Large artery properties and cardiovascular risk : a population study

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Large artery properties and cardiovascular risk:
a population study

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Large artery properties and cardiovascular risk: a population study

PROEFSCHRIFT

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Aan: mijn ouders
Harry en Floris

Abbreviations

BA	brachial artery
BMI	body mass index
CC	cross-sectional compliance
CCA	common carotid artery
D	diameter
DBP	diastolic blood pressure
DC	distensibility coefficient
FA	femoral artery
IDDM	insulin-dependent diabetes mellitus
InsR	insulin resistance
MAP	mean arterial pressure
PWV	pulse wave velocity
SBP	systolic blood pressure

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CHAPTER 1

Introduction

In Western countries cardiovascular disease remains the main cause of death in the population¹. Cardiovascular disease comprises several entities like myocardial infarction, heart failure, stroke and peripheral vascular disease. Several risk factors for the development of cardiovascular disease have been identified: age, male gender, blood pressure, hyperlipidemia, smoking, obesity and diabetes mellitus². The precise role of these risk factors in atherogenesis and how and why plaques form are still not fully understood. Large artery properties might also play a role in this process.

ATHEROSCLEROSIS

The earliest lesions of the arterial wall which are thought to relate to atherosclerosis are the fatty streaks, seen in children from three years of age. At about twenty years fibro-fatty plaques appear, consisting of a core of lipid and cellular debris, surrounded by a fibromuscular plaque, containing proliferated smooth muscle and collagen and elastic tissue². Later these plaques undergo progressive changes; hemorrhages and ulceration. These changes reduce the lumen size and predispose to thrombosis and plaque rupture, which may acutely occlude the arterial lumen.

Atherosclerosis mainly affects large arteries³ and is mostly located at branches or bifurcations. The cause of the development of atherosclerosis is unknown. One important theory is the response to injury theory; a disturbance in flow pattern causes chronic minimal injury to the endothelium, leading to the development of atherosclerosis^{2,4}. Most studies on atherosclerosis focus on atherosclerosis. Information on sclerosis, the stiffening of arteries, is more scarce⁵. According to a theory by O'Rourke, this stiffness can be caused by material fatigue of the arterial wall, caused by changes in arterial pressure during each heart cycle⁶.

1.2 LARGE ARTERY WALL PROPERTIES

1.2.1 Arterial tree

The arterial system is a complex network of elastic and muscular tubes, whose diameter varies with the pulsating pressure⁷. Large arteries have two special and specific functions; a conduit and a buffering function. The conduit function makes that blood from the heart is delivered from central to peripheral arteries with a minimal fall in mean arterial pressure. The conduit function is efficient because of wide arterial calibre and corresponding low resistance⁸. The buffering function dampens the pressure oscillations which are a consequence of the heart's intermittent action, making the flow to the tissues more continuous and less pulsatile. This latter function is a result of the visco-elastic properties of the arterial wall.

1.2.2 Definitions

Two important vessel wall properties are distensibility and compliance. In the literature the term arterial compliance often refers to compliance as well as distensibility. This confusion remained until a few years ago, since no good techniques were available to accurately measure both vessel wall properties separately. Compliance and distensibility are, however, quite different. Distensibility, defined as the relative change in volume per unit of pressure, reflects the strain on the arterial wall exerted by the stress⁹, while compliance, defined as the change in volume per unit of pressure, reflects the capacity to store volume^{7,10}. Arterial compliance

(C) is related to arterial distensibility (D) and arterial volume (V) by the formula $C=D \times V$ ⁷.

1.2.3 Clinical importance

Compliance reflects the buffering capacity of the artery ¹¹. Arterial compliance and total peripheral resistance are major determinants of cardiac afterload ¹¹. A decrease in compliance leads to an increase in pulse pressure (and systolic pressure) and contributes to a higher (mechanical) afterload of the heart ¹²⁻¹⁴. An increase in pulse pressure has been shown to be associated with an increased cardiovascular morbidity ¹⁵. An increase in cardiac afterload enhances the risk for cardiac hypertrophy and heart failure ¹⁶. By increasing pulse pressure, a decrease in arterial compliance may also have deleterious effects on coronary dynamics. It will lower diastolic pressure, while it increases systolic pressure, having practically no effect on mean arterial pressure levels and cardiac output. This means that coronary driving pressure may fall although oxygen requirements remain the same or may even increase because of cardiac hypertrophy and increased systolic pressure ¹⁷.

Distensibility is considered a determinant of pulsatile stress on the vessel wall. Pulsatile stress induces degeneration of vascular media ¹⁸. It is also thought to be a significant risk factor for endothelial lesions and plaque rupture, important features in atherosclerotic disease ¹⁹. Consequently preservation of vessel wall properties might be important in protecting the arterial wall at a particular arterial site ²⁰.

1.2.4 Determinants of large artery properties

Arterial distensibility has both structural and functional determinants: distensibility depends on the blood pressure level and on the intrinsic elastic properties of the material which composes the arterial wall and the amount of this material ¹³. The arterial wall is divided into three layers: the tunica intima, tunica media and tunica adventitia. The intima may contribute to arterial wall stiffness by releasing vasoactive substances such as nitric oxide and endothelin, which have effects on smooth muscle (see later). The tunica media comprises the largest part of the wall and is the principal determinant of the vessel's mechanical properties ⁷. Collagen and elastin are the predominantly elastic materials of the arterial wall. The arterial wall is regarded as a two phase structure: at low distending pressure the tension is borne by the relatively distensible elastin fibres, while at a high distending pressure the tension is mainly borne by the less extensible collagen fibres and the arterial wall becomes stiffer ^{13,21}. This means that the behaviour of arterial stiffness is non-linear and compliance and distensibility depend on the level of blood pressure, i.e. with an increase in blood pressure, the arterial wall becomes stiffer. The arterial tree is not a homogeneous system; the distribution of collagen and elastin differs between arteries. In the proximal aorta elastin is the dominant component, while towards the periphery collagen dominates ^{7,22-24}.

Another important constituent of the arterial wall is smooth muscle ⁷. Although smooth muscle is largely responsible for viscosity of the arterial wall, it also contributes to its stiffness by modulating the tension of elastic fibres ^{13,25} and by regulating arterial caliber and volume ²⁶. During contraction, the muscle transfers the circumferential tension from the collagen to itself and elastin, thereby increasing the extensibility of the vessel ²⁷. This effect is most marked in peripheral muscular arteries and least marked in the central elastic aorta ¹⁰. The nonlinear elastic behaviour of the arterial wall, nonuniform elastic properties of different arteries, different effects of smooth muscle on arterial stiffness and diameter, and viscosity of

the arterial wall makes it difficult to measure and interpret arterial wall properties. In the assessment of arterial wall properties important considerations are: which arterial territory was measured, at which pressure (isobaric) or pressure range (operating pressure) were the wall properties measured and has some medication, like vasodilatory drugs been used ?

1.2.5 Techniques to measure large artery properties

The first data on vessel wall properties were derived from isolated vessels²⁸, later followed by animal experiments²⁹⁻³¹. Since compliance in animals was estimated by invasive techniques and under anesthesia, these data cannot be fully extrapolated to the human, in vivo, situation. Nowadays different aspects of vessel wall properties can be measured in vivo using non-invasive techniques.

Total/Systemic compliance

Total or systemic arterial compliance (C) is an estimate of compliance of the whole arterial tree. Three methods are known. *Firstly* it has been estimated from stroke volume (SV) and pulse pressure (PP) by the formula $PP=SV/C$ ³². This method, however, does not take into account the velocity of ejection of the blood from the heart and the reflected waves. Total arterial compliance is also estimated via simple models of the arterial circulation, using analysis of the blood pressure wave. During diastole the aortic valves are closed, as a result of which the diastolic waveform can be considered as a response of the arterial system to the pressure changes occurring in systole³³. In this case the general shape of the pressure curve commonly assumes a simple monoexponential form. This monoexponential decline in pressure can be used to calculate arterial compliance, based on a "Windkessel model"³³ (*second method*) or an analog model, the electrical RC model, associating in series a single capacitance (C) and a single resistance (R) (*third method*)³⁴. Arterial compliance is the ratio between the time constant of the diastolic decay and the calculated vascular resistance³³⁻³⁵. The limitations of these models are that pressure oscillations are considered to occur simultaneously in all parts of the arterial tree. However, pressure changes do not occur at the same time, since pulse wave velocity varies between arteries. In addition, in these models wave reflections in the arterial tree are overlooked³⁶.

Regional compliance

Regional compliance describes compliance in an arterial segment. It can be calculated from arterial volume and distensibility. Regional distensibility can be assessed by measuring pulse wave velocity²². Distensibility (DC) and pulse wave velocity (PWV) are inversely related³⁷ by the Moens-Korteweg equation: $PWV=\sqrt{1/\rho DC}$, in which ρ is the blood density³⁸. Since diameter of an arterial segment is not constant, from PWV only regional distensibility and not regional compliance can be assessed accurately. Pulse wave velocity may be measured with transit time techniques. It is measured from the foot of pressure waves recorded at two points along the arterial tree and calculated as L/dt , where L is the distance between the two measuring sites and dt is the time delay^{7,39}. The distance is mostly measured with a tape measurer, which is not very precise. The PWV method also does not distinguish the increased pulse wave velocity due to general or more localized stiffening, for instance caused by local plaque formation⁴⁰. Pulse wave velocity is primarily determined by vascular elasticity, but the results are also affected by blood density, velocity of ejection, mean blood pressure and arterial wall

thickness⁴¹.

Local compliance

Noninvasive ultrasonic measurements of vessel diameter and diameter changes were first described by Arndt and coworkers, who used an A-mode technique⁴². Since this first publication several groups have developed different ultrasound techniques to measure local compliance non-invasively. These techniques were based on B-mode⁴³, M-mode^{44,45}, continuous wave⁴⁶, pulsed wave Doppler^{47,48} and multigate pulsed Doppler^{49,50}. Most of these techniques are time-consuming, inaccurate and have several limitations⁴⁰. In 1972, Hokanson developed a new method which accurately measured diameter changes during the heart cycle. This was possible by using the phase of the radiofrequency signal and positioning of windows at both arterial walls^{51,52}. A few years later Hoeks and coworkers developed a system based on tracking the position of the vessel wall during the heart cycle, using this radiofrequency signal^{40,50}. With this system diameter and stroke change in diameter of various large arteries can be measured accurately. Blood pressure is measured simultaneously. Assuming that during the heart cycle arteries predominantly change in diameter and not much in length, cross-sectional compliance, defined as arterial compliance per unit of length, can be used as an estimate of local compliance. From diameter, stroke change in diameter and pulse pressure cross-sectional compliance and distensibility coefficient can be calculated. Compared to other techniques, the advantage of this technique is that different vascular territories can be measured and both compliance *and* distensibility can be calculated.

Simultaneously Tardy and coworkers developed a new A-mode echo-tracking device to measure vessel wall properties of distal large arteries⁵³. With this technique radial artery diameter and stroke change in diameter are measured together with blood pressure measurements at the finger with a Finapres device^{54,55}. Lately, besides these ultrasound techniques, magnetic resonance imaging is also used to measure arterial dimensions^{56,57}. This method however is very expensive and time-consuming.

The weakness of the echo-tracking techniques is the assessment of pulse pressure at the site of the measurement. However if a good relation between pulse pressure in target and surrogate arteries exists, the error may be proportional. Consequently if pulse pressure in target and surrogate arteries behave similarly, results of comparative studies may demonstrate quite accurately changes in vessel wall properties, despite the fact that absolute values of vessel wall properties may be incorrect²⁰. Several studies described a good relation between carotid and brachial artery pulse pressure^{58,59}. It is however known that pulse wave reflections may boost pulse pressure in the carotid artery, but not in the brachial artery¹⁰. This may disturb the relation between brachial and carotid artery pulse pressures. The relation between brachial and carotid pulse pressure is also not constant, for example the timing and magnitude of pulse wave reflections can be altered by vasodilatory drugs, ageing, mental stress etc, leading to a different relation between brachial and carotid pulse pressure.

Until now no accurate method exists to measure blood pressure non-invasively at the carotid or femoral artery. A non-invasive technique to measure local pulse pressure has been proposed: applanation tonometry^{60,61}. Benetos and coworkers found a good correlation between brachial artery and femoral artery pulse pressure recorded with this technique²⁴. This method however requires a lot of skill and cannot be applied in all subjects (for instance obese subjects) and for all arteries. At the moment attempts are made to measure local pulse pressure

and diameter simultaneously with ultrasound techniques, but these methods still have to be evaluated⁹. Calculation of the pulse pressure of a central artery with the amplitude and contour of the pressure wave of a peripheral artery may also be promising⁶².

1.2.6 Variability

Blood pressure and heart rate vary over the day⁶³. A similar diurnal pattern has been found for vessel wall properties of elastic and muscular large arteries. Distensibility appears to decrease during the night, while diameter increases, resulting in no change in compliance from day to night⁶⁴. As a consequence in longitudinal studies, patients have to be measured at the same time of the day. This applies not only for local, but also for systemic and regional compliance. Apart from a day-night rhythm, also short-term variations in elastic properties have been reported⁶⁵. These short-term variations, observed in the femoral artery, could be caused by changes in vascular tone⁶⁵. Hayoz et al reported a vasomotion pattern in radial arteries of healthy volunteers; this fluctuation in diameter is flow-related⁶⁶.

The effect of vascular smooth muscle tone on arterial wall properties is not clear. Sympathetic stimulation, using mental stress and cold pressure tests, was found to increase⁶⁷ and decrease radial artery distensibility and compliance⁶⁸. The increase could be caused by the decrease in diameter, which unloads collagen fibers in favor of elastin. Subjects using the vasoconstrictor ergotamine, showed a lower carotid distensibility compared to subjects not taking it⁶⁹, while there was no difference in blood pressure or wall thickness. Smooth muscle relaxation with nitroglycerin increases brachial artery compliance, with no effect on brachial artery distensibility⁷⁰. Pharmacological blockade of the brachial plexus also increased radial artery compliance⁷¹, with no effect on arterial diameter. Modulators of vascular muscle tone may thus influence large artery function. The effect may depend on the vascular territory²⁰.

1.3 RELATION AND INFLUENCE OF CARDIOVASCULAR RISK FACTORS

This section describes not only the relation between vessel wall properties and well-known cardiovascular risk factors (hypertension, smoking, hyperlipidemia and diabetes mellitus), but also the relation with other factors that might directly or indirectly influence cardiovascular risk, such as age, gender and exercise.

1.3.1 Age

The effect of age on elastic properties of the arterial system was firstly investigated by Roy in 1880⁷². These studies were in vitro studies⁷³⁻⁷⁵, later followed by in vivo measurements using pulse wave velocity techniques^{22,41,76}. In the past decade several ultrasound studies concerning this issue have been described. Most of these studies focused on proximal, elastic arteries, like the aorta and common carotid artery. The major changes described with ageing are arterial dilatation, increase in wall thickness and decrease in elasticity^{22-24,41,49,73,76-83}. Aortic distensibility seems to reach its peak at about 10 years of age²², and starts to decrease in the 3rd age decade^{49,74}.

The mechanism by which ageing can cause a decrease in distensibility is not fully clear. There are several possibilities:

1. *Degeneration of elastic fibers and a parallel increase in collagen:* The cyclic stress on the elastic fibers can have a fatiguing effect ^{10,84}, which may result in fracturing of load-bearing elastic fibers with stretching and remodeling of the arterial wall ^{10,84}. This leads to a loss of elasticity and a parallel increase in collagen and mucopolysaccharide.

2. *Increase in vascular muscle mass:* With age vascular smooth muscle cells accumulate in the arterial wall, which may lead to a decrease in arterial distensibility.

3. *Atherosclerosis:* Development of atherosclerosis could play a role ^{84,85}. This is however contradicted by the fact that in a population without atherosclerosis (Chinese population) compliance also decreases with age ⁴¹.

4. *Early and advanced wave reflections:* Early wave reflections can increase pulse pressure, which could lead to a lower distensibility ⁸⁶.

The stiffening of the aorta and its major branches with age leads to a widening of pulse pressure and a progressive increase in systolic pressure ⁸⁷, implicating a higher cardiovascular risk.

The arterial tree comprises also (predominantly) muscular arteries, like the brachial and femoral arteries. Some smaller studies reported conflicting results on the effect of ageing on muscular arteries ^{24,51,77,80,83,88}. For instance some authors reported an increase in femoral diameter with age ^{51,80}, while others found no relation between age and arterial diameter ^{24,77}. From these studies it appears that ageing might have different effects on proximal and distal arteries, although other reasons, like differences in (small) study populations cannot be excluded.

1.3.2 Gender

Male gender is a cardiovascular risk factor, even after controlling for other risk factors ⁸⁹. Large artery wall properties differ between men and women. Women have smaller diameters of all arteries ^{23,24,75,77,90}. One of the explanations is that arterial calibre is influenced by body size (height) ^{78,91}, and the size of women is relatively smaller than men. The influence of gender on arterial stiffness is inconsistent across the published reports ^{22,24,57,78,90,92}. Again, most studies focussed on elastic arteries, while the effect of gender on muscular arteries is ill defined ^{77,88}. An explanation for the differences in large artery properties between men and women might be the effect of estrogens (see 1.3.10). The gender difference in vessel wall properties might contribute to the difference in cardiovascular risk between men and women.

1.3.3 Race

Prevalence of hypertension and mortality from hypertension related diseases (stroke) is higher among Africans than Caucasians ⁹³. Whether this is caused by an increased stiffness was investigated in a small number of studies. Two studies described no difference in aortic distensibility between Asian and Caucasian or Nigerian and Caucasian subjects, both living in the same country ⁹⁴. However in a recent cross-sectional study, aortic stiffness was lower in normotensive blacks than normotensive whites ⁹⁵. In hypertensive subjects however, blacks exhibited a higher stiffness than their white counterparts. In the latter study, several explanations for this phenomenon were given: different composition of the wall, different genetic factors (e.g. renin-angiotensin system), differences in vasodilatory capacity or differences in salt-sensitivity. Since the number of studies is small and the results of the studies inconsistent, further studies are necessary.

1.3.4 Hypertension

Hypertension, defined as a resting systolic blood pressure ≥ 140 mmHg and a diastolic blood pressure ≥ 90 mmHg⁹⁶, is a powerful and independent cardiovascular risk factor⁹⁷. Epidemiological studies have shown that mortality and morbidity caused by hypertension are better related with the systolic than with the diastolic blood pressure^{97,98}. This suggests that pulsatile stress (pulse pressure) plays an important role in the ill effects of hypertension. As mentioned before, arterial compliance is an important determinant of pulsatile stress. Blood pressure is known to be a major determinant of arterial distensibility²¹. A high blood pressure by itself can decrease arterial distensibility¹⁰. This was first appreciated by Frank in 1905^{99,100}. Since pathological arterial wall changes similar to those of ageing are seen in hypertensive subjects at an earlier age, hypertension is often considered to accelerate ageing of large arteries¹⁰¹. In general arterial distensibility and compliance of the elastic^{33,102-104} and muscular^{105,106} arteries, measured at operating pressure, are lower in hypertensive subjects. Arterial diameter increases in hypertension^{102,107}, possibly to compensate for the loss in distensibility, to limit the decrease in compliance. Two different mechanisms for a decrease in distensibility have been suggested: 1. structural changes due to arterial degeneration (primary defect) or 2. functional changes due to the distending pressure per se¹⁰¹.

No decrease in vessel wall properties of elastic^{101,106} and muscular¹⁰⁸⁻¹¹⁰ large arteries in hypertensive compared to normotensive subjects were shown, when the subjects had been studied at the same blood pressure (isobaric wall properties). This suggests that the decrease in wall properties seen in hypertensives could be explained by an increase in pressure per se and that mechanical alterations of conduit arteries are not causal in the development of hypertension. At the same mean arterial pressure, distensibility and compliance of the muscular radial artery in hypertensives were also equal or even higher compared to normotensives¹¹¹. The authors suggested this possible increase could be due to hypertension-related hypertrophy of vascular smooth muscle, which decreases the relative amount of collagen in the vessel wall¹¹¹. Later the same group discriminated different hypertensive patients: subjects with hypertrophy and subjects with remodeling of the radial artery¹¹². In the first group isobaric radial artery compliance was increased, while in the latter radial artery compliance was not different¹¹², indicating that compliance depends on the hypertrophy or remodeling pattern. In contrast to these results another study showed lower isobaric compliance and distensibility of the femoral artery in hypertensive subjects¹⁰⁶. The stiffening might thus not only be the result of pressure elevation, but can also be an intrinsic pressure-independent change of large artery properties caused by alterations of the vessel wall. These alterations could be functional or structural. Functional changes are increases in vasomotor tone, changes in endothelial function and activation of the renin-angiotensin system¹¹³. Structural changes include an increase in wall thickness¹¹³.

There also seems to be a difference between *essential hypertensives* and subjects with *systolic hypertension*, the first showing lower carotid artery wall properties and higher radial artery wall properties, while in the latter both are markedly reduced¹¹⁴.

The stiffening of the aorta and its major branches with hypertension has the same effect as the stiffening with age, namely a progressive increase in systolic pressure and widening of pulse pressure³⁹, leading to an increase of the cardiovascular risk. A recent report of the ARIC study showed that a decrease in carotid artery stiffness is associated with a higher risk to develop hypertension, suggesting that lower arterial elasticity is related to the development of

hypertension¹¹⁵.

Like in hypertension, also in **borderline hypertension** (blood pressure between 140/90 and 150/95 mmHg, subgroup of hypertension⁹⁶), compliance and distensibility of large arteries are diminished. This has been described for elastic¹¹⁶⁻¹²¹ as well as for muscular¹²¹ large arteries. Hypertensive subjects can be divided in sodium-sensitive and sodium-resistant subjects, based on the effect of a sodium load on blood pressure¹²². **Sodium-sensitive** borderline hypertensive subjects have lower compliance and distensibility of the carotid, brachial and femoral arteries compared to sodium-resistant subjects, deviating more from normal controls¹²¹. The mechanisms underlying these findings are however not clear¹²¹.

The results considering arterial compliance in subjects with a **family-history of hypertension**, show some discrepancy, with some reporting lower arterial compliance¹²³ and others with no difference compared to control subjects¹²⁴. A lower arterial compliance in these subjects could be due to environmental or genetic effects. Evidence for the latter is given by a study from Benetos et al, showing that AT1 receptor polymorphism (A-C polymorphism) might be involved: aortic stiffness was higher in CC compared to AA subjects, while aortic stiffness of AC subjects was intermediate¹²⁵.

Antihypertensive drugs have different effects on arterial compliance. Large artery compliance can be increased by calcium antagonists, angiotensin converting enzyme inhibitors, selective β_1 -blocking agents with vasodilating properties, diuretics containing thiazides and nitrates¹²⁶. This beneficial effect may, in part, be due to a decrease in blood pressure. The non-selective beta-blocker propranolol and the direct vasodilators of the hydralazine group and the centrally acting α_2 -agonist clonidine however do not increase arterial compliance, despite a marked fall in blood pressure¹²⁷. This suggests that these drugs might have a negative effect on large artery wall properties. Antihypertensive drugs might also have a direct positive action on the vessel wall. Evidence for this was given by a study showing a more pronounced increase in arterial compliance with the ACE inhibitor perindopril than with the combined diuretic amiloride-hydrochlorothiazide, with a similar decrease in blood pressure¹²⁸.

The effect of antihypertensive agents may also depend on the vascular territory. For instance the diuretic amiloride-hydrochlorothiazide did not change wall properties of the carotid artery, but did increase brachial artery wall properties¹²⁸. The effects of antihypertensive drugs on large artery properties also depend on the dose of the drug, the duration of treatment and the arterial state (age, coexistence of other diseases)²⁰. In addition the effect of antihypertensive drugs on arterial compliance can be different because of different effects on diameter and distensibility.

1.3.5 Heart rate

Tachycardia is strongly related to cardiovascular death¹²⁹. The number of studies on the relation between heart rate and arterial stiffness is small. Sa Cunha described a negative relation between heart rate and aortic stiffness and carotid and femoral distension, independent of age and blood pressure¹³⁰. Two recent studies in humans showed, with atrial pacing, a decrease in aortic distensibility and total arterial compliance^{131,132}. Part of this could have been explained by an increase in blood pressure. The relation between heart rate and vessel wall properties might be caused by a shortening of time available for recoil, resulting in arterial stiffening^{7,8}.

1.3.6 Obesity

Obesity is an independent risk factor for cardiovascular disease^{133,134}. Overweight non-smoking subjects have mortality rates up to 4 times higher than those for non-smoking subjects who are at desirable weight¹³⁵. Many studies have shown altered hemodynamics in obese subjects. Cardiac output, stroke volume and circulating blood volume increase with body weight¹³⁶⁻¹³⁸, while total peripheral resistance is often lower in obese subjects¹³⁶. Many obese subjects also show an increase in arterial blood pressure¹³⁶⁻¹³⁸, because total peripheral resistance did not decrease (enough) to counteract the increase in cardiac output.

The effect of obesity on large artery properties is not clear, some investigators found no effect of obesity on large artery properties, while others found a decrease or increase in arterial distensibility or compliance in obese subjects (Table 1).

Table 1. Studies on the effect of obesity on large artery properties

Author	Artery	Technique	D	DC	CC
Mujais ⁵⁷	aorta	PWV		=	
Kupari ¹³⁹	aorta	MRI		=	
Toto-Moukoko ¹⁴⁰	BA	PWV		↓	
Mangoni ¹⁴¹	RA	ultrasound	↑		↑
Oren ¹⁴²	SAC	PP/SV			↑
Resnick ¹⁴³	aorta	MRI		=	

D, diameter; DC, distensibility coefficient; CC, cross-sectional compliance; BA, brachial artery; RA, radial artery; SAC systemic arterial compliance; PWV, pulse wave velocity; PP/SV pulse pressure divided by stroke volume; MRI, magnetic resonance imaging; =, no change; ↑, increase; ↓, decrease

In the study by Resnick, aortic distensibility was significantly and inversely related to abdominal visceral fat¹⁴³. In two studies reduction in body weight led to an improvement of large artery properties^{140,144}. Yamashita found an increase in systemic arterial compliance with weight reduction, probably caused by a decrease in blood pressure¹⁴⁵. The reason for the inconsistency in the data is not known. The same holds for the possible cause of the changes in vessel wall properties in obese subjects. One explanation could be the coincidence of hyperinsulinemia in obese subjects¹⁴⁶, which seems to be related to arterial stiffness^{57,147,148}.

1.3.7 Hypercholesterolemia

Hypercholesterolemia is a well established risk factor for atherosclerosis¹⁴⁹. Different results on the relation between hypercholesterolemia and vessel wall properties were found, depending on the vascular territory (Table 2)

Table 2 shows there is a difference between mild hypercholesterolemia and familial hypercho-

lesterolemia (FH). The reduction in arterial diameter and compliance in FH, which is not seen in non-familial hypercholesterolemia, could be due to a genetic mechanism or due to persistent very high cholesterol levels ¹⁵². The effect of hypercholesterolemia might also be related to the duration of increased cholesterol levels.

Table 2 Effect of hypercholesterolemia on large artery wall properties

Author	Artery	Technique	Severity	D	DC	CC
Hayoz ¹⁵⁰	RA	ultrasound	mild	=	=	=
Kool ¹⁵¹	CCA BA FA	ultrasound	mild	=	=	=
				=	=	=
				=	↓	=
Avolio ⁴¹	aorta	PWV	mild		=	
Giannattasio ^{152, 155}	RA	ultrasound	mild familial	= ↓	 ↓	= ↓
Lehmann ¹⁵³	aorta	PWV	familial, young familial, adults		↑ ↓	
Iannuzzi ¹⁵⁴	aorta	ultrasound	children	=	=	
Toikka ¹⁵⁶	aorta	ultrasound/MRI	familial		=	
Tomochika ¹⁵⁷	aorta	ultrasound	familial	=	↓	
Pitsavos ¹⁵⁸	aorta	ultrasound	familial	=	↓	

↑, increase; ↓, decrease; =, no change compared with normocholesterolemic subjects; BA, brachial artery; CCA, common carotid artery; FA, femoral artery; RA, radial artery; D, diameter; DC, distensibility coefficient; CC, cross-sectional compliance; PWV, pulse wave velocity; MRI, magnetic resonance imaging

As can also be seen in Table 2, young subjects (4-20 years) with FH have significantly higher distensibility of the aorta ¹⁵³, while adult patients with FH have a significantly lower aortic distensibility than control subjects ¹⁵³. This could be due to the development of early stages of atherosclerosis in these patients, in which it has been suggested that possibly first an increase in distensibility is seen, followed by a decrease of distensibility later in the process ¹⁵⁹.

The change in vessel wall properties in subjects with FH is suggested to be caused by an (1) impaired function or secretion of endothelial relaxing factors, (2) an increased content of collagen and calcium subsequent to deposition of cholesterol in the vessel wall, (3) a potentiating effect of cholesterol on the responsiveness of vascular smooth muscle to sympathetic stimuli or (4) a toxic effect of oxidized lipoproteins ^{155,160}. The latter (oxidized LDL) is negatively associated with carotid and aortic distensibility in healthy men and subjects with FH ¹⁵⁶. The difference between non-familial and familial hypercholesterolemia and the effect of

duration of hypercholesterolemia could explain the inconsistent results.

Lately there is a lot of interest in the influence of *lipid-lowering therapy* on atherosclerotic lesions. This effect seems to be rather small ¹⁶¹. Most of these studies focused on the reversal of atherosclerotic plaques. There are only few studies about the effect of lipid-lowering drugs on vessel wall properties. Eight weeks of treatment with a HMG-coA reductase inhibitor did not improve large artery properties of the carotid, brachial and femoral arteries in mildly hypercholesterolemic patients ¹⁵¹. Since animal experiments have shown that reversal of changes in distensibility in atherosclerosis occur slowly, the duration of this therapy could have been too short to show an effect. A 6 month-treatment with another HMG-coA reductase inhibitor did also not improve vessel wall properties of the radial artery in hypercholesterolemic patients ¹⁵⁵, however after 24 months of therapy radial artery compliance was improved. This was also described for aortic stiffness after 13 months of therapy with a diet and a HMG-coA reductase inhibitor ¹⁵⁷.

1.3.8 Smoking

Cigarette smoking is a major risk factor for cardiovascular morbidity and mortality, independent of other risk factors ¹⁶². It is also the most preventable cause of cardiovascular mortality and morbidity. The long term risks of smoking are dose-related, the more one smokes, the greater the risk ¹⁶³. The effect of smoking however appears to be reversible; the risk for cardiac death in smokers was comparable to that in non-smokers within 1 year after stopping ¹⁶². This was not true for the risk of peripheral arterial disease, which was not completely reversed after cessation of smoking ¹⁶². Smoking has acute (sympathetic) effects on the systemic and coronary circulation: increase in heart rate, blood pressure and myocardial contractility ¹⁶³. Besides this, smoking has an effect on the endothelium, platelet function, hemostasis and lipid metabolism ¹⁶³. The relation between smoking and large artery stiffness is unclear. Impaired compliance of the arterial system of the lower leg has been described in a group of heavy smokers ¹⁶⁴. On the other hand similar vessel wall properties of the elastic aorta and muscular brachial artery in smokers and non-smokers have been reported ¹⁶⁵. The same result was described for total arterial compliance ¹⁶⁶. In addition, in a population study there was also no relation between smoking and aortic stiffness ⁵⁷.

Besides these cross-sectional studies concerning the chronic effect of smoking, there are also some studies about the acute effect of smoking on arterial wall properties. All of these studies reported increased arterial stiffness and decreased compliance of several different arteries after smoking a cigarette ^{165,167-171}. In some studies the effect was maintained for at least 20 minutes ¹⁷⁰. The decrease in distensibility was probably the resultant of the increase in blood pressure and an active stiffening, due to elevated muscular tone, which might be partially the result of activation of the sympathetic nervous system ¹⁷⁰. The increase in heart rate could also be an explanation. This means that after each cigarette the load on the arterial wall increases, which can lead to plaque rupture, an important feature in atherosclerotic disease.

In addition to the hazard of smoking for the smoker him/herself, passive smoking also seems to give an acute deterioration of aortic distensibility ¹⁷².

1.3.9 Diabetes mellitus

Diabetes mellitus is a well known risk factor for atherosclerotic diseases such as coronary

Type	Author	Artery	Technique	D	DC	CC	
IDDM + NIDDM	Woolam ¹⁷⁵ Scarpello ¹⁷⁶	BA BA TA	PWV PWV		↓ = = ↓		footulcer - footulcer +
IDDM	Oxlund ¹⁷⁷ Pillsbury ¹⁷⁸ Thordarson ¹⁷⁹ Lehmann ¹⁸⁰ Kool ¹⁸¹ Christensen ¹⁸²⁻¹⁸³ Berry ¹⁸⁴ Rydén Ahlgren ^{185,186} Lambert ¹⁸⁷ Zenere ¹⁸⁸ Giannattasio ¹⁸⁹	aorta BA aorta aorta aorta CCA FA BA FA total aorta CCA CCA FA aorta CCA RA	in vitro PWV ultrasound PWV ultrasound ultrasound SV/PP ultrasound ultrasound ultrasound ultrasound	 = = = = = = = = = = = = = = = =	↓ ↓ ↓ ↓ ↑ = = ↓ ↓ ↓/=	 = = = = ↓ ↓	F/M F/M microalb. normoalb. compl. no compl.
NIDDM	Lehmann ¹⁸⁰ Lo ¹⁹⁰ Wahlquist ¹⁹¹ McVeigh ¹⁹²	aorta aorta aorta total	PWV PWV PWV waveform		↓ ↓ ↓		=

Table 3 shows contradictory results. Some authors describe a lower arterial distensibility in diabetic patients^{175,178,179,182,190,191}, while other authors only found a lower distensibility of lower leg arteries in diabetic subjects with peripheral neuropathy and healed or ulcerated feet¹⁷⁶, or did not find a difference in arterial distensibility between diabetic patients and control subjects¹⁸¹. Lehmann and coworkers even described a more distensible aorta in uncomplicated type 1 diabetic patients compared to controls. This was particularly the case in type 1 diabetics, who were measured in the first year after diagnosis. This could be comparable to the increase in distensibility seen in young familial hypercholesterolemic patients¹⁵³. In this study diabetics and controls were however not matched for blood pressure, which could have influenced the results^{153,180}. Some authors also described a decrease in arterial compliance in diabetic patients¹⁸⁴, while others found not^{181,192}. A possible cause for the inconsistency in the results of studies about the effect of diabetes on large artery properties could be caused by the fact that most results are based on heterogeneous groups of patients with insulin and non-insulin dependent patients, with or without complications, with variable duration of disease, different types of medication and differences in regulation of the disease. Some authors namely found relations between arterial distensibility and glycemic control¹⁹⁰ or duration of disease^{177,179,182,185}. On the other hand this is disputed by others^{184,192}. The presence of complications, like microalbuminuria can also make a difference in the results^{187,188}. Besides this there also might be a gender-difference^{185,186}. It is not only unclear whether diabetic patients have altered vessel wall properties, the mechanism by which the disease contributes to the atherosclerotic process and the possible increased arterial stiffness is also not fully understood. Several mechanisms have been proposed: hemostatic abnormalities²⁶⁶, hyperinsulinemia¹⁹³, non-enzymatic glycosylation^{194,195}, changes in the autonomic nervous system¹⁹⁶ and clustering of other risk factors¹⁷³.

1.3.10 Neuroendocrine and metabolic factors

Estrogens

Vessel wall properties differ between men and women. In addition, stiffness of the aorta¹⁹⁷ and carotid artery^{197,198} is described to be higher in postmenopausal compared to age-matched premenopausal women. With these results in mind, several groups studied the effects of female hormones, like estrogen and progesterone.

There does not seem to be a relation between the menstrual cycle and arterial wall properties of the carotid and femoral arteries¹⁹⁹. Three months use of a third generation oral contraceptive also does not seem to influence these vessel wall properties²⁰⁰.

Several groups investigated the effect of estrogen replacement therapy with contradictory results. Some describe a positive effect of estrogens on distensibility of the aorta²⁰¹ and CCA^{202,203}, while others found no relation between estrogen replacement and distensibility of the aorta²⁰⁴, carotid^{205,206} or brachial arteries²⁰⁴. Several authors describe a positive effect of estrogen replacement therapy on systemic compliance^{201,202,204,206}. Since estrogens have a vasodilatory capacity²⁰⁷, the increase in compliance might be caused by vasodilation. Another evidence for this is the fact that the effect of estrogens on systemic compliance can be established in 4 weeks and also disappears after 4 weeks withdrawal^{201,208}. Estrogens, however, also have direct effects on the arterial wall: estrogens decrease collagen production and decrease the elastin/collagen ratio²⁰⁹. In one study it is suggested estrogens may protect against endothelial injury²¹⁰.

Since most hormone replacement therapy contains estrogens and progestins, the latter to prevent the risk of uterine cancer, the combination was also tested. One study found no difference in carotid artery distensibility between estrogens alone and the combination ²⁰³, while other studies described an attenuation of the estrogen effect on carotid artery distensibility and total arterial compliance with concomitant progestins ^{202,206}.

Insulin

Insulin is a growth promotor that can mediate structural changes of vascular wall tissue ¹⁴⁷. Recent data suggest a role for insulin in vascular changes. Some studies showed an inverse relation between insulin and aortic compliance ¹⁴⁷ and distensibility ⁵⁷, which was also found for distensibility of the common carotid artery ¹⁴⁸. On the contrary, a recent study described an increase in compliance of large arteries, caused by a vasodilation or increase in distensibility ²¹¹. The relation between insulin and large artery properties might also be gender-dependent: Giltay et al showed a negative relation between insulin and femoral artery wall properties in women, which was not found in men ²¹². Since no relation between insulin and carotid artery wall properties were found, neither in men nor women, the relation might also depend on the arterial territory ²¹². In conclusion, the exact relation between insulin and vessel wall properties has to be further elucidated.

Hormones of the renin-angiotensin system and sympathetic nervous system

Effector hormones of the sympathetic nervous system and renin-angiotensin system have been implicated as growth promoters that can lead to structural changes of vascular wall tissue ¹⁴⁷. Dimensions of large muscular arteries are influenced by vasoactive substances like *angiotensin*, *noradrenaline* and *atrial natriuretic peptide* ²¹³⁻²¹⁶, which could lead to altered vessel wall properties. In addition, Neutel and coworkers found a negative relation between *noradrenaline* and proximal arterial compliance, in normal subjects ¹⁴⁷.

Higher *aldosterone* plasma levels also tended to be associated with reduced total arterial compliance in normal subjects ¹⁴⁷, hypertensive subjects ²¹⁷, treated patients with congestive heart failure ²¹⁸ and subjects with primary hyperaldosteronism ²¹⁹. In the last study, compliance did not return to normal after treatment. The authors hypothesized two mechanisms which could be responsible: increased collagen deposition in the vessel wall or an increased responsiveness to adrenergic stimulation.

Hypopituitarism, Growth hormone, Thyroid hormone

Hypopituitary subjects, on routine hormone replacement have a higher mortality rate, caused by vascular disorders ²²⁰. Symptom-free hypopituitary women, but not men, also seem to have a lower carotid artery distensibility and compliance ²²¹. The subjects in the latter study were all growth-hormone deficient and had replacement of thyroxine, cortisol and sex-steroids. The cause of the altered wall properties in this study is not clear.

One explanation could be *growth hormone* deficiency, which is related to an increased cardiovascular risk ²²². It has been shown that symptom-free growth hormone deficient adults have less distensible arteries than controls. In addition they have higher cholesterol levels ¹⁵³. It is not clear whether the growth hormone deficiency per se, the hypercholesterolemia or the combination is the cause of the alteration in large artery properties.

Arterial distensibility of the carotid and radial artery also seems to be decreased in *hypothy-*

roid patients compared to age-matched controls ²²³. After replacement therapy with thyroid hormones distensibility returned to normal. The latter suggests more functional than structural changes, although structural changes, for instance accumulation of mucopolysaccharoid substances cannot be excluded.

Homocysteine

In the last decade, hyperhomocysteinemia has been recognized as a cardiovascular risk factor ²²⁴. Homocysteine for instance enhances smooth muscle proliferation ²²⁵. One study reported a link between homocysteine and PWV of the lower limb in subjects with end-stage renal disease ²²⁶. This was also reported for aortic stiffness in hypertensive patients ²²⁷. However, in a study by Smilde et al, in subjects with a genetically disordered homocysteine metabolism, the effect of homocysteine on arterial stiffness was only marginal ²²⁸. Homocysteine explained only a minor proportion of the variability in carotid artery distensibility and femoral artery compliance. This discrepancy could be explained by different arteries studied and different populations.

1.3.11 Exercise

Physical fitness and physical activity are associated with a decreased risk of cardiovascular disease and lower incidence of hypertension ²²⁹. Is this obtained by preservation of arterial distensibility and compliance? Cross-sectional studies comparing athletes and untrained subjects have found a higher aortic and brachial artery compliance in athletes ^{56,230} and trained cyclists ²³¹ respectively. In this latter study, cyclists had a larger diameter of the femoral artery compared to sedentary controls, but similar vessel wall properties. In hammer-throwers, diameter and compliance of the radial artery of the dominant arm were found to be increased compared to sedentary subjects, while this was not the case for the non-dominant arm ²³². This suggests training can increase local arterial diameter and compliance. Stiffness of the aorta and carotid artery is also described to be lower in trained postmenopausal women compared to sedentary women, with a similar blood pressure ¹⁹⁷. Not only very trained subjects seem to have less stiff arteries, also subjects with moderate activity (for instance dancing with sufficient activity to cause sweating) have a less stiff aorta compared to sedentary subjects ²³³. The increase of arterial distensibility with training might be due to a reduction of overall blood pressure, a decrease in smooth muscle tone, a reduced production of renin and angiotensin and/or a reduction in sympathetic effects. In addition it could also be a flow-dependent mechanism ²³². Besides this it could also be that athletes have a high arterial compliance for constitutional reasons rather than as a result of physical training. The study of the hammerthrowers does not support this, since the changes were only found in the dominant, trained arm ²³².

A study with a 4-week exercise programme showed an increase in arterial compliance, which decreased to baseline values after a 8-week sedentary period ²³⁴. In this study blood pressure was lowered, which could explain the results. Studies on the acute effects of exercise have shown an increase in aortic compliance in hypertensive subjects ²³⁵. In normotensives and mildly hypertensive subjects a decrease in aortic compliance has been shown ^{236,237}. An acute bout of exercise led to an increase in total arterial compliance and a decrease in aortic and femoral artery stiffness, which returned to normal after 1 hour ²³⁸. This suggests a change in vascular smooth muscle tone, leading to vasodilation. Another study however, showed no

effect of 6 weeks of moderate exercise training on blood pressure and vessel wall properties of the common carotid, brachial and femoral arteries²³¹.

On the contrary, a population study showed a positive relation between stiffness of the thoracic aorta and leisure-time physical activity, meaning that the thoracic aorta gets more stiff with physical activity⁵⁷. A recent study by Bertovic et al also reported a stiffer proximal aorta and leg arteries in strength-trained individuals compared to sedentary controls²³⁰. The authors of both studies suggest this might be explained by arterial fatigue, caused by repeated periods of increase in blood pressure during exercise^{57,230}.

1.3.12 Diet

Eating of *fish* can improve or preserve large artery vessel wall properties²³⁹. Pulse wave velocity of the aorta was smaller in subjects from fishing villages compared to farming villages, which means a lower arterial distensibility in the subjects from the farming villages. These effects of fish eating can be caused by fish oils, which might affect the arteriosclerotic process in a favourable way.²⁴⁰

Another dietary factor that might be important is the intake of *salt*. Compared to subjects with a high salt-intake, subjects with a low salt-intake have a better arterial distensibility²⁴¹. A low salt diet in normotensive adult subjects can result in a higher arterial distensibility, independently of the effect on blood pressure²⁴¹. As mentioned in the hypertension section, compared to sodium-resistant subjects, sodium-sensitive borderline hypertensive subjects have a lower compliance and distensibility of the carotid, brachial and femoral arteries¹²¹. The mechanisms underlying these findings are not clear¹²¹. Possible explanations are an increased activity of the sympathetic system or renin-angiotensin system or a decreased concentration of atrial natriuretic peptide¹²².

Recently 2 reports described a positive effect of *isoflavones* (in soybeans and red clover) on systemic arterial compliance in menopausal and perimenopausal women^{242,243}. The explanation might be that isoflavonoids have weak estrogenic activity.

1.3.13 Kidney diseases

Patients with end-stage renal failure have an increased cardiovascular risk. Several studies showed a larger diameter and decreased distensibility of elastic and muscular large arteries in patients on hemodialysis compared to control subjects, independently of blood pressure²⁴⁴⁻²⁴⁶. These altered vessel wall properties might be due to the long-existence of hypertension, lipid disorders, electrolyte disturbances, toxic effects of the uremia, the hypercalcemia after dialysis^{244,247} or the kidney disease per se²⁴⁶.

Subjects on long-treatment-time dialysis have less hypertension and cardiovascular complications as compared to the more usual short-treatment-time dialysis. However, even in this patients femoral artery distensibility and compliance, but not carotid artery distensibility and compliance were found to be reduced²⁴⁸. Three months after renal transplantation distensibility of the carotid artery is also, still, decreased. These patients were however on immunosuppressive therapy, which might have influenced the large artery properties²⁴⁹.

Another explanation could be hyperparathyroidism, which is often found in end-stage renal failure. Barenbrock et al described a significant negative relation between plasma parathyroid levels and carotid artery distensibility in renal transplant patients²⁵⁰. Since the effects were not related to calcium, blood pressure or arterial diameter, the authors suggest structural modifica-

tions of the wall ²⁵⁰.

1.3.14 Connective tissue disorders

Patients with elastic tissue disorders like Marfan have a decreased aortic distensibility ^{153,251,252}. This might be caused by an altered structure of the tunica media ²⁵¹. Patients with osteogenesis imperfecta also have a lower aortic distensibility ²⁵³. In subjects with Ehlers-Danlos syndrome, a condition associated with a collagen type III deficiency, arterial distensibility is improved, however at the expense of a weakened wall, leading to ruptures at an early age ²⁵⁴.

1.4 RELATION BETWEEN LARGE ARTERY WALL PROPERTIES AND ATHEROSCLEROSIS

Conflicting results have been reported regarding the arterial wall stiffness in atherosclerosis. Subjects with coronary artery disease have an abnormally rigid aorta ²⁵⁵⁻²⁵⁷. A decrease in arterial distensibility has also been reported in patients with arteriosclerosis obliterans (an atherosclerotic disease of the lower limbs) ²⁵⁸. One study described a close correlation between carotid artery stiffness in vivo and postmortem degree of atherosclerosis in this artery ²⁵⁹. These results suggest a decrease in arterial distensibility with atherosclerosis. Distensibility and compliance of the radial artery are, however, increased in subjects with peripheral vascular disease ²⁶⁰. This might be explained by 1) different structure of the artery, 2) some kind of compensation for the loss in central artery compliance.

How would atherosclerosis affect the wall? Atherosclerosis is a pleomorphic disorder, characterised by accumulation of lipid, thrombus, collagen and cellular components in the intima of the arterial wall ⁴. In experimental atherosclerosis in rhesus monkeys, Farrar et al showed a loss of aortic distensibility with the development of atherosclerosis, which was reversible with the regression of the atherosclerosis ¹⁵⁹. Surprisingly, during the induction of atheroma, the aorta firstly became more distensible, and then as focal lesions were formed, began to stiffen, ultimately becoming less distensible ¹⁵⁹. This result was confirmed by others ²⁶¹. The early phase of the atherosclerotic disease (atherosis) is due to the infiltration of LDL cholesterol into the intima and formation of foam cells ^{161,262}. This may lead to an increased distensibility. In older plaques, later sclerosis develops, due to laying down of collagen in the vessel wall ^{161,262} and arteries become stiffer ¹⁵³. Increased distensibility has thus been related to early stages of atherosclerosis. This means that the increased aortic distensibility found in early life (age 10-20) may be an early stage of atherosclerosis leading to stiffer arteries in later life ²². Consequently an increase and a decrease in distensibility can be an indication of atherosclerosis ²².

Avolio and coworkers were, however, unable to find a correlation between the degree of atherosclerosis and degree of arterial stiffening in two populations with a high and low incidence of atherosclerosis ⁴¹. The method used was, however, not able to detect early atherosclerotic lesions.

The possible stiffening of arteries in the development of atherosclerosis might not be a homogeneous process. Increased stiffness of the carotid artery was found at identifiable atherosclerotic lesions compared to places of the carotid walls nearby, where no lesion was visible ⁴⁴. In

a study on atherosclerotic lesions in the carotid artery bifurcation, distensibility was reduced at the site of the lesion, even when it was not associated with an intraluminal process ²⁶³. In conclusion, there is controversy about the effect of atherosclerosis on vessel wall properties. In a recent study by Blacher et al, arterial stiffness of the aorta in patients with end-stage renal failure, requiring hemodialysis, was a major predictor of all cause mortality and morbidity ²⁶⁴. The same author described a similar relation for hypertensive patients: a strong relation between aortic PWV and atherosclerotic alterations and a strong predictor of cardiovascular risk ²⁶⁵. A PWV > 13m/s even appeared a strong predictor of cardiovascular mortality ²⁶⁵. It is still not clear whether increased arterial stiffness is a risk factor contributing to the development of cardiovascular disease or is a marker of arterial disease. However, arterial stiffness measurements seem to be able to serve as tools for identifying patients at risk for cardiovascular disease. To further investigate this relation, longitudinal studies in unselected populations are necessary.

1.5 THIS THESIS

This introduction section shows that for most cardiovascular risk factors, results from studies on the relation between arterial wall properties and the risk factors are inconsistent. Explanations for this could be: different methods applied, small number of subjects and heterogeneous groups. In addition, vascular territories may behave differently.

To clarify the relation between vessel wall properties and different cardiovascular risk factors, the present thesis studies this relation in a random relatively large population sample and at different vascular territories.

The population sample and methods used in the studies of the present thesis are described in *chapter 2*.

Chapter 3 and 4 describe the relation between age and gender and large artery properties of the aorta, carotid, brachial and femoral arteries. Since one of the explanations for the observed gender-differences could be the influence of estrogen, in *chapter 5* the relation between menopause and large artery wall properties is studied.

Besides the influence of age and gender, we focused on the relation of vessel wall properties with metabolic risk factors, like obesity, insulin resistance and type 1 diabetes mellitus.

In *chapter 6*, the relation between obesity and large artery wall properties is described. Part of the results might have been caused by insulin resistance. In *chapter 7*, the relation between insulin resistance and vessel wall properties is studied.

Since the incidence of type I diabetes is 1:300, the number of subjects with type I diabetes in the study population was too small to study the effect of diabetes on vessel wall properties. This was studied in a different group of subjects. In *chapter 8*, vessel wall properties in different groups of IDDM patients were studied.

Finally *chapter 9* discusses the results of the studies published in this thesis and gives recommendations for future research.

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CHAPTER 2

Methods and Subjects

2.1 Population sample identification

Except for the study described in chapter 8, all studies in this thesis were performed in a random population sample. This population sample was identified in a rural area of Belgium ¹. The population sample was stratified by sex and age (20-39, 40-59, ≥ 60 years) in an attempt to recruit the same number of subjects in each stratum. From population registers a random sample of the households was drawn. All household members aged 20 years or older were eligible except if they were foreign nationals, or if the quota of their age-sex stratum had been fulfilled. At baseline (1985-1989), we invited 1419 subjects with a minimum age of 20 years, of whom 1107 (78%) took part. After excluding subjects who had died ($n=83$) and those who were severely ill ($n=3$) or had moved ($n=7$), 1014 subjects were eligible for a follow-up examination of whom, from 1991 to 1995, 823 (81%) participated. Of these participants, 209 subjects did not take part in the vascular measurements and 41 subjects were not actually examined because of technical and logistic problems. In the course of the present analysis a further 76 subjects were removed from the database, because vascular measurements were not available at all arteries studied: the common carotid, brachial and common femoral arteries. The number of subjects finally considered in the analysis totalled 250 men and 247 women.

Table 1. Characteristics of the study population

Item	Men	Women	P
N	250	247	
Age (years)	50 $\pm$ 13	50 $\pm$ 12	0.72
Body height (cm)	173 $\pm$ 7	161 $\pm$ 6	<.001
Body weight (kg)	78 $\pm$ 11	65 $\pm$ 11	<.001
Body mass index (kg/m ²)	26.0 $\pm$ 3.3	25.2 $\pm$ 4.0	.007
Blood Pressure (mmHg) [†]			
Systolic	132 $\pm$ 15	128 $\pm$ 18	.004
Mean	100 $\pm$ 10	96 $\pm$ 10	<.001
Diastolic	84 $\pm$ 10	81 $\pm$ 10	<.001
Heart rate (bpm)	61 $\pm$ 10	64 $\pm$ 10	.001
Smokers	84 (33.6)	76 (30.6)	0.50
Drinking alcohol	85 (34.0)	28 (11.3)	<.001
Antihypertensive treatment	37 (14.8)	40 (16.1)	0.87
Contraceptive pill		15 (9.0 [‡])	

Data are mean $\pm$ SD or number of subjects with percentage in brackets. Mean blood pressure = (2.DBP + SBP)/3. [†] Measured with a sphygmomanometer in sitting position. [‡] Percentage of women between 20-55 years of age with oral contraception.

2.2 Study design

All participants were asked to refrain from smoking, drinking caffeine containing beverages and heavy exercise for at least 3 hours before being examined. Firstly the participants were seated and were asked to relax for five minutes. Then sitting blood pressure was measured.

Afterwards the participants were interviewed about their current health status, smoking and drinking habits and intake of drugs.

After 15 minutes of supine rest in a quiet room vessel wall properties of the right elastic common carotid artery (CCA) and right muscular common femoral (CFA) and brachial (BA) arteries were measured. All measurements were made by the same observer, at an arterial segment which showed no echocardiographical signs of atherosclerosis in B-mode. Simultaneously with the assessment of the vessel wall properties blood pressure and pulse rate were recorded. PWV was calculated afterwards.

2.3 Blood pressure and heart rate

Sitting blood pressure was measured five times consecutively with a sphygmomanometer. Data of systolic and diastolic blood pressure are means of five measurements. This blood pressure was used for characterisation of the subjects. Mean blood pressure (MBP) was calculated as $(2 \cdot \text{DBP} + \text{SBP})/3$. This mean blood pressure was used as a possible confounding factor in the analyses.

Simultaneously with the vessel wall measurements, supine blood pressure and heart rate were measured at the left arm, with a semiautomated oscillometric device (Dinamap; Critikon, Tampa, Florida). Every 3 minutes recordings were made. At least 15 recordings were averaged and taken as the patient's reading. Pulse pressure of the brachial artery was calculated as systolic (SBP) minus diastolic (DBP) blood pressure. This pulse pressure was used for calculation of the vessel wall properties.

2.4 Vessel wall properties

2.4.1 Arterial compliance and distensibility

Vessel wall properties - compliance and distensibility - can be measured locally with a vessel wall movement detector system². This system consists of a conventional echo-imager system (Ultramark V; ATL, Bothell, Washington, USA), a data acquisition system, and a personal computer with an AD-card. With a 7.5 Mhz transducer the vessel of interest is visualized in B-mode (Fig.1). A line of observation or M-line is positioned perpendicularly to the artery. The echo-system is switched to M-mode, after which, by pressing on a footpedal, data are stored. During 5-6 seconds radiofrequency (RF) signals are digitised and stored in an internal buffer memory. This process is triggered by the R-top of a simultaneously recorded ECG, for a constant time-relationship between the distension curve and the ECG. The first RF-line is displayed on the computer screen. It is used to identify the wall-lumen interfaces. Two calipers (boxes, fig.2) are placed on the anterior and posterior wall of the vessel. The distance between these calipers corresponds to the initial diameter of the vessel lumen. This is the minimum diameter, measured at end-diastole. After this procedure the next RF-lines are transferred to the computer and processed to retrieve the movement of the arterial walls. The sample volumes are not fixed, but move along the beam, according to the detected movement (tracking principle).

Fig. 1 B-mode image of the common carotid artery of a young healthy volunteer

Fig. 2 An example of the digitized radiofrequency (RF) signal. The white boxes indicate the sample volumes and cover the anterior (left) and posterior (right) walls.

After processing of all RF-lines, the movement of the arterial walls during time is shown on the screen (Fig.3). The distension curve - the change in diameter during time - is obtained by the difference in movement between the anterior and posterior wall. From this distension curve, diameter (D) and change in diameter (ΔD) during each heart cycle can be obtained. Simultaneously with the vessel wall measurements arm blood pressure and heart rate are measured with a Dinamap (see section 2.3). Pulse pressure at the common carotid and common femoral arteries were obtained from calibration of the distension waveform.

Fig. 3 Displacement waveforms of the anterior (top) and posterior (middle) wall of the common femoral artery. The difference between these two is the distension waveform (bottom). The cross indicates the occurrence of the ECG trigger.

Fig. 4 Pressure wave. Y-axis: pressure, X-axis: time; P represents pulse pressure, A represents MAP-DBP.

Calibration procedure:

The calibration factor (CF) allows to calculate the pulse pressure at the target artery (PP tar) from the pulse pressure at the reference artery (PP ref) by the formula:

$$PP\ tar = CF \times PP\ ref$$

The calibration factor can be calculated from the pressure waveforms at the target and reference artery. In the pressure wave shown in figure 4, 'P' represents the pulse pressure and 'A' represents MAP minus DBP (MAP-DBP) respectively. 'P' and 'A' can be calculated from the pressure

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waveform in arbitrary units. 'A' is calculated by dividing the area under the pressure wave by time. This can be written by the formula:

$PP / (MAP-DBP) = P/A$, define $PA=P/A$, then:

$(MAP-DBP) = PP/PA$

As $(MAP-DBP)$ is assumed constant through the large artery tree, this formula holds for reference and target artery:

$PP \text{ tar}/PA \text{ tar} = PP \text{ ref}/PA \text{ ref} = (MAP-DBP)$

$PP \text{ tar} = PP \text{ ref} \times PA \text{ tar}/PA \text{ ref} = CF \times PP \text{ ref}$

The calibration factor $CF = PA \text{ tar} / PA \text{ ref}$

Likewise, instead of using the pressure waveform, in this thesis, the distension waveforms were used.

To calculate vessel wall properties - compliance and distensibility -, the assumption is made that an increase in arterial volume during systole is caused by an increase in cross-sectional area and not by a change in arterial length^{3,4}. Cross-sectional compliance is defined as the compliance/unit of length; it is the change in cross-sectional area per unit of pressure. It reflects the buffering capacity of an artery. Likewise, distensibility is defined as the relative change in cross-sectional area per unit of pressure. It reflects the elasticity of the wall of the artery. From D , ΔD and ΔP vessel wall properties can be calculated³:

Compliance coefficient (CC) = $\Delta V/L/\Delta P = \Delta A/\Delta P = \pi(2D.\Delta D + \Delta D^2)/4\Delta P$

Distensibility coefficient (DC) = $(\Delta A/A)/\Delta P = (2\Delta D.D + \Delta D^2)/(\Delta P.D^2)$

This device can be used to measure vessel wall properties of different superficial large arteries. In the studies described in this thesis the elastic common carotid artery and the muscular brachial and femoral arteries were measured. A reproducibility study has shown that with this system diameter and change in diameter during the heart cycle can be measured reproducibly. Intraobserver variability at the common carotid artery was less than 5% for diameter and less than 10% for compliance and distensibility. The results for the muscular arteries were somewhat less, but still lower than 15%⁵.

2.4.2 Pulse wave velocity

The vessel wall movement detector system also gives the delay time from the ECG-trigger (R-top) to the 10% level of the distension waveform of the artery that is measured at that time. This estimates the transit time of the pulse wave between the heart and the site of measurement. The difference between the transit times of the pulse wave from the heart to the femoral and carotid artery was used as an estimate of the carotido-femoral transit time (T). The distances from the sternal notch to the site of measurement of the common carotid artery and femoral artery were measured with a tape measurer. The difference between these two distances was used as the length of the carotido-femoral segment (L)⁶.

The average pulse wave velocity in this segment was calculated as:

$$PWV = L/T \quad (3)$$

which is an estimate of the stiffness of mainly the aortic pathway ⁷.

Pulse wave velocity is related to arterial distensibility (DC) by the formula:

$$PWV = \sqrt{1/\rho DC} \quad (\text{Moens Korteweg }^{8,9}) \quad (\rho = \text{blood density})$$

2.5 Data analysis

Database management and statistical analyses were performed with the SAS software (The SAS Institute Inc., Cary, North Carolina). The methods of data analysis are presented in the methods sections of each individual chapter. Data are mean $\pm$ SE, except for demographic values (mean $\pm$ SD). A p-value < 0.05 was considered as statistically significant. In the analyses, statistical adjustments were made for possible confounders: mean arterial pressure, pulse rate, body mass index, smoking, use of alcohol and antihypertensive treatment.

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CHAPTER 3

The effect of age on brachial artery wall properties differs from the aorta and is gender-dependent: a population study

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Abstract

Compliance and distensibility are wall properties of large arteries, which may play a role in cardiovascular disease. The purpose of this study was to investigate whether the influence of age on these vessel wall properties differs between vascular territories and is gender-dependent.

In a population sample of 497 men and women, age between 20-79 years, diameter, distensibility and compliance coefficient of the muscular brachial artery were measured with an echo-tracking device. Distensibility of the aorta was measured using pulse wave velocity. The effects of age and gender were assessed, adjusted for confounding factors like mean blood pressure, pulse rate, body mass index, smoking, alcohol intake and antihypertensive treatment.

Covariance analysis showed no relation between gender and distensibility of the elastic aorta. Distensibility of the muscular brachial artery was lower in men, while men had a larger diameter and larger compliance of the brachial artery. With age distensibility of the aorta decreased in both sexes to the same extent, while distensibility of the brachial artery did not change significantly. With age brachial artery diameter increased; this increase was more pronounced in women. In men brachial artery compliance did not change with age, while in women compliance of the brachial artery increased with age.

This study (1) confirms that distensibility of the aorta, an elastic artery, decreases with age. (2) In contrast to the aorta, after adjustment for confounding factors, in both men and women no relation exists between age and distensibility of the muscular brachial artery. (3) Brachial artery diameter increase with age is more pronounced in women than in men. (4) In contrast to the well-known decrease in arterial compliance of elastic arteries with age, brachial artery compliance is not decreased with age and even increased in women. In conclusion, the effect of age on large artery wall properties is not uniform, but depends on gender and vascular territory.

Introduction

Compliance and distensibility are vessel wall properties of large arteries. Arterial compliance, defined as the absolute change in volume per unit of pressure ($\Delta V/\Delta P$), reflects the buffering capacity of an artery; a decrease in compliance increases cardiac afterload and the risk of cardiac hypertrophy¹⁻³. Arterial distensibility, defined as the relative change in volume per unit of pressure ($(\Delta V/V)/\Delta P$), reflects mainly the elasticity of the wall, and is considered a determinant of strain on the vessel wall⁴. A local decrease in distensibility might be associated with an increased risk of arterial wall damage, an important feature in atherosclerotic disease⁵. Preservation of distensibility might be important in protecting the arterial wall against damage at a particular site⁶.

From 1880 on, several groups have investigated the effect of age on elastic properties of the arterial system⁷. The first studies were post mortem studies⁸⁻¹⁰, later followed by in vivo measurements of regional distensibility^{11,12}. At the age of twenty the vascular system is considered to be mature but it is unclear from which age distensibility starts to decrease. Several studies reported the influence of age on wall properties of elastic large arteries. It has been suggested that aortic distensibility reaches its peak at about 10 years of age¹¹, and starts to decrease in the 3rd age decade^{9,13}. With advancing age elastic arteries, like the aorta and common carotid artery dilate, become stiffer and show an increase in wall thickness^{8,11-18}. The arterial tree, however, not only comprises elastic, but also medium-sized muscular arteries, like the brachial artery. Whether the effect of age on arterial wall properties of these arteries is similar to the effect on elastic arteries is not known. In addition, no study investigated whether the effect of age is gender-dependent. The aim of the present study was to investigate the effects of age and gender on wall properties of the medium-sized muscular brachial artery compared to the elastic aorta in a general population.

Methods

A population sample of 250 men and 247 women were investigated¹⁹ (chapter 2).

Nurses who had previously visited the participants at home, measured sitting blood pressure conventionally with a sphygmomanometer and interviewed the participants about their current health status, smoking and drinking habits and intake of drugs.

After 15 minutes of supine rest in a quiet room aortic and brachial artery wall properties were measured. Vessel wall properties of the right brachial artery were measured with a vessel wall movement detector system²⁰ as described in chapter 2. Simultaneously with the vascular measurements, blood pressure was measured at the left arm, with a semiautomated device (Dinamap; Critikon, Tampa, Florida). Pulse pressure was calculated as SBP-DBP. ΔP during the heart cycle equals pulse pressure. From diameter, change in diameter during the heart cycle and pulse pressure, cross-sectional compliance and distensibility were calculated with the equations mentioned in chapter 2. This method has shown good reproducibility²⁰.

Vessel wall properties of the aorta were measured using pulse wave velocity. The delay times to the femoral and carotid artery was used as an estimate of the carotido-femoral transit time (T). The difference between the distances from the sternal notch to the site of measurement of the common carotid artery and femoral artery was used as an estimate of the length of the carotido-femoral segment (L_{ao})²¹. From this transit time and length, the pulse wave velocity of the aorta was calculated²² (chapter 2). Pulse wave velocity is related to arterial distensibility (DC) by the formula: $PWV = \sqrt{1/\rho DC}$ (Moens Korteweg^{23,24}) (ρ =blood density)

Database management and statistical analyses were performed with the SAS software (The SAS Institute Inc., Cary, North Carolina). The methods of analysis included Mann-Whitney-U tests for continuous variables and Chi-square tests for the dichotomous parameters. To test the influence of gender, an analysis of covariance was used with factors for mean arterial pressure (measured by sphygmomanometer), pulse rate, body mass index, smoking, use of alcohol and antihypertensive treatment. Factors with a p-value > 0.10 were dropped from the model. To get the relation between vessel wall properties and age, age was also added as a covariate. To investigate the difference of the age-effect among the sexes, the interaction of age and sex was also tested for. A p-value < 0.05 was considered as statistically significant.

The study was approved by the ethics committee of Leuven University and all subjects gave their written informed consent.

Results

The subjects, 250 men and 247 women, were 50±13 years old, with a range from 26-82 years (chapter 2). The distribution of age was similar among men and women: 6.0% were from 20 through 29 years old, 16.1% from 30 through 39, 31.5% from 40 through 49, 23.1% from 50 through 59, 16.3% from 60 through 69, and 7.0% were 70 years or older. The conventionally measured systolic and diastolic blood pressure was slightly higher in men than in women. Current smoking was reported by 160 participants (median 15 cigarettes a day; range 1-70) and 113 subjects reported regular alcohol consumption (median 20 g a day; range 1-196). A total of 77 subjects were taking antihypertensive treatment either in monotherapy or in combination. Of these, 36.4% (8 men and 20 women) were on diuretics, 57.1% (22 men and 22 women) on beta-blockers, 7.8% (4 men and 2 women) on angiotensin-converting-enzyme inhibitors and 26.0% (13 men and 7 women) on calcium antagonists.

Differences in vessel wall properties between men and women are shown in Table 1.

Table 1. Vessel wall properties in a random population

Artery	Unadjusted		p	Adjusted [†]		p
	Men N=250	Women N=247		Men N=250	Women N=247	
Aorta [‡]						
PWV (m/s)	7.0±1.9	6.7±2.1	**	7.4±2.4	7.2±2.2	
Brachial artery						
Diameter (mm)	4.55±0.60	3.65±0.57	***	4.52±0.48	3.68±0.48	***
DC (10 ⁻³ /kPa)	20.9±9.9	24.4±12.0	***	21.2±10.1	24.1±10.2	***
CC (mm ² /kPa)	0.33±0.13	0.25±0.12	***	0.33±0.12	0.25±0.12	***

Results are mean±SD. [†] Data adjusted for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and use of antihypertensive treatment. [‡] Measurements available in 242 men and 243 women. PWV: pulse wave velocity, Diameter: diameter, DC: distensibility coefficient, CC: cross-sectional compliance ; Statistical significance: ** p < .01, *** p < .001

Since vessel wall properties can be influenced by confounders, which might differ between men and women, values were calculated adjusted for confounders like mean arterial pressure, pulse rate, body mass index, smoking, use of alcohol and antihypertensive treatment. After adjustment, pulse wave velocity of the aorta, a measure of aortic distensibility, was not different between men and women. Distensibility of the brachial artery was larger in women ($p < .001$). But diameter and cross-sectional compliance of the brachial artery were smaller ($p < .001$) in women compared to men.

Descriptive analysis of the effect of age on vessel wall properties in men and women is shown in Fig. 1 and 2. Figures 1 and 2 show on the left the mean $\pm$ SEM of the vessel wall properties for each 10-year age class, before adjustment for confounders mentioned above.

Fig. 1 Association between age and pulse wave velocity of the aorta in the whole population sample. Results before (left) and after (right) adjustment for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and antihypertensive treatment. $\blacktriangle$ Men, $\triangle$ Women. Mean $\pm$ SEM.

In a further step of the analysis a linear as well as a curvilinear (i.e. including both age and the quadratic term of age) model were fitted to the relationships between age and large artery wall properties for men and women separately. These analyses showed that a linear model (Table 2a, unadjusted values) was sufficient to fit all age relationships. The relationship was also analysed after adjusting for the confounders (Table 2b, adjusted values). All individual data were recalculated according to the adjusted linear regression model and are shown in Fig. 1-2 (on the right).

Fig. 2 Association between age and vessel wall properties of the brachial artery in the whole population sample. Results before (left) and after (right) adjustment for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and antihypertensive treatment. ■ Men, □ Women. Mean $\pm$ SEM.

PWV of the aorta increased with age to the same extent in both sexes. Although visual inspection of adjusted data suggests a more pronounced decrease in brachial artery distensibility in women than in men, the linear regression model could neither in men nor in women show a statistically significant change in brachial artery distensibility with age (men: $p=0.76$; women: $p=0.61$) after adjustment for confounders (Table 2b). Visual inspection of the relation between age and brachial artery diameter or cross-sectional compliance is in accordance with the linear regression model: after adjustment for confounders (Table 2b) with advancing age brachial artery diameter increased more in women ($p=0.013$) than in men. Brachial artery compliance increased in women ($p=0.002$), while it remained unchanged in men.

Table 2a. Relation between vessel wall properties and age. Unadjusted

Artery	Men slope (age) ⁻¹ ·10 ⁻³	Women slope (age) ⁻¹ ·10 ⁻³	Gender difference regarding slope
Aorta ‡			
PWV (m/s)	90.0±7.6***	95.3±9.4***	n.s.
Brachial artery			
D (mm)	5.9±2.9*	19.8±2.6***	***
DC (10 ⁻³ /kPa)	-90.4±48.3*	-188.1±60.6**	n.s.
CC (mm ² /kPa)	n.s.	n.s.	n.s.

Regression coefficients±SE; ‡ Measurements available in 242 men and 243 women; PWV: pulse wave velocity, D: diameter, DC: distensibility coefficient, CC: cross-sectional compliance
n.s. non-significant, * $p < .05$; ** $p < .01$; *** $p < .001$

Table 2b. Relation between vessel wall properties and age. Adjusted †

Artery	Men slope (age) ⁻¹ ·10 ⁻³	Women slope (age) ⁻¹ ·10 ⁻³	Gender difference regarding slope
Aorta ‡			
PWV (m/s)	80.8±8.4***	76.9±9.4***	n.s.
Brachial artery			
D (mm)	4.3±2.6+	13.7±2.9***	*
DC (10 ⁻³ /kPa)	n.s.	n.s.	n.s.
CC (mm ² /kPa)	n.s.	2.1±0.7**	*

Regression coefficients±SE; † Adjusted for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and use of antihypertensive treatment.

‡ Measurements available in 242 men and 243 women; PWV: pulse wave velocity, D: diameter, DC: distensibility coefficient, CC: cross-sectional compliance ; n.s. non-significant, + $p < .1$, * $p < .05$; ** $p < .01$; *** $p < .001$

Discussion

The present study investigated whether the well known decrease in aortic distensibility with age was also present in the muscular brachial artery and whether it was similar in men and women. Changes in vessel wall properties with age are not only the effect of ageing, but can also be the effect of other, interrelating factors that change with age. From previous studies blood pressure, body mass index and antihypertensive treatment have been identified²⁵⁻²⁷ as confounding factors. The effect of other factors, like smoking and pulse rate, is not always clear²⁸⁻³⁰. In the present study, to get the relation between vessel wall properties and age, values were adjusted for mean auscultatory blood pressure, pulse rate, antihypertensive treatment, body mass index, smoking and use of alcohol for each gender.

Gender differences in a random population In this population sample distensibility of the aorta did not differ between men and women. Kupari³¹, who investigated men and women aged 36 and 37 years old, also reported a gender independency of the aortic stiffness. Laogun et al however showed a higher aortic distensibility in women between 15-45 years old compared to age-matched men¹¹. This contradictory result could be due to the use of a smaller study population in the latter study. In addition, in this study no corrections were made for confounders, like mean arterial pressure and body mass index; which are important determinants of large artery properties and often differ between men and women. Also in the present study, the unadjusted data showed a higher aortic distensibility in women, compared to men. However, after adjustment there was no difference anymore. In contrast to the aorta, distensibility of the muscular brachial artery was larger in women compared to men. The reason of this gender difference is not quite clear. One reason could be a difference in smooth muscle tone and vessel wall structure (elastin/collagen) between men and women, possibly related to hormonal influences, for instance effects of estrogen. Constitutional differences between men and women might also play a role. Diameter of the brachial artery was larger in men, compared to women. Other authors also showed larger diameters of different arteries in men^{10,14,15}. Since the caliber of vessels is related to body size (height and weight)^{16,32}, and the size of women is smaller than of men, this could explain the smaller vessel diameter in women³². Because of the larger diameter in men, compliance of the brachial artery was higher in men than in women, despite the lower distensibility of the brachial artery.

Effect of age and gender Distensibility of the aorta decreased with age in both sexes to the same extent. These results confirm earlier studies^{11,18}. Several studies showed that distensibility of another elastic artery, the carotid artery, also decreases with age^{13,18}. In contrast the present study showed that distensibility of the muscular brachial artery was not related with age as already observed by Kawasaki and coworkers¹⁸. In addition the present study showed that this was the case for both men and women.

The mechanism by which ageing causes a decrease in distensibility of the aorta and common carotid artery is not fully clear. Several hypotheses have been proposed. Firstly the fatiguing effect of cyclic stress on the elastic fibers could play a role^{33,34}. Ageing may lead to degeneration of the elastic fibers with stretching and remodeling of the arterial wall^{33,34}, resulting in a loss of elasticity and a parallel increase in collagen and mucopolysaccharides. This hypothesis is supported by the observation that the decrease in distensibility with age is proportional to the increase in collagen with age³⁴. Degeneration of elastin fibers may also explain arterial dilation with age. This dilation is greater in elastic than in muscular arteries, as would be predicted from theory. Secondly, with age vascular smooth muscle cells accumulate in the

arterial wall. Thirdly, atherosclerosis could play a role ^{34,35}. The exact relation between atherosclerosis and arterial wall stiffness is still unclear. Besides, it has been shown that also in a population without atherosclerosis compliance decreased with age ¹². Fourthly, early and advanced wave reflections, seen with increasing age, could boost pulse pressure and decrease distensibility ³⁶.

In the present population sample, the diameter of the brachial artery increased with age. The results about changes in diameter of the brachial artery with age are not consistent in the literature. Some authors have found an increase in diameter ¹⁸, while others have found no relation between age and arterial diameter ¹⁴. There also seems to be a gender difference; in the present study the increase in diameter of the muscular brachial artery was more pronounced in women than in men.

Compliance of the BA was not related with age in men. Surprisingly, compliance of the BA increased with age. This increase was statistically significant in women but not in men. The increase in compliance of the BA is caused by a larger diameter, without a statistical change in distensibility. The increase in arterial diameter with age is also found in other arteries ¹⁶⁻¹⁸. It has been suggested that the larger diameter with age is due to loss of elastic fibers in the arterial wall. Since brachial artery elasticity (reflected by distensibility) appears not significantly changed with age, an alternative explanation could be an adaptive remodeling of the brachial artery. If this latter hypothesis is true, then this adaptive remodeling of the brachial artery with age may be more pronounced in women than in men.

In conclusion, this study confirms that distensibility of the aorta, an elastic artery, decreases with age. This study shows that (1) in contrast to the aorta, after adjustment for confounding factors, in both men and women no relation exists between age and distensibility of the muscular brachial artery. (2) Brachial artery diameter increase with age is more pronounced in women than in men. (3) In contrast to the well-known decrease in arterial compliance of elastic arteries with age, brachial artery compliance is not decreased with age but even increased in women. (4) The effect of age on large artery wall properties is not uniform, but depends on gender and vascular territory.

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CHAPTER 4

Disparate effects of age and gender on the wall properties of elastic and muscular large arteries: a population study

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Abstract

Compliance and distensibility of large arteries may play a role in cardiovascular disease. The purpose of this study was to investigate how age and gender influence these vessel wall properties in different vascular territories.

In a population sample of 497 men (M) and women (F), ages 20-79 years, diameter, distensibility and cross-sectional compliance of the elastic common carotid artery (CCA), muscular brachial (BA) and femoral arteries (FA) were measured with an ultrasound device. The effects of age and gender were adjusted for confounding factors such as mean blood pressure, pulse rate, body mass index, smoking, alcohol intake and antihypertensive treatment.

With adjustment for confounders applied, in the 3 vascular territories men had a larger diameter and cross-sectional compliance of all arteries ($p < .001$). Distensibility was similar in both sexes with the exception of the brachial artery, which in men showed lower distensibility ($p < .01$). The diameter of the 3 arteries increased with age; for the muscular arteries (BA and FA) this increase was more pronounced ($p < .05$) in women than in men. In men the CCA had the largest percentage increase (15%) in diameter. Distensibility of the CCA and FA decreased with advancing age to a similar extent in both sexes. The percentage fall from the 3rd to the 8th age decade was larger ($p < .001$) for the CCA (M: 64%, F:60%) than for the FA (M:29 %, F:38%). Distensibility of the BA was not related to age. Cross-sectional compliance of the CCA decreased with age, more ($p < .01$) in men (50%) than in women (40%). Cross-sectional compliance of the FA was not statistically related to age. In women, cross-sectional compliance of the BA increased (20%) with age, in men there was no relation.

This study shows that the effect of age on large artery wall properties depends on (1) the vascular territory; with age arteries dilate and become stiffer, more in elastic than in muscular arteries. The effect of age on large artery wall properties also depends on (2) gender; the increase in diameter of muscular arteries is more pronounced in women.

Introduction

Arterial compliance (the buffering capacity of an artery, defined as the absolute change in volume per unit of pressure) and distensibility (reflecting largely the elasticity of the wall, defined as the relative change in volume per unit of pressure) can be indicative of early vascular changes and may play a role in atherosclerotic disease ¹⁻³.

Local distensibility and compliance can be assessed with ultrasonic wall-tracking techniques ⁴. Studies using these techniques revealed that large conduit arteries do not react identically to disease states. For instance, in hypertension distensibility and compliance of elastic arteries decrease ⁵, whereas compliance of the muscular radial artery does not ⁶. Several authors studied the effect of aging on large artery wall properties. With advancing age elastic arteries, like the common carotid artery dilate, become stiffer and show an increase in wall thickness ⁷⁻¹⁵. The influence of gender on these properties is inconsistent across the published reports ^{8,11,12,16,17}. The arterial tree, however, not only comprises elastic, but also (predominantly) muscular arteries, like the brachial and femoral arteries. Until now some smaller studies reported conflicting results on the effect of aging on muscular arteries ^{10,11,14,18,19}, whereas the effect of gender on these arteries also remains ill defined ^{10,19}.

The aim of the present study was to investigate the effects of age and gender on wall properties of three different vascular territories in a population sample: the common carotid artery, an elastic artery in which atherosclerosis is common, the common femoral artery, a muscular artery in which atherosclerosis is also common and the muscular brachial artery, an artery in which atherosclerosis is uncommon.

Methods

Vascular measurements were performed in 614 subjects from a random population sample ²⁰ (chapter 2). In the course of the present analysis a further 76 subjects were removed from the database, because vascular measurements were not available at all arteries studied. The number of subjects finally considered in the analysis totalled 250 men and 247 women.

All participants were asked to refrain from smoking, drinking caffeine containing beverages and heavy exercise for at least 3 hours before being examined. Firstly the sitting blood pressure was measured with a sphygmomanometer. Afterwards the participants were interviewed about their current health status, smoking and drinking habits and intake of drugs (chapter 2).

After 15 minutes of supine rest in a quiet room vessel wall properties of the right elastic common carotid artery (CCA) and right muscular common femoral (FA) and brachial (BA) arteries were measured with a vessel wall movement detector system ^{4,21} (chapter 2).

Simultaneously with the assessment of the vessel wall properties blood pressure and pulse rate were recorded with a semiautomated device (Dinamap; Critikon, Tampa, Florida). Brachial artery pulse pressure was defined as systolic minus diastolic blood pressure. Pulse pressure at CCA and FA were calculated by calibration of the distension curves (chapter 2).

Database management and statistical analyses were performed with the SAS software (The SAS Institute Inc., Cary, North Carolina). The methods of analysis included Mann-Whitney-U tests for continuous variables and Chi-square tests for the dichotomous parameters. To test the influence of gender and age, analysis of covariance was used with mean arterial pressure (sphygmomanometer), pulse rate, body mass index, smoking, use of alcohol and antihypertensive treatment as covariates. Factors with a p-value > 0.10 were dropped from the model. To

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investigate the difference of the age-effect among the sexes, the interaction of age and sex was also tested for. In order to test the null hypothesis of no difference between the arteries regarding the effect of age on wall properties, a multivariate analysis of variance was performed for each sex separately on the percentage differences, calculated versus the wall properties in the 3rd age decade. Data are mean $\pm$ SD for demographic values and mean $\pm$ SE for interactions. A p-value < 0.05 was considered as statistically significant.

Results

Demographics of the subjects are described in chapter 2. Values of the vessel wall properties in men and women are shown in Table 1. After adjustment for mean arterial pressure, pulse rate, body mass index, smoking, use of alcohol and antihypertensive treatment, diameters of the CCA, BA and FA were larger ($p < .001$) in men compared to women. Distensibility of the elastic CCA and muscular FA did not differ statistically between men and women, whereas distensibility of the muscular BA was larger ($p < .01$) in women. Cross-sectional compliance of CCA, BA and FA were smaller ($p < .001$) in women.

Table 1. Vessel wall Properties in a random population

Artery	Unadjusted			Adjusted [†]		
	Men	Women	p	Men	Women	p
Diameter						
Carotid artery	7.69 $\pm$ 0.81	6.90 $\pm$ 0.80	<.001	7.38 $\pm$ 0.96	7.03 $\pm$ 0.91	<.001
Brachial artery	4.55 $\pm$ 0.60	3.64 $\pm$ 0.57	<.001	4.52 $\pm$ 0.53	3.68 $\pm$ 0.53	<.001
Femoral artery	10.05 $\pm$ 1.08	8.53 $\pm$ 1.02	<.001	9.92 $\pm$ 1.06	8.47 $\pm$ 1.24	<.001
DC (10 ⁻³ /kPa)						
Carotid artery	21.3 $\pm$ 8.4	21.8 $\pm$ 8.6	.71	21.4 $\pm$ 9.6	21.3 $\pm$ 10.5	.89
Brachial artery	20.8 $\pm$ 9.9	24.4 $\pm$ 11.9	<.001	21.3 $\pm$ 10.1	23.9 $\pm$ 10.1	.005
Femoral artery	7.9 $\pm$ 4.1	8.9 $\pm$ 4.6	.02	8.1 $\pm$ 4.9	8.6 $\pm$ 4.9	.14
CC (mm ² /kPa)						
Carotid artery	0.97 $\pm$ 0.37	0.78 $\pm$ 0.26	<.001	0.97 $\pm$ 0.38	0.78 $\pm$ 0.41	<.001
Brachial artery	0.33 $\pm$ 0.13	0.25 $\pm$ 0.12	<.001	0.33 $\pm$ 0.12	0.25 $\pm$ 0.12	<.001
Femoral artery	0.61 $\pm$ 0.30	0.49 $\pm$ 0.22	<.001	0.59 $\pm$ 0.33	0.44 $\pm$ 0.35	<.001

Results are mean $\pm$ SD. [†] Data adjusted for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and use of antihypertensive treatment. DC: distensibility coefficient, CC: cross-sectional compliance

In a further step of the analysis a linear as well as a curvilinear (i.e. including both age and the quadratic term of age) model were fitted to the relationships between age and large artery properties for men and women separately (Table 2, unadjusted values). These analyses showed that a linear model was sufficient to fit all age relationships. These age-relationships were also analysed after adjusting for confounding factors (Table 2, adjusted values).

Results are shown in Fig. 1-2, as mean of each age decade and expressed as percentage difference compared to the 3rd age decade.

Table 2. Relation between vessel wall properties and age

slope $\dagger(\text{age})^{-1} \cdot 10^{-3}$	Unadjusted		Gender difference regarding slope	Adjusted [†]		Gender difference regarding slope
	Men	Women		Men	Women	
Diameter (mm)						
Carotid artery	26.7±3.5***	33.4±3.7***	.19	26.6±3.4***	32.1±3.8***	.28
Brachial artery	6.2±2.7*	19.8±2.9***	<.001	5.1±2.6+	14.3±2.8***	.02
Femoral artery	13.5±4.9**	35.90±5.2***	.002	13.2±4.9**	29.3±5.5***	.02
DC (10 ⁻³ /kPa)						
Carotid artery	-459.9±28.3***	-522.3±29.9***	.13	-440.8±26.2***	-440.2±29.4***	.99
Brachial artery	-94.1±52.9+	-183.5±55.8**	.25	n.s.	n.s.	-
Femoral artery	-54.0±20.4**	-136.8±21.5***	.005	-37.8±19.1*	-73.0±21.4***	.21
CC (mm ² /kPa)						
Carotid artery	-14.8±1.3***	-11.9±1.4***	.13	-14.2±1.2***	-9.1±1.4***	.005
Brachial artery	n.s.	n.s.	-	-0.2±0.6.	1.6±0.7*	.03
Femoral artery	-3.5±1.4*	-2.9±1.3*	.77	n.s.	n.s.	-

[†] Regression coefficients±SE; [†] Adjusted for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and use of antihypertensive treatment. DC: distensibility coefficient, CC: cross-sectional compliance; Statistical significance: n.s. non-significant;

* $p \leq .05$; ** $p < .01$; *** $p < .001$

Diameters of the CCA, BA and FA increased with advancing age in both men and women. The age-related increase in diameter of the muscular BA and FA was more pronounced ($p<.05$) in women than in men (Table 2). In men, after adjustment for confounders, the relative age-related dilatation of the CCA (15%) was more pronounced than that of the FA (3%, $p<.001$) or BA (10%, $p<.01$) (Fig 1). Distensibility of the CCA and FA decreased equally in both men and women, while distensibility of the BA did not change statistically with age. In both men and women the percentage fall in distensibility from the 3rd to the 8th age decade was larger ($p<.001$) in the CCA (M: 64%, F:60%) than in the FA (M:29%, F:38%) or BA (no relation with age) (Fig.1,2). In both men and women cross-sectional compliance of the CCA decreased with age, this phenomenon was more pronounced in men than in women ($p<.01$). Compliance of the FA was not statistically related to age. Compliance of the BA was also not correlated with age in men, but was positively correlated with age in women. In both sexes the percentage decrease in cross-sectional compliance of the CCA (M:50%, F:40%) was larger ($p<.001$) than in the FA (no significant relation with age) or BA (M:no relation, F: 20% increase with age).

Discussion

In the present population sample, in accordance with others^{10,11,17,22}, arterial diameter of all arteries was larger in men than in women. This could be explained by constitutional differences between men and women or the relatively smaller size of women compared to men^{12,23}. Distensibility of the CCA and FA did not differ between men and women, while distensibility of the muscular BA was larger in women compared to men. The reason of this gender difference and differences between arteries is not quite clear. Again constitutional differences might play a role. Another reason could be a difference in vessel wall structure (elastin/collagen) and smooth muscle tone between men and women. Hormones, like estrogen, could also play a role. Recent studies showed a lower CCA distensibility in postmenopausal women compared to premenopausal women of the same age²⁴ and a reduction of carotid artery wall stiffness by administration of estrogens to postmenopausal women²⁵. This suggests estrogens have a positive influence on arterial distensibility. Whether these effects are structural or more functional, for example by influencing arterial diameter has to be further elucidated.

Because of the larger diameter in men (and despite the lower distensibility of the BA), compliance of all three arteries was higher in men than in women, indicating men have a larger buffering capacity of large arteries.

One of the main findings of this study was that the effect of age depends on the vascular territory. In accordance to earlier studies^{11,12,14,26}, diameter of all arteries increased with age in both sexes. It has been suggested that the larger diameter with age is due to the loss of elastic fibers in the arterial wall. Whether the arterial dilatation is a consequence of lifelong cyclic stress or is a physiological adaptation to an increased stiffness is not known.

The relatively largest percentage increase in diameter was seen for the elastic CCA. This is in line with the statement that with age proximal, elastic arteries predominantly dilate, whereas peripheral, muscular arteries are more prone to wall thickening²⁷. On the other hand, percentage dilatation of the BA, a more muscular artery, was almost equal to that of the CCA. This suggests that at the BA, another vasodilatory mechanism than degeneration might be involved. In both men and women distensibility of the CCA and FA was negatively related with age,

whereas distensibility of the BA was not related with age in both sexes. A decrease in carotid artery DC was described before ^{8,13-15}. Earlier studies describing the relation between age and femoral artery DC show some discrepancies: some found no relation ^{11,14}, while others only found a relation in women ¹⁹. The mechanism by which aging causes a decrease in large artery distensibility is not fully clear. (1) Aging, meaning years of cyclic stress, may lead to degeneration of the elastin fibers with stretching and remodeling of the arterial wall ^{28,29}, resulting in a loss of elasticity and a parallel increase in collagen and mucopolysaccharide. This mainly occurs in the elastic arteries. (2) Vasodilatation per se can lead to a decrease in distensibility. (3) Another reason could be accumulation of vascular smooth muscle cells in the arterial wall. (4) Atherosclerosis could also play a role in the ageing process ^{28,30}. (5) Finally, early and advanced wave reflections, seen with increasing age, could boost pulse pressure and further decrease distensibility ³¹, especially of central arteries like the aorta and carotid artery.

In accordance to previous reports, in the present study distensibility was lower towards the periphery ^{8,11,27}. This has been attributed to differences in histopathological structures: in the proximal aorta elastin is the dominant component, whereas towards the periphery collagen dominates ^{8,11,22,32}. As stated, the present study shows that with ageing the largest percentage decrease in distensibility was seen in the central elastic CCA. This means that with advancing age the difference in stiffness between central and more peripheral arteries decreases. In addition, Van Merode et al described that the inhomogeneous distribution of wall elasticity along the femoral artery bifurcation in young subjects becomes more homogeneous in the older age ³³. This supports the idea, that in old age the aorta and large arteries will behave like a branching tube of common stiffness ³⁴. It might also indicate that smaller, more muscular arteries are capable to adapt to the decreased elasticity of the larger arteries, possibly by changing arterial tone.

Compliance of the CCA decreased with age in both men and women. This is caused by the large decrease in distensibility with age, which was not completely counteracted by the increase in diameter. Compliance of the FA was however not related with age in both sexes. Only a small number of studies exist on the effect of age on arterial compliance, confirming the present results on the CCA ^{11,16} and FA ^{11,19}. Compliance of the BA in men was also not related with age, whereas in women compliance of the BA increased with age. The more pronounced increase in BA compliance in women may result in a smaller loss of systemic arterial compliance with aging.

This brings us to the second main finding of our study, namely that the effect of age also is gender-dependent. Distensibility of all arteries decreased in both sexes to the same extent. Compliance of the CCA decreased more in men, than in women. As mentioned before, compliance of the BA increased in women and did not change in men. This increase in compliance of the BA is caused by an increase in diameter, without a statistical change in distensibility. The increase in brachial artery diameter, with no significant change in brachial artery elasticity (reflected by distensibility), suggests the increase in diameter is not totally due to a degeneration of elastic fibers, but is rather an adaptive remodeling process of the brachial artery. This vasodilation appears to be more pronounced in women, especially in the muscular BA and FA. This was not the case for the elastic CCA. Maybe estrogens also play a role in this process, since recent studies showed estrogens have a direct effect on the arterial wall, inducing vasodilation ³⁵. The increase in brachial artery compliance with age in women may limit the decrease in systemic arterial compliance.

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In conclusion, this study shows that [1] the effect of age on large artery wall properties depends on the vascular territory; with age arteries dilate and become stiffer, more in elastic than muscular arteries. [2] The effect of age on large artery wall properties also depends on gender; the increase in diameter of muscular arteries is more pronounced in women. [3] The present study confirms that vessel wall properties differ between men and women; men have a larger arterial diameter and compliance than women.

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Fig. 1 Differences between arterial territories. Association between age and vessel wall properties of the common carotid artery (CCA), brachial artery (BA) and common femoral artery (FA) in men, before (left) and after (right) adjustment for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and antihypertensive treatment. Data are shown as mean percentage difference compared to the mean of the third age decade. ● common carotid artery, ▲ femoral artery, ■ brachial artery.

Fig. 2 Differences between arterial territories. Association between age and vessel wall properties of the common carotid artery (CCA), brachial artery (BA) and common femoral artery (FA) in women, before (left) and after (right) adjustment for mean arterial pressure, pulse rate, body mass index, current smoking, current alcohol intake and antihypertensive treatment. Data are shown as mean percentage difference compared to the mean of the third age decade. ● common carotid artery, ▲ femoral artery, ■ brachial artery.

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CHAPTER 5

Menopause and the characteristics of the large arteries in a population study

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Abstract

In previous cross-sectional and longitudinal population studies, we found that the slope of systolic pressure on age was steeper in postmenopausal than in premenopausal women. We hypothesized that this observation could be due to a specific effect of menopause on the elasticity of the large arteries. We investigated 315 randomly selected women, ages 30 to 70 years. Based on 5.2 years of follow-up, 166 women were premenopausal and 149 menopausal (44 reaching menopause and 105 postmenopausal). These women were matched on age and body mass index with 315 men. We used a wall-tracking ultrasound system to measure the diameter, cross-sectional compliance and distensibility of the brachial and the common carotid and femoral arteries as well as carotid-femoral pulse wave velocity. Pulse pressure was determined from 24-hour blood pressure recordings. Both in menopausal women ($r=0.37$; $P<0.001$) and in matching male controls ($r=0.16$; $P=0.04$), pulse pressure widened with increasing age. The slope of the 24-hour pulse pressure on age was steeper in menopausal women than in their premenopausal counterparts (0.428 vs -0.066 mm Hg per year; $P=0.003$) and than in the male controls (0.428 vs 0.188 mm Hg per year; $P=0.06$). After adjustment for age, 24-hour mean pressure, body mass index, antihypertensive drug treatment, smoking and the use of oral contraceptives or hormonal replacement therapy, postmenopausal women showed a higher carotid-femoral pulse wave velocity (7.77 vs 6.71 m/s; $P=0.02$) and had a slightly greater diameter of the common carotid artery (7.09 vs 6.79 mm; $P=0.07$) than their premenopausal counterparts. After similar adjustments, menopausal class was not significantly associated with other vascular measurements in women or with any vascular measurement in control men. In conclusion, menopause per se may increase aortic stiffness. This phenomenon may contribute to the rise in systolic pressure and pulse pressure in women beyond age 50 and, in turn, may lead to a slight dilatation of the common carotid artery.

Introduction

Systolic pressure rises with age at least until the eighth decade of life ¹. However, until 50 to 60 years, systolic pressure is on average lower in women than in men, whereas the opposite is observed in older subjects ¹. Diastolic pressure on the other hand increases in both sexes only until middle age and thereafter levels off or even slightly declines. Thus, from 50 to 60 years onwards systolic pressure starts to rise and pulse pressure widens more rapidly in women than in men.

Whether menopause may accelerate the age-related increase in systolic pressure remains debated ². Most longitudinal surveys found that menopause is not associated with hypertension, while cross-sectional studies reported an elevated or unchanged blood pressure after menopause (for review, see reference 2). In a previous cross-sectional population study ³, we observed that systolic pressure rose 0.5 mm Hg per year more in women with natural or surgical menopause than in their premenopausal counterparts. In a subsequent longitudinal study ⁴, we found that over 5.2 years (median) of follow-up systolic pressure did not change in women who stayed premenopausal ($P=0.71$), but increased on average by 4 mm Hg in perimenopausal ($P=0.07$) and postmenopausal ($P=0.01$) women. Because similar changes were not observed for systolic pressure in men or for diastolic pressure in both sexes ⁴, we hypothesized that in older women the increase in systolic pressure and the widening of pulse pressure could be potentiated via a specific effect of menopause on the elasticity of the large arteries. We invited the subjects enrolled in our longitudinal study ⁴ for an extensive evaluation of the structural and functional properties of their large arteries ⁵. We report in this article our findings with regard to menopause.

Methods

Study population

We described the recruitment and follow-up of the participants in previous publications ⁴. At baseline (1985-1989), we invited 1419 randomly selected subjects with a minimum age of 20 years, of whom 1107 (78%) took part. After excluding subjects who had died ($n=83$) and those who were severely ill ($n=3$) or had moved ($n=7$), 1014 persons were eligible for a follow-up examination of whom, from 1991 to 1995, 823 (81%) participated. From our previous analysis on menopause and blood pressure ⁴, we excluded 76 subjects because of missing conventional or ambulatory blood pressure measurements and 117 because their age at follow-up was less than 30 years or exceeded 70 years. The 315 women included in the latter analysis ⁴ were matched on age and rank of body mass index at baseline with 315 men. These 630 subjects constitute the study population for this article.

Measurements at Follow-Up

Trained nurses measured the participants' sitting blood pressure at home ⁴. They determined systolic and phase V diastolic blood pressures 5 times consecutively to the nearest 2 mm Hg after the subjects had rested for 5 minutes. Within 1 week of the home visit the participants had their 24-hour blood pressure measured with SpaceLabs 90202 monitors (Redmond, WA) ⁶, programmed to obtain readings with an interval of 20 minutes from 8 AM until 10 PM and every 45 minutes from 10 PM to 8 AM. Standard cuffs had a 12 x 24 cm inflatable portion, but if upper arm girth exceeded 31 cm, larger cuffs with 15 x 35 cm bladders were employed. The same cuff size was used for all blood pressure measurements. The oscillometric Space-

Labs devices provided direct measurements of mean arterial pressure; pulse pressure was calculated as the difference between systolic and diastolic blood pressure.

A standardized questionnaire inquired into each person's medical and surgical history, smoking and drinking habits, intake of medications. We defined premenopause and postmenopause as an active menstrual cycle and continuous amenorrhea throughout follow-up. Women with periods at baseline but with amenorrhea at follow-up were classified as perimenopausal. Surgical menopause was diagnosed, if the menses had disappeared after bilateral oophorectomy. Follicle-stimulating hormone (FSH) was measured in the serum by an immunoradiometric assay.

After the participants had refrained from smoking and drinking alcohol or caffeine containing beverages for at least 3 hours, and after they had rested for 15 minutes in the supine position, the same observer (J.J.H.-S.) measured the vascular characteristics of the brachial and the common carotid and femoral arteries. A wall-tracking ultrasound system allowed to reproducibly ⁷ determine the vessel diameter during diastole and its change during the cardiac cycle ^{7,8}. depending on the vascular territory, the intra-observer coefficients of variation varied from 2.1 to 3.3% for diameter and from 9.2 to 12.8% for the changes in diameter ⁷. Simultaneously with the vascular measurements, blood pressure was recorded at 3-minute intervals at the left upper arm with a semi-automated device (Dinamap 845, Applied Medical Research Corporation, Tampa, FL). We extrapolated the local blood pressure in the common carotid and femoral arteries from the simultaneously measured brachial blood pressure by calibration of the arterial distension curves ^{9,10}. We then calculated the compliance and distensibility coefficients as the absolute and relative changes during the cardiac cycle in the cross-sectional area of the vessel per unit change in the local pulse pressure ⁷. From the delay between the R-wave trigger of the electrocardiogram and the 10% level of the ascending limb of the distension waveform in the carotid and femoral arteries, the ultrasound system also computed the carotid-femoral transit time ^{11,12}. From this interval and from the distance between the sternal notch and the site of the femoral measurements ^{11,12}, the carotid-femoral pulse wave velocity was calculated as an estimate of aortic stiffness ^{11,12}. For statistical analysis, we averaged the vascular measurements over 15 cardiac cycles.

Statistical analysis

The FSH distribution was logarithmically transformed. For between-group comparisons we used Student's t-test, analysis of variance and the χ^2 -statistic. We compared menopausal groups only if the P-value in the analysis of variance was less than 0.15. The statistical methods also included single and multiple linear regression. Regression slopes were compared across groups using the single model approach ¹³. Although we hypothesized that menopause would be associated with increased vascular stiffness, we used only 2-sided tests.

Results

Characteristics of the Subjects

The cohort had been followed for a median time of 5.2 years (range, 3.8-8.3 years) and included 166 premenopausal and 149 menopausal women. Of the latter group, 44 perimenopausal subjects had reached menopause during follow-up and 105 were postmenopausal since baseline. The serum FSH concentration (5th-95th percentile interval) in the premenopausal women was 5 (0-41) U/L; in the perimenopausal and postmenopausal groups, these levels

were 64 (31-143) U/L and 57 (8-126) U/L, respectively ($P < 0.001$ versus premenopausal subjects). Peri- and postmenopausal women showed higher conventional and ambulatory blood pressures and were more obese and shorter than their premenopausal counterparts (Table 1); for blood pressure and body height comparable trends were observed in the male controls.

Table 1 Characteristics of 315 women and 315 control men at follow-up

	Pre (n=166)	Peri (n=44)	Post (n=105)	P
Women				
Follow-up (y)	5.2±0.5	5.3±0.7	5.2±0.6	.43
Age (y)	41.0±5.6	52.2±4.9	61.2± 6.3	<.001
Body height (cm)	161.8±6.3	160.7±7.3	158.3±6.7	<.001
Body mass index (kg/m ²)	24.7±4.7	27.1±5.8	28.4±6.2	<.001
Home blood pressure (mm Hg)				
SBP	117.0±13.2	125.8±16.3	135.7±20.1	<.001
DBP	75.8±9.2	80.6±9.8	81.8±10.6	<.001
24-hour blood pressure monitoring (mm Hg)				
SBP	113.0±9.1	114.1±10.6	121.3±12.4	<.001
DBP	69.3±6.8	70.0±8.9	71.5±7.0	.06
MBP	83.5±7.2	84.8±8.7	88.4±9.2	<.001
PP	43.8±5.6	44.1±7.1	49.8±8.3	<.001
Men				
Follow-up (y)	5.3±0.6	5.3±0.4	5.2± 0.5	.27
Age (y)	40.8±6.5	52.9±5.1	62.2±6.6	<.001
Body height (cm)	175.2±6.7	170.7±6.6	170.2±7.0	<.001
Body mass index (kg/m ²)	26.2±3.8	26.3±3.4	26.4±3.2	.95
Home blood pressure (mm Hg)				
SBP	126.2±14.2	135.0±21.4	132.5±17.8	<.001
DBP	80.9±10.3	84.2±11.3	79.4±10.2	.04
24-hour blood pressure monitoring (mm Hg)				
SBP	119.7±8.9	123.8±14.4	120.9±11.8	.08
DBP	73.2±7.3	75.9±8.0	72.4±7.7	.04
MBP	87.7±7.5	91.5±9.9	87.7±8.2	.02
PP	46.5±5.3	47.9±8.4	48.5±8.7	.08

Values are means±SD. P values for the differences across 3 menopausal groups and 3 strata of male controls were derived by analysis of variance. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP pulse pressure

Of the premenopausal women, 36 (22%) were on oral contraceptives. Hormonal replacement therapy was used by 2 (5%) perimenopausal and 6 (6%) postmenopausal women. In the peri- and postmenopausal groups, menopause had been surgically induced in 5 (11%) and 22 (21%) subjects, respectively. Of the pre-, peri- and postmenopausal women 12 (7.2%), 8 (18.2%) and

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41 (39.0%) were on antihypertensive drug treatment; among the control men, these numbers were 12 (7.2%), 9 (20.5%) and 29 (27.6%), respectively. Less than 1% of all participants were on nitrates or coronary vasodilators.

Among women, the pre-, peri- and postmenopausal groups included 75 (45.2%), 12 (27.3%) and 16 (15.2%) smokers and 15 (9.0%), 1 (2.3%) and 9 (8.6%) individuals who consumed alcohol. Among men, these numbers were 67 (40.4%), 15 (34.1%) and 38 (36.2%) and 68 (41.0%), 13 (29.5%) and 24 (22.9%), respectively. Female and male smokers smoked 15 (median) gram tobacco per day (5th-95th percentile interval, 5-30 g/day). Among drinkers, alcohol consumption was similar in both sexes, averaging 15 (5-60) g/day).

Vascular Properties and Menopause

In exploratory analyses we first plotted the mean 24-hour pulse pressure by menopausal class at follow-up and by fourths of the age distributions in women and men separately (Figure 1). Single regression analysis showed that in premenopausal women the 24-hour pulse pressure was not correlated with age ($r=0.07$; $P=0.40$), whereas in the corresponding male controls the latter association was negative ($r=0.30$; $P<0.001$) because of the age-related increase in the 24-hour diastolic pressure.⁴ In menopausal women ($r=0.37$; $P<0.001$) and matching male controls ($r=0.16$; $P=0.04$) pulse pressure widened with increasing age. The slope of the 24-hour pulse pressure on age was steeper in the menopausal women than in their premenopausal counterparts (0.428 vs (0.066 mm Hg per year; $P=0.003$) and than in the male controls (0.428 vs 0.188 mm Hg per year; $P=0.06$).

Figure 1. 24-hour pulse pressure determined by ambulatory monitoring. Values are unadjusted means $\pm$ SE by fourths of the age distributions in 166 premenopausal and 149 peri- or postmenopausal women and in similar numbers of control men matched with the women on age and body mass index.

Before any adjustment, the arterial diameters of the brachial and the common carotid and femoral arteries increased with menopause in women, while compliance and distensibility of the common carotid and femoral arteries decreased (Table 2). In male controls comparable differences were observed but only for the carotid artery (Table 2). In women and control men, the carotid-femoral pulse wave velocity rose across the menopausal strata.

After cumulative adjustment for age, 24-hour mean pressure, body mass index, antihypertensive drug treatment, smoking and the use of oral contraceptives or hormonal replacement therapy (Table 3), the carotid-femoral pulse wave velocity increased ($P=0.03$) with menopause in women. A similar trend was noted for the diameter of the common carotid artery ($P=0.13$).

After adjustment for confounders (Figure 2), postmenopausal women showed a greater carotid-femoral pulse wave velocity (7.77 vs 6.71 m/s; $P=0.02$) and had a slightly wider diameter of the common carotid artery (7.09 vs 6.79 mm; $P=0.07$) than their premenopausal counterparts. With similar adjustments, menopause was no longer significantly associated with the other vascular measurements (Table 3). In control men, after adjustment for age, mean 24-hour pressure, body mass index, antihypertensive drug treatment and smoking, there were no differences across the 3 control groups (Table 3).

Differences Between Premenopausal and Postmenopausal Subjects

Figure 2. Mean differences (SE) in the diameter of the common carotid artery (left) and in carotid-femoral pulse wave velocity (right) between premenopausal and postmenopausal women and between corresponding male controls. The differences (P-values given) were adjusted for age, 24-hour mean pressure, body mass index, intake of antihypertensive drugs, smoking and in women also for the use of oral contraceptives or hormonal replacement therapy.

Table 2 Vascular characteristics by menopausal class before adjustment for confounders

	n	Pre mean±SD	n	Peri mean±SD	n	Post mean±SD	P
Women							
Brachial artery							
D (mm)	125	3.52±0.44	35	3.71±0.64	76	3.87±0.55	<.001
CC (mm ² /kPa)	125	0.24±0.11	35	0.22±0.11	75	0.26±0.13	.28
DC (10 ⁻³ /kPa)	125	25.1±13.0	35	21.4±10.9	75	22.5±9.94	.15
Common carotid artery							
D (mm)	132	6.61±0.63	35	7.14±0.76	78	7.31±0.85	<.001
CC (mm ² /kPa)	125	0.87±0.25	35	0.73±0.27	74	0.65±0.18	<.001
DC (10 ⁻³ /kPa)	125	25.1±6.7	35	18.1±5.80	74	15.7±5.0	<.001
Femoral artery							
D (mm)	123	8.26±0.89	31	8.66±0.94	65	9.03±1.04	<.001
CC (mm ² /kPa)	116	0.51±0.22	30	0.47±0.24	63	0.44±0.22	.12
DC (10 ⁻³ /kPa)	116	9.68±4.52	30	8.07±4.02	63	7.12±3.82	<.001
Aorta							
PWV (m/s)	122	6.00±1.25	31	6.59±1.06	61	8.13±2.81	<.001
Men							
Brachial artery							
D (mm)	125	4.56±0.58	32	4.55±0.57	81	4.56±0.62	.99
CC (mm ² /kPa)	125	0.33±0.13	32	0.31±0.11	81	0.33±0.15	.60
DC (10 ⁻³ /kPa)	125	20.1±10.3	32	19.6±8.93	81	20.9±10.0	.78
Common carotid artery							
D (mm)	125	7.48±0.63	32	7.95±0.88	82	8.00±0.78	<.001
CC (mm ² /kPa)	125	1.08±0.33	32	0.93±0.37	80	0.80±0.32	<.001
DC (10 ⁻³ /kPa)	125	24.7±7.2	32	18.6±5.6	80	15.8±5.77	<.001
Femoral artery							
D (mm)	121	9.97±0.97	28	9.93±0.93	70	10.26±1.32	.16
CC (mm ² /kPa)	120	0.63±0.29	28	0.59±0.33	69	0.59±0.30	.64
DC (10 ⁻³ /kPa)	120	8.39±4.09	28	7.75±4.25	69	7.24±3.72	.16
Aorta							
PWV (m/s)	120	6.31±1.26	26	7.37±1.73	65	7.95±2.14	<.001

P values for the differences across 3 menopausal groups and 3 strata of male controls were derived by analysis of variance; D, diameter; DC, distensibility coefficient; CC cross-sectional compliance; PWV, pulse wave velocity.

Table 3 Vascular characteristics by menopausal class after adjustment for age and other confounders

	Pre	Peri	Post	P
Women				
Brachial artery				
D (mm)	3.63±0.07	3.62±0.10	3.65±0.09	.96
CC (mm ² /kPa)	0.26±0.02	0.24±0.02	0.26±0.02	.52
DC (10 ⁻³ /kPa)	24.6±1.7	23.0±2.3	25.8±2.2	.54
Common carotid artery				
D (mm)	6.79±0.10	7.10±0.14	7.09±0.13	.13
CC (mm ² /kPa)	0.76±0.03	0.78±0.04	0.81±0.04	.71
DC (10 ⁻³ /kPa)	21.5±0.8	19.9±1.1	21.6±1.0	.25
Femoral artery				
D (mm)	8.17±0.13	8.19±0.19	8.47±0.18	.37
CC (mm ² /kPa)	0.47±0.03	0.45±0.05	0.45±0.04	.92
DC (10 ⁻³ /kPa)	9.10±0.63	8.71±0.89	8.52±0.84	.88
Aorta				
PWV (m/s)	6.71±0.26	6.73±0.37	7.77±0.36	.03
Men				
Brachial artery				
D (mm)	4.57±0.08	4.49±0.11	4.44±0.10	.62
CC (mm ² /kPa)	0.32±0.02	0.28±0.03	0.29±0.02	.52
DC (10 ⁻³ /kPa)	19.7±1.4	19.0±1.8	19.7±1.7	.93
Common carotid artery				
D (mm)	7.75±0.10	7.88±0.13	7.73±0.12	.56
CC (mm ² /kPa)	0.99±0.04	1.01±0.06	0.96±0.06	.77
DC (10 ⁻³ /kPa)	21.4±0.8	20.7±1.1	20.8±1.0	.86
Femoral artery				
D (mm)	9.96±0.16	9.77±0.23	9.92±0.21	.75
CC (mm ² /kPa)	0.59±0.04	0.57±0.06	0.55±0.06	.85
DC (10 ⁻³ /kPa)	8.14±0.56	7.80±0.81	7.39±0.74	.74
Aorta				
PWV (m/s)	7.19±0.23	7.25±0.34	7.34±0.32	.93

Values are least square means (±SE), adjusted for age, 24-hour mean pressure, body mass index, intake of antihypertensive drugs, smoking and in women also for the use of oral contraceptives or hormonal replacement therapy. P values for the differences across 3 menopausal groups and 3 strata of male controls were derived by analysis of variance. For the number of subjects included in each statistic, see Table 2. D, diameter; DC, distensibility coefficient; CC cross-sectional compliance; PWV, pulse wave velocity.

Discussion

In previous cross-sectional³ and longitudinal⁴ population studies, we found that the slope of systolic blood pressure on age was steeper in postmenopausal than in premenopausal women. The present article builds on this experience^{3,4} and shows that after adjustment for age and other confounding factors, aortic pulse wave velocity was greater in postmenopausal women than in their premenopausal counterparts, whereas this observation could not be reproduced in control men. It is plausible that menopause, by increasing the stiffness of the aorta, may contribute to the rise in systolic blood pressure and pulse pressure, which occurs in middle-aged and older women and which in turn may lead to a slight dilatation of the common carotid artery.

A limitation of our study was its observational nature and the relatively small sample size. On the other hand, its population-based design increased its external validity. To the best of our knowledge, our study was among the first to ascertain the presence of menopause in a prospective manner. The same investigator performed all vascular measurements. Women were matched on age and rank of body mass index at baseline with men drawn from the same community. We used a conservative statistical approach by limiting the number of comparisons between the menopausal groups based on the P-values in the analysis of variance and by using 2-sided tests. Our present findings suggest that in women menopause is associated with a loss of aortic elasticity, over and above the effects of aging. In an earlier hospital-based cross-sectional study, 14 women (n=104) showed at the level of the common carotid artery increased and earlier arterial wave reflections than men (n=119), because of their shorter body height and greater aortic tapering. In line with our findings, aortic pulse wave velocity rose with age in both sexes, but the increase was steeper in postmenopausal women than in age-matched men¹⁴. In premenopausal women greater distensibility of the brachial and femoral arteries partially compensated for the effects of shorter body height and enhanced aortic tapering, but after menopause this compensatory mechanism disappeared¹⁴. In the present population study, the analyses were adjusted for body mass index, hence for the inverse of body height (squared), but not for aortic tapering.

Several studies are in line with the present findings. Gangar et al⁵ found that the pulsatility index of the internal carotid artery was inversely correlated with the time elapsed since the last menstrual bleeding and that estrogen replacement therapy normalized the raised pulsatility index¹⁵. Westendorp et al found a decrease in distension of the common carotid artery in postmenopausal women compared to premenopausal women¹⁶. In the ascending aorta, Pines et al¹⁷ demonstrated a gradual decline in Doppler-derived peak flow velocity, flow velocity integral and mean flow acceleration in women who went through menopause. In an earlier study¹⁸ the same authors had shown that hormonal replacement therapy produced a significant improvement in these aortic flow measurements. Karpanou et al¹⁹ noticed that in hypertensive women reaching natural menopause, compared with age-matched hypertensive controls, aortic root function abruptly deteriorated as evidenced by significant declines in the distensibility and the cross-sectional compliance and by a rise in the aortic stiffness index¹⁹. Other studies are in keeping with our findings, but did not correct for the level of blood pressure²⁰⁻²² or reported that withdrawal of hormonal replacement therapy for 4 weeks resulted in a decrease of systemic arterial compliance and an increase in pulse wave velocity in the femoralis-dorsalis pedis region, but not in the aorto-femoral territory²².

Recent studies using ambulatory monitoring²³⁻²⁶ or automated blood pressure

self-measurement ²⁷ are in agreement with the hypothesis that estrogen deprivation, either at the onset of menstruation ²⁷ or in non-substituted postmenopausal normotensive ²⁴⁻²⁶ or hypertensive ²³ women, may increase blood pressure. Estrogens change the loading conditions on the elastin or collagen fibers or alter the structure of the vessel wall. Experiments in laboratory animals proved that estrogens dilate the large arteries ^{28,29}. In peri- and postmenopausal women ³⁰⁻³² they widen the smaller resistance vessels by mechanisms that include the protection of endothelial function ³¹ the potentiation of nitric oxide release ^{30,32} and the modulation of sympathetic reactivity ^{25,33}. Estrogens may also influence the visco-elastic properties of the arterial wall by changing the relative proportions of collagen and elastin ³⁴ by inhibition of smooth muscle cell proliferation, or by the prevention of atherosclerotic stiffening ³⁵. Menopause does not occur as a sudden event but as a continuous transition from a regular menstrual cycle to ovarian failure ². Thus, estrogen deficiency or hormonal replacement therapy may initially induce functional alterations, while structural vascular changes are more likely to contribute to long-term effects. For instance, Cohn et al ³⁶ found that in postmenopausal women with documented atherosclerosis, compared to healthy postmenopausal controls, oscillatory but not capacitive systemic arterial compliance was reduced. In conclusion, menopause per se may affect the stiffness of the aorta and the diameter of the common carotid artery. Estrogen deficiency may therefore contribute to the rise in systolic blood pressure and pulse pressure in women beyond age 50.

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CHAPTER 6

Obesity, fat distribution and vessel wall properties

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Abstract

Obesity is a well-known independent risk factor for the development of cardiovascular disease. Compliance (CC) and distensibility (DC) are wall properties of large arteries, which may play a role in cardiovascular disease. The purpose of this study was to investigate the relation between large artery wall properties and measures of obesity, such as body mass index (BMI), waist to hip ratio (W-H ratio) and thickness of skinfold. Since body height contributes to BMI, the effects of height were analysed separately.

In a population sample of 250 men (M) and 243 women (F), age between 20-79 years, diameter, DC and CC of the elastic aorta and common carotid artery (CCA) and muscular brachial (BA) and femoral arteries (FA) were measured with an echo-tracking device. The effects of height, body mass index (BMI), waist-to-hip ratio (W-H ratio) and skinfold thickness were assessed, adjusted for confounding factors.

In both sexes height was positively ($p < .05$) related to diameter of the CCA and FA. Also in both sexes height was positively related to carotid artery CC ($p < .05$), whereas at the femoral artery this positive relation was present only in men ($p < .01$). BMI was positively ($p < .01$) related to diameter of the CCA, BA and FA. Obesity was not significantly related to aortic stiffness. Except for carotid artery DC in women, BMI was negatively ($p < .05$) related to DC of CCA, BA and FA. In men, BMI was also negatively related to CC of the BA ($p < .05$) and FA ($p < .05$). An increased waist-to-hip ratio, i.e. an android body habitus, does not seem to be of importance for DC and CC in women. In men, it was negatively related to femoral artery DC and CC ($p < .01$). Skinfold thickness was negatively related to brachial artery DC in women ($p < .001$).

In conclusion the present study confirmed that height is a determinant of the buffering capacity of large arteries. The main findings of the study are that associations between obesity and arterial wall properties depend on the index of obesity, gender and the vascular territory. The majority of associations are found with BMI. BMI-based obese subjects have a larger arterial diameter and stiffer arteries in both sexes. Waist to hip ratio does not appear to be of importance in women, but in men it is associated with a lower femoral artery distensibility and compliance. Skinfold thickness is negatively associated with brachial artery distensibility in women, whereas it does not appear to be of importance in men.

Introduction

Obesity, generally defined as a body mass index greater than 27 kg/m² or a body weight greater than 120% of ideal, is common in Westernized societies with an overall prevalence of 30%¹. Obesity is a well-known independent risk factor for the development of cardiovascular disease^{2,3}. One of the possible targets of obesity-related risk is a change in vascular function.

Compliance and distensibility are vessel wall properties of large arteries, which might be important in the development of cardiovascular disease⁴. Compliance, defined as the absolute change in volume per unit of pressure ($\Delta V/\Delta P$), reflects the buffering capacity of the arterial system. Distensibility, defined as the relative change in volume per unit of pressure ($(\Delta V/V)/\Delta P$), reflects the elastic properties of the wall.

Little is known about the relation between obesity and vessel wall properties of large arteries. The few studies investigating the relation between obesity and large artery properties show different results⁵⁻¹⁰. This could be due to different techniques, small number of subjects, the involvement of different arteries and different definitions of obesity. Obesity can be expressed in different ways: body mass index (BMI), waist-to-hip ratio and thickness of skinfold. These indices do not describe the same entity. For example waist-to-hip ratio can differ substantially between two subjects with the same BMI, indicating a difference in fat distribution. The pattern of fat distribution itself also seems to add in the cardiovascular risk^{11,12}. Skinfold thickness is a measure of subcutaneous fat.

The aim of the present study was to investigate the relation between indices of obesity (BMI, waist-to-hip ratio and thickness of skinfold) and large artery wall properties of the aorta, common carotid, brachial and femoral arteries in a population sample. Since body height contributes to body mass, the relation between height and large artery wall properties was also studied.

Methods

Six hundred and fourteen people from a random population sample¹³ took part in vascular measurements (chapter 2). Of these participants 121 subjects were not included in the final analysis, because the necessary data were not complete, so the number of subjects finally considered in the analysis totalled 493 subjects (250 men and 243 women).

The cardiovascular examinations took place at a locally organised clinic. All participants were asked to refrain from smoking, caffeine containing beverages and heavy exercise for at least 3 hours before being examined. Data of systolic (SBP) and diastolic blood pressure (DBP) are mean of five measurements, measured conventionally with a sphygmomanometer. Mean blood pressure (MBP) was calculated as $(2 \times \text{DBP} + \text{SBP})/3$. A standardized questionnaire gave insight into their current health status, smoking and drinking habits and intake of drugs. Height and weight were measured. Body mass index (BMI) was calculated as $\text{weight}/\text{height}^2$. Waist circumference was measured with a tape measurer midway between the lower rib and the iliac crest. Hip circumference was measured at the point yielding maximum circumference over the buttocks. Waist-to-hip ratio (W-H ratio) was used as an indicator of centrally localized body fat distribution. Skinfold thickness, a measure of subcutaneous fat, was measured on the left arm, halfway between the upper arm, with a skinfold caliper (British Indicators LTD). After 15 minutes of supine rest in a quiet room vessel wall properties of the right elastic common carotid artery (CCA) and right muscular femoral (FA) and brachial arteries (BA) were measured with a vessel wall movement detector system¹⁴. The procedure and formulae

have been described earlier ¹⁵ (chapter 2).

With the vessel wall movement detector system also carotido-femoral transit time of the pulse wave (T) was recorded ¹⁶. The length of the carotido-femoral segment (L_{ao}) was measured with a tape measurer ¹⁷. From length and transit time, the average pulse wave velocity (PWV) in this segment was calculated ¹⁸. Pulse wave velocity is related to arterial distensibility (DC) by the formula: $PWV = \sqrt{1/\rho DC}$ (Moens Korteweg ^{19,20}) (ρ =blood density)

Database management and statistical analyses were performed with the SAS software (The SAS Institute Inc., Cary, North Carolina). The methods of analysis included Mann-Whitney-U tests for continuous variables and Chi-square tests for the dichotomous parameters. To test the influence of height, an analysis of covariance was used with factors for age, gender, mean arterial pressure, pulse rate, smoking, use of alcohol, total cholesterol and antihypertensive treatment. Factors with a p-value > 0.10 were dropped from the model. In addition, the same analysis with height as an additional confounding factor was repeated to investigate the effect of BMI, waist-to-hip ratio and skinfold thickness. To investigate which index of obesity was best related to large artery wall properties, an analysis of covariance with all indices of obesity was done. F values were used to show the importance of the factors to explain variance. Data are presented as mean $\pm$ SD for demographic values and mean $\pm$ SE for regression coefficients. A p-value < 0.05 was considered as statistically significant. The study was approved by the ethics committee of Leuven University and all subjects gave their written informed consent.

Results

Table 1. Demographic characteristics of the study population

	male	female	p
n	250	243	
Age (years)	50.4 $\pm$ 13.0	49.8 $\pm$ 12.3	.61
Body mass index (kg/m ²)	26.0 $\pm$ 3.3	25.2 $\pm$ 4.0	.005
Waist/Hip ratio	0.89 $\pm$ 0.09	0.83 $\pm$ 0.12	<.001
Skinfold	1.24 $\pm$ 0.47	2.01 $\pm$ 0.62	<.001
Blood Pressure (mmHg) [‡]			
Systolic	132 $\pm$ 15	128 $\pm$ 19	.003
Diastolic	84 $\pm$ 10	81 $\pm$ 10	<.001
Heart rate (bpm)	61 $\pm$ 10	64 $\pm$ 10	.001
Smokers	84 (33.6 %)	75 (30.9%)	.52
Drinking alcohol	85 (34%)	28 (11.5%)	<.001
Antihypertensive treatment	38 (15.2%)	38 (15.6%)	.89

Results are mean $\pm$ SD or number of subjects with percentage in brackets. [‡] Measured with a sphygmomanometer in sitting position. bpm, beats/minute

The 250 men and 243 women were between 26 and 79 years old (Table 1). Men had a larger body mass index, W-H ratio and blood pressure, while women had a larger skinfold thickness and heart rate. One hundred and fifty-nine participants smoked a median of 15 cigarettes per

day (range 1-70). One hundred and thirteen subjects drank a median of 20 g alcohol per day (range 1-196). A total of 76 subjects were taking antihypertensive treatment either in monotherapy or in combination. Vessel wall properties in this population are described in Table 2.

Table 2. Vessel wall properties in the study population

	male	female	p
PWV Aorta ¹	7.0±1.9	6.5±1.7	.002
Diameter (mm)			
CCA	7.71±0.79	6.92±0.78	<.001
BA	4.64±0.63	3.61±0.62	<.001
FA	10.06±1.11	8.49±1.09	<.001
Distensibility Coefficient (10 ⁻³ /kPa)			
CCA	21.4±8.4	21.9±8.6	.62
BA	20.8±10.0	24.4±11.8	<.001
FA	7.9±4.1	9.0±4.7	.012
Compliance Coefficient (mm ² /kPa)			
CCA	1.04±0.32	0.78±0.31	<.001
BA	0.33±0.16	0.21±0.16	<.001
FA	0.63±0.32	0.53±0.16	<.001

Results are mean±SD. ¹ Measurements available in 464 subjects. PWV: pulse wave velocity, CCA common carotid artery, FA common femoral artery, BA brachial artery

In both sexes, after adjustment for age, mean arterial pressure, pulse rate, smoking, use of alcohol, total cholesterol and antihypertensive treatment, height was positively related to carotid and femoral artery diameter and only in women to brachial artery diameter (Table 3).

Height was not related to arterial distensibility. In both sexes height was positively related to carotid artery CC, while only in men there was also a positive relation with femoral artery CC. In both sexes, after adjustment for the factors mentioned above, BMI was positively related to arterial diameter (Table 4). Except for carotid artery DC in women, BMI was negatively related to DC of all arteries. There was no relation with PWV of the aorta. Only in men, BMI was negatively related to CC of the FA and BA. W-H ratio was not related to vessel wall properties in women. In men W-H ratio was positively related to diameter of the CCA and BA, negatively related to DC of the BA and FA and to CC of the FA. Thickness of skinfold was in both sexes positively related to carotid artery diameter. In women skinfold thickness was negatively related to brachial artery DC. Skinfold thickness did not relate to arterial compliance in both sexes.

Table 5 shows the importance of the different indices of obesity as determinants of the large artery wall properties. W-H ratio was the more important determinant of FA compliance in men, whereas skinfold thickness was the most important determinant of BA distensibility in women. BMI was the most important determinant of all other arterial wall properties, which were related to obesity.

Table 3. Relation between arterial wall properties and height, after adjustment ¹

Slope ² (height (cm) ⁻¹).10 ²	male	female
PWV Aorta ³	n.s.	n.s.
Diameter (mm)		
CCA	1.6±0.7*	1.6±0.7*
BA	n.s.	1.2±0.5*
FA	4.1±1.0***	4.3±0.9***
Distensibility Coefficient (10 ⁻³ /kPa)		
CCA	n.s.	n.s.
BA	n.s.	n.s.
FA	n.s.	n.s.
Compliance Coefficient (mm ² /kPa)		
CCA	0.9±0.3***	0.5±0.2*
BA	n.s.	n.s.
FA	0.8±0.3**	n.s.

¹ adjustment for age, mean arterial pressure, heart rate, smoking, use of alcohol, total cholesterol and antihypertensive treatment. ² Regression coefficients ± SE. ³ Measurements available in 464 subjects. PWV pulse wave velocity, * p < 0.05, ** p < 0.01, *** p < 0.001, n.s. not significant.

Discussion

This is the first study investigating the association between three indices of obesity and wall properties of different arterial territories. Since body height contributes to body mass, we also analysed the effects of height separately.

The present study showed taller subjects have a higher compliance of the carotid and femoral arteries. This larger arterial compliance may contribute to a smaller cardiac afterload in taller men. This could explain why short men are more prone to ischemic heart disease ²¹. This larger compliance was the result of a larger diameter in taller subjects, which was also described by others ^{22,23}. This result could also partly explain the difference in arterial diameter between men and women, since most women are shorter than men.

Obesity can be defined in different ways. One of the most used indices is BMI. In the present study, the majority of associations between obesity and vessel wall properties were found for BMI.

In accordance with others ^{8,9,24}, in the present study, arterial diameter of all arteries studied was increased in subjects with a higher BMI. This can be the result of the hyperdynamic circulation in obese subjects; obese subjects have a higher cardiac output, stroke volume and circulating blood volume and lower peripheral resistance ²⁵⁻²⁸. This hyperdynamic circulation may cause flow-dependent vasodilation, leading to a larger arterial diameter.

BMI was negatively related to brachial and femoral artery DC in both men and women and carotid artery DC in men. However, like previous studies ^{5,7}, the present study did not find a relation between BMI and aortic distensibility. The exact cause of this higher arterial stiffness is not known. Several explanations could be hypothesized: (1) It could be a passive phenomenon, namely a consequence of the larger diameter in obese subjects. (2) The increased stiff-

ness could be caused by an increased size of adipocytes, which may affect the transmural pressure ⁶. (3) The increased stiffness could also be due to early atherosclerotic disease. It's however not clear whether a direct relation between obesity and atherogenesis exists. A recent report described an association between adipose tissue and C reactive protein, an inflammatory mediator, which may be directly involved in atherogenesis ²⁹. (4) It could also be an indirect relation; other factors, which often coincide with obesity, like hyperinsulinemia might be involved ^{7,30-32}. A decrease in DC may increase wall stress, which may lead to atherogenesis and cardiovascular events ³³.

Arterial compliance is determined by arterial diameter and distensibility. The increase in diameter in BMI-based obese subjects was often accompanied by a decrease in arterial distensibility. The net result was no change in arterial compliance of all three arteries in women. In men it resulted in a smaller arterial compliance of the muscular brachial and femoral arteries.

The associations between arterial wall properties and obesity, discussed so far, were based on obesity defined as a higher BMI. BMI is however not only an estimate of fat, it also comprises musculoskeletal mass. This means subjects with a high BMI can also be very well trained, non-obese subjects. Other estimates of obesity are waist-to-hip ratio and thickness of skinfold. The waist-to-hip ratio discriminates between fat deposited in the upper (android) and lower trunk (gynaecoid). Lately several reports showed that subjects with an android fat distribution have an increased cardiovascular risk, independent of BMI ^{11,12}. In the present study, waist-to-hip ratio was not significantly related to large artery wall properties in women. In men waist-to-hip ratio was negatively related to femoral artery distensibility and compliance. This is in line with an earlier study describing a negative relation between distensibility of the abdominal aorta and visceral fat accumulation ³⁴. Of all three indices of obesity, waist-to-hip ratio was also the most important determinant of femoral artery DC and CC in men, independent of BMI. The reason for this lower distensibility and compliance of the abdominal aorta and femoral artery is not clear. It has been suggested that it could be caused by the pressure of fat, surrounding the artery ³⁴.

Another method to assess fat distribution is by measuring skinfold thickness. In women thickness of skinfold was negatively related to brachial artery DC. Of the three obesity-indices studied, skinfold thickness was also the most important determinant of brachial artery DC in women. The cause of this is not clear, like for waist-to-hip ratio local pressure of fat might be hypothesized. This parameter does not seem to be of importance in determining large artery distensibility and compliance in men.

In conclusion, the present study confirmed that height is a determinant of the buffering capacity of large arteries. The main findings of the study are that associations between obesity and arterial wall properties depend on the index of obesity, gender and the vascular territory. The majority of associations are found with BMI. BMI-based obese subjects have a larger arterial diameter and stiffer arteries in both sexes. Fat distribution assessed by waist-to-hip ratio (an android body habitus) does not appear to be of importance in women, but in men it is associated with a lower femoral artery distensibility and compliance. Skinfold thickness is negatively associated with brachial artery distensibility in women, whereas it does not appear to be of importance in men. Whether the described effects are caused by obesity itself, i.e. local pressure of fat, or by concomitant factors like hyperinsulinemia and whether these changes are reversible remains to be further investigated.

Table 4. Relation between large artery wall properties and BMI, waist-hip ratio and skinfold thickness, after adjustment for confounding factors¹

	Men		Women	
	BMI kg/m ²	W-H ratio	BMI kg/m ²	W-H ratio
³ Slope.10 ²				
Pulse Wave Velocity (m/s) ²	n.s.	n.s.	n.s.	n.s.
Aorta				
Diameter (mm)				
CCA	4.4±0.7**	235.7±77**	21.6±11.2*	13.8±6.8*
BA	7.1±1.0***	296.5±59.6***	3.3±0.8***	n.s.
FA	6.8±2.1***	n.s.	5.6±1.4***	n.s.
Distensibility (10 ⁻³ /kPa)				
CCA	-21.1±10.3*	n.s.	n.s.	n.s.
BA	-82.4±17.6***	-2992±1000**	-46.3±18.3*	-327.7±11.9**
FA	-25.6±7.3***	-1162±4007**	-14.6±6.9*	n.s.
Compliance (mm ² /kPa)				
CCA	n.s.	n.s.	n.s.	n.s.
BA	-0.5±0.2*	n.s.	n.s.	n.s.
FA	-1.2±0.6*	-102.1±29.4***	n.s.	n.s.

¹ age, mean arterial pressure, heart rate, **height**, smoking, use of alcohol, total cholesterol and antihypertensive treatment.² Measurements available in 464 subjects. ³ Regression coefficients ± SE. PWV pulse wave velocity, CCA common carotid artery, BA brachial artery, FA femoral artery, BMI body mass index, W-H ratio waist to hip ratio, * p < 0.05, ** p < 0.01, *** p < 0.001, n.s. not significant.

Table 5. Covariance analysis with BMI, waist-hip ratio and skinfold thickness together, after adjustment for confounding factors¹

	Common Carotid Artery			Brachial Artery			Femoral Artery			Aorta	
	D (mm)	DC 10-3/kPa	CC mm2/kPa	D (mm)	DC 10-3/kPa	CC mm2/kPa	D (mm)	DC 10-3/kPa	CC mm2/kPa	PWV m/s	
Men											
R2	0.26	0.63	0.45	0.22	0.18	0.08	0.16	0.19	0.19	0.43	
Fvalues											
BMI	4.17	4.20	n.s.	30.02	22.02	3.93	18.11	12.25	n.s.	n.s.	
W-H ratio	n.s.	n.s.	n.s.	5.53	n.s.	n.s.	6.93	n.s.	12.03	n.s.	
Skinfold	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	
Women											
R2	0.31	0.61	0.38	0.26	0.18	0.08	0.33	0.23	0.11	0.42	
Fvalues											
BMI	4.13	n.s.	n.s.	17.27	5.14	n.s.	15.56	4.49	n.s.	n.s.	
W-H ratio	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	
Skinfold	n.s.	n.s.	n.s.	n.s.	8.58	n.s.	n.s.	n.s.	n.s.	n.s.	

¹ age, mean arterial pressure, heart rate, **height**, smoking, use of alcohol, total cholesterol and antihypertensive treatment. F value is shown if factor was significant in covariance analysis. PWV pulse wave velocity, D diameter, DC distensibility coefficient, CC cross-sectional compliance.
* p < 0.05, ** p < 0.01, *** p < 0.001, n.s. not significant.

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CHAPTER 7

Relation between insulin resistance and large artery properties

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Abstract

Changes in arterial wall properties, compliance and distensibility, can be related to cardiovascular disease. There is also evidence for a link between insulin resistance, hyperinsulinemia and macrovascular disease. Data on the relation between insulin resistance and large artery wall properties are scarce.

In a population sample of 463 men and women, age between 20-79 years and fasting glucose below 6.0 mmol/l, diameter, distensibility coefficient and cross-sectional compliance of the elastic common carotid artery and muscular brachial and femoral arteries were measured with an echo-tracking device. Distensibility of the aorta was measured using pulse wave velocity. The effects of insulin resistance, insulin and glucose were assessed, adjusted for mean blood pressure, pulse rate, body mass index, total cholesterol, smoking, alcohol intake and antihypertensive treatment.

In women insulin resistance, insulin (except for femoral artery diameter) and glucose were not related to large artery wall properties. In men, without adjustment for body mass index, insulin resistance was positively related to carotid ($p<.001$) and brachial artery ($p<.01$) diameter, and negatively related to brachial ($p<.05$) and femoral artery ($p<.01$) distensibility and femoral artery compliance ($p<.01$). After adjustment for BMI, insulin resistance was positively related to carotid artery diameter ($p<.001$) and negatively ($p<.01$) related to femoral artery compliance. The effects of insulin were comparable to the effects of insulin resistance. Glucose was negatively ($p<.05$) related to brachial artery compliance. BMI affected more arterial wall properties than insulin resistance.

In conclusion, the relation between insulin resistance and large artery wall properties is gender-dependent. In women, insulin resistance is not related to any of the large artery wall properties. The relation between insulin resistance and large artery wall properties in men depends on the vascular territory: compliance of the femoral artery was most affected by insulin resistance. Alteration of large artery properties in subjects with insulin resistance is probably due to increased insulin levels. Altered arterial wall properties in BMI-based obese subjects can only in part be attributed to an increase in insulin resistance.

Introduction

Changes in vessel wall properties of large arteries (compliance and distensibility) might play a role in the development of cardiovascular disease ¹. A decrease in compliance (change in volume per unit of pressure) increases cardiac afterload and the risk of cardiac hypertrophy ^{2,4}. A decrease in distensibility (relative change in volume per unit of pressure) is associated with an increased risk of arterial wall damage, an important feature in atherosclerotic disease ⁵.

Vascular disease is more frequently seen in patients with non-insulin dependent diabetes mellitus and even in prediabetic and insulin resistant subjects ⁶⁻⁹.

Insulin resistance is defined as a subnormal biological response to a given concentration of insulin. Insulin resistance can lead to (non-insulin dependent) diabetes mellitus, but is also found in apparently healthy subjects who maintain normal glucose levels by marked elevations of insulin secretion ¹⁰, causing hyperinsulinemia.

The relation between insulin and large artery wall properties has been studied ¹¹⁻¹⁴, showing no ¹⁴ or a positive relation ^{11,13,15,16} between insulin and arterial stiffness. It is not yet clear whether a relationship exists between insulin resistance and altered vessel wall properties. Until now, only one relatively small study described the relation between arterial stiffness of the carotid and femoral artery and insulin sensitivity in healthy subjects ¹⁶. There is however no study reporting the relation between insulin resistance and arterial wall properties at different arterial sites in a population.

The aim of the present study was to investigate the influence of insulin resistance (InsR) on large artery wall properties of different large arteries in a population sample of presumed healthy subjects with a normal fasting serum glucose level. In addition, we tried to reveal whether the effect was caused by insulin resistance per se or could be related to the influence of other factors like insulin, glucose or obesity. Since the relation between insulin and arterial stiffness seems to be gender-dependent ^{11,16}, men and women were analysed separately.

Methods

This study is also part of the population study ¹⁷. Of the participating subjects, 614 took part in the vascular measurements. One hundred and fifty one subjects were removed from the data base, because fasting glucose was equal or higher than 6 mmol/l (n=14) or insulin resistance was not estimated (n=17) or vascular measurements were not available at each of the three arteries studied. The number of subjects finally considered in the analysis totalled 232 men and 231 women.

Vessel wall properties of the right elastic common carotid artery (CCA) and right muscular femoral (FA) and brachial arteries (BA) were measured with a vessel wall movement detector system ¹⁸ according to a previously described protocol ¹⁹ (chapter 2). During these measurements blood pressure and pulse rate were recorded every 3 minutes with an appropriate sized cuff at the left arm with a semiautomated device (Dinamap; Critikon, Tampa, Florida). The mean of these recordings (at least 10) was taken as the subject's reading. Brachial artery pulse pressure was defined as systolic minus diastolic blood pressure. Pulse pressure at CCA and FA were calculated by calibration of the distension curves (chapter 2). With the vessel wall movement detector system it is also possible to measure carotido-femoral transit time of the pulse wave (T) ²⁰. The length of the carotido-femoral segment (L_{ao}) was measured with a tape measurer. From length and transit time, pulse wave velocity (PWV) of the aorta was calculated. Pulse wave velocity is related to arterial distensibility (DC) by the formula:

Large artery properties: effect of insulin resistance

$$PWV = \sqrt{1/\rho DC} \quad (\text{Moens Korteweg}^{21,22}) \quad (\rho = \text{blood density})$$

Subjects were visited at home after an overnight fast for venous blood sampling for glucose and insulin. Glucose was measured by a glucose oxidase method, plasma insulin levels were measured by RIA. Insulin resistance (InsR) was assessed by calculating the insulin resistance index^{23,24}:

$$\text{InsR} = [\text{Insulin}]/22.5 \times e^{-\ln[\text{Glucose}]}$$

For database management and statistical analyses the SAS software package (The SAS institute Inc., Cary, North Carolina) was used. The statistical models of the raw data of insulin resistance fitted better than the logarithmic transformed data. The methods of analysis included Mann-Whitney-U tests for continuous variables and Chi-square tests for the dichotomous parameters. To test the relation between insulin, glucose, insulin resistance and vessel wall properties, analyses of covariance were used. From the literature it is known that vessel wall properties are influenced by different factors like age, blood pressure and antihypertensive treatment²⁵⁻²⁷. Thus when studying the relation between InsR and large artery properties it is important to adjust for these factors. Adjustment was done for age, blood pressure, heart rate, antihypertensive treatment, total cholesterol, smoking and use of alcohol. Factors with a p-value > 0.10 were dropped from the model. Data are presented as mean ± SD for demographic values and mean ± SE for regression coefficients. A p-value < 0.05 was considered as statistically significant. The study was approved by the ethics committee of Leuven University and all subjects gave their written informed consent.

Results

Table 1. Characteristics of the study population

	Men	Women	p
n	232	231	
Age (years)	50.5±11	49.7±12.3	.55
Body mass index (kg/m ²)	25.9±3.4	25.1±4.0	.005
Blood Pressure (mmHg)#			
Systolic	131±14	128±19	.001
Diastolic	84±11	80±10	<.001
Pulse rate (bpm)	61±9	64±9	.001
Smokers	82 (35.3 %)	72 (31.2 %)	.34
Drinking alcohol	82 (35.3 %)	24 (10.4 %)	<.001
Antihypertensive treatment	34 (14.7 %)	35 (15.2 %)	0.88
Glucose (mmol/l)	4.9±0.5	4.8±0.5	<.001
Insulin (u/l)	8.2±4.4	8.2±4	.69
Total cholesterol (mmol/l)	5.7±1.0	5.7±0.8	.68
Insulin resistance	1.8±1.1	1.8±0.9	.65

Results are mean±SD or number of subjects with percentage within brackets. # Measured with a sphygmomanometer in sitting position. bpm beats/minute

Population Characteristics

Age ranged from 26 to 79 years (Table 1). One hundred and fifty four subjects currently smoked a median of 14 cigarettes a day (range 1-62). Alcohol drinkers consumed a median of 14 g a day (range 1-196). Fasting glucose ranged from 3.8 to 5.9 mmol/l, fasting insulin from 2.2 to 26.9 u/l. Vessel wall properties in this population are described in Table 2.

Table 2. Vessel wall properties in the population

	Men	Women	p
PWV aorta (m/s) ¹	7.0±2.0	6.6±1.8	.002
Diameter (mm)			
CCA	7.69±0.82	6.88±0.81	<.001
BA	4.57±0.60	3.64±0.55	<.001
FA	10.05±1.09	8.53±1.01	<.001
Distensibility Coefficient (10 ⁻³ /kPa)			
CCA	21.3±8.2	22.2±8.6	.35
BA	20.8±10.0	24.6±12.0	<.001
FA	8.0±4.2	8.9±4.6	.02
Compliance Coefficient (mm ² /kPa)			
CCA	0.97±0.35	0.80±0.26	<.001
BA	0.33±0.13	0.25±0.11	<.001
FA	0.62±0.31	0.49±0.22	<.001

Results are mean±SD. ¹Measurements available in 447 subjects. PWV pulse wave velocity, CCA common carotid artery, BA brachial artery, FA femoral artery.

Insulin resistance

Unadjusted data are shown in Table 3a for men and Table 3b for women. InsR did not relate to arterial diameter in women, while in men there was a positive relation between InsR and carotid (p<.001) and brachial artery (p<.01) diameter (Table 3). In both sexes a positive relation was found between InsR and PWV of the aorta (p<.01) and a negative relation with brachial (p<.01) and femoral (p<.01) artery DC. The same was found for carotid artery DC in men (p<.05). InsR was negatively related (p<.01) to femoral artery CC in both sexes and brachial artery CC in women (p<.05).

InsR often appears in obese subjects. Also in the present study, InsR was related to BMI (correlation 0.40, p < .001). By adjusting for BMI, we might underestimate the relation between InsR and large artery properties. We therefore performed two analyses: one adjusting for all confounding factors except for BMI and one with adjustment for all factors including BMI.

Without adjustment for BMI, in women, there were no significant relations between InsR and large artery wall properties. In men InsR was positively related to carotid (p<.001) and brachial artery (p<.01) diameter. InsR was or tended to be negatively related to distensibility of the aorta (p=.06), BA (p<.01) and FA (p<.05). There was also an inverse relation (p<.01) between InsR and femoral artery compliance and a trend for a negative relation with brachial artery compliance (p=.07).

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Table 3a Men: relation with Insulin Resistance, before and after adjustment ¹.

Slope ²	InsR Unadjusted	InsR Adjusted, without BMI	InsR Adjusted, with BMI	BMI (kg/m ²) Adjusted
PWV (m/s)				
Aorta ³	0.34±0.12 **	0.18±0.10+	0.18±0.10+	n.s.
Diameter (mm)				
Carotid artery	0.18±0.05 ***	0.17±0.05 ***	0.17±0.05 ***	0.041±0.014 **
Brachial artery	0.10±0.04 **	0.10±0.04 **	n.s.	0.067±0.011 ***
Femoral artery	n.s.	n.s.	n.s.	0.061±0.021 **
DC (10 ⁻³ /kPa)				
Carotid artery	-1.10±0.51 *	n.s.	n.s.	-0.23±0.10 *
Brachial artery	-1.83±0.61 **	-1.69±0.58 **	n.s.	-0.79±0.18 ***
Femoral artery	-0.69 **	-0.51±0.24 *	n.s.	-0.25±0.08 **
CC (mm ² /kPa)				
Carotid artery	n.s.	n.s.	n.s.	n.s.
Brachial artery	-0.015±0.008+	-0.013±0.008+	n.s.	-0.0043±0.0016 *
Femoral artery	-0.05±0.019 **	-0.051±0.018 **	-0.051±0.018 **	-0.013±0.0014 *

Table 3b Women: relation with Insulin Resistance, before and after adjustment ¹.

Slope ²	InsR Unadjusted	InsR Adjusted, without BMI	InsR Adjusted, with BMI	BMI (kg/m ²) Adjusted
PWV (m/s)				
Aorta ³	0.36±0.13 **	n.s.	n.s.	n.s.
Diameter (mm)				
Carotid artery	n.s.	n.s.	n.s.	0.20±0.10 *
Brachial artery	0.072±0.039+	n.s.	n.s.	0.038±0.009 ***
Femoral artery	n.s.	n.s.	n.s.	0.064±0.015 ***
DC (10 ⁻³ /kPa)				
Carotid artery	n.s.	n.s.	n.s.	n.s.
Brachial artery	-2.54±.83 **	n.s.	n.s.	-0.49±0.20 *
Femoral artery	-0.87±0.32 **	n.s.	n.s.	-0.18±0.07 *
CC (mm ² /kPa)				
Carotid artery	n.s.	n.s.	n.s.	n.s.
Brachial artery	-0.016±0.008 *	n.s.	n.s.	n.s.
Femoral artery	-0.45±0.015 **	n.s.	n.s.	n.s.

¹ adjustment was done for age, sex, mean blood pressure, BMI, heart rate, total cholesterol, smoking, use of alcohol and treatment of hypertension. ² Regression coefficients ± SE. ³ Measurements available in 223 men, 224 women. PWV pulse wave velocity, DC distensibility coefficient, CC cross-sectional compliance. * p < 0.05, ** p < 0.01, *** p < 0.001.

The results of the analysis with adjustment for BMI was similar for women. In men InsR was no longer related to brachial artery diameter, while there was still a positive relation with carotid artery diameter ($p < .001$). InsR was, except for a trend for the aorta, no longer significantly related to arterial distensibility. The (negative) relation between InsR and femoral artery compliance remained significant ($p < .01$).

BMI was associated with more arterial wall properties than insulin resistance (Table 3a-3b).

Insulin and Glucose

Insulin resistance is accompanied by increased serum levels of insulin and glucose. To investigate whether the relation between InsR and vessel wall properties in men can be explained by the increased serum insulin or glucose levels, two additional analyses were made, investigating the association between large artery wall properties and insulin and glucose respectively, again before and after adjustment for the possible confounding factors (Table 4a-b). In men, after adjustment, glucose tended to be inversely related to brachial artery DC ($p = .06$) and was inversely related to brachial artery CC ($p < .05$). The results for insulin were largely in accordance with the results for InsR. In women, insulin was only negatively related to femoral artery diameter ($p < .05$), while glucose was not related to any of the measured wall properties.

Table 4a Men: relation between insulin and glucose and large artery properties, before and after adjustment ¹.

Slope ²	Insulin Unadjusted (U/l)	Insulin Adjusted (U/l)	Glucose Unadjusted (mmol/l)	Glucose Adjusted (mmol/l)
PWV aorta ³	0.068±0.028*	0.044±0.023*	1.10±0.28***	n.s.
Diameter (mm)				
CCA	0.040±0.04***	0.041±0.011***	0.39±0.13**	n.s.
BA	0.02±0.009**	n.s.	n.s.	n.s.
FA	n.s.	n.s.	n.s.	n.s.
DC (10 ⁻³ /kPa)				
CCA	n.s.	n.s.	-4.72±1.27***	n.s.
BA	-0.40±0.1**	n.s.	-4.67±1.57**	-2.75±1.50+
FA	-0.17±0.06**	n.s.	-1.38±0.66*	n.s.
CC (mm ² /kPa)				
CCA	n.s.	n.s.	-0.13±0.056*	n.s.
BA	n.s.	n.s.	-0.051±0.020*	-0.040±0.020*
FA	-0.014±0.004**	-0.012±0.004**	-0.094±0.049+	n.s.

¹ adjustment was done for age, sex, mean blood pressure, BMI, heart rate, total cholesterol, smoking, use of alcohol and treatment of hypertension. ² Regression coefficients ± SE. ³ Measurements available in 223 men, 224 women. PWV pulse wave velocity, CCA common carotid artery, BA brachial artery, FA femoral artery. DC distensibility coefficient, CC cross-sectional compliance. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, n.s. not significant.

Table 4b **Women: relation between insulin and glucose and large artery properties, before and after adjustment ¹.**

Slope ²	Insulin Unadjusted (U/l)	Insulin Adjusted (U/l)	Glucose Unadjusted (mmol/l)	Glucose Adjusted (mmol/l)
PWV aorta ²	0.080±0.030**	n.s.	0.66±0.30*	n.s.
Diameter (mm)				
CCA	n.s.	n.s.	-2.74±1.41+	n.s.
BA	n.s.	n.s.	n.s.	n.s.
FA	n.s.	-0.032±0.016*	0.33±0.17*	n.s.
DC (10 ⁻³ /kPa)				
CCA	n.s.	n.s.	n.s.	n.s.
BA	-0.61±0.20**	n.s.	n.s.	n.s.
FA	-0.19±0.08*	n.s.	n.s.	n.s.
CC (mm ² /kPa)				
CCA	n.s.	n.s.	n.s.	n.s.
BA	-0.004±0.002*	n.s.	n.s.	n.s.
FA	-0.010±0.004**	n.s.	-1.57±0.75*	n.s.

¹ adjustment was done for age, sex, mean blood pressure, BMI, heart rate, total cholesterol, smoking, use of alcohol and treatment of hypertension. ² Regression coefficients ± SE. ³ Measurements available in 223 men, 224 women. PWV pulse wave velocity, CCA common carotid artery, BA brachial artery, FA femoral artery. DC distensibility coefficient, CC cross-sectional compliance. * p < 0.05, ** p < 0.01, *** p < 0.001, n.s. not significant.

Discussion

In the present study, the effects of insulin resistance, fasting insulin and fasting glucose on large artery wall properties of different arterial territories were studied in a random population with a normal fasting glucose. Since insulin resistance is often found in obese subjects, adjusting for BMI, the relation between the syndrome Insulin Resistance and large artery properties might be underestimated. To investigate this, an additional analysis without adjustment for BMI was done.

The main finding of the present study was the gender-related differences of the results. In women InsR was not related to any of the large artery wall properties. The same was true for glucose and, except for femoral artery diameter, also for insulin.

In men insulin resistance was negatively related to femoral artery compliance, meaning insulin resistant men have a lower femoral artery compliance. As in insulin resistant and diabetic patients early atherosclerosis occurs in the femoral artery and arteries of the lower limbs ²⁸, this altered femoral artery compliance might be an early feature or an indicator of an increased risk for atherosclerotic disease. A similar result was recently described in a clamp study ¹⁶. However in contrast to the present study, this negative relation between insulin resistance and femoral artery compliance relation was found only in women and not in men ¹⁶. Explanations could be: small number of subjects (17 men, 17 women) and a very different study population (young, non-obese subjects). Cross-sectional compliance is the resultant of diameter and

distensibility. InsR was also negatively related to distensibility of the femoral artery. Since diameter was not significantly changed, this suggests a really stiffer artery in insulin resistant men.

InsR was also negatively related to distensibility of the muscular brachial artery. This lower distensibility could be a passive phenomenon, due to vasodilation. Brachial artery diameter was namely also positively related to insulin resistance, but neither to insulin nor glucose serum levels. The relation disappeared after correction for BMI. This suggests that the larger BA diameter in insulin resistant subjects is related to the higher BMI. It has been shown that BMI-based obese subjects have a larger BA diameter (chapter 6). As obese subjects have a hyperdynamic relation, the increase in BA diameter might be due to flow-dependent vasodilation.

In men InsR was also positively related to carotid artery diameter. After adjustment for BMI, insulin resistant men still had a larger carotid artery diameter. This could be related to a higher blood pressure. Indications for this are a positive relation between InsR and heart rate and blood pressure, after adjustment for BMI (data not shown). As the larger diameter of CCA was also present for insulin alone, it could be due to insulin-induced vasodilation²⁹. Since carotid artery distensibility was not changed in InsR subjects, the larger diameter might also be caused by remodeling.

In a further step of the analysis the relation between glucose and insulin and vessel wall properties was investigated to see if the found relations were caused by insulin resistance *per se*.

The results for insulin were in accordance with the results for InsR. This similarity suggests most of the observed relations between InsR and large artery properties might be mainly the effect of insulin. As already mentioned, the literature concerning the relation between insulin and large artery wall properties is not clear. A recent study described an increase in compliance of large arteries after insulin infusion, caused by a vasodilation or increase in distensibility³⁰. Some studies showed a negative relation between insulin and distensibility of the aorta^{12,13} and common carotid artery¹¹, while others found no relation between aortic distensibility and insulin in healthy people¹⁴. An explanation for these discrepancies could be the fact that some studies presented results that were not adjusted for age and blood pressure. This is supported by a recent study by van Popele et al, which showed that the found relation between insulin and carotid artery distensibility disappears after adjustment for mean arterial pressure³¹.

The exact effect of insulin on the arterial wall is not fully elucidated. The direct action of insulin on arteries is vasodilation. Indirectly by increasing SNS activity, it causes vasoconstriction²⁹. The net effect of a chronic hyperinsulinemic state on arterial diameter depends on the weight of both mechanisms. Insulin is also assumed to be an atherogenic hormone: it increases the formation and decreases the regression of lipid plaques, it enhances proliferation of smooth muscle cells, it stimulates synthesis of connective tissue, it stimulates growth factors and it enhances cholesterol synthesis and increases low density lipoprotein activity³².

The fact that in women there was no relation between insulin and InsR and large artery properties may contribute to the findings of Modan et al, that hyperinsulinemia was associated with an increased cardiovascular risk in men, but not in women³³.

In men, there were no relations between glucose and carotid and femoral artery wall properties. These results are in accordance with a recent study, showing that in healthy men carotid artery wall properties are not influenced by acute systemic hyperglycemia³⁴. On the other

hand some studies suggest an increased stiffening of large arteries in hyperglycemic states, which might be caused by non-enzymatic glycosylation of collagen fibrils in the arterial wall³⁵. In the present study serum glucose was limited to 6 mmol/l.

BMI appears to affect more arterial wall properties than insulin resistance, indicating that the effects of obesity on large artery wall properties are only in part due to an increased insulin resistance.

In conclusion, [1] the relation between insulin resistance and large artery wall properties are gender-dependent. Insulin resistance, glucose and insulin are not related to large artery wall properties in non-diabetic women. [2] The relation between insulin resistance and large artery wall properties in men depends on the vascular territory. In men, compliance of the femoral artery was the most affected by insulin resistance. This altered femoral artery compliance might be an early feature or sign of an increased risk for atherosclerotic disease. [3] Alterations of large artery wall properties in subjects with an increased insulin resistance is probably due to the increased insulin levels. [4] As BMI affects more arterial wall properties than insulin resistance, altered arterial wall properties in obese subjects can only in part be attributed to an increased insulin resistance.

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CHAPTER 8

The effect of insulin-dependent diabetes mellitus on large artery wall properties

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Abstract

Subjects with insulin-dependent diabetes mellitus (IDDM) have an increased cardiovascular risk. Large artery wall properties (compliance (CC) and distensibility (DC)) may play a role in this process. In the present study diameter, DC and CC of the elastic common carotid artery (CCA) and muscular femoral (FA) and brachial (BA) arteries were measured with a vessel wall movement detector system in IDDM patients with different duration of disease and with (IDDM^{C+}) and without complications (IDDM^{C-}). In addition aortic pulse wave velocity, an estimate of aortic stiffness, was measured.

Brachial artery wall properties were not affected by diabetes mellitus. DC of the aorta was lower ($p < .001$) in IDDM patients than in control subjects. DC of the elastic CCA was lower in IDDM^{C+} compared to IDDM^{C-} and controls ($P < .01$). CC of the CCA was lower ($P < .01$) in the IDDM^{C+} group compared to IDDM^{C-} patients. In IDDM^{C-} compliance was even higher ($P < .01$) than in control subjects.

Duration of disease was negatively related to aortic and FA DC ($p < .001$), not to carotid artery DC. HbA1c was not related to any of the vessel wall properties measured.

In conclusion, diabetes affects wall properties of central arteries (aorta, CCA, FA), but not of the medium-sized BA. Large artery wall properties differ between complicated and uncomplicated IDDM patients. Distensibility and/or compliance of the aorta and carotid artery are lower in complicated IDDM. Compliance of the carotid artery of uncomplicated IDDM patients is even increased, suggesting that in an early phase of the disease arterial compliance may increase. Regulation of diabetes, expressed by HbA1c, does not influence arterial wall properties.

Introduction

Diabetes mellitus is a well known cardiovascular risk factor; it doubles the risk of cardiovascular disease in men and almost triples it in women ¹. This increase in risk is mainly caused by atherosclerosis. The mechanism by which the disease contributes to the atherosclerotic process is not fully understood. Compliance, the buffering capacity of an artery ², and distensibility, a determinant of strain on the vessel wall ³, are wall properties of large arteries, which can be involved in atherosclerotic disease. Large artery wall properties can be influenced by different disease states like hypertension and possibly also diabetes mellitus ^{4,5}. However, reports concerning large artery wall properties in diabetic patients show some discrepancies. Some studies found an increase in arterial stiffness ⁶⁻¹⁴, while others found no difference ^{12,15,16} or even a decrease in stiffness ^{15,16}. This could be explained by the fact that most reports concern heterogeneous patient groups with regard to type of diabetes mellitus, duration of disease, medication, existence of complications and glycemic control. In a study by Kool and coworkers, except for the femoral artery, no obvious differences were found in vessel wall properties of elastic and muscular large arteries between uncomplicated insulin dependent diabetic patients (IDDM) and matched control subjects ⁵. Distensibility of the femoral artery, an artery in which early atherosclerotic changes occur, was lower in the diabetic subjects ⁵. This suggests the presence of early (possibly atherosclerotic) changes in this artery, reflected by a decrease in distensibility. This study was however limited to uncomplicated IDDM and the number of patients was too small to detect a possible relation between arterial stiffness and duration of disease.

The aim of the present study was to investigate large artery wall properties in insulin-dependent diabetic patients with different duration of disease and with and without complications. Since different arteries may behave differently ^{5,17}, we studied two predominantly elastic arteries (common carotid artery and aorta, both prone for the development of atherosclerosis) and two muscular arteries (the femoral artery, also an artery in which atherosclerosis develops and the brachial artery, an artery in which atherosclerosis is less pronounced).

Methods

Subjects

One hundred and four insulin-dependent diabetic (IDDM) patients (68 men, 36 women) were recruited from four outpatient clinics. IDDM was defined as onset of disease before 30 years of age in combination with insulin dependence from diagnosis. Two groups of IDDM patients were selected: 56 subjects with uncomplicated IDDM, with different duration of disease (IDDM^{C-}) and 26 subjects with IDDM with complications (IDDM^{C+}). Uncomplicated IDDM was defined as diabetes without retinopathy, (micro)albuminuria, or clinical signs of neuropathy. Complicated IDDM was characterized by microalbuminuria / nephropathy, retinopathy or both. Retinopathy was determined by an ophthalmologist using direct and indirect ophthalmoscopy and fundus photography within six months before or three months after the measurements. Microalbuminuria was determined in three 24 hour urine samples, collected within 3 months before or after the vascular measurements. Subjects were classified as having microalbuminuria if 2 out of 3 samples contained >3 mg albumin/mmol creatinine but < 25 mg albumin/mmol creatinine, while macroalbuminuria was defined as ≥ 25 mg albumin/mmol creatinine. The control group included 82 apparently healthy volunteers (44 men, 38 women). Subjects were matched for age, gender, body mass index and mean arterial pressure.

Exclusion criteria for all subjects were: intake of any medication other than insulin or oral contraceptives (17 female diabetic subjects and 6 control subjects), pregnancy, ankle/arm index (Doppler) < 0.95, hypertension (defined as > 160/95 mmHg) at the time of the study, hyperlipidemia (cholesterol $\geq$ 8mmol/l, mean of 2 values, measured within 6 months prior to the study), any cardiovascular event 6 months prior to the study and atherosclerotic plaques in the arteries of interest, as detected by ultrasound during the examination. All patients received appropriate insulin treatment. In addition, all patients regularly controlled their own blood glucose. The study was performed in accordance with the principles of the Declaration of Helsinki (revised 1983) and was approved by the local Ethics Committees of the participating clinics. Informed consent was obtained from all subjects.

Study design

Subjects did not take a meal or inject insulin within 3 hours before the examination. In addition subjects refrained from smoking, taking caffeine and heavy exercise for at least 3 hours before examination. At the start of the study the actual blood glucose was determined (One Touch 2; Lifescan, Tilburg, The Netherlands). Measurements were performed if blood glucose levels were within acceptable limits ($\geq$ 4 mmol/l and $\leq$ 11 mmol/l). If a subject suffered from symptomatic hypoglycemia or blood glucose was below 3 mmol/l or above 15 mmol/l, the measurements were postponed. If blood glucose was between 3 and 4 mmol/l, subjects were given 10 ml glucose 50% intravenously and if blood glucose was between 10 and 15 mmol/l, subjects were given insulin (Actrapid^R, 1 Unit/20kg weight) intravenously. Fifteen minutes after injection of glucose or insulin, a second measurement of blood glucose was done. If the subject still had a blood glucose below 4 mmol/l or above 11 mmol/l, measurements were postponed. Before and after the measurements blood was drawn to measure glucose. Blood glucose data reported are the mean of these two samples.

Vascular measurements

Blood pressure and pulse rate were recorded every 3 minutes at the left arm with a semiautomated device (Dinamap; Critikon, Tampa, Florida). The mean of these recordings ($\pm$ 15) was taken as the subject's reading. Brachial artery pulse pressure was defined as systolic minus diastolic blood pressure. Pulse pressure at the common carotid and femoral arteries were calculated by calibration of the distension curves (chapter 2).

After 15 minutes of supine rest in a quiet room vessel wall properties, i.e. diameter (D), distensibility coefficient (DC) and compliance coefficient (CC) of the right elastic common carotid artery (CCA) and right muscular common femoral (CFA) and brachial (BA) arteries were measured with a vessel wall movement detector system^{18,19}. All measurements were made by the same observer. With the vessel wall movement detector system it is also possible to measure carotido-femoral transit time (T)¹⁹. Carotido-femoral length was measured with a tape measurer (L_{ao})²⁰. The average pulse wave velocity (PWV) in this segment was calculated as:

$$PWV = L_{ao}/T$$

which is an estimate of the stiffness of mainly the aortic pathway²¹. Pulse wave velocity is related to arterial distensibility (DC) by the formula:

$$PWV = \sqrt{1/\rho DC} \quad (\text{Moens Korteweg }^{22,23}) \quad (\rho = \text{blood density})$$

Laboratory tests

HbA1c was measured by high-performance liquid chromatography (Diamat, Biorad Laboratories, Richmond, Ca, USA) and obtained within 6 weeks before the start of the measurements. Urinary albumin excretion was measured by an immunoturbidimetric method. Glucose was measured by a glucoseoxydase method.

Statistical analysis

For database management and statistical analysis the SAS software package (The SAS institute Inc., Cary, North Carolina) was used. Study groups and patient characteristics were analysed by means of chi-square tests for categorical data. For continuous data the Kruskal-Wallis test for overall comparisons and the Mann-Whitney test for pairwise comparisons were used. To investigate the relation between arterial wall properties and duration of diabetes, HbA1c, blood glucose level and complications, a covariance analysis was used. Adjustments were made for possible confounding factors: age, sex, body mass index, mean arterial pressure, heart rate, smoking and total cholesterol. Factors with a p-value > 0.10 were dropped from the model. From this analysis also the estimated large artery properties after adjustment were calculated. Data are presented as mean $\pm$ SD for demographic values or as mean $\pm$ SE for other data. A p-value < 0.05 was considered as statistically significant.

Results**Characteristics of the IDDM patients and control subjects**

IDDM patients with complications were older and had a higher MAP and heart rate compared to IDDM patients without complications and to control subjects (Table 1). Glycaemic control did not differ between the two IDDM groups. HbA1c ranged from 3.7 through 13.2%. Mean blood glucose levels during the measurements were between 3.9 and 10.9 mmol/l and were also comparable in both IDDM groups. Of the diabetic patients with complications, 12 had retinopathy, 6 microalbuminuria, 4 both retinopathy and microalbuminuria and 4 both retinopathy and macroalbuminuria. Mean 24 hour albumin excretion was 33 ± 42 mg/mmol creatinine.

Vessel wall properties of the IDDM patients and control subjects

Data before adjustment for confounding factors are shown in Table 2. Data after adjustment are shown in Table 3. After adjustment, diameter of the CCA was larger in IDDM than in control subjects. In contrast, diameter of the FA tended to be smaller in IDDM patients. Diameter of the carotid and femoral arteries did not differ significantly between IDDM^{C+} and IDDM^{C-}. Brachial artery diameter did not differ significantly between the 3 groups. PWV of the aorta was higher in IDDM patients than in controls, indicating a lower DC. DC of the elastic CCA was lower in IDDM^{C+} compared to IDDM^{C-} and controls. DC of the muscular BA and FA did not differ significantly between the groups. CC of the CCA was lower in the IDDM^{C+} group compared to IDDM^{C-} patients, but in IDDM^{C-} compliance was higher than in control subjects. CC of the BA and FA did not differ significantly between the three groups.

Table 1. Characteristics

	Control subjects	IDDM patients		p overall	p 1-2	p 1-3	p 2-3
		no complications	with complications				
Sex (M/F)	44/38	52/24	14/12	.16			
Age (years)	33±7	30±9	39±10	.001	.05	.01	<.001
Body Mass Index (kg/m ²)	24.5±3.6	23.8±3.0	23.8±2.6	.53			
Mean arterial pressure (mmHg)	86±9	87±7	93±10	.005	.39	.003	.003
Heart rate (beats/min)	65±10	67±10	76±13	<.001	.11	<.001	.005
Smokers	22 (27%)	26 (34%)	11 (39%)	.39			
cigarettes/day	15±14	14±17	12±11	.70			
Cholesterol (mmol/l)	5.0±0.9	4.7±1.0	5.1±1.0	.10			
Duration of disease (years)	-	12±8	25±9	-			<.001
HbA1c (%)	-	8.2±1.5	8.2±1.7	-			.69
Mean glucose (mmol/l)	-	9.1±3.8	8.8±3.9	-			.68
Insulin use (units/day)	-	57±16	47±17	-			.005

Data are mean±SD. P overall, statistical difference between the three groups. If P overall < .05, statistical difference between each of the groups is shown. P1-2, statistical difference between control subjects and uncomplicated IDDM patients; P1-3, statistical difference between control subjects and IDDM patients with complications; P2-3, statistical difference between IDDM patients with and without complications; M, male; F, female. IDDM, insulin dependent diabetes mellitus.

Table 2. Vessel wall properties. Differences between IDDM patients with and without complications and control subjects.

	Control subjects	IDDM patients no complications	IDDM patients with complications	p overall	p 1-2	p 1-3	p 2-3
Common Carotid Artery							
Diameter (mm)	6.72±0.62	6.92±0.72	7.19±0.69	.01	.17	.004	.03
DC (10-3/kPa)	29.7±8.2	32.9±9.0	21.4±8.8	<.001	.04	<.001	<.001
CC (mm2/kPa)	1.06±0.33	1.20±0.27	0.84±0.27	<.001	<.001	.005	<.001
Brachial Artery							
Diameter (mm)	3.85±0.64	3.83±0.65	4.02±0.74	.40			
DC (10-3/kPa)	25.9±13.7	24.2±9.2	19.3±8.6	.02	.98	.01	.01
CC (mm2/kPa)	0.29±0.14	0.27±0.12	0.24±0.09	.63			
Common Femoral Artery							
Diameter (mm)	9.25±1.30	9.05±1.16	8.86±1.23	.38			
DC (10-3/kPa)	9.7±5.1	10.6±5.4	7.7±4.8	.009	.25	.02	<.01
CC (mm2/kPa)	0.63±0.31	0.66±0.29	0.44±0.25	<.001	.26	.001	<.001
Aorta							
PWV (m/s)	5.6±1.0	6.0±0.9	7.9±2.9	<.001	.01	<.001	<.001

Data are mean ± SD. DC, distensibility coefficient. CC, cross-sectional compliance. PWV, pulse wave velocity. P overall, statistical difference between the three groups. If P overall < .10, statistical difference between each of the groups is shown. P1-2, statistical difference between control subjects and uncomplicated IDDM patients; P1-3, statistical difference between control subjects and IDDM patients with complications; P2-3, statistical difference between IDDM patients with and without complications.

Table 3. Vessel wall properties, after adjustment for confounders¹. Differences between IDDM patients with and without complications and control subjects.

	Control subjects	IDDM patients no complications	IDDM patients with complications	P overall	P 1-2	P 1-3	P 2-3
Common Carotid Artery							
Diameter (mm)	6.66±0.05	6.94±0.06	7.11±0.11	<.001	<.001	<.001	.19
DC (10-3/kPa)	30.3±0.7	31.7±0.8	26.6±1.2	.003	.19	.009	<.001
CC (mm2/kPa)	1.03±0.03	1.16±0.03	0.97±0.05	.001	.002	.34	.002
Brachial Artery							
Diameter (mm)	3.76±0.05	3.75±0.05	3.96±0.09	.11			
DC (10-3/kPa)	25.6±1.1	23.6±1.2	21.7±2.0	.19			
CC (mm2/kPa)	0.27±0.01	0.26±0.01	0.25±0.02	.52			
Common Femoral Artery							
Diameter (mm)	9.12±0.10	8.84±0.11	8.68±0.21	.08	.06	.06	.49
DC (10-3/kPa)	9.8±0.5	10.6±0.6	8.6±1.0	.25			
CC (mm2/kPa)	0.62±0.03	0.63±0.03	0.50±0.05	.12			
Aorta							
PWV (m/s)	5.6±0.1	6.2±0.1	6.5±0.2	<.001	<.001	<.001	.21

Results are lsmeans±SE, ¹ age, sex, BMI, MAP, heart rate, smoking and total cholesterol. DC, distensibility coefficient. CC, cross-sectional compliance. PWV, pulse wave velocity. P overall, statistical difference between the three groups. If P overall < .10, statistical difference between each of the groups is shown. P1-2, statistical difference between control subjects and uncomplicated IDDM patients; P1-3, statistical difference between control subjects and IDDM patients with complications; P2-3, statistical difference between IDDM patients with and without complications;

IDDM-patients: Relation between vessel wall properties and 'markers' of disease

To investigate the relation between large artery properties and 'markers of disease', like HbA1c, analysis of covariance was used with the following explanatory variables: age, sex, body mass index, mean blood pressure, total cholesterol, smoking, duration of disease, HbA1c, blood glucose (mean of two values, before and after the measurements), normal use of insulin, complications, extra infused glucose and extra infused insulin. As there were no relations between brachial artery wall properties and any of the markers of disease, data of the brachial artery are not shown in Table 4. HbA1c was not related to any of the vessel wall properties measured. Duration of disease was not related to arterial diameter. There was a negative relation between duration of disease and DC of the FA and aorta ($p < .001$). Duration of disease was negatively related to CC of the FA ($p = .008$). Blood glucose was positively related ($p = .02$) to femoral artery diameter. It was negatively related to DC of the FA ($p = .01$) and DC and CC of the CCA ($P = .009$, $p = .04$ resp.). There was a negative relation between the daily dose of insulin and DC ($p = .01$) and CC of the FA ($p = .009$). There was a negative relation between the presence of complications and DC and CC of the CCA ($p = .002$, $p = .04$ resp.). This was probably caused by the subjects with retinopathy, since in a further analysis the same results were found for subjects with retinopathy. Microalbuminuria was not related to arterial stiffness.

Table 4. IDDM patients. Relation between vessel wall properties and 'markers' of disease, after correction for confounders¹

slope ²	Duration	HbA1c	Glucose	Insulin	Complications
PWV (m/s)					
Aorta	.15±.04***	n.s.	n.s.	n.s.	n.s.
Diameter (mm)					
Carotid artery	n.s.	n.s.	n.s.	n.s.	n.s.
Femoral artery	n.s.	n.s.	.048±.021*	n.s.	n.s.
DC (10 ⁻³ /kPa)					
Carotid artery	n.s.	n.s.	-.41±.15**	n.s.	-4.84±1.48**
Femoral artery	-.23±.06***	n.s.	-.28±.11*	-.077±.031*	n.s.
CC (mm ² /kPa)					
Carotid artery	n.s.	n.s.	-.012±.006*	n.s.	-.12±.06*
Femoral artery	-.009±.003**	n.s.	n.s.	-.004±.002**	n.s.

¹ age, sex, BMI, MAP, heart rate, smoking, total cholesterol, extra infused glucose, extra infused insulin. ² Regression coefficients ± SE. CCA, common carotid artery; D diameter, DC, distensibility coefficient. CC, cross-sectional compliance. PWV, pulse wave velocity. n.s. not significant. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Discussion

The present study showed that the effect of diabetes on large artery properties depends on the vascular territory. In contrast to the central aorta, carotid and femoral arteries, vessel wall properties of the medium sized brachial artery were not influenced by diabetes mellitus. In accordance with an in vitro study^{14,24}, stiffness of the aorta was higher in both diabetic

groups. Stiffness of the carotid artery was only higher in complicated, but not uncomplicated IDDM. This is in agreement by a recent study of Giannattasio et al.¹⁴

In accordance to Kool and Lambert^{5,25}, the present study showed a larger carotid artery diameter in diabetic compared to control subjects, whereas, also confirming earlier studies^{5,26}, femoral artery diameter tended to be lower in diabetics compared to controls. Since during the early stages of atherosclerosis, arterial diameter may become increased²⁷, this larger carotid artery diameter could be an expression of atherosclerosis. Further in the atherosclerotic process, probably because of increasing intima-media thickness of the wall, diameter decreases. This could explain the decrease in femoral artery diameter in diabetic subjects. This confirms the hypothesis that in diabetics atherosclerosis occurs earlier in the femoral artery than carotid artery²⁸. Another explanation for the decrease in femoral artery diameter could be an increased tone, caused by an increase in noradrenaline content²⁹. This was not confirmed by the results of the brachial artery. In addition, a recent study by Vervoort et al showed a decrease in sympathetic drive in noncomplicated type 1 diabetic patients³⁰.

Compliance of the carotid artery was lower in complicated compared to uncomplicated IDDM patients. Carotid artery compliance of uncomplicated diabetics was even higher compared to control subjects, suggesting that in an early phase of the disease arterial compliance may increase. Lehmann et al reported a similar finding for the aorta in diabetic subjects in the first year after diagnosis¹⁵. The difference in carotid artery compliance between uncomplicated and complicated IDDM can explain why some authors did find a difference in arterial compliance between IDDM patients and control subjects¹³ and others did not^{5,25}.

The observed difference in vessel wall properties between uncomplicated and complicated diabetic subjects could be caused by a different duration of disease, which was twice as high in the complicated IDDM. In this study, duration of disease was related to aortic stiffness. However, in accordance with other studies^{5,13}, there was no relation between carotid artery diameter and distensibility and duration of disease. This suggests that other factors also might play a role.

The exact pathogenesis of macrovascular disease in diabetes is unknown. One of the hypotheses is that hyperglycemia causes formation of advanced glycosylation end-products^{31,32}, leading to stiffer arteries. This might imply a relation between arterial wall properties and glycemic control. In accordance with several other studies^{5,6,13,25,33}, HbA1c, an estimate of regulation during the last 6 weeks, was not significantly related with any of the measured vessel wall properties. Blood glucose during the investigation was positively related to femoral artery diameter and negatively related to distensibility of the carotid and femoral arteries and compliance of the carotid artery. Since no relation with HbA1c was found, this suggests a more (sub) acute effect of hyperglycemia. This is in contradiction with a recent clamp study, showing that in healthy men carotid artery wall properties were not influenced by acute, artificially induced systemic hyperglycemia³⁴.

Another hypothesis explaining the relation between diabetes and macrovascular disease concerns hyperinsulinemia³⁵. In the present study, daily dose of insulin was negatively related to femoral artery distensibility and compliance. One explanation could be a vasoconstrictive effect of insulin³⁶, although this was not observed at the other muscular artery, the brachial artery. Another explanation could be more structural changes caused by insulin.

Presence of complications was a determinant of carotid and aortic stiffness (negative relation) and carotid artery compliance. In a sub-analysis in the subjects with complications, for all

these three vessel wall properties (DC aorta, DC and CC of the CCA), retinopathy appeared to be the complication explaining the relation. In other words, subjects with retinopathy have stiffer elastic arteries. In contrast to Zenere³³ and in agreement with Lambert¹¹, no relation between arterial stiffness and microalbuminuria was found. However, for definite conclusions the number of subjects (six) was too small and a study in a larger patient group is necessary. This might be very difficult, since nowadays in an early stage, all patients with microalbuminuria are treated with ACE-inhibitors, which also have effects on large artery wall properties.

In conclusion, the main findings of this study are [1] the effect of diabetes depends on the vascular territory; diabetes affects wall properties of central arteries (aorta, CCA, FA), but not of the medium-sized brachial artery. [2] Large artery wall properties differ between complicated and uncomplicated IDDM patients. Distensibility and/or compliance of the elastic aorta and common carotid artery are lower in complicated IDDM. [3] Compliance of the carotid artery is increased in uncomplicated IDDM patients, suggesting that in an early phase of the disease arterial compliance may increase.

In addition the present study confirms that regulation of diabetes, expressed by HbA1c, does not influence arterial wall properties.

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CHAPTER 9

General discussion

9.1 Introduction

In the last two decades there has been a lot of interest in large artery wall properties and their relation with cardiovascular disease and risk. Several new techniques to measure these wall properties have been developed. A number of studies focussed on the relation between cardiovascular risk factors and large artery wall properties, for instance studies on hypertension^{1,2} and smoking³⁻⁵. With the rise in number of studies, also discrepancies are seen (chapter 1). Several explanations for these inconsistencies can be given. [1] Different methods have been used, measuring different entities. [2] There is still indistinctness in the terminology used. [3] Small number of subjects, because of which there is sometimes not enough power. [4] Some studies, like those on diabetes mellitus, concern heterogeneous groups. [5] In addition, associations may differ between arterial territories. For instance two studies by Kool et al showed an influence of hypercholesterolemia and diabetes mellitus on the femoral, but not on the carotid and brachial arteries^{6,7}. Taking this into account, in the present thesis investigations were done in a population sample of more than 500 subjects. Different vascular territories were studied: elastic and muscular arteries, in which atherosclerosis is or is not common.

9.2 Associations between large artery wall properties and cardiovascular risk factors

9.2.1 Associations in a random population sample

In addition to the factors mentioned in 9.1, most large artery studies reported, combine men and women or concern only men or only women. However, females have a lower risk of cardiovascular disease compared to males⁸. Large artery wall properties also seem to differ between men and women. In addition also the influence of cardiovascular risk factors might be gender-dependent. In the population studies described in the present thesis, we therefore chose to analyse men and women separately.

9.2.1.1 Associations in men

As can be seen from Table 1, the relation between cardiovascular risk factors and large artery properties differs between the vascular territories.

Aging has a negative effect on the distensibility of the aorta, common carotid and femoral arteries, while this is not the case for the brachial artery (chapter 3 and 4). At young age, the central arteries have the largest distensibility. Since with aging the largest decrease in distensibility is seen in the aorta and common carotid artery, this means that with age, the difference in stiffness between central and more peripheral arteries decreases and the arterial tree will behave as a branching tube of common stiffness. With age arteries also dilate, although more pronounced in elastic than muscular arteries. This dilatation is suggested to be caused by repetitive strain causing fragmentation of elastin⁹. From a completely different point of view it also could be suggested that it is a physiological adaptation (remodeling) to an increased stiffness of the central arteries. Evidence for the latter is the fact that the increase in diameter of the brachial artery from the 3rd to the 8th age decade is 10% in men and 24% in women, whereas for the carotid artery the percentages are respectively 15% and 28%. This increase in diameter for the brachial artery is more than expected on the basis of degeneration. This

suggests a vasodilatory mechanism to maintain the buffering capacity of the arterial tree.

Table 1 Relation between cardiovascular risk factors and large artery properties in men

	Diameter (mm)			DC ($10^{-3}/\text{kPa}$)				CC (mm^2/kPa)		
	CCA	FA	BA	aorta	CCA	FA	BA	CCA	FA	BA
Age	↑↑	↑	↑	↓↓	↓↓	↓	=	↓	=	=
InsR	↑	=	=	(↓)	=	=	=	=	↓	=
InsR-BMI	↑	=	↑	(↓)	=	↓	↓↓	=	↓	(↓)
Insulin	↑	=	=	↓	=	=	=	=	↓	=
Glucose	=	=	=	=	=	=	(↓)	=	=	↓
Height	↑	↑	=	=	=	=	=	↑	↑	=
BMI	↑	↑	↑	=	↓	↓	↓↓	=	↓	↓
W-H ratio	↑	=	↑	=	=	↓	↓↓	=	↓	=
Skinfold	↑	=	=	=	=	=	=	=	=	=

DC distensibility coefficient, CC cross sectional compliance, CCA common carotid artery, FA femoral artery, BA brachial artery, InsR insulin resistance, InsR-BMI relation with insulin resistance, not corrected for body mass index, BMI body mass index, W-H ratio waist to hip ratio, ↑ positive relation, ↓ negative relation, = not related, (↓) tended to be negatively related

Obesity is a cardiovascular risk factor and lately it has become clear that especially the distribution of fat (waist-hip ratio) seems to be important. In the present population sample we analysed the relation between different measures of obesity and large artery wall properties (chapter 6). BMI-based obese subjects have a larger arterial diameter and stiffer arteries. This, however, does not hold for the aorta. In men an android body habitus, reflected by an increased waist to hip ratio, was associated with lower femoral artery distensibility and compliance. Why is obesity related to larger and stiffer arteries? Hypotheses are: [1] hyperdynamic circulation, leading to a flow-dependent vasodilation and as a result stiffer arteries, [2] atherosclerosis, [3] the effect of other coinciding factors like hyperinsulinemia, [4] transmural pressure of adipocytes. The latter could also explain why there is especially a relation between an android body habitus and lower femoral artery distensibility and compliance. The consequence of this relation and the question whether these changes are reversible have to be further investigated. A recent study showed that loss of weight increased carotid artery distensibility at operating pressures, but not under isobaric conditions. This suggests that the decrease in distensibility with weight loss is probably due to the decrease in blood pressure¹⁰.

Since one of our hypotheses was that the relation between obesity and large artery properties could be explained by other factors, like insulin resistance, this was investigated in a study described in chapter 7. The study showed that altered wall properties in obese subjects can only partly be attributed to insulin resistance. This means that further research is necessary to fully explain the increase in arterial stiffness in obese subjects is necessary. It was also shown that alterations in large artery wall properties in insulin resistant men are probably due to insulin. The present results suggest insulin itself, and not only glucose, has to be further

investigated for its role in cardiovascular disease.

9.2.1.2 Associations in women

As can be seen from Table 2, compared to Table 1, the results of the studies confirmed the hypothesis that the influence of risk factors on large artery properties is gender-dependent.

Table 2 Relation between cardiovascular risk factors and large artery properties in women

	Diameter (mm)			DC(10 ⁻³ /kPa)				CC (mm ² /kPa)		
	CCA	FA	BA	aorta	CCA	FA	BA	CCA	FA	BA
Age	↑	↑	↑	↓↓	↓↓	↓	=	↓	=	↑
Menop.	(1)	=	=	↓	=	=	=	=	=	=
InsR	=	=	=	=	=	=	=	=	=	=
InsR-BMI	=	=	=	=	=	=	=	=	=	=
Insulin	=	↓	=	=	=	=	=	=	=	=
Glucose	=	=	=	=	=	=	=	=	=	=
Height	↑	↑↑	↑	=	=	=	=	↑	=	=
BMI	↑↑	↑	↑	=	=	↓	↓↓	=	=	=
W-H ratio	↑	=	=	=	=	=	=	=	=	=
Skinfold	=	=	=	=	=	=	↓	=	=	=

DC distensibility coefficient, CC cross sectional compliance, CCA common carotid artery, FA femoral artery, BA brachial artery, InsR insulin resistance, InsR-BMI relation with insulin resistance, not corrected for body mass index, BMI body mass index, W-H ratio waist to hip ratio, ↑ positive relation, ↓ negative relation, = not related

The effect of age differs between men and women. The most catching result is an increase in brachial artery compliance with age in women, but not in men. This increase in compliance is the result of a larger increase in diameter of the brachial artery, which also accounts for the femoral artery, both muscular arteries. This increase in diameter is much larger in women compared to men, while the decrease in distensibility is about equal in men and women. This could also point to an active, remodeling mechanism, and suggests that women more than men can compensate for the loss in compliance in the more central arteries.

One explanation for the gender difference could be the influence of hormones, mainly estrogens, of which it is believed that they provide protection against cardiovascular disease ¹¹. Estrogens are described to have direct effects on the vessel wall, for instance inducing vasodilation ¹² and changing the elastin-collagen ratio ¹³. In the present thesis, to elucidate more about the role of estrogens in women, the effect of menopause was studied (chapter 5). Menopause was negatively related to aortic stiffness, but not related to stiffness of the other arteries. This difference between arteries could be one of the explanations for the discrepancy in the reports on the effects of estrogens on arterial distensibility : some describe a positive effect of estrogens on distensibility of the aorta ¹⁴, while others found no relation between

estrogen replacement and distensibility of the aorta ¹⁵ (chapter 1). A similar contradiction was found by two studies on the relation between large artery properties and the menstrual cycle. One study described no relation between the menstrual cycle and carotid and femoral artery stiffness ¹⁶, while another study described fluctuations of radial artery distensibility throughout the menstrual cycle ¹⁷. The role of sex hormones on large artery wall properties has to be further investigated. If there is a clear positive relation, it could be an additional argument for supplementation of estrogens to (post)menopausal women.

In women obesity is also related to arterial diameter and distensibility; however, the influence seems to be much larger in men. In women, there was no relation between an android body habitus and large artery wall properties.

Insulin resistance, of which it is suggested to be linked to abdominal obesity, was not significantly related to large artery wall properties in women, whereas it was in men. Insulin and glucose itself were also not related to large artery wall properties. This is in accordance with a study showing no relation between insulin and cardiovascular risk in women ¹⁸. This gender-difference and the meaning of it in relation with non-insulin dependent diabetes mellitus has to be further investigated.

9.2.2 Associations in insulin-dependent diabetes mellitus

Since the number of patients with insulin-dependent diabetes mellitus was too small in the random population sample, IDDM patients from different clinics were selected. Several previous studies investigated the effect of diabetes on large artery wall properties, with contradictory results. One of the main explanations of this is probably the fact that heterogeneous patient groups were used (chapter 1). In addition to an earlier study by Kool et al ⁷, who investigated young, uncomplicated IDDM patients, we conducted a study in IDDM patients with and without complications (chapter 8). Unfortunately, because of the number of patients, it was not possible to analyse men and women separately.

Table 3 Relation between diabetes mellitus and large artery wall properties

	Diameter (mm)			DC(10 ⁻³ /kPa)				CC (mm ² /kPa)		
	CCA	FA	BA	aorta	CCA	FA	BA	CCA	FA	BA
IDDM no compl.	↑	(↓)	=	↓	=	=	=	↑	=	=
IDDM compl.	↑↑	(↓)	=	↓↓	↓	=	=	=	=	=

DC distensibility coefficient, CC cross sectional compliance, CCA common carotid artery, FA femoral artery, BA brachial artery, IDDM insulin-dependent diabetes mellitus, compl. complications, ↑ positive relation, ↓ negative relation, = not related, (↑) tended to be positive related

Insulin-dependent diabetes mellitus affects central arteries (aorta, CCA, FA), but not the brachial artery. This is in accordance with other studies, showing that alterations in vessel

wall properties can be heterogeneous along the arterial tree. In uncomplicated IDDM patients carotid artery compliance was even increased, suggesting an increase in arterial compliance in the early phase of the disease. Something similar has also been described by other authors in IDDM patients¹⁹ and in subjects with familial hypercholesterolemia²⁰. These results suggest that early in the disease large artery properties already change. An hypothesis for this increase could be the development of atherosclerosis. In experimental atherosclerosis in rhesus monkeys, Farrar et al showed that during the induction of atheroma, the aorta firstly became more distensible, and then as focal lesions were formed, began to stiffen²¹.

Vessel wall properties also differ between complicated and uncomplicated IDDM. Part of this, but not all can be explained by different duration of disease. Similar results were described in a recent study by Giannattasio et al²². There are many hypotheses about the underlying mechanisms. Regulation of diabetes, estimated by HbA1c did not appear to be of importance. This is in contrast to what was expected, since many studies put emphasis on the importance of a good (meaning: low) HbA1c. A recent experimental study showed an increase in arterial distensibility with breakers of advanced glycation products²³. Unfortunately these products are still not available for humans. Further research is necessary to reveal the underlying mechanisms and to investigate whether the process can be delayed.

9.2.3. Most important conclusions from the present studies

In the present population sample, in accordance with all other studies, men have a larger diameter and larger arterial compliance (chapter 3 and 4). Distensibility of the aorta, carotid and femoral arteries did not differ between the genders, while brachial artery distensibility was larger in women compared to men. The results of the studies in this thesis show that vessel wall properties not only differ between men and women, but also the influence of physiological and pathological influences seems to differ. This is in accordance to two earlier studies, which described a clear difference between men and women; one study concerning the relation between IDDM and arterial stiffness²⁴, the other between insulin sensitivity and arterial stiffness²⁵. This implies that in future, where possible, men and women should be analysed separately.

Another important finding from our studies is that the influence of physiological and pathological influences is dependent on the vascular territory. The effect of age, gender, obesity, insulin resistance and diabetes mellitus differs between arteries (this thesis). For age, hypertension and diabetes mellitus, this was also suggested in earlier papers^{7,22,26,27}. Explanations for these differences can be: [1] different composition of the wall (elastic vs. muscular), [2] amplification of pulse pressure, due to pulse wave reflections, [3] standing position, because of which the pressure in the lower limbs is higher. In conclusion, when studying the influence between cardiovascular risk factors and vessel wall properties, it is important to be aware of the fact that large arteries may behave differently. This means that multiple sites have to be measured for characterisation of large artery wall properties.

9.3 Large artery wall properties as a marker for cardiovascular risk

[1] From the studies in this thesis and others (chapter 1), it can be concluded that most cardiovascular risk factors are related to arterial stiffness. These relations can be determined by structural or functional factors. An example of a structural relation is the effect of age²⁸.

The acute effect of smoking on large artery properties is an example of a functional relationship²⁹. These relations are dependent on gender and vascular territory.

[2] Most associations found between large artery wall properties and cardiovascular risk factors are found for the aorta, common carotid and femoral arteries. These are also the arteries most prone for atherosclerosis.

[3] Several cardiovascular risk factors, for instance insulin resistance, seem to affect large artery wall properties in men, but not in women. This is in accordance with the finding that females have a lower cardiovascular risk compared to males⁸.

The above three points are arguments for an association between large artery wall properties and cardiovascular risk. Recently two studies agreed with this hypothesis. They showed that aortic stiffness was a major predictor of cardiovascular morbidity and mortality in patients with end-stage renal failure, requiring hemodialysis³⁰ and hypertensive patients³¹. This means that measurements of large artery wall properties probably can serve to identify patients at risk for cardiovascular disease. However which arteries have to be measured and whether increased arterial stiffness is a risk factor contributing to the development of cardiovascular disease or is a marker of arterial disease is still not clear. However, in both conditions it can be used as a marker for cardiovascular risk.

9.4 Future research

9.4.1 Assessment of local pulse pressure

Lately there is more and more interest in pulse pressure as an independent cardiovascular risk factor³². This widening of pulse pressure is caused by arterial stiffness. Especially after the age of 50-60 years, pulse pressure, and thereby cardiovascular risk, increases.

In large arteries mean arterial pressure is constant, whereas pulse pressure varies³³. As a consequence, the use of pulse pressure in one artery as a surrogate for pulse pressure in the target artery might be erroneous. Ideally, vessel wall movement should be related to pulse pressure measurements obtained simultaneously and at the same site. Unfortunately this is not always possible. If a good relation between pulse pressures in target and surrogate arteries exists, the error may be proportional. Consequently if pulse pressures in target and surrogate arteries behave similarly, results of comparative studies may demonstrate quite accurately changes in vessel wall properties, despite the fact that absolute values of vessel wall properties may be incorrect³⁴.

Several studies described a good relation between carotid and brachial artery pulse pressures^{35,36}. It is, however, known that pulse wave reflections may boost pulse pressure in the carotid artery, but not in the brachial artery³⁷. This may disturb the relation between brachial and carotid artery pulse pressures.

In the last decade, a new non-invasive technique to measure local pulse pressure has been proposed: applanation tonometry^{38,39}. Benetos and coworkers found a good correlation between brachial artery and femoral artery pulse pressure recorded with this technique⁴⁰. However, several authors have found the magnitude of the pulse pressure obtained by applanation tonometry to be unreliable^{41,42}. A new promising method might be assessment of local pulse pressure by calibration of the tonometer pressure wave. This is based on the observation that mean blood pressure is constant through the large artery tree and that diastolic pressure does not change substantially^{42,43}. Applanation tonometry cannot be applied to all subjects

and all arterial sites⁴³. It requires a solid background (bone) to flatten the arterial wall and lean skin, to avoid cushioning of the pressure pulse. For instance, in obese subjects applanation tonometry is often inaccurate at a majority of arterial sites. In addition, performing measurements simultaneously with vessel wall movement detection, measurements have to be done at the contralateral site. In older subjects with atherosclerotic plaques this can introduce errors. In addition, for the carotid artery this is not possible. Thus measurements are done consecutively, which might also introduce errors.

Alternatively, pulse pressure based on calibration of arterial distension waves can be used and show good accuracy (chapter 2). This latter method was used in the studies described in this thesis. Comparing the data and analyses before and after calibration of the pulse pressure showed comparable trends. As could be expected for the relations between age and distensibility of the carotid artery, the slope was steeper after calibration (unpublished data).

This calibration however, does not mean the final solution. Future research must focus on techniques to measure pulse pressure locally and simultaneously with vessel wall movement detection.

9.4.2 Associations with other cardiovascular risk factors

Besides the risk factors studied in this thesis, there are also other risk factors that have to be (further) investigated: physical activity, mental stress, heart rate variability. There are also risk factors which have already been investigated, however with contradictory results, or only in one vascular territory. These factors, for instance smoking and hyperlipidemia, also have to be examined more thoroughly. In addition attention should focus on newly recognized risk factors that are currently under investigation, such as hyperhomocysteinemia. Until now, three studies investigated the relation with large artery properties with different results⁴⁴⁻⁴⁶. Again this could be explained by different arteries studied and different populations. This means further investigation is necessary.

Besides studying risk factors separately, also the effect of interactions between risk factors, for instance obesity, insulin resistance and hypertension, on large artery properties needs to be studied.

Future studies should also focus on genetic factors. There is already evidence for a relation between AT1 receptor polymorphism and aortic stiffness⁴⁷. A recent study by Hanon et al found a relation between apolipoprotein E polymorphism and carotid artery wall hypertrophy, but no relation with carotid and radial artery wall properties⁴⁸. This field of genetics should be further explored. This should be done for example in family studies. May be in future it is possible to link genotype with phenotype.

9.4.3 Use of vessel wall properties as a marker for cardiovascular risk

Besides the cross-sectional study, also longitudinal studies are necessary, to try to elucidate if measurement of vessel wall properties can be used as a marker of cardiovascular risk. First the risk has to be established. Early detection of increased arterial stiffness can possibly be used to identify subjects at risk for the development of cardiovascular disease.

Secondly, to identify subjects at risk, normal values for large artery wall properties should be agreed upon. To achieve this, more population studies should be conducted, or data from several groups, using the same technique, pooled to achieve large numbers of subjects.

Knowing the normal values, subjects with stiffer arteries than their age-matched counterparts can be identified.

9.4.4 New approaches for the treatment of high pulse pressure

As stated in the introduction, vessel wall properties can probably be influenced by drugs. In future, research should focus on the development of new drugs which act more specifically upon large artery properties. For instance drugs, which decrease arterial stiffness without a substantial effect on resistance vessels. An example of such a drug is sinitrodil ⁴⁹. This is a new NO donor, with a higher selectivity for large arteries than for resistance vessels. This means a decrease in pulse pressure, without a substantial decrease in mean and diastolic blood pressure. This is very promising, especially for subjects with coronary artery disease, in which we want a decrease of the pulse pressure, however with maintenance of the diastolic pressure for coronary perfusion.

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CHAPTER 10

Summary

Summary

Compliance and distensibility are vessel wall properties of large arteries which may play a role in cardiovascular disease. Arterial compliance reflects the buffering capacity of an artery; a decrease in compliance increases cardiac afterload and the risk of cardiac hypertrophy. Arterial distensibility reflects mainly the elasticity of the wall. A local decrease in distensibility might be associated with an increased risk of arterial wall damage, an important feature in atherosclerotic disease.

In *chapter 1* the definitions and determinants of these vessel wall properties are described. This chapter also reviews the relations between cardiovascular risk factors and large artery wall properties. From this review it can be concluded that for most cardiovascular risk factors results from studies on the relation between arterial wall properties and these risk factors are inconsistent. Explanations could be: different methods applied, small number of subjects, heterogeneous groups and possible differences between vascular territories.

To clarify the relation between vessel wall properties and different cardiovascular risk factors, in the present thesis the relation between cardiovascular risk factors and arterial diameter, distensibility and compliance coefficient of different vascular territories (the elastic aorta and common carotid artery and the muscular brachial and femoral arteries) was studied in a population sample of 497 men and women, age between 20-79 years.

Chapter 2 describes the population sample and methods used in the different studies.

In *chapter 3 and 4*, the influence of age and gender on the vessel wall properties of different vascular territories was investigated. After adjustment for possible confounding factors, i.e. mean blood pressure, pulse rate, body mass index, smoking, alcohol intake and antihypertensive treatment, covariance analysis showed that men had a larger diameter and compliance of all arteries. Distensibility was similar in both sexes with the exception of the brachial artery, which in men showed lower distensibility. The effect of age on large artery wall properties is not uniform, but depends on the vascular territory; with age arteries dilate and become stiffer, more in elastic than in muscular arteries. The effect of age on large artery wall properties also depends on gender; the increase in diameter of muscular arteries is more pronounced in women. In contrast to the well-known decrease in arterial compliance of elastic arteries with age, brachial artery compliance is not decreased with age and even increased in women.

The relation between menopause and large artery properties was investigated in a group of pre- and postmenopausal women and compared with men (*chapter 5*). Menopause per se was positively related to aortic stiffness. This may contribute to the rise in pulse pressure in women beyond age 50. Menopause was not related to stiffness of the other arteries.

Associations between obesity and arterial wall properties depend on the index of obesity, gender and the vascular territory (*chapter 6*). The majority of associations are found with body mass index (BMI). BMI-based obese subjects have a larger arterial diameter and stiffer arteries in both sexes. An android body habitus, i.e. an increased waist to hip ratio, does not appear to be of importance in women, but in men it is associated with a lower femoral artery distensibility and compliance. Skinfold thickness is negatively associated with brachial artery distensibility in women, whereas it does not appear to be of importance in men.

Altered arterial wall properties in BMI-based obese subjects can only in part be attributed to an increase in insulin resistance (*chapter 7*). The relation between insulin resistance and large artery wall properties is also gender-dependent. In women, insulin resistance is not related to any of the large artery wall properties. The relation between insulin resistance and

large artery wall properties in men depends on the vascular territory: compliance of the femoral artery was most affected by insulin resistance. Alteration of large artery properties in subjects with insulin resistance is probably due to increased insulin levels.

Insulin-dependent diabetes mellitus affects wall properties of central arteries (aorta, common carotid artery and femoral artery), but not of the medium-sized brachial artery (*chapter 8*). Large artery wall properties differ between complicated and uncomplicated IDDM patients. Distensibility and/or compliance of the aorta and carotid artery are lower in complicated IDDM. Compliance of the carotid artery of uncomplicated IDDM patients is even increased, suggesting that in an early phase of the disease arterial compliance may increase. Part of these results could be explained by a longer duration of disease. Regulation of diabetes, expressed by HbA1c, does not influence arterial wall properties.

In *chapter 9* the main conclusions from the studies are discussed. An important finding from our studies is that the influence of physiologic and pathologic influences is dependent on gender and vascular territory. In addition arguments are given for the use of large artery wall properties as a marker of cardiovascular disease. In this chapter also suggestions for future research are given.

CHAPTER 11

Samenvatting

Compliantie en distensibiliteit zijn vaatwandeigenschappen van grote slagaders (arteriën). Arteriële compliantie bepaalt het bufferend vermogen van een arterie, d.w.z. in welke mate de arterie het slagvolume van het hart kan opvangen en geleidelijk kan afgeven aan de perifere weefsels. Een verminderde compliantie leidt tot een toename in nabelasting van het hart en verhoogt het risico op hypertrofie van het hart. Arteriële distensibiliteit is een maat voor de elasticiteit van de vaatwand. Een locale afname van de distensibiliteit geeft een toename van de stress op de vaatwand en is geassocieerd met een verhoogd risico op vaatwandschade. Een vermindering van compliantie en distensibiliteit zijn geassocieerd met een verhoogd cardiovasculair risico.

In *hoofdstuk 1* worden de definities van de vaatwandeigenschappen beschreven en factoren die deze vaatwandeigenschappen bepalen/beïnvloeden. In dit hoofdstuk wordt er ook een overzicht gegeven van de relaties tussen bekende cardiovasculaire risicofactoren en de vaatwandeigenschappen. Uit dit overzicht blijkt dat er voor de meeste risicofactoren discrepanties bestaan tussen de resultaten van de verschillende studies. Verklaringen hiervoor kunnen zijn: [1] verschillende onderzoeksmethoden, [2] kleine aantallen personen per studie, [3] heterogene groepen en [4] mogelijk bestaan er ook verschillen tussen de arteriën onderling.

In dit proefschrift wordt gekeken naar de relaties tussen cardiovasculaire risicofactoren en diameter, compliantie en distensibiliteit van respectievelijk de grote buikslagader (aorta), de halsslagader (arteria carotis), de liesslagader (arteria femoralis) en de armslagader (arteria brachialis) in een populatiestudie.

Hoofdstuk 2 beschrijft de opzet van het onderzoek, de methoden die gebruikt zijn voor de metingen en de opbouw van de populatie, die bestaat uit een groep van 497 mannen en vrouwen, in de leeftijd van 20-79 jaar.

Hoofdstuk 3 en 4 beschrijven de invloed van leeftijd en geslacht op de arteriële vaatwandeigenschappen. Er werd gecorrigeerd voor mogelijk beïnvloedende factoren, zoals gemiddelde bloeddruk, hartfrequentie, gewicht (body mass index), roken, alcoholgebruik en gebruik van bloeddrukverlagende middelen. Covariantie analyse liet zien, dat mannen in vergelijking met vrouwen een grotere diameter en compliantie hebben van alle bestudeerde arteriën. De distensibiliteit was gelijk, met uitzondering van de arteria brachialis, waarvan de distensibiliteit bij mannen lager is dan bij vrouwen. Het effect van leeftijd op de vaatwandeigenschappen is niet eenduidig, maar hangt af van de arterie; met de leeftijd dilateren arteriën en worden stijver, meer in elastische dan in musculaire arteriën. Het effect van de leeftijd hangt ook af van het geslacht; de toename in diameter van musculaire arteriën is groter bij vrouwen dan bij mannen. In tegenstelling tot de bekende afname in arteriële compliantie van elastische arteriën met de leeftijd, neemt de compliantie van de arteria brachialis bij mannen niet af met de leeftijd en bij vrouwen zelfs toe.

De relatie tussen menopauze en vaatwandeigenschappen is onderzocht in een groep postmenopauzale vrouwen en vergeleken met een groep premenopauzale vrouwen en een groep mannen (*chapter 5*). Er was een positief verband tussen menopauze zelf en de stijfheid van de aorta. Dit zou (mede) een verklaring kunnen zijn voor de toename in polsdruk die gezien wordt bij vrouwen na de leeftijd van 50 jaar. Menopauze was niet gerelateerd aan de stijfheid van één van de andere arteriën.

Overgewicht, ofwel obesitas, kan op verschillende manieren gedefinieerd worden. o.a. d.m.v. de body mass index (BMI), huidploidikte en taille-heup ratio. Het verband tussen obesitas en vaatwandeigenschappen is afhankelijk van de bepaling van de obesitas, het

geslacht en de arterie die gemeten is (*chapter 6*). De meeste associaties worden gevonden met de body mass index. Mensen met overgewicht, gebaseerd op een te hoge BMI, hebben arteriën met een grotere diameter en een lagere distensibiliteit. Dit geldt zowel voor mannen als voor vrouwen. Een androïde (mannelijke) lichaamsbouw, dat wil zeggen een hoge taille-heup ratio, lijkt bij vrouwen niet van belang te zijn. Bij mannen is het geassocieerd met een lagere distensibiliteit en compliantie van de arteria femoralis. Bij vrouwen is er een negatief verband tussen huidploidikte en distensibiliteit van de arteria brachialis, terwijl dit bij mannen niet van invloed lijkt.

Personen met een hoge BMI zijn vaak ook ongevoeliger voor insuline: insuline-resistent. De verandering in arteriële vaatwandeigenschappen bij personen met een hoge BMI kan slechts voor een deel verklaard worden door insuline-resistentie (*chapter 7*). De relatie tussen insuline-resistentie en vaatwandeigenschappen is geslachtsafhankelijk. Bij vrouwen is er geen relatie tussen insuline-resistentie en vaatwandeigenschappen, terwijl er bij mannen wel een relatie is. Deze relatie is echter 'arterie-afhankelijk': de compliantie van de arteria femoralis wordt het meest beïnvloed door insuline-resistentie. De verandering in vaatwandeigenschappen als gevolg van insuline-resistentie wordt waarschijnlijk bepaald door de hyperinsulinemie.

Insuline-afhankelijke diabetes mellitus (IDDM) heeft een invloed op de centrale arteriën (aorta, arteria carotis, arteria femoralis), maar niet op de middelgrote arteria brachialis (*chapter 8*). Er bestaat een verschil in vaatwandeigenschappen tussen IDDM-patiënten met en zonder complicaties. Distensibiliteit en/of compliantie van de aorta en arteria carotis zijn lager bij IDDM patiënten met complicaties. De compliantie van de arteria carotis bij IDDM patiënten zonder complicaties is juist toegenomen. Dit suggereert dat in een vroege fase van de ziekte arteriële compliantie kan toenemen. Een deel van deze resultaten kan verklaard worden door een langere ziekteduur bij patiënten met complicaties. De regulatie van de diabetes, weerspiegeld door een laag HbA1c, heeft geen invloed op de arteriële vaatwandeigenschappen.

In *hoofdstuk 9* worden de belangrijkste conclusies uit dit proefschrift besproken. Een belangrijke conclusie is, dat de invloed van fysiologische en pathologische invloeden verschilt tussen mannen en vrouwen en ook tussen de verschillende arteriën. Daarnaast worden in dit hoofdstuk ook argumenten gegeven voor het gebruik van vaatwandeigenschappen als risicofactor voor of juist als uiting van cardiovasculaire ziekte. In dit hoofdstuk worden tenslotte ook suggesties gegeven voor vervolgonderzoek.

Dankwoord

Dankwoord

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Curriculum Vitae

Curriculum Vitae

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