10 Arterial Flow, Pulse Pressure and Pulse Wave Velocity in Men and Women at Various Ages

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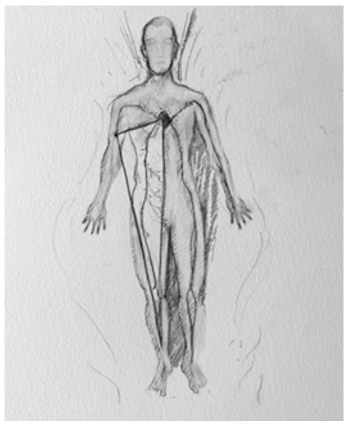

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Abstract

The increase in pulse pressure (PP) that occurs with advancing age is predominantly due to reduced arterial distensibility leading to decreased aortic compliance, particularly in the elderly, in whom high blood pressure mainly manifests as isolated systolic hypertension. Since age-related changes in stroke volume are minimal compared with changes in PP, PP is often considered a surrogate measure of arterial stiffness. However, since PP is determined by both cardiac and arterial function, a more precise and reliable means of assessment of arterial stiffness is arterial pulse wave velocity (PWV), a parameter that is only dependent on arterial properties. Arterial stiffness as measured by PWV has been

P. L. M. Kerkhof, V. M. Miller (eds.), *Sex-Specific Analysis of Cardiovascular Function*,
Advances in Experimental Medicine and Biology 1065, https://doi.org/10.1007/978-3-319-77932-4_10

found to be a powerful pressure-related indicator for cardiovascular morbidity and mortality. We analyzed PP and PWV in men and women of various age groups in healthy volunteers as well as cardiac patients with different types of diseases. The findings identified several striking sex-specific differences which demand consideration in guidelines for diagnostic procedures, for epidemiological analysis, and in evaluation of therapeutic interventions.

Keywords

Pulse pressure · Blood pressure · Aging arterial system · Arterial compliance · Sex-specific analysis · Pulse wave velocity · Cardio-ankle vascular index · Augmentation index

Basic Components: Pressure, Diameter, Flow

Characteristics of pulsatile pressure and flow are important physical attributes for investigation of vascular physiology. Physical aspects of relationships of pressure and flow are most pronounced in the systemic arterial vasculature because of the relatively high pressure levels and the strong pulsatile nature of these phenomena [1]. While it is important to continuously record the frequency-dependent characteristics of pressure and flow waveforms, in humans such accurate measurements are only feasible during catheterization. Much progress in the field has been based on early investigations performed in chronically instrumented animals quantifying pulsatile phenomena in arteries [2] and vascular and ventricular function [3, 4]. An example is presented in Fig.10.1, showing aortic diameter, flow, and left ventricular (LV) pressure and ECG, all sampled at 250 Hz. Using similar techniques, simultaneous aortic pressure and diameter have been measured to calculate viscoelastic properties of the aorta in fetal sheep, exercising lambs and adult animals [5]. Pulsatile

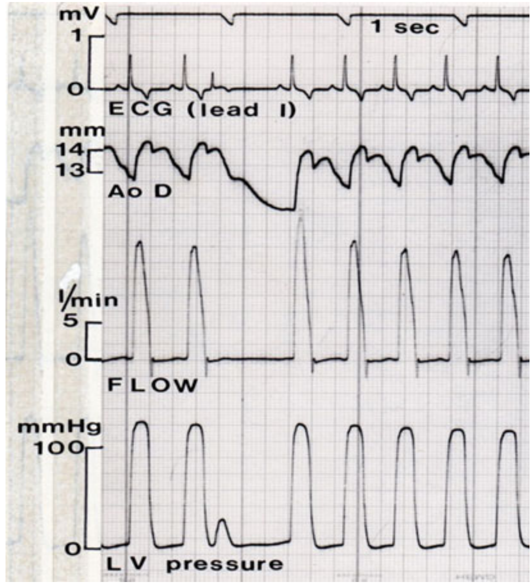


Fig. 10.1 Various calibrated recordings obtained from a chronically instrumented conscious dog. They include left ventricular (LV) pressure, proximal aortic (Ao) diameter (D), and aortic root flow. The registration shows a spontaneous premature beat with reduced ventricular pressure generation which fails to open the aortic valve. As a result there is no aortic flow, while the aortic diameter continuous to relax leading to a transient increase of peak flow during the next beat. (Data from [4])

properties of the arterial system interact with the pumping behavior of the ventricle, implying that the study of ventricular-arterial coupling attracted considerable interest, also by clinicians. A popular approach to study coupling refers to the ratio of ventricular and effective arterial elastance [6]. However, if simply defined as the ratio of SV and ESV, then this index does not reveal anything that is superior to the (problematic) metric of ejection fraction. In the present survey, we will not address these aspects and limit ourselves to arterial pressure and its derived metrics.

In clinical practice, one often has to rely on noninvasive measurements yielding systolic pressure (Ps) and diastolic pressure (Pd) and their difference, Ps-Pd, the pulse pressure (PP). An elevated PP is a powerful independent predictor of cardiovascular end points in the elderly

[7]. This has been confirmed in large cohorts such as the Framingham Heart Study [8]. The important observation is that whereas systolic pressure continues to rise with age in both men and women, diastolic pressure increases up to the age of 55 and then decreases. It is at this age that the systolic pressure for men and women diverge, with women showing a steeper increase with age [9] (Fig. 10.2). In addition, males and females also show different degrees of pressure pulse amplification between the aorta and brachial artery as observed in a large global survey of central aortic blood pressure which aimed to established reference values in a healthy population [10].

From youth to middle age, men consistently have significantly higher systolic and diastolic pressures than women. The significantly increased PP in women after age 55 is clearly observed in these healthy subjects, due to a greater increase in systolic pressure and similar decrease in diastolic pressure as compared with men.

In a recent study [11], four-dimensional (4D) flow MRI at 1.5T and 3T was used for the assessment of three-dimensional (3D) blood flow in the thoracic aorta in 98 healthy subjects (aged 9–78 years, 41 women). Subjects were categorized into age groups with divisions at 15, 20, 40, and 60 years. Data analysis included the 3D segmentation of the aorta, aortic valve peak velocity, mid-ascending aortic diameter (normalized by BSA), and calculation of flow velocity distribution descriptors (mean, median, standard deviation, incidence of velocities >1 m/s, skewness, and kurtosis of aortic velocity magnitude). Men and women revealed significant

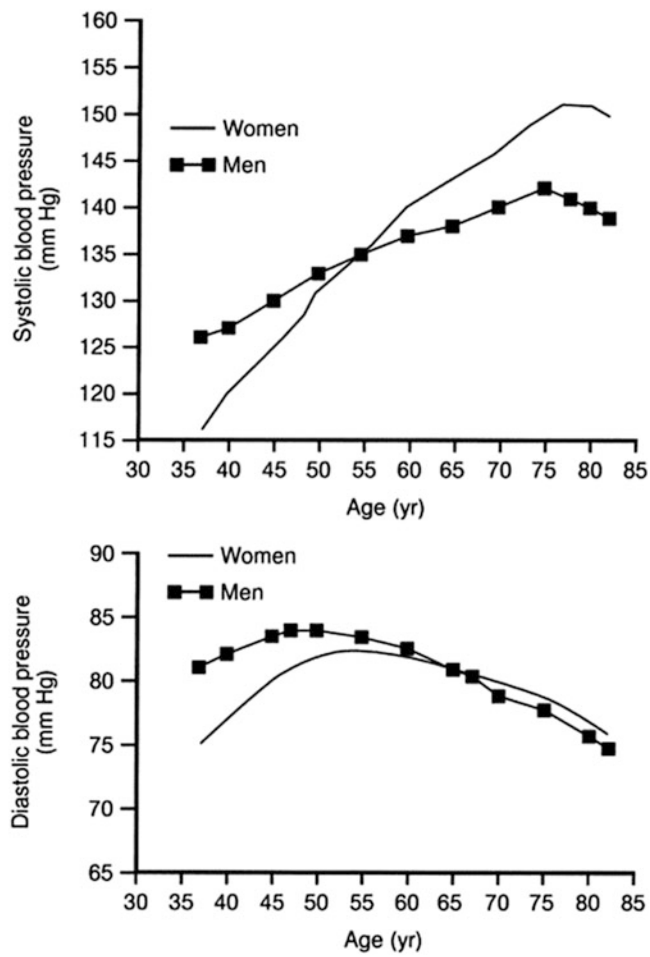


Fig. 10.2 The significant increase in pulse pressure in women compared to men after age 55 in healthy subjects is due to a greater increase in systolic pressure and similar decrease in diastolic pressure. (Data From [9], reproduced with permission)

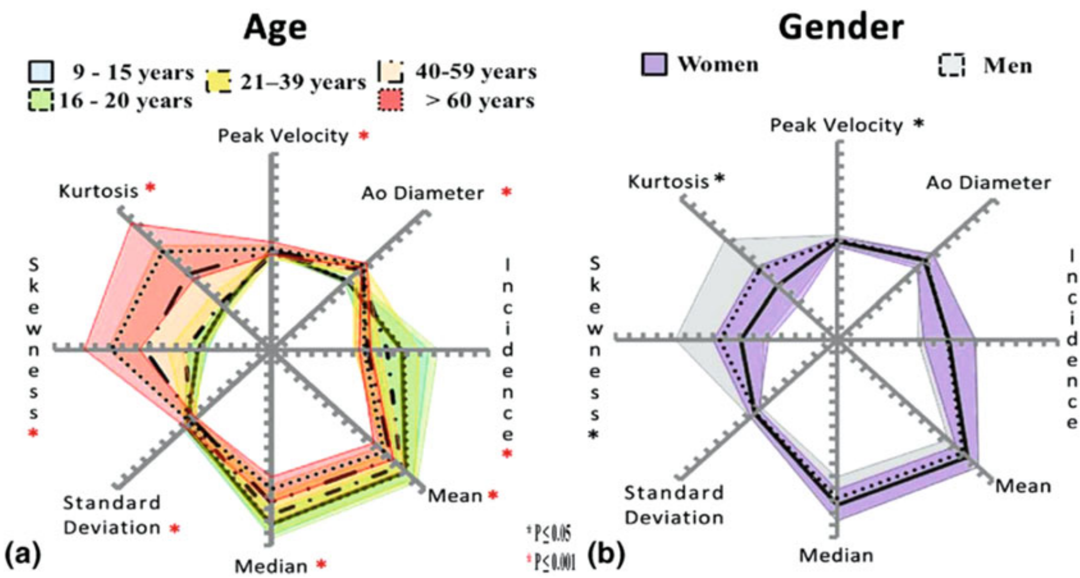


Fig. 10.3 Spider plots showing that the velocity magnitude distribution analysis of values for aortic blood flow depends on age and sex in healthy humans. Individuals (N = 98) were subdivided into five age groups (panel **a**), while analysis was carried out separately for men and women (N = 41) in (panel **b**). (Data from [11], reproduced with permission)

differences ($p \leq 0.05$) for peak velocity, incidence, mean, median, standard deviation, and skewness, all adjusted by heart rate. Results are graphically summarized in Fig. 10.3. The authors conclude that age and sex should be considered for assessment of the impact of cardiovascular disease on aortic blood flow.

Methods to Study Vascular Properties

Arterial Pressure and PWV in Humans

Population Studies

In population studies, blood pressure measurements were performed with conventional brachial cuff sphygmomanometry using auscultatory or oscillometric methods. PWV measurements were performed as a means of noninvasive assessment of arterial stiffness. Increased arterial stiffness and reduced large artery compliance have been found in large population studies with different prevalence of hypertension [12]. PWV is readily obtained during measurement of arterial pulses; it has become a most commonly measured index of vascular stiffness. In experimental studies, PWV has been found to increase with increasing pressure and also increase in wave reflections. In this context, PWV is most commonly measured from foot-to-foot pulse transit time (PTT) over a given distance (d) and computed as PWV = d/PTT. When the pressure wave is available, pulse wave analysis is performed to obtain a central aortic pressure waveform using mathematical transformations [13] from which wave indices are obtained such as augmentation index (AIx) to quantify the effect of increased systolic pressure augmentation due to wave reflections. AIx is calculated from the ratio of augmented pressure from the first systolic shoulder and PP. Similar analysis using central aortic wave components has been shown to discriminate the potential for predisposition to myocardial ischemia in women in a study of 1628 cardiology outpatients (590 females) [14].

The population studies reported are from a cohort of healthy volunteers (N = 987) with no hypertension or diabetes, nor clinically detectable heart disease, and not taking medication that would be interfering with cardiac function.

Pressure-Independent Measure of Arterial Stiffness: Pulse Wave Velocity and Cardio-Ankle Vascular Index

Since PWV as a measure of arterial stiffness is pressure dependent, a pressure-independent index, the cardio-ankle vascular index (CAVI), has been developed [15] and provides a measure of arterial stiffness based on ECG, heart sounds, and PTT of brachial and ankle pulses (indicated as T in Fig. 10.4). However, due to the inherent assumptions involving underlying relationship between pressure and diameter and measurement of reference pressure, the measurement as proposed still contains some residual pressure dependency. Methods have been recently proposed to correct for this form conventional measurements of CAVI [16].

Studies in Children

In children studies reported here, similar techniques in adults were used for measurement of

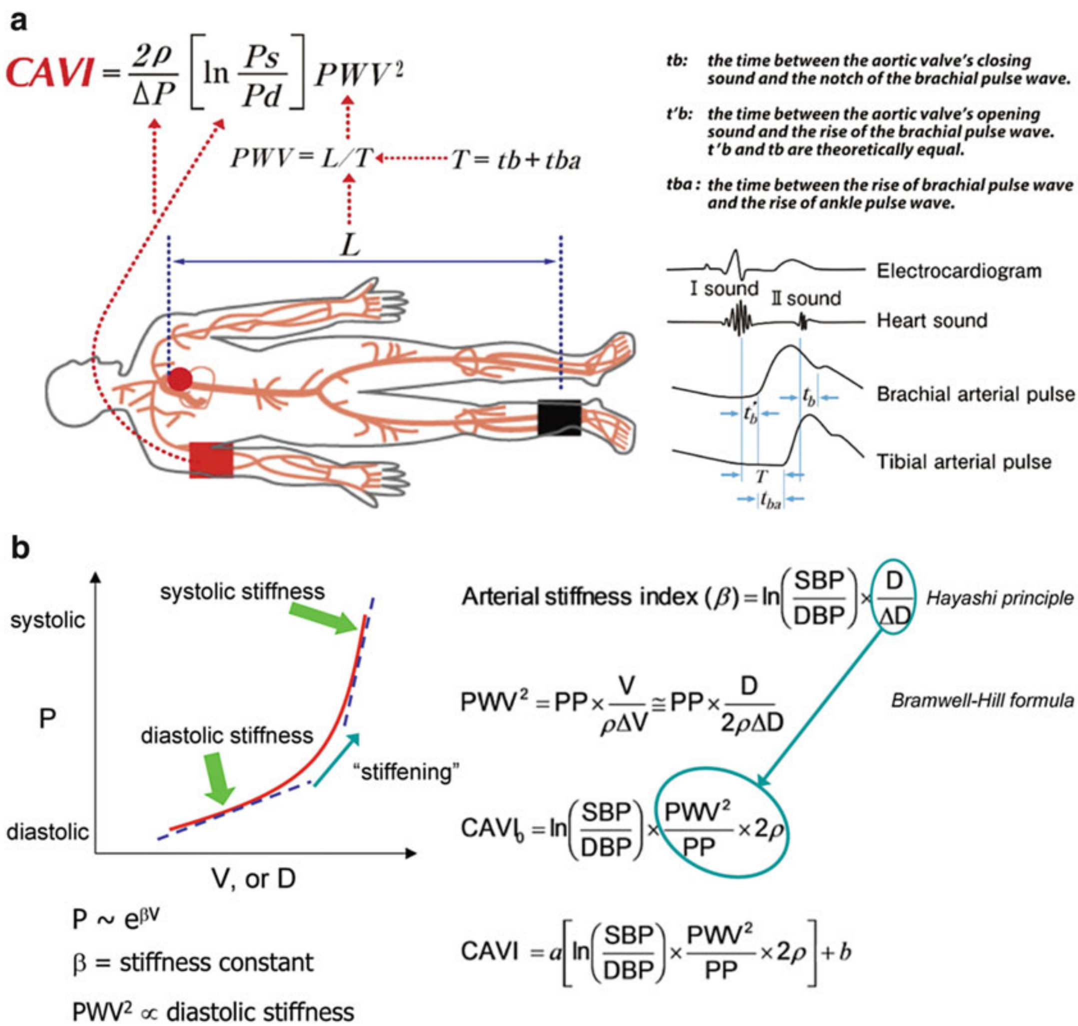


Fig. 10.4 (**a**) Method for measurement of cardio-ankle vascular index (CAVI). Principles and calculations used to define CAVI are based on capture of the aortic valve closure using a microphone and wave analysis using cuffs on the arm and leg. [Data from [17], with permission]. (**b**) Theoretical association of quantities associated with CAVI in relation to the nonlinear relationship between pressure and vessel diameter. (Data from [18], reproduced with permission)

blood pressure and PWV. However, since the transfer function techniques are validated only for adult subjects for determination of central aortic pressure [13], some studies have used the carotid waveform as a surrogate of the central aortic pressure wave [19, 20].

Catheterization Studies

Blood pressure was measured invasively in patients admitted to the catheterization laboratory for evaluation of chest pain and dyspnea. Prior to biplane angiography, blood pressure was recorded in the proximal aorta by an intra-arterial fluid line connected to an external pressure transducer (Statham P23Db). With lines thoroughly flushed, the manometer system has an adequate frequency response for reliable measurement of peak pressures and detection of pulse waveform features. LV volumes were determined by the area-length method.

Results

Populations Studies

The clinical and hemodynamic characteristics for the healthy cohort (N = 987) are described in Table 10.1. Men have higher brachial systolic and diastolic pressures compared to women, with both having similar brachial PP. However, for similar brachial PP and lower aortic PWV, women have higher central aortic PP. Relationships between components of blood pressure, PWV, and age are given in the various panels of Figs. 10.5 and 10.6.

Figure 10.7 shows the blood pressure component associated with CAVI, which slightly but significantly declines with age, although it is generally higher in women for the younger range. However, CAVI value is lower in women at all ages from a study in a large urban Japanese cohort

Table 10.1 Clinical and haemodynamic characteristics of 987 healthy subjects

Characteristics	Men (n = 475)	Women (n = 512)
Anthropometrics		
Age, y	45.4 ± 14.4	46.0 ± 14.1
Body weight, kg	82.9 ± 13.0	68.7 ± 13.4‡
Body height, cm	177.7 ± 6.7	164.4 ± 6.7‡
Body mass index, kg/m^2	26.2 ± 3.80	25.4 ± 4.49‡
Brachial systolic BP, mm Hg	129.1 ± 13.9	122.8 ± 15.2‡
Brachial diastolic BP, mm Hg	83.0 ± 9.8	77.7 ± 9.0‡
Brachial PP, mm Hg	46.2 ± 10.8	45.0 ± 11.5
MAP, mm Hg	101.4 ± 10.3	95.7 ± 10.5‡
Heart rate, beats/minute	62.6 ± 8.6	65.9 ± 9.1‡
Questionnaire data		
Current smoking, n (%)	94(19.8)	90 (17.6)
Drinking alcohol, n (%)	414 (87.2)	316 (61.7)‡
Hypertensive, n (%)	139 (29.3)	79 (15.4)‡
Central haemodynamics and stiffness		
Central PP, mm Hg	34.6 ± 10.8	37.0±12.9†
Pulse wave velocity, m/s	7.34 ± 1.57	6.91±1.53‡

Values are mean (±SD) or number of subjects (%). †$P \leq 0.01$; ‡$P \leq 0.001$; *BP* blood pressure, *MAP* mean arterial pressure, *PP* pulse pressure
Data in table from T. Kuznetzova

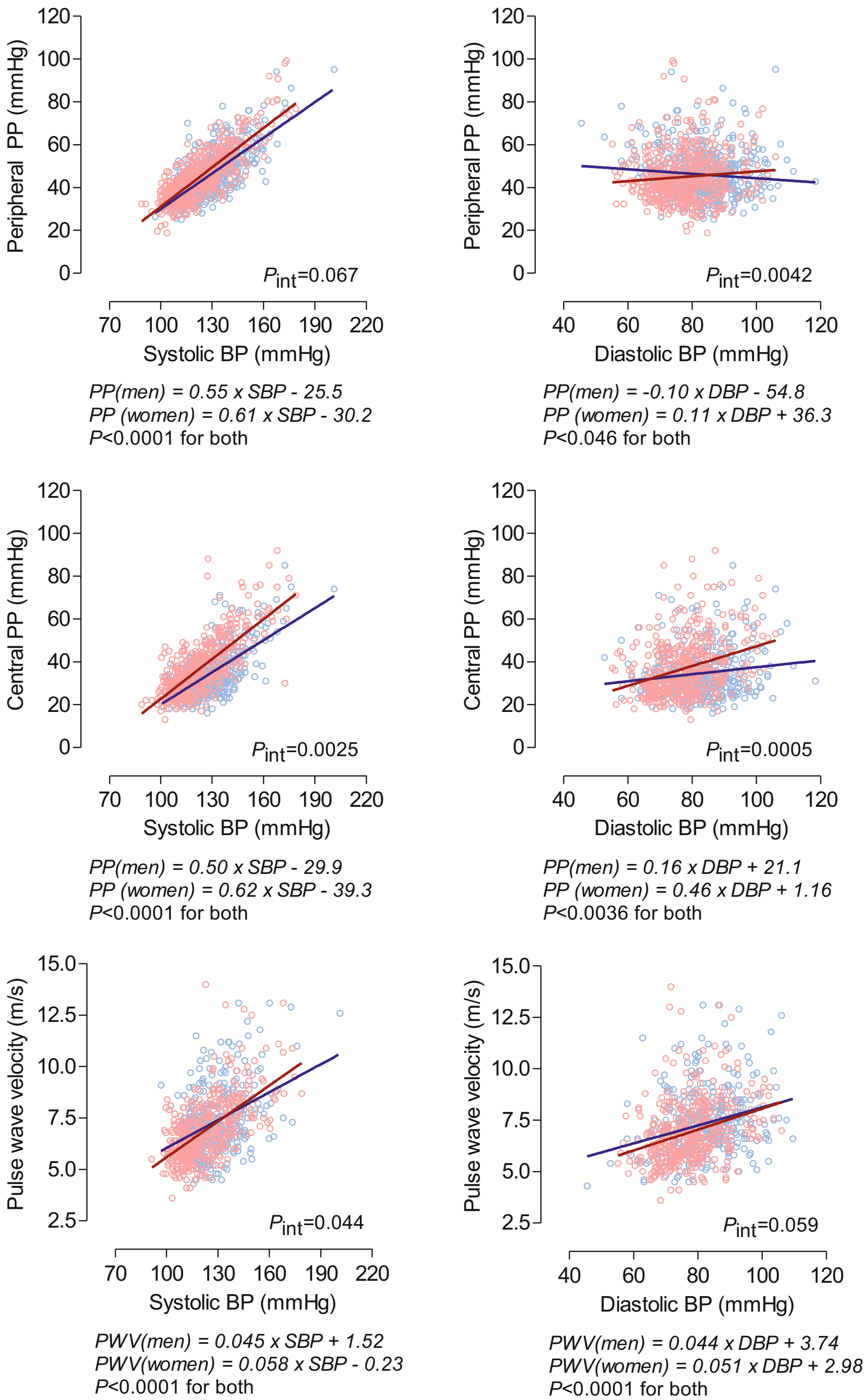


Fig. 10.5 Univariate correlations between central hemodynamics and arterial stiffness with peripheral BP components in men (blue) and women (red)

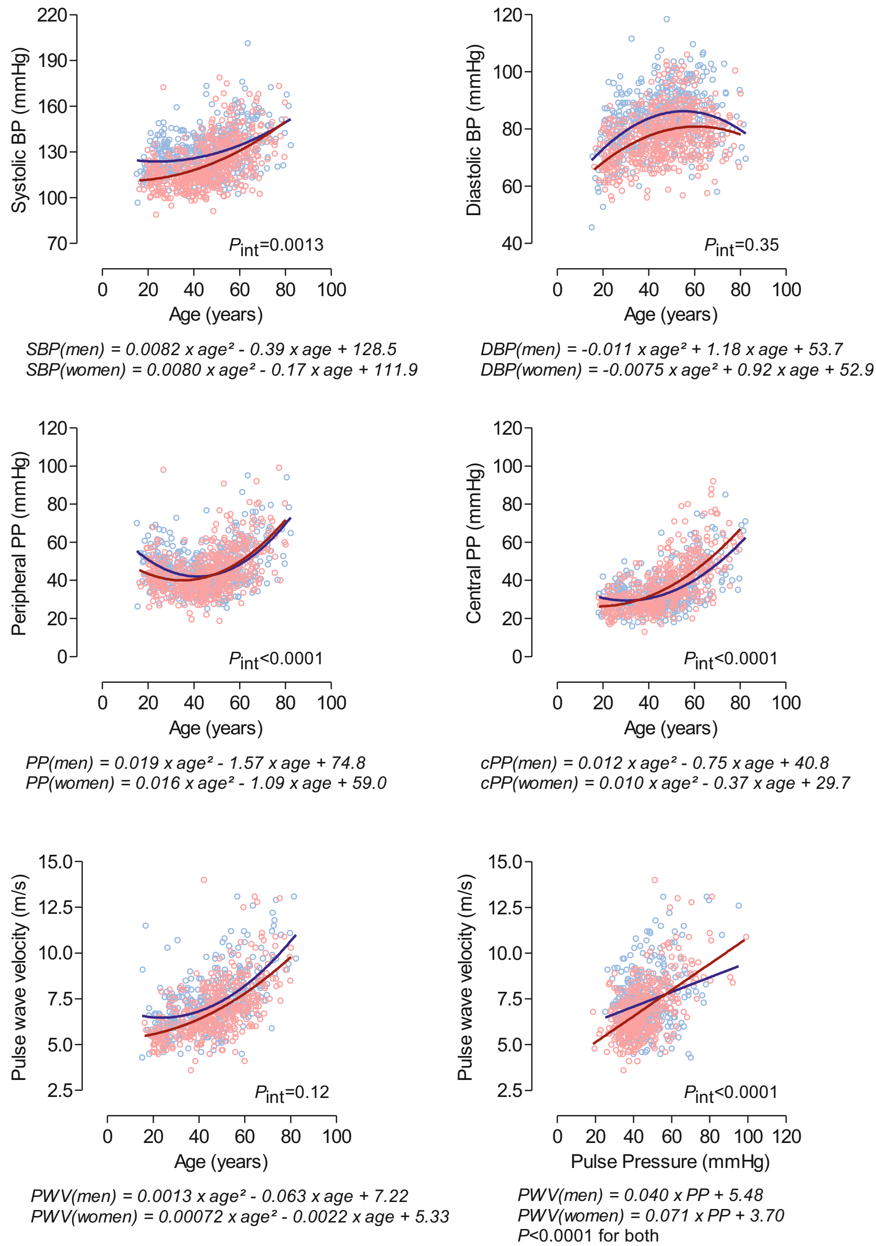


Fig. 10.6 Univariate correlations of peripheral BP components, central hemodynamics, and arterial stiffness with age in healthy men (blue) and women (red)

(N = 32,627) [15] (Fig. 10.8). (Note: Figs. 10.7 and 10.8 show different variables on the ordinate). Other studies show that a high CAVI in women is associated with a greater left ventricular mass index [21].

As seen in Table 10.1, women have similar brachial PP compared to men but greater central aortic PP. This can be explained by a relatively higher systolic augmentation in women as shown in Fig. 10.9 between second and seventh decades.

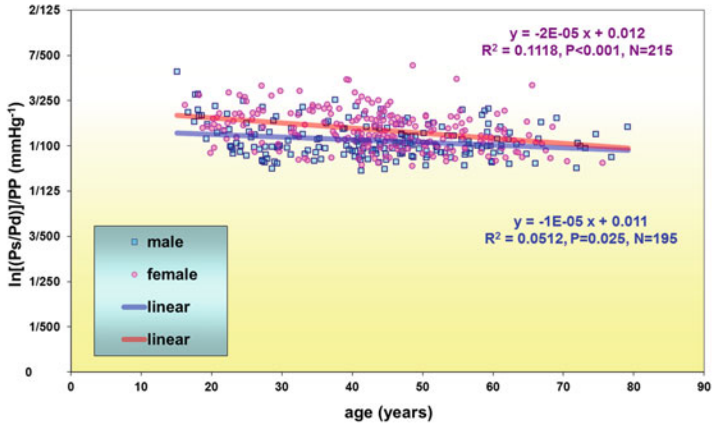


Fig. 10.7 Distribution of the pressure-associated component of the cardio-ankle vascular index (CAVI) versus age in healthy individuals shown for males and females separately. CAVI is obtained by multiplication with pulse wave velocity squared. (Data from T. Kuznetsova)

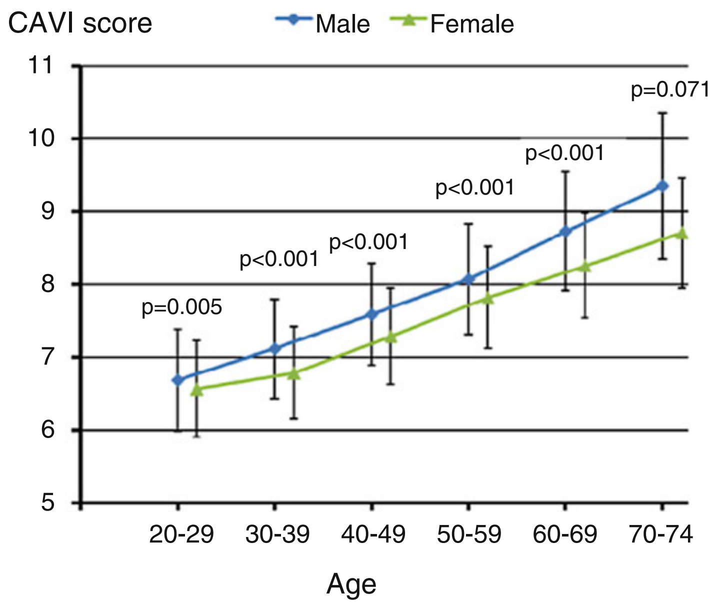


Fig. 10.8 CAVI scores by age between males and females in subjects free from cardiovascular risk. Data from a large urban Japanese population ($N = 32{,}672$) [15]

Studies in Children

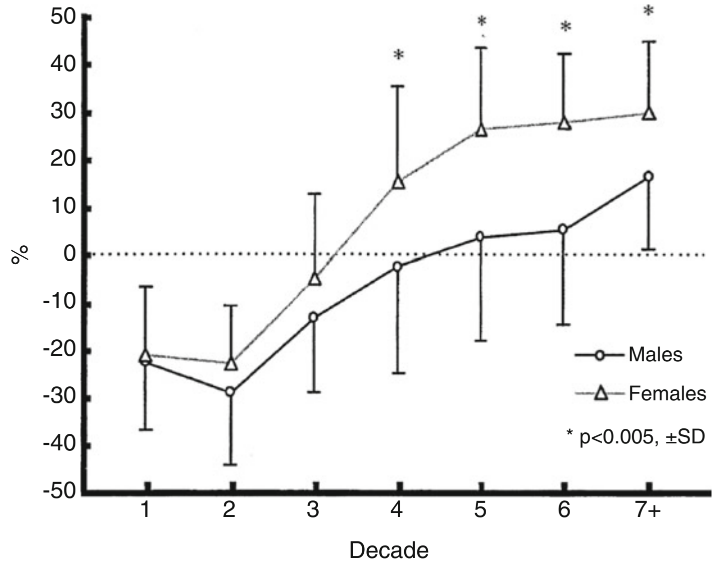
Sex Differences in Blood Pressure in Children and Adolescents

Blood pressure in children and young adults tends to increase in both males and females. However, changes are more varied during puberty given the different rates of growth in both sexes. A study in over 32,000 normal-weight Chinese adolescents (aged 12–17 years) [23] shows marked differences in systolic and diastolic pressure between males and females when controlling for age and height (Fig. 10.10).

A study in Australian children assessed the differences in blood pressure and components of PP (augmentation index) at age 8 [19]) and then again at age 14 [20]. At age 8, there was no difference in systolic or diastolic pressure and height and weight similar for boys and girls. However, girls had a relatively higher systolic augmentation than boys. This was similar at age 14, with a statically different lower height in girls.

The relatively higher systolic augmentation of central aortic pressure seen in prepubescent girls compared to boys is continued through the growth phase and into adulthood (Fig. 10.9)

Fig. 10.9 Central aortic augmentation index in male and females in each age decade. (Data from [22], reproduced with permission)



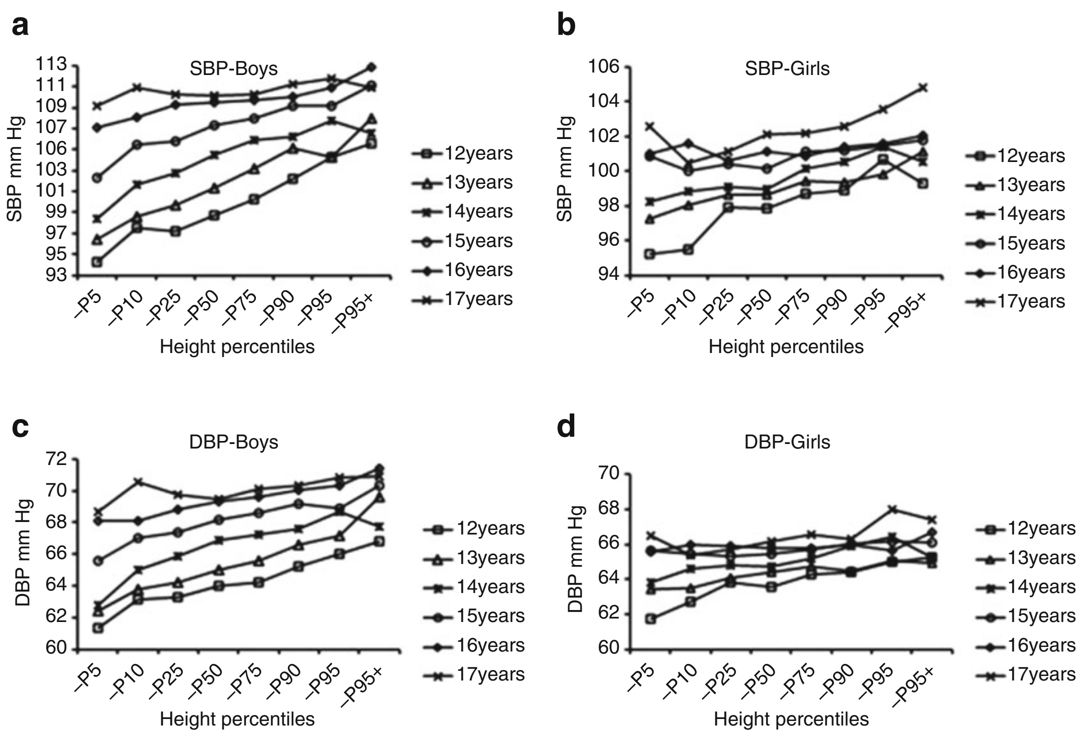


Fig. 10.10 Height percentiles and mean systolic (SBP) and diastolic (DBP) blood pressure for boys and girls for 12–17 years. SBP and DBP increased with height in each age group among boys and girls. Height percentiles in each age group were closely associated with SBP and DBP ($p < 0.01$ or $p < 0.05$) in both boys and girls. (Data from [23])

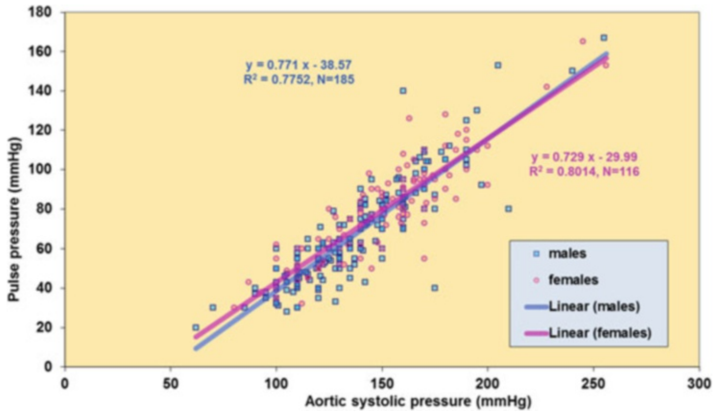


Fig. 10.11 The pulse pressure (PP) as related to systolic arterial pressure in cardiac patients (M vs F)

Table 10.2 Blood pressure components in a similar cohort of boys and girls at age 8 and followed up at age 14

	Age 8			Age 14		
	Boys	Girls	*p*	Boys	Girls	*p*
Height (m)	1.29 ± 0.06	1.28 ± 0.06	ns	1.66 ± 0.80	1.60 ± 0.0.06	<0.001
Weight (kg)	29.4 ± 6.7	28.9 ± 6.7	ns	59.2 ± 13.88	58.4 ± 12.32	ns
bSBP mmHg	100 ± 7	101 ± 7	ns	115 ± 10.3	113 ± 9.5	ns
bDBP mmHg	59 ± 6	60 ± 5	ns	64 ± 6.0	66 ± 7.1	ns
cSBP mmHg	93 ± 8	95 ± 8	ns	102.8 ± 12.53	100.1 ± 10.52	ns
AIx@75 (%)	−18 ± 11.0	−13.1 ± 9.0	<0.001	−32.3 ± 12.37	24.5 ± 12.14	<0.001
cAP mmHg	−6.1 ± 3.8	−4.2 ± 3.2	<0.001	−11.4 ± 6.54	−8.5 ± 5.36	<0.01

Data from [19, 20]

bSBP Brachial systolic pressure, *bDBP* brachial diastolic pressure, *cSBP* central (carotid) systolic pressure, *AIx* augmentation index at heart rate of 75 bpm, *AP* augmentation pressure

[22]. In this study significant differences are found after the fourth decade, suggestive of the time when systolic pressure in females overtakes than in males (Fig. 10.2, Table 10.2).

Catheterization Studies

Figures 10.11, 10.12, 10.13, 10.14, and 10.15 present relationships of invasive pressure measurements in a cohort of cardiac patients (n = 301) evaluated during catheterization procedures. Table 10.3 summarizes pressure data (systolic, diastolic, mean, and pulse pressure) obtained in the proximal aorta, stratified for sex. All measures, apart from diastolic pressure, are significantly different when males and females are compared. Despite the higher afterload (as reflected by mean aortic pressure), women have a higher ejection fraction (EF). Figure 10.16 shows how peripheral resistance (Rs, calculated as mean pressure divided by cardiac output) relates to arterial compliance (C, based on PP and stroke volume). The curves for men and women almost coincide, with no significant differences for Rs and C.

Discussion

Systolic Pressure, Diastolic Pressure, and Pulse Pressure

The chapter has presented data on arterial function parameters such as blood pressure and arterial stiffness measures for men and women over the adult lifespan and also in children and adolescents. Measurements were performed noninvasively in population cohorts and invasively in patients during cardiac catheterization.

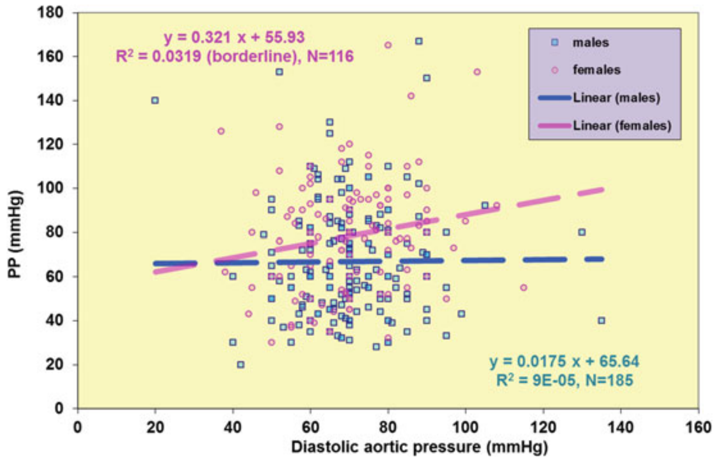


Fig. 10.12 The pulse pressure (PP) as related to diastolic arterial pressure in cardiac patients (M vs F)

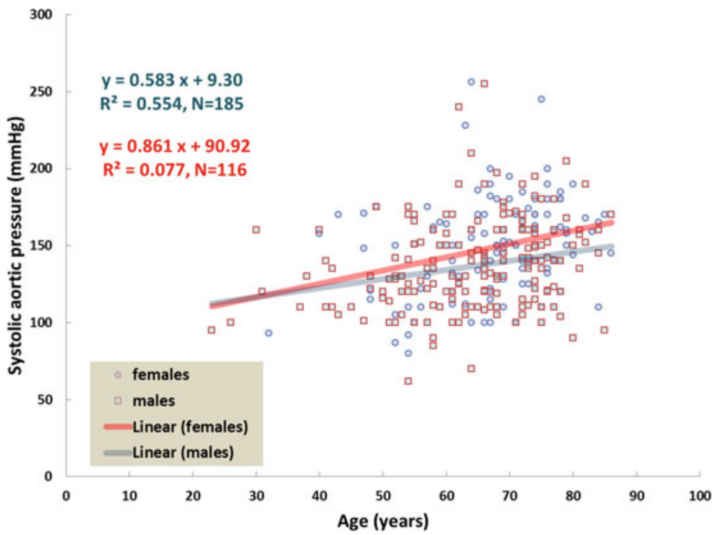


Fig. 10.13 The systolic pressure, Ps, as related to age in cardiac patients (M vs F)

The heart and the arterial system interact dynamically on a beat-to-beat basis. No attempt is made here to separate the components of pulsatile pressure and flow due to the contraction of the left ventricle from those of the arterial system. We addressed how systolic pressure, diastolic pressure, and PP are affected by age and sex in healthy and cardiovascular disease states; PWV is selected as an index of vascular stiffness, as it is solely dependent on the properties of the arterial system.

The principal reason many consider the importance of systolic pressure over diastolic pressure is that systolic pressure is associated with ventricular ejection and is the principal driving pressure for perfusion [1]. Additionally, it has long been thought that systolic time index is critical in determining the energy expenditure of the heart. Thus, a higher systolic arterial pressure signals a greater afterload to ventricular ejection.

The increase in PP is also predominantly due to an increase in systolic pressure, as we have shown here (Fig. 10.6). Note that when systolic pressures are mostly within the normal range, there is little observed difference between the sexes, but the differences become striking at higher pressure

Fig. 10.14 The diastolic pressure, Pd, as related to age in cardiac patients (M vs F)

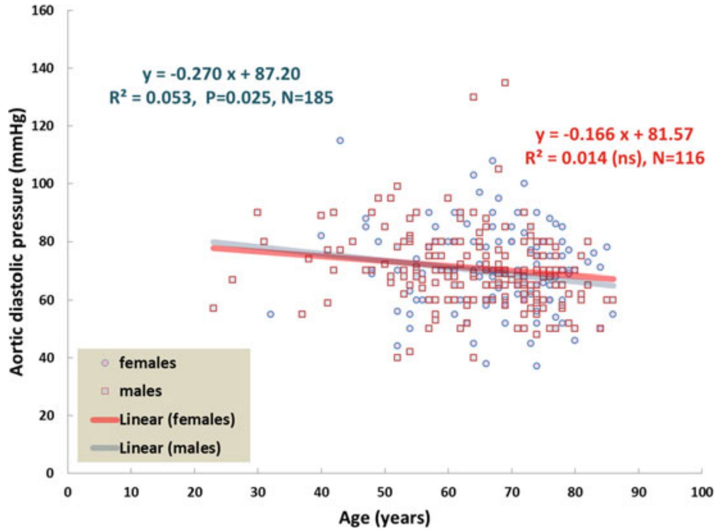


Fig. 10.15 The pulse pressure as related to age in cardiac patients (M vs F)

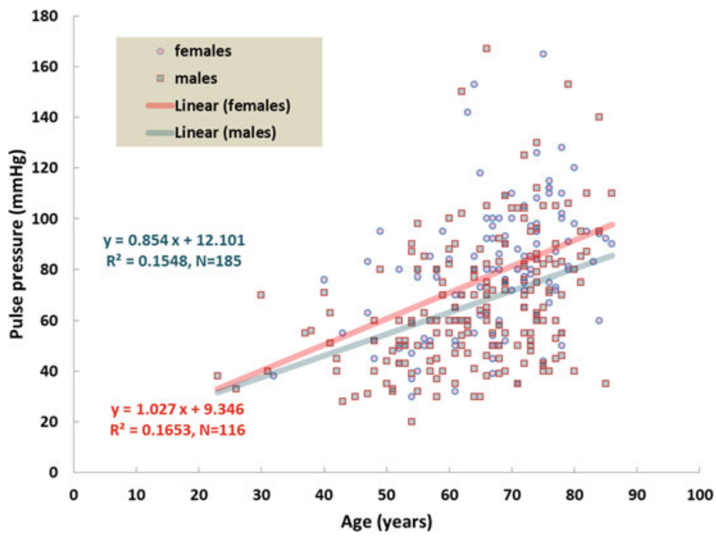
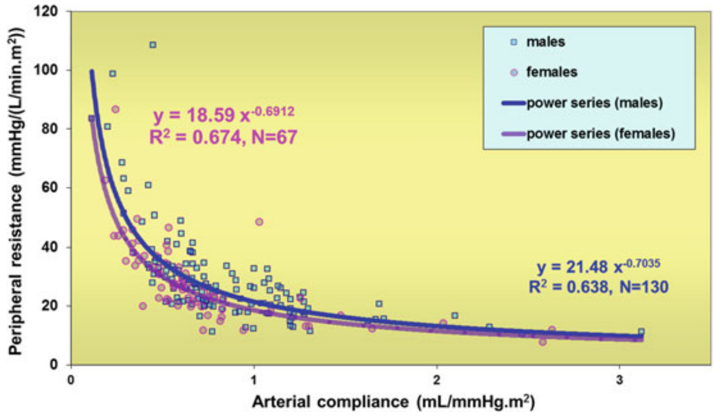


Table 10.3 PP statistics for the 301 cardiac patients (185 males)

	Ao-meanP mmHg	LVEF %	Ao-SBP mmHg	Ao-DBP mmHg	Ao-PP mmHg
Males					
Mean	95.1	61.7	136.7	69.9	66.9
SD	16.4	17.9	29.2	13.8	25.6
Females					
Mean	100.4	70.3	148.9	70.4	78.5
SD	18.3	16.7	31.4	14.2	25.6
p	0.011	<0.001	<0.001	0.76	<0.001

SD Standard deviation, *Ao-SBP* Aortic systolic pressure, *Ao-DBP* Aortic diastolic pressure, *Ao-PP* Aortic pulse pressure, p values designates level of significance for difference between males and females

Fig. 10.16 The asymptotic inverse relationship between peripheral resistance, Rs, and arterial compliance, C, in male and female heart failure patients. Calculations based on mean arterial pressure, cardiac output, stroke volume, and pulse pressure. Average values for Rs and C do not differ for males and females



levels. Of course, these relations may be altered in differing pathological conditions.

The American Heart Association defines hypertension as a systolic/diastolic pressure greater than 140/90 mmHg (recently [late 2017] revised to 130/80 mmHg). With age, the tendency toward hypertension is only related to systolic pressure from the Framingham Study, particularly for elderly women (Fig. 10.2). Since there is a decline in diastolic pressure, PP is greater with age and much more significantly so in elderly women than men (Fig. 10.2). Our findings support this view (Figs. 10.5 and 10.6). The increase in PP is mostly due to significantly increased systolic pressure. Such increase in PP is exaggerated further with a greater increase in systolic pressure (Fig. 10.5), rather than the decrease in diastolic pressure. It is this large increase in systolic pressure with increasing age that isolated systolic hypertension (ISH) has been found to be more prevalent in the elderly (also from the Systolic Hypertension in the Elderly Program or (SHEP) study [24]. And the rate of ISH is higher in women than men. ISH is generally defined as a blood pressure greater than 160/90 mmHg.

In cardiac patients, the increase in PP due to the increase in systolic pressure is accentuated (greater slope; Fig. 10.11 vs Fig.10.5), although the differences between sexes are small. This is due to compounded arterial hypertension in many such cardiac patients (Fig. 10.11). The somewhat muted increase in diastolic pressure (Fig. 10.12) showed significant differences among the sexes. Since aortic diastolic pressure serves as the perfusion pressure to the coronary arteries, cardiac patients with hypertension do not receive the benefit of increased coronary perfusion pressure. This aspect is also clear from our data (Fig. 10.14). The higher overall PP in female cardiac patients with associated hypertension may signal a higher overall mortality in this group of elderly women.

Increased PP and PWV, both of which have been shown to be directly related to increased vascular stiffness, are major risk factors of coronary heart disease and stroke. It should be noted here that PWV measured over a long distance is less characteristic of the individual or regional arterial stiffness [1, 25]. In this regard, the CAVI can be said to provide a measure of “average” arterial stiffness over the measurement distances or pulse transmission path.

Central and Peripheral Arterial Function

Overall arterial function is essentially determined by the compliance of the large arteries and resistance of the peripheral vessels, as characterized by the Windkessel model. Peripheral muscular arteries are stiffer than central aorta. As such, the increased stiffness found in hypertensive patients is mostly due to reduced compliance in the aorta rather than that in peripheral arteries, (e.g., radial or femoral arteries). The elastic modulus is much higher in these peripheral arteries than in the central aorta, for both sexes [26]. Thus, a change in increased PWV is less if measured in the radial artery of hypertensive patients than that in the central aorta.

Characterization of the arterial system by the Windkessel model is prescribed by the diastolic aortic pressure decay time constant τ, i.e., the product of total peripheral resistance (Rs) and total arterial system compliance. Since the aorta contributes largely to the total arterial compliance, (C) has been used to reflect the compliance of the aorta. Since $\tau = \mathrm{Rs}\ \mathrm{C}$, the relation between Rs and C is curvilinear or, more precisely, inverse asymptotic, as seen in Fig. 10.16. Rs is defined as the ratio of mean pressure to mean flow in this context. Thus, for any given mean pressure or peripheral resistance, total arterial compliance is lower in females than in males. This sex difference is significant at increased vascular stiffness or greatly reduced compliance. Reduced aortic compliance has been found in coronary artery disease patients [27], thus it is not surprising that Fig. 10.16 reflects greatly reduced compliance values as compared with normal in both male and female patients with heart failure. Systolic hypertension, which is prevalent in the elderly, has been found to be associated with a much greater reduction in arterial compliance than a moderate increase in peripheral resistance [28, 29].

Increased pulse wave reflections are associated with a reduced arterial compliance and exhibit a greater influence on the pressure pulse than that by peripheral resistance [30]. Wave reflection also has considerable impact on the propagating pulse wave [31]. Although not equivalent, AIx has been more popularly used in the clinical setting to describe the effect of wave reflections.

AIx measured in central arteries, such as the carotid artery [22], showed increasing values of AIx with age. The difference in AIx between male and female is more striking with each increasing decade (Fig. 10.9). Again, this reflects the increased systolic pressure augmentation in women, especially beyond age 55, as we also found here.

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