Vascular function in the metabolic syndrome and the effects on skeletal muscle perfusion: lessons from the obese Zucker rat

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Abstract

The increased prevalence of obesity in Western society has been well established for many years, and with this trend, the prevalence of other associated pathologies including insulin resistance, dyslipidaemia, hypertension and the genesis of a pro-inflammatory and prothrombotic environment within individuals is also rapidly increasing, resulting in a condition known as the metabolic syndrome. From a physiological perspective, one of the most severe consequences of the metabolic syndrome is a progressive inability of the cardiovascular system to adequately perfuse tissues and organs during either elevated metabolic demand and, if sufficiently severe, under basal levels of demand. For the study of the metabolic syndrome, the OZR (obese Zucker rat) represents an important tool in this effort, as the metabolic syndrome in these animals results from a chronic hyperphagia, and thus can be an

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excellent representation of the human condition. As in afflicted humans, OZR experience an attenuated functional and reactive hyperaemia, and can ultimately experience an ischaemic condition in their skeletal muscles at rest. The source of this progressive ischaemia appears to lie at multiple sites, as endothelium-dependent vasodilator responses are strongly impaired in OZR, and specific constrictor processes (e.g. adrenergic tone) may be enhanced. Whilst these active processes may contribute to a reduction in blood flow under resting conditions or with mild elevations in metabolic demand, an evolving structural alteration to individual microvessels (reduced distensibility) and microvascular networks (reduced microvessel density) also develop and may act to constrain perfusion at higher levels of metabolic demand. Given that constrained muscle perfusion in the metabolic syndrome appears to reflect a highly integrated, multi-faceted effect in OZR, and probably in humans as well, therapeutic interventions must be designed to address each of these contributing elements.

What constitutes the metabolic syndrome?

Whilst numerous challenges to public health exist within Western society, one of the most problematic in this regard is the increased prevalence and incidence of overweight and obesity. Using guidelines established by the Centers for Disease Control, overweight is considered to be represented by a BMI (body mass index) between 25 and 30 kg/m² in adults, or body mass in excess of the 95th percentile in paediatric populations, with obesity being defined as a BMI in excess of 30 kg/m² in adults [1]. Based on 1999–2002 NHANES (National Health and Nutrition Examination Survey) data, approx. 135 million American adults are classified as overweight, with approx. 63 million of these individuals classified as obese [1]. What is even more of a concern than the prevalence of overweight and obesity in Western society are recent trends demonstrating an increased incidence of these conditions. Comparisons between the 1971–1974 and 1999–2002 NHANES data sets, shows the incidence of obesity increased from 12.1% to 27.6% in men, whilst women demonstrated an increase from 16.6% to 33.2% over that same period, with comparable patterns evident in paediatric populations [1,2].

Whilst an increased prevalence of obesity represents a profound challenge for public health, a major concern over the development of the overweight/obese condition is that it predisposes individuals for the development of established cardiovascular disease risk factors, including dyslipidaemia, hypertension and impaired glycemic control. When combined, these myriad conditions create a multi-pathology state known as the metabolic syndrome (also termed Syndrome ‘X’ or insulin resistance syndrome). Specifically, the metabolic syndrome is defined as the combined presentation of three or more of: (i) abdominal obesity (waist circumference ≥ 102 cm in males; ≥ 88 cm in females), (ii) atherogenic dyslipidaemia (triglycerides ≥ 150 mg/dl; high-density lipoprotein cholesterol ≤ 40 mg/dl; 50 mg/dl in women), (iii) elevated blood pressure.
(≥130/85 mmHg), (iv) insulin resistance or glucose intolerance (fasting glucose ≥110 mg/dl), (v) the presence of a prothrombotic state (e.g. high fibrinogen), and (vi) the presence of a proinflammatory state (e.g. elevated C-reactive peptide).

A recent study has demonstrated that the prevalence of the full metabolic syndrome is also increasing consistently within the American population, as between NHANES III (1988–1994) and NHANES IV (1999–2002), the age-adjusted prevalence of the metabolic syndrome increased from 24% to 27%, with the most dramatic increases identified among the female population, where the increase was 23.5% [3].

**What are the implications of the metabolic syndrome for outcomes in human populations?**

For cardiovascular health, the most profound implication of evolution of the metabolic syndrome is an increased likelihood for the development of peripheral vascular disease [4], a condition associated with compromised perfusion of the affected limbs and tissues, leading to impaired function and a progressive deterioration in tissue viability. Within humans, the numbers of studies that have focused on the vascular consequences of the full metabolic syndrome, and on mechanisms underlying identified impairments, are limited. As such, it is necessary to examine previous studies wherein a ‘reduced’ model of the metabolic syndrome is present (i.e. specific elements of the metabolic syndrome only) and to draw inferences from these results. Almost universally, previous studies have identified that with the progression of the metabolic syndrome, as well as with each of the contributing elements to it, perfusion of multiple tissues can be profoundly compromised [5,6]. In humans, the skeletal muscle constitutes approx. 40% of body mass and is a principle determinant of peripheral insulin sensitivity [7]. Consequently, deficits in skeletal muscle perfusion and the corresponding diminution of insulin and substrate diffusion from the intravascular space have been identified as a primary factor in the pathogenesis of the metabolic syndrome [5,6,8].

**Vasodilation**

One of the most commonly identified dysfunctions within vascular tissue with either the metabolic syndrome, or the contributing elements to it, is a compromised vasodilation in response to an imposed physiological (e.g. reactive hyperaemia, elevated metabolic demand) or pharmacological (e.g. infusion of endothelium-dependent agonists) challenge. As an example, Hamdy et al. [9] demonstrated in patients with the metabolic syndrome that brachial artery flow-mediated dilation was impaired relative to normal subjects, whereas responses to an exogenous NO (nitric oxide) donor was normal. Partial alleviation of the severity of the metabolic syndrome through weight reduction and chronic exercise improved brachial arterial flow-mediated dilation, although these effects were not associated with an improvement in
microvascular reactivity [9]. Likewise, others have shown that infusion of endothelium-dependent vasodilators, such as acetylcholine, methacholine and insulin, result in blunted increases in limb perfusion in patients with the metabolic syndrome relative to control subjects, whereas vasodilator responses via endothelium-independent mechanisms were intact [10]. Importantly, whilst this impairment in endothelium-dependent vasodilation in humans afflicted with the metabolic syndrome is via a NO signalling mechanism, this impairment in NO signalling can adversely impact vascular smooth muscle cell proliferation/migration, platelet aggregation/thrombosis, monocyte/macrophage adhesion and inflammation throughout the circulation.

Vasoconstriction
In conjunction with depressed endothelium-dependent vasodilation, enhanced vasoconstriction could also limit skeletal muscle perfusion during the metabolic syndrome. For example, it has been suggested that in addition to decreased bioavailability of NO, there is a corresponding increase in the production of the potent vasoconstrictor ET-1 (endothelin-1). Indeed, higher circulating concentrations of ET-1 are reported to occur in patients with the metabolic syndrome [11], and Cardillo et al. [12] reported that there is an increased vasoconstrictor tone mediated through endogenous ET-1 in type II diabetic patients. In addition, previous studies have suggested that an increased production of vasoconstrictor prostanoids and angiotensin II [13], as well as activation of the sympathoadrenal system [14], have also been postulated as mechanisms constraining skeletal muscle perfusion in the metabolic syndrome.

Vascular structure
Several lines of evidence indicate that there are changes in arterial vascular structure in the metabolic syndrome that could serve to limit skeletal muscle perfusion. Clinical studies have demonstrated that increases in arterial pulse wave velocity are positively correlated with the cluster of features associated with the metabolic syndrome, and are frequently indicative of increases in the mechanical stiffness of arteries [15]. Further, increased arterial wall thickness is likely to be partially related to elevated concentrations of insulin through direct trophic effects on smooth muscle cells, as well as by the generation of reactive oxygen species, protein kinase C and activation of nuclear factor-κB to stimulate vascular smooth muscle cell growth, migration and proliferation. Further, Fossum et al. [6] reported a positive association between the appearance of peripheral structural vascular changes in the forearm and insulin resistance that could limit perfusion. This effect could clearly be mediated by decreases in arterial diameter and microvessel density.

Validity of the Zucker rat as a model of the metabolic syndrome
The OZR (obese Zucker rat; fa/fa) represents a key animal model in the study of the metabolic syndrome. The fa mutation represents an autosomal recessive
locus on chromosome 5, and with both copies present, the leptin receptor gene is not properly encoded [16]. Heterozygotes (fa/+) exhibit no phenotypic anomaly, and are not distinguishable from the control lean Zucker rat (+/+). Owing to this dysfunctional leptin receptor gene, the OZR demonstrates an impaired satiety reflex and a chronic elevation in food intake. As a result, OZR rapidly develop profound obesity, exhibited through both hypertrophy and hyperplasia of adipocytes, as well as many of the subsequent disease states associated with chronic obesity, including insulin resistance and profound hypertriglyceridaemia [16]. Additionally, OZR can develop a moderate, clinically relevant form of hypertension [17–19], and ongoing studies suggest that OZR exist in a profound proinflammatory and prothrombotic [20] state, with expressions of plasminogen, plasminogen activator inhibitor-1 and C-reactive peptide all consistently elevated above that in controls.

Given that OZR develops its systemic pathologies through a chronic hyperphagia, this genesis of the metabolic syndrome is highly relevant to the human condition. Further, OZR experience a prolonged period of hypertriacylglyceridaemia and insulin resistance prior to the overt development of type II diabetes mellitus, as is frequently the case in obese humans. The degree of hypertension that does develop in OZR can best be described as mild to moderate, which is also in keeping with the levels of hypertension identified in most humans afflicted with the metabolic syndrome. Finally, the recent identification of a proinflammatory and prothrombotic environment within OZR has also demonstrated striking parallels to the conditions of the human metabolic syndrome. Taken together, these elements support the contention that OZR represent an appropriate model for studying the genesis, outcomes and potential treatment for the metabolic syndrome in humans.

**Perfusion abnormalities in the OZR**

Under resting conditions, skeletal muscle arteriolar perfusion in OZR has consistently been demonstrated to be reduced versus levels determined in controls, and this has been demonstrated in both trans-illuminated cremaster [21] and spinotrapezius muscle preparations [22]. These observations have translated to bulk perfusion of *in situ* whole skeletal muscles. Work from Frisbee’s group has consistently demonstrated that perfusion of gastrocnemius muscle was reduced in OZR as compared with that identified in the lean Zucker rat counterparts [23,24].

As one of the hallmark characteristics of the metabolic syndrome in humans afflicted with this condition is the progressive inability to match muscle perfusion with metabolic demand, hyperaemic responses in skeletal muscle of OZR in response to physiological and pharmacological stimuli has received additional attention in recent years and is a vital avenue for ongoing investigation. In a recent study of reactive hyperaemia in skeletal muscle of OZR, it was suggested that the total perfusion response following removal of the occlusive stimulus was reduced in obese animals relative to that in controls [25].
The investigation of functional or active hyperaemia, points directly to the ability of the skeletal muscle circulation to alter perfusion appropriately to match convective and diffusive substrate exchange with metabolic intensity. Using *in situ* spinotrapezius muscle, Hester’s group has determined that functional hyperaemia within single arterioles of OZR is attenuated as compared with that in lean Zucker rats (Figure 1), and that these impairments were correlated with impaired dilator responses to acetylcholine [26]. Ongoing studies using the *in situ* gastrocnemius muscle preparation have demonstrated that this constrained active hyperaemia is also evident at the level of bulk perfusion to skeletal muscle [23,24 and (Figure 2)]. When taken together, these results suggest that impaired active hyperaemia within skeletal muscle of OZR may be present regardless of the severity of metabolic demand and may also be independent of the type of muscle contraction imposed [23,24]. However, given that OZR continue to grow and that daily activity levels are not markedly different between lean Zucker rats and OZR at 14 weeks of age [10], it is unlikely that this ischaemia is sufficient to compromise growth or normal daily activity. However, with stronger elevations in metabolic demand, impaired perfusion of skeletal muscle in OZR may contribute to the genesis of premature fatigue development [24].

**Vascular basis for perfusion abnormalities**

**Vasodilator reactivity**

One of the most consistent observations regarding altered vascular function within OZR is an impaired endothelium-dependent vasodilation within not only the skeletal muscle circulation, but also within resistance arterioles of other multiple organs [27,28], suggesting the likelihood of common
Figure 2. Change in developed tension (A), muscle blood flow (B) and mean vascular resistance during contraction (C) of in situ gastrocnemius muscle of LZR and OZR

Muscles were stimulated to contract via the sciatic nerve at 60 isometric titanic contractions/min (2003 ms, 503 Hz). Data are presented as means ± S.E. *P < 0.05 versus LZR control. Reproduced from Frisbee (2003) Am. J. Physiol. Regul. Integr. Comp. Physiol. vol. 285, pages R1124–R1134, with permission from The American Physiological Society.
mechanisms underlying this compromised behaviour. As examples, within cremaster or spinotrapezius muscles of OZR, dilator responses to elevated wall shear rate [21 and (Figure 3)] and challenge with acetylcholine [21,26] or arachidonic acid [21,22], have consistently been demonstrated to be reduced below that determined in lean rats. The impairments to endothelium-dependent dilation have also been verified using isolated skeletal muscle arterioles by several investigators. Johnson et al. [18] demonstrated that gracilis muscle resistance arterioles from OZR manifest an impaired dilation to application of acetylcholine and elevated perfusate flow rate, results that are consistent with previous studies demonstrating an impaired endothelium-dependent dilation of isolated arterioles in response to acetylcholine, reduced oxygen tension and arachidonic acid [21,23] in OZR versus lean rats. Whilst isolated reports of an impaired vasodilation in response to endothelium-independent stimuli

Figure 3. The change in arteriolar diameter (A) and wall shear rate (B) for in situ cremasteric arterioles of LZR and OZR after 120 s of physical occlusion of a parallel arteriole

*P < 0.05 versus LZR. Reproduced from Frisbee and Stepp (2001) Am. J. Physiol. Heart Circ. Physiol. vol. 281, pages H1304–H1311, with permission from The American Physiological Society.
exist [23], the overwhelming majority of the literature suggests that dilator reactivity following direct activation of the smooth muscle is near normal across vascular beds within OZR [18,26,27].

As many of the studies cited above have employed shear-induced and acetylcholine-induced dilation, both highly dependent on the appropriate production and bioavailability of NO from the endothelium, several studies have targeted these processes in terms of elucidating mechanisms of the impaired response in OZR. Fulton et al. [29] demonstrated that eNOS expression patterns, phosphorylation and binding to Hsp90 (heat shock protein 90) are not altered in OZR relative to controls, and concluded that mechanisms underlying the reduced vascular reactivity to endothelium- and NO-dependent stimuli must lie elsewhere, citing possible cofactor or substrate bioavailability limitations or elevated scavenging actions of superoxide anion. As an elevation in vascular oxidant stress in OZR manifesting the metabolic syndrome has been well documented, several investigators have pursued this avenue of investigation, treating these animals with an array of oxidative radical scavengers in an attempt to restore NO bioavailability and vascular reactivity. In general, treatment of OZR with antioxidants has improved vasodilator responses to NO-dependent stimuli in isolated microvessels [21,24] and using in situ preparations [21], suggesting that endothelium-dependent dilator reactivity can be improved by acute treatment with oxidative radical scavengers which, by extension, implicates oxidative radical scavenging of endothelium-derived NO as a key contributor to compromised dilator responses in OZR. Interestingly, a recent study by Geakelman et al. [30] provided insight into this area as they determined that chronic treatment of Zucker diabetic fatty rats (which develop type II diabetes mellitus more rapidly than do OZR), with a peroxynitrite scavenger improved acetylcholine-induced dilation of renal arteries/arterioles. These results raise an important issue of which process is more relevant to the reduced dilator reactivity in OZR, a reduction in NO bioavailability or the generation of peroxynitrite. This may be a key consideration in that Brzezinska et al. [31] identified that peroxynitrite can selectively antagonize the calcium-activated potassium ($K_{Ca}$) channels in smooth muscle cells, preventing membrane hyperpolarization in the face of elevated calcium and impairing the ability of the muscle cell to relax. The importance of oxidant stress-based reductions in NO bioavailability in terms of the regulation of functional hyperaemia and the matching of muscle perfusion with metabolic demand has recently been brought into question. Whole body acute reductions in vascular oxidant stress (via intravenous infusion of antioxidants), whilst improving depressor responses to methacholine, had no discernible impact on metabolic demand-induced increases in skeletal muscle perfusion [24].

A number of other mechanisms have been investigated in OZR that could contribute to a reduction in NO bioavailability and compromised arterial/arteriolar dilator reactivity, including increased expression and activity of protein
kinase βII acting to constrain stimulus-induced NO formation [27], the role of haem oxygenase derived carbon monoxide production as a contributor to inhibiting NO synthase [18 and (Figure 4)].

In terms of arachidonic acid metabolism, whereas comparable evidence supporting an oxidant stress-based mechanism for NO scavenging has also been postulated to exist with regard to eicosanoid bioavailability [24], a recent study has demonstrated that the reduced dilation of in situ spinotrapezius muscle arterioles with arachidonic acid in OZR was partially restored following treatment of the muscle with the PGH₂–TxA₂ (prostaglandin H₂–thromboxane A₂) receptor antagonist SQ-29548 [22], suggesting that an inappropriate activation of vasoconstrictor pathways may contribute to the impaired dilator responses determined in these animals.

**Vasoconstrictor reactivity**

Although having received considerably less attention, there is evidence that pathways associated with vasoconstriction may also be markedly altered in OZR and that these may exhibit a much stronger influence on the evolving ischaemia in skeletal muscle of these animals than do pathways of vasodilation. Whilst isolated reports of increased vascular tone exist due to an increased myogenic activation [24] and an elevated expression and activity of serotonin [32] and endothelin receptors [33] and in skeletal muscle have
been reported, it is unclear how these results would impact skeletal muscle perfusion, as the necessary analyses have not been performed.

With development of obesity, an increased adrenergic activity is frequently observed [34], which can have a profound impact of the perfusion of tissues which are sensitive to adrenergic modulation. Carlson et al. [35] demonstrated that, with development of the metabolic syndrome in OZR, sympathetic nervous system activity was elevated as compared with levels in control animals. Building from this, Stepp and Frisbee [36] determined that norepinephrine-induced constriction of skeletal muscle resistance arterioles was increased in OZR relative to that in lean animals, and that intravenous infusion of the $\alpha_1$-adrenoreceptor antagonist prazosin caused a pronounced dilation of \textit{in vivo} arterioles, significantly greater than in controls. Further, Schreihofer et al. [37] determined that phenylephrine-induced elevation in vascular resistance in the hindlimb of OZR was greater than that in lean Zucker rats. Attempts at elucidating the mechanism underlying this increased adrenergic reactivity of skeletal muscle resistance arterioles in OZR have only recently been undertaken, although Naik et al. [38] has provided evidence suggesting that RhoA-kinase may play a significant role in increasing the sensitivity of the contractile machinery of the vascular smooth muscle cell of OZR in response to elevations in intracellular calcium levels.

Recent studies have begun to elucidate the significance of this increased adrenergic reactivity of the skeletal muscle microvessel of OZR for muscle perfusion. In \textit{in situ} gastrocnemius muscle of OZR, the increased adrenergic vasoconstriction contributes to reduced skeletal muscle perfusion at rest, and in response to mild and moderate elevations in metabolic demand, as intravenous infusion of adrenergic antagonists restored perfusion in OZR to levels that were near those in control animals [23]. This study also clearly demonstrated that with high metabolic demand, adrenergic constraint on functional hyperaemia was not present. Additional recent studies have provided evidence suggesting the increased adrenergic reactivity of the skeletal muscle resistance arterioles contributes to both a premature reduction in skeletal muscle perfusion with incremental haemorrhage [39] and a reduced reactive hyperaemic response following removal of brief periods of serial vascular occlusion [25] in OZR.

**Structural remodeling**

Several studies have consistently determined that passive (i.e. pressurized in a calcium-free environment) diameter of skeletal muscle resistance arterioles of OZR was reduced below that in lean animals [40,41]; not a surprising observation given that many of the contributing elements to the metabolic syndrome have been previously identified as being associated with altered arteriolar wall mechanics. In OZR manifesting the metabolic syndrome, these alterations include significant reductions in arteriolar wall incremental distensibility and left-shifting of the circumferential wall stress versus strain relationship ([40] and (Figure 5)). The skeletal muscle microcirculation of OZR
is also altered at the network level of resolution, as capillary density in muscle of these animals is significantly reduced versus that in controls [17, 40, 42]. When taken together, reduced vascular distensibility and microvascular rarefaction result not only in an increased minimum vascular resistance of the skeletal muscle of OZR [40] and (Figure 6)), but can also contribute to a blunted functional hyperaemia of skeletal muscle at higher levels of metabolic demand [24]. Recent studies exploring mechanisms underlying skeletal muscle microvascular rarefaction in OZR suggest that this reduction in microvessel density is closely associated with the severity of insulin resistance, and may be independent of the development of hypertension [17]. Further, whilst it has been suggested that rarefaction in OZR is closely aligned with a chronic reduction in vascular NO bioavailability [43], recent observations from Geakelman et al. [30] suggest that the generation of peroxynitrite from the scavenging of NO by superoxide could underlie the pattern of reduced microvessel density in these animals, as chronic treatment with a peroxynitrite scavenger prevented renal microvascular rarefaction in OZR.

**Systemic cardiovascular control**

A recent study has identified additional elements to the global cardiovascular system within OZR that may contribute to the ischaemic perfusion of skeletal muscle at rest and with elevated metabolic demand. Schreihofer et al. [37] made an initial observation that blood and plasma volumes of

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**Figure 5. Circumferential wall stress versus strain relationship of isolated gracilis muscle first-order arterioles from LZR and OZR under Ca\(^{2+}\)-free conditions**

\(^*P < 0.05\) versus the slope coefficient (\(\beta\)) describing this relationship for arterioles from LZR. Reproduced from Frisbee (2003) *Am. J. Physiol. Heart Circ. Physiol.*, vol. 285, pages H104–H111, with permission from The American Physiological Society.
OZR are reduced as compared with lean Zucker rats, despite corrections for the increased adiposity. In addition to this, Frisbee demonstrated that the ability of OZR to tolerate incremental haemorrhage, largely dependent on rapid sympathetic neural responses, was impaired relative to that in lean Zucker rats [39]. Further, data presented in this study [39] suggest that the impaired ability to tolerate incremental haemorrhage may have been a function of the reduced circulating blood volume and an imbalance in the sympathetic neural responses to the hypovolaemia. Specifically, the skeletal muscle circulation received an immediate and pronounced elevation in vasoconstrictor tone of adrenergic origin, whilst in contrast adrenergic constriction of the splanchnic circulation was both delayed and blunted in magnitude [39]. It is possible that this reduction in circulating blood volume

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Figure 6. Perfusion pressure (A) and calculated vascular resistance (B) within pump-perfused gastrocnemius muscles of LZR and OZR
Gastrocnemius muscle mass was not different between LZR (2.35±0.13 g) and OZR (2.29±0.15 g). Data (means±S.E.) are presented from perfusion of a maximally dilated microvascular bed at a constant volume flow rate of 0.5, 1.0, 1.5 or 2.0 ml/min. *P<0.05 versus LZR at that perfusion rate. Reproduced from Frisbee (2003) Am. J. Physiol. Heart Circ. Physiol., vol. 285, pages H104–H111, with permission from The American Physiological Society.
in OZR, acting in combination with an altered distribution of sympathetic neural tone may contribute to the underperfusion of skeletal muscle at rest and with elevated metabolic demand.

**Clinical implications and therapeutic interventions**

Several tentative conclusions can be drawn regarding processes that negatively impact muscle perfusion in OZR. Foremost, impaired endothelium-dependent dilation has been clearly demonstrated in skeletal muscle arterioles of OZR. However, whilst it is clear that acute interventions such as correcting oxidant stress, inhibiting protein kinase C, antagonizing PGH$_2$–TxA$_2$ receptors, or blocking endogenous carbon monoxide production can improve arteriolar dilation in response to specific pharmacological stimuli, the importance of these processes in terms of the matching of perfusion with metabolic demand is less clear.

With regard to constrictor reactivity, the impact of enhanced responses to adrenergic stimulation may reduce resting perfusion and constrain functional hyperaemia at low to moderate elevations in metabolic demand in OZR. Whilst recent studies have implicated specific signalling pathways increasing the sensitivity of the smooth muscle contractile machinery to elevated calcium concentration as contributing to this enhanced adrenergic vascular tone, this is an area of investigation that warrants future investment. Additional investigation into other pathways of constrictor reactivity in OZR which, although identified, have not been fully verified with regard to the regulation of skeletal muscle perfusion, including increased myogenic activation, increased constrictor prostanoid generation, increased serotonin receptor expression and increased endothelin receptor expression and activity, require future validation.

Investigation into vascular structural alterations with genesis of the metabolic syndrome and the role of these alterations into the regulation of tissue perfusion has recently come under more intense investigation. However, it has rapidly become clear that skeletal muscle circulation of OZR experiences numerous alterations to its structure, including a reduced resistance arteriolar distensibility and a progressive rarefaction of microvascular networks. Whilst treatments designed to improve vascular wall stiffness are not uncommon in the clinical setting (e.g., angiotensin converting enzyme inhibitors) [19], therapeutic interventions designed to improve tissue vascularity and blunt microvascular rarefaction have been less well explored. However, given the potential importance of a maintained vascular NO bioavailability for the maintenance of microvessel density, developing therapeutic interventions into the protection of microvessel network structure, and not simply dilator reactivity or wall stiffness may prove to be a highly beneficial avenue for future investigation.

**Conclusions**

As both the prevalence and the incidence of the full metabolic syndrome, and the individual systemic pathologies that comprise it, are growing rapidly
in Western society, the impact of this trend on afflicted individual mortality and morbidity will also become more severe. Given that one of the most clearly demonstrated outcomes of the metabolic syndrome is the progressive development of peripheral vascular disease, ongoing study into the nature of this evolving dysfunction and the interaction of specific mechanisms that underlie it will continue to be critical arenas for future investigation. Further, an understanding of how vascular reactivity (both dilator and constrictor) combines with vascular structure (at the individual vessel and vascular network levels of resolution) for the integrated regulation of perfusion will be vital for the development of effective interventional strategies and therapeutic regimes.

Summary

- Owing to chronic hyperphagia, the OZR represents an excellent model of the metabolic syndrome in humans, as it progressively develops obesity, insulin resistance dyslipidaemia, moderate hypertension and represents a proinflammatory and prothrombotic environment.
- In OZR, resting skeletal muscle blood flow is reduced below that in normal control animals. Functional and reactive hyperaemic responses in skeletal muscle are also blunted, with a myriad of contributing mechanisms.
- Endothelium-dependent dilation of skeletal muscle microvessels is impaired in OZR, although dilation in response to endothelium-independent stimuli appears to be intact. The consequences of this impairment to dilator reactivity for skeletal muscle perfusion are presently unclear.
- Skeletal muscle microvessel constriction in response to adrenergic agonists is enhanced in OZR manifesting the full metabolic syndrome, and this has the potential to constrain skeletal muscle perfusion at rest and with mild to moderate elevations in metabolic demand.
- Structural alterations to the skeletal muscle microcirculation in the OZR, including reduced microvessel wall distensibility and microvessel density elevate minimum vascular resistance and may constrain blood flow with higher elevations in metabolic demand.

References


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