Mechanisms of coronary microvascular adaptation to obesity

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METABOLIC SYNDROME (MetS) is associated with a clustering of cardiovascular risk factors in individuals that may greatly increase their risk of developing ischemic heart disease and heart failure. Abnormalities in the vasomotor function of the coronary microvessels occur in MetS, and in some instances these abnormalities represent important markers of risk or may even contribute to the pathogenesis of myocardial dysfunction. Obesity and its related metabolic dysfunction are the driving forces in the prevalence of MetS. It is believed that obesity has detrimental effects on cardiovascular function, but its overall impact on the vasomotor regulation of small coronary arteries is still debated. Emerging evidence indicates that in obesity coronary arteries adapt to hemodynamic changes via maintaining and/or upregulating cellular mechanism(s) intrinsic to the vascular wall. Among other factors, endothelial production of cyclooxygenase-2-derived prostacyclin and reactive oxygen species, as well as increased nitric oxide sensitivity and potassium channel activation in smooth muscle cells, have been implicated in maintaining coronary vasodilator function. This review aims to examine studies that have been primarily focused on alterations in coronary vasodilator function in obesity. A better understanding of cellular mechanisms that may contribute to coronary microvascular adaptation may provide insight into the sequence of pathological events in obesity and may allow the harnessing of these effects for therapeutic purposes.

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Data obtained in animal models of MetS also indicate that the presence of fasting hyperglycemia, hence the presence of manifest diabetes, impairs coronary vasodilation to agonists and to increases in intraluminal flow (24, 26, 31, 99, 135). Oltman et al. (120) have demonstrated that in Zucker diabetic fatty (ZDF) rats coronary arteriolar dilation to ACh is diminished, whereas dilation in prediabetic, younger (8- to 12-wk-old) animals is preserved. Of note, in prediabetic obese Zucker rats or in animals fed a high-fat diet, with mild elevation of fasting glucose levels, impaired vasodilator function has been reported in vessels from the mesentery (120), cerebral (43, 44), and skeletal muscle vascular beds (41, 48). In contrast, in the obese Zucker rats and also in animals fed a high-fat diet, recent studies found preserved (70, 78, 91) or even augmented coronary dilations (123). Thus it seems that during the progression of MetS, while coronary vasomotor function is protected before the development of type 2 diabetes, peripheral microvessels exhibit impaired vasomotor regulation.

To address this discrepancy, it has been posited that, compared with the vascular beds of the periphery, coronary microvessels are more “resistant” to the development of vasomotor dysfunction (88). This implies that coronary vessels either have efficient mechanisms, which protect their vasomotor function, or that coronary vessels have mechanisms that can actively compensate for the loss of vasomotor pathways as metabolic disease progresses (50, 138). Since in the coronary circulation oxygen extraction is near maximal (141), any impairment in arteriolar dilator function could have significant consequences on myocardial perfusion. As described by Chilian et al. (28, 80), the coronary circulation matches blood flow with oxygen requirements by coordinating the resistances within different-sized vascular beds, each governed by distinct regulatory mechanisms. Such integration in the coronary circulation is believed to be advantageous because the system does not rely on a single mechanism of control, i.e., myogenic, flow or metabolic regulation of vascular resistance (109). An integration of vasomotor regulatory systems in the coronary circulation seems especially important in obesity and MetS, conditions in which metabolic and hemodynamic changes require adaptation of coronary vasomotor regulation.

In MetS, there could be several factors that can be implicated in necessitating adaptation of coronary vessels. In MetS, the impact of these pathological factors is difficult to discern, owing to the close interrelationships between obesity, insulin resistance, type 2 diabetes, hypertension, and other known and as yet unidentified pathological factors (34, 35). Yet, several previous and recent studies raised the possibility that the early adaptation of the coronary circulation can be attributed specifically to obesity and/or obesity-related changes in metabolic and hemodynamic regulation. On the other hand, adaptive vasomotor responses in the coronary circulation may decline as MetS progresses and other comorbid diseases develop, such as severe insulin resistance, hypertension, and fasting hyperglycemia (diabetes). This may lead to limited vasomotor function (both dilator and constrictor functions can be diminished at an advanced state of a disease) of coronary microvessels that are primarily responsible for adjusting cardiac perfusion to actual metabolic demand (Fig. 1).

**Obesity and Cardiovascular Regulation**

This review makes no attempt to provide a detailed description of the impact of obesity on complex hemodynamic regulation or the functional and structural changes of the heart but refers to a comprehensive recent review (1). Of particular importance is the widely accepted view that obesity is independently associated with left ventricular hypertrophy. A large body of evidence indicates that an increase of left ventricular mass, in the long term, leads to diastolic and systolic cardiac contractile dysfunction in obese patients (1). It has been also posited that “uncomplicated” (lack of comorbid conditions such as hypertension, diabetes, etc.) obesity-associated increases in left ventricular mass can be appropriate for body size (75). Thus early “physiological” adaptation of cardiac function can be envisioned, which will accommodate for the higher hemodynamic and metabolic demand in obesity. It is known that any increase in body mass (muscular or adipose tissue) requires a higher cardiac output and expanded intravascular volume to meet the elevated metabolic requirements (95). It is also believed that obesity is associated with a hyperdynamic circulation and increased cardiac output (95). Correspondingly, a study by Jern et al. (79) has demonstrated that cardiac output and stroke volume were positively related to body mass index (BMI) but inversely to waist-to-hip ratio. They also found that total peripheral resistance was inversely correlated to BMI, whereas the high waist-to-hip ratio was associated with higher systemic vascular resistance (79). This implies that increased BMI can be associated with increased cardiac output and lower peripheral vascular resistance but that visceral obesity, which
is the case in many obese patients, is associated with lower cardiac output and higher total peripheral resistance. Whether these changes can be attributed to an altered cardiac structure or contractile dysfunction or whether they can be related to alterations in the function of coronary and peripheral resistance vessels is not known. The impact of obesity on complex cardiovascular regulation over the course of progression of MetS clearly requires further mechanistic investigations.

Impact of Obesity on Coronary Vasodilator Function

Morphological changes in microvessels are quite rare in obesity prior to the development of hyperglycemia. Obesity-related pathological alterations, including atherogenic dyslipidemia, insulin resistance, and hyperinsulinemia, are believed to impair the vasomotor function of small arteries. However, blood flow to the various organs systems is rarely impaired in obesity, unless atherosclerosis of the arteries develops. Throughout life, organs receive normal or even greater than normal blood flow in obese subjects (66). Yet, convincing evidence of the impact of obesity on vasomotor regulation of coronary microvessels is lacking at present. Such demonstration is hampered by issues regarding direct investigation of coronary microcirculation both in humans and animal models (28, 124) and also by the impact of several, combined risk factors present in obesity.

Studies on obese patients. Central obesity was found to be associated with reduced bradykinin- or hyperemia-induced forearm blood flow (67, 146). It has been shown that obese children already exhibit impaired brachial artery relaxation to hyperemic flow (84). Forearm resistance vessels also exhibited reduced ACh- and nitric oxide (NO)-donor (sodium nitroprusside)-induced dilations in obese humans (133). Interestingly, it has been posited that body fat distribution, rather than body weight increase, is responsible for the impaired brachial artery dilation (67) and elevation of peripheral vascular resistance in obesity (79), an idea that is further supported by a theoretical analysis using physiological measurements obtained in obese patients (46).

Only a limited number of studies are available that have investigated alterations in the vasomotor responses of coronary microvessels in obese patients. Because other studies (2, 139) demonstrated a close association between coronary vasomotor function and relaxation of brachial artery, it was speculated that obesity may also adversely affect coronary dilations. Indeed, myocardial blood flow, as measured by positron emission tomography, was found to be significantly reduced in postmenopausal women with obesity, which was negatively correlated with waist-to-hip ratio (100). Moreover, the study by Fulop et al. (50) found that in isolated coronary arterioles of normotensive patients, obesity was associated with a reduction of agonist-induced coronary dilations. These observations are in line with the literature, suggesting the detrimental effects of obesity on vasomotor responses (67, 84). However, the study by Fulop et al. (50) found that in the simultaneous presence of hypertension and obesity, coronary arteriolar dilations to bradykinin and the NO donor sodium nitroprusside were markedly enhanced and also that these dilations were positively correlated with BMI in these patients. Alterations in coronary arterioles were mirrored in large peripheral arteries in that there was a positive correlation between the flow-mediated and nitroglycerin-induced dilations of the brachial artery (50). In other studies, coronary microvessels dissected from the hearts of diabetic patients also exhibited preserved (108) or even enhanced, endothelium-dependent dilations (138).

These observations indicated that obesity, especially in the presence of comorbidities, such as hypertension and diabetes, is not necessarily associated with impaired vasodilator function of coronary microvessels. On the contrary, it is possible that the presence of obesity potentially has a key role in maintaining and augmenting the vasodilator capacity of coronary microvessels. Interestingly, clinical studies (64, 65, 73) in obese patients with coronary heart disease have found an unexpectedly favorable prognosis on acute cardiovascular outcome, with the worst prognosis associated with either underweight or morbidly obese patients. Although obesity is widely accepted as a risk factor for coronary heart disease and heart failure, emerging evidence supports a protective role of obesity once patients have developed cardiovascular disease (65, 73). Whether this protection can be related, at least in part, to the adaptive responses in the coronary vascular beds is yet to be tested in future investigations.

Studies in animal models of obesity. Before providing a description of animal studies of obesity, it is important to briefly highlight the models frequently used to study obesity-related nonvascular and vascular pathologies. In evaluating the results obtained in animal models of obesity, it is also important to bear in mind that similar to the situation in humans, obesity is frequently associated with comorbid diseases, such as elevated blood pressure. Also, it is important to note that even in the absence of fasting hyperglycemia, animals with insulin resistance are usually characterized by elevated postprandial glucose levels; thus the potential pathological role of high glucose concentrations cannot be entirely excluded. In commonly used animal models, obesity develops on the basis of mutations in the leptin gene or the leptin receptor, genetic constellations that are relatively rare in humans with obesity. For instance, in ob/ob mice (leptin gene deficient) obesity and hyperinsulinemia develop shortly after weaning. In db/db mice (leptin receptor deficient) fasting hyperglycemia develops as early as 6–7 wk of age. The obese Zucker rat has a similar genetic abnormality in leptin signaling and exhibits obesity and insulin resistance with no or relatively mild fasting hyperglycemia, as they age. The JCR:LA-cp rat is also characterized by obesity, insulin resistance, hyperinsulinemia, and hypercholesterolemia. Furthermore, high-fat feeding has been used to study the vascular effects of obesity in different animals.

The vasomotor dysfunction described in animal models of obesity is similar in characteristics that are observed in obese patients. This similarity also applies to the discrepant findings obtained in various vascular beds in different models of obesity (Table 1). In the obese, JCR:LA-cp rats, an impaired endothelium-dependent relaxation of aorta to A23187 (17) and reduced dilations of mesenteric arteries to ACh (118) have been reported. Reduced mesenteric (112) and skeletal muscle (41) arteriolar dilation to ACh was also found in rats fed a high-fat diet. In obese Zucker rats, it has been reported that in mesenteric arterioles endothelium-dependent relaxation to ACh was preserved at 20 wk old but was reduced in 32-wk-old animals (137). In a similar experimental design, Oltman et al. (120) investigated the progression of coronary and mesenteric arte-
Coronary arterioles from female pigs have also been reported (12). Hydroxyl radical-induced relaxation in the femoral artery has been observed in mice fed a high-fat diet, an enhanced endothelium-dependent, independent vasodilations in the femoral artery has been reported earlier by Auguet et al. (4). In studies of both 20- and 32-wk-old obese Zucker rats animals, (137) found that relaxation of aorta to ACh is enhanced at the ages of both 20- and 32-wk-old obese Zucker rats animals, results similar to those observed earlier by Auguet et al. (4). In mice fed a high-fat diet, an enhanced endothelium-dependent, hydroxyl radical-induced relaxation in the femoral artery has been also reported (12). Coronary arterioles from female pigs fed a high-fat diet exhibited only modest impairment of dilation to bradykinin (70), whereas coronary dilations to ACh were preserved in the obese Zucker rats (85) and in rats fed a high-fat diet (78). More intriguing, Prakash et al. (123) reported that ACh-induced dilations of coronary arterioles from obese Zucker rats were markedly enhanced (>25% increase in diameter, compared with lean animals). These latter observations imply that although coronary dysfunction progresses with obesity, coronary vasodilator function can be preserved or even augmented at early phases of the disease.

Collectively, on the basis of these aforementioned human and animal studies, it is likely that coronary microvessels adapt to obesity by maintaining or enhancing their dilator function to increase coronary blood flow to higher metabolic demand. Emerging evidence indicates that hemodynamic adaptation is not a passive phenomenon but requires active participation of various cellular pathways, also at microvascular level. Understanding these cellular mechanisms seems important, not only because they provide insight into the sequence of pathological events in obesity, but also because they could be harnessed for therapeutic purposes.

Table 1. Human and animal studies investigating the impact of obesity on endothelium-dependent and endothelium-independent vasodilations

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<tr>
<th>Vascular Bed</th>
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<td>Auguet et al. (4)</td>
<td>aorta (20 wk)</td>
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<td>Subramanian et al. (134)</td>
<td>mesenteric (20 wk)</td>
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<tr>
<td>Subramanian et al. (134)</td>
<td>mesenteric (30 wk)</td>
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<td>Young et al. (153)</td>
<td>mesenteric (12 wk)</td>
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<td>Oltman et al. (117)</td>
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<td>Brunner et al. (17)</td>
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<td>Brunner et al. (17)</td>
<td>perfused heart</td>
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FMD, flow-mediated dilation; BK, bradykinin; NONO, spermine NONOate.

Emerging evidence indicates that hemodynamic adaptation is not a passive phenomenon but requires active participation of various cellular pathways, also at microvascular level. Understanding these cellular mechanisms seems important, not only because they provide insight into the sequence of pathological events in obesity, but also because they could be harnessed for therapeutic purposes.
Cellular Mechanisms of Vascular Adaptation in Obesity

NO-soluble guanylate cyclase-cGMP pathway. The vascular endothelium produces and secretes numerous compounds that regulate a variety of physiological functions, including vaso-motor tone, coagulation, inflammation, permeability, and cell adhesion (144). Among others, NO is considered to be one of the key molecules in maintaining normal vascular homeostasis and it is a major contributor to the maintenance of adequate coronary microvascular tone (98). Solid evidence indicates that type 2 diabetes is associated with impaired bioavailability of NO both in conduit vessels and resistance arteries (8, 48, 70, 99, 128, 136, 147). Studies (42, 48, 113) have also demonstrated that obese subjects exhibit a reduced NO-mediated, agonist-induced dilation of cerebral, mesenteric, coronary, and skeletal muscle microvessels. Interestingly, Brandes et al. (15) reported that reduced endothelial NO production by acute administration of an NO synthase inhibitor in wild-type mice or chronic deficiency of NO in eNOS knockout mice increases NO sensitivity of vascular smooth muscle cells in response to exogenous NO donors. They proposed that an increased sensitivity of soluble guanylate cyclase (sGC) to NO may compensate for the reduced NO synthesis (15). Because administration of exogenous NO decreased sGC activity acutely and over time sGC protein expression (130), it has been posited that NO may play an important, negative feedback regulatory role in the catalytic activity of the sGC; hence, any reduction of NO level may lead to an enhancement of the sensitivity of sGC to NO. To test this hypothesis, Jębelowszki et al. (78) provided evidence for an enhanced NO sensitivity of coronary arterioles isolated from obese rats fed a high-fat diet. They found that the enhanced sensitivity of coronary arterioles to NO was associated with increased activity of sGC in coronary arterioles in which a reduced NO bioavailability was also detected (78). Similar results were obtained in humans, showing that NO donor-induced coronary arteriolar and also brachial artery dilations were enhanced in patients with obesity and hypertension (50). Enhanced dilations of coronary arterioles to the NO donor sodium nitroprusside have been also described in female pigs fed a high-fat diet (155) and in mesenteric arterioles of obese Zucker rats (120).

Although it seems plausible that the lack of NO release may lead to an enhanced activity of sGC in vascular smooth muscle cells (15), other studies (18, 154) demonstrated that an acute exposure to reactive oxygen species (ROS), i.e., H$_2$O$_2$, could also lead to activation of sGC, contributing to the relaxation of the bovine pulmonary artery. Moreover, Bauersachs et al. (10) have shown that rats with heart failure exhibit increased expression of sGC, which was due to the enhanced vascular superoxide anion production. Since obesity is also associated with oxidative stress (41, 120), it is likely that ROS, in addition to their effect in reducing NO availability, may play a role in the activation of sGC, a hypothesis that has yet to be tested.

Collectively, these data suggest that an impaired endothelial NO availability in coronary arterioles can be associated with an enhanced sensitivity to NO in vascular smooth muscle cells and that this mechanism may lead to compensation of the reduced NO-mediated vascular signaling in obesity. On the other hand, it has been demonstrated that oxidative and nitrosative stress can lead to inactivation of sGC over time (111); thus the question remains to be answered to what extent and how long upregulation of sGC may compensate for the reduced NO-mediated vascular signaling, as obesity and MetS progress.

Endothelium-derived hyperpolarizing factor potassium channel activation in obesity. It is known that in addition to NO other mechanisms may contribute to dilations of coronary microvessels, such as the endothelium-derived hyperpolarizing factor (EDHF; Ref. 108). There is a paucity of data in the literature investigating alterations in EDHF-mediated coronary microvascular responses in obesity. Unlike NO, EDHF-mediated arteriolar dilation is believed to be less sensitive to oxidative stress, and dilations mediated by EDHF can persist and may compensate for the loss of other vasodilator pathways in obesity. For example, a study by Wolfe and de Wit (152) found that mice even under severe hypercholesterolemic conditions (ApoE and LDL receptor-deficient mice fed a high-cholesterol diet) exhibited a preserved EDHF-mediated, endothelium-dependent dilation to ACh in the cremaster muscle arteriole in vivo. Moreover, the study by Ellis et al. (38) found an augmented, EDHF-mediated vasodilation of small mesenteric arterioles both in wild-type and LDL receptor knockout female mice fed a high-fat diet. It is known that opening of the Ca$^{2+}$-activated potassium (K$_{Ca}$) channels (small, intermediate, and large conductance K$_{Ca}$ channels) plays a crucial role in EDHF-mediated vasodilation (19, 22, 37, 108). Thus it can be assumed that the K$_{Ca}$ channel function is preserved in obesity. Correspondingly, in the study by Ellis et al. (38) the augmented, EDHF-mediated dilations to ACh were effectively blocked by the K$_{Ca}$ channel inhibitors apamin and charybdotoxin in mesenteric arteries of high-fat diet-treated mice. In contrast, in fructose-fed, insulin-resistant (but not obese) rats Miller et al. (104) reported that ACh-induced small coronary artery dilation was reduced due to decreased responses by K$_{Ca}$ channels. In mesenteric arterioles of type 2 diabetic ZDF rats, Burnham et al. (20, 21) demonstrated previously that the large conductance BK$_{Ca}$ channel-mediated and also the small conductance SK$_{Ca}$ channel-mediated arteriolar relaxations are significantly impaired, but no abnormalities in BK$_{Ca}$ and SK$_{Ca}$ channel function were detected in younger (5–6 wk old) animals that already developed insulin resistance. Yet, a very recent study by Young et al. (156) demonstrated that nondiabetic obese Zucker rats exhibit a reduced EDHF-mediated dilation in small mesenteric arteries, but this alteration was due to the impaired connexin-dependent cell-to-cell signaling, rather than changes in K$_{Ca}$ channel function. Collectively, a limited number of studies indicate that EDHF-mediated, K$_{Ca}$ channel-dependent dilation may be impaired in peripheral vessels in obesity, but future studies are needed to confirm this phenomenon in coronary microvessels, both in humans and animal models.

ROS in coronary microvascular adaptation. Oxidative stress occurring in response to hyperglycemia (6–9, 14, 40, 129) and hypertension (76, 142, 143) is considered to be one of the key factors leading to microvascular vasomotor dysfunction in advanced stages of MetS. Evidence supports that even before the development of fasting hyperglycemia and manifest type 2 diabetes, hyperinsulinemia (42) and obesity (41, 43) are also associated with an increased vascular production of ROS. Studies aiming to detect the impact of free radical production on coronary arteriolar dilations, however, yielded conflicting results in animal models of obesity. Oltman et al. have found that a free radical scavenger, tiron, restored dilations of coro-
nary arterioles to the level of lean animals (120), suggesting a crucial role for \( \text{ROS} \) in reducing \( \text{ACH} \)-induced responses. Rats fed a high-fat diet exhibited enhanced vascular production of \( \text{ROS} \), which was associated with reduced \( \text{ACH} \)- and histamine-induced arteriolar dilations of skeletal muscle arterioles; and the responses were restored by the ROS scavenger, tiron (41). In contrast, Katakam et al. (85) and Jebelovszki et al. (78) were unable to demonstrate impaired coronary dilation of obese Zucker rats and rats fed a high-fat diet, in spite of the presence of enhanced ROS production in these models. Although studies found that ROS-dependent inactivation of NO leads to a reduced agonist-induced dilation of cerebral, mesenteric and skeletal muscle microvessels (6, 14, 48), these latter observations indicated that coronary arteriolar dilations can be resistant to oxidative stress, but the nature of mechanism(s) responsible for this “resistance” remained obscure.

One theory that may explain these discrepant findings is the high subcellular and cellular compartmentalization of ROS production. Normally, effective antioxidant systems (SOD isoforms, catalase and glutathione peroxidase etc.) limit ROS production, for instance, by preventing the interaction between superoxide anion and NO (153). During pathological conditions, such as in obesity, the production of ROS may exceed the capacity of antioxidant mechanisms, which could have detrimental effects on vasomotor regulation, such as reduced availability of NO. The above-described experimental evidence showing that responsiveness of vascular smooth muscle cells to exogenous NO may be preserved or could be augmented in obesity, however, indicated that the excess production of ROS is mainly localized to endothelial, but not vascular smooth muscle cells in coronary microvessels.

On the other hand, emerging evidence indicates that ROS may act as a positive regulator of endothelial signaling pathways, both under normal and pathological conditions (63, 94). For instance, Matoba et al. demonstrated that a major dilator factor released from the endothelium of porcine coronary microvessels is the ROS derivate, \( \text{H}_2\text{O}_2 \) (101). Coronary arteriole microvessels from the human heart, likely to be affected by existing disease such as obesity, also generate \( \text{H}_2\text{O}_2 \) from endothelial cells, as a major contributor of coronary arteriolar dilations (107). Thus in addition to inhibitory action of superoxide anion on NO, \( \text{H}_2\text{O}_2 \) may actively participate in endothelium-dependent vasodilation. The underlying mechanism of \( \text{H}_2\text{O}_2 \)-mediated dilation varies, but studies show that, \( \text{H}_2\text{O}_2 \) exerts its vasodilator effects via activating \( \text{K}_{\text{Ca}} \) channels (32, 101, 107). Thus it has been proposed that \( \text{H}_2\text{O}_2 \), via inducing \( \text{K}_{\text{Ca}} \) channels-mediated endothelium-dependent hyperpolarization, potentially acts as an EDHF (45, 131). Other studies demonstrated that \( \text{H}_2\text{O}_2 \)-derived vasodilation is mediated through the release of NO from the endothelium (72) or is partially mediated by cGMP release in vascular smooth muscle cells (49). Regardless of the mechanisms of action, endothelial production of \( \text{H}_2\text{O}_2 \) can be one of the key molecules, which may compensate for the loss of dilator function of coronary arterioles and may contribute to vascular adaptation during the progression of obesity (Fig. 2).

Uprregulation of COX-2 and coronary adaptation. It is clear that several cardiovascular diseases are associated with a state of chronic, low-level inflammation (58, 96). A crucial role of COX-derived prostaglandins in vascular inflammatory responses has been well established (115). A possible role for prostaglandin-mediated, low-level vascular inflammation has been also described in type 2 diabetes and obesity (52, 69, 70, 134, 150). Recently, a great deal of attention has been devoted to the complexity of molecular events regulating vascular prostaglandin synthesis. For a long time, it was the view that COX-1 was constitutively expressed in most tissues, such as vascular endothelial cells, and was involved in the maintenance of cellular homeostasis (105, 106, 145). In contrast, the expression of COX-2 is very low in the endothelium and in smooth muscle cells under normal conditions (33). Importantly, COX-2 can be readily upregulated by inflammatory, mitogenic, and physical stimuli (121). Obesity and type 2 diabetes are associated with low-grade vascular inflammation; thus it is possible that changes in vascular prostaglandin synthesis can be altered in these diseases and that the changes can be attributed to alterations in the vascular expression of COX-2. Correspondingly, recent studies (5, 62) provided evidence that COX-2 protein expression is elevated in the aorta of mice with obesity and type 2 diabetes. Also, in diabetic patients vascular expression of COX-2 was found to be markedly elevated in coronary arterioles, which was associated with the enhanced production of dilator prostaglandins, most likely prostacyclin (\( \text{PGI}_2 \)) or \( \text{PGE}_2 \) (138). These dilator prostaglandins, known to be essential in the mediation of dilator responses elicited by bradykinin, are key vasoactive mediators involved in the regulation of coronary flow (29, 60).

A growing body of evidence indicates that COX-2-derived \( \text{PGI}_2 \) production in endothelial cells is an important homeostatic response to accommodate the enhanced aggregability of circulating platelets (59) and vasomotor dysfunction of coronary arterioles (138) (Fig. 2). Whether upregulation of COX-2 and consequently enhanced \( \text{PGI}_2 \) production contribute to maintained coronary dilations in obesity has yet to be elucidated. Moreover, the potential mechanism(s) responsible for the upregulation of COX-2 requires further investigation. The key role for high glucose concentrations in COX-2 expression seems to be established (30, 87). It has been found that in high-glucose-treated mesangial (87) and endothelial cells (30) increased production of the superoxide anion was primarily responsible for the enhanced COX-2 expression. Furthermore, it has been demonstrated that proinflammatory cytokines, such as IL-1\( \beta \) and TNF\( \alpha \), potentially induce COX-2 expression (105) by stabilizing COX-2 mRNA and enhancing transcription through NF-\( \kappa B \) or peroxisome proliferator-activated receptor-\( \gamma \) (PPAR\( \gamma \); Ref. 122). In this context, a previous study (103) also identified a region of the COX-2 gene promoter containing a PPAR-response element in human epithelial cells. It has been found that in rat vascular smooth muscle cells in culture, the PPAR\( \gamma \) activator rosiglitazone increased the expression of phospholipase A\_2 and COX-2 (13). In contrast, in vascular smooth muscle cells in culture PPAR\( \gamma \) activation inhibited ANG II-induced COX-2 expression (74). These findings indicate a potential impact of PPAR\( \gamma \) activation on COX-2 expression and prostaglandin formation. Hence, studies have yet to be performed to elucidate the specific roles of PPAR\( \gamma \) in the regulation of vascular expression of COX-2 and altered synthesis of \( \text{PGI}_2 \), which may affect platelet aggregation and also coronary vasomotor responses in obesity. These studies also underline the need for clinical investigations addressing the possible effects of drugs interfering with COX-2-
mediated and/or PPARγ-dependent prostaglandin synthesis, particularly in obese patients.

Role of adipocyte-derived factors in vascular adaptation. Adipocytes perform an important endocrine function by secreting numerous cytokines, hormones, and bioactive peptides (81). Upon secretion into the bloodstream, adipocyte-derived signaling molecules (e.g., adiponectin, leptin, resistin, TNFα, etc.) could have an important impact on other tissues such as muscle and liver to regulate energy homeostasis and metabolism (81). In obesity, this normal function of adipocytes can be altered and can easily result in reduced adiponectin (82) and elevated levels of leptin, resistin, and TNFα (11). Alterations in adipokine levels have been implicated in the development of vascular dysfunction in obesity, and they may also exert effects on endothelial- and smooth muscle-dependent vasoregulatory mechanisms in coronary arteries.

In this context, it has been shown that leptin incubation promotes oxidative stress in cultured endothelial cells (92). Knudson et al. (90) reported that leptin, at higher concentrations (625 pmol/l), significantly attenuated dilation to ACh in isolated coronary rings of normal dogs. Animals fed a high-fat diet had elevated leptin levels, but they exhibited a preserved coronary dilation to ACh (89). Moreover, in porcine coronary arteries exposure of another adypokine, resistin elicited a reduced dilation to bradykinin, via eliciting oxidative stress (93). Dick et al. (36) also found reduced bradykinin-induced dilations of dog coronary arteries exposed to resistin, but the effect was independent from free radical production and was not affecting endothelial production of NO or PGI2. These animal studies indicated that circulating adipokines, such as leptin and resistin, may exhibit adverse effects on coronary vasodilator responses in obesity. Although higher leptin concentrations were found to be associated with impaired arterial distensibility in healthy adolescents (132), acute, subcutaneous administration of leptin unexpectedly increased flow-mediated dilations of brachial artery in nonobese adults (16). Also, in obese women leptin concentrations did not predict the impaired flow-mediated dilations of the brachial artery (119). Clearly, further studies are needed to solve this existing discrepancy between animal studies and human observations.

A growing body of evidence indicates, on the other hand, that perivascular adipose tissue through releasing a transferable nonlipid factor may induce vasorelaxation and may counteract agonist-induced vasoconstrictor responses (97, 127). In this context, Gao et al. (53, 55) have reported that perivascular adipose tissue releases a relaxing factor that induces endothelium-dependent relaxation of the rat aorta or the human internal thoracic artery through NO release and KCa channel activation. Interestingly, they also proposed a potential involvement of H2O2 in this process, which may also activate sGC in the
vascular smooth muscle cells (53). Somewhat contradictory, the same group (54) reported that an increased production of superoxide anion from perivascular fat augmented the contractile responses of mesenteric arteries.

It remained, however, unclear whether phenotypic changes of perivascular adipocytes may differently affect vasomotor responses, as obesity progresses. Interestingly, the vasorelaxant effect of perivascular adipose tissue was attenuated in spontaneously hypertensive rats in the study by Galvez et al. (51). Although these aforementioned observations indicate adverse effects of circulating adipokines, such as leptin and resistin on coronary vasomotor function, they raise the possibility that perivascular fat, via activating vasodilator mechanisms in vascular endothelial cells, can be protective (Fig. 2). Whether the vasomotor effects of perivascular fat-derived factors, via activating endothelium- and smooth muscle-dependent cellular pathways, are contributing to coronary microvascular adaptation in obesity and whether this regulatory function changes as obesity progresses requires further investigation.

Summary and Clinical Implications

Although obesity is widely accepted as a risk factor for coronary heart disease and heart failure, evidence (64, 65, 73) also supports a role for obesity in cardiovascular protection. A growing number of recent reports document a statistically significant survival benefit in obese patients once they have been diagnosed with cardiovascular diseases. The conclusion that obesity may both elicit cardiovascular disease and protect from cardiovascular death now clearly requires further investigation at the cellular, molecular, and systematic levels. On the basis of the above-described studies, it is possible that vascular oxidative stress and low-grade vascular inflammation contribute to coronary microvascular adaptation, which can be attributed specifically to obesity. Understanding the sequence of pathological events in obesity-related microvascular dysfunction and adaptation might provide a rationale for therapeutic interventions, and it might as well harness these effects for therapeutic purposes.

There are promising pharmacological interventions that may prevent and/or restore coronary arterial dysfunction, such as the use of statins (61) and the PPARγ activator insulin sensitizers thiazolidinediones early on in obesity (71, 77). On the other hand, it is possible that interfering with adaptive signaling mechanisms in the coronary arteriolar wall may provide further burden to those mechanisms that are maintaining vascular function in disease. For instance, upregulation of COX-2 in the endothelium and vascular bed specific production of dilator and antithrombotic prostacyclin may serve to maintain vascular homeostasis in patients with atherosclerosis (3, 47, 59). Recent population-based studies (27, 57, 86) suggest the need for extra caution when using selective COX-2 inhibitors and nonsteroidal anti-inflammatory drugs in patients with cardiovascular risk factors. Experimental and clinical studies emphasize the importance of those investigations that strive to elucidate the specific effects of prostaglandin synthesis inhibitors in the regulation of cardiovascular function in obesity. Furthermore, although high levels of ROS have been shown to impair vascular function in several pathological conditions and oxidative stress can be considered a negative modulator of vasomotor function (23), recent interventional clinical trials yielded largely negative results, and there has even been some suggestion of harmful effects (151). For example, the Heart Outcomes Prevention Evaluation (HOPE) Trial assessed the antioxidant vitamin E in high-risk patients with cardiovascular disease and diabetes and found no effect on cardiovascular outcomes (68). Even worse, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial found an increased risk for coronary events in subjects receiving vitamin-E or β-carotene, as antioxidants (125, 126, 148). More concerning yet, an increased harm from supplemental vitamin E, vitamin A, and β-carotene is indicated by the meta-analysis of 15 clinical trials on cardiovascular outcomes (149). Further studies are needed to solve the current paradox of pharmacological interventions likely to be affecting prostaglandin metabolism and the oxidant status of the coronary arteriolar wall.

GRANTS

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REFERENCES

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