Summary

In the present thesis we have investigated whether there is a role for microvascular dysfunction as a potential pathophysiological mechanism in linking obesity with insulin resistance and hypertension, all components of the metabolic syndrome and important cardiovascular risk factors. Defects in muscle microvascular function may contribute to insulin resistance through impaired availability of glucose and insulin to peripheral muscle cells and to elevated blood pressure through an increase in peripheral vascular resistance. In addition, insulin resistance and hypertension develop in situations of elevated cortisol levels. In this thesis we have studied whether associations between cortisol and these components of the metabolic syndrome may be, at least in part, explained by microvascular dysfunction. Finally, microvascular defects in the kidney are thought to play a role in the initiation and maintenance of salt sensitivity of blood pressure through the induction of renal vasoconstriction and interstitial inflammation. Salt sensitivity of blood pressure is a cardiovascular risk factor per se and is also closely related to insulin resistance and hypertension. Microvascular dysfunction not confined to a single organ may underlie these latter relationships. A better understanding of the role of microvascular function in associations between cardiovascular risk factors mentioned above may initiate further studies after microvascular function as a preventive or therapeutic target.

Several animal and human studies have suggested that insulin redirects blood flow from non-nutritive vessels to nutritive capillary beds, thereby enhancing the access of insulin and glucose to peripheral muscle cells. Insulin-mediated effects on microvascular perfusion have never been studied directly by intramuscular measurements in humans. In chapter 2, we showed that insulin affected human intramuscular microvascular perfusion as measured directly with the laser Doppler technique. Systemic hyperinsulinaemia increased two different measures of intramuscular microvascular perfusion: reactive hyperaemia after arterial occlusion and vasomotion. First, hyperinsulinaemia increased the maximal reactive response in intramuscular laser Doppler perfusion following arterial occlusion and reduced the time needed to reach this maximal response. Second, hyperinsulinaemia enhanced intramuscular microvascular vasomotion, in a way indicative of an increase in the contribution of endothelial and neurogenic activity. Also, we confirmed previous findings of stimulatory effects of insulin on total limb blood flow and skin microvascular perfusion. Taken together, these data show that the vascular effects of insulin in humans are not limited to total blood flow and the skin microvascular perfusion, but extend to microvascular perfusion in the muscle.

Obesity is associated with an increased risk of developing insulin resistance, hypertension and microangiopathy. We hypothesised that obesity is associated with microvascular dysfunction and that this contributes to the development of these obesity-associated disorders. In chapter 3, we demonstrated that obesity in humans is indeed characterised by defects in skin microvascular function, i.e. postocclusive capillary recruitment and endothelium-dependent vasodilation. Also, impairment of these measures of microvascular function was associated with elevated blood pressure and insulin resistance in both lean and obese women together. In addition, obesity-associated microvascular defects could be shown not only at resting conditions but also during systemic hyperinsulinaemia. Furthermore, in chapter 4, we described that local and direct insulin-induced vasodilatory effects on the skin microvasculature are impaired in obesity. In the same chapter, we demonstrated obesity-associated defects in microvascular vasomotion. More precisely, obesity was characterised by reduced overall microvascular vasomotion in a way that is indicative of altered endothelial and neurogenic activity. Thus, our data demonstrate that obesity is clearly associated with defects in microvascular function. In addition, obesity is characterised not only by reduced peripheral glucose uptake, i.e. metabolic insulin resistance, but also by impaired insulin-induced microvascular effects, so-called microvascular insulin resistance. These phenomena may be functionally coupled, because the latter may limit availability of glucose and insulin.
to muscle cells and, consequently, may explain part of the obesity-associated reduction in peripheral glucose uptake. Also, obesity-associated defects in microvascular function may contribute to the development of hypertension and disease entities that are wholly or in part caused by microangiopathy, notably retinopathy, nephropathy and heart failure.

Central adiposity is associated with cardiovascular risk independently of overall adiposity. Part of this association may be explained by enhanced secretion of cytokines by visceral adipocytes resulting in a general proinflammatory state. Microvascular dysfunction may link specifically central adiposity with cardiovascular risk factors, such as insulin resistance and hypertension. In chapter 5, we showed that in adults visceral adiposity as measured with MRI was inversely associated with capillary recruitment, independently of total body adiposity. Also, in both adults and children, truncal subcutaneous adipose tissue using skinfold measurements was inversely related to capillary recruitment. Furthermore, in adults, the association between visceral adiposity and capillary recruitment could, at least statistically, be partly explained by a composite inflammatory score, containing information about plasma C-reactive protein, interleukin-6 and tumour necrosis factor-α. These data in adults suggest a role for visceral adiposity and its associated proinflammatory state in capillary perfusion. Also, our findings in children and adults suggest that not only visceral but also truncal subcutaneous adiposity is detrimental for capillary perfusion and that this process may start before puberty. These observations underline the necessity for interventions in childhood to prevent truncal obesity and its associated cardiovascular risk.

Obese individuals are exposed to daylong increased systemic FFA concentrations. Previous studies have shown that elevation of FFA concentrations resulted in insulin resistance and elevated blood pressure whereas lowering of FFA concentrations increased insulin sensitivity. Therefore, FFA-induced modulation of microvascular function may contribute to obesity-associated insulin resistance, hypertension and microangiopathy. In chapter 6, we demonstrated that in lean women, acute elevation of FFA levels impaired microvascular function, i.e. postocclusive capillary recruitment and endothelium-dependent vasodilation, both in the basal state and during hyperinsulinaemia. In parallel, overnight lowering of FFA levels in obese women improved capillary recruitment both in the basal state and during hyperinsulinaemia. This suggests that elevated FFA levels in obesity may contribute to microvascular dysfunction. Furthermore, in lean and obese women, changes in FFA levels were inversely associated with changes in capillary recruitment and insulin-mediated glucose uptake. Moreover, in lean and obese women, these changes in microvascular function could statistically explain approximately 29% of the association between changes in FFA levels and changes in insulin-mediated glucose uptake. These data further support functional coupling between insulin’s stimulatory microvascular and metabolic effects by concomitant changes in both effects during FFA elevation and lowering. Furthermore, they underline the importance of microvascular dysfunction as a partial explanation for FFA-induced insulin resistance in obesity.

Situations of endogenous and exogenous cortisol access are characterised by elevation of blood pressure and insulin resistance. Cortisol-related impairments of microvascular function may explain part of the cortisol-induced hypertension and insulin resistance. In chapter 7, we provided evidence of an inverse association between urinary cortisol and skin capillary recruitment in healthy women, but not in men. Furthermore, linear regression analyses showed that, in women, capillary recruitment explains approximately 37% of the cortisol-blood pressure relationship. These findings in healthy women suggest that interventions directed at preservation or improvement of microvascular function may be worthwhile in women in whom cortisol excess is to be expected.

Microvascular injury to the kidney is thought to play a role in the initiation and maintenance of salt sensitivity of blood pressure. Therefore, generalised microvascular dysfunction may contribute to the development of salt sensitivity, insulin resistance and hypertension, and may thus link these cardiovascular risk factors. In chapter 8, we demonstrated a strong inverse linear association between capillary recruitment and endothelium-dependent vasodilation in the skin microvasculature on the one
hand and salt sensitivity of blood pressure on the other hand. Also, we confirmed previous findings that salt sensitivity of blood pressure is inversely associated with insulin sensitivity and positively associated with blood pressure. More importantly, we demonstrated that the relationship of salt sensitivity with both insulin sensitivity and blood pressure is largely, at least statistically, dependent on microvascular function. These data are in agreement with a potential central role for generalised microvascular dysfunction as a link between salt sensitivity, insulin resistance and hypertension.