Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in premenopausal women. It is associated with an increased risk of diabetes type 2 and cardiovascular diseases. In part, this may be due to the fact that PCOS is often associated with obesity. (Central) obesity itself is also associated with metabolic and cardiovascular risk factors. However, a substantial number of women with PCOS are not obese. Therefore, the question arises whether such women are also at a greater risk of diabetes type 2 and cardiovascular disease, i.e. whether PCOS increases these risks independently of the presence of obesity.

To gain more insight into these issues, the general purpose of the present thesis was to assess insulin sensitivity, micro- and macrovascular function in lean and obese women with and without PCOS. We were interested in the metabolic and vascular function in these women because vascular dysfunction and metabolic insulin resistance are associated with type 2 diabetes and cardiovascular diseases. Chapter 1 contains the outline of the present thesis and chapter 2 provides a description of the methods used for the assessment of vascular function and metabolic insulin resistance.

Before starting the measurements of the vascular- and metabolic function in women with PCOS, two methodological issues were a main concern to us. First, as obesity plays a (central) role in the development of cardiovascular risk factors in women with PCOS, we were interested in whether BMI is a valid separator. In chapter 3 we validated simple anthropometric measurements with the gold standard technique for determining body fat (distribution), Dual-energy X-ray absorptiometry (DXA). We showed that, in Dutch Caucasians, truncal skinfolds, waist circumference and BMI were positively correlated with central fat mass as measured by DXA. We preferred to use BMI instead of skinfolds or waist circumference as separator in our studies because this measure allowed us an easier comparison of our data with the existing literature in which BMI is predominantly used. However, in future studies waist circumference is still preferable particularly when the effect of central fatness on cardiovascular risk factors is studied.

Second, since menstrual-cycle-related female sex hormones changes can affect microvascular and metabolic function, we investigated this issue in chapter 4. We showed that, in healthy ovulatory women, microvascular function do not demonstrate a clear menstrual cycle-dependent variation. We also did not find cycle-dependent variation in insulin sensitivity (i.e. metabolic function), or blood pressure. Therefore, in future studies, microvascular function as presented in chapter 4, do not necessarily need to be standardized with regard to a specific phase of the menstrual cycle.

Chapter 5, 6 and 7 represents the studies which where performed to investigate the general purpose of the present thesis as stated above. In chapter 5 we measured the microvascular function as the response of endothelium-dependent vasodilatation on insulin in lean and obese women with and without PCOS. Furthermore, insulin sensitivity was determined with the gold standard, i.e isoglycemic hyperinsulinemic clamp technique. We demonstrated two key findings that first, obese as compared to lean women were characterized by an impairment of the endothelial microvascular response to insulin (microvascular insulin resistance). Second, only obese and not lean women had metabolic insulin resistance. In addition, PCOS per se was accompanied by aggravation of metabolic insulin resistance only in the obese women. In other words, the presence of PCOS per se was not accompanied by microvascular- and metabolic insulin resis-
tance. However, PCOS in the presence of obesity were more metabolic insulin resistant as compared to obese controls.

In chapter 6 we measured the microvascular function as the response of capillary recruitment on insulin, *i.e.* insulin-induced capillary recruitment in stead of endothelium-dependent vasodilatation. We provide evidence that both lean and obese women with PCOS are characterized by impaired insulin-induced capillary recruitment. In addition, we demonstrated that insulin-induced capillary recruitment is a determinant of glucose uptake in lean, but not in obese women with or without PCOS. However, despite the fact that PCOS *per se* demonstrated an impaired insulin-induced capillary recruitment, obesity remains to have the largest effect on glucose uptake (*i.e.* metabolic insulin resistance). Furthermore, our data provide correlative evidence that hyperandrogenism in PCOS may contribute to insulin resistance.

Next to the microvascular function, we were interested in the macrovascular function in lean and obese women with PCOS. In chapter 7 we therefore investigated stiffness of the carotid, femoral and brachial arteries, and of the aorta. The main finding of this study was that (central) obesity, but not PCOS, was associated with greater arterial stiffness. In addition, PCOS had no discernible influence on the association between obesity and increased arterial stiffness. Taken together, these results suggest that any greater arterial stiffness in young women with PCOS is conferred by the effects of obesity, not by PCOS itself.

Finally, chapter 8 provides a general discussion of the results in the present thesis, discusses the issue if we should screen PCOS women for cardiovascular risk factors and provides future strategies for further research of cardiovascular health in women with PCOS.