Review

Preserved coronary arteriolar dilatation in patients with type 2 diabetes mellitus: Implications for reactive oxygen species

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Abstract:

Type 2 diabetes mellitus is associated with clustering of cardiovascular risk factors that may greatly increase individuals' risk of developing coronary artery disease. Type 2 diabetes is believed to impair coronary function. However, its impact on the vasomotor function of coronary resistance vessels in humans is still debated. Reduced, preserved or even augmented dilations of coronary arterioles have been reported in subjects with type 2 diabetes. Interestingly, recent studies have suggested that reactive oxygen species (ROS), particularly hydrogen peroxide, may compensate for the loss of the vasodilatory function of coronary microvessels during disease development. Recent interventional clinical trials have yielded largely negative results, and there has even been some suggestion of harm caused by attempts to reduce ROS. Thus, it is possible that interference with ROS-related signaling might paradoxically temper the function of coronary microvessels, predisposing patients to myocardial ischemia. In this review, we aim to highlight current findings supporting a potential role for ROS in preserving coronary arteriolar dilation in type 2 diabetes mellitus.

Key words: diabetes, coronary, arteriole, H₂O₂, antioxidant

Changes in vasomotor function of coronary arterioles in type 2 diabetes

Type 2 diabetes mellitus is associated with a markedly increased incidence of ischemic heart disease, accounting for approximately 70% of deaths in the diabetic population [49]. The development of macrovascular disease, such as atherosclerotic plaque formation and atherothrombosis is common among patients with diabetes mellitus, and contributes to the increased incidence of myocardial infarction [4]. Although acute and chronic ischemic syndromes are

commonly a result of coronary, flow-limiting, atherosclerotic plaques in epicardial coronary arteries, about 10 to 20% of patients undergoing cardiac catheterization are found to have normal coronary angiograms [10]. Nitenberg et al. have demonstrated that despite the presence of angiographically normal coronary arteries, the coronary flow reserve is reduced in diabetic patients [38]. Thus, it has been suggested that in diabetes patients, epicardial atherosclerosis may not be the only underlying pathophysiology resulting in abnormal coronary flow reserve, but that a role for the reduced dilatory capacity of coronary microvessels may also exist [37, 38].

Strong evidence suggests that coronary microcirculation is compromised in diabetes mellitus [9, 11, 12, 32, 44]. Before the morphological changes take place [18, 19, 26, 45, 57], vasomotor dysfunction of microvessels may occur, which is considered to be one of the early alterations that occur in several cardiovascular diseases, as outlined by many recent reviews [9, 11, 12, 29, 32, 44]. In humans with diabetes mellitus, impaired vasomotor function of the large conductance arteries is established [14]. However, a limited number of studies are available describing alterations in vasomotor responses of coronary microvessels in diabetic patients. Similar to findings in the peripheral vessels of type 2 diabetic subjects, an impaired dilatory function of coronary arterioles can also be hypothesized. This idea was supported by a study from Gutterman's laboratory showing impaired dilation of human coronary arterioles in response to hypoxia in diabetic patients [35]. Interestingly, the authors have also found that endothelium-derived hyperpolarizing factor (EDHF)-mediated dilation in response to bradykinin was similar in diabetic and non-diabetic patients [35]. Data from our laboratory showed an enhanced bradykinin-induced dilation of coronary microvessels dissected from the hearts of diabetic patients [47] and also in coronary arterioles from patients suffering from obesity and hypertension [21]. In line with these observations, there are other reports showing preserved [24, 30] and even augmented [39] coronary dilations in animal models of type 2 diabetes. In part, these apparently conflicting data can be explained by species differences, the size of coronary vessels studied, the duration of type 2 diabetes and the degree of hyperglycemia. To address some of these controversial findings, it has recently been suggested by Tune et al. that, as compared to the vascular beds of the periphery, coronary microvessels are more "resistant" to changes in the vasomotor function in diseases [29]. This suggests that coronary vessels possess mechanisms that can operate efficiently to protect vasomotor function, such as maintaining vasodilatory responses and/or limiting vasoconstrictor pathways. Indeed, under physiological conditions in the coronary arteriole, many potent vasoconstrictors of the periphery such as norepinephrine and angiotensin II, can cause substantial vasodilation [46, 58]. On the basis of recent studies, we propose that coronary arterioles exhibit effective mechanisms that can compensate for the loss of vasodilator pathways in type 2 diabetes [21, 47].

Impact of oxidative stress on endothelium-dependent vasomotor function in coronary arterioles

Oxidative stress occurring in response to hyperglycemia [1, 2, 5, 42], hyperinsulinemia [17] and hypertension [27, 50, 51] is considered to be one of the key factors leading to microvascular disease in patients with type 2 diabetes mellitus. Strong evidence supports that type 2 diabetes is associated with an increased production of reactive oxygen species (ROS) that, *via* interfering with nitric oxide (NO) signaling, are responsible for the reduced bioavailability of NO [48]. In this context, we demonstrated previously that in type 2 diabetic rats, vascular production of ROS is markedly elevated due to the increased activity of vascular xanthine oxidase activity. This phenomenon results in impaired NO availability and consequently, reduced agonist-induced dilations of skeletal muscle microvessels [16]. Interestingly, in the same animal model, we observed that, in spite of the reduced NO bioavailability, dilation of coronary arterioles to ACh is preserved [28]. These findings indicate the possibility that in coronary arterioles of type 2 diabetic rats, unlike in peripheral arterioles, mechanisms intrinsic to the vascular wall are activated to compensate for the reduced NO availability and preserve vasodilation, although the nature of these mechanisms is not completely understood.

Emerging evidence indicates that ROS act in the vasculature by modulating specific redox-sensitive signal transduction pathways under normal and pathological conditions [22, 31]. For instance, Matoba et al. demonstrated that a major dilation factor released from the endothelium of porcine coronary microvessels is the ROS derivate, H_2O_2 [33]. Coronary arterial microvessels from the human heart – likely to be affected by existing disease – also generate H_2O_2 from endothelial cells, as a major contributor to coronary arteriolar dilation [34]. In this context, we have demonstrated that mice with type 2 diabetes exhibit markedly increased H_2O_2 production in the arteriolar wall [15]. Thus, in addition to inhibiting endothelial generation of NO, H_2O_2 may actively participate in endothelium-dependent vasodilation mechanisms in type 2 diabetes mellitus. The mechanism of H_2O_2 -mediated dilation is not completely understood, but studies have shown that, by activating calcium-activated potassium channels, H_2O_2 hyperpolarizes vascular

smooth muscle cells and therefore potentially acts as an EDHF [13, 33, 34]. Other studies have demonstrated that H_2O_2 -induced vasodilation is mediated through the release of NO from the endothelium [25] or is partially mediated by cGMP release [20]. Regardless of the mechanisms of action, H_2O_2 can be considered a key molecule involved in the mechanism of compensation for the loss of NO-mediation of coronary microvessels during the development of type 2 diabetes mellitus.

Impact of oxidative stress on coronary arteriolar smooth muscle cells – a role for soluble guanylate cyclase activation

Brandes et al. reported that both acute cessation of endothelial NO production in wild type mice and chronic deficiency of NO in eNOS knockout mice increase the NO sensitivity of vascular smooth muscle cells in response to nitrovasodilator agents [6]. They proposed that an enhanced sensitivity of soluble guanylate cyclase (sGC) to NO may compensate for the reduced NO availability [6]. In this context, it has been also found that administration of exogenous NO decreased sGC activity acutely and decreased its protein expression over time [43]. These findings indicate that NO may play an important regulatory role on the catalytic activity of the sGC; hence, any reduction of NO level may lead to an enhancement of the sensitivity of sGC to NO. In this context, results from our laboratory have provided evidence for enhanced NO sensitivity of coronary arterioles isolated from type 2 diabetic rats, in which we also found reduced NO bioavailability [28]. Interestingly, we have obtained similar results in humans, demonstrating that coronary arteriole, and also brachial artery, dilations in response to a NO donor are enhanced in patients suffering from obesity and hypertension [21]. Enhanced dilations of coronary arteries in response to the NO donor sodium nitroprusside have been also described in female pigs fed a high fat diet, whereas NO-mediated coronary dilations in response to bradykinin were blunted [56]. Collectively, these data suggest that an impaired NO availability in coronary microvessels may be associated with an enhanced sensitivity to NO and that this mechanism may be responsi-

ble, in part, for the maintained dilation capacity of coronary arterioles in type 2 diabetes.

An intriguing question thus arises: what are the exact origin and nature of the factor(s) that contribute to the enhanced vascular sensitivity to NO? It seems plausible that the lack of NO may lead to enhanced sGC activity in vascular smooth muscle cells [6]. Although it has been proposed that oxidative and/or nitrosative stress can lead to inactivation of sGC in long-term [36], other studies have demonstrated that acute exposure to H_2O_2 can lead to activation of sGC, contributing to the relaxation of the bovine pulmonary artery [7, 55]. Moreover, Bauersachs et al. have shown that myocardial infarct-induced ischemic heart failure in rats leads to the upregulation of both vascular eNOS and sGC expression in association with an increased vascular superoxide production [3]. Thus, it is likely that ROS, in addition to the above described effect on NO availability, may play a role in the activation of sGC in the coronary microvessels, a hypothesis which has yet to be tested. Furthermore, it remains unclear to what extent and for how long up-regulation of sGC can contribute to the maintenance of NO-mediated arteriolar vasomotor responses.

Clinical implications

The above-described studies suggest that in type 2 diabetes mellitus, oxidative stress in the coronary microvascular wall may not only be an undesirable by-product, but a homeostatic response to the “diabetic” environment. Although high levels of ROS have been shown to impair vascular function in several pathological conditions, and that oxidative stress can be considered a negative modulator of vasomotor function [8], recent interventional clinical trials yielded largely negative results in response to antioxidant treatment, with some suggestion of potential harm [54]. For example, the Heart Outcomes Prevention Evaluation (HOPE) trial assessed vitamin-E treatment in high-risk patients with cardiovascular disease and diabetes mellitus and found no effect on cardiovascular outcomes [23]. Worse, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial found an increased risk for coronary events in subjects receiving vitamin-E or beta-carotene as antioxidants [40, 41, 52]. Of greater concern was that an

increased degree of harm from supplemental vitamin-E, vitamin-A, and beta-carotene was indicated by a meta-analysis of 15 clinical trials on cardiovascular outcome [53]. Thus, it is possible that interfering with ROS-dependent vascular responses may add further burden to those mechanisms that maintain vascular functions in diseased conditions. Further studies are needed to solve the current paradox of the roles of oxidative stress, antioxidants and cardiovascular risk in type 2 diabetes mellitus.

In summary, we propose that ROS, particularly H₂O₂, may compensate for the reduced NO availability in humans with type 2 diabetes mellitus, thereby contributing to the maintenance of coronary arteriole dilation. By interfering with ROS-related vascular signaling mechanisms, e.g. the administration of antioxidants such as vitamin-E, might paradoxically temper the vasodilatory function of coronary microvessels, predisposing diabetic patients to myocardial ischemia.

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