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Peripheral Blood Flow Regulation in Human Obesity and Metabolic Syndrome

Jacqueline K. Limberg^{1,3}, Barbara J. Morgan², and William G. Schrage³

¹Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA

²Department of Orthopedics and Rehabilitation, University of Wisconsin – Madison, Madison, WI, USA

³Department of Kinesiology, University of Wisconsin – Madison, Madison, WI, USA

Abstract

Both obesity and metabolic syndrome are important cardiovascular disease risk factors. In this review, we will explore the hypothesis that young obese adults and adults with metabolic syndrome exhibit alterations in blood flow regulation that occur prior to the onset of overt cardiovascular dysfunction.

Keywords

Exercise; Skeletal Muscle; Functional Sympatholysis; Endothelium-Dependent Vasodilation; Muscle Sympathetic Nerve Activity; Oxidative Stress

Introduction

Over 60% of the United States population is overweight or obese, and over one third exhibit metabolic syndrome (i.e. pre-diabetes) (38). Both obesity and metabolic syndrome are important cardiovascular disease risk factors. Due to drastic increases in the incidence of both obesity and metabolic syndrome in recent years, there is a clear need for effective interventions aimed at preventing and reducing the negative cardiovascular effects associated with these conditions. Regular exercise holds promise as an effective non-pharmacological approach to reducing the impact of obesity and metabolic syndrome on cardiovascular disease risk (8). Surprisingly, little is known about how cardiovascular control is altered in human obesity at rest or how obesity alters the vascular responses to exercise. Adequate blood flow is critical to ensure that oxygen supply matches metabolic demand [Reviewed in (25, 29)]. In this way, even small impairments in local skeletal muscle blood flow at rest and/or during exercise may have important negative consequences on muscle oxygenation, blood pressure regulation, glucose delivery, and waste removal [Reviewed in (25, 29)]. Based on our work in the field, *we hypothesize obese adults and adults with metabolic*

Corresponding Author: Jacqueline K. Limberg, Ph.D. Department of Anesthesiology, Mayo Clinic, 200 1st Street SW; Rochester, MN, Phone: 507-255-8380; Fax: 507-255-7300; Limberg.Jacqueline@mayo.edu.

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syndrome exhibit altered neural and vascular control of blood flow at rest and in response to exercise, prior to the onset of overt cardiovascular disease (Figure 1). In light of this, the present review explores recent work examining changes in control of the skeletal muscle circulation that occur with obesity and metabolic syndrome, and the potential implications on cardiovascular health.

The Significance of Studying Human Obesity

Over the past 30 years, the prevalence of obesity in the United States has more than doubled (38). Obesity is a progressive condition and has been linked with increased incidence of a variety of other conditions associated with cardiovascular disease, including hypertension, dyslipidemia, and hyperglycemia. This disease clustering was first defined as “Metabolic Syndrome” by the World Health Organization in 2001 (5, 16). The presence of metabolic syndrome significantly increases a person's risk of developing atherosclerotic cardiovascular disease, type 2 diabetes, and related complications that include, but are not limited to: insulin resistance, cardiac arrhythmias, heart failure, renal failure, diabetic cardiomyopathy, fatty liver disease, and sleep apnea (5, 16). Insight into the pathophysiology of human obesity and/or metabolic syndrome has been challenging due to the varying degrees of the condition as well as the prolonged time-course of disease progression. For example, individuals may exhibit impaired vascular control mechanisms many years prior to the manifestation of overt dysfunction identified in clinical examinations. Therefore, a greater mechanistic understanding is necessary to elucidate factors contributing to the early progression of obesity-related vascular dysfunction, describe the time-course of the development of overt cardiovascular disease, and determine how this vascular dysfunction impacts related complications in at-risk individuals. Such understanding will be integral to identifying potential therapeutic targets to mitigate the negative impact of obesity and metabolic syndrome on the cardiovascular system.

Obesity Alters Peripheral Blood Flow Regulation

Local blood flow control within the skeletal muscle circulation is a balance of vasoconstriction and vasodilation with the goal of matching oxygen delivery and metabolic demand. In response to acute stress (e.g. exercise), the relationship between blood flow and oxygen consumption remains relatively constant in healthy individuals, such that delivery is proportional to demand [Reviewed in (25, 29)]. Until recently, very little work had assessed how vascular control may be altered in obese humans; however, animal models of obesity and metabolic syndrome (e.g. Obese Zucker Rat) support the concept of impaired blood flow regulation [Reviewed in (13)].

The Obese Zucker Rat is commonly used to study the physiological consequences of obesity and metabolic syndrome. These animals present with inactive leptin receptors, resulting in hyperphagia (overeating), leading to a model very similar to human obesity and metabolic syndrome – including the development of obesity, hypertension, dyslipidemia, and hyperglycemia (13). These obese animals also exhibit a variety of vascular control abnormalities, including increased sympathetic activity, increased vasoconstriction, and impaired vasodilatory mechanisms (including impaired endothelium-dependent vasodilation, vascular smooth muscle dysfunction, decreased nitric oxide availability, etc) (13). As a

result, Obese Zucker Rats consistently exhibit impaired total blood flow as well as impaired flow distribution within the skeletal muscle circulation both at rest and in response to acute stressors (e.g. hypoxia, simulated exercise) (15). Additional data suggest such impairments in skeletal muscle perfusion likely contribute to increased muscle fatigability, as well as impaired glucose uptake, waste removal, and altered blood pressure regulation (14). Consistent with this notion, adults with metabolic syndrome exhibit impaired glucose handling, exaggerated blood pressure responses to exercise, and reduced exercise tolerance (36, 43).

Increased Sympathetically-Mediated Vasoconstriction at Rest in Obesity

Obese humans and those with metabolic syndrome are known to exhibit increased muscle sympathetic nerve activity, a physiologic factor which has been linked to increased rates of cardiovascular morbidity and mortality (28). The exact mechanisms behind this increase are unknown; however a rise in sympathetic activity may occur in response to changes in body composition, altered insulin signaling, and/or changes in central autonomic regulation. Chronic sympathetic activation can affect neurovascular coupling, resulting in altered neurotransmitter release, receptor number/affinity, and/or signaling within the vascular smooth muscle. Consistent with this concept, animal models of metabolic syndrome exhibit increased sympathetic activity in addition to increased basal α -adrenergic receptor-mediated vasoconstriction when compared with healthy control animals (37, 40).

We recently sought to translate such findings in humans. Data from our lab showed that adults with metabolic syndrome exhibit higher sympathetic nervous system activity (as assessed using the technique of microneurography, Figure 2A), as well as greater vasoconstrictor responsiveness to intra-arterial infusion of an α_2 -adrenergic receptor agonist [Figure 2B, (35)]. These data are indicative of increased sympathetically-mediated vasoconstriction in adults with metabolic syndrome and are consistent with reports of greater sympathetic support of blood pressure in human obesity (7). Our results (Figure 2C and 2D) are also consistent with data demonstrating a lack of α_1 -adrenergic receptor down-regulation in response to increased sympathetic activity in a canine model of metabolic syndrome (9).

Despite support within the animal literature, our findings disagree with much of what we understand about neurovascular control in healthy young and/or aging individuals. For example, young healthy adults exhibit a balance between sympathetic nervous system activity and α -adrenergic mediated vasoconstriction at rest such that those with chronically higher sympathetic activity exhibit lower vascular-adrenergic responsiveness [Figure 2C, (6)]. Similarly, older men with increased levels of sympathetic nervous system activity are less responsive to α -adrenergic agonists and thus exhibit blunted sympathetically-mediated vasoconstriction at rest when compared with younger adults (10). Many speculate this to be the result of chronic increases in sympathetic activity and resultant adrenergic receptor desensitization or downregulation. Interestingly, the inverse relationship between sympathetic activity and α -adrenergic mediated vasoconstriction is absent in human metabolic syndrome (Figure 2D), highlighting that human metabolic syndrome is a unique pathophysiological phenotype that cannot be merely described as “early vascular aging”. With this in mind, the uncoupling between elevated sympathetic activity and

vasoconstriction in metabolic syndrome may have important implications in the progression towards overt cardiovascular disease and diabetes. In support of this idea, previous work has shown α -adrenergic responsiveness to be maintained in healthy obesity (1), but increased with type 2 diabetes (21).

Sympathetically-Mediated Vasoconstriction, Exercise, and Blood Flow

Exercise tolerance is reduced in obese individuals (36, 43), which may be the result of poor regulation of peripheral blood flow. Consistent with this, animal models of obesity and metabolic syndrome suggest impairments in neural control of the circulation at rest extend into exercise. For example, blood flow responses to simulated exercise are impaired in the Obese Zucker Rat, and these impairments are abolished with an α -adrenergic receptor-blocking drug (i.e. phentolamine) (11, 40). Based on our work in resting humans (35), we hypothesized blood flow responses to acute exercise would be reduced in human obesity and/or metabolic syndrome. Surprisingly, and in direct contrast to data from animals, we have consistently found that young obese individuals and/or individuals with metabolic syndrome do not exhibit impairments in whole limb blood flow responses to acute exercise, and under certain conditions blood flow responses may actually be *higher* when compared to non-obese control subjects [Figure 3, (31, 33, 34)]. These data are not only in contrast with the majority of animal work, but also disagree with previous work conducted in humans (17, 27). There are many potential reasons for this discrepancy, with the most obvious being that very few, if any, research groups examined blood flow responses to exercise in younger (<35 years) obese individuals independent of other comorbidities (e.g. diabetes). In this way, the body of literature is supportive of progressive and/or time-dependent alterations in vascular control as it relates to human obesity.

This led us to question “*what is happening during the early stages of obesity that may contribute to preserved blood flow responses to exercise in the face of altered neurovascular control?*” We initially proposed that obese individuals may exhibit augmented “functional sympatholysis”. “Functional sympatholysis” is a term used to describe a relative reduction in sympathetically-mediated vasoconstriction during exercise. For example, a given level of sympathetically-mediated vasoconstriction is observed at rest which is important in ensuring appropriate blood flow (41). With exercise, specific metabolic (e.g. adenosine, potassium, lactate) and other sympatholytic factors (e.g. nitric oxide, prostacyclin, ATP) blunt sympathetically-mediated vasoconstriction in active skeletal muscle, which allows blood flow to be redirected to appropriately meet metabolic demand (41). Interestingly, when we examined functional sympatholysis in obese humans with metabolic syndrome, we found the degree of functional sympatholysis was similar to that of healthy lean control subjects (30, 34). This suggests adults with metabolic syndrome do not exhibit increased sympatholytic factors which could contribute to increased perfusion during exercise. Thus, contrary to our initial hypothesis, augmented sympatholysis cannot explain the observed preserved and/or higher blood flows with exercise (Figure 3). Subsequently, we asked the question: *Are higher blood flow responses to exercise necessarily “beneficial”? Or could relatively “normal” flows in the face of altered vascular control mechanisms be a sign of early and potentially negative neurovascular adaptations?*

Obesity and Altered Blood Flow Distribution

Although the majority of work in humans examines whole-limb blood flow (e.g. arm, leg) when exploring vasodilatory responses to exercise (10, 31), it is important to acknowledge that all blood flow is not created equal. Specifically, blood flow is not uniformly distributed among and within working muscles (26) and the exact pattern of flow distribution is difficult to assess. With this in mind, we speculate preserved and/or increased whole-limb blood flow responses to exercise in human metabolic syndrome [Figure 3, (31, 33, 34)] may be the result of altered blood flow distribution. Impaired distribution, or greater blood flow to inactive skeletal muscle fibers and/or non-metabolically active tissues (e.g. skin, adipose tissue), may require larger increases in total limb flow in order to meet oxygen needs of contracting skeletal muscle. Along these lines, recent research in obese animal models uncovered extensive perfusion-demand mismatch resulting in higher flow dispersion in the animal model of metabolic syndrome when compared with controls (15). Higher whole limb blood flows in some animal models of metabolic syndrome (2, 42) support this concept. In our own research, we demonstrated greater clonidine-mediated (primarily α_2 -adrenergic) vasoconstriction in metabolic syndrome adults when compared with age-matched, healthy controls (34). Alpha-2 adrenergic receptors are thought to be metabolically sensitive and may play an important role in functional sympatholysis by limiting blood flow to inactive tissues and directing flow toward more metabolically stressed muscle fibers. Although blood flow distribution was not directly assessed in our experiments, the combined observations (higher whole limb blood flow and greater α_2 -mediated vasoconstriction during exercise in adults with metabolic syndrome) are consistent with the concept of unfavorable blood flow distribution and are in agreement with results from the Obese Zucker Rat (15).

In general, concrete observations regarding flow distribution in humans are limited; however, some recent work employing Positron Emission Tomography offers insight into tissue-specific blood flow during exercise. This technology determines flow patterns based on the kinetics of specific tracers labelled with radioisotopes in tissues of interest. Using Positron Emission Tomography, researchers have uncovered important roles for sympathetically-mediated vasoconstriction (19) and nitric oxide-mediated vasodilation (20) in blood flow heterogeneity at rest and during exercise. Together, these data support the idea that impairments in the normal function of the sympathetic nervous system and/or important vasodilatory pathways (e.g. nitric oxide) may contribute to impairments in effective tissue perfusion distribution (20). Consistent with this, impairments in blood flow distribution in the Obese Zucker Rat can be returned to normal with pharmacological inhibition of sympathetically-mediated vasoconstriction (14). Therefore, not only does sympathetic inhibition improve total flow, it also improves blood flow distribution. However, this is only true in the proximal circulation [at the level of 1A-2A arterioles, (4, 14)] (Figure 4A and B).

As suggested above, a strong body of literature also supports an important role for nitric oxide in normal blood flow responses to exercise. Thus reduced nitric oxide bioavailability may significantly impact whole-limb blood flow, as well as blood flow distribution, in response to exercise. For example, improvements in nitric oxide bioavailability (via antioxidant-mediated scavenging of free radicals with a superoxide dismutase mimetic, TEMPOL) have been shown to improve whole-limb blood flow, as well as blood flow

distribution within the distal (3A-4A) arterioles of the Obese Zucker Rat (Figure 4A and B) (4, 14). Interestingly, although both phentolamine and TEMPOL improve whole-limb blood flow (Figure 4C), it is not until the two are combined (phentolamine + TEMPOL) that muscle fatigue/tension development is improved [Figure 4D, (14)]. Collectively these data suggest: 1) blood flow distribution is impaired in models of obesity/metabolic syndrome, 2) sub-optimal blood flow distribution is the result of both increased sympathetically-mediated constriction and decreased vasodilatory mechanisms (via increased oxidative stress and decreased nitric oxide bioavailability) (Figure 4A and B), and 3) the relative influence of these mechanisms (sympathetic vasoconstriction, reactive oxygen species) varies along the arterial tree (Figure 4A and B), and treating both is necessary in order to improve blood flow distribution and, in turn, muscle fatigability (Figure 4D). All of these concepts must be taken into account as we seek to: 1) further define relationships among human obesity, metabolic syndrome, and cardiovascular risk, and 2) develop new therapeutic strategies for preventing or reversing obesity- and metabolic syndrome-related impairments in vascular function. However, the subclinical nature of such changes and the anatomical divergence of dysfunctional mechanisms add to the complexity of this pathological condition and create a unique challenge in the development of therapeutic strategies.

Oxidative Stress, Inflammation, and Impairments in Vasodilatory Mechanisms in Obesity

As noted above, we have not observed large group differences in measures of vascular function in young obese humans or adults with metabolic syndrome (31, 33, 34). However, recent data from our group suggest unique phenotypes exist within groups of obese individuals which appear to drive impairments in subclinical measures of vascular function. For example, in addition to increases in activity of the sympathetic nervous system (discussed in detail above), obesity has been associated with chronic low-grade inflammation, increased levels of pro-inflammatory cytokines, and increases in oxidative stress. Consistent with this, we recently demonstrated that endothelial-dependent vasodilation is preserved, on average, in young obese individuals and individuals with metabolic syndrome (32). However, those individuals with the greatest level of oxidative stress exhibit the lowest peak response to endothelial and vascular smooth muscle stimulation (indicative of microvascular impairments) (32). Additionally, our recent data support the idea that chronic inflammation plays a role in determining how quickly the blood flow response to exercise reaches steady-state (Figure 5A). Specifically, those individuals with high C-reactive protein levels (a measure of systemic inflammation) require more time to achieve steady-state exercise blood flow [Figure 5B, (33)]. Functionally, a delayed vasodilator response to exercise may result in earlier onset of fatigue and poor exercise tolerance (22), which has important clinical implications. Interestingly, this impairment is reversed with acute infusion of Vitamin C (a potent antioxidant) (33). Collectively, these findings expose a potential relationship between inflammation, oxidative stress, and the time-course of the exercise vasodilator response in human obesity and metabolic syndrome (32, 33).

Lastly, despite relatively preserved exercise blood flows in obese individuals (Figure 3), we have also observed relationships between regular physical activity and blood flow responses to exercise. When we examine the relationship between the hemodynamic response to

exercise and levels of physical activity (determined by self-report) in the same cohort, we find that adults reporting lower levels of regular physical activity tend to exhibit improvements in exercise blood flow following infusion of Vitamin C (33). Although speculative, these results suggest that sedentary behaviors, rather than obesity-related disease *per se*, contribute to oxidative stress-mediated impairments in vascular responses to exercise. Along these lines, physical activity has been shown to increase production of endogenous antioxidant enzymes, which may be important to counteract the presence of chronic and/or exercise-mediated production of reactive oxygen species (23). Consistent with this idea, low levels of physical activity are associated with increased oxidative stress, inflammation, impaired endothelial function, and increased cardiovascular disease risk (39). Taken together, increased physical activity and/or other interventions focused on improving sub-clinical risk factors (e.g. inflammation, oxidative stress) are likely important targets which could attenuate the impact of obesity and metabolic syndrome on the cardiovascular system in certain individuals.

Obesity and Metabolic Syndrome: A Progressive Condition

As noted above, although it is commonly thought that peripheral vascular function is impaired in human obesity, our lab has consistently shown that blood flow responses to exercise are preserved [Figure 3, (31, 33, 34)]. Additionally, young, otherwise healthy obese individuals exhibit relatively preserved endothelial and smooth muscle function (18, 32) and the few impairments we have observed appear to be related to the progression of the disease, including: 1) sedentary behaviors, 2) mild increases in oxidative stress, and/or 3) mild increases in inflammation (Figure 5B). Further, although we have observed higher sympathetic nervous system activity and sympathetically-mediated vasoconstriction in obese adults with metabolic syndrome (34, 35), this is not a consistent finding (30). With this, sympathetic activity is also known to be highly variable between individuals and is strongly correlated with specific disease factors (e.g. insulin resistance, systemic inflammation, circulating leptin, etc) (28) – with higher sympathetic activity observed with increasing number of comorbidities. Together, these data highlight the likely progressive and individually-variable impact of obesity and/or metabolic syndrome on the peripheral vasculature. It is also important to note the potential for sex and age differences in sympathetic nervous system activity and neurovascular control (3, 24).

Consistent with the idea of prolonged, sub-clinical disease progression, Frisbee and colleagues (2016) recently published an elaborate study utilizing eight rat models spanning the progression of cardiovascular disease from “healthy” (Lean Zucker Rat) animal models to those consistent with “high peripheral vascular disease risk” (Obese Zucker Rat, Dahl Salt-Sensitive Rats) (12). At mild-levels of disease risk (e.g. Sprague-Dawley rats on high-salt or high-fructose diets), they observed a reduction in bioavailable nitric oxide. With the introduction of hypertension, adrenergic vasoconstriction was increased. Interestingly, and consistent with human work from our lab, blood flow responses to simulated exercise were not significantly altered with mild-or-moderate disease risk, although there were changes indicative of heterogeneous perfusion within resting and contracting skeletal muscle (12). This recent work strongly supports early, sub-clinical aspects of the obesity process which may be strong predictors of skeletal muscle microvascular pathology and poor health

outcomes associated with obesity and metabolic syndrome (12). With this in mind, efforts to develop quantitative methods for assessing blood flow distribution within human skeletal muscle must be given high priority. Without them, a complete understanding of the effects of obesity and metabolic syndrome on vascular function and cardiovascular risk may not be possible.

Conclusion/Summary

In conclusion, we leave the readers with four take-home points:

1. Increased sympathetically-mediated vasoconstriction, in addition to increases in inflammation and/or oxidative stress significantly impact local blood flow regulation in obese adults and adults with metabolic syndrome and may have important implications for overall vascular health early in the disease process.
2. Neither obesity nor metabolic syndrome is a homogeneous disorder and therefore, the quest for insight into the pathophysiology of these two conditions is challenging due to varying severities and uncertain rates of progression.
3. A complex array of subtle, sub-clinical changes likely have a big impact on vascular function, but may take time to develop and/or require multiple insults (i.e. comorbidities) in order to progress to the point of obvious impairment. Thus, individuals may exhibit altered vascular control mechanisms many years prior to the manifestation of overt dysfunction.
4. Physical activity and/or other interventions focused on reducing sympathetic activity, oxidative stress, and/or systemic inflammation are likely effective targets which could attenuate the impact of obesity and metabolic syndrome on the cardiovascular system and, in turn, slow the progression toward devastating effects of obesity-related cardiovascular disease.

Taken together, we are beginning to establish an emerging story where differences in blood flow, vascular heterogeneity, and individual sensitivity to sub-clinical changes significantly impact vascular control. These intriguing results provide ample opportunities to continue to explore the complex interplay between potentially dysfunctional mechanisms in future work.

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Summary

The present review explores the hypothesis that young obese adults and adults with metabolic syndrome exhibit impaired peripheral blood flow regulation.

Key Points

- Regulation of blood flow within the skeletal muscle vasculature involves a balance between vasoconstriction and vasodilation, with the goal of matching oxygen delivery and metabolic demand.
- Even small impairments in local skeletal muscle blood flow may have negative consequences on muscle oxygenation, blood pressure regulation, glucose delivery, and waste removal.
- In this review, we highlight how increased sympathetically-mediated vasoconstriction, in addition to increases in inflammation and/or oxidative stress, significantly impact local blood flow regulation in obese adults and adults with metabolic syndrome.

Figure 1. Novel Hypothesis

Blood flow control within the skeletal muscle vasculature is a balance of vasoconstriction and vasodilation, with the goal of matching oxygen delivery with metabolic demand. We explore the hypothesis that young obese adults with metabolic syndrome exhibit sub-clinical alterations in neurovascular control of the peripheral circulation, including increased sympathetic activity, increased local vasoconstriction, and decreased vasodilatory mechanisms - which may contribute to impairments in blood flow regulation at rest and in response to exercise.

Figure 2. Altered neurovascular control of the circulation at rest in human metabolic syndrome

We observed higher sympathetic nervous system activity (as assessed using the technique of microneurography, Fig 2A), as well as greater vasoconstrictor responsiveness to intra-arterial infusion of an α_2 -adrenergic receptor agonist in adults with metabolic syndrome [$*p < 0.05$ vs Control, Fig 2B, (35)]. These data are indicative of increased sympathetically-mediated vasoconstriction in adults with metabolic syndrome. Furthermore, whereas young healthy adults exhibit an inverse relationship between sympathetic nervous system activity and α -adrenergic mediated vasoconstriction (Fig 2C), such relationships were found to be absent in human metabolic syndrome (Fig 2D). [Adapted from (35). Copyright © 2012 John Wiley and Sons. Used with permission.]

Figure 3. Exercise blood flow is preserved in human obesity and metabolic syndrome

Although we hypothesized blood flow responses to acute exercise are likely reduced in human obesity and/or metabolic syndrome, we have consistently found that young obese individuals and/or individuals with metabolic syndrome do not exhibit impairments in total blood flow responses to acute exercise, and under certain conditions blood flow responses may actually be *higher* than in non-obese control subjects (31, 33, 34). [Adapted from (33). Copyright © 2014 the American Physiological Society. Used with permission.]

Figure 4. Impaired blood flow distribution in animal models of metabolic syndrome and contributing mechanisms

LZR = lean Zucker rat, OZR = obese Zucker rat. Animal models of metabolic syndrome exhibit impaired distribution of blood flow that can be returned to normal with inhibition of sympathetically-mediated vasoconstriction (α -adrenergic inhibitor, phentolamine) at the level of the proximal 1A arterioles [$*p < 0.05$ vs No Change; Fig 4A and 4B, (4, 14)]. Despite improvements in whole-limb blood flow with phentolamine (Fig 4C), impairments in blood flow distribution distally in the 4A arterioles are not improved until antioxidant-mediated scavenging of free radicals (with TEMPOL) [$*p < 0.05$ vs LZR, $\dagger p < 0.05$ vs OZR; Fig 4B, (4, 14)]. Furthermore, it is not until both of these maneuvers (phentolamine + TEMPOL) are used in sequence are improvements in muscle fatigue/tension development observed [$*p < 0.05$ vs LZR, $\dagger p < 0.05$ vs OZR; Fig 4D, (14)]. [Adapted from (4). Copyright © 2013 the American Physiological Society. Used with permission.] [Adapted from (14). Copyright © 2011 John Wiley and Sons. Used with permission.]

Figure 5. Variability in human obesity and role of systemic inflammation

Although we have not observed large group differences in measures of vascular function in young obese humans or adults with metabolic syndrome (18, 32), recent data from our group suggest unique phenotypes exist within groups of obese individuals which appear to drive impairments in subclinical measures of vascular function. For example, individuals with high C-reactive protein (a measure of systemic inflammation) require more time to achieve steady-state exercise-mediated vasodilation ($\dagger p < 0.10$ vs CRP < 3 mg/L) [Mean Response Time = calculated as the time to achieve $\sim 63\%$ of the increase in forearm vascular conductance to steady-state, analyzed in 3-second bins during 5-minutes to dynamic forearm exercise.]. This finding highlights the potential heterogeneous nature of human obesity, as well as potential relationships between inflammation and vascular function. [Adapted from (33). Copyright © 2014 the American Physiological Society. Used with permission.]