Central hemodynamics and arterial function
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Chapter 1

General introduction and outline of the thesis

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GENERAL INTRODUCTION

Cardiovascular risk factors
Cardiovascular disease (CVD) is worldwide one of the leading causes of death. With the introduction of blood pressure and cholesterol lowering medication, platelet aggregation inhibitors and glucose lowering therapy the incidence of cardiovascular events has decreased substantially. The residual risk of cardiovascular disease remains substantial. Presently, in the Netherlands CVD is the second most common cause of death (www.cbs.nl). To further optimize treatment and/or to prevent CVD we need to refine our tools to determine which subjects are at risk and should receive treatment. This risk stratification is traditionally based on the assessment of cardiovascular risk factors. The INTERHEART study convincingly showed that nine potentially modifiable risk factors for cardiovascular disease are associated with more than 90% of the risk of an acute myocardial infarction.1 These risk factors are hypertension, abnormal lipids, smoking, diabetes, abdominal obesity, psychosocial factors, diet (consumption of fruits and vegetables), use of alcohol, and physical activity. The predictive value of these nine risk factors is consistent across men and women, young and old and among different ethnic groups. Clinically the Framingham risk score and the European Systemic Coronary Risk Evaluation (SCORE) are used to predict the risk of cardiovascular disease. These risk scores incorporate most but not all of the modifiable risk factors from the INTERHEART study. There are, however, groups that are not adequately identified by these risk scores. Younger persons, persons with only one risk factor and persons with rare genetic or congenital disorders affecting the cardiovascular system might not be identified with the traditional risk factor approach, although they might benefit from early cardiovascular prevention. Furthermore, most cardiovascular events occur in subjects who are categorized as low-risk according to the above mentioned risk scores. There is therefore a need to improve the prediction of CVD for the individual person to be able to identify those who might benefit most from treatment.

Central blood pressure and wave reflection
Improving risk stratification begins with optimizing assessment of individual risk factors. Just as there is discussion which physical measure best describes obesity and which lipid parameter is the best representative of dyslipidemia and has the highest predictive power of CVD, there has been debate which blood pressure component (systolic, diastolic or pulse pressure) yields the best predictive value for cardiovascular disease. Not only are the different blood pressure components debated, but also the location of the blood pressure measurement. Although it has long been realized that systolic blood pressure differs among the arterial system, treatment of hypertension has since the last 100 years been based on blood pressure readings from the brachial artery. Central aortic blood pressure, which is the blood pressure in the proximal aorta, however, may better reflect the blood pressure burden on the heart and brain and is therefore thought to be a better predictor of organ damage and cardiovascular events than peripheral
Systolic blood pressure amplifies when going from the heart to more distant arteries, while diastolic blood pressure remains constant. Pulse pressure as the difference between systolic and diastolic blood pressure therefore increases. This is known as pulse pressure amplification. The difference between peripheral and central blood pressure is explained by a phenomenon called pulse wave reflection. Pressure waves generated by contraction of the left ventricle, called forward waves, travel down the aorta and its main branches with a certain speed. They reflect at points where there is a discontinuity - branches or changes in diameter (reflection points) - and travel back to the heart as backward waves. Thus, pressure waves measured anywhere in the arterial system are the result of the interaction between forward and backward waves. The timing of forward and backward waves determines the height of the pressure wave and thus systolic and pulse pressure. Early or enhanced wave reflection causes increased central systolic pressure, which results in increased load to the left ventricle. Augmentation index (Alx) is a measure of wave reflection and is determined by heart rate, aortic stiffness and reflection site. These three factors can be pharmacologically modified. First, wave reflection and therefore Alx increases when heart rate is lowered as a result of prolonged ejection time causing a greater portion of the backward wave to arrive in late systole. This is for example seen during treatment with beta-blockers. Second, arterial stiffness is, among other factors, dependent on distending pressure and sympathetic tone of the artery. The speed by which pulse waves travel down the aorta and the arterial system, or pulse wave velocity (PWV), is a measure of arterial stiffness. Pharmacological agents that are able to lower blood pressure and/or sympathetic tone could decrease arterial stiffness and theoretically alter wave reflection. Finally, Alx can be changed by modifying the reflection site. Because Alx is the sum of different forward and backward waves, the location and contribution of the different reflection sites to Alx is difficult to establish. It is known that besides major bifurcations, the main reflection sites are thought to be high resistance small arteries and arterioles. Agents such as angiotensin II and noradrenalin induce vasoconstriction and have been shown to increase Alx, whereas vasodilators, such as nitroprusside and calcium channel blockers lower Alx.

Differences in peripheral and blood pressure are not only relevant because of the differences in predictive value of cardiovascular events, but even more because peripheral and central pressure can be altered differentially with antihypertensive agents. The landmark Conduit Artery Function Evaluation (CAFE) study has shown that beta-blocker/diuretic based treatment lowered peripheral blood pressure to the same extent as calcium channel blocker (CCB)/angiotensin converting enzyme (ACE) inhibitor based treatment, but importantly the latter treatment lowered Alx and central blood pressure significantly more. Interestingly, cardiovascular morbidity and mortality was significantly lower with CCB/ACE inhibitor treatment compared to beta-blocker/diuretic treatment.
Arterial structure and function

There are numerous markers of (subclinical) organ damage that are known to predict and are causally related to cardiovascular endpoints such as myocardial infarction and stroke: 1) left ventricular hypertrophy (LVH), 2) intima media thickness of the carotid artery (cIMT) and 3) pulse wave velocity (PWV). The combined European Society of Cardiology and European Society of Hypertension guideline on the treatment of hypertension acknowledges the added value of these markers of subclinical organ damage by allocating persons with subclinical organ damage to higher risk categories. The value of these risk markers at improving individual cardiovascular risk prediction is, however, still debated.

Atherosclerosis is a slow process and most individuals remain asymptomatic at its early stages. Intermediate or surrogate markers of atherosclerosis, such as cIMT are used to assess the burden of atherosclerosis. cIMT is measured non-invasively with ultrasonography and is a measure of carotid artery wall thickening, which is independent of classic cardiovascular risk factors. It is used as an intermediate endpoint in studies evaluating the effect of an intervention designed to counteract the ongoing process of atherosclerosis. Increased cIMT is associated with an increased risk, whereas regression of cIMT is associated with a reduction in cardiovascular events. The presence of plaques and stenoses, rather than just thickening of the carotid artery is associated with dramatically increased cardiovascular risk.

Where cIMT is a measure of atherosclerosis representing structural changes in the arterial wall, PWV is a measure of arterial stiffness describing more functional alterations of the arterial wall. PWV is considered the gold standard of non-invasive arterial stiffness measurements. PWV is an independent predictor of cardiovascular mortality. Possibly PWV could help identify persons at risk for cardiovascular disease. Two studies have shown that a high PWV, in subjects with a low SCORE risk (<5%) or with a low Framingham risk was a strong predictor for cardiovascular events, suggesting a better risk prediction by PWV in these individuals. Disagreement between risk score and PWV, especially in subjects with low risk scores implies that PWV is particularly useful in younger subjects, since age is the major contributor in these models. Whether PWV indeed improves risk stratification needs to be confirmed in prospective studies. PWV can be reduced by lowering blood pressure and there is some evidence that statin therapy improves PWV. An important issue that needs to be addressed in this respect is whether improvement in PWV will translate into a reduction in CVD.

Aims

To better appreciate the value of central blood pressure, wave reflection and large artery stiffness in the prediction of cardiovascular risk, the first aim of this thesis is to study central hemodynamics and large artery function with the use of non-invasive measurements in patients characterized by inherited structural and anatomical large artery abnormalities or a
genetic predisposition to these abnormalities. The second aim is to study the differential effects of both non-pharmacological and pharmacological interventions on peripheral and central hemodynamic and large artery function in subjects at risk of CVD. The third aim of our study came out of our observation that wave reflection appeared to decrease upon standing, a finding we thought counterintuitive at first. In the final part of this thesis we aim to further explore these findings and hypothesize on the possible pathophysiological mechanisms underlying the decline in wave reflection after postural change.

OUTLINE OF THE THESIS

This thesis describes the use of different non-invasive techniques to measure central hemodynamics and large artery structure and function. Part I of the thesis presents a series of studies focussing on central hemodynamics and large artery characteristics in patients with a congenital or genetic predisposition to structural and functional large artery abnormalities. In chapter 2 we examine structural and functional large artery alterations in carriers of a mutation in the lecithin:cholesterol acyl transferase (LCAT) gene and therefore lifelong exposed to low HDL-c levels. There is discussion whether LCAT mutation carriers have an increased risk of cardiovascular disease. We address this issue by measuring carotid artery thickness with 3.0 Tesla MRI and ultrasound, as a measure of atherosclerotic organ damage, in LCAT carriers and matched controls. In chapter 3 we investigate whether the structural abnormalities observed in LCAT mutation carriers were associated with functional changes in large arteries by measuring PWV. In chapter 4 we investigate micro- and macrovascular function in patients with Fabry disease, an X-linked hereditary lysosomal storage disorder caused by a deficiency of α-galactosidase A that leads to accumulation of globotriaosylceramide in various organs and tissues, including the arterial wall. In chapter 5 we examine whether apparently healthy asymptomatic first degree relatives of patients with premature coronary artery disease show signs of increased large artery stiffness and whether this is associated with coronary artery calcifications. Chapter 6 describes structural and functional alterations in patients with surgically corrected aortic coarctation. It has previously been shown that post-coarctectomy patients have enhanced wave reflection. We assess whether this can be pharmacologically modified with vasodilatory agents such as salbutamol and nitroglycerine. In chapter 7 we extend our research in post-coarctectomy patients by assessing determinants of enhanced wave reflection and by examining whether enhanced wave reflection is associated with cIMT and left ventricular mass as indicators of organ damage.

In Part II we assess peripheral and central hemodynamics in a number of intervention studies. In chapter 8 we assess the blood pressure lowering effects of cocoa in a double-blind placebo-controlled three-period cross-over trial. In chapter 9 we study the differential effects
of intravenous labetalol and sodium nitroprusside on peripheral and central hemodynamics in the immediate treatment of malignant hypertension. In chapter 10 we compare in a cross-over study the effects of carvedilol and metoprolol in heart failure patients and assess whether common genetic variants in the beta2-adrenergic receptor can mediate the treatment response. Chapter 11 describes the changes in hemodynamics and autonomic balance after gastric bypass surgery in morbidly obese persons.

Part III explores the effects of postural change from supine to standing on wave reflection. In chapter 12 we investigate the influence of increased peripheral resistance from supine to standing on wave reflection and the effects of age in this response to postural change. We elaborate on the wave reflection response during postural change in chapter 13. We investigate whether different angles of head up tilt will lead to a gradual decrease in wave reflection. Finally, in chapter 14 we set out to test our hypothesis that the reduction in wave reflection during standing partially depends on the beta2-adrenergic receptor and whether persons with specific haplotypes of the beta2-adrenergic receptor show an altered wave reflection response upon standing.
References


