Microvascular Dysfunction
A Potential Pathophysiological Role in the Metabolic Syndrome

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Obesity and a central body fat distribution, hypertension, insulin resistance, glucose intolerance, dyslipidemia, and proinflammatory and prothrombotic factors are all part of the metabolic syndrome. The metabolic syndrome defines a clustering of metabolic risk factors which confers an increased risk for type 2 diabetes and cardiovascular disease. In the past years a large amount of research has been aimed at elucidating the pathophysiology underlying this clustering of risk factors, because a better understanding may lead to new therapeutic approaches that specifically target underlying causes of the metabolic syndrome.

Recently, it has become clear that microvascular dysfunction, by affecting both pressure and flow patterns, may have consequences not only for peripheral vascular resistance, but also for insulin-mediated changes in muscle perfusion and glucose metabolism, providing a novel pathophysiological framework for understanding the association between hypertension, obesity, and impaired insulin-mediated glucose disposal.

The present article examines recent data concerning the role of microvascular dysfunction as an explanation for the associations among hypertension, obesity, and impaired insulin-mediated glucose disposal.

Description of the Microcirculation
An exact definition of the microcirculation is elusive. Morphologically, the microcirculation is widely taken to encompass vessels <150 μm in diameter. It therefore includes arterioles, capillaries, and venules. Alternatively, a definition based on arterial vessel physiology rather than diameter or structure has been proposed. By this definition, all arterial vessels that respond to increasing pressure by a myogenic reduction in lumen diameter are included in the microcirculation. Such a definition would include the smallest arteries and arterioles in the microcirculation in addition to capillaries and venules. Small arterial and arteriolar components should, therefore, be considered a continuum rather than distinct sites of resistance control.

A primary function of the microcirculation is to optimize nutrient and oxygen supply within the tissue in response to variations in demand. A second important function is to avoid large fluctuations in hydrostatic pressure at the level of the capillaries causing disturbances in capillary exchange. Finally, it is at the level of the microcirculation that a substantial proportion of the drop in hydrostatic pressure occurs. The microcirculation is therefore extremely important in determining overall peripheral vascular resistance.

Microvascular Dysfunction in Hypertension and Obesity
In hypertension, the structure and function of the microcirculation are altered. The mechanisms regulating vasomotor tone are abnormal, leading to enhanced vasoconstriction or reduced vasodilator responses. Moreover, there are anatomic alterations in the structure of individual precapillary resistance vessels, such as an increase in their wall-to-lumen ratio. Finally, there are changes at the level of the microvascular network involving a reduction in the number of arterioles or capillaries within vascular beds of various tissues (eg, muscle and skin), so called vascular rarefaction. In obese individuals similar defects in the microcirculation can be demonstrated. In addition, measures of obesity in healthy individuals are strongly related to skin microvascular function. In adults, visceral adiposity as measured with MRI and truncal subcutaneous adipose tissue using skinfold measurements are inversely associated with capillary recruitment.

Taken together, microvascular dysfunction in different tissues has been established in both hypertension and obesity.

Microvascular Dysfunction as a Cause of Hypertension
In most forms of experimental and clinical hypertension, cardiac output is close to normal and the peripheral vascular resistance is increased in proportion to the increase in blood pressure. The increase in total peripheral vascular resistance is likely to reflect changes in vessels ranging from 10 to 300 μm in diameter. In several tissues capillary density has

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been found to correlate inversely with blood pressure in hypertensive and normotensive subjects.\textsuperscript{2-5, 7} Whereas it has been known for many years that increased wall-to-lumen ratio and microvascular rarefaction can be secondary to sustained elevation of blood pressure,\textsuperscript{3} there is also evidence that abnormalities in the microcirculation precede and thus may be a causal component of high blood pressure. Microvascular rarefaction, similar in magnitude to the rarefaction observed in patients with established hypertension, can already be demonstrated in subjects with mild intermittent hypertension and in normotensive subjects with a genetic predisposition to high blood pressure.\textsuperscript{3, 5, 6} Moreover, in hypertensive subjects, capillary rarefaction in muscle has been shown to predict the increase in mean arterial pressure over 2 decades.\textsuperscript{9} More recently, a smaller retinal arteriolar diameter has been shown to predict the occurrence and development of hypertension in a prospective population-based study of normotensive middle-aged persons.\textsuperscript{10} In addition, calculations by mathematical modeling of in vivo microvascular networks predict an exponential relationship between capillary and arteriolar number and vascular resistance. Total vessel rarefaction up to 42\% (within the range observed in hypertensive humans) can increase tissue vascular resistance by 21\%. Thus, it seems likely that microvascular abnormalities can both result from and contribute to hypertension, and a “vicious cycle” may exist in which the microcirculation maintains or even amplifies an initial increase in blood pressure. However, according to the Borst-Guyton concept, chronic hypertension can occur only if renal function is abnormal with a shift in the renal pressure-natriuresis relationship. In the absence of the latter, increased peripheral resistance only temporarily raises blood pressure, to be followed by an increase in renal sodium excretion restoring blood pressure toward normal. Importantly, therefore, subtle renal microvascular disease\textsuperscript{11} as well as a reduced number of nephrons\textsuperscript{12} may reconcile the Borst-Guyton concept with the putative role of vessel rarefaction in the etiology of high blood pressure. This may also explain the observed salt sensitivity of blood pressure in insulin resistance subjects.\textsuperscript{13}

It is important to realize that a decreased capillary density also affects the spatial pattern of flow in the microvascular bed, causing a nonuniform distribution of blood flow among exchange vessels. This nonuniform distribution of flow among vessels, which can be defined as some vessels receiving more and some less of their appropriate fraction of total flow, has been invoked to explain phenomena such as flow-limited muscular performance\textsuperscript{14} and suboptimal capillary transport of small solutes.\textsuperscript{15} This, with a special emphasis on insulin and glucose, will be discussed in more detail in the next section. In addition, microvascular dysfunction may contribute to various kinds of end-organ damage (eg, retinopathy, lacunar stroke, microalbuminuria, en heart failure).\textsuperscript{3}

In summary, microvascular dysfunction, in particular rarefaction, by affecting both pressure and flow patterns, may have consequences not only for peripheral vascular resistance and blood pressure, but also for muscle perfusion and metabolism.

**Microvascular Dysfunction as a Cause of Insulin Resistance**

Insulin resistance is typically defined as decreased sensitivity and/or responsiveness to metabolic actions of insulin that promote glucose disposal. A major action of insulin in muscle tissue involves translocation of glucose transporters to the plasma membrane and activation of downstream pathways of glucose metabolism.\textsuperscript{16} The glucose transporter protein is considered to be rate-limiting for insulin-stimulated glucose uptake in the muscle.\textsuperscript{16} However, before insulin interacts with the receptor on the plasma membrane, insulin and glucose must be delivered to the muscle cells in normal amount and time-course. In the past years, there has been an increasing interest in these precellular steps, in particular with regard to the possible contribution of insulin-mediated changes in muscle blood flow to insulin-mediated glucose uptake.

Insulin increases total blood flow and blood volume in skeletal muscle.\textsuperscript{5, 17} Mainly because the ability of insulin to dilate skeletal muscle vasculature is impaired in a wide range of insulin-resistant states (eg, hypertension, obesity, type 2 diabetes), it has been hypothesized that vasodilatory and metabolic actions of insulin (ie, glucose disposal) are functionally coupled.\textsuperscript{4, 17-19} However, despite the compelling nature of these findings, the concept that insulin might control its own access and that of other substances, particularly glucose, has been vigorously challenged. In experiments with lower doses of insulin and shorter time courses of insulin infusion, it was shown that insulin-mediated changes in total blood flow appear to have time kinetics and a dose dependence on insulin different from those for the effect on glucose uptake. In addition, studies in which glucose uptake has been measured during hyperinsulinemia and manipulation of total limb blood flow with different vasodilators have shown that total limb blood flow could be increased in either normal or insulin-resistant individuals, yet there was no increase in insulin-mediated glucose uptake.\textsuperscript{4} Recently, it has been demonstrated that induction of endothelial dysfunction with subsequent impairment of insulin-induced increases in total limb blood flow do not decrease insulin-mediated glucose uptake.\textsuperscript{20} These discrepant findings have been ascribed to the fact that various vasoactive agents may change total flow but have distinct effects on the distribution of perfusion within the microcirculation. Clark and colleagues have introduced the concept that distribution of blood flow in nutritive compared with nonnutritive vessels, independent of total muscle flow, may affect insulin-mediated glucose uptake.\textsuperscript{4} By elegant studies in rats, applying different techniques to measure capillary recruitment (1-methylxanthine metabolism) and microvascular perfusion (contrast-enhanced ultrasound [CEU] and laser Doppler flowmetry), they could demonstrate that insulin mediates changes in muscle microvascular perfusion consistent with capillary recruitment.\textsuperscript{4} This capillary recruitment is associated with changes in skeletal muscle glucose uptake independently of changes in total blood flow, requires lower insulin concentrations than necessary for changes in total blood flow, and precedes muscle glucose disposal.\textsuperscript{4, 19} Recently, the effects of systemic insulin infusion on transport and distribution kinetics of the extracellular marker [14C]inulin were studied in an animal...
model that allowed access to hindlimb lymph, a surrogate for interstitial fluid. Insulin, at physiological concentrations, augments the access of the labeled insulin to insulin-sensitive tissues. In addition, they demonstrated that access of macromolecules to insulin-sensitive tissues is impaired during diet-induced insulin resistance. These studies supported the concept that the in vivo effect of insulin is determined, at least in part, by the effect of insulin to reach metabolically active tissues by changing local blood flow distribution patterns. The presented data led to the hypothesis that insulin redirects blood flow from nonnutritive vessels to nutritive capillary beds, resulting in an increased and more homogeneous overall capillary perfusion termed “functional capillary recruitment”. The latter would enhance the access of insulin and glucose to a greater mass of muscle for metabolism. Consistent with such a mechanism in humans, insulin increases microvascular blood volume as measured with CEU or positron emission tomography and concomitantly enhances the distribution volume of glucose in human muscle. In obese subjects, the insulin-stimulated muscle microvascular recruitment is impaired. We have shown, by directly visualizing capillaries in human skin, that systemic hyperinsulinemia is capable of increasing the number of perfused capillaries. This insulin-dependent capillary recruitment is impaired in obese insulin-resistant subjects. Additional insight into the complex relationships among vasodilation, blood flow velocity, and capillary recruitment was gained through measurement of the capillary permeability-surface area product (PS) for glucose and insulin. PS for a substance describes its capacity to reach the interstitial fluid. This depends on the permeability and the capillary surface area, which in turn depends on the amount of perfused capillaries. A recent investigation using direct measurements of muscle capillary permeability showed that PS for glucose increased after an oral glucose load, and a further increase was demonstrated during an insulin infusion. The increase of PS was exerted without any concomitant change in total blood flow. It was concluded that the insulin-mediated increase in PS seen after oral glucose is important for the glucose uptake rate in normal muscle. Interestingly, PS for glucose is subnormal under steady-state insulin clamp conditions in insulin-resistant type 2 diabetic subjects. Moreover, a close and positive correlation was demonstrated between the rate of muscle glucose uptake and PS for glucose. A stimulated uptake of glucose and insulin in the absence of an increased PS would, hypothetically, lead to depletion of these substances in the interstitium. Importantly, at steady state, the interstitial muscle insulin and glucose concentrations nevertheless were normal in the type 2 diabetes group. The concomitant cellular insulin resistance leading to a subnormal glucose uptake rate may balance the low transcapillary transport rate of glucose and insulin so that the interstitial fluid concentrations stay normal. The importance of the perturbed capillary recruitment for the reduction in glucose uptake is, however, evident because a normal increase in PS in type 2 diabetes muscle would lead to supernormal interstitial concentrations.

The effect of insulin on capillary recruitment may be attributable to insulin-mediated effects on precapillary arteriolar tone and/or on arteriolar vasomotion. These effects can be studied by laser Doppler flowmetry. It has been shown that laser Doppler flow measurements in the constant-flow erythrocyte-perfused rat hindlimb correlate with changes in muscle metabolism, indicating the ability of this technology to measure erythrocyte movement both proportional to nutritive flow and separate from total flow. In rat muscle in vivo, physiological hyperinsulinemia induced an increase in the laser Doppler signal that is consistent with nutritive flow recruitment without a change in total flow. Making use of iontophoresis and laser Doppler flowmetry, we have demonstrated that locally applied insulin induces microvascular vasodilation in human skin independently of the systemic effects of insulin. In obesity, this local effect of insulin on the microcirculation is impaired compared with healthy controls (RT de Jongh et al, unpublished data, 2006). In addition, we have demonstrated that systemic hyperinsulinemia influences microvascular vasomotion in human skin and muscle. Vasomotion, the rhythmic fluctuations of microvascular blood flow, may be an important determinant of the spatial and temporal heterogeneity of microvascular perfusion and, therefore, of the number of perfused capillaries. The origin and control of microvascular vasomotion is still a matter of debate. A central neurogenic regulatory mechanism is suggested by synchronicity on contralateral limbs and by the suppressive effect of central sympathectomy. However, local administration of vasoactive substances such as acetylcholine and sodium nitroprusside directly influences vasomotion. Furthermore, vasomotion has been shown in isolated small arteries, indicating a local regulatory mechanism. In view of these considerations, it can be suggested that vasomotion is regulated by both local vasoactive substances and influences of the central nervous system. The contribution of different regulatory mechanisms can be investigated by analyzing the contribution of different frequency intervals to the variability of the laser Doppler signal. Our data suggest that an insulin-mediated effect on microvascular vasomotion occurs by increasing endothelial and neurogenic activity, and that particularly the contribution of endothelial and neurogenic activity to microvascular vasomotion is impaired in insulin-resistant obese individuals (RT de Jongh et al, unpublished data, 2006).

These data illustrate the importance of the microcirculation in regulating nutrient and hormone access to muscle, and raise the possibility that any impairment in capillary recruitment may cause an impairment in glucose uptake by muscle.

Impairment of Insulin-Mediated Capillary Recruitment: Possible Mechanisms

Vascular Insulin Resistance

Insulin-stimulated glucose uptake in skeletal muscle and adipose tissue is mediated by translocation of the insulin-responsive glucose transporter GLUT4 to the cell surface. This requires phosphatidylinositol 3-kinase (PI3-kinase)–dependent signaling pathways that involve the insulin receptor, insulin receptor substrate-1 (IRS-1), PI3-kinase, phosphoinositide-dependent kinase-1 (PDK-1), and Akt. Ras/MAP kinase pathways do not contribute significantly to insulin-
stimulated translocation of GLUT4, but are important for insulin-mediated regulation of growth and mitogenesis. Interestingly, the vascular actions of insulin that stimulate the production of NO require PI3-kinase–dependent insulin-signaling pathways that bear striking similarities to metabolic insulin-signaling pathways (Figure 1). Moreover, the MAP-kinase branch of insulin signaling controls secretion of endothelin-1 (ET-1), a strong vasoconstrictor, by the endothelium. Insulin therefore has opposing hemodynamic actions on vessels. In vessels of healthy rats, insulin has no net effect on vessel diameter, because of a balance between stimulation of two pathways—NO-mediated vasodilation and ET-1-mediated vasoconstriction. Insulin stimulates activation of endothelial NO synthase: the signaling pathway is through IRS-1, PI3-kinase, and Akt. However, if this pathway is inhibited, the arteriole constricts, a response mediated by ET-1 through the Ras/MAP-kinase and extracellular signal-related kinase-1/2 (ERK1/2) pathway. These observations imply a dual insulin signaling mechanism in vessels—one pathway stimulating synthesis of NO, the other ET-1 release. In obese rats, these signaling pathways are selectively impaired: insulin-mediated activation of the ET-1 pathway is impaired, but insulin-mediated activation of ERK1/2 is intact. In line with this evidence, we have recently found insulin-induced, ET-1–dependent vasoconstriction in skeletal muscle arterioles of obese rats (Eringa et al, unpublished data, 2005). Recent experimental studies in rats demonstrate that endothelin-1 infusion in vivo severely blunted the increased capillary recruitment and limb blood flow caused by insulin. These effects of endothelin-1 were accompanied by increased blood pressure and reduced muscle glucose uptake. In addition, insulin resistance in spontaneously hypertensive rats is associated with endothelial dysfunction characterized by imbalance between NO and ET-1 production. Moreover, obese, hypertensive humans show an insulin-induced vasoconstriction as well as increased ET-1–dependent vasoconstrictor tone and decreased NO-dependent vasodilator tone at the level of the resistance arteries. Thus, shared insulin-signaling pathways in metabolic and vascular target tissues with complementary functions may provide a mechanism to couple the regulation of glucose with hemodynamic homeostasis. The net hemodynamic action of insulin is dependent on a balance between its vasodilator and vasoconstrictor effects.

**Obesity-Related Endocrine Signaling**

Dysfunction at the level of both the resistance vessels and the nutritive capillary beds develops progressively along with an increase in adiposity. This close association between measures of adiposity and microvascular function suggests communicative pathways between adipose tissue and the microvasculature. Adipose tissue and in particular visceral adipose tissue cells secrete a variety of bioactive substances called adipokines such as free fatty acids (FFA), adiponectin, leptin, resistin, angiotensinogen, and tumor necrosis factor-α (TNF-α). Here we will focus on the role of FFAs and TNF-α.

By use of magnetic resonance spectroscopy, FFA-induced insulin resistance in humans has been shown to result from a significant reduction in the intramyocellular glucose concentration, suggestive of glucose transport as the affected rate-limiting step. The current hypothesis, supported by data from protein kinase theta (PKC-θ) knock out mice, proposes that fatty acids on entering the muscle cell activate PKC-θ as either fatty acyl-coenzyme A (CoA) or diacylglycerol. PKC-θ activates a serine kinase cascade leading to the phosphorylation and inactivation of IRS-1 by tyrrosine phosphorylation. Because the technique of magnetic resonance spectroscopy only identifies a gradient from extracellular to intracellular glucose in muscle cells, it re-
mains to be proven that the gradient did not occur between the plasma and interstitial glucose and thus reflects a rate-limiting step of glucose delivery induced by fatty acids. Interestingly, studies suggest that glucose delivery contributes to sustaining the transmembrane glucose gradient and, therefore, is a determinant of glucose transport. This would be consistent with the finding in rats that FFA elevation concomitantly impairs insulin-mediated muscle capillary recruitment and glucose uptake. In addition, we have demonstrated that in lean individuals, FFA elevation induces skin microvascular dysfunction and reduces whole body glucose uptake, whereas in obese individuals FFA lowering has the opposite effect (Figure 2). Moreover, changes in capillary recruitment statistically explained ~29% of the association between changes in FFA levels and insulin-mediated glucose uptake. A defect involving fatty-acid–induced impaired insulin signaling through the same PKC-θ mechanism in endothelial cells, which in turn may negatively influence the balance between insulin-mediated vasodilation and vasoconstriction, may be responsible for the impaired capillary recruitment.

Increased production of the proinflammatory cytokine TNF-α is associated with obesity-related insulin resistance as well as obesity-related hypertension. In rats, TNF-α elevation concomitantly impairs insulin-mediated muscle capillary recruitment and glucose uptake. In addition, in humans, circulating TNF-α levels are associated with reduced whole body glucose uptake and skin capillary recruitment. In isolated skeletal muscle resistance arteries, we could demonstrate that TNF-α impairs the vasodilator effects but not the vasoconstrictor effects of insulin through activation of intracellular enzyme c-Jun N-terminal kinase (JNK) and impairment of insulin-mediated activation of Akt. This selective inhibition of the vasodilator effects of insulin results in insulin-mediated vasoconstriction in the presence of TNF-α. JNK has been shown to regulate whole-body insulin sensitivity as well as insulin-mediated cell signaling. In conclusion, both FFAs and TNF-α are likely candidates to link visceral adipose tissue with defects in microvascular function, at least in part by influencing insulin signaling and thereby the vascular effects of insulin.

We have recently hypothesized an alternative communicative pathway between adipose tissue and the microvasculature. Obese Zucker rats are characterized by a well-circumscribed depot of fat cells around the origin of the nutritive arteriole supplying the cremaster muscle whereas lean rats are not. Adipokines released by these fat cells may directly inhibit vasodilatory pathways distal in the arteriole and thereby cause loss of blood flow in the nutritive capillary network supplied by this arteriole. In this hypothesis, which remains to be tested, adipokines released from periarteriolar fat depots have a local rather than a systemic vasoregulatory effect, which we named “vasocrine”.

**Insulin Resistance, Arterial Stiffness, and Microvascular Function**

Arterial stiffness has recently been recognized as an important cardiovascular risk factor. All classic risk factors, including age, hypertension, diabetes, smoking, and low-density lipoprotein (LDL) cholesterol, are determinants of arterial stiffness. In the Atherosclerosis Risk in Communities Study, the fasting insulin concentration was positively corre-
lating with several indexes of arterial stiffness. This relationship was independent of age, cigarette-years, and cholesterol and suggested, assuming fasting hyperinsulinemia to be a marker of insulin resistance, that insulin resistance may contribute to stiffening of large arteries. Indeed, subsequent cross sectional epidemiological data suggest that insulin resistance and arterial stiffness are related. Moreover, the metabolic syndrome is associated with an increased progression of aortic stiffness with age. In addition, insulin has direct effects on large arteries resulting in decreased augmentation of central aortic pressure as a result of reduced pulse wave reflection from the periphery. This hemodynamic effect of insulin is blunted in obese insulin-resistant subjects. Unlike the effect of insulin on peripheral resistance and positively associated with insulin-mediated glucose uptake. Unlike the effect of insulin on peripheral resistance vessels, which occurs only after a number of hours and at physiologically, the effect of insulin on arterial stiffness occurs rapidly and well within the physiological range comparable to insulin’s effects on the microcirculation.

Interestingly, relations between microvascular function, aortic stiffness, and pressure pulsatility have been reported. In the Framingham Heart Study offspring cohort increased aortic stiffness was associated with higher forearm vascular resistance at baseline and during reactive hyperemia, and with blunted flow reserve during hyperemia. Moreover, aortic stiffening is accompanied by microcirculatory structural or functional remodeling beyond that which is explained by contemporaneously measured cardiovascular risk factors. One interpretation is that microvascular damage may result from increased aortic stiffness and elevated forward wave amplitude or from increased transmission of a given forward wave into the microcirculation. Consistent with this hypothesis, prior studies in animal models have shown that locally induced isolated alterations in pressure pulsatility have major effects on microvascular structure and function. Another interpretation is that abnormalities in the microcirculation and, therefore, in peripheral vascular resistance, lead to the perturbations in aortic stiffness. Recent careful observations by Christensen and Mulvany have confirmed that pulsatility penetrates much deeper in the microvasculature than was previously supposed. It has, therefore, been hypothesized that structural alterations (rarefaction) leading to changes in the architectural design of the distal vascular tree influence pulse pressure and the augmentation index beyond the Windkessel (compliance, resistance) paradigm. The biophysical basis of this influence is still poorly explored, although recent studies suggest a possible role for microvascular branching angles and related geometric parameters in hypertension-related cardiovascular disease.

**Perspectives**

The pathophysiological basis of the metabolic syndrome is multiple and complex. There is increasing evidence that microvascular function is a potential factor explaining the clustering of several components of the metabolic syndrome such as hypertension, obesity, and insulin resistance (Figure 3). Also, microvascular defects play an important role in the end-organ damage associated with the metabolic syndrome and may contribute to macrovascular dysfunction, although further studies will have to elucidate the physiological mechanisms underlying relationships between these two segments of the circulation. Thus, the microcirculation may present a promising future therapeutic and preventative target in the metabolic syndrome. Hence, clarification of pathophysiological pathways that contribute to microvascular dysfunction is essential. This review discusses the potential role for defects in intracellular insulin signaling and obesity-related endocrine signaling therein. These pathways are worth more detailed studies in the future to develop targeted interventions for microvascular dysfunction.

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**Disclosures**

None.

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