Central hemodynamics and arterial function
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SUMMARY

Chapter 1 provides an introduction to this thesis. At first the pitfalls of current cardiovascular risk scores are discussed. This is followed by a short description of the value of central hemodynamics in assessing cardiovascular risk and effects of treatment. Finally, the value of PWV and its association with other indicators of subclinical organ damage is discussed.

Part I of the thesis presents a series of studies focusing on central hemodynamics and arterial structure and function in patients characterized by congenital abnormalities in or a genetic disposition to abnormalities in large artery structure and function.

In chapter 2 we investigated structural large artery alterations in lecithin:cholesterol acyl transferase (LCAT) gene mutation carriers. These patients have a lifelong exposure to low HDL-cholesterol levels, a strong predictor of cardiovascular disease. Whether LCAT mutation carriers have an increased risk of CVD is under dispute. We assessed IMT and plaque components of the carotid arteries using ultrasound and 3T MRI in LCAT mutation carriers and compared them to healthy age-matched controls. LCAT gene mutation carriers exhibited increased carotid artery wall thickening and had a higher total volume of atherosclerotic plaque components compared to age-matched healthy controls. The structural changes in the carotid arteries remained significant after adjustment for other cardiovascular risk factors pointing towards an increased cardiovascular risk in carriers of a LCAT gene mutation and low HDL-cholesterol.

In chapter 3 we assessed whether the observed structural changes in LCAT mutation carriers were associated with functional alterations of large arteries. We assessed large artery stiffness by non-invasive measurement of PWV. We showed that aortic PWV is increased in LCAT mutation carriers compared to age and sex matched controls, indicative of increased arterial stiffness. This difference remained significant in multivariate analysis and after exclusion of patients with CVD. In addition we demonstrated a strong correlation between arterial stiffness and thickness of the carotid arterial wall as assessed by ultrasound and 3T MRI showing that alterations in large artery function and structure coincide in this atherosclerotic phenotype.

In chapter 4 we investigated micro- and macrovascular function of 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. We found that IMT was increased and FMD was decreased in male Fabry patients compared to matched controls, whereas no difference in IMT and FMD was found in females. Disease severity, as assessed by lysoGb3, was associated with increasing IMT in
female patients. In males, however, lysoGb3 did not predict IMT. In both males and females, increases in plasma lysoGb3 were associated with lower FMD.

In chapter 5 we examined structural large artery alterations as assessed by PWV in patients with premature coronary artery disease and their first degree relatives by comparing them to first degree relatives and unrelated controls. We showed that PWV is increased in both patients with premature coronary artery disease and their first degree relatives who were free from CVD. This difference remained after correction for other cardiovascular risk factors. These data imply that apparently healthy asymptomatic first degree relatives of patients with premature coronary artery disease have increased structural large artery abnormalities indicative of increased arterial stiffness and early vascular aging.

In chapter 6 we studied wave reflection in adult post-coarctectomy (CoA) patients, a relatively common congenital heart defect characterized by a stenosis in the aortic arch. Despite successful surgical repair, adult CoA patients have an increased risk of cardiovascular disease and decreased life expectancy compared to the general population. Intra-arterial measurements have shown that blood pressure waves are altered in patients with aortic coarctation and that the change in pressure waveform may be explained by early and increased reflection of the pressure waves on the stenosis. We non-invasively assessed AIx, a measure of wave reflection, by applanation tonometry in CoA patients without hypertension or recoarctation. We showed that CoA patients had higher AIx compared to matched controls. In order to assess whether AIx can be pharmacologically modified in CoA patients we used salbutamol, a beta adrenergic agonist and nitroglycerine, a venous and arterial vasodilator to assess whether the wave reflection in CoA patients can be modified. At baseline and after administration of salbutamol and nitroglycerine AIx remained higher in CoA patients. The mean decrease in wave reflection for salbutamol was comparable between the groups. However, nitroglycerine reduced wave reflection to a larger degree in CoA patients than in control patients. This suggests that the increased wave reflection in CoA patients can, at least in part, be influenced by pharmacologically induced vasodilatation.

In chapter 7 we extended our study in CoA patients by assessing determinants of wave reflection and by examining the association between wave reflection and carotid IMT and LVM as markers of organ damage. Besides age and DBP, patch angioplasty type of surgery was an independent predictor of AIx in multivariate analysis. This supports the concept that enhanced wave reflection is partially caused by early reflection of pressure waves on the reconstructed and scarred aortic arch in CoA patients, because less elastic synthetic materials are used in the patch angioplasty procedure. Despite the increase in AIx we previously observed in CoA patients, AIx was not an independent predictor of carotid IMT or LVMI.
In Part II we assessed peripheral and central hemodynamics in a number of intervention studies.

Chapter 8 describes the findings of a study on the possible blood pressure lowering effect of cocoa. The consumption of cocoa has been associated with a decreased risk of cardiovascular morbidity and mortality. One of the mechanism by which cocoa could exert its presumed beneficial effects on cardiovascular disease is by lowering blood pressure. Theobromine, a phosphodiesterase inhibitor, which is present in cocoa in high concentrations, might contribute to the presumed blood pressure lowering effects of cocoa. In a double-blind placebo-controlled three-period cross-over trial we assigned healthy individuals with high-normal and stage 1 hypertension to a random treatment sequence of dairy drinks containing (1) placebo, (2) flavanol-rich cocoa with natural dose consisting of 106 mg theobromine or (3) theobromine enriched flavanol-rich cocoa with 979 mg theobromine. Participants were treated for three weeks with a two week wash-out period. Natural dose theobromine cocoa did not significantly change either 24-hour ambulatory or central systolic blood pressure, whereas theobromine enriched cocoa significantly increased 24-hour ambulatory systolic blood pressure while lowering central systolic blood pressure. We found no evidence for any antihypertensive effect of flavanol-rich cocoa. In contrast, theobromine enriched cocoa had a differential effect peripheral and central blood pressure. How these differential effects translate to the risk of CVD needs further exploration.

In Chapter 9 we studied the differential effects of intravenous labetalol and sodium nitroprusside (SNP) on peripheral and central blood pressure in the immediate treatment of malignant hypertension. The treatment of malignant hypertension calls for instant lowering of blood pressure. Guidelines advice to lower MAP by 25%, because larger reductions of MAP have been associated with symptomatic hypoperfusion of the brain, resulting in cerebral damage and even death. In this study we showed that during the treatment of malignant hypertension with labetalol or SNP aimed at a 25% reduction in MAP Labetalol gave a greater reduction in peripheral SBP and PP than treatment with SNP. Pulse pressure amplification did not change with labetalol, but increased with SNP. So, depending on the choice of antihypertensive drugs central pulsatile blood pressure components are not fully appreciated when looking at peripheral pressures. In the labetalol group, peripheral and central PP were lowered equally as can be appreciated from the unchanged PPA. On the other hand, when treatment with SNP would have been targeted at peripheral SBP, central SBP would have been lower than desired because of the increase in PPA. The possibly larger than expected reductions in central pressure are especially relevant in disease states with disturbed cerebral autoregulation such as malignant hypertension, where an uncontrolled drop in blood pressure might lead to cerebral hypoperfusion.
In chapter 10 we continued to study differences in peripheral and central blood pressure, this time in heart failure patients. One of the characteristics of heart failure is activation of the sympathetic nervous system. Beta-blockers inhibit the adverse effects of the sympathetic nervous system. They are therefore considered the cornerstone of pharmacological treatment of heart failure patients. In hypertensive patients, third generation (vasodilatory) beta-blockers, such as nebivolol and carvedilol, have been shown to reduce central blood pressure to a greater extent than first and second generation beta-blockers, such as atenolol and metoprolol. This may, at least in part, be caused by differences in heart rate reduction. In this cross-over study we investigated whether carvedilol lowers peripheral and central blood pressure more than metoprolol in heart failure patients when titrating for the same heart rate. A possible determinant of the blood pressure response to carvedilol may include common genetic variations in the beta2-adrenergic receptor gene (ADRB2). Two highly prevalent single nucleotide polymorphisms, Arg16Gly and Gln27Glu in the ADRB2 receptor gene, are associated with altered receptor trafficking and downregulation. These two polymorphisms form three common haplotypes (Arg16/Gln27, Gly16/Gln27 and Gly16/Glu27). Individuals homozygous for the Gly16/Glu27 haplotype show increased vasodilation in response to the beta2-receptor agonist isoproterenol compared to Arg16/Gln27. In young individuals the Arg16/Gln27 has been associated with higher blood pressures. Our second aim was, therefore, to assess whether common functional beta2-adrenergic receptor haplotypes mediate treatment response. Our study showed that compared to metoprolol, carvedilol lowered peripheral and central blood pressure to a similar extent while aiming at a similar rate. The higher blood pressure levels with metoprolol treatment were most pronounced in Arg16/Gln27 carriers.

Body weight is associated with blood pressure and losing weight will lead to a reduction in blood pressure. In obese persons, gastric bypass surgery induced weight loss has shown to decrease blood pressure. In chapter 11 we aimed learn more about the hemodynamic changes and baroreflex cardiovascular control involved by assessing the effects of weight loss six weeks after Roux-en-Y gastric bypass surgery on baroreflex sensitivity, systemic hemodynamics and the relation between peripheral and central blood pressure in 15 patients. Roux-en-Y gastric bypass surgery led to a 13±5 kg (10%) decrease in weight after six weeks and a significant decrease in blood pressure. The blood pressure reduction is caused by a marked decrease in cardiac output, while systemic vascular resistance slightly increased. Baroreflex sensitivity, as a measure of autonomic balance, significantly improved after surgery. Overall gastric bypass surgery led to an improved hemodynamic profile and the enhanced baroreflex sensitivity suggests a change in autonomic balance towards increased parasympathetic heart rate control.

Part III explores the effects of postural change from supine to standing on wave reflection.
It has previously been shown that during 60° head up tilt wave reflection decreases compared to supine position. In chapter 12 we investigated the influence of increased peripheral resistance from supine to standing on wave reflection and the effects of age in this response to postural change. In 15 healthy older and 15 younger individuals aortic pressure and flow were calculated from finger pressure during supine rest and active standing. Then from aortic pressure and flow forward and backward pressure waves, reflection magnitude (ratio of backward and forward pressure waves), augmentation index, and peripheral resistance were derived. Both in the healthy older and younger subjects, upon standing, peripheral resistance increased, whereas reflection magnitude and augmentation index decreased. The opposite changes in reflection magnitude and peripheral resistance suggest that reflection and pressure augmentation are not solely dependent on peripheral resistance.

In chapter 13 we elaborated on the wave reflection response to postural change. We studied hemodynamics and wave reflection, calculated from continuous finger arterial pressure monitoring, during different angels of head up tilt in ten healthy volunteers. We showed that from supine position to 30 and 70 degrees head up tilt and active standing (90º) Alx and the reflection magnitude (RM) gradually decreased in the presence of increasing systemic vascular resistance, stroke volume and heart rate decreased.

Finally, in chapter 14 we set out to test our hypothesis that the reduction in wave reflection during standing partially depends on ADRB2 mediated vasodilation and that Arg16Gln27 carriers show a blunted wave reflection decrease upon standing compared to Gly16Glu27 carriers. As in chapter 12 and 13 we showed in this study that from supine to standing total peripheral resistance increased while wave reflection decreased. Wave reflection and hemodynamic response to standing, however, were not different between subjects homozygous for Gly16Glu27 or Arg16Gln27 haplotype. We speculate that the change in body position might have an effect on wave reflection through changes in arterial diameter and function.

PERSPECTIVES

The general aim of this thesis was to study whether central hemodynamics and arterial stiffness provide additional value over peripheral blood pressure in the prediction and treatment of cardiovascular risk by studying phenotypes which are characterized by early vascular ageing or anatomic abnormalities of the aorta. In addition we explored the effect of different pharmacological agents on peripheral and central hemodynamics. We have shown that apparently healthy and asymptomatic subjects with inherited low HDL-cholesterol, Fabry disease and persons with a family history of premature coronary artery disease show signs of early vascular aging and should be considered at increased risk of cardiovascular disease. We showed that
antihypertensive interventions, either with nutraceuticals or pharmacological agents, might have a differential impact on peripheral and central hemodynamics. The implications of these findings and future perspectives will be discussed below.

**Arterial stiffness**

Large artery stiffness increases with age and is the principal determinant of isolated systolic hypertension (ISH) and hypertension-related cardiovascular morbidity and mortality. ISH is more difficult to treat than combined systolic-diastolic hypertension. In the past two decades the focus of hypertension research has therefore shifted towards the predictive value of arterial stiffness indices. There are several methods to measure arterial stiffness. PWV is considered the gold standard arterial stiffness measurements. Both in hypertensive patients and in the general population PWV has been shown to predict cardiovascular morbidity and mortality independent of (and beyond) blood pressure and other cardiovascular risk factors.\(^1\)\(^,\)\(^2\) PWV is therefore increasingly used in prospective observational studies and clinical trials. We showed that 1) LCAT mutation carriers have increased PWV and cIMT compared to age matched controls, 2) Fabry patients have increased cIMT but no significant increase in PWV and 3) first degree relatives of patients with premature coronary artery disease have increased PWV compared to healthy controls. Thus arterial stiffness seems to be a distinct entity that is not always associated with structural large artery abnormalities. Possible implementation of PWV measurements in the follow up of subjects at risk of cardiovascular disease should therefore be further studied.

Before PWV measurements can be implemented in clinical practice to assess cardiovascular risk, however, several issues need to be addressed. First, the different systems to measure PWV that are commercially available show important differences in absolute values of PWV. These values mainly differ because of differences in 1) mathematical ways of determining the beginning of the pulse wave and 2) measuring the path length of the pulse waves. These issues have been addressed by calculating equations to convert between the different algorithms of foot-of-the-wave assessment and between the different path lengths.\(^3\)\(^,\)\(^4\) This approach is far from perfect and true standardisation between the different methodologies should be implemented. Second, reference values for PWV are urgently needed to identify individual patients at risk for cardiovascular disease. Recently, a collaboration has generated normal and reference values of PWV per age decade and blood pressure category.\(^5\) With these reference values individualized risk prediction becomes feasible. However, there is debate whether implementing PWV in the clinical work-up of patients will improve risk stratification. A recent analysis from the Rotterdam study showed that PWV measurements in an elderly population (n= 2849, mean age 72 years) was significantly associated with cardiovascular risk, but did not improve risk stratification.\(^6\) However, in a middle-aged population (n=1968, age 41-71 years) PWV measurements were independently associated with cardiovascular disease and significantly improved cardiovascular risk prediction, especially in subjects with low estimated cardiovascular disease risk (<5%
cardiovascular mortality in 10 years according to SCORE). Furthermore a recent analysis from the Framingham Heart Study (mean age 63 years) showed that risk of cardiovascular disease increased by 48% per SD increase in PWV. The group of asymptomatic first degree relatives of patients with premature coronary artery disease described in chapter 5 are a perfect example of an apparently low risk group according to traditional risk score, who do show signs of early vascular aging and might therefore be at increased risk of cardiovascular disease and should receive close follow up and possibly early preventive (pharmacological) interventions. Finally, it is still unclear whether identification and treatment of persons at high-risk for cardiovascular disease based on PWV measurements will lead to improved outcome since prospective intervention studies are missing.

In conclusion the added value of PWV seems to be in risk stratification of individuals with a low risk according the traditional risk scores. This should be assessed in prospective studies.

Central hemodynamics

Central hemodynamic measurements provide a unique opportunity to study the pathophysiological mechanisms behind cardiovascular diseases and treatment strategies. The pivotal question is whether central blood pressure and wave reflection provide added value over peripheral blood pressure components in clinical practice. In other words: should we convince family physicians, internists, cardiologists or any other medical professional involved in the prevention and/or treatment of cardiovascular disease to perform central blood pressure measurements in stead of or next to ‘normal’ brachial blood pressure readings? Clearly, there is more and more epidemiological evidence that central blood pressure is a better predictor of cardiovascular morbidity and mortality than peripheral or brachial blood pressure. The added value, however, seems small. Apart from the fact that there still are technical issues about the correct way of calibrating central pressure readings, there have so far been no clinical end-point studies in which treatment was guided by central rather than peripheral blood pressure measurements. Although effective treatment options, including lifestyle modifications and pharmacological agents to lower blood pressure and reduce target organ damage are available, one of the biggest problems is low awareness and control of hypertension. A population based study in the US demonstrated that only 36.8% of hypertensive patients have controlled blood pressure values. Compared to the US these figures for Europe are even worse. The main focus of clinicians should be on controlling hypertension in general, rather than on fine tuning treatment. Nevertheless, there are clinical situations were the additional value of central blood pressure may be of particular interest. There are individuals, mainly young men, who have brachial systolic hypertension, but normal central blood pressures. This is called spurious systolic hypertension or pseudo systolic hypertension of youth and has been attributed to extreme pulse pressure amplification and low wave reflection, because of highly elastic arteries. This view, however, has been argued by suggesting increased elevated stroke volume and/or aortic stiffness, which have been observed in young systolic hypertensives, contributed
Because central blood pressure and echocardiograms were normal in these patients, they are likely not at increased risk for cardiovascular disease, although this also is debated. Estimating central blood pressure using applanation tonometry may be an excellent way of identifying these patients, who may not benefit from blood pressure lowering treatment, but long term follow-up studies assessing the risk of hypertension and cardiovascular disease are lacking.

Furthermore there is some evidence that agents that exert a greater effect on central blood pressure may give additional cardiovascular protection. For example, the CAFE study has shown that although beta-blocker/diuretic based treatment lowered peripheral blood pressure to the same extent as CCB/ACE-inhibitor based treatment, central blood pressure was significantly lower in the latter group. It was also observed that cardiovascular morbidity and mortality was significantly lower with CCB/ACE inhibitor treatment, but the link between the lower central blood pressure and the reduction in cardiovascular events has never formally been established. Therefore it is great importance that clinical trials provide evidence that central blood pressure guided therapy gives a reduction in cardiovascular morbidity and mortality compared to peripheral blood pressure guided therapy, before we implement central hemodynamics in clinical practice. Perhaps new devices that have been developed to assess the 24 hour ambulatory central blood pressure profile can contribute to this.