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TOPICAL REVIEW

Arterial blood pressure measurement and pulse wave analysis—their role in enhancing cardiovascular assessment

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Abstract

The most common method of clinical measurement of arterial blood pressure is by means of the cuff sphygmomanometer. This instrument has provided fundamental quantitative information on arterial pressure in individual subjects and in populations and facilitated estimation of cardiovascular risk related to levels of blood pressure obtained from the brachial cuff. Although the measurement is taken in a peripheral limb, the values are generally assumed to reflect the pressure throughout the arterial tree in large conduit arteries. Since the arterial pressure pulse becomes modified as it travels away from the heart towards the periphery, this is generally true for mean and diastolic pressure, but not for systolic pressure, and so pulse pressure. The relationship between central and peripheral pulse pressure depends on propagation characteristics of arteries. Hence, while the sphygmomanometer gives values of two single points on the pressure wave (systolic and diastolic pressure), there is additional information that can be obtained from the time-varying pulse waveform that enables an improved quantification of the systolic load on the heart and other central organs. This topical review will assess techniques of pressure measurement that relate to the use of the cuff sphygmomanometer and to the non-invasive registration and analysis of the peripheral and central arterial pressure waveform. Improved assessment of cardiovascular function in relation to treatment and management of high blood pressure will result from future developments in the indirect measurement of arterial blood pressure that involve the conventional cuff sphygmomanometer with the addition of information derived from the peripheral arterial pulse.

Keywords: arterial pressure, sphygmomanometer, hypertension, ageing, cardiovascular risk, pulse pressure, heart rate, pulse waveform, pulse wave

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analysis, transfer function, radial pulse, carotid pulse, central aortic pressure, arterial impedance, pulse wave velocity, arterial stiffness, pulse amplification, vascular haemodynamics

1. Introduction

From antiquity, the presence of the arterial pulse has been understood as a fundamental sign of life. Many cultures and civilizations developed qualitative interpretations of changes in the *texture* and *strength* of the arterial pulse and the associated change in health and disease (Leake 1962). The *textural* changes in the arterial pulse were illustrated in graphical form by the various mechanical devices developed in the 19th century where sensors, placed mainly on the wrist, responded to movement associated with cardiac ejection, and levers amplified the signal which was traced on a rotating smoked drum (figure 1). These were the first ever signals displaying time-related changes in a physiological parameter and that could be recorded and compared with signals at different times or in different subjects (Fishman and Richards 1964). Thus, the shape of the arterial pulse wave became a parameter that aided both clinical description and diagnosis, using the technique of sphygmography (Mackenzie 1902, Mahomed 1872, Marey 1863). Although many of these signals were faithfully recorded, they were essentially qualitative illustrations which did not describe the *strength* of the arterial pulse. Pulse *strength*, related to the force exerted over a given area of the arterial wall, was quantified by indirect means at the cusp of the 19th and 20th centuries with the development of the brachial cuff and the auscultatory technique to produce the sphygmomanometer (Riva-Rocci 1896, Korotkoff 1905). This enabled pressure measurement in terms of the height of a column of mercury, where values of pressure (in relation to atmospheric pressure) were associated with the peak (systolic pressure) and trough (diastolic pressure) of the arterial pressure pulse. There has been very little change to the fundamental technology and operation of the sphygmomanometer since its original development and, together with the simple thermometer and stethoscope, ranks among the most ubiquitous physiological measurement instrument in medicine.

The conventional sphygmomanometric measurement of brachial cuff systolic and diastolic pressure has been used to quantify levels of arterial pressure associated with cardiovascular risk and progression of age-related pressure levels in individuals and populations (O'Brien and Fitzgerald 1994). Epidemiological studies have now convincingly demonstrated that lowering arterial pressure, by whatever means, in hypertensive individuals is a powerful contributor to reduced cardiovascular risk at any age (MacMahon *et al* 1990). These studies have all been conducted using the conventional brachial cuff sphygmomanometer, where values of systolic and diastolic pressure are taken to represent the pressure load in large conduit arteries supplying peripheral vascular beds and organs. However, due to wave propagation properties of systemic arteries, the arterial pressure pulse alters its frequency characteristics as it travels away from the heart to the periphery and the pulse alters its wave contour and generally becomes amplified (Mills *et al* 1970, Milnor 1982, Nichols and O'Rourke 2005). The amount of amplification and change in wave contour is a function of the spectral content of the pulse at the aortic root and the degree of impedance mismatch along the specific arterial path, which can be represented using a transfer function. For the brachial artery, the transfer function shows an increase in modulus from unity at zero frequency with a peak of 2.5–3.0 at around 4 Hz, after which it declines at higher frequencies (Chen *et al* 1997, Karamanoglu *et al* 1993). Hence, the pulse pressure present in the arteries of the brachial vasculature is generally not the

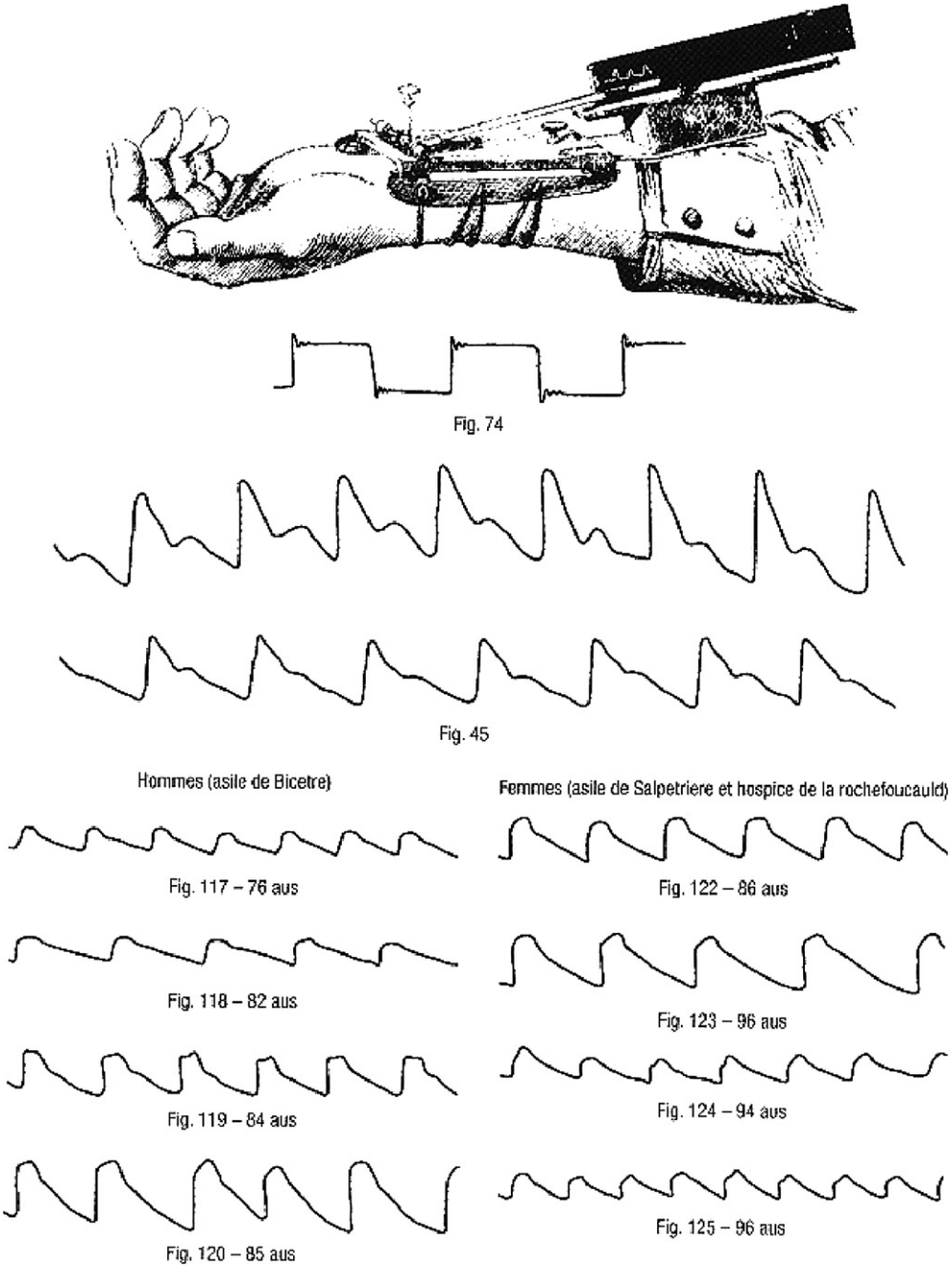

Figure 1. Pulse tracings obtained by Marey using the sphygmograph (Marey 1863) (top). Below the illustration of the sphygmograph is a square wave test to determine frequency response. Sphygmograms are shown for two young adults. Nichols and O'Rourke (2005), with permission.

same as that in the central aorta. Due to anatomical proximity, the pulsatile stress on organs such as the heart, brain and kidney is determined more closely by the central aortic pulse pressure than by the peripheral pulse pressure (O'Rourke and Safar 2005).

The observation of significant differences between the peripheral and central pressure pulse has lead to a body of work in the last 20 years where the central pressure can be estimated from the peripheral pulse wave shape recorded non-invasively. This can be achieved by means of a mathematical model of the arterial path in the upper limb (Chen *et al* 1997, Karamanoglu *et al* 1993, O'Rourke and Gallagher 1996, Pauca *et al* 2001) or from non-invasive recordings of the carotid pressure pulse (Salvi *et al* 2004) or carotid diameter waveforms (Van Bortel *et al* 2001). Recent studies in large populations using these techniques have established the importance of central pressure in the proper assessment of anti-hypertensive agents and in improved stratification of cardiovascular risk (McEniery *et al* 2008, Roman *et al* 2007, Williams *et al* 2006). Furthermore, studies on the use of beta-blockers for the treatment of high blood pressure (Bangalore *et al* 2007) have shown that in patients with uncomplicated hypertension, the use of beta-blockers is associated with increased risk of stroke compared with other antihypertensive agents. Lowering of arterial pressure with beta-blockers is also associated with reduced regression of end-organ effects such as the reduction of left ventricular hypertrophy (Dahlöf *et al* 2002). Whilst some of the effects may be related to pharmacological action, an important factor is related to the actual measurement of arterial pressure in the arm using the conventional sphygmomanometer. In the case of beta-blockers, this relates to the fact that similar values of systolic and diastolic pressures between individuals, or with treatment, can be associated with different heart rates (Dahlöf *et al* 2002, Williams *et al* 2006), and so with different spectral content of the arterial pressure waveform (Nichols and O'Rourke 2005). Hence, similar peripheral (arm) systolic and diastolic pressures are associated with different central aortic pressures. This means that while peripheral systolic blood pressure would seem to be lowered, central systolic pressure is lowered to a much lesser extent. This may explain, in part, the pressure-related increased risk of stroke and the lack of regression of ventricular hypertrophy (Bangalore *et al* 2007, Devereux *et al* 2002, Pedersen and Cockcroft 2009, Williams *et al* 2006, Kelly *et al* 1990).

The implication of the work related to central aortic pressure is that conventional measurements of blood pressure using the brachial cuff may need to be re-evaluated with respect to assessment of cardiovascular risk, improved risk stratification and especially in relation to proposed guidelines for treatment of high blood pressure (Avolio 2008, McEniery *et al* 2008). However, while the cuff sphygmomanometer has recognized limitations (section 3), there is no other method that can readily give similar measures of systolic and diastolic pressure non-invasively and that can be applied in clinical situations with relative ease. This topical review will assess the techniques of pressure measurement that combine the use of the cuff sphygmomanometer with information contained in the arterial pressure waveform and also examine related methodologies. That is, it will assess the possibility that for improved assessment of cardiovascular function, the indirect measurement of blood pressure be conducted with the conventional cuff sphygmomanometer and the detection of the peripheral pulse waveform. It will also examine other methodologies relating blood pressure and waveform analysis.

2. A brief history of the measurement of blood pressure

The physiological measurement of blood pressure involves the quantification of the distending pressure on the wall of blood vessels due to the volume of blood contained in the distensible vascular space and the additional volume ejected by the contracting ventricle. The first documented direct measurement of arterial blood pressure was performed by Stephen Hales in 1733 (Geddes 1970). The pressure in the carotid artery of a horse was obtained by insertion of a tube directly in the vessel and then measuring the height of the blood column. Although

this direct method gave accurate and reliable measurements (Geddes 1970), and while it was suitable for animal experimentation and for invasive measurements in human subjects when combined with mechanical manometers, it was not practical for routine clinical use. This resulted in a search for a practical means of obtaining a registration of the pulse that could be felt externally by using a series of mechanical levers and transducers. Many mechanical techniques were developed, involving placement of cupped devices on locations where the pulse could be palpated (Mahomed 1872, Marey 1863). However, the most significant advance came with the use of the brachial cuff by Riva-Rocci (1896), and the subsequent description of the auscultatory phenomena associated with the change in cuff pressure by Korotkoff (1905). The auscultatory methodology became the standard for routine non-invasive measurement of arterial blood pressure.

The new-found possibility of collecting data in terms of numbers that could be associated with clinical outcomes opened up the possibility of obtaining quantitative calculations of risk (Postel-Vinlay 1997). In this regard, the contributions of life insurance companies to the epidemiology of largely asymptomatic levels of arterial blood pressure and cardiovascular risk were fundamental in establishing normal population levels of blood pressure and levels of risk, as these would presumably impact on life insurance premiums (Postel-Vinlay 1997). Thus, the quantitative measurements of systolic and diastolic pressure obtained by the brachial cuff sphygmomanometer became the basis for clinical decisions. Cuff brachial systolic and diastolic pressure also guided epidemiological studies concerning cardiovascular risk factors associated with elevated arterial pressure (Kannel *et al* 1976), classification of normal and abnormal levels of blood pressure in terms of 'normotensive' and 'hypertensive' clinical associations, pharmacological studies for anti-hypertensive therapies and the production of guidelines for clinicians to treat high blood pressure (Chobanian *et al* 2003, Mancia *et al* 2007).

3. The sphygmomanometer

The description of the sphygmomanometer can be found in many fundamental texts in physiology and medical instrumentation (Geddes 1970, Webster 1997) and basic reviews (O'Brien and Fitzgerald 1994). In this section, brief descriptions will be given to complement the use of the device in association with the arterial pulse wave.

3.1. Mode of operation

3.1.1. Palpation. The palpation method is based on the original technique of Riva-Rocci (1896), where the brachial cuff is inflated to obliterate the peripheral pulse. The cuff is gradually deflated until the peripheral pulse is again felt at the radial artery. The cuff pressure at which the pulse is initially felt is the systolic pressure. With this method, it is not possible to determine diastolic pressure as there is no other means to determine the trough of the pulse since the pulse can be felt continuously following cuff deflation.

3.1.2. Auscultation. The information required for estimation of diastolic pressure became available with Korotkoff's observation that sounds heard through the stethoscope placed over the brachial artery change: they appear and disappear as the brachial cuff is gradually deflated (Korotkoff 1905). Although the origin of the Korotkoff (K) sounds entails a complex interaction between generation of turbulent flow due to arterial obstruction and vibration of the arterial wall (Conrad *et al* 1980, Ur and Gordon 1970), the cuff pressure at which the sounds are initially heard correspond to arterial systolic pressure, and when they disappear, to diastolic

pressure. One of the characteristics of the K-sounds is that they continue for some time during cuff deflation below diastolic pressure. Hence a more formal description of the phases of the K-sounds is employed to standardize measurement (Geddes 1970, O'Brien and Fitzgerald 1994). The spectrum of the K-sounds is divided into five different phases—phase I: appearance of the sound with a 'snapping' characteristic; phase II: continuous persisting murmurs; phase III: increasing of sound intensity above that of phase II; phase IV: muffling of sounds; phase V: cessation of sounds. Recommendations for determinations of diastolic pressure are to use phase V; however, if sounds persist, phase IV should be used (dable Educational Trust Ltd 2009). The sounds can be detected with a stethoscope in manual recordings and the operator makes decision in associating the cuff pressure reading with the specific sounds. In automatic devices, the sounds are detected by microphones and computerized algorithms are used for associated cuff pressures (O'Brien *et al* 2001a). The 'auscultatory gap', where the sounds in phases I and II disappear and reappear, can be a source of error, especially for systolic pressure determination (Blank *et al* 1991). In these cases, the palpatory method can be used to determine systolic pressure. The causes of the auscultatory gap have been found to be multifactorial with possible effects of respiration. However, studies have shown a significant association with vascular wall properties, with suggestions that the presence of the auscultatory gap, in itself, may have a prognostic significance (Cavallini *et al* 1996).

3.1.3. Oscillometry. The oscillometric method involves the analysis of the oscillations in the cuff pressure (the oscillogram) during deflation of the cuff (Geddes 1970, O'Brien and Atkins 1995a, O'Brien *et al* 2001a, 2001b). Compared to the mean cuff pressure, the oscillations are relatively small. When the oscillogram is plotted as a function of mean cuff pressure, the oscillation amplitude increase from zero to a maximum and then decrease to a smaller value or zero. The pressure at maximum amplitude corresponds to the vascular unloading condition of minimal (or zero) transmural arterial pressure. At this pressure, there is maximal wall expansion and the cuff pressure is equal to the mean arterial pressure (Geddes 1970). To obtain systolic and diastolic pressure, the oscillogram is analysed to obtain characteristic points that can be identified to correlate with these pressures. Systolic pressure is generally easily identified as the cuff pressure where the oscillations begin. Diastolic pressure does not always correspond with the disappearance of the oscillations and devices employ proprietary algorithms to identify this pressure value (O'Brien and Atkins 1995a, 1995b). Some studies have found an association of osillometric pulse pressure with central aortic pressure, presumably due to an underestimation of brachial pressure with the oscillometric device used in the study (Borow and Newburger 1982).

3.2. Manual and automatic devices

3.2.1. Manual. Manual devices employ a cuff wrapped around a limb with the operator palpating a peripheral pulse downstream from the site of the cuff (palpation technique) or listening for the K-sounds with a conventional stethoscope (auscultatory technique). The cuff pressure is read off from a column of mercury or, where mercury has been phased out, on an aneroid manometer with an analogue or digital readout. The accuracy of the reading depends on the precision of the discrimination of the K-sounds as well as the rate of cuff deflation. Guidelines for blood pressure measurement recommend a cuff deflation rate of 2–3 mmHg per heart beat (dable Educational Trust Ltd 2009).

3.2.2. Automatic. Automatic measurement of blood pressure became possible with the development of microprocessor technology where specific algorithms can be programmed

in software and applied to digital signals. Automatic devices employ the auscultatory or oscillometric techniques. The K-sounds are detected by a microphone with sufficient frequency response to cover the spectral range for all phases of the K-sounds, which is in the range 30–300 Hz (Allen *et al* 2004). A computer algorithm matches the sound characteristics with the cuff pressure. The cuff deflation rate is preset and under microprocessor control. Commercial devices preferentially use the oscillometric technique, as only a single pressure sensor is required to detect the cuff pressure and oscillations during cuff deflation. Since the actual measurement in the technique is mean pressure, with systolic and diastolic pressure being derived, there is only a certain number of commercial devices that are recommended by professional societies (Association for the Advancement of Medical Instrumentation 2008, O'Brien *et al* 1993b, 2001b, 2002).

The development of fast processors and relatively inexpensive mass storage media in recent years has enabled improvements in techniques for better estimation of arterial pressure with automatic devices. Some modifications to the brachial cuff employ wrist cuffs or incorporate fuzzy logic algorithms so as to provide better estimates with repeated measurements in the same subject (Ilman *et al* 2007, Jilek and Fukushima 2007, Omboni *et al* 2007, Verdecchia *et al* 2006). These techniques have also enhanced the application of ambulatory blood pressure measurements (ABPM). Pressure measurements obtained from conventional cuff-type ABPM devices have been extended to calculate vascular stiffness indices based on relative changes of mean and pulse pressure (Adiyaman *et al* 2008, Dolan *et al* 2006a, 2006b, Hansen *et al* 2006, Li *et al* 2006, Toribatake and Komine 2009). A number of studies have been conducted to assess whether this technique could offer a method for the evaluation and comparison of arterial stiffness in addition to direct pulse wave velocity measurement (Baumann *et al* 2008, Jerrard-Dunne *et al* 2008, Schillaci and Parati 2008, Westerhof *et al* 2007).

3.3. Standardization of measurement

The measurement of arterial pressure is a simple and practical means to obtain one of the most basic quantitative parameters in clinical medicine. However, it is subject to a range of possible errors due to the interaction of the operator with all components of the sphygmomanometer system, such as proper application of the cuff, selection of cuff size, fiducial auscultation of sounds, cuff deflation rates and reliable analysis of the oscillogram. In addition, systematic validation studies indicate that not all devices meet the recommended criteria for equivalence with intra-arterial measurements (Ochiai *et al* 1997, Raftery and Ward 1968).

3.3.1. Evaluation standards and protocols. Standards for evaluation of blood pressure measurement devices are set by professional societies. At present there are three principle societies that have issued recommendations: the Association for the Advancement of Medical Instrumentation (AAMI) (Association for the Advancement of Medical Instrumentation 2008), the British Hypertension Society (BHS) (O'Brien *et al* 1990, 1993b) and the European Society of Hypertension (ESH) (O'Brien *et al* 2002).

The original standard for validation of electronic or automated sphygmomanometers as used with an occluding cuff was published by the AAMI in 1986, with subsequent revisions (Association for the Advancement of Medical Instrumentation 2008, White *et al* 1993). The specific methodology requires tests to be conducted in 85 subjects with three measurements in each subject. The criteria state that the 255 measurements should give a mean difference of $<\pm 5$ mmHg and a standard deviation of 8 mmHg for systolic and diastolic pressure. The BHS criteria are established from the AAMI protocols with three measurements in 85

subjects with the addition of cumulative percentage of differences between a reference and the device being tested. The different categories or differences are 5, 10, 15 mmHg that determine the grade of classification (O'Brien *et al* 1990, 1993b). The ESH attempted to simplify the BHS procedures by reducing the protocol to two parts, with 15 and 18 subjects in each. Similar category differences as the BHS are used for validation criteria (O'Brien *et al* 2002).

Information regarding all aspects of sphygmomanometric measurement of blood pressure, ranging from specifications and testing of commercial devices, standardization of measurement techniques and a continuously updated list of relevant publications techniques, is contained in a comprehensive online resource based on the broad and long experience of Dr Eoin O'Brien in the field of arterial blood pressure measurement (dable Educational Trust Ltd 2009). The content is regularly updated and is rich in quantitative data. Devices are classed in specific categories: (1) devices for clinical use: manual, mercury sphygmomanometers, aneroid sphygmomanometers, automated devices for clinical use; (2) self-measurement devices: upper arm cuff devices, wrist devices, devices for community use; (3) ambulatory blood pressure measurement (ABPM) devices: devices for intermittent measurement; continuous measurement. All of these classes of devices have linked tables of specific devices and manufacturers classified as 'recommended', 'questionable' and 'not recommended', based on an evaluation of a set of standardized criteria based on the international protocol (IP) approved by the European society of Hypertension, the British Hypertension Society and the Association for the Advancement of Medical Instrumentation Standards (Association for the Advancement of Medical Instrumentation 2008, O'Brien *et al* 1993b, 2002).

3.4. Limitations of indirect measurement of arterial blood pressure

The theory of non-invasive measurement of arterial pressure is robust (Geddes 1970, Webster 1997). It predicts that features of the K-sounds or the oscillogram are closely associated with specific levels of cuff pressure which are related to intra-arterial pressure. However, since it is the cuff pressure which is actually measured, the associations are dependent on the transduction process, whose fidelity cannot be readily determined. It is assumed that if all the correct steps are taken, the cuff pressure is a reliable measurement of arterial pressure. However, there is a general tendency for cuff pressure to underestimate true arterial systolic pressure independent of device (Borow and Newburger 1982, Hunyor *et al* 1978) with increased variability during exercise (Gould *et al* 1985). Although an association is found between cuff pressure and intra-arterial pressure under optimum measurement conditions (Breit and O'Rourke 1974, O'Brien *et al* 2002, Ochiai *et al* 1997), the relation between peripheral blood pressure and central aortic pressure as a measure of left ventricular load is subject to a range of physiological variations.

Figure 2 shows the correspondence between invasively measured radial artery pressure and aortic pressure (Pauca *et al* 1992). This study in adult subjects (age 48–77 years) showed a mean difference in the systolic pressure of 12 mmHg (range −7 to 31), in the diastolic pressure of −1.0 mmHg (range −5 to 3) and in the mean pressure of −0.8 mmHg (range −5 to 3). The large scatter in systolic pressure results in a wide variation in pulse pressure. In addition to the methodological aspects of obtaining accurate measurement of pressures to correspond with intra-arterial pressure, the physiological phenomenon of the variable difference between central aortic and peripheral systolic pressure (figure 2) presents a potential limitation in using the conventional cuff sphygmomanometric pressure as a surrogate measure of left ventricular load, and as a fundamental descriptor of cardiovascular risk (McEniery *et al* 2008). The following sections 3.4–6 describe methods of pulse wave analysis such that additional information can be obtained from the continuous recording of the peripheral pressure

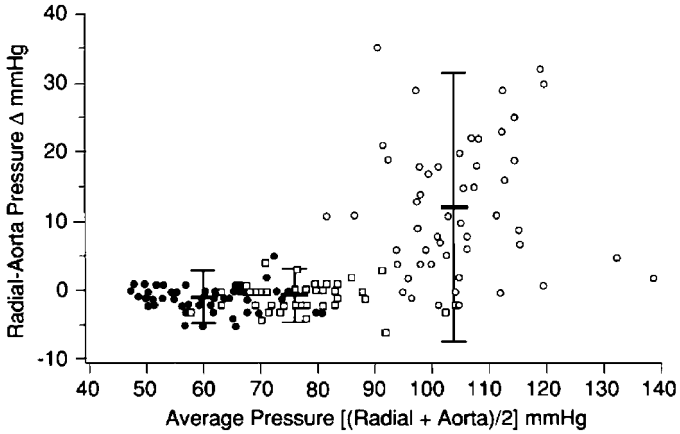

Figure 2. Differences between invasive values of systolic (open circles), mean (open squares) and diastolic (closed circles) pressure between direct intra-arterial measurements of blood pressure, plotted against the average of the two pressures. Bars represent 2 standard deviations. The mean difference for mean and diastolic pressures is around zero, whereas the mean difference for systolic pressure is 12 mmHg, with a large scatter. Pauca *et al* (1992), with permission.

pulse to complement the quantitative information provided by the cuff sphygmomanometer to estimate central aortic pressure non-invasively as well as extracting quantitative data from the morphological features of the arterial pressure pulse.

4. The arterial pulse

4.1. Background

The history of diagnosis from the radial pulse dates back several thousand years (Leake 1962). Palpation of the radial artery pulsations is one of the four main methods used in traditional Chinese medicine patient evaluation (King *et al* 2002). Despite such a long history, the first actual recordings of the arterial pulse contour were not made until 1863 by E J Marey, who created a device which used a mechanical membrane and lever system to write the radial pulse waveform directly to smoked paper (Marey 1863). The original recordings are depicted in figure 1. Marey's sphygmographs were copied and improved upon by others for several decades (Mackenzie 1902, Mahomed 1872). The first practical arterial occlusive device was made in 1876 by von Basch (Geddes 1970), but widespread use of cuffs did not occur until around 1900, following the seminal publication by Riva-Rocci (1896). Sphygmographs eventually lost ground to electrocardiograms for cardiac rhythm analysis and occlusive cuffs for blood pressure measurement around 1920 (Geddes 1970, O'Brien and Fitzgerald 1994, Postel-Vinlay 1997) and were considered to be a superseded technology for many years. Pressman and Newgard (1963) rediscovered the sphygmogram by using the technique of applanation tonometry to measure arterial pressure wave shapes in 1963. It is the basis of the widely used type of transducers for accurate, non-invasive detection of peripheral arterial pressure wave shape (Matthys *et al* 2008, McEniery *et al* 2008). Penaz (1973) later introduced the vascular unloading method of measuring continuous blood pressure and its contour non-invasively in the finger using the photoplethysmographic technique.

4.2. Generation of the arterial pressure pulse and wave propagation

The systemic arterial pressure pulse is generated by left ventricular ejection into the arterial tree. The increase in blood volume in the aorta causes a transient increase in pressure which depends on the ability of the arterial wall to expand as well as the amount of volume loss through the peripheral beds perfusing the tissue. To a first approximation, the change in volume (ΔV) is related to the change in pressure (ΔP) through the arterial compliance (C) (equation (1)):

$$C = \frac{\Delta V}{\Delta P} \tag{1}$$

where C is the lumped compliance term in the classical Windkessel model which discharges through the peripheral resistance (R) (Chemla *et al* 1998, Frank 1899, Sagawa *et al* 1990, Westerhof *et al* 2009). However, this only defines a scalar quantity and does not account for time-dependent changes of the pulse over distance. Notwithstanding, it is clear from this simple model that if the elastic storage capacity of the aorta decreases, such as that in increased arterial stiffening due to age (Avolio *et al* 1983, 1985, Kelly *et al* 1989a), a greater pressure pulse will be generated for the same stroke volume.

To account for pulse wave propagation, relationships based on oscillatory concepts have been developed, where magnitude of the pressure pulse (P) and the time course during the cardiac cycle are determined by the relationship between the flow rate (Q) and the arterial input impedance (Z_{in}) (McDonald 1968). The concept of impedance is only strictly expressed in the frequency domain, so the relationship is expressed for respective harmonics (ω) of pressure and flow (equation (2)):

$$P(\omega_i) = Z_{\text{in}}(\omega_i) \cdot Q(\omega_i) \tag{2}$$

where $i = 1, 2, 3, \ldots, N$.

$P(\omega_i)$ and $Q(\omega_i)$ are the sinusoidal components of the time-varying signals $P(t)$ and $Q(t)$ described for the period of the cardiac cycle. The complete arterial pulse can be described by at most the first ten harmonics ($N = 10$), as over 95% of the energy is in the first five to eight harmonics (Milnor 1982).

Arterial impedance is a complex quantity with modulus and phase. It is determined entirely by the physical properties of the arteries and blood. Womersley's solution of the fluid motion equations in cylindrical conduits resulted in closed form equations describing the derivation of oscillatory flow velocity from pressure gradient and dimensions of the tube and properties of the fluid (Womersley 1955, 1957b). This both facilitated the calculation of flow velocity profiles along the cross-section of the tube and produced a closed-form expression for the longitudinal impedance (relation of flow and pressure gradient over a given length) and tube characteristic impedance (Z_0, determined by blood properties and wall properties of the segment of a given length) (Nichols and O'Rourke 2005). For a uniform arterial segment of length L and terminated by a terminal impedance Z_T, the reflection coefficient (Γ) for each harmonic component (ω) is defined as

$$\Gamma(\omega) = \frac{Z_T(\omega) - Z_0(\omega)}{Z_T(\omega) + Z_0(\omega)}. \tag{3}$$

The pulse transmission along the tube length is determined by the propagation coefficient (γ) such that the transmission ratio of the pressure pulse at length L (P_L) to that at the input (P_0) is

$$\frac{P_L}{P_0} = \frac{1 + \Gamma}{e^{\gamma L} + \Gamma\, e^{-\gamma L}} \tag{4}$$

where γ is determined by the elastic and geometric properties of the arterial segment as well as density and viscosity of blood, and all terms (P_L, P_0, γ, Γ) are a function of frequency (ω) (Nichols and O'Rourke 2005, Taylor 1966b).

Equation (4) indicates that the presence of wave reflection due to impedance mismatch (equation (3)) will alter the relationship between the input and output pressure pulse in a uniform tube. This will also be modified by the elastic properties and dimensions of the artery and the density and viscosity of blood. Thus, according to the theory of wave propagation (Womersley 1957a, Taylor 1966a, 1966b), the presence of changes in arterial elasticity and dimensions along the arterial tree will produce changes in the magnitude and phase of the frequency components of the pressure pulse between two points, with the result that, for the same mean pressure, the pulse pressure and the wave shape will be different. This has implications for the measurement of peripheral pressure and in its use as a surrogate measure of central aortic pressure. However, the relation between central and peripheral pressure can be quantified in terms of mathematical representations of the frequency-dependent transfer function with aortic pressure as input and peripheral pressure as output (section 5). The inverse model (with peripheral pressure as input) then allows the estimation of the central pressure pulse from the time function of the peripheral pulse.

5. Pulse wave analysis

5.1. Background

The essentially periodic characteristics of cardiac ejection can be analysed by means of Fourier analysis of oscillatory time-dependent functions of arterial pressure and flow, and relationships expressed in the frequency domain as described in equations (2)–(4) (Milnor 1982). The inherent assumptions in the concept of impedance and wave transmission are that the system is linear and in steady state oscillation (Nichols and O'Rourke 2005, Womersley 1957a, Taylor 1966b, 1966a). That is, a specific component of pressure is uniquely related to the same harmonic component of flow determined by the vascular impedance at that frequency. Similarly, a specific harmonic component of distal pressure is uniquely related to the same harmonic component of proximal pressure as determined by the vascular transmission values of modulus and phase at that frequency. Although blood flow in elastic arteries does not strictly obey the properties of linearity (Atabek and Lew 1966, Ling *et al* 1973) and steady state oscillation, the contribution of nonlinearities under normal operating conditions is relatively small. In the canine system, using intermodulation frequency methods, the contribution of nonlinearities to pressure and flow total power was of the order of 1% and 2% respectively (Dick *et al* 1968). These effects were also measured in conscious animals to quantify wall viscoelasticity (Armentano *et al* 1995). *In vitro* studies of the human aorta showed a pressure-dependent compliance of the thoracic aorta over the cardiac cycle (Langewouters *et al* 1985), although aortic pressure and diameter waveshapes show a large degree of similarity (Studinger *et al* 2000). In terms of energy transfer, the major energy component responsible for flow is potential energy. Kinetic energy provides a much smaller component, approximately 5% of total energy (Milnor 1982). Thus, the effect of factors that contribute to nonlinearity is relatively small and so the assumption of linearity greatly facilitates the analysis by enabling the derivation of closed-form relations (equations (2)–(4)).

Other methods of characterising the arterial pulse waveform include wavelet transforms (De Melis *et al* 2009, Leonard *et al* 2004) and wave intensity analysis (WIA) (Parker and Jones 1990). WIA does not require the assumption of steady state oscillation. It considers the pressure wave as a series of wavefronts of solitary waves (Jones *et al* 2002, Koh *et al*

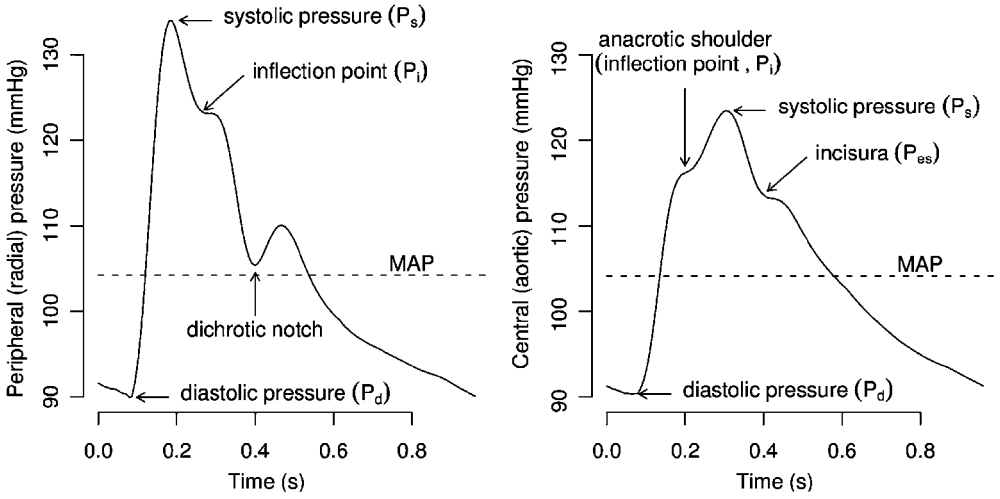

Figure 3. Features of the radial pulse wave and corresponding central aortic pressure wave. Radial pressure wave was recorded from a 50 year old male, BMI of 23.72 kg m^{-2}, and central pressure wave derived using an aortic-radial transfer function. MAP: mean pressure.

1998, Parker 2009, Parker and Jones 1990, Wang *et al* 2009, Zambanini *et al* 2005). This analysis is entirely in the time domain and uses the concept of compression and expansion waves (Parker 2009). For normal operating conditions, the frequency and time analysis methodologies give complementary information (Hughes and Parker 2009). However, there is recent interest in recasting the Windkessel concept so as to provide an alternative interpretation of the quantification of the principal factors that contribute to the morphology of the arterial pulse (Tyberg *et al* 2008, 2009).

5.2. Pulse waveform features

The time course of the pressure pulse waveform at the aortic root is determined by the pattern of ventricular ejection and the elastic and geometric properties of the arterial tree (Milnor 1989). During the cardiac cycle, the waveform exhibits prominent features that can be used as descriptors of the pressure pulse. In the ascending aorta (figure 3), peak pressure (P_s) occurs after peak flow due to the capacitive (storage) effects of the ascending aortic segment. The first inflection generally coincides with the time of peak flow velocity (at pressure value of P_i), at time Ti, at approximately 30% of the ejection duration (Westerhof *et al* 2006). The ratio of the augmented component of pressure described as $(P_s - P_i)/(Ps - P_d)$ is defined as the augmentation index (AIx). AIx has been found to have a significant heritability factor and shows changes with age (Kelly *et al* 1989a, McEniery *et al* 2005, Snieder *et al* 2000). It is generally negative in young individuals and increases to positive values with increasing age due to significant changes in the waveform morphology brought about by changes in structural components of the arterial system affecting pulse wave propagation (Kelly *et al* 1989a, Murgo *et al* 1980) (figure 4). It was conceived as a parameter associated with ventricular–vascular coupling (Yaginuma *et al* 1985). Modelling studies have also assessed the contribution of ventricular ejection to systolic pressure augmentation (Karamanoglu and Feneley 1999, 1997).

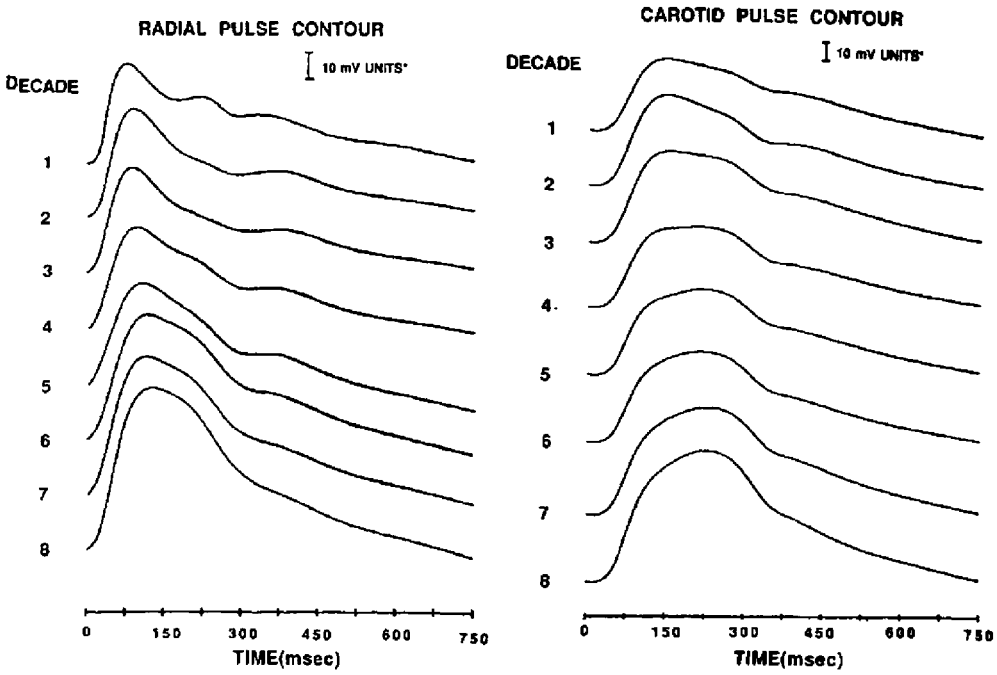

Figure 4. Ageing changes in the peripheral (radial) and central (carotid) arterial pulse in humans. Pulse waveforms obtained by applanation tonometry. Note the increase of late systolic augmentation with age. Kelly *et al* (1989a), with permission.

The radial pulse is also characterized by a number of waveform features (figure 3). The minimum point in the pressure waveform corresponding to diastolic pressure (P_d) is often equated to that in the aorta (or in the carotid artery) and together with mean pressure is used as a calibration reference (Kelly and Fitchett 1992, Verbeke *et al* 2005). The first peak in the waveform corresponds to systolic pressure (P_s) and is different to that in the central pulse, with a large variation in the difference (figure 2). An inflection (P_i) occurs late in systole and is usually lower than P_s but may form a local maximum higher than P_s in cases of high arterial stiffness, as seen with advancing age (Kelly *et al* 1989a). It is also related to systolic peak in the aorta (Takazawa *et al* 2007). A local minimum near the end of systole, the dichrotic notch, (often incorrectly called the incisura) strongly correlates with the timing of the incisura obtained from the aortic or carotid pressure pulse, and therefore corresponds to aortic valve closure, and can be used to obtain systolic duration (Gallagher *et al* 2004).

5.2.1. Peripheral pulse for estimation of arterial elastic properties. Since the development of applanation tonometry for arterial pulse detection (section 5.3), various permutations of tonometry and other methods of pulse detection have been developed that utilize waveform features for the estimation of arterial elastic properties. The CVProfilor device (Hypertension Diagnostics Inc., Eagan, MN, USA) mechanically braces the tonometer against the site of measurement to allow hands-free operation of the tonometer. The device uses a parametric model fit to the diastolic portion of the pressure pulse to determine central and peripheral compliance (Duprez *et al* 2004, Finkelstein *et al* 1988, Finkelstein and Cohn 1992). This technique has been used in studies of ageing and other factors that alter arterial distensibility (McVeigh *et al* 1999, 2002) and has been proposed to have prognostic potential (Cohn 1999).

However, one of the inherent limitations of this method is that it requires an estimation of stroke volume. This is achieved by use of average values of stroke volume scaled for anthropometric features, age and gender (Finkelstein *et al* 1988). While this may be suitable for normal conditions, errors in estimates of compliance values would occur for interventions causing significant physiological changes in stroke volume. Other applications use calibrated non-invasive subclavian pressure pulses in association with transesophageal echocardiography for diameter measurements to determine aortic elastic properties (Lang *et al* 1994).

5.2.2. Second derivative methods. Waveform features utilizing the second derivative of the photoplethysmographic (PPG) signal (section 5.3) are used to investigate cardiovascular function (Takazawa *et al* 1998). The features consist of inflection points and five sequential waves, designated *a, b, c, d* and *e*. The *a, b, c* and *d* waves occur in systole and *e* in diastole. The height is expressed in relation to the height of the *a*-wave, and extensive use has been made of these features to quantify changes in arterial parameters (Bortolotto *et al* 2000, Hashimoto *et al* 2002, Takada *et al* 1996, Takazawa *et al* 1998). The ratios b/a and d/a have been shown to have a strong relationship with age and d/a with systolic augmentation index derived from the central aortic pressure (Takazawa *et al* 1998). Because there is a known association of age and pulse wave velocity, the study by Hashimoto *et al* (Hashimoto *et al* 2002) examined the relationship between absolute values of d/a and b/a with pulse wave velocity. An age index (AGI) was also determined as $(b - c - d - e)/a$ (Hashimoto *et al* 2002, Takazawa *et al* 1998). Although these investigations report significant associations between PPG waveform features as determined by second derivatives and properties of arterial function, it is important to recall that the features of the arterial pulse are also determined by cardiac function. Thus, reduced cardiac contractility would also be manifested as a change in the derived indices (*a–e*), and this could constitute a source of error (Avolio 2002).

5.3. Pulse waveform detection

5.3.1. Applanation tonometry. Of all the many and varied techniques employed for non-invasive detection of the arterial pressure pulse, applanation tonometry has the widest application in devices that perform pulse wave analysis (see related device information in tables 1–3). The strict definition of a tonometer is essentially any instrument that measures pressure or tension. The specific application of 'applanation' tonometry, however, is one where a curved surface is flattened, such that the wall tension is effectively reduced to zero and there is transmission of the internal force to the external transducer (Drzewiecki *et al* 1983). This found specific application in the field of ophthalmology, where intraocular pressure (IOP) can be determined by a force transducer applanating the cornea (Goldmann and Schmidt 1957, Mackay and Marge 1960). The governing relationships are based on the Imbert–Fick principle which states that the internal pressure (P_i) in a spherical body consisting of an infinitely thin, dry and elastic membrane wall is the ratio of the applied force (F_a) and the area of the applanated surface (A) [$P_i = F_a/A$] (Mackay and Marge 1960). Although the Imbert–Fick principle requires ideal conditions such as thin wall, with correct applanation of the corneal surface and with accurate calibration, it is possible to determine IOP and quantify changes.

The theoretical basis for arterial applanation tonometry which was developed from the ocular application was also applied specifically to arteries. The models developed by Pressman and Newgard (1963, 1965) included properties of the transducer elements and the overlying tissues where the uniform compressible tissue surrounding the elastic artery can be represented

Table 1. Validation and selected clinical studies for applanation tonometry methods of the arterial pulse. Peer reviewed references are drawn from the PubMed database on device name and manufacturer search terms, and from the company websites.

Method	Device (manufacturer)	Calculated and estimated variables	Device validation studies	Selected clinical studies
Radial applanation tonometry	SPT-301 with data acquisition system (Millar Instruments)	–	(Kelly *et al* 1989b)	(Kelly *et al* 1989a, Wilkinson *et al* 2002a)
Radial, carotid and/or femoral applanation tonometry with calibration to oscillometric brachial pressure cuff measurement	Avidenz; BPro; Pulse Traxer (HealthStats)	Ambulatory blood pressure	(Nair *et al* 2008, Ng *et al* 2004)	–
	HEM-9000AI (OMRON)	AIx, cardiac afterload	(Takazawa *et al* 2007)	(Minami *et al* 2009)
	Complior (Artech Medical)	PWV; derived central pulse pressure; arterial stiffness index	(Huck *et al* 2007, Millasseau *et al* 2005, Podolec *et al* 2007, Rajzer *et al* 2008, Salvi *et al* 2008)	(Asmar 1999, Polonia *et al* 2009, Scuteri *et al* 2009)
	CVProfilor (Hypertension Diagnostics Inc.)	Capacitive and oscillatory compliance; systemic vascular resistance; vascular impedance; LVED; CO	(Prisant *et al* 2001b)	(Prisant *et al* 2001a, 2002)
	Diagnostic Applanation Tonometry (Specaway)	PWV; Windkessel compliance; AIx; Max dp/dt; diastolic time index; derived central aortic pressure	(Karamanoglu 1997)	(Longo *et al* 2006)

Table 1. (Continued.)

Method	Device (manufacturer)	Calculated and estimated variables	Device validation studies	Selected clinical studies
	PP-1000, GAON21A (Hanbyul Meditech)	PWV; AIx	(Lee and Park 2009)	(Shin *et al* 2009)
	PulsePen (DiaTecne)	AIx; LVED	(Salvi *et al* 2004, 2008)	(Alecu *et al* 2006, 2008)
	SphygmoCor (AtCor Medical)	PWV; derived aortic PWV; derived central aortic pressure; AIx; LVED; population averages	(Adji and O'Rourke 2004, Crilly *et al* 2007, Huck *et al* 2007, Magometschnigg 2005, Millasseau *et al* 2005, Papaioannou *et al* 2004, Rajzer *et al* 2008, Savage *et al* 2002, Sharman *et al* 2006, Soderstrom *et al* 2002, Wilkinson *et al* 1998)	(Dawson *et al* 2009, Gedikli *et al* 2009, McEniery *et al* 2008, Polonia *et al* 2009)
	T-Line (Tensys Medical)	Ambulatory blood pressure	(Szmuk *et al* 2008)	–
	Vasotrac (Medwave)	Ambulatory blood pressure	(Ahn and Jung 2006, Belani *et al* 1999a, 1999b, Cua *et al* 2005, Findlay *et al* 2006, Hager *et al* 2008, McCann *et al* 2005)	(Schultz *et al* 2007)
	VP2000 (OMRON-Colin)	PWV; LVED; AIx;	–	(Sugawara *et al* 2007)

AIx: augmentation index; LVED: left ventricular ejection duration; CO: cardiac output; PWV: pulse wave velocity.

Table 2. Validation and selected clinical studies for pressure cuff measurement techniques to detect and monitor the arterial pressure and pulse. Peer reviewed references are drawn from the PubMed database on device name and manufacturer search terms, and from the company websites.

Method	Device (manufacturer)	Calculated and estimated variables	Device validation studies	Selected clinical studies
Oscillometric pressure cuff	DP200M, DP5000A (Dynapulse)	Peripheral compliance and resistance; 24 h blood pressure; central blood pressure; LVED; CO; left ventricular contractility	(Goonasekera *et al* 1998, Motiwala *et al* 2006)	(Neutel *et al* 2004, Shrestha *et al* 2008, Urbina *et al* 2005)
	MS-2000 (Cardiovision)	Arterial stiffness index; ankle-brachial index	(Sharma *et al* 2005)	(Park *et al* 2005)
	VP1/2000 (OMRON-Colin)	Ankle-brachial index	(Cortez-Cooper *et al* 2003)	(Cook *et al* 2006)
Brachial pressure cuff with automated Korotkoff sound detection	Diasys Integra (Novacor)	QKd; 24 h ambulatory blood pressure	(Barthelemy *et al* 1991, Mora-Macia *et al* 1993, O'Brien *et al* 1991a, 1991b, 1992, O'Brien *et al* 1993a)	(Baguet *et al* 2005, Gosse *et al* 2005, Mallion *et al* 2000, Olsen *et al* 2002)
Servonulling plethysmo-manometer finger cuff	Finometer, Portapres (Finapres Medical Systems)	AIx; total peripheral resistance; pulse rate variability; baroreflex sensitivity; CO	(Birch and Morris 2003, Guelen *et al* 2003, 2008, Hehenkamp *et al* 2002, Panerai *et al* 2008, Parati *et al* 1989, Penzel 1995, Penzel *et al* 1992, Schutte *et al* 2004, Silke and McAuley 1998, Zion *et al* 2003)	(Chacon *et al* 2008, Grassi *et al* 2009, Lavinio *et al* 2007)

Table 2. (Continued.)

Method	Device (manufacturer)	Calculated and estimated variables	Device validation studies	Selected clinical studies
	Nexfin (BMEYE)	AIx; cardiac after load	(Akkermans *et al* 2009, Eeftinck Schattenkerk *et al* 2009, Lemson *et al* 2009)	(Okamoto *et al* 2009)
	Task Force Monitor (CNSystems)	Cardiac output; continuous blood pressure waveform	(Fortin *et al* 2006)	(Gratze *et al* 2005, Cornolo *et al* 2006, Boysen *et al* 2007)
Sub-diastolic limb pressure cuffs	Atherowin, Periscope (Genesis Medical Systems)	Ankle-brachial index; arterial stiffness index; estimated carotid-femoral PWV	(Naidu *et al* 2005)	–
	VaSera (Fukuda Denshi)	Ankle-brachial index; cardio-ankle vascular index	(Huck *et al* 2007, Shirai *et al* 2006)	(Goernig *et al* 2008, Toribatake and Komine 2009, Yambe *et al* 2004)
	Vicorder (Skidmore Medical)	PWV; peripheral pressures	(Hickson *et al* 2009a)	–
Supra-systolic brachial pressure cuff	Arteriograph (TensioMed)	Central pressure; estimated aortic PWV; AIx; systolic and diastolic area index;	(Baumann *et al* 2008, Magometschnigg 2005, Rajzer *et al* 2008)	(Hlimonenko *et al* 2007)
	Pulsecor (Pulsecor)	AIx; reflected wave transit time	(Payne *et al* 2007a)	–

AIx: augmentation index; LVED: left ventricular ejection duration; CO: cardiac output; PWV: pulse wave bvelocity.

Table 3. Validation and selected clinical studies for flow and flow volume measurement techniques to monitor the arterial pulse. Peer reviewed references are drawn from the PubMed database on device name and manufacturer search terms, and from the company websites. Numerous validation studies have been conducted on Doppler (Hoskins 2008) and PPG techniques (Allen 2007). However, limited validation and clinical studies conducted to date have been found for the specific devices listed in the table.

Method	Device (manufacturer)	Calculated and estimated variables	Device validation studies	Selected clinical studies
Flow Doppler	PulseTrace PWV (Cardinal Health—Micromedical)	PWV	(Salvi *et al* 2008)	–
	Vicorder (Skidmore Medical)	Ankle-brachial index	–	–
Photoplethysmography	Atherowin (Genesis Medical Systems)	Peripheral flow volume, ankle-brachial index, stiffness index	–	–
	OPV-1500 Life Scope (Nihon-Kohden)	Pulse wave transit time	(Ishihara *et al* 2004)	–
	PulseTrace PCA2, (Cardinal Health—Micromedical)	Stiffness index; reflection index	(Chowienczyk *et al* 1999, Millasseau *et al* 2002)	(Brillante *et al* 2009, Millasseau *et al* 2000)
	Vicorder (Skidmore Medical)	Peripheral flow volume	–	–
Plethysmography with sub-diastolic finger cuff	Endo-PAT2000, Watch-PAT200 (Itamar Medical)	Peripheral volume pulse	(Selamet Tierney *et al* 2009)	(Peled *et al* 2009, Yinon *et al* 2006)

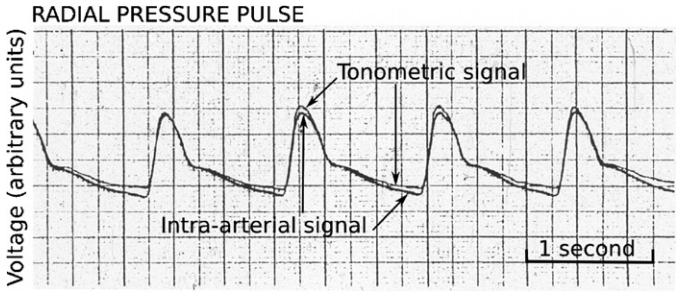

Figure 5. Comparison of non-invasive tonometric radial pulse with the intra-arterial pressure pulse obtained with a 1 F micro-tip pressure sensor at the same location in the wrist, introduced via the femoral artery (Avolio and Takazawa 1996).

by linear springs. Furthermore, the deflections caused by the application of the tonometer were assumed to be small, allowing nonlinearities to be neglected. The elastic artery was also represented by a spring model (Pressman and Newgard 1963). This model was further developed (Drzewiecki 1979, Drzewiecki and Noordergraaf 1979, Drzewiecki *et al* 1983), where the artery was represented by a cylindrical tube instead of a spring model. The overlying tissue and skin layer was neglected and the artery was assumed to be thin walled and with isotropic and homogeneous wall properties. By assuming a uniform deformation along the length of the arterial segment, the contact stress, as a function of distance from the centre of the circular artery, was calculated using curved beam mechanics (Drzewiecki *et al* 1983). This elaborate analysis indicates the importance of correct placement of the sensor to obtain zero contact stress so that only the internal blood pressure is detected with sufficient hold-down force, but no additional deformational stress.

The application of the applanation tonometry principle to arteries followed directly from the ocular application, given the propensity for circular arterial segment to be flattened by an external force. However, this requires a rigid support for the artery. The most accessible and suitable anatomic location is the wrist, where the radial pulse can be readily palpated. The main sensor types are the single sensor at the end of a hand-held pencil-type holder where the element consists of a piezoresistive transducer with dimensions much smaller than the arterial diameter, or an array of sensors strapped over the radial artery where the optimum signal is selected using computer-based algorithms (Matthys and Verdonck 2002, Sato *et al* 1993).

As in the ocular application, the original aim was to obtain actual calibrated measurements of arterial pressure using the principles of applanation tonometry (Pressman and Newgard 1963, 1965). In theory, this was deemed to be possible by eliminating the contact stress (Drzewiecki *et al* 1983). However, the practical application of this has not proved entirely successful (Matthys *et al* 2008). As yet, there is no reliable and reproducible tonometric technique able to quantify the intra-arterial pressure in a way to match the sphygmomanometer with respect to the ease of use (Matthys and Verdonck 2002). Notwithstanding the inability to obtain calibrated pressure values, the applanation principle is highly effective in recording the time-related change in intra-arterial pressure (Kemmotsu *et al* 1991a, 1991b). Thus, for an uncalibrated signal, the non-invasive tonometric pulse is similar to the intra-arterial pressure pulse. Figure 5 shows the strong correspondence between the non-invasive tonometric radial artery pulse and the pressure measured with an intra-arterial 1 F micro-tip sensor located directly beneath the tonometer. This property of arterial applanation tonometry has enabled the accurate registration of the peripheral pulse. This has resulted in the development of devices that combine pulse wave analysis and the cuff sphygmomanometer (tables 1–3)

Although the tonometric sensor is in solid state and with a high-frequency response (in the kHz range), the overall response is determined by the transducer and the coupling to the artery through the surrounding tissue. For a multi-sensor array device, the frequency response of the sensor is given as being flat for 0–50 Hz for a pressure applied directly to the sensor, although a much lower flat frequency response between was found for the complete system (Sato *et al* 1993). However, a good agreement was found with intra-arterial pressure waves with largest discrepancies occurring in early systole.

5.3.2. Modified tomometric devices. Difficulties are encountered with methods that are prone to the tonometer being displaced when the subject moves, leading to loss of the pulse signal. The Bpro and PulseTraxer devices (HealthSTATS International Pty Ltd, Singapore) use a hemispherical tonometer, which, according to manufacturer specifications, provides less sensitivity to exact positioning over the artery, facilitating measurements over longer periods and 24 h monitoring of the pulse (Ng *et al* 2004). Recent studies have shown the utility of adaptive filtering techniques for noise cancellation in the tonometric signal due to motion artefact (Ciaccio and Drzewiecki 2008). Other devices employ computerized control systems to place an array of tonometric sensors on the strongest pulse detection point upon the wrist, subsequently choosing the optimal transducer element in the array to monitor the strongest waveform amplitude (HEM-900AI, OMRON) (table 1).

5.3.3. Vascular unloading methods. The volume clamp, or vascular unloading method introduced by Penaz (1973), measures continuous peripheral arterial blood pressure. The method is incorporated in a range of devices (see table 2). A photoplethysmography approach is used at the distal part of the phalanges to monitor vascular volume. Changes in vascular volume are compensated through a servo-nulling principle by adjustment of a pressure cuff around the phalanges. The finger cuff pressure required to maintain the constant blood volume is the instantaneous arterial pressure in the finger and describes a calibrated finger pressure pulse (Imholz *et al* 1998, Wesseling 1996). The device can be uncomfortable when used for long periods as the finger cuff pressure is greater than venous pressure and occludes venous return. The Portapres and other similar devices (e.g. BMV, CnSystems) attempt to alleviate this problem with alternate measurement on two fingers. Recent developments in the technology have shown an improvement in the association between finger pressure and brachial cuff pressure values (Eeftinck Schattenkerk *et al* 2009).

The finger-cuff device gives a calibrated continuous recording of arterial pressure. It has been used extensively for applications requiring beat-to-beat information such as quantification of baroreceptor function and obstructive sleep apnoea (Bonsignore *et al* 2002, Omboni *et al* 1993, Parati *et al* 1989, 1997) as well as in microgravity simulations for space missions (Iwase *et al* 2000, Kamiya *et al* 2000, Voogel *et al* 1997).

5.3.4. Fluid-filled pulse detectors. A fluid-filled sensing apparatus placed over the radial artery is the basis of the Vasotrac system (Medwave Inc, Danvers, USA) and operates by a method similar to oscillometry (Belani *et al* 1999a). A pressure ramp is applied from a low pressure to systolic or supra-systolic level. The mean pressure is determined as the pressure corresponding to the maximum pulse amplitude. Systolic and diastolic pressures are estimated from waveform features using patented algorithms. The continuously varying force means the device does not continuously measure blood pressure but provides a pulse waveform approximately every 15 s that corresponds well with those measured using applanation tonometry (Avolio *et al* 2003) and invasive pressures (Ahn and Jung 2006). However, there are

some limitations in obese subjects (Hager *et al* 2009). The varying force also makes it suitable for measurements over extended time periods as it does not permanently occlude blood flow. It is also less sensitive to positioning errors.

5.3.5. Cuff devices for the detection of the arterial pulse. The arterial pulse can also be measured using a volume displacement technique in a statically inflated limb pressure cuff. Small oscillations in the cuff caused by arterial pulsations within the area covered by the cuff are detected by a piezo-electric pressure sensor. The Vicorder device (Skidmore Medical) (table 3) inflates pressure cuffs to sub-diastolic levels for the detection of the arterial pulse at the brachial, femoral and carotid regions. The Arteriograph (Tensiomed) measures the terminal arterial pulse against a brachial pressure cuff inflated to super-systolic pressure, associating features of the terminal pulse with arterial stiffness parameters such as augmentation index and pulse wave velocity (Hlimonenko *et al* 2007). Similar techniques of supra-systolic cuff inflation are employed in the Pulsecor device (table 2) using a wideband external pulse (WEP) measurement with a broad bandwidth piezoelectric sensor located over the brachial artery under the distal edge of a sphygmomanometer cuff. The WEP signal is similar to the first derivative of the intra-arterial pressure signal and tracks changes following use of vasoactive agents (Payne *et al* 2007a).

5.3.6. Photoplethysmography. A common method for pulse wave recording is monitoring of the finger blood volume through photoplethysmography (PPG). Allen (2007) has provided an extensive review on the broad field of PPG and its applications in physiological measurement and clinical use. Although the origins of the PPG are not fully established, the availability of low cost components and microprocessor technology has seen resurgence in the technique, employed in various commercial devices encompassing blood oxygen levels, transit time, cardiac output and beat-to-beat changes in arterial pressure, thus enabling studies of autonomic function. The reader is referred to the in-depth review by Allen (2007) on the use of PPG as an extension of the features of the non-invasive arterial pulse as discussed in this present topical review. Recent studies have highlighted the use of the PPG signal in relation to characterizing changes in blood volume (Middleton *et al* 2008 2009). Other studies extended the use of the PPG waveform to the detection of ventricular ejection times and pulse transit times during tilt manoeuvres (Chan *et al* 2007a, 2007b, 2008). A number of studies by Millasseau *et al* have made extensive use of the PPG signals for pulse waveform analysis and quantification of vascular function (Alty *et al* 2007, Broyd *et al* 2005, Millasseau *et al* 2000, 2002, 2003a, 2003b, 2006).

6. Transfer functions

6.1. Background

Transfer functions are mathematical entities used to describe a system in terms of the relationship between input and output signals. If the input is a flow signal and the output is pressure, the transfer function between flow and pressure measured at the same location and at the same time is the impedance of the system (Z_{in}), described in equation (2) as the ratio of the frequency components of pressure and flow (section 4.2) (Milnor 1989, Nichols and O'Rourke 2005). If the input is a pressure signal (P_0) and the output is another pressure signal (P_L) measured at the same time but at a different location separated by a finite distance (L), the transfer function (TF) is the ratio of the frequency (ω) components of the output and input pressure signals ($\mathrm{TF}(\omega) = P_L(\omega)/P_0(\omega)$). From equation (4) (section 4.2), it is seen

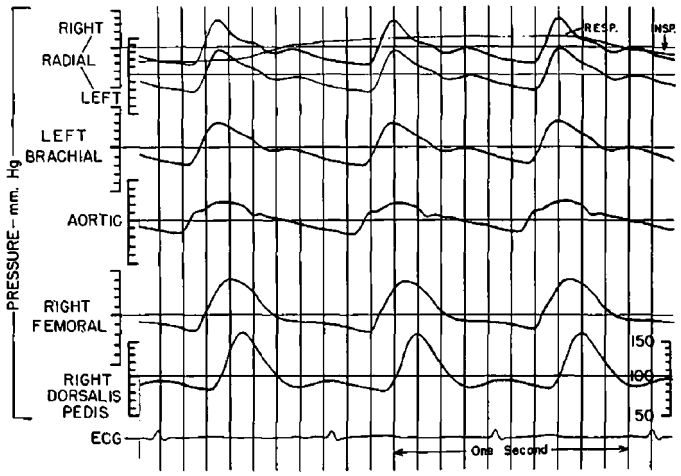

Figure 6. The following is an account of the change in the arterial pulse at different anatomical sites as eloquently described by Kroeker and Wood (1955): '... a series of simultaneously recorded pulses in a 31 year old healthy subject. There is a gradual increase in the time interval between the peak of the R wave in the electrocardiogram and the onset of the pulse wave and a gradual increase in pulse pressure, especially the systolic peaks, toward the periphery. The anacrotic shoulder is present in the aortic pulse but barely visible in the femoral pulse. There is a secondary wave following the primary peak but preceding the dicrotic notch in the brachial-radial system and there is an absence of this wave in the femoral-dorsalis pedis system. The incisura, sharp and short in the aortic pulse, is lost during transmission of the pulse wave peripherally. The dicrotic notch, which is drawn out and deep in the brachial-radial system, is practically nonexistent in the femoral and so drawn out and deep in the dorsalis pedis pulse that it approaches end diastolic pressures'. (With permission.)

that the TF is a function of the distance (L), the propagation coefficient (γ), which depends on arterial geometric and elastic properties defining pulse wave velocity, and the reflection coefficient (Γ). Like impedance, the TF is a complex quantity expressed as modulus and phase as a function of frequency. The high frequency phase delay is related to the pulse wave velocity between the two measuring sites (Nichols and O'Rourke 2005). TFs are described in the frequency domain (Chen *et al* 1997, Karamanoglu *et al* 1993) or as autoregressive functions (Fetics *et al* 1999). They can also be developed as closed form filter functions such as neural networks and Chebychev filters (Qasem *et al* 2001a, 2001b, Qasem 2002), in the time domain using peripheral pressure and wave velocity (Stergiopulos *et al* 1998) or multichannel adaptive algorithms (Hahn *et al* 2006, Swamy *et al* 2006). The following sections review the development of the transfer function between central and peripheral pressure with the aim to determine central aortic pressure by means of the peripheral (radial) arterial pressure pulse wave shape using the sphygmomanometric cuff measurements as calibration.

6.2. The relation between central and peripheral pressure pulse

A salient characteristic of the pressure pulse is that it changes shape as it travels away from the heart. In large arteries, mean pressure is essentially constant. Hence, shape changes are such that the total waveform area over one cardiac period is constant, and this generally results in a change of pulse height. These changes were documented in the early studies of Kroeker and Wood (1955, 1956) in which simultaneous measurements of arterial pressure were obtained using intra-arterial catheters. Figure 6 illustrates these changes with a description by the

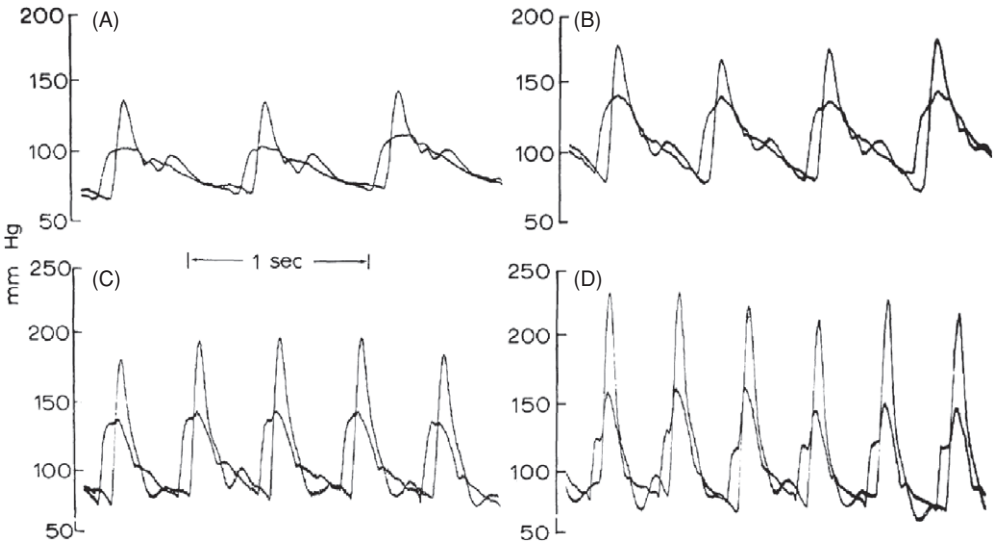

Figure 7. Simultaneous direct recordings of intra-arterial pressure in the aorta (smaller pulse) and radial artery (larger delayed pulse) in a 24 year old male during graded exercise. A: rest; B: 28.2%; C: 47.2%; D: 70.2% of maximal oxygen uptake. Note the increase in difference in pulse pressure between aorta and radial artery with increasing heart rate. Rowell *et al* (1968), with permission.

authors of the morphological changes referring to the pulse waveform features as shown in figure 3. These studies are significant as they illustrate the different time delay and the marked difference in pulse pressure at different anatomical sites. The importance of these observations is in the large differences in peak peripheral pressure as surrogate values of aortic pressure and thus the peak load on the ejecting ventricle. The difference is exaggerated in exercise as in the studies by Rowell *et al* (1968) where radial pulse pressure can be more than double the aortic pulse pressure (figure 7).

6.3. Brachial transfer function

Studies employing direct intra-arterial measurements of blood pressure such as those of Kroeker and Wood (1955, 1956) and Rowell *et al* (1968) highlighted the importance of understanding the fundamental physiological mechanisms to explain the difference between central and peripheral systolic pressure and pulse contour. This, of course, is significant in relating the conventional cuff measurements in the arm to cardiovascular function. Many modelling studies, involving simple tube models, showed the change in arterial pulse and pulse amplitude amplification due to elastic and geometric non-uniformity, such that pulse amplification can occur with progressive stiffening (Avolio 1980, Karamanoglu *et al* 1994, 1995, Taylor 1964, 1966a, 1966b, Westerhof *et al* 1969). O'Rourke (1970) investigated the influence of ventricular ejection on the transmission ratio of pulse pressure between the aorta and brachial pulse. The transmission ratio is, in effect, related to the modulus of the transfer function of the brachial system. Subsequent studies by Lasance *et al* (1976), although principally aimed at using the peripheral pulse for estimation of stroke volume, showed a frequency dependence of TF modulus and phase delay.

The development of pulse-sensing techniques has made it possible to detect the peripheral pulse with a high degree of accuracy. Although many devices use the finger as the site for

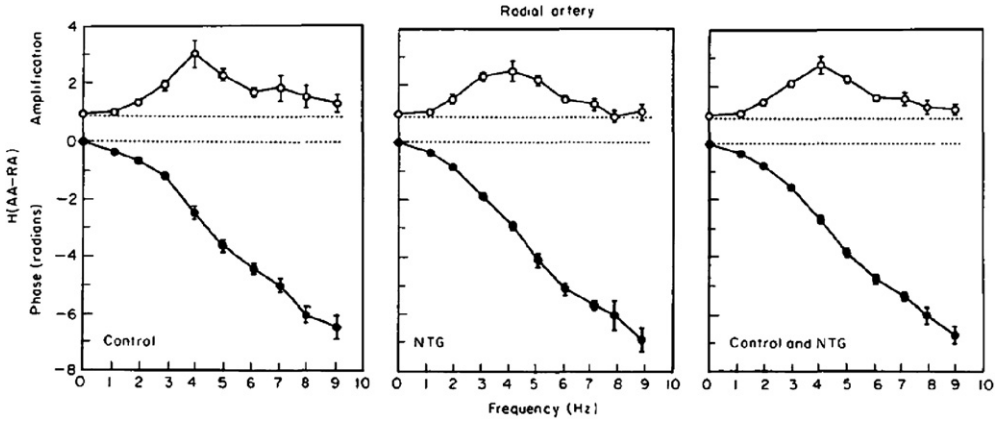

Figure 8. Amplitude and phase of transfer functions between the aorta and radial artery for control conditions (left), following administration of sublingual nitroglycerin (NTG, centre) and both combined (right). Karamanoglu *et al* (1993), with permission.

pulse detection, the assumption is that there is an association between the volume pulse usually detected in the finger (Allen 2007) and the pressure pulse in the large arteries. The most reliable registration of the peripheral arterial pulse is where it can be palpated and readily accessible, usually the wrist. Thus, from the early systems which employed mechanical levers to register the pulse at the wrist (Marey 1863) (figure 1), the resurgence of the recording of the radial pulse through the application of the technique of arterial tonometry (section 5.3) has made a significant contribution in advancing the field of blood pressure measurement by providing a reliable signal that can be analysed to estimate central aortic pressure non-invasively.

Tonometry of the radial artery has enabled the application of the brachial transfer function, determined by invasive catheter measurements, for non-invasive determination of the aortic pressure pulse and, in combination with the brachial cuff sphygmomanometer, to provide calibrated values. The study by Karamanoglu *et al* (1993), where intra-arterial pressures were measured directly by high-fidelity catheter-tipped transducers, showed that the modulus and phase of the brachial TF was relatively constant under control conditions and following administration of sublingual glycerol trinitrate (GTN). Although GTN resulted in a reduction in systemic mean pressure, the overall frequency did not change markedly, especially at low frequencies (below 4 Hz), the bandwidth containing most of the energy of the arterial pulse (Milnor 1982) (figure 8). In this bandwidth, the combined results in both aortic-brachial and aortic radial TF showed a close correspondence with results from other previous studies (Kroeker and Wood 1955, Remington and Wood 1956, Rowell *et al* 1968).

The study by Karamanoglu *et al* (1993) formed the basis for the development of a generalized transfer function where it was proposed that it could be applied to adults for the non-invasive estimation of central aortic pressure. Since its early use and initial prospective validation using invasive measurements at rest (Chen *et al* 1997, Fetics *et al* 1999, Pauca *et al* 2001) and during exercise (Dawson *et al* 2009, Sharman *et al* 2006, 2008), there has been substantial debate on the generalized transfer function concept regarding the use of essentially a constant mathematical filter in all adult subjects, irrespective of age and gender (Adji and O'Rourke 2004, Agabiti-Rosei *et al* 2007, Avolio *et al* 2004, Cloud *et al* 2003, Dart *et al* 2007, Hope *et al* 2007, Lehmann 2001). There have been attempts at individualization and development of group-specific transfer functions (Chen *et al* 1997, Fetics *et al* 1999, Hope *et al*

2002, 2007, Segers *et al* 2007a, Westerhof *et al* 2008). While it is recognized that there are necessary individual differences, the constancy of the TF at low frequencies makes the TF essentially a robust low pass filter, with relatively low mean differences between estimated and derived pulse pressure (Pauca *et al* 2001). Furthermore, the TF validation procedures included considerable changes in vascular haemodynamics, as occur in the Valsalva manoeuvre (Chen *et al* 1997). As with the vasodilatory effects of GTN (Karamanoglu *et al* 1993), the generalized transfer function tracked changes in central systolic and diastolic pressure with marked decreases in systemic mean pressure due to altered intra-thoracic pressure during forced expiration against a closed glottis as occurs during a Valsalva manoeuvre (figure 9). Transfer functions derived for specific groups such as diabetics (Hope *et al* 2004b) or sub-maximal exercise (Payne *et al* 2007b) have shown average differences of less than 5% for systolic pressure estimates when compared to the generalized transfer function. These findings are in agreement with recent studies analysing pulse wave propagation in the human arm which have shown that individualization of the TF would produce minimal effect in adults (Westerhof *et al* 2008). Other techniques have been proposed for the non-invasive estimation of central aortic pressure from the analysis of the pressure signal in the brachial artery (Marmor *et al* 1987, Sharir *et al* 1993), but these have not gained widespread use.

7. Central aortic pressure

7.1. Background

Since the early development and validation of transfer function models as non-invasive means of obtaining central aortic pressure from the peripheral arterial pulse (Chen *et al* 1997, Fetics *et al* 1999, Karamanoglu *et al* 1993, Karamanoglu and Feneley 1996, 1997, Pauca *et al* 2001), there has been a surge of activity in the use of pulse wave analysis for the determination of vascular parameters to complement the conventional blood pressure measurement by the cuff sphygmomanometer. The information contained in tables 1–3 represents the broad range of methods and devices that utilize continuous measurement of the arterial pressure pulse, some of which estimate central aortic pressure and others determine pulse transit time for calculation of pulse wave velocity. The list of methodologies and devices in tables 1–3 is by no means exhaustive but illustrates the current status and activity in the field, indicating the increasing interest in the addition of pulse waveform information to the conventional measurements of arterial pressure by the cuff sphygmomanometer.

Since the publication of recent large trials on anti-hypertensive treatment and specific endpoints such as the LIFE study (Dahlöf *et al* 2002), the CAFE study (Williams *et al* 2006), the Strong Heart study (Roman *et al* 2007) and the REASON study (de Luca *et al* 2004a, 2004b, London *et al* 2004, Mallion *et al* 2004), there has been broad acceptance that central aortic pressure is a parameter that can improve cardiovascular risk stratification. Although there is an increasing number of methodologies (tables 1–3), the principal techniques involve the use of the brachial generalized transfer function (Chen *et al* 1997, Karamanoglu *et al* 1993) or the calibration of the tonometric carotid pulse using brachial cuff mean and diastolic pressures (Salvi *et al* 2004). A third method is emerging which equates the pressure at the inflection point of the radial artery (radial P_i, figure 2) to the aortic systolic pressure (Adji *et al* 2007, Munir *et al* 2008, Pauca *et al* 2004, Takazawa *et al* 2007). A modification of this method is now being incorporated in devices using a multi-sensor array for detection of the radial pulse (table 1). Whereas the generalized transfer function and the carotid method would always provide a value of central systolic pressure, the inflection point method relies on the actual presence and detection of the inflection, a feature that is not always present

(Melenovsky *et al* 2007), especially at high heart rates and estimates may have increased error at low systolic pressure (Hickson *et al* 2009b).

7.2. Central aortic pressure and pulse wave amplification

The general increase in the wall elastic modulus and relative wall thickness with respect to vessel caliber of the arterial tree with distance from the aorta results in increasing arterial stiffness and so pulse wave velocity (Avolio 1980, 1995, Taylor 1966a, 1966b, Virmani *et al* 1991, Westerhof *et al* 1969). This has the property of producing frequency-dependent transfer functions of modulus and phase, where the modulus is essentially unity at very low frequencies and increases to a peak, then decreases at higher frequencies (Chen *et al* 1997, Karamanoglu *et al* 1993). For given values of pulse wave velocities, the frequency of the peak modulus depends on the length of the arterial segment (Milnor 1982). In adults, the mean length of the arm does not have large variations with age, since the wingspan is proportional to height and mean height varies little with age (Han *et al* 1997, Sorkin *et al* 1999). Brachial pulse wave velocity also changes little with age compared to pulse wave velocity in the aortic trunk (Avolio *et al* 1983, 1985). Hence, the peak of the modulus of brachial transfer function in adults occurs at a relatively constant frequency of mean value around 4 Hz (figure 8). This means that different frequency components will be amplified or attenuated to different degrees. Hence, the amplification of the propagated pressure pulse depends on the spectral content of the aortic pulse, and so the shape of the pulse wave. These considerations, therefore, become important when associating the pressure as measured by the brachial cuff sphygmomanometer to central properties such as peak load on the ejecting ventricle.

7.3. Central aortic pressure and effect of heart rate

Implicit in the frequency spectrum of the brachial transfer function is that amplification of the arterial pulse between proximal and distal sites depends on heart rate. This is due to the fact that the first harmonic of the pulse waveform contains the bulk (60–75%) of the total energy (Milnor 1989). Hence, the first harmonic, and therefore heart rate, is the major contributor to amplification of the pressure pulse. This implies that the association of central and peripheral pulse pressure depends on heart rate (Avolio and Benetos 2006, Wilkinson *et al* 2002b). Since diastolic pressure is essentially similar in central and peripheral large arteries (figure 2), the variability in amplification is manifest as differences in systolic pressures. Hence, similar systolic and diastolic pressures as measured with the brachial cuff at different heart rates would be associated with different systolic pressure in the central aorta. This effect can be detected by use of information available from the arterial pressure pulse waveform, in addition to the sphygmomanometer cuff measurements. The amplification ratio to peripheral sites is also age dependent (O'Rourke *et al* 1968) due to changes in waveform morphology with age (figure 4). Studies using a brachial transfer function and atrial pacing showed that pulse amplification (A) between the derived central aorta and radial artery was estimated as 39% for a heart rate of 65 beats min^{-1} increasing to 95% for 120 beats min^{-1}, giving a relationship between A and heart rate (HR, beats min^{-1}) of $A = 0.01\text{HR} + 0.76$ (Wilkinson *et al* 2002b).

The heart rate effect on pulse amplification becomes an important factor in assessing ventricular load, especially peak load due to systolic pressure, for conditions where there are large changes in heart rate, such as exercise (Rowell *et al* 1968) (figure 7), or large scale studies where anti-hypertensive agents also affect heart rate and where small differences become highly statistically significant. Results of the LIFE study in over 9000 hypertensive subjects show that an angiotensin receptor-blocking agent (losartan) has virtually identical effects on brachial

blood pressure reduction as a beta-blocking agent (atenolol) for a follow-up period of 5 years (Dahlöf *et al* 2002). For a similar reduction in blood pressure, losartan produced additional beneficial and pressure-independent effects such as improved regression of left-ventricular hypertrophy (Dahlöf *et al* 2002, Devereux *et al* 2002). However, the reduction in heart rate with atenolol was of the order of some 6 beats min^{-1}. This means that although brachial pulse pressure was identical for both agents, pulse amplification was greater with losartan; hence, aortic pulse pressure would be lower. Central aortic pressure was not measured in the LIFE study. For a given diastolic pressure, and using the regression relation between pulse amplification and heart rate (Wilkinson *et al* 2002b), the increase in central systolic pressure associated with beta-blocker treatment is estimated at approximately 3 mmHg (Avolio and Benetos 2006). In the subsequent CAFE study, where central aortic pressure was estimated from the radial pulse wave in over 2000 subjects (Williams *et al* 2006), central systolic pressure was found to be an average of 4.3 mmHg higher for the beta-blocker (atenolol) treatment compared to the calcium channel blocker treatment (amplodipine), despite similar brachial cuff pressures over a 4 year follow-up. Further analysis of the LIFE data (Fyhrquist *et al* 2005) has shown that in patients with hypertension and left ventricular hypertrophy, there were significantly higher risks for the primary composite end point, stroke and total mortality in the highest quartile of pulse pressure with atenolol-based treatment compared to the lowest quartile. The risks increased with pulse pressure for both losartan and atenolol with a trend of lower values of risk for losartan.

The observations from the LIFE (Dahlöf *et al* 2002, Devereux *et al* 2002, Fyhrquist *et al* 2005) and CAFE (Williams *et al* 2006, 2009) studies, large long-term follow-up studies addressing the efficacy of anti-hypertensive treatments, are important in terms of highlighting the information obtained from the conventional brachial cuff measurements and that obtained from the combination of the cuff measurements with the pulse waveform. The conclusions drawn from the similar cuff measurements in the LIFE study would be that the end-organ effects such as regression of left ventricular hypertrophy are pressure-independent effects and are essentially due to the treatment (Dahlöf *et al* 2002). However, with the inclusion of the arterial pulse and estimation of central pressures, it is seen that with treatments that alter heart rate, similar brachial cuff systolic pressure is associated with a different central aortic systolic pressure, and so with different peak systolic load on the left ventricle. In these studies, these effects persisted for 4–5 years; hence, conditions such as regression of left ventricular hypertrophy may not necessarily be pressure independent.

7.4. Calibration methods for non-invasive estimation of central pressure

The arterial pulse can be detected with various non-invasive methodologies as described in section 5.3. While the pulse waveform can be registered with a high degree of accuracy, the output voltage of the transducer system requires a calibration factor for conversion to pressure units (mmHg). However, since the only method for non-invasive measurement of arterial pressure is essentially based on limb cuffs (brachial or finger), the association of measured and estimated central pressure values will depend on the specific comparison made using non-invasive brachial cuff values with intra-arterial values, given the inherent errors associated with the cuff sphygmomanometer (section 3). This has particular significance when comparing central pressure estimated with a brachial transfer function and the peripheral pulse calibrated with cuff values (Cloud *et al* 2003, Davies *et al* 2003, Davies and Struthers 2003, Lehmann 2001, Takazawa *et al* 1996). Thus, it is important to distinguish the errors inherent in the algorithm used to estimate central aortic pressure (e.g. transfer functions using the entire peripheral pulse (section 5) or regression models using specific waveform features

(Melenovsky *et al* 2007, Munir *et al* 2008, Takazawa *et al* 2007)) from errors due to calibration (Papaioannou *et al* 2006). Studies validating transfer functions with fluid-filled manometers for invasive central and peripheral pressures and measuring gauge pressures (i.e. calibrated to atmospheric pressure) have shown good overall agreement between measured and estimated systolic pressure (Pauca *et al* 2001).

The practicalities of calibrating a peripheral (mainly radial or carotid) pulse waveform determine the ease of application of pulse wave analysis for estimation of central aortic pressure. The convention of calibrating the radial pulse to the measured brachial cuff systolic and diastolic pressure has been addressed in terms of determining a small but significant brachial-radial pulse amplification (Verbeke *et al* 2005). Potential errors due to pulse amplification can be reduced by using diastolic and mean pressure values for calibration (Kelly and Fitchett 1992, Salvi *et al* 2004, Segers *et al* 2007a, 2007b, Van Bortel *et al* 2001). However, this also introduces an additional source of error with respect to the determination of mean pressure. The conventional rule of equating mean pressure to diastolic pressure +1/3 pulse pressure has been questioned when compared to integration of the pulse waveform (Bos *et al* 2007). Notwithstanding the potential errors in the calculation of mean pressure from systolic and diastolic values, an oscillometric device actually produces a measurement, not estimation, of mean pressure (section 3.1), so this would add to the reliability of the calibration.

When central aortic pressure is estimated from a radial pulse using a transfer function of the form shown in figures 9 and 10, the calibration factor is common to both peripheral and central pulse pressure. Hence, ratios of central and peripheral pulse pressures are essentially calibration independent since the relationship between the pulse frequency components is determined by the dimensionless quantity of the modulus of the transfer function. This has been used to quantify changes in large populations in terms of age and gender (McEniery *et al* 2008).

7.5. Pulse wave amplification and clinical guidelines for the management of high blood pressure

7.5.1. Guidelines. The Seventh Report of the Joint National Committee (JNC7) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure published in 2003 (Chobanian *et al* 2003) provided a new set of guidelines for the prevention and management of hypertension by producing new classifications of hypertension in terms of cardiovascular risk. The JNC7 guidelines stated that over an age of 50 years, systolic pressure >140 mmHg is a better predictor of cardiovascular risk than diastolic pressure and classed as hypertensive. The risk of cardiovascular disease begins at a blood pressure of 115/75 mmHg and doubles with each increment of 20/10 mmHg. Those classed as normotensive at an age of 55 years have a 90% lifetime risk for developing hypertension. Those with a systolic pressure of 120–139 mmHg or a diastolic pressure of 80–89 mmHg should be considered as prehypertensive and require health-promoting lifestyle modifications to prevent cardiovascular disease. Hypertension, defined as 140/90 mmHg, would require treatment with appropriate combination of anti-hypertensive agents, depending on other associated conditions such as kidney disease or diabetes. Because of the ageing population, these classifications made a large proportion of the normal asymptomatic population 'prehypertensive' (Norton *et al* 2008).

The publication of the Guidelines for the Management of Arterial Hypertension by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) in 2007 (Mancia *et al* 2007) has broken new ground in attempts at incorporating expanded categories of levels of arterial pressure based on cardiovascular risk. The Guidelines underscore the reconsideration of the early concept of assessing high blood pressure simply on levels of

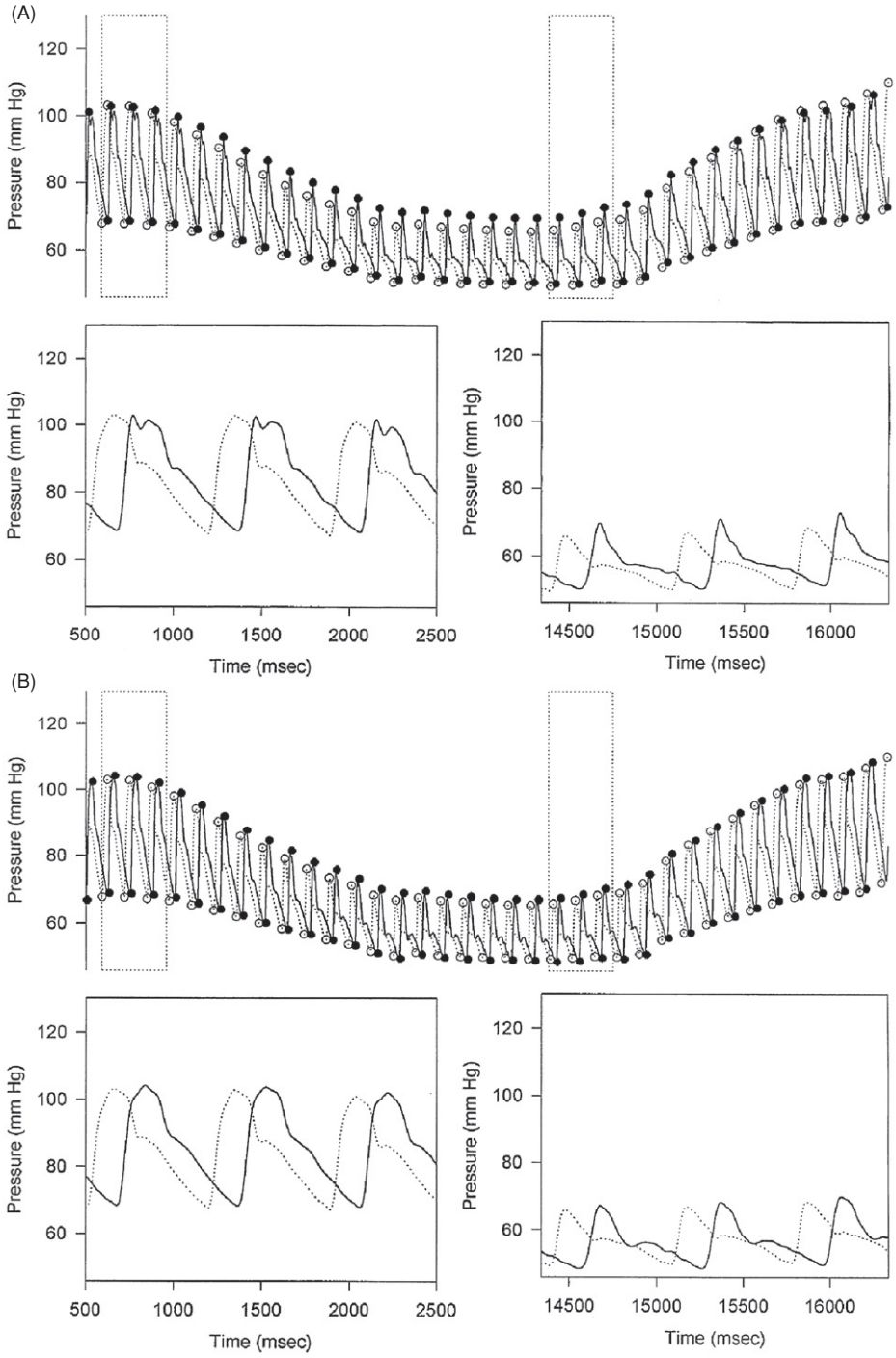

Figure 9. Comparison of invasively measured aortic pressure and estimated aortic pressure from the radial pulse. The estimated pressure tracked the aortic pressure pulse over a range of arterial pressure levels obtained with a Valsalva manoeuvre. Panels (A) and (B) indicate the use of general and individual transfer functions, respectively. Chen *et al* (1997), with permission.

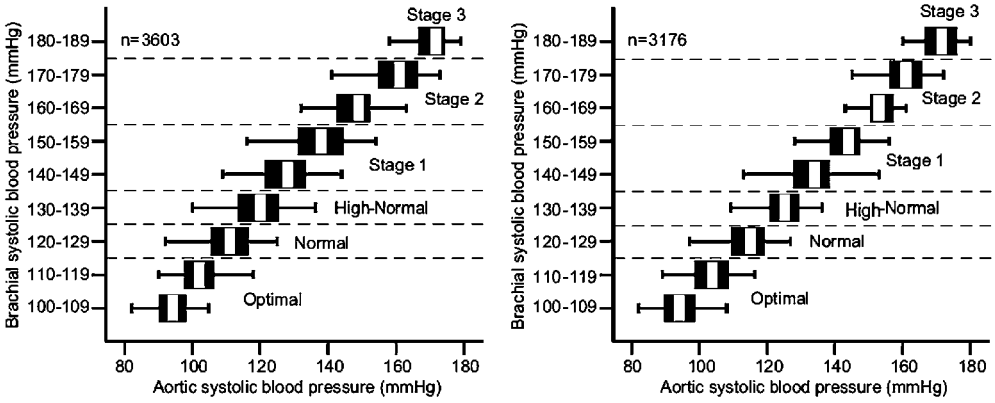

Figure 10. Box plot of aortic systolic pressure per 10 mmHg increments in brachial systolic pressure in men (left, $n = 3603$) and women (right, $n = 3176$). The vertical line within the box represents the median, the box represents the interquartile range (50% of the distribution) and the whiskers represent the range of values. The dashed lines indicate blood pressure classifications according to the 2007 European Society of Hypertension and of the European Society of Cardiology guidelines Mancia *et al* (2007). McEniery *et al* (2008), with permission.

diastolic pressure, with inclusion of systolic pressure as a parameter in classification categories. This was based on results of many randomized trials showing conclusively that cardiovascular morbidity and mortality have a continuous relationship with both diastolic and systolic pressure (Lewington *et al* 2002, MacMahon *et al* 1990) to values as low as 110–115 mmHg (systolic) and 70–75 mmHg (diastolic). This continuous relationship, together with the known unimodal distribution of arterial blood pressure in the population (Pickering 1968), puts into question the very usage of the term 'hypertension' as a condition related to some disease process. However, the Guidelines explain its continued use due to the widely accepted terminology but qualify its interpretation in terms of associated risk factors and still utilize categories of hypertension in terms of arterial blood pressure levels and related treatment options.

In contrast to the JNC7 Guidelines, the ESH/ESC Guidelines do not have any prehypertension categories and use the following definitions and classifications of arterial blood pressure (mmHg) as measured by the conventional cuff sphygmomanometer for systolic (Ps) and diastolic (Pd) pressure: *Optimal*: Ps: <120 and Pd <80; *Normal*: Ps:120–129 and/or Pd: 80–84; *High Normal*: Ps:130–139 and/or Pd: 85–89; *Grade 1 Hypertension*: Ps: 140–159 and/or Pd: 90–99; *Grade 2 Hypertension*: Ps: 160–179 and/or Pd: 100–109; *Grade 3 Hypertension*: Ps $\geqslant 180$ and/or Pd $\geqslant 110$; *Isolated Systolic Hypertension*: Ps $\geqslant 140$ and Pd <90.

The Guidelines also consider the possibility of pulse pressure being a significant parameter with age-dependent effects being more prominent in the elderly and middle aged (after age 50–55 years) (Benetos *et al* 1997, Blacher *et al* 2000, Darne *et al* 1989, Dart and Kingwell 2001, Franklin *et al* 1999, Gasowski *et al* 2002). The possibility that central pressure may also be relevant is also considered in terms of the different effect on central aortic pressure by conventional anti-hypertensive agents (Morgan *et al* 2004), effects not readily seen by brachial cuff measurements (Williams *et al* 2006).

Although there is a general trend for cuff systolic pressure to underestimate true systolic pressure and thus the cuff measurement may approach invasive measurements of central aortic systolic pressure (Gould *et al* 1985, Hope *et al* 2004a, Hunyor *et al* 1978, Kayrak *et al* 2008, Ochiai *et al* 1997, Raftery and Ward 1968, Borow and Newburger 1982), it is the relative difference that is relevant in comparing measurements of central and peripheral pressure

as left ventricular load, and so determination of cardiovascular risk. It is well established that physiological pulse amplification of the aortic pressure pulse occurs in the brachial and radial arteries (Kroeker and Wood 1955, Pauca *et al* 1992, Rowell *et al* 1968). Hence, since guidelines for treatment and management of high blood pressure are all based on brachial cuff measurements, the relevant central pressure is that which is relative to non-invasive measurement by the conventional cuff sphygmomanometer.

7.5.2. Pulse amplification. To date, guidelines for management and treatment of high blood pressure as a significant cardiovascular risk factor are based on blood pressure values obtained with a brachial cuff sphygmomanometer, as are calculations of cardiovascular risk (Chobanian *et al* 2003, Kannel *et al* 1976, MacMahon *et al* 1990, Mancia *et al* 2007, Pickering *et al* 2005). However, given the variable difference between central and peripheral systolic pressure (figure 2), there is a large range of values of central pressure that would correspond to a given value of peripheral systolic pressure. As described in section 5, this relationship depends on the pulse waveform, and so the relative magnitude and phase of the frequency components of the pressure wave. Thus, the amplification of the arterial pressure pulse between the aorta and the upper limb is a significant factor in determining the relationship between the pressure actually affecting the ejecting ventricle and the values of peripheral pressure relevant to the specific categories of risk established by the guidelines (Jankowski *et al* 2008, Mahmud and Feely 2003, Protogerou *et al* 2007, Vergnaud *et al* 2008, Wilkinson *et al* 2002c). Pulse pressure amplification and hypertension have been addressed in a recent review (Avolio *et al* 2009). Amplification has also been addressed in relation to antihypertensive treatment (Protogerou *et al* 2009).

Methodologies employing both the cuff sphygmomanometer and transfer functions to determine central aortic pressure from the brachial cuff pressure measurement and the tonometric radial artery pressure pulse have been used in the study by McEniery *et al* (2008) in over 10 000 adults of age range 18–101 years. This is the largest study of its kind using both conventional pressure measurements and pulse waveform data. This study provides quantitative analysis on the role of central aortic pressure as an improved measure of the haemodynamic burden on the ejecting ventricle. It addresses the interpretation of guidelines for management of hypertension as a cardiovascular risk factor with blood pressure as determined from the conventional brachial cuff. An important feature of the study is that it addressed the difference between central (cPP) and peripheral pulse pressure (pPP). The ratio cPP/pPP is independent of calibration (section 7.4) and depends only on the reliable detection of the peripheral pressure pulse and the methodology used to estimate the central aortic pressure pulse. A considerable variability in the ratio of cPP/pPP was found for different age groups (figure 10). This variability determines the extent of overlap of central pressure values between the categories describing the various levels of cuff blood pressure as defined by the recent ESH-ESC Guidelines for management of hypertension (Mancia *et al* 2007). Findings suggest that, on systolic values alone, 32% of males and 10% of females would be considered to have *normal* brachial systolic pressures, and therefore not treated, but would be classified as having *Stage 1 Hypertension* based on equivalent central aortic systolic pressure, and so would be considered for treatment. A key implication of this study is that while brachial cuff pressure will continue to be used as the most practical surrogate measure of arterial blood pressure, other useful and relevant information may be obtained from the registration of the arterial pulse waveform. Furthermore, while central pressure values may be estimated with regression models that do not necessarily include the time varying pulse waveform, these do not explain the whole variation. It has been shown (Camacho *et al* 2004, Walsh 2006) that stepwise multiple regression models, including height, weight, heart rate, systolic and

diastolic cuff pressure and age, explain 76% of the variability. This agrees with the figure of 73% obtained in the study by McEniery *et al* (2008) and implies that the entire peripheral pulse waveform is required for a reliable estimation of central aortic pressure. This has further implications on the heart rate dependence on pulse amplification (Wilkinson *et al* 2002b) in individual pressure measurements and subsequent classification according to guidelines.

The study by McEniery *et al* (2008) highlights the necessity to quantify the value of central aortic pressure, given the increasing interest in the field. Although the cross-sectional design presents a limitation, the overall results indicate that it can form an important platform on which to launch further investigations on the relevance of central blood pressure. The study describes, for the first time, the unique feature of using the physiological phenomenon of the variable difference of the pulse pressure between the aorta and upper limb arteries and is used to quantify the role of central aortic pressure estimated from measured values of conventional brachial cuff pressure and a peripheral pulse waveform.

8. Summary

This review addresses the topic of non-invasive measurement of arterial blood pressure. The overall approach has been to review the field in terms of the established methodology of the brachial cuff sphygmomanometer and to provide information on the use of the arterial pulse waveform. The cuff sphygmomanometer is a fundamental instrument in clinical medicine. It has played a major role in quantifying the cardiovascular risk associated with elevated arterial pressure. However, while the limitations have long been recognized, there is no other modality offering a readily accessible means of obtaining quantifiable information on levels of arterial blood pressure. This review assesses the possibility that the combination of the conventional cuff sphygmomanometer with the pulse waveform can provide a markedly improved means of non-invasive characterization of cardiovascular function and better stratification of cardiovascular risk.

There is much published material on the use and operation of the sphygmomanometer and the registration of the arterial pulse in a wealth of research papers, textbooks and topical reviews. This present review makes use of the broad range of this material but places emphasis on the emerging field of pulse wave analysis and its application in a range of medical devices. A significant application of pulse wave analysis is in the non-invasive estimation of central aortic pressure. While there is a large amount of data on the use of brachial systolic and diastolic pressures and their therapeutic and prognostic value, similar data on central pressure are not yet available. However, evidence showing the importance of central pressure is emerging from a number of trials addressing the efficacy of anti-hypertensive agents and the effect on end organs. Given the increasing interest in the use of pulse wave analysis in the medical devices industry, the robust combination of the cuff sphygmomanometer and the arterial pulse waveform could herald a paradigm shift in the management of arterial blood pressure as a risk factor for cardiovascular disease.

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