In line with Guyton's work, the goal of our research was to explore in three European populations whether the properties of large arteries are associated with renal sodium handling, which itself changes with environmental factors and with variation in a large number of genes. Before engaging in the genetic analyses proper, we first studied the familial aggregation and the heritability of arterial properties. In all our analyses, we accounted for relatedness among participants and for covariables and confounders.

In a first study, we compared the arterial characteristics and blood pressure (BP) in normotensive offspring of two normotensive parents (OFF/NT) and normotensive offspring, who had at least one hypertensive parent (OFF/HT). We measured peripheral pulse pressure (PPp) by conventional and 24-h ambulatory BP. A SphygmoCor device was used to determine the central (CAIx) and peripheral (PAIx) augmentation indexes, central pulse pressure (PPc), and aortic pulse wave velocity (aPWV). Compared with OFF/NT (n=59; 16 to 34 years of age), the OFF/HT (n=174; 17 to 40 years) had higher ($0.14<P<0.0007$) BP and PPp on conventional measurement (121/75 vs. 114/71 mm Hg and 46 vs. 42 mm Hg) as well as on 24-h ambulatory monitoring (118/70 vs. 114/67 mm Hg and 48 vs. 47 mm Hg). OFF/HT, compared with OFF/NT, also had higher ($0.05<P<0.0008$) PPc (28 vs. 26 mm Hg), PAIx (54.7% vs. 44.9%), CAIx (108.8% vs. 99.8%), and aPWV (7.4 vs. 6.6 m/sec). However, complex adjustment including mean arterial pressure and age removed the differences between the offspring in CAIx, PAIx, and aPWV.

In a family-based population sample consisting of 204 parents (mean age, 51.7 years) and 290 offspring (29.4 years), we investigated the heritability and familial aggregation of PPp, CAIx, PAIx and aPWV. We partitioned the phenotypic correlation between these traits into shared genetic and environmental components. We found significant heritability for PPp, CAIx, PAIx, and mean arterial pressure ranging from 0.37 to 0.41; $P\leq0.0001$. The parent-offspring correlation coefficients were significant for all arterial indexes ($r\geq0.12$; $P\leq0.02$) with the exception of PPc ($P=0.90$). The sib-sib correlations were also significant for CAIx ($r=0.22$; $P=0.001$). The genetic correlation between aPWV and the other arterial indexes were significant ($\rho G\geq0.29$, $P<0.0001$). The corresponding environmental correlations were only significantly positive for PPp ($\rho E=0.10$. $P=0.03$).

In the Flemish population sample, we also ultrasonographically measured diameter, cross-sectional compliance (CC) and distensibility (DC) of the carotid, brachial, and femoral arteries. In multivariable-adjusted analyses of 1069 untreated subjects (mean age, 41.6 years), CC and DC of the femoral artery increased with higher fractional distal sodium reabsorption (RNadist), as assessed by the clearance of endogenous lithium. Differences associated with a 1-SD change in RNadist were 51.7 mm2/kPa □10-3 ($P=0.0002$) and 0.56□10-3/kPa ($P=0.004$) for femoral CC and DC, respectively. In women as well as in men, a 1-SD increment in fractional proximal sodium reabsorption (RNaprox) was associated with decreases in femoral and brachial diameter, amounting to 111.6 □m ($P=0.003$) and 52.5 □m ($P=0.016$), respectively. There was no consistent association between the properties of the elastic carotid artery and renal sodium handling.

In 1126 subjects from the same Flemish population (mean age, 43.8 years), we investigated whether arterial characteristics are related to the genes encoding ADD1 (Gly460Trp), ADD2 (C1797T) and ADD3 (A386G). In single gene analyses, brachial diameter was 0.15 mm ($P=0.0022$) larger, and brachial CC and DC were 0.017 mm2/kPa ($P=0.0029$) and 1.55 10-3/kPa ($P=0.013$) lower in ADD3 AA than ADD3 GG homozygotes with an additive effect of the G allele. In multiple-gene analyses,

the association of brachial diameter and DC with the ADD3 G allele only occurred in ADD1 GlyGly homozygotes. Otherwise, the associations between the arterial phenotypes in the three vascular beds and the ADD1 or ADD2 polymorphisms were not significant. There was no evidence for population stratification ($0.07 \leq P \leq 0.96$). Transmission of the mutated ADD3 G allele was associated with smaller brachial diameter in 342 informative offspring (–0.12±0.04 mm; P=0.0085) and in 209 offspring, who were ADD1 GlyGly homozygotes (–0.14±0.06 mm; P=0.018). Finally, in 1064 Flemish subjects (mean age, 43.6 years), we assessed the multiplegene effects of ADD1 (Gly460Trp), AGT (C–532T and G–6A) and AT1R (A1166C). In ADD1 Trp allele carriers, but not in ADD1 GlyGly homozygotes (P-value for interaction ≤0.014), femoral CC was significantly higher (0.74 vs. 0.65 mm2/kPa; P=0.020) in carriers of the AT1R C allele than in AT1R AA homozygotes, with a similar trend for femoral DC (11.3 vs. 10.2 10-3/kPa; P=0.055). Family-based analyses confirmed these results. Brachial diameter (4.35 vs. 4.18 mm) and plasma renin activity (PRA, 0.23 vs. 0.14 ng/ml/h) were increased ($P \leq 0.005$) in AGT CG haplotype homozygotes compared with non-carriers, whereas the opposite was true for brachial DC (12.4 vs. 14.4 10-3/kPa; P=0.011). There was no interaction between AGT and any other gene in relation to the measured phenotypes.

In conclusion, in this doctoral dissertation, we demonstrated significant familial aggregation and significant heritability of arterial properties. We also noticed that higher RNadist was associated with higher femoral CC and DC, and that higher RNaprox was associated with decreased diameters of muscular arteries. The aforementioned observations justified our analyses of genes, which are involved in renal sodium handling. In ADD1 GlyGly homozygotes, the properties of the brachial artery were related to the ADD3 (A386G) polymorphism. Furthermore, ADD1 and AT1R interactively determined the elastic properties of the femoral artery. There was a single-gene effect of the AGT promoter haplotypes on brachial properties and PRA. Overall, our findings suggest, that there might be a genetically determined influence of renal sodium handling on arterial properties, or vice versa, or that common genetic pathways might influence both arterial and renal function.