Chapter 14
Hypertension

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Learning outcomes

1. Define hypertension.
2. Describe the causes, risk factors and treatment of hypertension.
3. Describe isolated and mixed hypertension and the relationship with age.
4. Describe the typical change in blood pressure which occurs with ageing, as a result of arterial stiffening.
5. Describe arterial remodelling following a medium-term (weeks) change in blood pressure.
6. Describe invasive and non-invasive methods for the measurement of blood pressure.
7. Describe estimation of central pressure from a radial artery tonometry.

Hypertension is an elevated blood pressure which arises as a result of a number of haemodynamic changes. Ageing can also leads to elevated blood pressure. This chapter will consider hypertension and the effect of ageing on blood pressure.

14.1 Hypertension

As blood pressure is a continuous variable and is normally distributed in the population, any definition of hypertension is purely arbitrary. This is compounded by the fact that epidemiological data indicate a continuous relationship between blood pressure and the risk of stroke/heart attack. However, a level of ≥140 mmHg

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systolic and/or ≥90 mmHg diastolic, measured in the arm, is commonly used to 'define' hypertension, as it is a level above which we know that lowering blood pressure brings benefit. 'Ideal' blood pressure is considered to be <120/80 mmHg.

Hypertension is common, affecting up to a third of the adult population in the UK. In the majority of cases (90–95 %), there is no clear underlying cause—so-called primary or 'essential' hypertension. This is thought to result from a combination of life style factors including excess salt intake, reduced level of exercise and stress in genetically susceptible individuals. In rare cases, causes can be identified—so-called secondary hypertension and this offers the possibility of a cure. Causes of secondary hypertension include kidney disease, rare endocrine disorders such as Conn's syndrome, pregnancy and drugs including the oral contraceptive pill, antidepressants and cocaine.

Hypertension is a major risk factor for stroke, heart attack, kidney disease and aneurysm formation. Increased central pressure (i.e. pressure in the ascending aorta) means that the heart must work harder to eject blood into the aorta which if sustained over many years can lead to diminished heart function and eventually heart failure. Increased blood pressure in arteries is associated with increased circumferential stress which leads to a reduction in nitric oxide production, promoting plaque formation, with greater risk of rupture of atherosclerotic plaque and aneurysm. Overall, hypertension is the most common modifiable risk factor for premature death across the world. This is the reason that there is considerable clinical attention on reduction of blood pressure in the population.

Treatment of hypertension mostly involves changes to lifestyle (increased exercise, reduction in salt content of food) and medication.

Physiologically, it is important to think about the two components of blood pressure when trying to identify the underlying pathophysiological causes of hypertension (Fig. 14.1).

- Pulsatile—i.e. the pulse pressure (difference between systolic and diastolic blood pressure). The principal determinants of pulse pressure are the stroke volume and the stiffness of the large arteries.

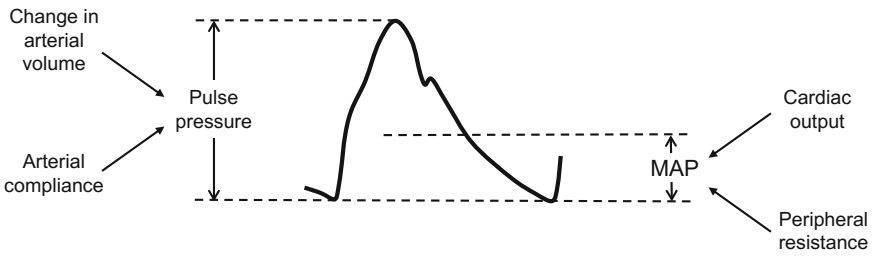

Fig. 14.1 Haemodynamic influences on pulse pressure and mean pressure. From; Koeppen BM, Stanton BA; Berne & Levy Physiology, Updated Edition, 6th Edition; Berne RM et al. Physiology. Philadelphia, PA: Copyright Elsevier (2010), with permission from Elsevier

- Static or 'steady-state'—represented by the mean arterial pressure. The determinants of the mean arterial pressure are cardiac output and peripheral vascular resistance:

$$\text{mean arterial pressure} = \text{cardiac output} \times \text{peripheral vascular resistance} \quad (14.1)$$

Essential hypertension is characterised by changes in one or more of the haemodynamic determinants of blood pressure. Interestingly, which of these components is responsible for hypertension is strongly influenced by age. In adolescents and young adults (<30 years), the principal haemodynamic disturbance is an increased stroke volume. Peripheral vascular resistance is relatively normal, as is arterial stiffness. The result is that young people tend to present with an elevated pulse pressure—so-called isolated systolic hypertension (high systolic but normal or low diastolic pressure) (Fig. 14.2). Over time, cardiac output falls to normal or subnormal levels, and peripheral vascular resistance rises, probably due to remodelling of small resistance vessels. Consequently, pulse pressure is relatively normal, but mean pressure is elevated, and this gives rise to elevation in systolic and diastolic pressures—so-called 'mixed' systolic/diastolic hypertension (Fig. 14.2), which is by far the most common form of hypertension in middle-aged individuals.

In older adults (>50 years), isolated systolic hypertension is again the most common form of hypertension, but arterial stiffening is the principal haemodynamic disturbance, causing an exaggerated increase in pulse pressure as the large arteries

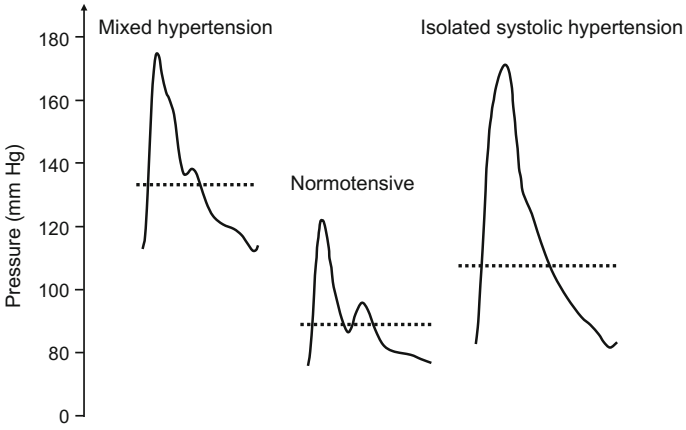

Fig. 14.2 Pressure waveforms for typical examples of mixed hypertension and isolated systolic hypertension; compared to normotension. Reproduced with permission from; McEniery CM, Wilkinson IB, Avolio AP; Age, hypertension and arterial function; Clinical and Experimental Pharmacology and Physiology. 2007;34:665–671; reproduced with permission. © 2007 The Authors Journal compilation © 2007 Blackwell Publishing Asia Pty Ltd., with permission from John Wiley and Sons

Table 14.1 summarises the relationship between haemodynamics and hypertension with age

Age	Principal haemodynamic disturbance	Predominant form of hypertension
<30 years	Increased stroke volume	Isolated systolic hypertension
30–50 years	Increased peripheral resistance	Mixed (systolic/diastolic) hypertension
>50 years	Increased arterial stiffness	Isolated systolic hypertension

can no longer effectively buffer the cyclical changes in blood pressure during each cardiac cycle. Indeed, this demonstrates the importance of normal arterial compliance. Table 14.1 summarises the relationship between haemodynamics and hypertension with age.

It is important to understand that systolic pressure is not constant along the arterial tree. Moving from the aorta to the peripheral arteries, where we tend to measure blood pressure, systolic pressure rises by up to 30 mmHg due to increased vessel stiffness and wave reflections. In contrast, diastolic pressure falls by 1–2 mmHg. This difference between aortic and brachial pressure is important because the heart, brain and other major organs are exposed to aortic not brachial pressure, and certain drug therapies exert differential effects on peripheral and central pressure.

14.2 Ageing and Blood Pressure

With increasing age arteries get stiffer. This is illustrated in Fig. 14.3, and this leads to an increase in systolic central blood pressure as shown in Fig. 14.7. Published data on brachial pressure with age is given in Burt et al. (1995) for a USA population (Fig. 14.4). Herbert et al. (2014) present data on change in central pressure with age from data collected worldwide. Data on the change in the rate of hypertension with age for different parts of the world is provided by Kearney et al. (2005). They note lower overall rates (15–27 %) in Eastern and some developing countries. The highest rates were in established market economies (37 %), former socialist economies (37 %) and Latin America and the Caribbean (37 %). Wilkinson and McEniery (2012) noted that some populations have a much lower change of pressure with age identifying a rural community in China (Avolio et al. 1985), and a tribe in Cameroon living a hunter-gatherer lifestyle (Lemogoum et al. 2012) in this context. This leads to the idea that there is stiffening as a natural consequence of ageing and stiffening as a pathological process associated with disease (Wilkinson et al. 2012). This is illustrated in Fig. 14.5. The 2 processes are the following:

- *Biological increase in stiffness with age*. The repeated cyclic stress on the elastic fibres in the arterial wall leads to fibre fracture and loss of elasticity (O'Rourke 1990). Cyclic fatigue is commonly seen in engineering where repeated stretching and unstretching of materials many millions of times eventually lead

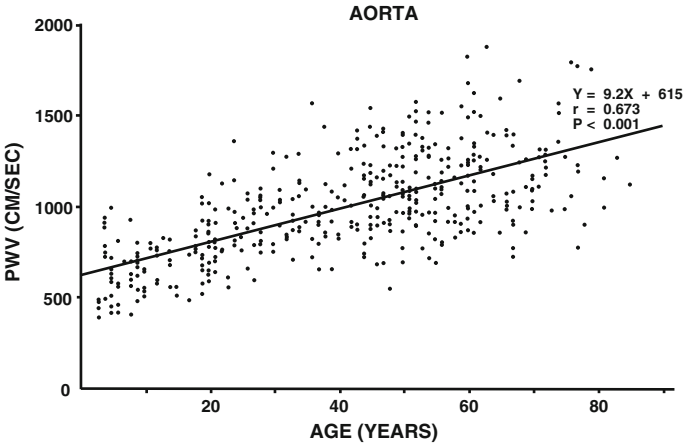

Fig. 14.3 Aortic PWV, measured between base of the neck and groin for all subjects (both male and female subjects) between ages 3 and 89 years. Individual values were determined as the average of 10 pairs of pulses simultaneously recorded with identical transcutaneous Doppler transducers. From; Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF; Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation. 1983;68:50–58; with permission from Wolters Kluwer Health, Inc.

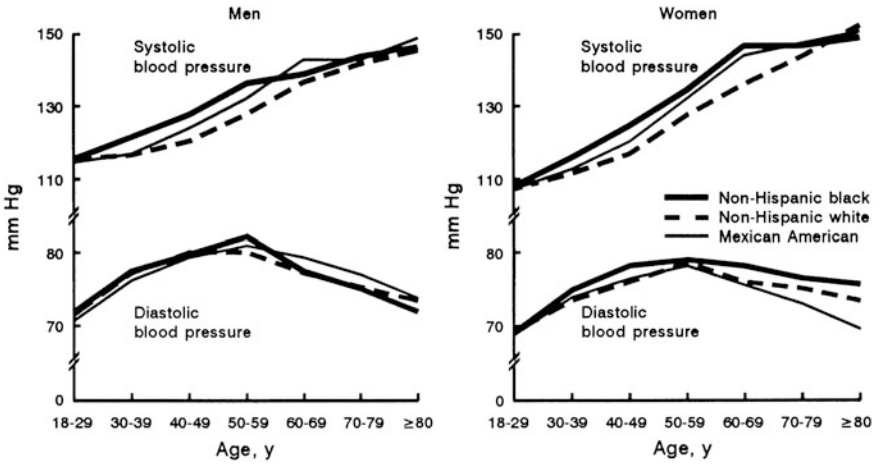

Fig. 14.4 Mean systolic and diastolic blood pressures by age and race/ethnicity for men and women, US population 18 years of age and older. From; Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M et al.; Prevalence of hypertension in the US population. Results from the Third National Health and Nutrition Examination Survey. 1988–1991. Hypertension. 1995;25:305-313; © 1995 American Heart Association, Inc., with permission from Wolters Kluwer Health, Inc.

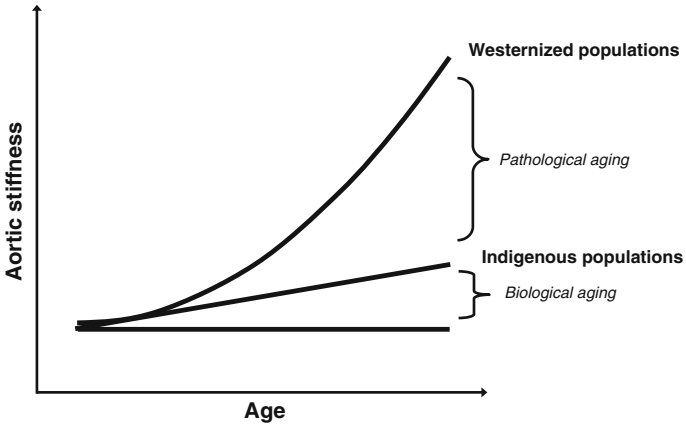

Fig. 14.5 Schema demonstrating pathological versus biological vascular ageing. From; Wilkinson IB, McEniery CM. Arteriosclerosis: inevitable or self-inflicted? Hypertension. 2012;60:3–5; © 2012 American Heart Association, Inc., with permission from Wolters Kluwer Health, Inc.

to fracture of the material. In the human over a single decade, the elastic fibres in the artery wall will stretch and unstretch over 300 million times. This effect is also more marked at higher pressures. A measure of the degree of cyclic stretch fatigue is the product of age times pulse pressure times heartrate.

- *Pathological increase in stiffness with age*. Diseases such as diabetes and aspects of Western lifestyle such as high salt intake, along with genetic predisposing factors, lead to biological changes in the vessel wall and increase in stiffness.

Biological and pathological factors form a vicious circle in which there continues to be increase in stiffness and pressure over time (Fig. 14.6) both of which contribute to the formation of atherosclerosis.

14.3 Pressure and Stiffness

Blood pressure is inextricably linked to arterial stiffness, mainly stiffness of the aorta. This section will examine what happens to blood pressure as the stiffness of the aorta increases.

14.3.1 Role of PWV in Determining Pressure

It will be recalled from Chap. 4 that the blood pressure waveform (pressure–time) is a composite of the forward going pressure wave and the reverse going pressure

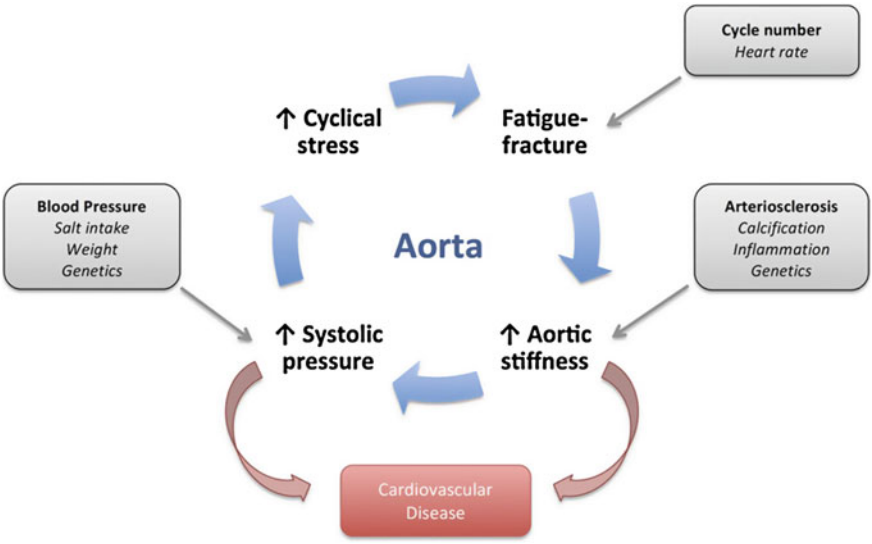

Fig. 14.6 The vicious circle of arteriosclerosis. Fatigue fracture of the elastic elements in the aorta leads to elevated systolic pressure and thus increased cyclic stress—setting up a vicious circle. Factors driving blood pressure elevation lead to increased systolic pressure, thereby accelerating the process, as do the factors driving arteriosclerosis. Ultimately, elevated systolic pressure and increased stiffness both lead to cardiovascular disease. From McEniery CM, Wilkinson IB. The pressures of ageing. Hypertension 2013;62:823–824. © 2013 American Heart Association, Inc., with permission from Wolters Kluwer Health, Inc.

wave. The pressure wave from the heart travels down the aorta and returns after being reflected from the distal arteriolar beds. The time at which the reverse going wave returns is determined by the pressure wave speed (the pulse wave velocity, PWV) in the aorta. The PWV is in turn determined by the stiffness, wall thickness and diameter of the aorta through the Moens–Korteweg equation described in Chap. 4 and reproduced below.

$$\mathrm{PWV} = \sqrt{\frac{Eh}{d\rho}}, \tag{14.2}$$

where E is elastic modulus of the artery, h is wall thickness, d is diameter and ρ is density of blood.

The effect of increased stiffness on the pressure waveform is illustrated in Fig. 14.7. In this example, increasing stiffness arises through ageing (discussed in Sect. 14.2). At higher stiffness, the amplitude of the reverse going pressure wave is greater and the reverse wave returns earlier in the cardiac cycle leading to augmentation of the overall pressure.

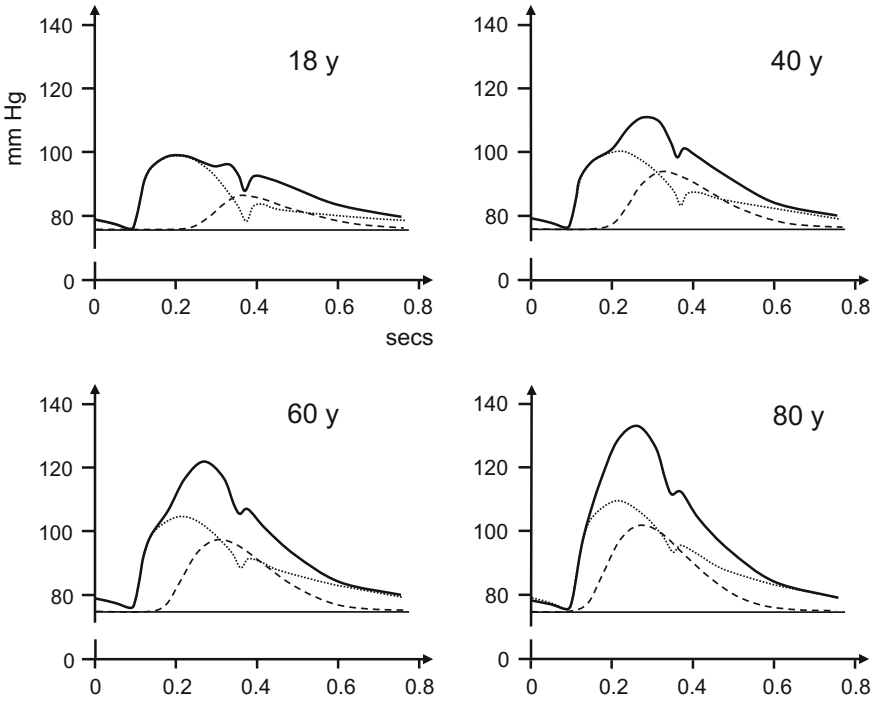

Fig. 14.7 Changes in the central pressure waveform with age. This is divided into forward (*dotted lines*) and reflected (*dashed lines*) pressure waves. The resultant pressure (*solid lines*) is the summation of forward and reflected waves. The reflected wave component increases in amplitude with age and also returns earlier, both effects leading to increase in systolic pressure. Redrawn with permission from images from Atcor Medical, West Ryde, NSW 2114, Australia

14.3.2 Pressure and Remodelling

Let us consider the case where there is a medium-term (weeks to months) increase in blood pressure as a result of disease or lifestyle. Figure 14.8 shows the pressure–stiffness curve of the aorta. The resting pressure of this particular individual is 95/65; well within what is classified as the 'normal' range. During the cardiac cycle the aorta stiffness will change as pressure changes from 2.2 to 2.6 units in Fig. 14.8. Suppose that the pressure increases due to some change in lifestyle or due to disease; this is shown in an exaggerated manner where the new blood pressure is 175/100. The artery is now operating in the stiffer part of the curve with the new stiffness changing from 2.7 to 3.1 units during the cardiac cycle. There is an associated increase in PWV which acts to exacerbate the increase in systolic pressure through the processes mentioned above. If the blood pressure increase is sustained long-term, then the artery will remodel to normalise circumferential stress. However, this is achieved through wall thickening which itself will lead to

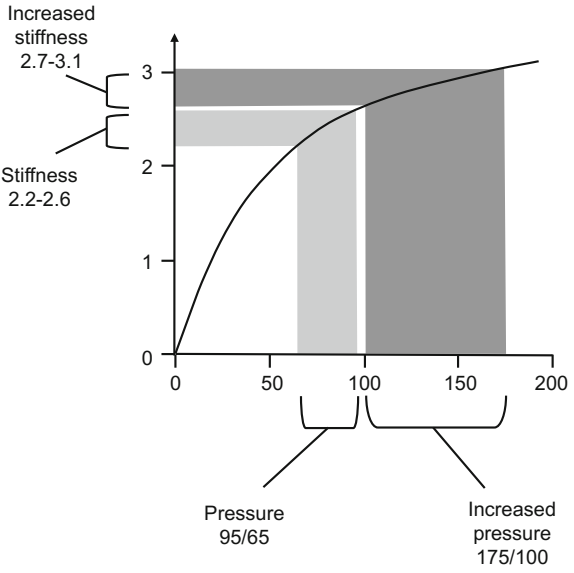

Fig. 14.8 Pressure–stiffness curve for an artery. In this example, pressure of 95/65 is associated with stiffness of 2.2–2.6 units. Increase in pressure to 175/105 is associated with stiffness of 2.7–3.1 units

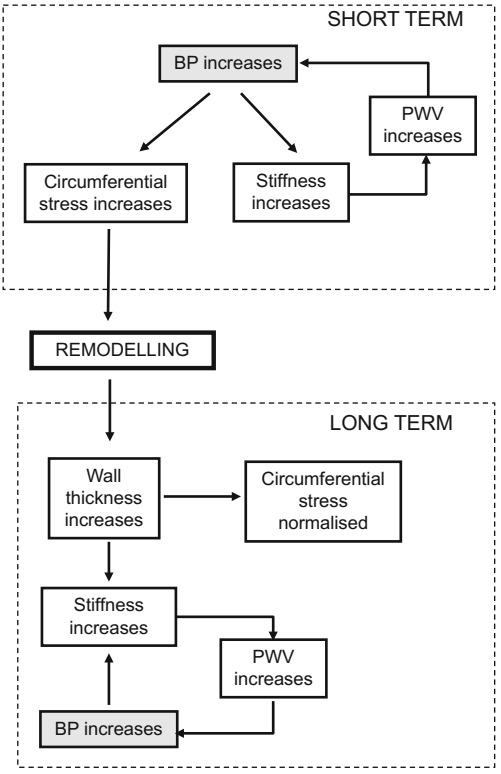

Fig. 14.9 Changes to the artery resulting from medium-term (weeks–months) change in blood pressure

long-term increase in stiffness, in PWV and in systolic pressure. A medium-term decrease in blood pressure, through medication, exercise or reduction in psychological stress will result in the opposite. These processes are illustrated in Fig. 14.9.

14.4 In Vivo Measurement of Pressure

14.4.1 Invasive Measurement

Direct measurement of blood pressure requires an arterial puncture and insertion of a catheter. The tip of the catheter is directed by the operator to the site of interest (e.g. the coronary artery), usually under X-ray guidance. The original methodology was based on a flexible membrane within the catheter tip with pressure variations transmitted along a fluid-filled column to a pressure sensor which was located in a control unit into which the catheter was plugged. These have several disadvantages including the need to flush the vessel to remove air bubbles and motion artefacts. There is also signal attenuation and overshoot leading to an inaccurate pressure trace. Modern catheters used in clinical practice have used measurement of pressure at the catheter tip using, for example, a piezoelectric transducer (Millar Instruments) (Fig. 14.10). The direct measurement enables an improved frequency response and more accurate recording of pressure (Fig. 14.11). An early paper which described catheter-tip pressure measurement is Millar and Baker (1973). Reviews of invasive pressure measurement are provided by Zimmer and Millar (1998) and Papaioannou et al. (2009).

14.4.2 Non-invasive Measurement—Pressure Cuff

Measurement of blood pressure in the brachial artery is undertaken using a cuff wrapped around the arm. The cuff is inflated to above systolic blood pressure then gradually deflated allowing blood to flow in the artery. The pressure in the cuff is traditionally measured using a mercury manometer with a stethoscope used to monitor the sounds arising from the occlusion and re-establishment of blood flow. Using this method the systolic and diastolic pressure can be identified. Blood flow may also be measured using Doppler ultrasound allowing identification of the point of systole (where blood just begins to flow) but not diastole.

Automated monitoring of blood pressure may be performed by examining the pressure oscillations in the cuff as the cuff pressure is released. A pressure sensor is used to monitor cuff pressure and signal processing is used to extract the systolic and diastolic blood pressures. These are referred to as NIBP (non-invasive blood pressure) devices.

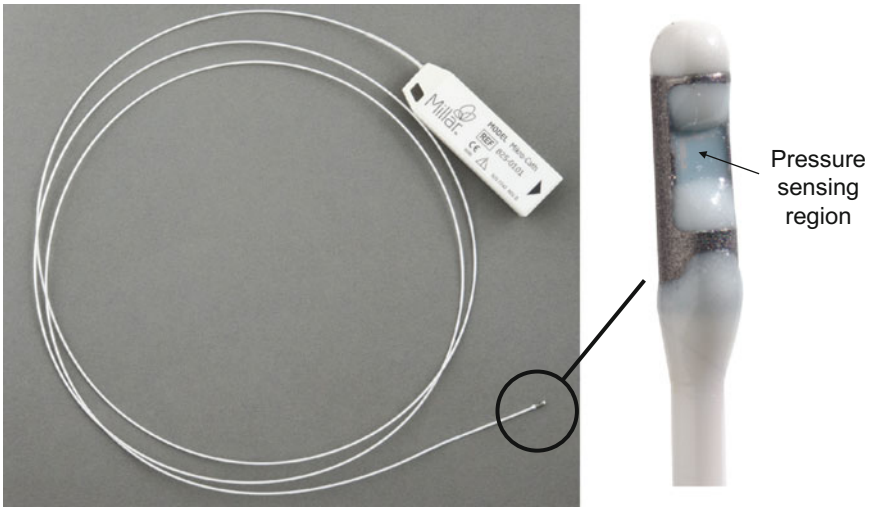

Fig. 14.10 Pressure catheter for measurement in arteries. The catheter tip showing the pressure measuring region is shown. This is the Mikro–Cath pressure catheter; images kindly provided by Millar Inc. (Houston, Texas, USA)

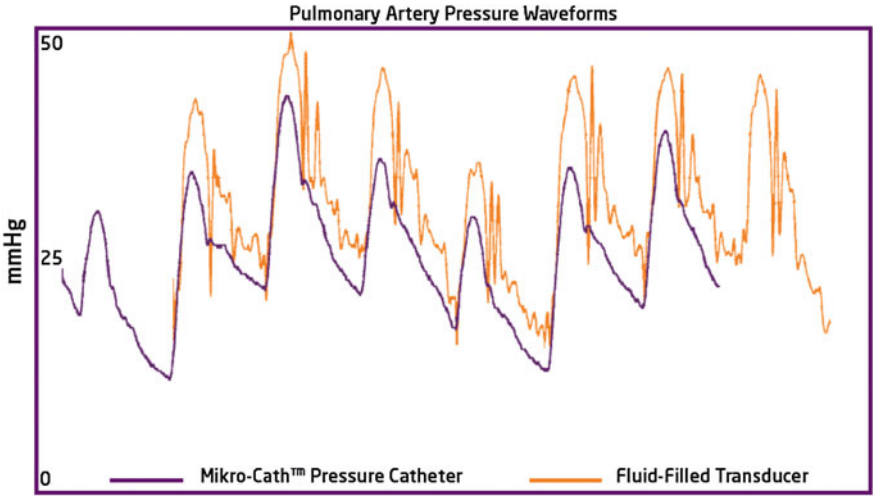

Fig. 14.11 Comparison of pressure waveforms measured using a fluid-filled transducer and a solid-state transducer (Mikro–Cath, Millar Inc.). Images kindly provided by Millar Inc. (Houston, Texas, USA)

Though cuffs are mostly used in the arm they can also be used in the leg, though this is not commonly done outside of a few research labs.

14.4.3 Non-invasive Measurement—Applanation Tonometry

The term 'tonometry' refers to measurement of pressure, the term 'applanation' means to flatten. Applanation tonometry concerns the measurement of arterial pressure using a probe containing a pressure sensor in which the probe is pressed onto the skin over the artery causing (at least to some degree) flattening of the surface of the artery against the probe and against the bone. The pressure variations from the artery are transmitted through the overlying tissues and detected by the pressure sensor. This technique is applicable to arteries which are close to the surface, so the radial and brachial arteries in the arm, the carotid artery in the neck and the common femoral artery in the leg. The blood pressure is obtained as a function of time; however, this is uncalibrated. In the brachial or radial artery, the blood pressure may be calibrated using pressure measurements taken using an arm cuff.

The main interest for applanation tonometry has been the estimation of the central pressure waveform from the radial waveform. The central pressure waveform is estimated using a transfer function approach developed by O'Rourke and colleagues (Karamanoglu et al. 1993). This has been validated against invasive measurements (Pauca et al. 2001; Chen et al. 1997; Gallagher et al. 2004). Reviews of the development and clinical application of applanation tonometry are provided

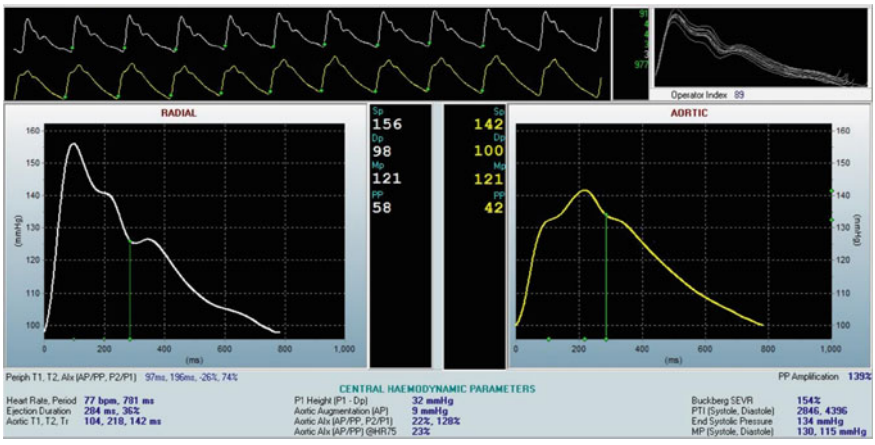

Fig. 14.12 Radial artery pressure waveform obtained using a Sphygmocor applanation tonometry system and the calculated central pressure waveforms

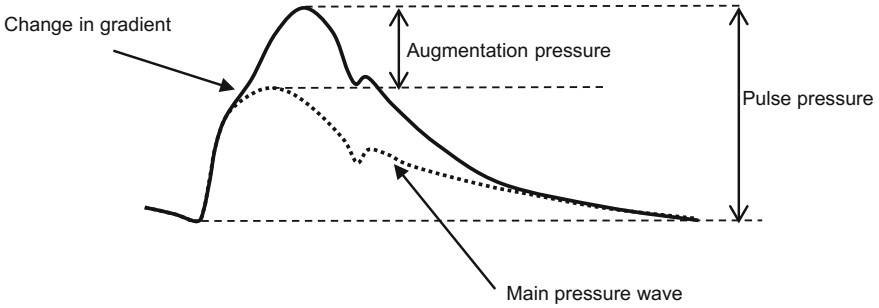

Fig. 14.13 Measurement of pressure required in calculation of augmentation pressure

by O'Rourke and Gallagher (1996), O'Rourke et al. (2001), Wilkinson et al. (1998), Nelson et al. (2010) and Kim and Braam (2013).

Figure 14.12 shows typical radial artery waveforms and the calculated central pressure waveforms. An index 'augmentation index' may be measured (Fig. 14.13) which describes the increase in pressure arising from the reflected wave component:

$$\text{Augmentation index} = \text{augmentation pressure}/\text{pulse pressure}$$

The augmentation pressure is the difference between the peak pressure which would have occurred in the absence of reflected waves and peak pressure in practice (Fig. 14.13). These are often referred to as the first and second peaks. In some cases, these peaks can be clearly distinguished allowing estimation of the augmentation pressure from the pressure waveform. However in most cases there is no second peak. Instead, there is a slight change in the pressure gradient (labelled on Fig. 14.13) which may be difficult to detect with accuracy. In practice, commercial devices such as the Sphygmocor (AtCor Medical, Sydney, Australia) calculate the main and reflected pressure components and use these to estimate the augmentation pressure.

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