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HEART OF THE MATTER: CORONARY DYSFUNCTION IN METABOLIC SYNDROME

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Abstract

Metabolic syndrome (MetS) is a collection of risk factors including obesity, dyslipidemia, insulin resistance/impaired glucose tolerance, and/or hypertension. The incidence of obesity has reached pandemic levels, as ~20–30% of adults in most developed countries can be classified as having MetS. This increased prevalence of MetS is critical as it is associated with a two-fold elevated risk for cardiovascular disease. Although the pathophysiology underlying this increase in disease has not been clearly defined, recent evidence indicates that alterations in the control of coronary blood flow could play an important role. The purpose of this review is to highlight current understanding of the effects of MetS on regulation of coronary blood flow and to outline the potential mechanisms involved. In particular, the role of neurohumoral modulation via sympathetic α-adrenoceptors and the renin-angiotensin-aldosterone system (RAAS) are explored. Alterations in the contribution of end-effector K^+, Ca^{2+}, and transient receptor potential (TRP) channels are also addressed. Finally, future perspectives and potential therapeutic targeting of the microcirculation in MetS are discussed.

Keywords

coronary circulation; neurohumoral factors; obesity; renin-angiotensin-aldosterone axis; sympathetic activation

1. Introduction

Metabolic syndrome (MetS) is a group of risk factors including obesity, dyslipidemia, insulin resistance/impaired glucose tolerance, and/or hypertension accompanied by pro-inflammatory and thrombotic states [1]. The incidence of obesity has reached pandemic levels, as ~20–30% of adults in most developed countries can be classified as having MetS [1;2]. The increased prevalence of MetS is important as it is associated with a 2-fold increased risk for cardiovascular disease, 5-fold increased risk for type 2 diabetes mellitus,

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and 1.5-fold increase in all-cause mortality [3–5]. Critically, the prevalence of coronary disease and heart failure is significantly elevated in patients with MetS [3;6–8]. Given that heart disease remains a leading cause of death around the world [1], elucidating mechanisms by which MetS increases cardiovascular risk is essential for developing future treatments and preventing this global epidemic.

Alterations in the control of coronary blood flow could underlie increased cardiovascular morbidity and mortality in the MetS. Regulation of myocardial oxygen delivery is critical to overall cardiac function as the heart has limited anaerobic capacity and maintains a very high rate of oxygen extraction at rest (70–80%) [9–12]. Thus, the myocardium is highly dependent on a continuous supply of oxygen to maintain normal cardiac output and blood pressure. MetS impairs the ability of the coronary circulation to regulate vascular resistance and balance myocardial oxygen supply and demand [13–15]. Coronary microvascular dysfunction in MetS is evidenced by reduced coronary venous PO_2 [13–15], diminished vasodilation to endothelial-dependent and independent agonists (i.e. flow reserve) [16–21], and altered functional and reactive hyperemia [13–15;22;23]. Importantly, these changes occur prior to overt atherosclerotic disease and have been associated with left ventricular systolic and diastolic contractile dysfunction in humans [24–28] and animal models of MetS [13;29–31].

The purpose of the present review is to highlight current understanding of the effects of MetS on regulation of coronary blood flow and outline potential mechanisms involved. In particular, pathophysiologic roles of neurohumoral modulation via sympathetic α-adrenoceptors and the renin-angiotensin-aldosterone system (RAAS) are explored. In addition, the contribution of end-effector K^+, Ca^{2+}, and transient receptor potential (TRP) channels are addressed. Finally, future perspectives and potential therapeutic targeting of the microcirculation in MetS are discussed. Other recent reviews of microvascular dysfunction in MetS include those by Knudson *et al*. [32], Hodnett and Hester [33]; Frisbee [34]; Stepp *et al* [35;36]; Serne *et al* [37]; Bagi [38] and Krentz *et al* [39]; Liu and Gutterman [40].

2. Coronary blood flow in MetS

2.1 Resting flow and vasodilator responses

There is little change in baseline coronary blood flow in either animals [13–15;22;41–45] or humans [16–19;46] with MetS. While myocardial perfusion is equivalent, myocardial oxygen consumption (MVO_2) is elevated in proportion to increases in stroke volume, cardiac output, and blood pressure; i.e. characteristic “hyperdynamic circulation” [13;30;31;46;47]. Basal coronary venous PO_2 is reduced in MetS, indicating an imbalance between coronary blood flow and myocardial metabolism [13–15]. These findings suggest that the MetS forces the heart to utilize its limited oxygen extraction reserve by affecting one or more primary determinants of coronary flow, including: 1) myocardial metabolism; 2) arterial pressure; 3) neuro-humoral, paracrine and endocrine influences; and 4) myocardial extravascular compression [9;10]. As addressed below, MetS increases sympathetic output [48–51] and activates the RAAS [15;52–55], increasing blood pressure, myocardial oxygen demand, and coronary vascular resistance. The determinants of coronary flow in MetS are also influenced by diminished nitric oxide (NO) bioavailability [36;56–59] and augmented endothelial-dependent vasoconstriction [43;60–64]. However, despite these changes it is not surprising that basal coronary flow is largely unaffected by MetS, as it is well established that inhibition of NO synthesis [65–69] or endothelin-1 receptors [63;70–72] does not alter myocardial perfusion in normal, lean subjects. To date, no studies have specifically examined the effects of MetS on myocardial compressive forces.

MetS attenuates coronary flow responses to pharmacologic vasodilator compounds such as acetylcholine, adenosine, papaverine, and dipyridamole [16–20;45;73]. Decreases in coronary flow reserve directly correlate with waist-to-hip ratio [74], body mass index [17], blood pressure [20], degree of insulin resistance [16;20], and the clinical diagnosis of MetS [18]. Interestingly, our data indicate that specific receptor subtypes and downstream K^+ channels involved in coronary microvascular dilation are altered in Ossabaw swine with early-stage MetS, prior to any absolute change in coronary flow reserve [44]. In contrast, decreased coronary flow reserve is evident in swine with later-stage MetS [41;73;75] and worsens with the onset of type 2 diabetes [16;17]. Exact mechanisms underlying impaired pharmacologic coronary vasodilation in MetS have not been clearly defined, but are likely related to altered functional expression of receptors and ion channels [41;44;45;73;76;77], endothelial and vascular smooth muscle function [36;56;77;78], paracrine and neuro-endocrine influences [32;48–50;54;79;80], structural remodeling of coronary arterioles [35;81;82], and/or microvascular rarefaction [83–85].

2.2 Coronary response to increases in cardiac metabolism

Energy production of the heart is almost entirely dependent on oxidative phosphorylation for contraction in relation to ventricular wall tension, myocyte shortening, heart rate, and contractility [9]. Since the heart maintains a very high rate of oxygen extraction at rest, increases in myocardial energy production must be met by parallel increases in myocardial oxygen delivery [9–11;86]. Exercise is the most important physiologic stimulus for increases in coronary blood flow, as many of the primary determinants of myocardial oxygen demand are elevated by β-adrenoceptor signaling [9;86]. Data from our laboratory indicate that MetS impairs the ability of the coronary circulation to adequately balance myocardial oxygen delivery with myocardial metabolism at rest and during exercise-induced increases in MVO_2. In particular, coronary vasodilation in response to exercise is attenuated in Ossabaw swine with MetS. This effect is evidenced by reduction of the slope between coronary blood flow and aortic pressure, which supports that exercise-mediated increases in vascular conductance are attenuated in MetS (Fig. 1A). Diminished local metabolic control of the coronary circulation is also evidenced by decreased coronary blood flow at a given coronary venous PO_2 (Fig. 1B), an index of myocardial tissue PO_2 which is hypothesized to be a primary stimulus for metabolic coronary vasodilation [9–11]. Importantly, coronary venous PO_2 is also depressed by MetS relative to alterations in MVO_2 (the primary determinant of myocardial perfusion) both at rest and during exercise (Fig. 1C). Together, these findings demonstrate coronary microvascular dysfunction in MetS leads to an imbalance between coronary blood flow and myocardial metabolism that could contribute to the increased incidence of cardiac contractile dysfunction and the onset of myocardial ischemia in obese patients [1;3;7;8]. This point is supported by an ~25% reduction in baseline cardiac index (cardiac output normalized to body weight) and a marked increase in myocardial lactate production (onset of anaerobic glycolysis) in swine with the MetS [13].

2.3 Coronary response to myocardial ischemia

Coronary vasodilation in response to myocardial ischemia is a critical mechanism increasing oxygen delivery to the heart to mitigate ischemic injury and infarction [87;88]. To address the effects of MetS on ischemic vasodilation, we examined coronary flow responses to a 15 sec occlusion in anesthetized, open-chest lean and MetS Ossabaw swine [22]. Representative tracings illustrating reactive hyperemia in lean vs. MetS swine are shown in Fig. 2A. Because coronary reactive hyperemia varies directly with baseline blood flow, estimating overall repayment of incurred oxygen debt is critical for analyzing ischemic dilator responses [87;88]. Our finding that vasodilation in response to cardiac ischemia is impaired by MetS, relative to the deficit in coronary blood flow (i.e. repayment/debt ratio; Fig. 2B), is consistent with decreased reactive hyperemia of peripheral vascular beds in

obese humans [89;90]. We propose that impaired ischemic dilation in MetS could exacerbate myocardial injury in patients with flow-limiting atherosclerotic lesions or acute coronary thrombosis.

In summary, microvascular dysfunction in MetS upsets the balance between coronary blood flow and myocardial metabolism as well as impairs blood flow responses to pharmacologic vasodilator compounds (coronary flow reserve), exercise-induced increases in MVO_2 (physiologic stimuli), and cardiac ischemia (pathophysiologic stimuli). Potential mechanisms underlying these key alterations in the control of coronary blood flow are explored below.

3. Neurohumoral modulation of coronary flow in MetS

3.1 Sympathetic control of coronary blood flow

MetS is associated with sympathetic hyperactivity, as numerous studies have documented increased plasma and urinary catecholamines, sympathetic nerve activity, and cardiac autonomic activity [48–52;91;92]. Potential components of MetS that might contribute include increased plasma insulin, adipokines, nonesterified fatty acids, proinflammatory cytokines, as well as activation of RAAS, baroreflex impairment, and obstructive sleep apnea [48;50]. Sympathetic activation has important effects on the coronary circulation through direct actions on vascular α- and β-adrenoceptors and indirect initiation of local metabolic vasodilator mechanisms secondary to increases in contractility, heart rate, and arterial pressure [9;11;12;93]. It is well accepted that direct α-adrenoceptor mediated vasoconstriction limits myocardial flow in both normal and hypoperfused hearts [94–101] and that “feedforward” β-adrenoceptor vasodilation contributes to increased coronary blood flow when the sympathetic nervous system is activated, as during exercise [96;97;102;103]. Therefore, alterations in these opposing autonomic influences could play a key role in coronary microvascular dysfunction in MetS.

Vasoconstriction mediated by α-adrenoceptors is augmented by MetS in both coronary [42;104] and peripheral vascular beds [105–107]. Recent findings from Grisk *et al.* who documented that α_1-adrenoceptor mediated vasoconstriction is enhanced in isolated coronaries from Wistar Ottawa Karlsburg W rats [104], are consistent with *in vivo* data from our laboratory which demonstrated increased coronary constriction to the α_1-adrenoceptor agonist methoxamine in MetS dogs (Fig. 3A) [42]. Importantly, no differences in α_2-adrenoceptor mediated coronary vasoconstriction or expression of α_{1B}- or α_{1D}-adrenoceptors were noted in lean vs. MetS canines. Thus, MetS is associated with increased coronary α_1-adrenoceptor signaling that likely contributes to the imbalance between myocardial oxygen supply and demand, especially during heightened sympathetic activity. Given that α-adrenoceptor inhibition improves myocardial perfusion and cardiac contractile function clinically [108;108–111], therapeutic strategies to diminish coronary α_1-adrenoceptor activation could improve cardiovascular outcomes in patients with MetS.

Sympathetic vasodilation mediated by β-adrenoceptors is also diminished in MetS as D'Angelo *et al.* recently showed that an exaggerated blood pressure response to acute stress in obese Zucker rats is related, at least in part, to blunted β-adrenoceptor dilation [112]. Decreased vasodilation to the β-agonist isoproterenol has also been observed in isolated coronary arterioles [104]. However, the extent to which altered sympathetic β-adrenoceptor expression and/or signaling contribute to coronary vascular dysfunction in MetS *in vivo* has not been investigated.

3.2 RAAS and coronary blood flow

There is substantial evidence that MetS activates the RAAS and that effects of angiotensin II on vascular tone, inflammation, vascular remodeling, thrombosis, and plaque stability are central to the pathogenesis of cardiovascular disease [15;52–55]. Although angiotensin II has very modest effects on the coronary circulation in normal hearts [15;113;114], vasoconstriction to angiotensin II is enhanced in disease states associated with chronic RAAS activation [15;115;116]. Our data support this hypothesis, as increased circulating angiotensin II in our canine model of MetS was accompanied by increased angiotensin II type 1 (AT_1) receptor-mediated coronary vasoconstriction (Fig. 3B) [15]. This augmented constriction directly corresponded with a ~40% increase in coronary AT_1 receptor expression, while coronary AT_2 receptor expression was unchanged. Importantly, inhibition of AT_1 receptor-mediated coronary vasoconstriction with telmisartan significantly improved the balance between myocardial oxygen supply and demand in MetS animals at rest and during exercise-induced increases in MVO_2.

Increases in aldosterone signaling have been linked with impaired vascular function, pro-atherosclerotic gene expression, vascular smooth muscle proliferation, and calcification, as well as diminished cardiac and renal function [117–120]. With regard to the coronary circulation, aldosterone produces dose-dependent vasoconstriction *in vivo* in open-chest dogs [121], *in vitro* in isolated perfused rat hearts [122], and in isolated coronary arterioles [123]. Interestingly, this non-genomic effect of aldosterone is blunted by inhibition of AT_1 receptors [123;124] and endothelial denudation [123], but is unaffected by blockade of mineralocorticoid receptors with spironolactone [121;123]. Coronary effects of aldosterone also appear to be augmented in disease states such as hypertension [123] and to worsen contractile function during cardiac ischemia [121]. Although clinical trials have established a beneficial effect of aldosterone antagonism on cardiovascular morbidity and mortality in myocardial infarction and heart failure [55;125], pathophysiologic consequences of elevated coronary mineralocorticoid receptor stimulation in MetS have not been examined. We propose one mechanism by which increases in angiotensin II and aldosterone impair control of coronary blood flow in MetS is through alterations in the expression of microvascular ion channels and receptors. This hypothesis is discussed in detail below. Together, these findings implicate upregulation of the RAAS in MetS-induced coronary vascular dysfunction and provide strong rationale for future clinical studies with AT_1 and mineralocorticoid receptor antagonists in patients with MetS.

4. Coronary ion channel dysfunction in MetS

4.1 Smooth muscle K^+ channels in MetS

Coronary smooth muscle cells express a variety of K^+ channels, which regulate membrane potential and vascular tone [77]. Major types include voltage-dependent (K_V), large conductance, Ca^{2+}-activated (BK_{Ca}), ATP-sensitive (K_{ATP}), and inwardly rectifying (Kir) K^+ channels, but other channels such as IK_{Ca} and SK_{Ca} are functionally expressed in the coronary circulation [126].

K_V channels are activated in the physiological range of membrane potential and thus have been implicated in the control of coronary blood flow [77]. In particular, our laboratory previously demonstrated that K_V channels regulate coronary blood flow at rest, during ischemia, and with increasing MVO_2 in normal-lean animals [127–131]. More recently, we documented that induction of the MetS markedly attenuates coronary vascular smooth muscle K_V current and expression of $K_V1.5$ channels [118], which is consistent with recent preliminary data indicating that metabolic coronary vasodilatation is reduced in $K_V1.5$ knockout mice [132]. Importantly, these changes in functional expression of K_V channels were directly associated with reductions in coronary blood flow, vascular conductance, and

coronary venous PO_2 in swine with the MetS [127]. Although the specific mechanisms underlying the impairment of coronary K_V channels in MetS are unclear, there is evidence that dyslipidemia, hyperglycemia, hypertension, and/or oxidative stress may contribute [133–139]. Activation of the sympathetic nervous system, RAAS, and PLC-PKC signaling pathways could also be involved [77;140;141].

Compared to K_V channels, BK_{Ca} channels activate at more depolarized membrane potentials [41], but also respond to local Ca^{2+} signaling [73]. Recently, we found that the MetS significantly attenuates coronary BK_{Ca} channel function, as evidenced by a reduction in vasodilation to the BK_{Ca} channel agonist NS1619 (Fig. 3D) [41]. This decrease in vasodilation corresponded with reductions in coronary vascular smooth muscle BK_{Ca} current (Fig. 3C) and a paradoxical increase in BK_{Ca} channel α and β1 subunit expression [41]. Decreases in total K^+ current and spontaneous transient outward currents, which are elicited by Ca^{2+} sparks and indicative of BK_{Ca} channel activation, have also been reported in coronary microvessels of diabetic dyslipidemic swine [73;142]. Studies in obese, insulin resistant rat models also support these findings and suggest that the reductions in BK_{Ca} current are related to alterations in the regulatory β_1 subunit [143]. Although diminished BK_{Ca} channel function in obesity/MetS is well established, data fail to support a significantly role for BK_{Ca} channels in the control of coronary blood flow at rest, during increases in MVO_2 or during cardiac ischemia in lean or MetS animal models [22;41]. However, BK_{Ca} channels have been shown to modulate coronary endothelial-dependent vasodilation in normal-lean subjects [144;145]. Thus, we propose that decreases in BK_{Ca} channel function likely contribute to coronary endothelial dysfunction observed in the setting of the MetS (see recent review by Belin de Chantemele and Stepp [146]), but play little role in the overall impairment of coronary vascular function.

Evidence that coronary K_{ATP} channels are altered by MetS also exists as we recently documented that the functional contribution of K_{ATP} channels to coronary vasodilation in response to 2-chloroadenosine or a brief coronary artery occlusion (i.e. coronary reactive hyperemia) is significantly diminished in MetS vs. lean Ossabaw swine [22;44]. Decreases in K_{ATP} channel function have also been reported in the skeletal muscle microcirculation of obese Zucker rats [33] and in the coronary circulation of diabetic humans [147]. In contrast, other investigations have shown an increased role for coronary K_{ATP} channels in hypercholerestolemic swine [148] and type-1 diabetic dogs [149;150]. Overall, more studies are needed to understand the mechanisms by which the MetS affects coronary smooth muscle K_{ATP} channels. Particularly needed are direct measurements of K_{ATP} channel activity and subunit expression. The same is true of Kir channels, which are highly expressed in autoregulatory beds such as the coronary circulation and tend to increase in abundance with decreasing vessel diameter [151]. While studies indicate roles for Kir in the regulation coronary arteriole diameter and blood flow [152], the impact of MetS on Kir channel function is unknown.

4.2 Ca^{2+} channels in MetS

L-type ($Ca_V1.2$) Ca^{2+} channels are the predominant voltage-dependent Ca^{2+} channel expressed in coronary smooth muscle [153]. Ca^{2+} regulates contraction and gene expression; therefore, alterations in L-type channel function by MetS could have many consequences [154–156]. In particular, increased activation of vasoconstrictor pathways (e.g. α_1 adrenoceptors, AT_1 receptors) along with decreased function of smooth muscle K^+ channels (e.g. BK_{Ca} channels, K_V channels) would serve to augment L-type Ca^{2+} channel activity and vasoconstriction [77]. Data from our laboratory support this hypothesis as we previously demonstrated that the MetS increases intracellular Ca^{2+} concentration [41], L-type Ca^{2+} channel current (Fig. 3E) and arteriolar vasoconstriction to the L-type Ca^{2+} channel agonist Bay K 8644 [32] (Fig. 3F). We also found that coronary vasodilation in response to the L-

type Ca^{2+} channel antagonist nicardipine is markedly elevated in obese dogs with the MetS [32]. These findings are in contrast with earlier studies which documented reductions in L-type Ca^{2+} channel current in hypercholesterolemic and/or diabetic dyslipidemic swine [157;158]. Taken together, these data indicate that the entire MetS milieu is critical in determining the overall functional expression of L-type Ca^{2+} channels in the coronary circulation. Whether increases in L-type Ca^{2+} channel activation contribute to the impaired control of coronary blood flow at rest or during increases in MVO_2 in the MetS merits further investigation.

4.3 TRP channels in MetS

Transient receptor potential (TRP) channels are non-selective channels permeable to monovalent and divalent cations. Thus, changes in the function or expression of TRP channels could alter intracellular Ca^{2+} levels directly, indirectly or through membrane potential and the regulation of L-type Ca^{2+} channel activity. Several TRP subfamilies are expressed in vascular smooth muscle, including TRPC (canonical) and TRPV (vanilloid) channels in the coronary circulation.

TRPC channels are expressed throughout the vasculature and are activated by G protein-coupled receptors and receptor tyrosine kinases [159]. Selective TRPC subtypes regulate vascular tone in response to phenylephrine [160;161], hypoxia [162] and have been shown to be the predominant source of Ca^{2+} entry in response to endothelin-1 stimulation in rabbit coronary smooth muscle [163]. Although the exact role of TRPC channels in the control of coronary blood flow has not been extensively examined, data from the Sturek laboratory indicate that the MetS significantly augments TRPC1 expression and store operated Ca^{2+} entry in coronary smooth muscle [164;165]. TRPC1 is also upregulated following vascular injury [166;167] and inhibition of TRPC1 attenuates neointimal growth [168;169]. Thus, alterations in TRPC activity and expression have been implicated in smooth muscle Ca^{2+} dysregulation and proliferation in MetS.

TRPV channels are activated by various stimuli including capsaicin, lipids, acid, heat, shear stress, and hypoosmolarity [159]. To date, those best characterized are TRPV1 and TRPV4. TRPV1 is present in primary afferent capsaicin-sensitive neurons projecting to cardiac tissues [159]. Capsaicin causes vasodilation, but many studies fail to distinguish direct vascular effects of capsaicin from TRPV1-dependent release of CGRP and/or substance P. However, recent data from our laboratory indicate that TRPV1 channels are functionally expressed in the coronary circulation, and that the MetS significantly impairs endothelial-dependent responses to capsaicin administration [75]. This decrease in TRPV1-mediated dilation was directly associated with diminished coronary TRPV1 protein expression and capsaicin-induced divalent cation influx in endothelial cells. TRPV4 functions in flow-mediated dilation of coronary arterioles [170], a response that is impaired in MetS [171]. These findings indicate that TRP channel dysfunction could be an important mechanism underlying impaired vascular reactivity and disease that should be further explored.

5. Conclusions and future perspective

Investigations to date have demonstrated that the MetS has profound effects on the regulation of coronary blood flow (see schematic diagram in Fig. 4). We propose that therapies targeting of angiotensin/AT_1 receptors, mineralocorticoid receptors, and/or sympathetic activation of α_1-adrenoceptors are likely to be effective in attenuating cardiovascular complications associated with the MetS as such treatments would not only target vasoconstrictor pathways, but key signaling pathways that influence the functional expression of downstream K^+ and Ca^{2+} channels. However, much research is needed to more clearly elucidate the mechanisms underlying coronary microvascular dysfunction in

the MetS and to determine the efficacy and cardiovascular outcomes of targeted therapies in these patients.

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Abbreviations

MetS	metabolic syndrome
TRP	transient receptor potential
NO	nitric oxide
RAAS	renin-angiotensin-aldosterone system
MVO_2	myocardial oxygen consumption
TRP	Transient receptor potential

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RESEARCH HIGHLIGHTS

- Metabolic syndrome impairs the balance between myocardial oxygen supply and demand.
- Obesity impairs coronary response to exercise, ischemia, and vasodilator agonists.
- Increased neurohumoral and RAAS activation limits coronary blood flow.
- Alterations in functional expression of coronary ion channels are explored.

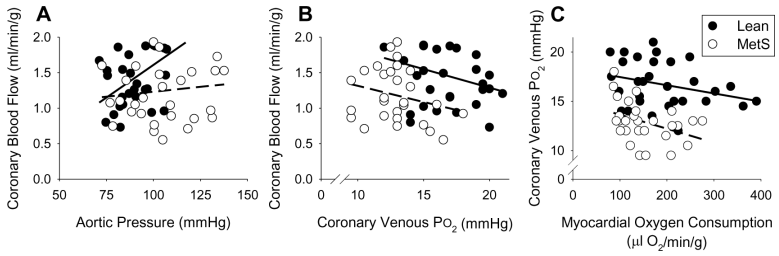

Fig. 1.

Effects of metabolic syndrome on coronary blood flow at rest and during exercise. (**A**) Reduction of the slope between coronary blood flow and aortic pressure indicates that exercise-mediated increases in vascular conductance are significantly attenuated by the MetS. (**B**) Diminished local metabolic control of the coronary circulation is also evidenced by decreased coronary blood flow at a given coronary venous PO_2, an index of myocardial tissue PO_2 that is hypothesized to be a primary stimulus for metabolic coronary vasodilation. (**C**) Imbalance between myocardial oxygen supply and demand in MetS is evidenced by the reduction of coronary venous PO_2 relative to alterations in MVO_2 (the primary determinant of myocardial perfusion) both at rest and during exercise.

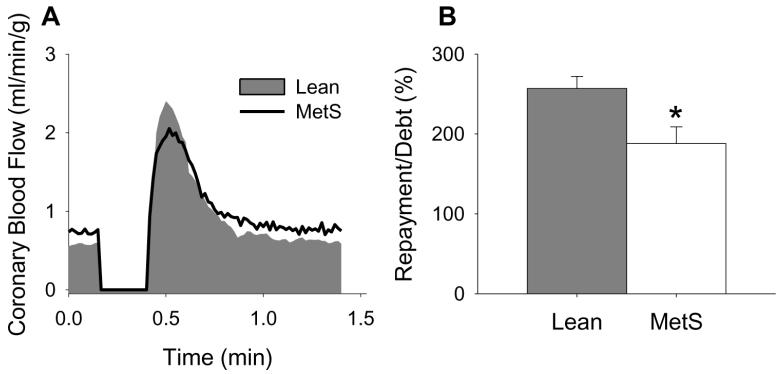

Fig. 2.

Effect of the metabolic syndrome on coronary vasodilation in response to cardiac ischemia. (**A**) Representative tracings illustrating reactive hyperemic responses in lean and MetS swine. (**B**) Coronary vasodilation in response to cardiac ischemia is impaired by metabolic syndrome as evidenced by the significant reduction in percent repayment of incurred coronary flow debt (i.e. repayment/debt ratio). * $P < 0.05$ vs. lean-control.

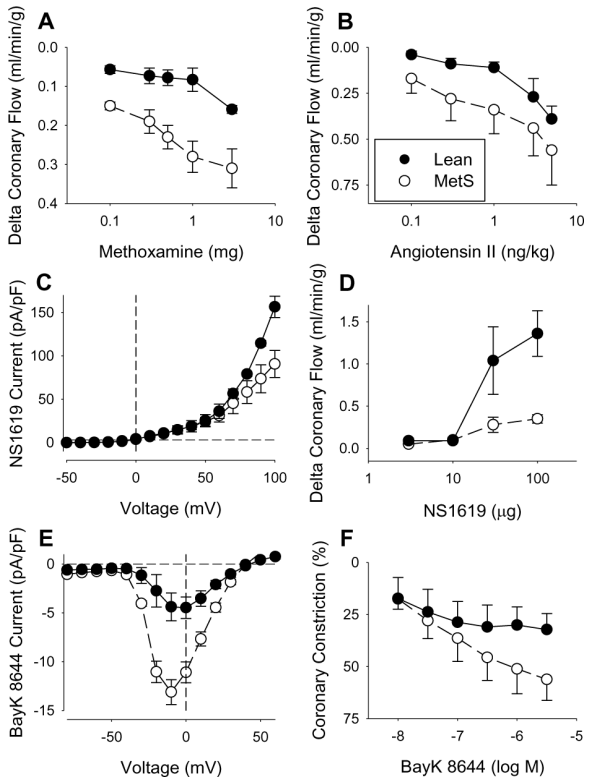

Fig. 3.

Effect of metabolic syndrome on neurohumoral-mediated coronary vasoconstriction and ion channel function. (**A**) Increased coronary constriction to the α_1-adrenoceptor agonist methoxamine in obese dogs. Data from reference [42]. (**B**) Augmented angiotensin II type 1 (AT_1) receptor-mediated coronary vasoconstriction in obese dogs with the MetS. Data from reference [15]. (**C**) Reductions in coronary vascular smooth muscle BK_{Ca} current in response to the BK_{Ca} channel agonist NS1619 directly correspond with (**D**) diminished coronary vasodilation to NS1619 in MetS swine. Data from reference [41]. (**E**) Increases in coronary vascular smooth muscle L-type Ca^{2+} channel current activation in response to Bay K 8644 are associated with (**F**) augmented coronary arteriolar vasoconstriction to Bay K 8644 in obese dogs. Data from reference [32].

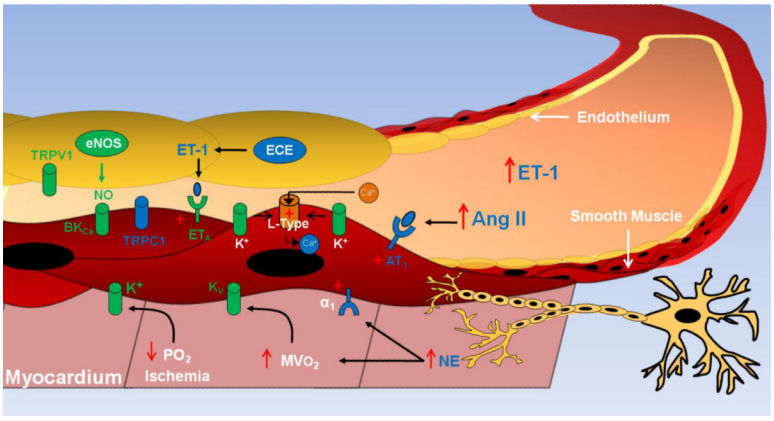

Fig. 4.

Schematic diagram illustrating mechanisms by which the metabolic syndrome impairs control of coronary blood flow in response to increases in myocardial oxygen consumption (MVO_2) or a brief coronary artery occlusion (i.e. decrease PO_2/ischemia). Factors, receptors and ion channels that are downregulated in metabolic syndrome are depicted in green. Factors, receptors and pathways that are upregulated in metabolic syndrome are depicted in blue and/or with + symbol. ET-1 (endothelin-1); Ang II (angiotensin II); AT_1 (angiotensin II type 1 receptor); α_1 (α_1 adrenoceptor); NE (norepinephrine); TRP (transient receptor potential channel); BK_{Ca} (large conductance, Ca^{2+} activated K^+ channel); ET_A (endothelin type A receptor). eNOS (endothelial nitric oxide synthase); ECE (endothelin converting enzyme).