms are then transformed by a transfer function

to give aortic AIx. No comparative studies between Vicorder® and tonometry have been done in pregnancy. In a non-pregnant cohort of COPD patients, AIx measurements significantly correlated between Vicorder® and SphygmoCor®, however limits of agreement were only -10.42-9.02%, with co-efficient of reproducibility of 27.9%[24]. Vicorder® values were lower but there was satisfactory agreement[24].

Arteriograph® obtains AIx from calculating the pressure difference (amplitude difference between the start of a first wave P1 and the start of a second reflected wave P2) in relation to the pulse pressure (PP). The brachial artery waveform readings allow AIx calculation: AIx (%) = [(P2 - P1)/PP] × 100 and thus provides the brachial AIx without applying a transfer function. Similarly, there are no validation studies of Arteriograph® in pregnancy, however it has been widely used in pregnancy research[7, 25, 26], and validated against aortic AIx obtained by cardiac catheterisation in a non-pregnant cohort[13].

The advantages and disadvantages of commonly used devices for PWV and AIx are presented in Table 1.

Endothelial function

The endothelium lines the internal surface of arteries and is sensitive to changes in haemodynamic signals and responds by releasing a number of vasodilator substances, the most potent of which is nitric oxide, NO, or vasoconstrictors. Endothelial injury with resulting dysfunction is associated with atherosclerosis and cardiovascular events[27].

Endothelial function is commonly examined by upper arm flow-mediated dilatation (FMD) or forearm blood flow (see Table 2 for comparison of advantages of techniques). Brachial artery FMD correlates with measures of coronary endothelial function[28,29]. Normal arteries dilate 10%- 15% depending on the position of the cuff and equipment used. By definition, if vasodilation does not reach 5%, there is overt endothelial dysfunction[29].

FMD measurement

FMD measurements as described by Celermajer et al[30] has been extensively used with good reproducibility and low inter-observer variability[31]. This technique requires an ultrasound system equipped with a high-frequency linear vascular probe, vascular software for 2D and colour Doppler imaging, and an internal ECG monitor so that each image frame of blood flow can be synchronized to the cardiac cycle. A stereotactic probe-holding device will limit measurement error by micro-movements of probe by the operator.

With the subject lying supine, a baseline longitudinal image of the brachial artery with clear anterior and posterior intimal interfaces between the lumen and vessel wall is first acquired. Then, arterial occlusion is created by a forearm blood pressure cuff inflated to suprasystolic pressure for a standardized length of time. Subsequent cuff deflation induces a brief high-flow state through the brachial artery (reactive hyperaemia) and the resulting increase in shear stress causes endothelium-dependent vasodilation. The longitudinal image of the artery is recorded continuously from 30 seconds before to 2 min after cuff deflation. This continuous imaging period should be sufficient to capture peak arterial dilatation, which is reported to occur around 57 ± 15 seconds in pregnant women[32]. At least 10 min of rest is needed after reactive hyperaemia before another image is acquired to reflect the reestablished baseline conditions.

If endothelium-independent vasodilation response is to be tested, an exogenous NO donor (usually nitroglycerine-NTG spray or sub-lingual tablet) is administered prior to the steps above, to determine maximum obtainable vasodilator response 3-4 minutes after NTG administration. The observed endothelium-independent vasodilation reflects vascular smooth muscle function.

FMD is calculated as a percentage change from baseline diameter to the peak diameter in response to reactive hyperaemia using the following equation:

FMD (%) = [(peak diameter- baseline diameter)/ baseline diameter] x 100.

Forearm blood flow measurement

Studies have variably used either upper arm or forearm cuff occlusion, and although there is no consensus as to which technique provides more precise information, forearm blood flow measurement is generally considered the 'gold standard' for endothelial function testing. Rresistance vessel function in the forearm is assessed by strain-gauge venous impedance plethysmography. This works on the underlying principle that if venous return from the arm is obstructed and arterial inflow continues unimpeded, the forearm swells at a rate proportional to the rate of arterial inflow[33]. The procedure is generally carried out in the following way: a wrist cuff is inflated to suprasystolic pressure and 60 seconds allowed before measurements commenced. A second cuff is placed around the upper arm and inflated to about 40mmHg (higher than venous pressure but lower than diastolic pressure) at intervals of 10 seconds with 5 seconds deflation, allowing venous emptying whilst not impeding arterial inflow. The arms are positioned above the heart using pads and cushions. A strain gauge is placed around the widest part of the arm and the changes in circumference (which reflect changes in forearm volume) are measured.

This test is most useful when comparing dose-response relationships of different drugs within a single study, however major drawbacks include reproducibility (due to variations in arterial pressure, initial forearm blood flow and forearm size) and more invasive nature compared with FMD.

Application of arterial function studies in pregnancy

In normal pregnancy, there is a significant reduction in unadjusted aPWV from pre-conception to the second trimester (although the reduction is not significant using MAP-adjusted PWV). PWV remains low or increases slightly in the third trimester and returns to baseline in the post-partum period[34, 35]. Aortic AIx adjusted for heart rate (AIx-75) in normal pregnancy follows a similar pattern to PWV, with the most significant changes occurring between pre-pregnancy and the early first trimester[36]. FMD is reported to increase in pregnancy until 32 weeks and decreases significantly at 36+ weeks[37, 38].

Studies of arterial stiffness in complicated pregnancies have been largely focused on pre-eclampsia, intra-uterine growth restriction (IUGR), pre-term birth and gestational diabetes (GDM) [7, 26, 39, 40]; disorders that are associated with higher future CV event risk for the mother.

Arterial function in hypertensive disorders of pregnancy

All parameters of arterial stiffness in pre-eclamptic women have been found to differ significantly from normal pregnancies. In a systematic review of 23 studies evaluating the effect of preeclampsia on arterial stiffness, women with preeclampsia had elevated arterial stiffness both during and after pregnancy, and to a greater extent than in gestational hypertension (GH). More severe presentations of preeclampsia was associated with a greater degree arterial stiffness[41]. It should be noted however, that only a few studies in the review adjusted arterial stiffness measurements for important variables of maternal heart rate or blood pressure. Significantly higher levels of aortic PWV and AIx have also been observed in the sub-clinical stage (as early as 11 weeks) of pre-eclampsia[23, 40]; the magnitude of PWV increase in these early phases was similar to that seen in established pre-eclampsia. Cross-sectional and longitudinal studies that assess arterial stiffness in these early sub-clinical stages have shown the potential for arterial stiffness indices as a screening test to predict subsequent development of early and late-onset pre-eclampsia, especially when combined with other maternal variables such as central systolic blood pressure[7, 40].

Lower FMD has been found in the first and second trimesters among high-risk women who subsequently developed preeclampsia, compared to controls[42, 43]. An increase in FMD 4-6 weeks post-partum in women who had preeclampsia, has been observed, suggesting a partial reversal of the endothelial dysfunction[44]. Very few studies of endothelial function within pregnancy have included both endothelial dependant and endothelial independent measurements, and this may affect findings as both processes are intricately related, and have large variations in pregnancy[19].

Arterial function in fetal growth restriction

Very few studies have examined PWV in isolated IUGR. In one which reported on small for gestational age babies (which may have included a sub-set of IUGR), no differences were found in PWV recorded in the first trimester[45]. A relationship between PWV (third trimester) and birth weight in normal pregnancies was found, with an increase of 1 m/sec in PWV associated with a decrease in birth weight centiles by 17.6%[46]. In pregnant women with chronic hypertension who subsequently develop both superimposed preeclampsia and fetal growth restriction aortic AIx-75 was a determinant of birth weight, and was the only significantly elevated haemodynamic parameter in patients who developed fetal growth restriction but not superimposed preeclampsia[47]. Aortic AIx, while normal in women with normotensive SGA pregnancies, was elevated in women who later presented with pre-eclampsia and SGA fetuses. In postnatal women whose pregnancies were affected by IUGR, there was a persistent difference in FMD compared to controls, whether hypertensive or not[48]. This difference was not seen when comparing glyceryl trinitrate (GTN) responsiveness between the two groups; suggesting they are due to endothelial rather than vascular smooth muscle dysfunction.

Arterial function in diabetes in pregnancy

Arterial stiffness indices are higher in women with established GDM and in those with pre-existing type 2, but not type 1, diabetes mellitus[49, 50]. Furthermore, women who develop GDM have increased arterial stiffness, which are evident from the first trimester of pregnancy, suggesting its potential predictive value[26]. Possible mechanisms to explain these associations include alterations in the composition of the extracellular matrix and arterial remodeling due to hyperglycemia, and oxidative stress, leading to arterial stiffening. Additionally, diabetes is associated with reduced nitric oxide production, which may impair endothelial function.

Recommendations for assessing arterial function in pregnancy

- Due to the rapid responses of sympathetic activity and the arterial system to internal and external influences, as many variables as possible should be standardised across all tests.

- Before any measurements are performed, adequate acclimatisation to the room in which the tests are carried out should be allowed. In general, participants rest in the position in which the tests are to be carried out (e.g. supine or sitting) for at least 5 minutes before commencement of the tests. For FMD measurements, a resting position of about 20 minutes is recommended[51].

- Room temperature should be set at approximately 22-24°C to control for orthostatic changes. As several medications that are taken in pregnancy can affect arterial function, it is generally recommended that participants refrain from taking medication for at least 4 half-lives of the drug prior to testing, where possible. Drug and vitamin intake over the last 24 hours should be recorded, and co-related to the results.

- It is recommended that participants abstain from caffeinated drinks at least 4 hours, and smoking for 12 hours prior to haemodynamic testing.

- In pregnancy, caval compression from the weight of the gravid uterus can affect circulating haemodynamics, therefore it is recommended that tests are carried out in the left lateral position. If longitudinal studies are done, this position should also be standardized even when the participant is not pregnant or in the first trimester.

- Comparison of results should also be adjusted for any neuro-hormonal perturbations associated with pregnancy and fertility e.g. phase of menstrual cycle if considering pre-conception studies, or breastfeeding if considering post-partum assessments. Participants that have undergone hormonal stimulation such as follicular priming in IVF may have very different haemodynamics[52], and this should be taken into account if comparing against women with spontaneous conceptions.

Recommendations for future research

- Arterial function testing in pregnancy has largely been focused on identifying different haemodynamic signatures in pathological pregnancies. More large scale studies are needed to assess and validate the role of arterial function parameters in predicting pregnancy complications, as well as assessing its prognostic value, whether on its own, or in combination with other biophysical and biochemical markers of metabolic dysfunction.

- Additionally, there lacks an understanding of arterial function changes pre-conception and in very early pregnancy in relation to pathological pregnancies, and therefore longitudinal pre-conception work is needed.

- There have been a few studies[53, 54] assessing the impact of therapy in pregnancy on arterial function, but larger scale studies would be helpful in evaluating how and to what extent the maternal arterial system responds, and whether treatment options can be adjusted to optimise clinical outcomes.

- To improve the understanding of changes in arterial stiffness, independently of confounding factors e.g. maternal heart rate or blood pressure which can change significantly in disorders such as pre-eclampsia, studies should report appropriately adjuster parameters alongside raw data.

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Table 1 Devices for measuring arterial stiffness (Pulse wave velocity [PWV] and augmentation index [AIx]). All devices tabulated are non-invasive, and none have been validated against invasive techniques in pregnancy.

Technique	Advantages	Disadvantages
Mechanotranducer Complior® (Alam Medical, France)	• Widely used in the first few epidemiological studies that demonstrated predictive value of PWV in cardiovascular disorders (CVDs). • Simultaneous recording of central and peripheral signal. • Portable device	• Errors associated with distance estimation signal
Oscillometric fluid distension • Arteriograph® (Tensiomed, Hungary) • Vicorder® (Skidmore Medical, UK)	• Affordable • Non-invasive • Good intra-observer variability • Can obtain AIx and central systolic blood pressure(BP)	• Vicorder not yet been validated against invasive techniques for arterial function testing
Tonometry SphymoCor® (AtcCor Medical, Australia)	• Used in many large observational studies linking arterial function to CV events	• Expensive • Measured distance is an estimation of the true distance and largely depends on body habitus

Tonometry **Omron HEM-9000AI**® **(Omron Healthcare, Japan)**	• Similar to SphymoCor and can obtain AIx and central systolic BP • Portable	• Cannot obtain PWVcf or central blood pressures
Ultrasound	• Can analyse waveforms simultaneously or separately using ECG synchronisation	• Requires extensive training • User-dependent variability
Photoplethysmography **PulseTrace PCA 2 and** **PulseTracePWV**® **(Micro Medical, UK)**	• More suitable for use in overweight populations	• Only give information on waveforms at peripheral body sites; information on central arterial waveforms less reliable • Inferior quality of waveform obtained from finger probe
Cardio-ankle vascular **index**® **VaSera System** **(Fukuda Denshi, Japan)**	• Records distensibility of whole aortic-iliac, femoral-tibial system	• Needs further validation process in comparison to PWVcf

Table 2. Techniques for measuring endothelial function

Technique	Advantages	Disadvantages
Flow mediated dilatation	• Non-invasive • Predicts outcome • Relatively quick assessment	• Considered a less precise method of assessment • Expensive collateral equipment
Forearm blood flow	• Currently gold standard • Allows assessment of basal nitric oxide (NO) • Strong co-relation with cardiovascular (CV) outcomes	• Invasive • Requires specialist research setting • Time-consuming

Figure Legends:
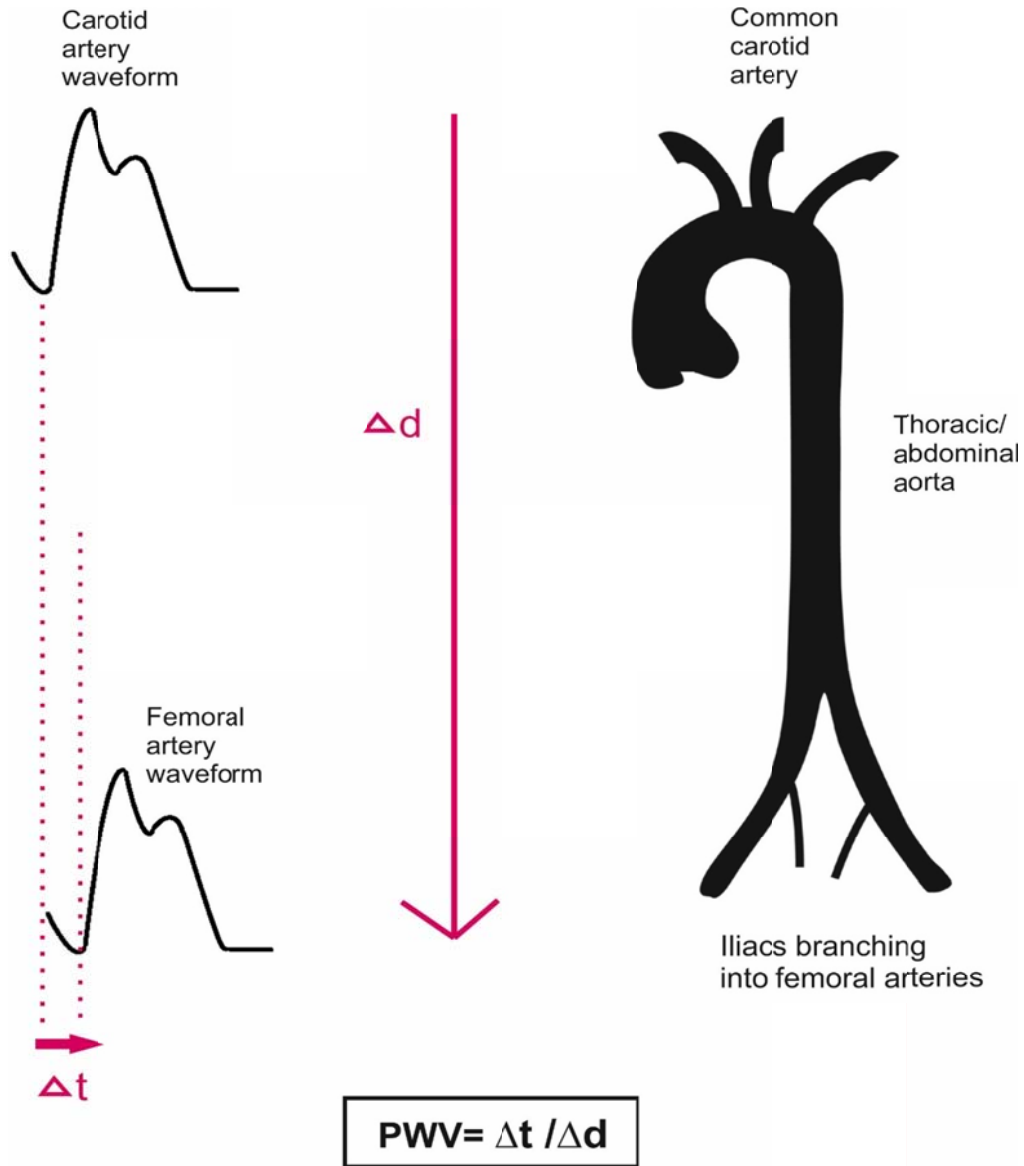
Figure 1: Foot to foot measurement of carotid femoral pulse wave velocity

Figure 2: The arterial waveform complex

Figure 1: 'Foot to foot' measurement of carotid-femoral pulse wave velocity

Figure 2. The arterial waveform complex