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TOPICAL REVIEW

Photoplethysmography and its application in clinical physiological measurement

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Abstract

Photoplethysmography (PPG) is a simple and low-cost optical technique that can be used to detect blood volume changes in the microvascular bed of tissue. It is often used non-invasively to make measurements at the skin surface. The PPG waveform comprises a pulsatile ('AC') physiological waveform attributed to cardiac synchronous changes in the blood volume with each heart beat, and is superimposed on a slowly varying ('DC') baseline with various lower frequency components attributed to respiration, sympathetic nervous system activity and thermoregulation. Although the origins of the components of the PPG signal are not fully understood, it is generally accepted that they can provide valuable information about the cardiovascular system. There has been a resurgence of interest in the technique in recent years, driven by the demand for low cost, simple and portable technology for the primary care and community based clinical settings, the wide availability of low cost and small semiconductor components, and the advancement of computer-based pulse wave analysis techniques. The PPG technology has been used in a wide range of commercially available medical devices for measuring oxygen saturation, blood pressure and cardiac output, assessing autonomic function and also detecting peripheral vascular disease. The introductory sections of the topical review describe the basic principle of operation and interaction of light with tissue, early and recent history of PPG, instrumentation, measurement protocol, and pulse wave analysis. The review then focuses on the applications of PPG in clinical physiological measurements, including clinical physiological monitoring, vascular assessment and autonomic function.

Keywords: ageing, artery, autonomic function, blood pressure, cardiac output, cardiovascular, diabetes, endothelial function, heart rate, infrared, microcirculation, photoplethysmography (PPG), pulse wave analysis, Raynaud's phenomenon, vascular disease, vein

1. Background to the topical review

Photoplethysmography (PPG) is an optical measurement technique that can be used to detect blood volume changes in the microvascular bed of tissue (Challoner 1979). It has widespread clinical application, with the technology utilized in commercially available medical devices, for example in pulse oximeters, vascular diagnostics and digital beat-to-beat blood pressure measurement systems. The basic form of PPG technology requires only a few opto-electronic components: a light source to illuminate the tissue (e.g. skin), and a photodetector to measure the small variations in light intensity associated with changes in perfusion in the catchment volume. PPG is most often employed non-invasively and operates at a red or a near infrared wavelength. The most recognized waveform feature is the peripheral pulse, and it is synchronized to each heartbeat. Despite its simplicity the origins of the different components of the PPG signal are still not fully understood. It is generally accepted, however, that they can provide valuable information about the cardiovascular system (Kamal *et al* 1989).

This review has two parts. An introductory section describes the basic principle of PPG operation, light interaction with tissue, early and recent history of PPG, instrumentation, measurement protocol, and pulse wave analysis. The second section reviews current and potential clinical applications in physiological measurement under the categories of clinical physiological monitoring, vascular assessment and autonomic function.

2. Photoplethysmography

2.1. The photoplethysmography waveform

The pulsatile component of the PPG waveform is often called the 'AC' component and usually has its fundamental frequency, typically around 1 Hz, depending on heart rate (figure 1). This AC component is superimposed onto a large quasi-DC component that relates to the tissues and to the average blood volume. This DC component varies slowly due to respiration, vasomotor activity and vasoconstrictor waves, Traube Hering Mayer (THM) waves and also thermoregulation (Burton 1939, Burton and Taylor 1940, Hertzman and Dillon 1940b, Hertzman and Roth 1942a, 1942b, 1942c, Hertzman and Flath 1963, Hyndman *et al* 1971, Peñáz 1978, Ahmed *et al* 1982, Harness and Marjanovic 1989, Nitzan *et al* 1996b, 1996a, general thermoregulatory pulse changes in Shusterman *et al* (1997), Schultz-Ehrenburg and Blazek (2001), Nitzan *et al* (2001)). These characteristics are also body site dependent (Allen and Murray 2000b). With suitable electronic filtering and amplification both the AC and DC can be extracted for subsequent pulse wave analysis.

2.2. Optical considerations of the origins of the photoplethysmography waveform

The interaction of light with biological tissue is complex and includes the optical processes of (multiple) scattering, absorption, reflection, transmission and fluorescence (Anderson and Parrish 1981). Several researchers have investigated the optical processes in relation to PPG measurements (Hertzman and Randall 1948, Brown *et al* 1965, D'Agrosa and Hertzman 1967, Weinman 1967, Zweifler *et al* 1967, Challoner 1979, Ochoa and Ohara 1980, Nijboer *et al* 1981, Roberts 1982, Lindberg and Öberg 1993, de Trafford and Lafferty 1984, Kamal *et al* 1989). They have highlighted the key factors that can affect the amount of light received by the photodetector: the blood volume, blood vessel wall movement and the orientation of red blood cells (RBC). The orientation effect has been demonstrated by recording pulsatile waveforms from dental pulp and in a glass tube where volumetric changes should not be

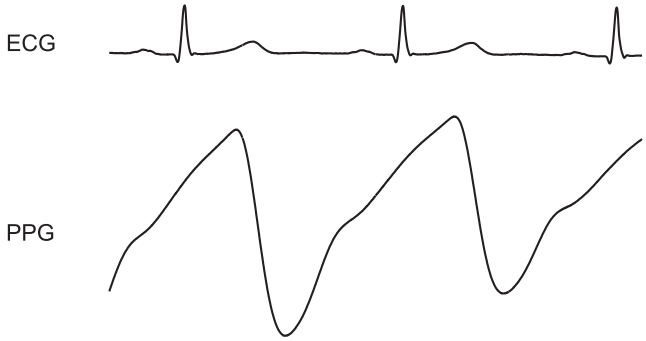

Figure 1. The pulsatile (AC) component of the PPG signal and corresponding electrocardiogram (ECG). The AC component is actually superimposed on a much larger quasi-DC component that relates to the tissues and to the average blood volume within the sample. It represents the increased light attenuation associated with the increase in microvascular blood volume with each heartbeat. In practice, the PPG waveform is often inverted.

possible, and more recently by Näslund *et al* (2006) who detected pulsatile waveforms in bone. The recorded pulses do bear a direct relationship with perfusion, and the greater the blood volume the more the light source is attenuated. However, attempts at pulse amplitude quantification ('calibration') have been largely unsuccessful (Hertzman 1938, Challoner and Ramsay 1974, Jespersen and Pedersen 1986, Cejnar *et al* 1993).

The wavelength of optical radiation is also important in light–tissue interactions (Cui *et al* 1990), and for three main reasons: (1) *The optical water window*: the main constituent of tissue is water that absorbs light very strongly in the ultraviolet and the longer infrared wavelengths. The shorter wavelengths of light are also strongly absorbed by melanin. There is, however, a window in the absorption spectra of water that allows visible (red) and near infrared light to pass more easily, thereby facilitating the measurement of blood flow or volume at these wavelengths. Thus, the red or near infrared wavelengths are often chosen for the PPG light source (Jones 1987), (2) *Isobestic wavelength*: significant differences exist in absorption between oxyhaemoglobin (HbO_2) and reduced haemoglobin (Hb) except at the isobestic wavelengths (Gordy and Drabkin 1957). For measurements performed at an isobestic wavelength (i.e. close to 805 nm, for near infrared range) the signal should be largely unaffected by changes in blood oxygen saturation, and (3) *Tissue penetration depth*: the depth to which light penetrates the tissue for a given intensity of optical radiation depends on the operating wavelength (Murray and Marjanovic 1997). In PPG the catchment (study) volume, depending on the probe design, can be of the order of 1 cm^3 for transmission mode systems. PPG can provide information about capillary nutritional blood flow and the thermoregulatory blood flow through arterio-venous anastomosis shunt vessels.

2.3. Early and recent history of photoplethysmography

This paragraph gives a brief summary of the early history of PPG and is taken from the excellent review article by Challoner (1979). In 1936 two research groups (Molitor and Kniazuk of the Merck Institute of Therapeutic Research, New Jersey, and Hanzlik *et al* of Stanford University School of Medicine) described similar instruments used to monitor the blood volume changes in the rabbit ear following venous occlusion and with administration of vasoactive drugs. Molitor and Kniazuk also described recordings made with a reflection mode PPG system from human fingers. A pioneer who helped establish the PPG technique was Alrick Hertzman from the Department of Physiology at St. Louis University School of

Medicine, St. Louis, MO. In 1937, Hertzman and his colleagues published their first paper on PPG describing the use of a reflection mode system to measure blood volume changes in the fingers induced by the Valsalva manoeuvre, exercise and with exposure to cold. This excellent contribution to the field demonstrated the potential clinical utility of the technique. In 1938, Hertzman undertook a validation of the PPG technique by comparing blood volume changes with those measured simultaneously by mechanical plethysmography. Preliminary observations on the PPG technique were also reported in the same year by Matthes and Hauss. Hertzman and Dillon (1940a) split the AC and DC components with separate electronic amplifiers and monitored vasomotor activity. Potential sources of error with the technique have been identified by Hertzman (1938), who emphasized that good contact with skin was needed, but without excessive pressure that would result in blanching. He advised that movement of the measurement probe against the skin should be avoided. These observations led to the development of elaborate positioning devices. Illumination was identified as another important design consideration. Hertzman also used a battery powered torch bulb which was less than ideal because of its relatively wide spectrum, particularly in the infrared because of local tissue heating, errors due to the effects of oxygen saturation, and the widespread illumination which can mix skin microvascular blood flow with larger vessel signals. Furthermore, constant light intensity could not be guaranteed.

In more recent decades the desire for small, reliable, low-cost and simple-to-use non-invasive (cardiovascular) assessment techniques are key factors that have helped re-establish photoplethysmography. Advances in opto-electronics and clinical instrumentation have also significantly contributed to its advancement. The developments in semiconductor technology, i.e. light emitting diodes (LED), photodiodes and phototransistors, have made considerable improvements in the size, sensitivity, reliability and reproducibility of PPG probe design. A major advance in the clinical use of a PPG-based technology came with the introduction of the pulse oximeter as a non-invasive method for monitoring patients' arterial oxygen saturation (Aoyagi *et al* 1974, Yoshiya *et al* 1980). There have also been considerable developments in computer-based digital signal processing and pulse wave analysis.

2.4. Photoplethysmography instrumentation

Modern PPG sensors often utilize low cost semiconductor technology with LED and matched photodetector devices working at the red and/or near infrared wavelengths (*CIE* IR-A near infrared band 0.8 to 1 μm, Duck (1990)). An excellent review of optical sensor technology for PPG and pulse oximetry applications is written by Webster (1997).

The choice of light source is important (Burke and Whelan 1986, Lindberg and Őberg 1991, Ugnell and Öberg 1995). LEDs convert electrical energy into light energy and have a narrow single bandwidth (typically 50 nm). They are compact, have a very long operating life ($>10^5$ h), operate over a wide temperature range with small shifts in the peak-emitted wavelength, and are mechanically robust and reliable. The averaged intensity of the LED should be constant and preferably be sufficiently low to minimize excessive local tissue heating and also reduce the risk of a non-ionizing radiation hazard. The choice of photodetector is also important (Weinman and Fine 1972, Fine and Weinman 1973). Its spectral characteristics are chosen to match that of the light source. A photodetector converts light energy into an electrical current. They are compact, low-cost, sensitive, and have fast response times. Near infrared devices can be encased with daylight filters. The photodetector connects to low noise electronic circuitry that includes a transimpedance amplifier and filtering circuitry.

A high pass filter reduces the size of the dominant DC component and enables the pulsatile AC component to be boosted to a nominal 1 V peak-to-peak level. Carefully

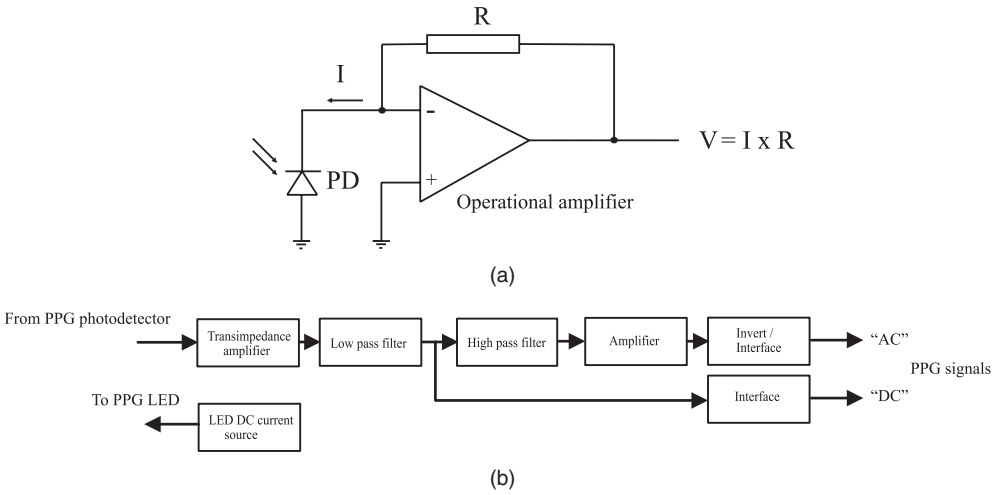

Figure 2. Electronic building blocks used in a typical PPG measurement system. (a) A transimpedance (current-to-voltage) amplifier stage that converts light intensity at the photodiode (PD) to an amplifier output voltage ($V = I \times R$, transimpedance gain proportional to feedback resistor value R). (b) The signal conditioning stages surrounding the transimpedance amplifier which include low pass filtering, high pass filtering and further amplification, inversion and signal interfaces. The AC component and a measure of the DC component are available for pulse wave analysis. A constant current driver stage for the PPG LED is also shown.

chosen filtering circuitry is also needed to remove the unwanted higher frequency noise such as electrical pick up from (50 Hz) mains electricity frequency interference. Figure 2(a) shows a transimpedance amplifier design and figure 2(b) shows the signal conditioning stages surrounding this, including low pass filtering, high pass filtering and further amplification, signal inversion and signal interface. The choice of high pass filter cut-off frequency is particularly important and is often a design compromise; excessive filtering can distort the pulse shape but too little filtering can result in the quasi-DC component dominating over the AC pulse (Allen and Murray 2003, 2004). This example system shows a constant current driver stage for the PPG probe LED.

There are two main PPG operational configurations: transmission ('trans-illumination') mode operation where the tissue sample (e.g. fingertip) is placed between the source and detector, and reflection ('adjacent') mode operation where the LED and detector are placed side-by-side. Clearly, transmission mode PPG imposes more restrictions than the reflection mode PPG on the body locations available for study. The PPG probe should be held securely in place to minimize probe-tissue movement artefact. There are other sources of artefact that need to be considered in the measurement technology. For example, artefact can arise from ambient light interference but can be reduced in several ways: by suitable probe attachment to the skin (e.g. using a dark Velcro wrap-around cuff), by further shading of the study site area and performing measurements in subdued lighting, and by electronic filtering (e.g. light modulation filtering, Webster (1997)). Ambient light interference in PPG-based systems has also been discussed by Hanowell *et al* (1987).

Many of the studies reported in the PPG literature are for a single site, often the ear, finger or toe, where pulses can easily be detected (including Stern (1974), Barnes *et al* (1977a, 1977b), Sherebrin and Sherebrin (1990), Allen and Murray (1993), Chowienczyk *et al* (1999), Hahn *et al* (1999), Bortolotto *et al* (2000), Foo *et al* (2006), Millasseau *et al* (2006)). Many other skin measurement sites are available for vascular assessment (Tur *et al* 1983). The supraorbital

artery, just above each eye has been studied (Lee *et al* 1981), as well as measurements on the skin above key arterial landmarks (Loukogeorgakis *et al* 2002). There have also been studies published which investigated PPG pulses at two sites simultaneously (Dillon and Hertzman 1941, Nijboer and Dorlas 1985, Cooke *et al* 1985, Grossmann *et al* 1987, Okada *et al* 1986, Porret *et al* 1995, Nitzan *et al* 1998b, 1998a, 2001). Three channel PPG research systems have been described by Evans and Geddes (1988) and four channel research systems by Buchs *et al* (2005) and Erts *et al* (2005). Multiple finger site pulse data have also been reported by Dyszkiewicz and Tendera (2006). Six channel PPG data have been published for simultaneous multi-bilateral site PPG data measurements (i.e. the right and left ear lobes, index fingers or thumbs, and great toes) (Allen *et al* 2000, 2002, 2003, 2004, 2005, 2006). Technically, Allen and Murray (2000a) have emphasized the importance of the electronic and optical matching of pulse amplifier channels to allow the best chance for right-to-left side physiological differences to be detected with confidence. A multi-bilateral site PPG pulse measurement and analysis system and example pulse recording from a healthy subject are shown in figure 3. PPG systems are also available commercially. Examples include the Skidmore Medical Ltd. Vicorder, the Cuban Biofísica Médica ANGIODIN® PD 3000, and the VIASYS Healthcare MicroLite™ and VasoGuard™ systems. These lists are not exhaustive.

Other emerging technologies include PPG imaging technology, telemedicine and remote monitoring. Schultz-Ehrenburg and Blazek (2001) and Huelsbusch and Blazek (2002) investigated an experimental cooled near infrared CCD PPG imaging system for studying skin blood flow and related rhythmical phenomena. The aim of the technology was to obtain new insights into normal physiological tissue perfusion and detect changes associated with ulcer formation and wound healing. In 2005, Wieringa *et al* described a contactless multiple wavelength PPG imaging system whose main application is the remote imaging of arterial oxygen saturation (SpO_2) distribution within tissue. The system acquires movies of two-dimensional matrix spatially resolved PPG signals at three wavelengths (660 nm, 810 nm and 940 nm) during changes in respiration. A tissue oxygen image might be useful in many areas of medical diagnostics, for example in quantifying tissue viability. PPG has considerable potential for telemedicine including the remote/home health monitoring of patients. Miniaturization, ease-of-use and robustness are key design requirements for such systems. This is illustrated with finger ring-based PPG sensors for monitoring beat-to-beat pulsations (Rhee *et al* 2001, Zheng and Zhang 2003) and the need for motion artefact reduction, optimal sensor placement and minimizing battery power consumption. Innovative LED and photodetector array technology has been incorporated into a PPG finger sensor and palm-sized home health monitor to enable the pulse, oxygen saturation and respiration to be measured along with haematocrit derived from optical characteristics at five different wavelengths (569, 660, 805, 904 and 975 nm) (Yoon *et al* 2005). Preliminary clinical testing showed that the haematocrit was within $\pm 10\%$ of the gold standard value. Respiratory information was extracted using digital filtering techniques and blood oxygen saturation (SpO_2) predicted using the standard ratio for the red and near infrared wavelengths.

2.5. Measurement protocol and reproducibility

Reproducibility is very important in clinical physiological measurement, for example in giving confidence in detecting significant responses to therapy. Many factors affect reproducibility, including the method of probe attachment to tissue, probe–tissue interface pressure, pulse amplifier bandwidth, minimization of movement artefact, subject posture and relaxation, breathing, wakefulness, room temperature and acclimatization (Teng and Zhang 2006, Zhang and Zhang 2006). As yet, however, there are no internationally recognized standards for clinical PPG measurement. Published research tends to be based on studies using quite

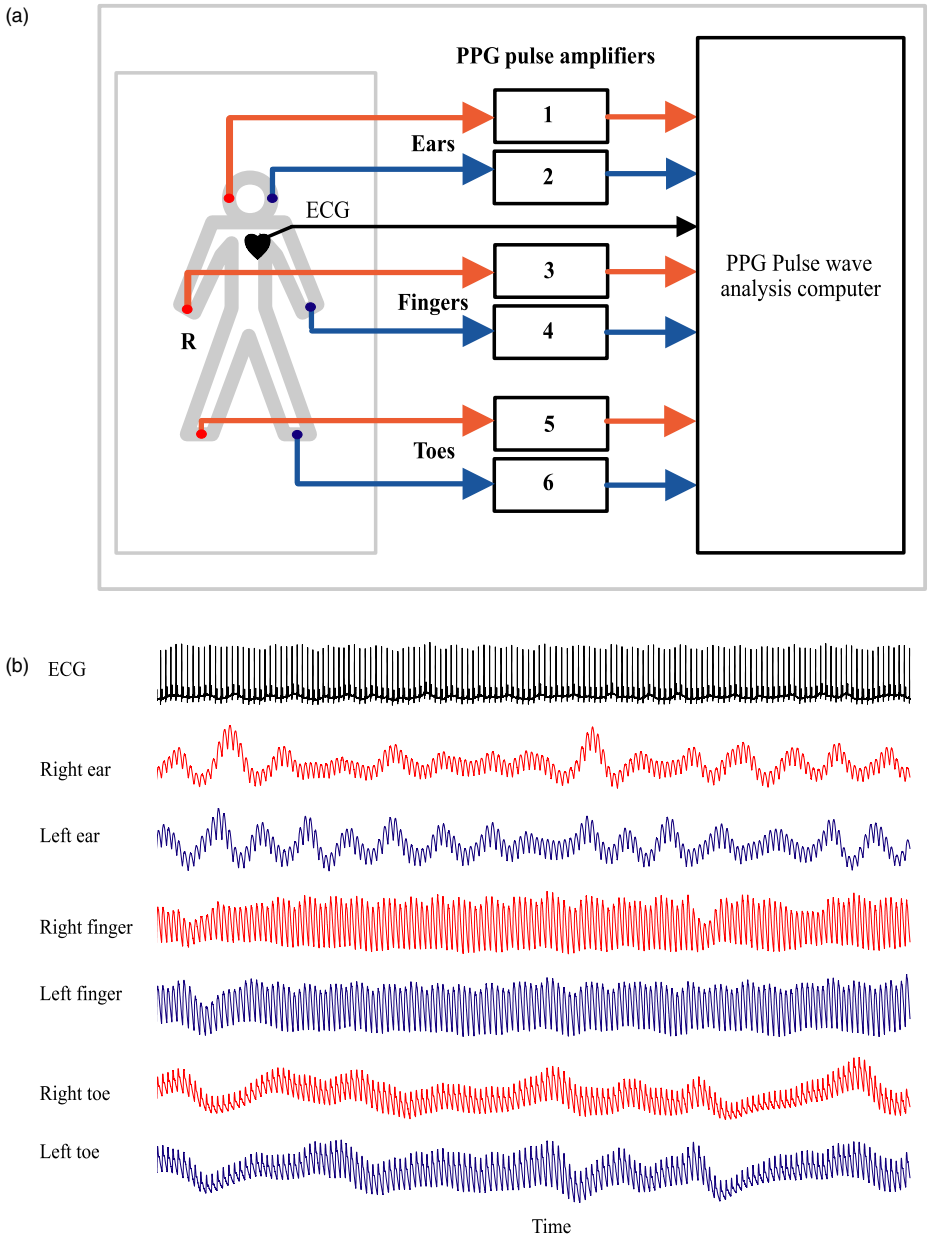

Figure 3. Multi-bilateral site photoplethysmography. (a) An overview of a six channel PPG measurement and analysis system, giving capability for pulses to be compared between the right and left sides and between head to foot sites (Allen *et al* 2006). (b) An example recording made from the right and left ear lobes, index fingers, and great toes of a healthy subject. There is similarity in the pulse characteristics between the right and left body sides but clear differences between the proximal and distal measurement sites. However, the degree of right to left side similarity in the high and low frequency components of the PPG waveform can be reduced in patients with vascular disease (Allen and Murray 2000a) and also in patients with autonomic dysfunction (Buchs *et al* 2005).

differing measurement technology and protocols, thereby limiting the ease with which PPG physiological measurements can be replicated between research centres.

There are a limited number of studies quantifying the repeatability or reproducibility of PPG measurements. An important study by Jago and Murray (1988) addressed the uncertainty in PPG measurements for a group of healthy adult subjects. They studied the repeatability of PPG pulse transit time (PTT) measurements made from the ear, thumb and toe sites both within session and between sessions held on separate days. Measurements at individual sites and bilateral (right–left) side differences were both assessed. The results showed the importance of controlling for factors such as posture, ambient temperature, relaxation and acclimatization. Bilateral measurements were generally more repeatable than individual site measurements since heart rate, respiration and blood pressure factors tend to affect both sides of the body simultaneously.

There have also been a limited number of studies published that quantify the complex physiological variability in PPG waveforms measured at different body sites. Applications that utilize the beat-to-beat variation in PPG characteristics include the assessment of autonomic dysfunction and cardiovascular ageing (see section 3.3). It can also be useful, however, to obtain an averaged pulse measure to represent an individual subject/site. An averaging period covering at least 60 heartbeats has been suggested to improve confidence in the single timing, amplitude or shape measurements extracted from the PPG pulse (Allen 2002).

2.6. Photoplethysmography pulse wave characterization and analysis

2.6.1. Pulse wave characterization. Two important characteristics of the PPG AC pulse waveform were described by Hertzman and Spealman (1937). The appearance of the pulse was defined as two phases: the anacrotic phase being the rising edge of the pulse, and the catacrotic phase being the falling edge of the pulse. The first phase is primarily concerned with systole, and the second phase with diastole and wave reflections from the periphery. A dicrotic notch is usually seen in catacrotic phase of subjects with healthy compliant arteries.

It is useful also to consider the blood pressure pulse and its propagation along individual arteries. The pressure pulse wave is known to change in shape as it moves toward the periphery and undergoes amplification and alterations in its shape and temporal characteristics. These changes are thought to be largely due to reflection of the pulse wave and the tapering down of the arteries towards the periphery. Pulse propagation in arteries is further complicated by frequency dependent phase distortion. These phenomena have been described by O'Rourke and Gallagher (1996) and are discussed in the wider literature on pulse. The blood pressure pulse has similarities with the PPG blood volume pulse, with similar changes occurring in vascular disease, such as damping and a loss of pulsatility. The damping has been associated with a reduction in vessel compliance and increased peripheral resistance, although these changes have yet to be fully explained.

The potential of PPG for assessing vascular disease was recognized many decades ago. In 1940b, Hertzman and Dillon compared PPG to mechanical plethysmography in arteriopaths and in normal control subjects. They derived a crest time measurement from the rising edge of the pulse waveform and normalized this to the heart rate. The crest time was prolonged in patients with vascular disease or hypertension. The potential for extracting diagnostic information from the PPG pulse has been reviewed by Murray and Foster (1996). From the literature, many features have been investigated (figure 4), including beat-to-beat PPG rise time, PTT, amplitude, shape, and the variability in each of these. The pulse shape (contour) can also be described after normalization in pulse width and height (Allen and Murray 2003).

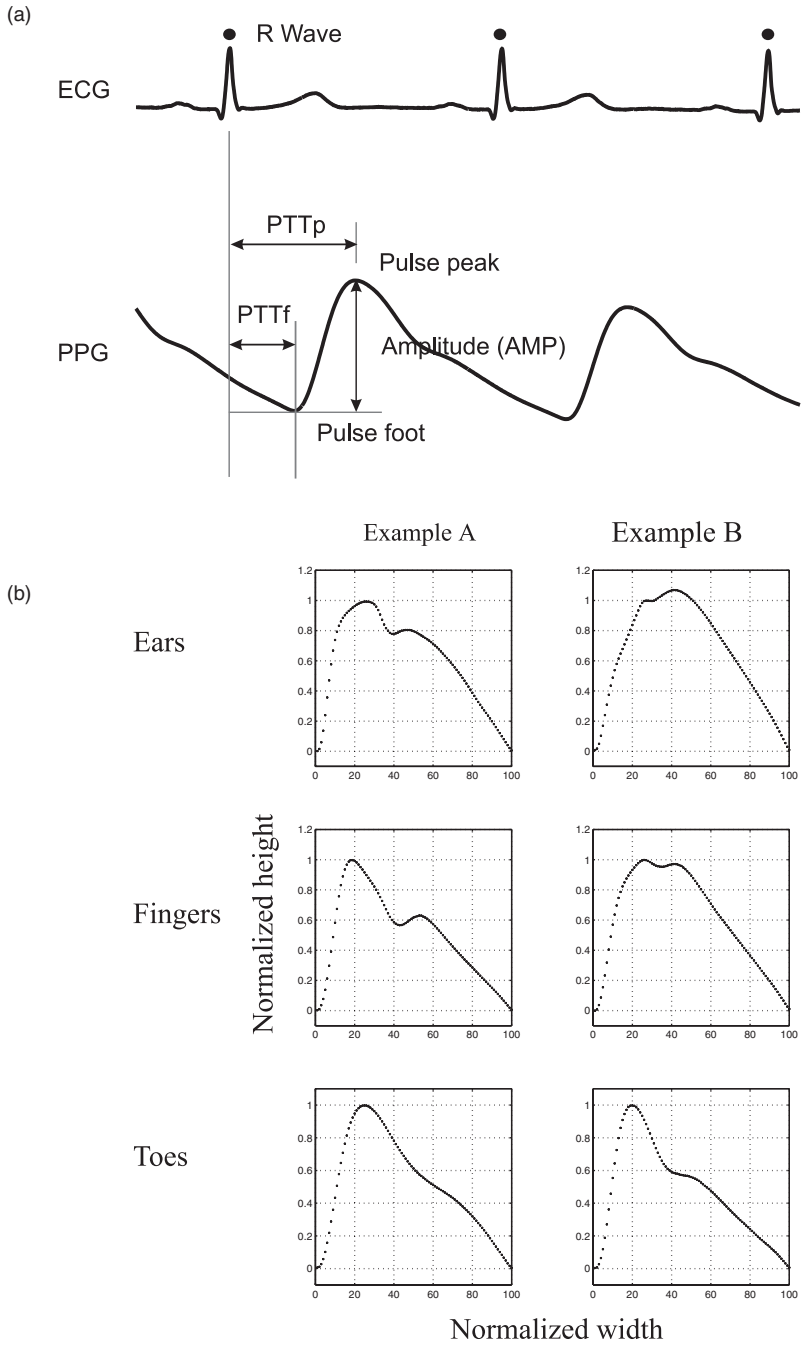

Figure 4. Characterization of PPG pulse timing, amplitude and shape features. (a) Key pulse landmarks can automatically be identified using a pulse wave analysis computer to give beat-to-beat pulse transit time to the foot of the pulse (PTTf), pulse transit time to the peak of the pulse (PTTp), and foot-to-peak amplitude (AMP). The pulse landmarks can then be used to calculate the normalized pulse contour. Contour examples are given in (b) for two different healthy subjects (Allen and Murray 2003).

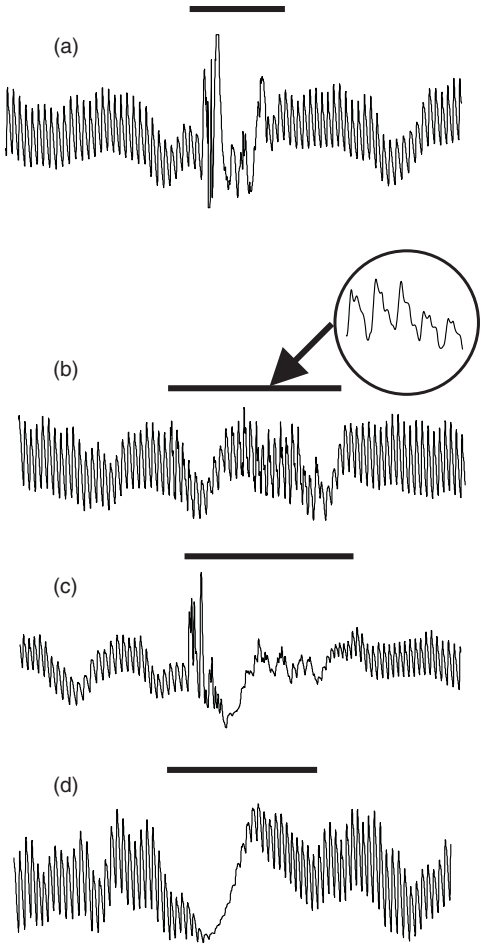

Figure 5. Examples of the types of measurement artefact and the extremes in physiological variation that can be seen in PPG recordings. Each recording is from the index finger site over a period of 1 min and the artefact/physiological events are marked. (a) An episode of gross movement artefact or PPG probe cable tugging lasting approximately 15 s. (b) Hand or finger tremor, (c) a bout of coughing, and (d) marked changes in the breathing pattern (a deep gasp or yawn). These types of artefact and physiological variation should be considered with the measurement protocol and subsequent pulse wave analysis.

2.6.2. Pulse wave analysis. Manual measurement and feature extraction techniques were often used in the very early days of pulse wave analysis, using various media including chart recorder paper and ruler or photographic recording/magnetic tape (e.g. Hertzman and Spealman (1937), Dillon and Hertzman (1941), Simonson (1956), Corte (1979), Cooke *et al* (1985), Sherebrin and Sherebrin (1990)). Recent developments in computing technology and software data analysis tools have enabled the sophisticated pre- and post-processing of physiological waveforms. MATLAB (MathWorks Inc.) is a digital signal processing environment that is well suited to pulse wave analysis algorithm prototyping, and often appears in the PPG literature.

It is well established that PPG measurements are quite sensitive to patient and/or probe–tissue movement artefact (see examples in figure 5). The automatic detection of such motion

artefact, and its separation from good quality although highly variable pulse recordings, is a non-trivial exercise in computer signal processing. Computer-based filtering, feature extraction and waveform averaging have also been employed in PPG pulse wave analysis, including the analysis of frequency (de Trafford *et al* 1982, Okada *et al* 1986, Nitzan *et al* 1994, Bernardi *et al* 1996, Grohmann *et al* 1996a, 1996b, Larsen *et al* 1997, Sherebrin and Sherebrin 1990), joint-time frequency (Yan *et al* 2005), artificial neural network (Allen and Murray 1993, 1995, 1996, 1999, Weng *et al* 1998), systems identification and transfer function modelling (Cohn *et al* 1995, Allen and Murray 1993, 1995, 1996, McVeigh *et al* 1999, Millasseau *et al* 2000), principal component analysis (Enríquez *et al* 2002), nonlinear and chaos theory (Christ *et al* 1997, Bhattacharya *et al* 2001), cross correlation (Allen and Murray 2000a, Drinnan *et al* 2001) and double differentiation (acceleration plethysmogram, Takada *et al* (1996–97), Takazawa *et al* (1998), Bortlotto *et al* (2000)).

3. Clinical applications

PPG has been applied in many different clinical settings, including clinical physiological monitoring (blood oxygen saturation, heart rate, blood pressure, cardiac output and respiration), vascular assessment (arterial disease, arterial compliance and ageing, endothelial function, venous assessment, vasospastic conditions, e.g. Raynaud's phenomenon, microvascular blood flow and tissue viability) and autonomic function (vasomotor function and thermoregulation, blood pressure and heart rate variability, orthostatic intolerance, neurology and other cardiovascular variability assessments). This section reviews each of these areas with a view to demonstrating the widespread use of the optical technology in medicine and also its considerable potential for further innovation and application.

3.1. Clinical physiological monitoring

3.1.1. Blood oxygen saturation. Pulse oximetry is said to represent one of the most significant technological advances in clinical patient monitoring over the last few decades (Webster 1997). It utilizes PPG measurements to obtain information about the arterial blood oxygen saturation (SpO_2) as well as heart rate (Aoyagi and Miyasaka 2002). It has widespread application in many different clinical settings, including hospital, outpatient, sports medicine, domiciliary use, and in veterinary clinics. In the early 1990s pulse oximetry became a mandated international standard for monitoring during anaesthesia. An excellent review of the technique can be found in Kyriacou (2006) where he described the basic principle of operation, measurement technology and its clinical applications. Earlier reviews of pulse oximetry have been written by Kelleher (1989) and Severinghaus and Kelleher (1992).

SpO_2 can be determined by shining red and then near infrared light through vascular tissue, with rapid switching between the wavelengths. The amplitudes of the red and near infrared AC signals are sensitive to changes in SpO_2 because of the differences in the light absorption of HbO_2 and Hb at these two wavelengths. From their amplitude ratio, and corresponding PPG DC components, SpO_2 can be estimated. This process usually involves an empirically derived calibration factor (Webster 1997). There is the assumption that the pulsatile component of the PPG signal results solely from the arterial blood volume changes with each heartbeat. Limitations of pulse oximetry are that the technique relies upon a peripheral pulse to be present, oxygen saturation readings can be affected by dyshaemoglobinaemias, and its accuracy can fall off at low saturation levels (Kyriacou 2006). Advanced computer algorithms have been developed to try to overcome the problem of movement artefact affecting the measurement

reliability. This includes the Masimo SET technology (Goldman *et al* 2000, Hayes and Smith 2001).

Pulse oximeters can measure SpO_2 using both the reflection and transmission modes of operation (Mendelson and Ochs 1988). Central body measurement sites have also been investigated, including oesophageal oxygen saturation monitoring to overcome the problem of finger pulse loss associated with intra-operative peripheral cooling (Kyriacou *et al* 2002, Kyriacou 2006). Another recent and exciting development in pulse oximetry is the non-invasive measurement of venous oxygen saturation using external artificial perturbations applied close to the PPG probe (VENOX Technology, Chan *et al* (2003), Echiadis *et al* (2005)).

3.1.2. Heart rate. The heart rate is an important physiological parameter to measure for a wide range of clinical settings, including hospital-based and ambulatory patient monitoring. The AC component of the PPG pulse is synchronous with the beating heart and therefore can be a source of heart rate information. In pulse oximetry systems this information is often displayed alongside the SpO_2 level. The main problem is that confidence in the rate parameter can be reduced when there is significant movement artefact or cardiac arrhythmia.

Computer algorithms have been investigated to improve the reliability of heart rate detection. These include simple digital filtering and zero crossing detection to separate heart rate and respiratory components from the ear PPG signal (Nakajima *et al* 1996). Johansson *et al* (1999) have described a PPG-based device for heart rate (and respiration) monitoring in neonatal care units, and tested on PPG and ECG derived heart rate data acquired continuously over 8 hour sessions. High quality ECG recordings were obtained for 77% of the measurements. In these periods, excluding those disturbed by offset adjustment of the PPG signal (6%), the PPG heart rate included approximately 1% false negative and also 1% false positive beats. More sophisticated algorithms have been applied to extract heart rate information from PPG waveforms, including time-frequency techniques based on the smoothed Wigner Ville distribution (Yan *et al* 2005). The accuracy in measuring heart rate was evaluated by comparing pulses from the study hand at rest or undergoing controlled hand movements, with the pulses measured from the contralateral and stationary reference hand. The time-frequency approach showed significant improvement over two traditional approaches (i.e. weighted moving average (WMA) and fast Fourier transform (FFT)) for measurements obtained during finger bend manoeuvres. The mean absolute pulse rate error reduced to 6 beats per minute (bpm) compared with 16 bpm for WMA and 11 bpm for FFT. In comparison with other heart rate measurement technologies good agreement by Bland and Altman analysis (Bland 1995) has been demonstrated between pulse oximetry and radial piezoelectric pulsations at the radial artery (Foo and Lim 2006c).

Automatic assessment of the reliability of reference heart rates from patient vital-signs monitors incorporating both ECG and PPG based pulse measurements has been proposed by Yu *et al* (2006). They expressed reliability as a quality index for each reference heart rate. The physiological waveforms were assessed using a support vector machine classifier and the independent computation of heart rate made by an adaptive peak identification technique that filtered out motion-induced noise. The method was evaluated in 158 randomly selected 7 s data samples from trauma patients collected during helicopter transport. When the results of the algorithm were compared with the manual analysis performed by human experts at least 92% of cases could be matched. In the remaining 8% of cases the algorithm inferred a less conservative signal quality, as mainly attributed to ambiguously labelled waveform samples. If the ambiguous waveforms were re-labelled then the mis-classification rate fell from 8% to 3%. Automatic heart rate detection systems for sleep studies have also been developed. Foo and Wilson (2006) utilized a dual measurement approach comprising an accelerometer

movement detector and a zero phase filter for enhancing the PPG signals in poor perfusion states. A decision matrix selected the appropriate technique to dynamically improve the PPG signal to noise ratio. The maximum error rate when compared to ECG heart rate measurement was less than 8%.

3.1.3. Blood pressure. Arterial blood pressure is also a very important clinical parameter to measure. Examples include the tracking of beat-to-beat blood pressure (or related surrogate pressure measurements) in autonomic function studies and also limb/digital blood pressure measurements in vascular disease studies. Several approaches to non-invasive PPG-based blood pressure measurements have been described in the literature and these are summarized below.

Finapres™ (for FINger Arterial PRESsure) technology was introduced in the early 1980s enabling the measurement of the arterial pressure waveform at the finger on a continuous beat-by-beat basis. The method is based on the dynamic (pulsatile) vascular unloading of the finger arterial walls using an inflatable finger cuff with built-in PPG sensor (Peñáz 1973). A substantial number of comparative and methodological studies have been published on the technology, including a general review by Imholz *et al* (1998). Here, the main clinical applications for the technology focused on anaesthetic monitoring and autonomic function testing. The Finapres™ system is no longer commercially available, although alternative blood pressure devices have been introduced: the Portapres and Finometer systems (Finapres Medical Systems BV, Holland) and the Task Force Monitor system (CNSystems Medizintechnik, GmbH). A system overview of the Task Force Monitor is shown in figure 6 and illustrates how simple PPG-based technology can be incorporated into sophisticated clinical cardiovascular assessment tools.

Surrogate pulse measures of blood pressure have also been investigated, including tracking beat-to-beat changes in pressure using the PTT (Naschitz *et al* 2004, Payne *et al* 2006). PTT is usually calculated from the ECG R wave to the foot of the PPG pulse although sometimes the Q wave or a fraction of the pulse risetime is selected as the timing reference point. Chen *et al* (2000) described a method of combining high frequency information in the PTT and the lower frequency information in an intermittently acquired systolic blood pressure (SBP) measurement. The predicted SBP changes were compared with measured pressure changes and the error remained within $\pm 10\%$ for 98% of measurements. Payne *et al* (2006), however, noted the significant contribution of the cardiac pre-ejection period to PTT, potentially limiting its ability to track SBP in a clinical setting. To help limit the influence of pre-ejection, Foo *et al* (2006) has introduced the vascular transit time (VTT), defined as the difference between phonocardiography heart sounds and the foot of the PPG waveform. In its validation, a series of arm raise manoeuvres on healthy subjects found an improvement in the correlation coefficient (r) of transit time with SBP ($r^2 = 0.82$). A recent innovation for the home monitoring of SBP is the prototyping of a toilet seat fitted with PPG sensor and ECG electrodes (Kim *et al* 2006). Blood pressure was estimated using an algorithm based on the pulse arrival time and was compared with conventional arm blood pressure measurements. Their approach showed promise as a method for home monitoring of blood pressure.

Non-invasive blood pressure measurements are often used in the assessment of peripheral vascular disease, for calculation of the ankle brachial pressure index (ABPI) (Yao *et al* 1969). Limb pressures are traditionally measured using Doppler ultrasound, however, this is relatively expensive compared to PPG and requires an acoustic coupling gel. Upper and lower limb SBPs have also been measured using PPG and ankle/arm pressure cuffs (Nielsen *et al* 1973, McGuigan *et al* 2002, Laurent *et al* 2005, Jonsson *et al* 2005a, 2005b). In 2005b, Jonsson *et al* compared PPG and standard Doppler ultrasound measurements of ABPI and found no

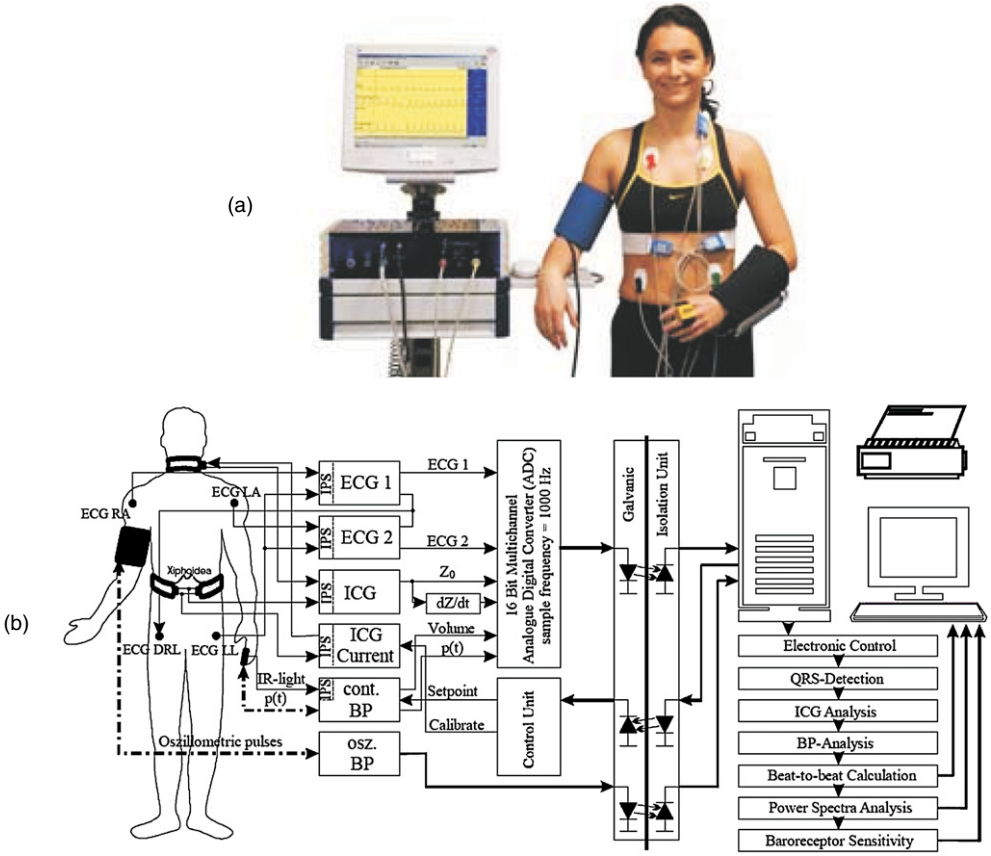

Figure 6. Cardiovascular assessment system incorporating PPG-based non-invasive beat-to-beat blood pressure measurement technology (Task Force Monitor system, CNSystems Medizintechnik, GmbH). Its method of blood pressure measurement is based on the development of the dynamic (pulsatile) vascular unloading of the finger arterial walls using an inflatable finger cuff with built-in PPG sensor (Peñáz 1973). (a) A patient fitted with the blood pressure cuff unit with dual finger PPG probe, blood pressure pneumatic and electrical interface unit, and computer signal conditioning processing system for the physiological signals: blood pressure, ECG, impedance cardiography (ICG); (b) a schematic to demonstrate the complexity of the overall measurement system. (Figures are courtesy of CNSystems Medizintechnik, GmbH.)

significant difference between techniques, with Bland and Altman 95% limits of agreement (Bland 1995) of −0.19 to +0.16 for visual inspection of the pulse trace and −0.18 to +0.28 for automated pulse detection. An example of a commercial device for automatic PPG-based limb pressure measurement is the Vascular Assist^{TM} vascular assessment system (Huntleigh Healthcare, UK).

Ankle cuff pressure measurements are not always possible because of arterial rigidity (‘calcification’), for example in patients with advance renal disease or diabetes mellitus. Toe blood pressures can be measured instead (Leskinen *et al* 2002). In the study by Hirai and Kawai (1977) a PPG probe was attached distally to an occluding pressure cuff, and found good agreement with strain gauge plethysmography and Doppler ultrasound techniques. Toe pressures have also been assessed using audio-photoplethysmography (Fronek *et al* 1994), where the pulse drives an audio oscillator enabling the operator to

audibly locate the point at which the pulse is restored following cuff release. PPG-based toe pressures have been used as a standard to validate new optical approaches to digital blood pressure measurement, including laser Doppler flowmetry based methods (Ubbink 2004).

Nitzan *et al* (2005) have studied the effects of external pressure on arteries distal to the pressure cuff during sphygmomanometry. Bilateral PPG waveforms were measured on the fingers of healthy male subjects during the slow release of cuff pressure. Significant time delays were found between the pressure measurement arm and control arm, even at sub-diastolic pressures of 50 mmHg. Significant bilateral differences in amplitude were also detected throughout the measurement cycle. These findings were attributed to changes in compliance of the conduit and small arteries with cuff inflation and deflation. Zheng *et al* (2005) have also investigated the relationship between external sub-systolic cuff pressures and PTT. Various proximal/distal arm pressure cuff configurations, including the equivalent of a whole arm cuff, were investigated across a range of study pressures (0–30 mmHg in 10 mmHg steps). The whole arm cuff produced the greatest mean increase in PTT (18 ms at 30 mmHg). The results agreed with theory; when the external cuff pressure increases for a constant arterial blood pressure, the arterial wall compliance increases which leads to an increase in PTT.

3.1.4. Cardiac output. For the resting healthy adult the volume of blood pumped by the heart is in the region of 5 litres per minute but can be impaired in patients with cardiovascular disease. Its accurate, reliable and non-invasive measurement is therefore very important clinically. However, there is ongoing discussion in the literature in regard to the accuracy of PPG-based cardiac output assessments (Azabji Kenfack *et al* 2004).

The stroke volume can be estimated from PPG-derived pulse contour analysis on a beat-by-beat basis (where cardiac output = stroke volume multiplied by heart rate). Several methods have been explored, including the Pressure Recording Analytical Method (PRAM, Romano and Pistolesi (2002)) and the ModelFlow^{TM} method (TNO Biomedical Systems and Finapres Medical Systems BV, Holland) (Harms *et al* 1999). PRAM has been compared with gold standard direct-oxygen Fick and thermodilution methods (Romano and Pistolesi 2002) in order to validate the technique for non-invasive beat-to-beat monitoring of cardiac output. The Bland and Altman 95% limits of agreement (Bland 1995) across a range of cardiac outputs (range 2.3 to 7.4 l min^{-1}) were $\pm$0.9 l min^{-1} (Giomarelli *et al* 2004) and (range 1.8 to 10.4 l min^{-1}) were $\pm$0.6 l min^{-1} (Scolletta *et al* 2005), with no significant mean differences between the techniques. The ModelFlow^{TM} method of stroke volume estimation utilizes a non-linear adaptive 3-element Windkessel model to mimic specific properties of the aortic input impedance to estimate aortic blood flow on a beat-by-beat basis. These elements represent the characteristic impedance, Windkessel compliance and peripheral resistance. In comparison with thermodilution (Modelflow^{TM}—thermodilution) the 95% limits of agreement across the range of cardiac outputs (6.4 $\pm$1.1 l min^{-1}) were $-$4.6 to +1.1 l min^{-1} with mean difference of $-$1.7 l min^{-1} (Remmen *et al* 2002). The exercise study by Tam *et al* (2004) introduced an independent calibration method (i.e. open-circuit acetylene uptake) and found that the 95% limits of agreement ranged from $-$6.6 to +7.1 l min^{-1} with elimination of bias offset. From these data they concluded that Modelflow^{TM} was an accurate procedure for measuring cardiac output in humans both at rest and during exercise, and could be used for routine clinical purposes. In relation to cardiotherapy both Butter *et al* (2004) and Whinnett *et al* (2006) have shown the potential benefits of finger PPG for cardiac resynchronization therapy to optimize cardiac output and function.

3.1.5. Respiration. Physiological monitoring of breathing interval (respiratory rate) is important in many clinical settings, including critical and neonatal care, sleep study assessment and anaesthetics. Respiration causes variation in the peripheral circulation, making it possible to monitor breathing using a PPG sensor attached to the skin. The low frequency respiratory-induced intensity variations (RIIV) in the PPG signal are well documented (includes key workers, Johansson *et al* (1999) and Nilsson *et al* (2000)). It is considered that RIIV includes contributions from the venous return to the heart caused by alterations in intra-thoracic pressure and also changes in the sympathetic tone control of cutaneous blood vessels. The physiological mechanisms relating to the RIIV are, however, not fully understood.

In a study by Johansson and Öberg (1999a) the RIIV signal was digitally extracted from forearm PPG measurements and compared with simultaneous invasive venous blood pressure measurements and also the calibrated inspired volume respiration. The extraction algorithm was centred on a bandpass filter design (0.13–0.48 Hz, Bessel 16th order). A high correlation was obtained between waveforms for the normal volunteers studied, although an absolute measurement of the respiratory volume from RIIV was not possible. Johansson and Öberg (1999b) then modelled the dynamics of the system using a Windkessel and compartmental modelling approach. Coherence has also been shown between forearm RIIV waveforms and changes in central and peripheral venous pressures, arterial pressure, tidal volume and respiratory rate by Nilsson *et al* (2003a, 2003b, 2005), for spontaneous breathing and also for positive pressure ventilation under anaesthesia. The highest RIIV amplitudes were observed with the higher tidal volumes, lower respiratory rates and during mainly thoracic breathing. Coherence has also been tested against trans-thoracic impedance measurements (Nilsson *et al* 2000) and a CO_2 reference (Nilsson *et al* 2006). The phase relationships between RIIV and the pressure and volume variables appear complex, and have been further investigated by Nilsson *et al* (2003b). A clearer understanding of these lower frequency components of the PPG waveform is warranted. Consider the recent study by Nitzan *et al* (2006) where the respiratory-induced variations in the finger PPG waveform were observed even when an arm blood pressure cuff was pressurized to well above the SBP, giving further evidence for autonomic nervous system involvement.

Various other RIIV extraction algorithms have been investigated: Neural network based pattern recognition algorithm extracted RIIV from reflection mode PPG measurements at the forehead and giving low error classification rates in the region of 10% (Johansson 2003). Zero phase digital filter extraction of the breathing interval (BI) in children (Foo and his co-workers 2005) where the mean BI was significantly related during tidal breathing and also with externally applied inspiratory resistive loading. Wavelet transformation of the PPG signal has facilitated automated estimation of the respiratory rate (Leonard *et al* 2006).

Changes in pulse timing characteristics with breathing have also been studied. This includes using the PTT to track arousals during obstructive sleep apnoea, and leading to a clinically useful non-invasive measure of inspiratory effort in patients with sleep-related breathing disorders (Pitson *et al* 1994, 1995). Slow paced breathing and deep inspiratory gasp challenges in autonomic function testing can also induce significant changes in the PTT (Drinnan *et al* (2001) and Allen *et al* (2002), respectively).

3.2. Vascular assessment

3.2.1. Arterial disease. In the peripheral circulation, atherosclerosis of increasing severity can lead progressively to exercise induced leg pain ("intermittent claudication"), rest pain, and tissue damage in the form of ischaemic ulceration or gangrene (Kester and Leveson 1981).

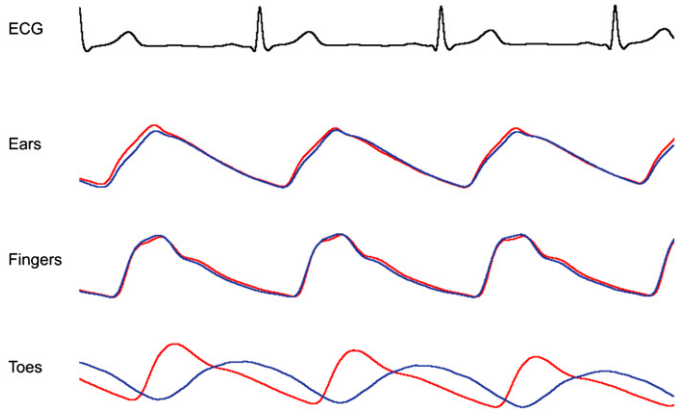

Figure 7. Example of a multi-bilateral site PPG pulse recording in a patient with unilateral lower limb peripheral arterial occlusive disease. The pulses are shown for the right and left ear lobe, index finger, and great toe sites, for a period of several seconds. They show the damping, relative delay between legs, and the reduction in amplitude for the toe pulse from the affected side. The clear bilateral similarity of the pulses at the ear and finger sites is consistent with there being no significant proximal arterial disease.

Atherosclerosis is also called peripheral arterial occlusive disease (PAOD) whose prevalence increases with ageing, especially from the fourth or fifth decade of life (Hertzer 1991). PAOD is also associated with increased risk of coronary artery disease and stroke, and even the relatively milder degrees of PAOD can significantly interfere with the lifestyle and well-being of patients. It is important therefore to establish the exact cause of a patient's symptoms since other conditions such as musculo-skeletal/spinal disease, and venous disease may also produce the symptoms of claudication (Barnes 1991). Disease detection with PPG is possible because the peripheral pulse usually becomes damped, delayed and diminished with increasing severity of vascular disease (Heck and Hall 1975, Osmundson *et al* 1985, Kvernebo *et al* 1989). Figure 7 shows the bilateral dissimilarity in right and left toe pulses in a patient with arterial disease. The majority of published papers appear to have focused on the utility of PPG for lower limb disease detection. Many different features of the pulse have been explored, including risetime, frequency characteristics, width/height ratio, amplitude and shape, as summarized below.

Simonson *et al* (1955) investigated the *risetime* of the PPG pulse during reactive hyperaemia in healthy subjects and in those with Buerger's disease. They showed the relative changes in timing with advancing age and also that the pulse becomes dampened when the circulation is compromised, with changes related to disease severity rather than type of vascular pathology. In 1976, Oliva *et al* used Fourier transform based *frequency analysis* to distinguish between legs having healthy arteries and those with atherosclerosis. The fundamental frequency and lower harmonics from patient pulses were compared against normative range values, giving a diagnostic accuracy of 89%. In 1990, Sherebrin and Sherebrin also utilized frequency analysis and showed that the higher harmonic frequencies diminish with age, consistent with the loss of the dicrotic notch feature in older subjects. This study was also important because it considered normative age-related pulse characteristics and protocol issues for obtaining good quality recordings. PPG pulse frequency characterization can also be found in Grohmann *et al* (1996a, 1996b). Oliva and Roztocîl (1983) have also looked at simple analysis methods, including a single pulse measure calculated from the width at two thirds of the foot-to-peak height and normalized to pulse interval. This technique detected 81% of

stenotic and 100% of occlusive disease. Angiography was the gold standard implying that only patients having higher grade disease were studied. Healthy control subjects were not screened with angiography giving some uncertainty in the diagnostic specificity. In 1996, Carter and Tate investigated the utility of toe pulse *amplitude* for disease detection and proposed that amplitude was a valuable feature for discriminating limbs with major disease. They also commented that the pulse amplitude was related to skin temperature. Therefore, unless thermal acclimatization is incorporated into the protocol then healthy subjects with a degree of cold sensitivity could also register as having blocked arteries. There is growing evidence that the *shape* of the pulse contains valuable diagnostic information for vascular assessments. However, the PPG pulse shape can be difficult to describe mathematically. One approach is to use artificial neural network (ANN) technology since it has the capability to allow non-linear classification of 'hard-to-define' physiological signals, and also has great potential for de-skilling in clinical PPG assessments. An ANN pulse shape classifier developed by Allen and Murray (1993) produced a diagnostic accuracy of 90% in a pilot study of lower limb arterial disease detection. A prospective assessment of the technique in a larger group of subjects (266 legs) produced an accuracy of 80% (Allen and Murray 1995, 1996). The strength of this approach was its classification sensitivity compared to the gold standard ABPI test for vascular disease.

Multi-body site PPG measurements have been proposed for peripheral vascular disease detection. In 2000a, Allen and Murray demonstrated the considerable similarity in bilateral (right and left body side) PPG characteristics at three main peripheral sites, i.e. the ear lobes, thumb pads and great toe pads. Cross correlation analysis quantified the degree of similarity in normal subjects compared to the dissimilarity in a patient with unilateral arterial disease. This study also described the technical requirements for a multi-site PPG measurement system, including the need for electronic matching of the PPG channels allocated to the right and left body sides so that detected bilateral differences were likely to be related to pathology rather than to artefact. Normative multi-site PPG data have been established for pulse timing characteristics (Allen and Murray 2002) and pulse shape characteristics (Allen and Murray 2003). Allen *et al* (2005, 2006) have also quantified the diagnostic value of bilateral PPG assessments for detecting arterial disease, using age-matched normative data as a reference (table 1), and also the relative merit of different pulse features on diagnostic accuracy (table 2). The shape index (SI) was introduced as a measure of the abnormal distortion of the pulse contour and provided the greatest accuracy ($>$90% and giving substantial agreement by the Kappa statistic with the ABPI). Simple timing differences between the right and left side pulse feet were also good at detecting the higher grade disease. The potential for using bilateral (right and left side) PTT differences to detect lower limb disease has also been described in important contributions to the literature by Insall (1991), Erts *et al* (2005) and Spigulis (2005). Further research is warranted to determine if multi-bilateral site PPG measurements can reliably locate disease within an arterial segment or assess responses to vascular therapy.

Carotid artery disease has been assessed by supraorbital PPG, detecting haemodynamically significant disease with an accuracy of 88% (Barnes *et al* 1977a, Lynch *et al* 1981). Oculoplethysmography as an adjunct to angiography detected carotid occlusive arterial disease again with an accuracy close to 90% (Kartchner *et al* 1976, Rasmussen *et al* 1981, Lane *et al* 1984). Occlusive disease in the upper limb arteries is relatively rare, although multi- bilateral site PPG technology may prove to have a role here. The prevalence of thoracic outlet arterial compression has been studied with simple unilateral PPG measurements to Adson's, costoclavicular, and hyperabduction manoeuvres (Gergoudis and Barnes 1980). Further research is warranted since measurements consistent with arterial obstruction were found in a significant number of healthy subjects.

Table 1. Normative toe PPG pulse characteristics (95% confidence interval ranges), for timing (PTTf and PTTp, pulse transit times to foot and peak respectively, and risetime) amplitude (AMP) and shape (shape index, SI). The data and methods are from Allen *et al* (2005).

Pulse measure	Right and left legs	Absolute differences between right and left legs
PTTf (ms)	233–330	0–17
PTTp (ms)	431–582	0–50
Risetime (ms)	172–278	0–40
AMP (V, and ratio)	0.03–0.84	1.0–3.3
SI (normalized area units)	0.0–0.71	0.0–0.28

Table 2. Accuracy of bilateral PPG toe pulse assessments in detecting lower limb peripheral arterial occlusive disease (Allen *et al* 2005). The shape index (SI) quantified the degree of abnormal pulse distortion and was the best overall feature at separating healthy control subjects from patients with arterial disease. The accuracy (A) was greater than 90% (i.e. for ABPI < 0.9). SI also gave the highest Kappa statistic (agreement beyond chance) with substantial agreement between techniques. The diagnostic specificity (Sp) and sensitivity (Se) are also shown. SI was also 100% sensitive in detecting the higher grade disease. Simple bilateral pulse transit time differences also performed well at detecting the higher grades of disease (i.e. for ABPI < 0.5).

Disease grade and site comparison	Pulse measure	Sp (%)	Se (%)	A (%)	Kappa statistic (agreement class)
Individual leg, for ABPI < 0.9	Shape index (SI)	90.6	88.9	90.2	0.75 (substantial)
Individual leg, for ABPI < 0.5	Shape index (SI)	90.6	100.0	91.8	0.70 (substantial)
Bilateral side difference, for ABPI < 0.9	Pulse transit time (PTTp)	93.3	75.0	87.9	0.70 (substantial)
Bilateral side difference, for ABPI < 0.5	Pulse transit time (PTTf)	93.3	92.9	93.3	0.77 (substantial)

3.2.2. Arterial compliance and ageing. The process of hardening ("stiffening") of the arteries has been shown to start from around the first or second decades of life in healthy subjects, and it can be accelerated by medical conditions including renal disease and diabetes mellitus (Avolio *et al* 1983). Objective assessment of vascular ageing is very important since arterial stiffness is associated with hypertension, a risk factor for stroke and for heart disease. The stiffer the artery the faster the pulse will travel through it to the periphery, i.e. pulse wave velocity (PWV) increases (Bramwell and Hill 1922, Eliakim *et al* 1971). In addition, augmentation of the forward pressure pulse wave by a fast returning reflected wave is also another key feature that can be found in subjects with arterial stiffening. These age-related phenomena have also been explored by investigating PPG pulse timing and shape characteristics.

Generally, the PTT is inversely related to the PWV (Gizdulich 1984). However, the PTT includes the time from the ECG QRS waves to the blood ejection from the left ventricle. Nevertheless, it has been put forward as a surrogate and non-invasive measure of arterial compliance. PTT has been shown to decrease with age at the ear, finger and toe sites (Allen and Murray 2002) and with the greatest age-associated effect for the toe site (figure 8(a)). The dominance of the age-related reduction in aortic compliance may explain this finding for the toes. In the same year Nitzan *et al* (2002) also published age-related changes in PTT differences between finger and toe sites for adults. Foo *et al* (2005a, 2005b) have demonstrated that PTT increases with age in children and have explored the different confounding factors including height and growth (arterial path length) and blood pressure. The transit time of the pulse between two points along an arterial segment can also be used to assess arterial stiffening. In an important study by Loukogeorgakis *et al* (2002) PWV was assessed using transcutaneous PPG measurements of the pulse wave delay time between different points along an arterial segment. The technique was successfully validated using comparative non-invasive Doppler

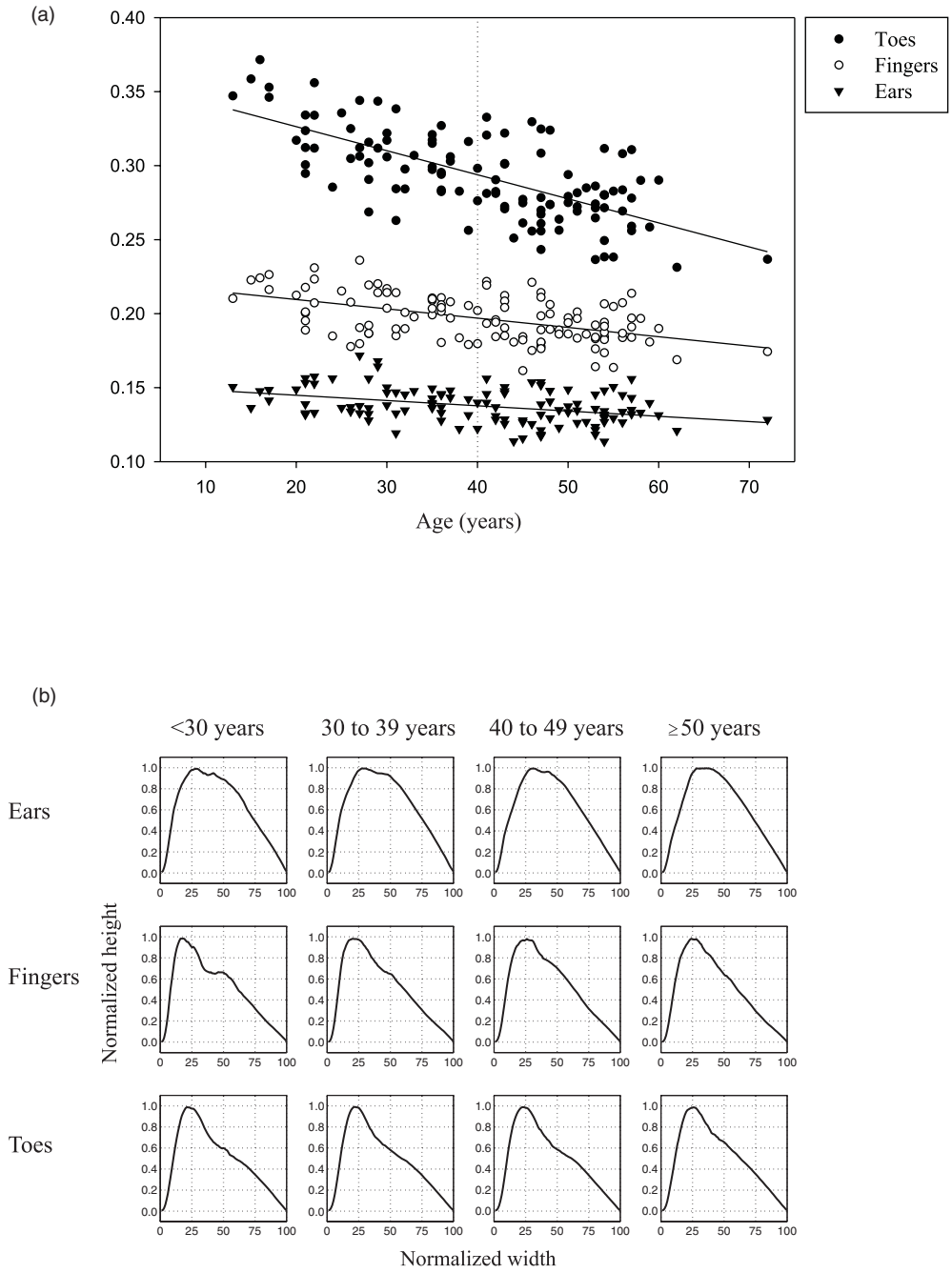

Figure 8. Changes in the PPG pulse characteristics with advancing age, for (a) pulse transit time (PTT) (Allen and Murray 2002) and (b) normalized pulse shape (Allen and Murray 2003). Each normalized shape plot is formed from the average of at least 20 subjects. The age-related reductions in PTT are greatest at the toe site, and consistent with the reported dominant ageing effect in the aorta. The gentle triangulation in normalised pulse shapes with advancing age can also be seen.

ultrasound blood flow waveforms and intra-operative arterial pressure waves. Repeatability data were also reported. Other workers investigating pulse transit time differences between body sites and arterial compliance include: Tsai *et al* (2005), Foo and Lim (2006b) and Zheng *et al* (2006).

Age-related changes in the pulse shape characteristics can also yield valuable diagnostic information about the cardiovascular system. A significant contribution to the literature has come from Millasseau, Chowienczyk and their co-workers, including the excellent review paper on contour analysis of the PPG pulse waveform measured at the finger (Millasseau *et al* 2006). This gave a succinct history of the topic and highlighted the resurgence of interest in PPG-based pulse wave analysis, and with recognition of the clinical importance of arterial stiffness. There have been many developments since the 1940's in this pulse shape analysis. It appears that digital volume pulse (DVP) contour analysis was initiated by Dillon and Hertzman (1941) who described pulse shape in terms of the crest time and dicrotic notch height. Characteristic changes in crest time and 'triangulation' of the DVP were noted in patients with hypertension and arterioslcerosis. The tendency of the notch to rise with systemic vasoconstriction and decrease after inhalation of the vasodilator amyl nitrate was also reported. This degree of dicroticism has been used as a sensitive indicator of the vasomotor effects of drugs. Four classes of DVP have been described by Dawber *et al* (1973) giving characteristic shapes with advancing age and/or the presence of vascular disease. Allen and Murray (2003) demonstrated the age-related trend towards PPG pulse triangulation at the ear and toe sites as well as the finger site (figure 8(b)). Millasseau *et al* (2002) quantified the PPG finger pulse shape using the large artery Stiffness Index and the Reflection Index to give information representing arterial stiffness and vascular tone, respectively. The Stiffness Index is calculated from the body height divided by the time delay between the pulse systolic peak and the inflection point of the reflection wave (units m/s), and the Reflection Index is calculated as the percentage ratio of the height of the diastolic notch to the peak pulse height (PulseTrace system, Micro Medical Ltd., Kent). The PPG pulse shape has also been converted to an acceleration plethysmogram to evaluate ageing and vascular disease in the cardiovascular system (Takada *et al* 1996–97). Their approach uses the second derivative of the finger PPG waveform to stabilize the baseline and enable the individual waves to be visualized. Four wave patterns were categorized and shown to be significantly associated with age and also with a biological marker for atherosclerosis. Takazawa *et al* (1998) have clinically investigated the effects of vasoactive agents and vascular ageing on these signal components by splitting it into four separate systole waves (named a–d) and a diastole wave (named e). Specific combinations of wave features were reported to be useful for investigating vasoactive drugs and also vascular ageing. Their derived ageing index was higher in subjects having diabetes mellitus, hypertension, hypercholesterolemia and ischaemic heart disease than for age-matched healthy control subjects. Other researchers have recently reported its potential clinical value for assessing vascular ageing and risk for coronary heart disease (Bortolotto *et al* 2000, Hashimoto *et al* 2005, Otsuka *et al* 2006).

The PPG pulse shape has also been compared with the blood pressure pulse shape in studies of arterial compliance. López-Beltrán *et al* (1998) formed a peripheral vascular compliance index from PPG signals and found significant differences between young and old subjects at low mean arterial pressures and also during a cold-pressor challenge. Transfer function analysis also offers some insight into the dynamic behaviour of the pulse. With the blood pressure pulse (from Finapres™ technology) selected as the input to the cardiovascular model and the PPG pulse at the finger as its output, systems identification methods enable the model parameters to be estimated and tracked in time (Allen and Murray 1999). In this study both simple linear and complex nonlinear neural network-based linear models were

explored for calculating static and dynamic system time constants (i.e. surrogate measures relating to compliance and resistance). By comparing the root mean squared (RMS) error difference between measured and predicted PPG waveforms the neural network approach gave the best shape modelling performance. The relationship between Finapres™ pressure and PPG volume pulses has been shown to provide transfer function gain and phase data for different frequencies in the physiological range (Millasseau *et al* 2000). In this study the volume pulse formed the model input and pressure pulse the model output. Healthy subjects were compared with patients having hypertension. Changes in the model to the vasodilator, sublingual nitroglycerin, were also investigated. It was found that neither the drug nor hypertension had an overall effect on the transfer function model.

PPG has been used experimentally to assess the viscoelastic properties of blood vessels including the volume elastic modulus of finger arteries (arterial pulse pressure related to PPG volume change, at specific transmural pressures, Shimazu *et al* (1986)). The volume change ratio and pulse pressure in the finger arteries were simultaneously determined by a combined transmission type near infrared PPG sensor and volume oscillometric sphygmomanometer fitted with water-filled occlusive pressure cuff. The volume elastic modulus was then determined at a range of transmural pressures. The cuff pressure was automatically inflated at a rate of 3–5 mmHg/heartbeat from 0 to 300 mmHg and the changes in pulse amplitude with vascular unloading compared to baseline levels. Systolic and mean arterial blood pressures were estimated at the points of disappearance of pulsation and at maximum pulsation, respectively. A clear difference in volume elastic modulus was found between a young subject and an old subject (33 and 65 years of age). Measurements were also compared with the local PWV in the finger giving a correlation coefficient close to 0.9. Kawarada *et al* (1986) automated the technique to derive the volume elastic modulus parameter in the finger of patients with congestive heart failure and also the forelegs of hyperlipidaemic rabbits with experimental atherosclerosis. The animal experiments evaluated the usefulness of the instrument for long-term tracking of changes in arterial properties. Progressive changes in the volume elastic modulus/transmural pressure relationship were observed during the long-term feeding of the cholesterol-rich diet in the rabbits. In the congestive heart failure patients the administration of the vasodilatator, isosorbinate dinitrate, reduced the volume elastic modulus at each set level of transmural pressure. Other workers have used a variety of physiological challenges to perturb the vascular system to assess arterial viscoelasticity, including PPG responses to a local vibration challenge (Peñáz *et al* 1997).

3.2.3. Endothelial function. The endothelium is the layer of thin specialized epithelium, comprising a single layer of cells that line the interior surface of blood vessels to form an interface between the circulating blood in the lumen and the vessel wall. These cells line the entire circulatory system, from the heart to the smallest capillary. Endothelial cells are involved in many aspects of vascular biology, including vasoconstriction and vasodilatation, blood clotting, atherosclerosis, angiogenesis, and inflammation and swelling. Endothelial dysfunction is considered to be an early event in atherosclerosis and correlates with major risk factors for cardiovascular disease.

Endothelial function is often assessed non-invasively by ultrasound brachial artery diameter measurement before and after several minutes of blood flow occlusion to the arm (Celemajer *et al* 1992). The change in arterial diameter gives a measure of flow-mediated vasodilatation. The technique, however, is operator dependent and requires high cost ultrasound imaging instrumentation which could limit its usefulness for routine clinical assessments. PPG has also shown potential for the assessment of endothelial function but is much less costly than the ultrasound approach. Shape-related information can be extracted

from the PPG waveform to quantify vasodilatatory effects with reactive hyperaemia, etc. This analysis could include comparing the height of the reflected peak relative to the systolic peak or quantifying the degree of maximal pulse damping.

The potential for PPG assessments to assess vasodilatation has been demonstrated using haemodynamic responses to nitroglycerin (NTG) therapy (Lund 1986). A well-considered PPG measurement protocol was described whereby changes in the dicrotic notch feature of the finger and toe pulse were studied over several hours to give information about the degree and length of vasodilatation with vasoactive drug. Other workers assessing the effects of vasodilator therapy include Ruiz-Vega *et al* (1998), comparing the relative height of the dicrotic notch in relation to foot-to-peak pulse amplitude over time. The finger DVP contour has the potential to help investigate endothelial-dependent dilatation in patients with type II diabetes mellitus (Chowienczyk *et al* 1999). In 2001, Gopaul *et al* (2001) also detected endothelial dysfunction in diabetic patients using the PPG derived reflection index (Millasseau *et al* 2002). There have been several other important pulse wave analysis studies reported recently but with the pulse measurements obtained using applanation tonometry instead of PPG, these include Wilkinson *et al* (2002) and Lind *et al* (2003). It is likely that the literature on PPG-based endothelial function assessment will develop considerably.

3.2.4. Venous assessment. The DC component of the PPG waveform can be used for the non-invasive assessment of lower limb chronic venous insufficiency (CVI). CVI often results in the reflux of blood through damaged valves in the legs on standing. Changes in the limb blood volume with posture can be tracked with PPG because of the associated changes in light absorption. This approach is sometimes referred to as light reflection rheography (LRR) (Belcaro *et al* 1998, Nicolaides 2000, Incze *et al* 2003). LRR has been compared successfully with the gold standard invasive ambulatory venous pressure measurement (Abramowitz *et al* 1979) with the time for the PPG signal to recover to baseline following tip-toe exercises correlating well with the pressure assessment. An example of LRR measurement and corresponding PPG venous traces in health and CVI are shown in figure 9 (Rheo Dopplex™ vascular assessment system, Huntleigh Healthcare, UK). Other researchers have compared PPG assessments and discussed their relative merits with other non-invasive assessments, including colour duplex ultrasound and air plethysmography (Marston 2002). Examples of where venous PPG has been used clinically include: assessing microcirculatory responses to phlebotropic agents in the treatment of leg ulcers (Guillot 1994), assessing age-related changes in calf muscle pump function (Stucker *et al* 2005), investigating the effect of body position on measurement reproducibility (Sam *et al* 2006), assessing improvements in deep vein reflux following varicose vein surgery (Ciostek *et al* 2004) and evaluating the haemodynamic performance of football players and wrestlers (Sophromadze *et al* 2006).

3.2.5. Vasospastic conditions, e.g. Raynaud's phenomenon. The vasospastic or cold sensitivity condition known as Raynaud's phenomenon has been investigated using a variety of optical measurement techniques, including PPG. Cooke *et al* (1985) characterized the PPG pulse shape in healthy subjects and Raynaud's patients and found that both the pulse amplitude and the slope of the rising edge were good markers for the condition. PPG amplitude also correlated well with thermographic assessments. They also reported the loss of the dicrotic notch in patients with Raynaud's secondary to systemic sclerosis and associated this with reductions in vessel compliance. Pulse amplitude changes with cold exposure have shown potential for assessing 'vibration white finger' (VWF, also known as hand arm vibration syndrome—HAVS) (Bogadi-Šara and Zavalić 1996). This approach has been extended to multi-channel finger PPG assessments by Dyszkiewicz and Tendera (2006). In the latter study

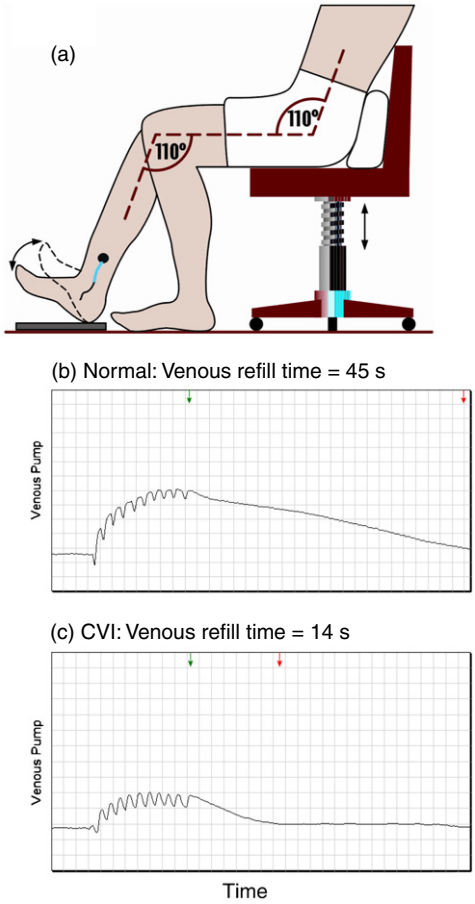

Figure 9. DC PPG for lower limb venous assessment (light reflection rheography, LRR). The PPG probe is attached to the ankle and the patient performs a series of controlled dorsiflexions of the foot whilst sitting in the position shown in (a). Venous pump traces obtained using the Rheo Dopplex^{TM} vascular assessment system are shown for (b) a healthy subject and (c) for a patient with chronic venous insufficiency (CVI). In CVI patients the time to recover to baseline levels, i.e. the venous refill time, is shorter and typically less than 20 s. Furthermore, the efficiency of the venous calf/foot pump mechanism can be impaired in patients with venous disease. (Figures are courtesy of Huntleigh Healthcare, UK.)

good sensitivity was reported compared with palesthesiometry, a visual test of skin appearance following hand cooling, and an industrial health questionnaire.

Other experimental PPG-based systems have been designed to understand the mechanisms of vasospasm. The vasomotor control system has been modelled by de Trafford *et al* (1982) where thermal stimuli were applied to the study hand at different frequencies and the changes in PPG characteristics measured on the contralateral side. Raynaud's patients had different entrainment responses to healthy subjects. In 1986, Tordoir *et al* investigated a multi-finger PPG-based system that measured digital SBPs during air cooling or heating of the hand. Finger responses from primary Raynaud's patients were different to those with digital arterial occlusive disease. Furthermore, significant pressure drops occurred at the finger of the occlusive disease group with cooling, whereas primary Raynaud's patients did not show a significant pressure change overall. Novel sensors with Peltier finger heater/cooler devices can facilitate nailfold capillary visualization of red blood cell velocity for comparison with PPG

throughout a finger temperature challenge cycle (Hahn *et al* 1999). Blood vessel vasoactivity following cold challenge stress testing has also been studied by Evans and Geddes (1988). Notably, good correlations have been found in Raynaud's assessments between low-cost PPG and laser Doppler flowmetry during controlled heating and cooling of the hand (Suichies *et al* 1992).

3.2.6. Microvascular blood flow and tissue viability. Many techniques have been proposed for the assessment of the microcirculation, including radioisotope clearance, infrared thermography, capillaroscopy, laser Doppler flowmetry, transcutaneous oxygen pressure, histology, spectrophotometry, ultrasonography, PPG and (non-contact) PPG imaging technology. The relative merits of these techniques can be studied from papers by Almond and Cooke (1989), Swain and Grant (1989), Malvezzi *et al* (1992), Brumen *et al* (1994), Agache and Dupond (1994), Midttun and Sejrsen (1996), Schultz-Ehrenburg and Blazek (2001) and Huelsbusch and Blazek (2002).

Both the anatomy and physiology of microvascular blood flow are complex, with regional differences across the body for the nutritional and thermoregulatory vascular systems. As an example of the complexity of microvascular blood flow Tur *et al* (1983) have quantified the basal perfusion of the microcirculation as a function of anatomic position for measurements collected from more than fifty skin surface sites of healthy subjects. Higher regions of perfusion were noted at the ears, fingers, palms and face. The amplitude of the PPG pulse often correlated with laser Doppler blood flow.

Measurement of the tissue perfusion is important for the clinical assessments of viability and healing. Perfusion of oxygen-carrying blood is vital for the preservation of tissue. In plastic surgery the post-operative PPG monitoring of tissue perfusion can detect early problems in free tissue transfer enabling early intervention and salvage (Jones *et al* 2000). In a study by Stack *et al* (2003) normative data were established for viable flaps from various donor sites and incorporated these into a hand-held computer for clinical use, reporting excellent results and with PPG performing better than duplex ultrasound measurements. Interruption of the blood supply to the tissues can also lead to pressure sores (Taha 1991). However, objective assessment methods are needed to better understand tissue perfusion and local ischaemia. Murray and Marjanovic (1997) have demonstrated differences in the tissue occlusion pressure as a function of PPG LED wavelength. Their findings could help in developing better methods to predict who might be more at risk of getting these sores. The role of PPG wavelength in perfusion measurement has also been discussed by de Trafford and Lafferty (1984), Giltvedt *et al* (1984), Cui *et al* (1990) and Sandberg *et al* (2005).

Lee *et al* (1979) showed the potential of PPG as an objective measure of the healing potential of tissue. If the PPG signal was pulsatile then healing was indicated with conservative management, if non-pulsatile then healing was likely to fail. Similarly, PPG assessments of dental pulp tissue viability have demonstrated pulsatile waveforms synchronous with a finger PPG reference in healthy subjects and the loss of pulsatility in patients with nonvital dental pulp (Miwa *et al* 2002). Interestingly, there was a significant negative correlation between the tooth PPG signal and subject age in those with healthy teeth. Studies of the blood have also been undertaken. A rheological study by Aldrich *et al* (2002) showed promise for the identification of abnormal haemoglobin concentrations in patients with anaemia by comparing the ratio of pulsatile changes in light attenuation to the changes in light path length.

3.3. Autonomic function

It has already been stated that the PPG signal is composite in nature and has low frequency components relating to respiration, blood pressure control and thermoregulation, as well as

the high frequency components relating to the heart synchronous pulse waveform (Murray and Foster 1996). There is considerable interest in the PPG technique applied to autonomic function including studying the variability of these signal components at the different body sites.

3.3.1. Vasomotor function and thermoregulation. Nitzan and his co-workers have contributed substantially to the PPG literature with many of their research papers focusing on the low frequency and spontaneous fluctuations of the signal. A variety of pulse wave analysis techniques have been used, including power spectral and correlation analysis, to characterize the beat-to-beat PPG amplitude variations attributed to sympathetic activity (Nitzan *et al* 1994, 1996b, 1996a, 2001), as well as the left body side similarity in low frequency characteristics (Nitzan *et al* 1998b, Khanokh *et al* 2004). Further evidence that these fluctuations are linked to the sympathetic nervous system has been demonstrated by the increase in PTT following epidural anaesthesia treatment (Babchenko *et al* 2000) and the reduction in low frequency variability following thoracic sympathectomy (Nitzan *et al* 2001). The degree of bilateral dissimilarity in the PPG low frequency characteristics for diabetic patients with neuropathy has also been measured (Nitzan *et al* 1998a, Buchs *et al* 2005), with the average right to left finger pulse low frequency baseline correlation significantly reduced from 0.93 ($\pm$0.05) in non-diabetic subjects to 0.78 ($\pm$0.22) in diabetic subjects, and the average right to left toe pulse low frequency baseline correlation significantly reduced from 0.93 ($\pm$0.06) to 0.81 ($\pm$0.17). Similar reductions in correlation were found for the pulse amplitude. The right-left correlation also decreased with disease duration. In the patient group the correlation data were clearly skewed in distribution. Other researchers have investigated the low frequency variation in PPG waveforms, including Evans and Geddes (1988), Kamal *et al* (1989), Barron *et al* (1993), Porret *et al* (1995), Bernardi *et al* (1996), Allen and Murray (2000b), Drinnan *et al* (2001) and Tanaka and Sawada (2003).

Autonomic characteristics of the PPG signal during anaesthesia have shown the relative stability of ear and finger waveforms measured at different stages of the procedure, with variability attributed to vasoconstrictor activity less apparent at the ear site (Nijboer and Dorlas 1985). Larsen *et al* (1997) undertook spectral analysis of beat-to-beat changes in the PPG AC and DC components at the ear and finger sites and compared resting healthy subjects with patients undergoing anaesthesia. At rest, the majority of spectral power was in the low (thermoregulatory) frequency band (<0.08 Hz), with associated fluctuations greater at the finger than at the ear. Low and mid frequency bands were reduced during anaesthesia but the high frequency band attributed to ventilation was maintained. Quantification of PPG waveforms in this way could help to better understand the physiological processes and stages during anaesthesia.

The inter-relationship between sympathetic wave characteristics and changes in finger temperature, in response to a deep inspiratory gasp manoeuvre, have been considered by Allen *et al* (2002). The measurement protocol included contralateral hand warming to reduce spontaneous fluctuations in skin blood flow, as recommended by Khan *et al* (1992). The relative delays between minimal finger PPG amplitude at vasoconstriction and the corresponding fall in finger pulp skin temperature were quantified for healthy male subjects. Both within-session and between-session gasp response repeatability data were provided for the test. An example of the changes in PPG pulse and the beat-to-beat PTT with this protocol is shown in figure 10. Rauh *et al* (2003) also showed that PPG was useful for detecting the gasp response and that there was a significant correlation between PPG and laser Doppler flowmetry techniques. They found a continuous increase in the correlation coefficient from the first to the final fifth gasp performed. Interestingly, Kistler *et al* (1998) showed that vasoconstrictor waves

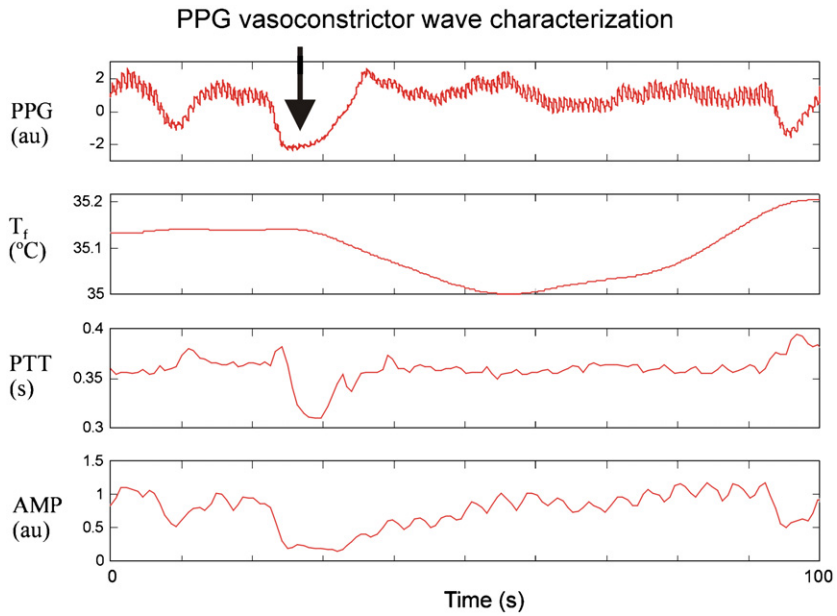

Figure 10. PPG characteristics during a deep inspiratory gasp manoeuvre. The inter-relationships between gasp and beat-to-beat changes in pulse transit time (PTT) and foot-to-peak amplitude (AMP in arbitrary units, au) can be studied. The gasp-induced reductions in PTT and AMP can clearly be seen along with the respiratory-related variations both before and after recovery from the gasp. The dynamic relationship between the finger pad skin temperature (T_f) and the pulse timing and amplitude characteristics could warrant further investigation. (Example recording taken from Allen *et al* (2002).)

at the finger are more easily demonstrable when the fingertip temperature is above 32 °C. The deep inspiratory gasp reflexes certainly warrant further evaluation, particularly in female subjects and in different autonomic patient groups. Potential clinical applications include the assessment of secondary Raynaud's phenomenon and complex regional pain syndrome (CRPS).

3.3.2. Blood pressure and heart rate variability. The physiological control of heart rate and blood pressure is very important in maintaining blood pressure homeostasis, and is often characterized by the baroreflex sensitivity (BRS, unit ms/mmHg). BRS can be attenuated in cardiovascular disease. Its non-invasive assessment is possible using beat-to-beat peripheral arterial blood pressure waveforms measured using finger-pressure cuff/PPG technology (Peñáz 1973, Imholz *et al* 1998). It has already been stated in the section on blood pressure measurement that there are several devices that can be used for this purpose, including the Finapres™ system. The value of simple and low cost PPG surrogate measures of arterial blood pressure have also been explored for BRS type studies, including the PTT. A degree of coherence between PTT and SBP variability has been shown and that the signals are inversely correlated (Naschitz *et al* 2004, Payne *et al* 2006). Further research is needed though before PTT information can be included in routine clinical autonomic studies. The heart rate and its variability are much more straightforward since they can easily be extracted from PPG pulse signals.

As well as the deep inspiratory gasp challenge in autonomic function testing (Allen *et al* 2002, Rauh *et al* 2003) slow paced breathing can be performed. This exercise should induce

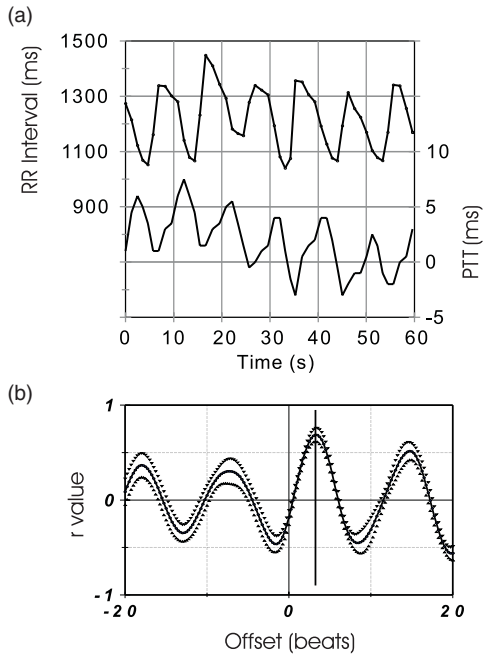

Figure 11. PPG characteristics during a slow paced breathing exercise (0.1 Hz) with (a) beat-to-beat changes in PTT and ECG RR interval. (b) Summary of the cross correlation analysis for recordings from 15 healthy subjects. The PTT lags the RR interval changes with a mean offset of 3.2 heartbeats (Drinnan *et al* 2001) (range shown is mean correlation coefficient (r) $\pm$ standard error of the mean).

periodic and synchronous blood pressure (PPG pulse) and heart rate changes. The study by Drinnan *et al* (2001) showed that PTT at the finger (and ECG RR interval) is clearly modulated by paced breathing (rate 0.1 Hz). Here, the incremental PTT and RR interval values were calculated on a beat-to-beat basis using an overlapping waveform morphology technique and their variability summarized using simple statistics. The phase differences between the signals were calculated using cross correlation analysis and a strong relationship found overall, with changes in PTT lagging changes in RR by approximately 3 heartbeats (figure 11).

3.3.3. Orthostasis. Assessment of orthostasis is a growing research area in autonomic function testing, for example in falls and syncope clinics. Changes in pulse with orthostatic stress have been assessed by several researchers. Nasimi *et al* (1991) investigated sympathetic neuropathy in patients with diabetes mellitus by monitoring PPG frequency characteristics throughout a supine-to-standing posture challenge. A significant difference in the lower frequency components with standing was found in healthy subjects, but with less change detected in the patient group. Nasimi *et al* (1992) also investigated periodic posture stimulation on local vasomotor reflexes. They applied a periodically controlled pulley-tracked movement to the study leg and detected the entrainment across a range of frequencies by both finger and toe PPG, and largely independent of breathing input. Linder *et al* (2006) have also investigated beat-to-beat changes in the ear and finger pulses on standing and have related these to heart rate dynamics. Other areas where assessment of orthostasis is important include military and space research. Jaron *et al* (1987) assessed acceleration tolerance using a reflection PPG probe placed in a region above the superficial temporal artery, and correctly identifying approximately 80% of peripheral light loss ('greyout') events.

3.3.4. Neurology. Brain autonomic control is reported to be asymmetrical, with the left hemisphere affecting predominantly parasympathetic function and the right hemisphere affecting predominantly sympathetic function. In migraine patients autonomic function can be assessed by measuring the trigemino-parasympathetic reflex to vasodilator response at the forehead with bilateral PPG. In the study by Avnon *et al* (2003) the cranial parasympathetic function differed among patients with various migraine types, with bilateral sufferers having the greatest amount of vasodilatation and unilateral sufferers the least. In a study by Komatsu *et al* (2003) the second derivative of the PPG pulse (i.e. the acceleration photplethysmograph) at the finger had significantly different wave features in migraine sufferers during headache-free periods compared to control subjects. Avnon *et al* (2004) studied left- and right-sided migraineurs outside migraine attacks and found that the left-sided group had significantly higher parasympathetic vasodilatation, although the somato-sympathetic vasoconstriction reflex at the finger was similar for both groups. PPG therefore shows considerable potential for neurological assessment, with the capability to give new insights into the physiology and pathophysiology of the central and peripheral nervous systems.

3.3.5. Other cardiovascular variability assessments. Dutch and Redman (1983) studied cardiovascular activity during psychological stressors with significant PTT decreases measured during the cold-pressor test, reaction-time task, video game and problem solving. Vascular tone, that is the degree of vasoconstriction experienced by a blood vessel relative to its maximally dilated state, has also been assessed in patients with haemorrhagic shock (Miyagatani *et al* 1999), following mood changes whilst listening to music (Matsuura 2002), genital haemodynamics in sexual dysfunction (Prause *et al* 2005, Brauer *et al* 2006), physiological studies (Foo and Lim 2006a, Foo *et al* 2006), haemodialysis (Burkert *et al* 2006), and the ambulatory monitoring of patients prone to hypoglycaemic events (Harris *et al* 1996).

4. Summary

This review has introduced the technique of photoplethysmography and has demonstrated its great potential for use in a wide range of clinical measurements. A main focus has been the assessment of the cardiovascular system. In recent years there has been a resurgence of interest in the technique, and driven by the demand for low cost, simple and portable technology for the primary care and community based clinical settings, the availability of low cost and small semiconductor components, and the advancement of computer-based pulse wave analysis techniques. PPG-based technology can be found in a wide range of commercially available medical devices for measuring oxygen saturation, blood pressure and cardiac output, assessing autonomic function and also detecting peripheral vascular disease. This success is despite the characteristics of the PPG waveform not being fully understood. Challenges remain with the technology, including the standardization of measurements, improving repeatability, and establishing comprehensive normative data ranges for comparison with patients and for evaluating responses to therapy. Future research is also likely to see developments in the measurement and analysis technology, including PPG imaging, simple endothelial dysfunction assessments, and home diagnostics.

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