

Optical Techniques in the Assessment of Peripheral Arterial Disease

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Abstract: A variety of optical techniques have been developed over the years for experimental use in vascular disease, mainly for the assessment of lower limb peripheral arterial disease (PAD). Optical techniques have several advantages over more traditional experimental approaches. Photoplethysmograph (PPG) was one of the earliest methods used for this purpose; PPG satisfies many of the conditions for a non-invasive technique to estimate skin blood flow using infrared light, not only for research but also in clinical practice. PPG is a promising, safe and easy-to-use tool for diagnosis and early screening of various atherosclerotic pathologies and could be useful for regular GP-assessment or even self-monitoring of PAD at home or during individual physical exercises. This review discusses the application of PPG in the assessment of PAD.

Keywords: Peripheral arterial disease, ankle brachial pressure index, optics, plethysmograph and photoplethysmograph.

INTRODUCTION

It is estimated that peripheral arterial disease (PAD), a manifestation of systemic atherosclerosis, occurs in approximately 12% of the adult population, affecting about 10 million people in the United States [1, 2]. The prevalence of PAD increases with advancing age; almost 20% of people over the age of 70 years have the disease. The most common symptom associated with mild to moderate atherosclerotic PAD is intermittent claudication (annual incidence of 2% in persons over 65 years) [3]. The severity of PAD is closely associated with increased risk of myocardial infarction (MI), ischemic stroke, and death from vascular causes. The lower the ankle brachial pressure index (ABPI), the greater the risk of vascular events [4, 5]. Patients with critical leg ischaemia (the most severe clinical manifestation of PAD), who have the lowest ABPI values, have an annual mortality of 25% [6]. Therefore, the early diagnosis of PAD is essential to reduce morbidity and mortality. Non-invasive methodologies in the vascular laboratory play an important role in the evaluation and early detection of this condition [7]. Current non-invasive monitoring include: pressure (at rest and post-exercise), volume changes, blood flow velocity, temperature and oxygen tension [8, 9]. This review targets the emerging optical technologies based on the application of Photoplethysmography (PPG) in the assessment of PAD, principally early disease.

PLETHYSMOGRAPHY

Plethysmograph (PG) is a combination of the ancient Greek words 'plethysmos', meaning increase, and 'grapho' is the word for write, and is an instrument mainly used to

determine and register the variations in blood volume or blood flow in the body which occur with each heartbeat. PPG was one of the earliest methods devised for measuring blood flow in the extremities, having first been employed for this purpose around the turn of the century [9]. By 1938 Hertzman found a relationship between the intensity of back-scattered light and blood volume in the skin [8]. Indeed much of our basic knowledge of vascular physiology and pathophysiology has been derived from PPG studies. Table 1 shows the development of these methodologies. These include: air [10], water [11], impedance [12], photoelectric [13] and strain gauge [14].

PHOTOPLETHYSMOGRAPHY

Photoplethysmography (PPG) is an optical technique which typically operates using infrared light, allowing the transcutaneous registration of venous and/or arterial blood volume changes in the skin vessels. The complex interaction between the heart and connective vasculature are the components of the mechanism that generates the PPG signal.

METHODOLOGY

The fundamental of this technology is the detection of the dynamic cardiovascular pulse-wave, generated by the heart, as it travels throughout the body. The cardiovascular pulse wave is propagated by the elastic nature of the peripheral arteries, as they are excited by the contractions of the heart. The heart instigates a pulse pressure wave that travels throughout the arteries into deeper vasculature. Generally, the illuminating PPG wavelength is chosen to provide weak absorption in tissue, yet stronger absorption by blood, to provide a high degree of optical contrast. Infrared radiation is often employed and provides a convenient illumination source. It provides a signal proportional to changes in skin blood volume [15]. The wavelength of the light used is crucial when determining the parameters of interest – wave-

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Table 1. Types Plethysmography, Methodology and Clinical Applications

Types	Methodology	Outcomes	Major Applications
Photoelectric	Infrared densitometer (light-emitting diode)	Backscattered signal denotes red blood cell volume	Measures pulses, erythrocyte oxygen saturation, and volume (measuring ABPI to detect PAD)
Strain gauge	flexible tube filled mercury or gallium (Changes in the length of column of mercury)	Change in arterial or venous volume	Differentiates spasm from obstruction, estimates change in venous and arterial blood volume (evaluate PAD and DVT)
Air	An air-filled cuff (Pneumatic compression)	Change in venous volume	Estimates venous outflow and presence of reflux
Water	A self-sealing chamber filled with water (Volume displacement)	Change in venous volume	Estimates venous outflow and occlusive arterial disease
Impedance	Low frequency alternating current applied through electrodes (Ohm's law)	Estimates venous volume and measures emptying time in extremities	Estimates venous outflow and occlusive arterial disease (PAD and DVT)

Table 2. Summary of the Clinical Use of PPG

Therapy	Diagnosis	Evaluation
Treatment of skin disorders	Pulse counter in anaesthesia and intensive care	Action of drugs on circulation
PUVA for psoriasis	Heart rate meters in sport centres	To predict vessel graft occlusion in vascular surgery
Photodynamic therapy of cancer	Vascular changes in mental stress	To predict vessel graft occlusion in plastic surgery
Photodynamic therapy for jaundice in newborn	Raynaud's phenomenon	Assessment of post-phlebotic syndrome
Portwine stain coagulation	To predict ovulation in females	

lengths between 650-950 nm are commonly used because they combine good penetration with good contrast between the dark vessels (veins and arteries) and the light tissue. In this wavelength range haemoglobin in the blood absorbs much more strongly than the remaining tissue. Light is reflected after it reaches the skin and part of the light penetrates into deeper layers where it may be either scattered or absorbed.

Absorption is predominant in the epidermis and upper dermis, whereas scattering is predominant in deeper layers [16]. While absorption is due to specific chromophores such as water, haemoglobin and melanin, scattering is caused by the different refractive indices of tissue components such as cell organelles and membranes. In the dermis, collagen fibres are believed to be a major source of light scattering [17]. In the epidermis, the major absorbing entity in this spectral region is melanin. For example: the wavelength of 400-600 nm is absorbed in the dermis by blood chromophores: haemoglobin, oxyhaemoglobin, bilirubin and carotene. A weak absorption by blood occurs at wavelengths of 700-1300 nm with a low scattering in the dermis. A decreased absorption of the skin in the visible spectral region is caused by a considerably lower amount of biologically important chromophores in comparison with ultraviolet (UV) radiation (mela-

nin, DNA, urocanic acid and aromatic amino acids) [18]. The signal produced by PPG also depends on the location and the properties of the subject's skin at that site, including skin structure, blood oxygen saturation, blood flow rate and temperature [19]. Furthermore, the amount of reflected light varies with the number of red blood cells in the cutaneous microcirculation. Slight dilatation and contraction of arterioles and capillaries during each cardiac cycle attenuate light reflection.

PPG requires a light source and a detector, and their relative positions may vary. Differing PPG sensors have been designed with different aims: reflection mode (the light source and the detector are placed side by side with mean volume of interaction between infrared photons and measuring up to 4 mm in tissue depth) allows placing on virtually any tissue site [20] or transmission mode (light source and the detector opposite each other on the skin surface, illuminating a large tissue volume for strong signals) typically for application on the peripheral digits, or with fibre optic lines (Fig. (1)) for use in highly magnetic environments such as MRI. In quantitative PPG the optical illumination in the measuring area is automatically adjusted for each different type of skin until a predetermined level of reflected light is reached. With this technology, PPG measurements are inde-

pendent of skin colour, thickness and individual blood volume [21]. The PPG signal consists of AC and DC components (Fig. (1)). The AC component (for arterial pulse detection) is synchronous with the heart rate and depends on the pulsatile blood volume changes [22,23]. It has been suggested that the AC component is related to pulsatile blood volume changes because of varying lumen of the vessel and red cell orientation during each cardiac cycle [24, 25]. Conversely, the DC component (commonly used for venous evaluation) of the signal varies slowly and reflects variations in the total blood volume of the examined tissue [19].

THE APPLICATIONS OF PPG

PPG is mainly used to assess venous function non-invasively [26, 27]. For example, the muscle pump test (assessment of calf pump failure in chronic venous insufficiency), vein occlusion test (thrombotic obstruction) and venous resting pressure test. However, PPG can also be used to assess PAD [28]. For example, the perfusion tests [7, 29].

Peripheral pulses can be described in various ways, including timing, amplitude and shape characteristics to represent delay, diminishing and damping respectively, with arterial disease. There are few data in the literature, however, quantifying the normal ranges of pulse characteristics and how these change in vascular patients [28]. PPG has been used to measure the peripheral pulse; it can provide important information about the cardiovascular system [30]. Furthermore, these pulse signals can easily be obtained from the

tissue pads of the ears, fingers and toes where there is a high degree of superficial vasculature [31, 32]. This technique is simple and inexpensive, and can provide valuable information about the peripheral circulation [33]. Table 2 summarises clinical use of PPG.

PPG AND ANKLE BRACHIAL PRESSURE INDEX

PPG can be used to detect PAD [34, 35]. It has been used as a pulse detector, particularly to measure ankle systolic blood pressure in suspected arterial disease since the resting ABPI is the best indicator of arterial occlusive disease of the lower extremity [29]. PPG has also been used in conjunction with thigh occlusion cuffs to evaluate peripheral arterial flow (toe pulse) during treadmill exercises and reactive hyperaemia [36, 37]. One study used PPG to evaluate ABPIs calculated from ankle pressure measurements using an alternate technique with an inherent possibility of automation [38]. A PPG probe, integrated with the cuff was validated against the conventional colour Doppler pen for blood flow detection in intensive care patients and healthy volunteers. The major advantage of this PPG method is the possibility to automate the measurement procedure, and thereby decrease observer dependency. This study showed that the sensitivity and specificity for identification of vascular disease were identical between the two measurements. Another study used a new PPG probe specially designed for the detection of arterial blood flow at the ankle. This probe is positioned underneath a standard pneumatic cuff, serving for future stan-

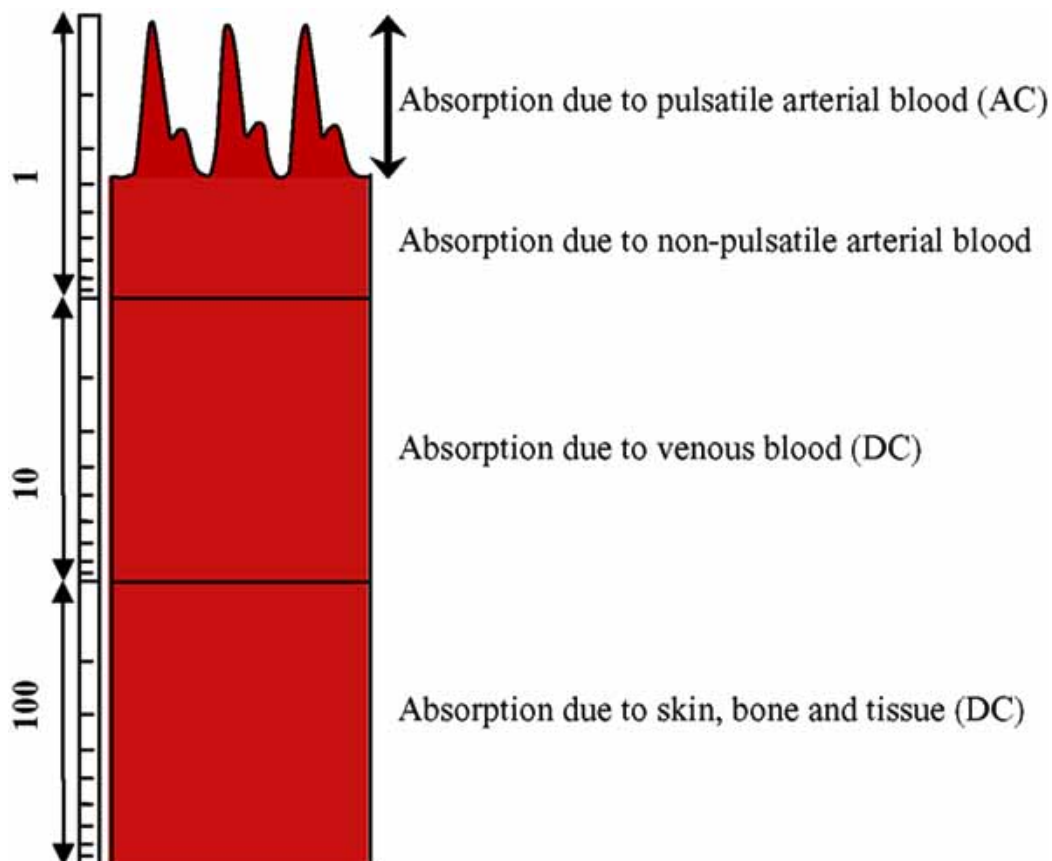


Fig. (1). The steady and pulsatile components of the PPG signal.

dardization of cuff application and automation of the pressure measurements [39]. This showed that systolic ankle pressure measurements could become less operator dependent [40]. These findings are encouraging and motivate continued development of the PPG technique. But both the colour Doppler and the PPG methods suffer the limitations associated with the use of a pneumatic cuff, which might produce invalid blood pressures in subjects with stiff ankle arteries (e.g. diabetics) [38].

PPG can use the measurements of skin perfusion to assess the ischaemia of the lower limb, and its use is generally limited to the determination of relative changes in skin perfusion to a limited depth during a single application [41]. A system has also been developed for non-invasive monitoring of blood flow in the anterior tibial muscle [42]. These studies indicate that, depending on the optical geometry of the probe and wavelength, blood flow signals can be extracted from blood vessels in deep structures and this can be manifested by the mechanical force due to geometric realignment. In particular, changes in the optical probe coupling, anatomy of the patient or optical properties of the tissue can induce motion artefacts individually or in a combined fashion.

THE APPLICATIONS OF PPG IN PAD WITH ARTERIAL STIFFNESS

Arterial stiffness increases with age, diabetes mellitus, hypercholesterolemia, hypertension and end-stage renal disease [43]. Since changes in arterial stiffness may precede the clinical manifestations of cardiovascular disease, indices of arterial stiffness may be utilized to monitor the preclinical progression of arteriosclerosis [44]. It has been used to assess radial artery compliance in long standing hypertensive patients [45]. PPG was also used to demonstrate changes in the arterial pressure/volume relationship (arterial elasticity) in healthy volunteers and compare them with patients with coronary atherosclerosis. There was an association between a reduction in arterial elasticity and atherosclerosis [46]. Arterial stiffness can be derived from measurements of the pulse wave velocity (PWV) using PPG [47]. One study used PPG to measure PWV fingers and toes in 20 young healthy subjects with those performed in 40 patients with atherosclerotic cardiovascular disease and including patients with intermittent claudication. This study showed that the PWV correlates with age and atherosclerosis [48]. A digital volume pulse (DVP) or as it also called arterial PPG can be obtained using PPG [22]. The DVP can be rapidly and simply detected by measuring the transmission of infrared light through the finger pulp [49], and has a strong correlation with arterial stiffness and central augmentation index (measurement of systemic arterial stiffness derived from the ascending aortic pressure waveform) [50]. Central pulse pressure and the augmentation index may therefore provide a more composite index of arterial compliance and hence be a better surrogate marker of whole body compliance than exclusively large artery measures, such as central PWV. Furthermore, increased arterial stiffness has been consistently demonstrated in type 2 diabetes and has also been proposed as independent risk factor for vascular disease [51]. A previous study demonstrated that the contour of DVP is similar to that of a peripheral pressure pulse [22]. The contour of the DVP is determined by the systemic circulation including pressure wave

reflection and PWV in the aorta and large arteries [22, 49, 52].

PPG AND THE ASSESSMENT OF DRUG ACTION

PPG was a useful tool to assess digital vascular resistance in a randomized study where patients (n=28) with essential hypertension took isradipine or atenolol [53]. PPG was also used to evaluate cutaneous microcirculation of the skin in patients with venous insufficiency and leg ulcers when taking Daflon 500 mg [54] or pentoxifylline [55].

PPG was used to monitor the beneficial effects of anti-hypertensive therapy on the systemic vasculature, particularly for elderly women in whom enhanced vasoreactivity may contribute to excessive cardiovascular morbidity and mortality [56]. It has also been used for the non-invasive monitoring of cerebral perfusion when administering anti-hypertensive therapy in elderly patients [57].

Using PPG in comparison with invasive arterial cannulation was equivalent in measuring the response to exogenous angiotensin. However, the reliability and reproducibility of PPG measurement appear to be more satisfactory [58].

PPG was also used to compare the pharmacokinetic and pharmacodynamic characteristics of angiotensin II receptor antagonists [59].

Some studies used PPG and computer-supported infrared thermographic imaging to distinguish the antinociceptive effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the treatment of acute pain [60].

Some studies have even used the optical technique to assess statin therapy by measuring the improvement in arterial compliance in patients with atherosclerosis and/or diabetes [61]. Furthermore, the non-invasive measurement of local arterial compliance using PPG may be a useful adjunct for cardiovascular risk assessment early in the course of the disease as well as for monitoring vascular response to therapy [62].

OTHER IMPLICATIONS OF PPG

PPG is also used in pulse oximetry to monitor arterial oxygen saturation (SpO₂) during anaesthesia and in intensive care units [63]. Another study [64] evaluated the response of different instruments designed to measure skin blood flow, using a simple animal model. Of these, PPG was the most sensitive to small decreases in perfusion, being able to detect a stenosis even before it became haemodynamically critical. This sensitivity arises from PPG using the pulsatile component of the distal pressure, which has been shown to be more sensitive to energy dissipation by stenosis than comparisons of absolute pressure [64]. The pulse wave transit time (PWTT) delay obtained from analysis of bilateral PPG signals seems to be a useful parameter for the assessment of unilateral arterial stenosis [65].

PPG and tonometric principles have been used in the measurement of baroreflex sensitivity (BRS) both of which have been shown to be practical and safe [66].

PPG is also promising in determining the prognosis of surgery for thoracic outlet syndrome [67]. PPG and laser

Doppler flowmetry (LDF) were used to measure changes in perfusion of the distal lower limb of a pig, in response to a stenosis created in the external iliac artery. PPG was more sensitive than the LDF to a small reduction in perfusion pressure [68]. Existing non-invasive PPG technology is also suitable for monitoring haemoglobin concentrations in blood flowing through accessing catheters during haemodialysis [69, 70] or apheresis [71], but truly non-invasive techniques have not proven to be accurate enough under other circumstances. Furthermore, PPG has been proposed as a candidate non-invasive technique for quantitative measurement for haemoglobin to eliminate the need for blood sampling, but it is limited by uncertainty regarding the effective light path length [72].

There is a high prevalence of PAD among patients with chronic renal failure (CRF) [73, 74]. One study recommended the use of PPG to measure ABPI and toe brachial index (TBI) in the evaluation of PAD in patients with CRF [75]. Whereas, another study showed an early involvement of the peripheral circulation (measuring forearm vascular blood flow and forearm vascular resistance) using PPG in association with increased urinary albumin excretion in normotensive and hypertensive patients [76].

DISCUSSION

The advantage of PPG methodology that it is completely automated and once the photosensor device is placed on the toe, the operator's hands are free. One study compared Doppler to PPG measurements showed that PPG waveform can be obtained in all but extremely advanced disease [77]. They were able to obtain pressure measurements by PPG in all four limbs in which the Doppler failed because of advanced occlusive disease or dense calcification in the posterior tibial artery or dorsalis pedis artery. The same limitations are seen with both methods in limbs with very high systolic arterial pressures, obesity or oedema, resulting in arterial incompressibility [78]. This study concluded that detection of low signal by infrared PPG is a simple and quick method that is comparable with the traditional Doppler signal and there is virtually no difference in the calculated ABPIs in either normal subjects or patients [77].

A weakness of PPG is measuring blood flow in deeper tissue. Although, a recent study showed that PPG can be potentially used non-invasively in the measurement of local muscle perfusion, some considerations still have to be accounted for, such as the influence of temperature on blood perfusion [79]. Therefore, current commercially available PPG systems are still inappropriate for monitoring deeper tissues [80]. A method that non-invasively monitors variations in muscle blood perfusion without causing trauma or pain is preferable to the current conventional method. There is a clinical need to monitor different physiological parameters from deeper laying tissues and vessels. For example, near-infrared spectroscopy (NIRS) is used to obtain information about tissue oxygenation from deeper vascular compartments in both cerebral [81] and muscle tissue [82, 83]. In comparison to LDF signal, PPG measurements demonstrated significant differences between both perfusion disorders throughout the entire observation period. This study sug-

gested that PPG may be reliably used to differentiate between arterial and venous perfusion disorders [84].

Furthermore, the potential of the multi-channel PPG technique for clinical sensing and monitoring seems quite promising, especially regarding early detection and assessment of cardiovascular pathologies [65, 85]. The PPG method is simple and has the advantage of automation and operator convenience. It is more forgiving in the non-compliant patient, and is able to detect low signal more accurately than the Doppler probe. This technique is highly accurate for measurements of systolic arterial pressures and calculation of ABPIs. Although, its use is still limited to research may also be developed to be used in primary care on a routine basis [78].

CONCLUSIONS

Non-invasive optical techniques have become a common method of assessing peripheral vascular function because there is no risk for the patient, and less expense in comparison with duplex scanning. PPG occupies a unique position among these methods. PPG has found considerable use in the field of non-invasive physiological monitoring and the most successful application of PPG in this century is pulse oximetry. Ultimately, the low-cost and simplicity of this optical-based technology could offer significant benefits to healthcare (e.g. in primary care where non-invasive, accurate and simple-to-use diagnostic techniques are desirable). The further development of PPG together with its non-invasive nature can place this methodology among other tools used in the management of vascular disease.

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