Impaired dilation of coronary arterioles during increases in myocardial O$_2$ consumption with hyperglycemia

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Am J Physiol Endocrinol Metab 279: E868–E874, 2000.—Previous studies showed that nitric oxide (NO) plays an important role in coronary arteriolar dilation to increases in myocardial oxygen consumption (MV˙O$_2$). We sought to evaluate coronary microvascular responses to endothelium-dependent and to endothelium-independent vasodilators in an in vivo model. Microvascular diameters were measured using intravital microscopy in 10 normal (N) and 9 hyperglycemic (HG; 1 wk alloxan, 60 mg/kg iv) dogs during suffusion of acetylcholine (1, 10, and 100 μM) or nitroprusside (1, 10, and 100 μM) to test the effects on endothelium-dependent and -independent dilation. During administration of acetylcholine, coronary arteriolar dilation was impaired in HG, but was normal during administration of nitroprusside. To examine a physiologically important vasomotor response, 10 N and 7 HG control, 5 HG and 5 N during superoxide dismutase (SOD), and 5 HG and 4 N after SQ29,548 (SQ; thromboxane A$_2$/prostaglandin H$_x$ receptor antagonist) dogs were studied at three levels of MV˙O$_2$: at rest, during dobutamine (DOB; 10 μg · kg$^{-1}$ · min$^{-1}$ iv), and during DOB with rapid atrial pacing (RAP; 280 ± 10 beats/min). During dobutamine, coronary arterioles dilated similarly in all groups, and the increase in MV˙O$_2$ was similar among the groups. However, during the greater metabolic stimulus (DOB+RAP), coronary arterioles in N dilated (36 ± 4% change from diameter at rest) significantly more than HG (16 ± 3%, P < 0.05). In HG+SQ and in HG+SOD, coronary arterioles dilated similarly to N, and greater than HG (P < 0.05). MV˙O$_2$ during DOB+RAP was similar among groups. Normal dogs treated with SOD and SQ29,548 were not different from untreated N dogs. Thus, in HG dogs, dilation of coronary arterioles is selectively impaired in response to administration of the endothelium-dependent vasodilator acetylcholine and during increases in MV˙O$_2$.

coronary microcirculation; diabetes; dobutamine; superoxide; SQ29,548; superoxide dismutase

DIABETES MELLITUS IS ASSOCIATED with increased morbidity and mortality, largely as a result of cardiac events. Although patients with diabetes mellitus have an increased incidence of atherosclerosis, not all cardiac complications can be explained by atherosclerosis of coronary conduit vessels (17). Patients with diabetes mellitus have a higher incidence of exercise intolerance than nondiabetic patients (1). Nahser et al. (22) reported that, in patients without significant coronary artery disease, coronary flow reserve and coronary vascular responses to pacing are impaired in diabetic patients compared with nondiabetic patients. Thus coronary vasodilation induced by metabolic stimuli is impaired by diabetes through mechanisms that cannot be explained by obstructive coronary artery disease.

The normal response of the coronary circulation to increases in metabolic demand is a reduction in coronary vascular resistance. We have recently demonstrated that coronary arteriolar dilation during increases in myocardial oxygen consumption are mediated in large part by release of nitric oxide (NO), an endothelium-derived relaxing factor (9), suggesting that the endothelium plays a pivotal role in metabolic arteriolar dilation. Studies in diabetic animals (19, 21, 26, 29, 32) and of diabetic patients (12, 24) have shown impaired endothelium-dependent relaxation. Endothelial dysfunction in diabetes may be mediated by several different mechanisms including increased release of an endothelium-derived constricting factor (21, 29, 30) and increased production of reactive oxygen species (26, 31), which may interfere with NO (11, 25) or may alter arachidonic acid metabolism, favoring production of vasoconstricting, rather than vasodilatory, prostanoids (15). Vasoconstrictor prostanoids are produced in excess in diabetes (21, 29, 32) and attenuate endothelium-mediated dilation in rabbit aorta (30, 32). Administration of scavengers of oxygen radicals restores normal vasodilation to endothelium-dependent agents both in vitro (26, 31) and in vivo (2). It is not entirely clear which radical species are involved, but superoxide anion reacts directly with NO to produce the less potent dilator peroxynitrite (28). More recently, Katusic et al. (15) have shown that superoxide generation with xanthine/xanthine oxidase causes production of thromboxane A$_2$/prostaglandin H$_2$. 

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Because metabolic coronary dilation is mediated in part by endothelium-dependent mechanisms and because endothelial dependent mechanisms are impaired in diabetes, we considered the possibility that the coronary arteriolar response to metabolic stimuli is impaired during prolonged hyperglycemia. Thus the first objective of this study was to examine endothelium-mediated dilation during hyperglycemia in our in vivo model. Next, we sought to test the hypothesis that coronary microvascular dilation during increases in myocardial oxygen consumption (MVO₂) is impaired with prolonged hyperglycemia. Because vasoconstrictor prostanooids and reactive oxygen species are involved in impaired endothelium-dependent vasodilatation in diabetes, our final objective was to test the hypothesis that vasoconstrictor prostanooids and/or reactive oxygen species mediate the impaired coronary microvascular responses to increases in MVO₂ during prolonged hyperglycemia.

METHODS

Model of Prolonged Hyperglycemia

Adult mongrel dogs (n = 26, body wt 3–8 kg) were injected with a single injection of alloxan monohydrate (60 mg/kg iv). Alloxan was prepared as a 6% solution in a citrate buffer (pH 4.0–4.5), as described by Engerman et al. (10) and as previously used in our laboratory (16). Animals were allowed only water during the 24 h before injection and were fed immediately after injection. Hydration status, serum electrolytes, blood urea nitrogen (BUN), creatinine, and blood glucose were closely monitored between injection and experimental day. All experiments involving hyperglycemic animals were performed 6–8 days after alloxan injection. Animals were included in the hyperglycemia group if their glucose was >200 mg/dl when tested 3–4 days after alloxan injection. All animals studied were free from volume depletion, electrolyte disturbances, and renal dysfunction.

General Surgical Preparation

Dogs were sedated with ketamine (15 mg/kg sc) and acepromazine (0.2 mg/kg sc), and anesthetized with α-chloralose (60 mg/kg iv) and urethan (150 mg/kg iv). Additional doses of chloralose and urethan were given as needed to maintain a surgical depth of anesthesia. Both femoral arteries (PE-205) and one femoral vein (PE-150) were cannulated for hemodynamic monitoring, measurement of arterial blood gases, and drug and fluid administration, respectively. Dogs were ventilated with a high-frequency jet ventilator synchronized to the cardiac cycle, as previously described (4, 5, 18). The ventilator settings were adjusted to maintain physiological blood gases and pH at all times. Small doses of sodium bicarbonate were administered as needed to correct metabolic acidosis. Arterial blood gases were measured with a Radiometer OSM2 calibrated for canine blood.

A left thoracotomy was performed, and the heart was suspended in a pericardial cradle. Catheters (PE-150) were inserted into the coronary sinus via the left jugular vein and into the left atrial appendage for administration of fluorescein-labeled dextran and radiolabeled microspheres. A 5-French catheter (Millar Instruments, Houston, TX) was placed in the left ventricle via the left atrial appendage for recording left ventricular pressure and dP/dt. Snares were placed around the descending thoracic aorta and the inferior vena cava to control arterial pressure. Pacing electrodes were attached to the left atrial appendage and connected to a Grass stimulator (Grass Instruments, Quincy, MA), which was used to control heart rate. The epicardial surface was kept moist by suffusion of warmed oxygenated Krebs solution (in mM: NaCl 118.3, KCl 4.7, CaCl₂ 2.5, MgPO₄ 1.2, NaHCO₃ 25, KH₂PO₄ 1.2) at 2 ml/min bubbled with 20% oxygen, 5% carbon dioxide, and 75% nitrogen. Body temperature was maintained (37 ± 1°C) with a servo-controlled thermal blanket.

Microvascular Preparation

Coronary microvascular diameters were measured by intravital microscopy (Zeiss, Germany) with epi-illumination of the cardiac surface by a computer-controlled strobe (Chadwick Helmut, Almonte, CA). The strobe was triggered using the left ventricular dP/dt signal to flash once per cardiac cycle in late diastole. Fluorescein isothiocyanate dextran (mol wt 487,000, Sigma Chemical, St. Louis, MO) was injected into the left atrium to illuminate the microvascular lumen and to differentiate arterioles from venules by sequence of illumination. A Zeiss Neufluora (6.3X, n.a. = 0.02) objective was used; when coupled with a 6.3X relay lens, microvascular diameters can be measured with 2.5-μm resolution. Digital images were captured with a video camera and stored on computer disk. Images were later recalled on a high-resolution monitor, and the microvascular diameters were measured using a digitizing tablet and a computer to calculate the internal vessel diameter in micrometers. Details of the system have been described previously (4, 5, 18). All vessel measurements represent the mean of at least three images obtained at steady state for each experimental condition.

Myocardial Perfusion and Oxygen Consumption

Myocardial perfusion was measured with the radiolabeled microsphere technique, as previously described (5). Radiolabeled microspheres (15.5 μm: 141Ce, 65Nb, 46Sc, 113Sn, 85Sr) were injected into the left atrial appendage during withdrawal of two reference samples from the aorta via the femoral artery catheters at a fixed rate (1.4–2.5 ml/min). At the end of the experiment, the heart was excised, and left ventricular tissue samples, excluding the papillary muscles, were obtained from the region of the studied vessels. The radioactivity contained in each sample was counted by a germanium crystal gamma counter (Canberra Industries, Meriden, CT). Myocardial blood flow (ml/min) was calculated with the formula

$$MBF = \frac{(Cm \times WR \times 100)}{Cr}$$

where Cm is radioactivity per weight in grams of tissue, WR is the withdrawal rate of the reference aortic blood samples in ml/min, and Cr is the total radioactivity of the reference blood samples. A minimum of 400 microspheres was contained in each sample.

Left ventricular arterio-venous oxygen difference (avO₂D, ml/l) was determined with the formula

$$avO₂D = 1.36[(Hgbₐ \times O₂Satₐ) - (Hgbₐ \times O₂Satₐ)]$$

where Hgbₐ and Hgbᵥ are arterial and coronary sinus hemoglobin concentrations in g/l and O₂Satₐ and O₂Satᵥ are arterial and coronary sinus hemoglobin oxygen saturations (%), respectively. Myocardial oxygen consumption (MVO₂, ml/min⁻¹ · 100 g⁻¹) was determined with the formula

$$MVO₂ = avO₂D \times MBF/100$$
CORONARY ARTERIOLE RESPONSES IN HYPERGLYCEMIA

To test the hypothesis that endoperoxides (thromboxane A2, prostaglandin H2) are responsible for impaired responses to increases in MVO2 during prolonged hyperglycemia, a dobutamine and RAP protocol described in protocol 2 was performed.

Protocol 4: role of superoxide anion in impaired metabolic dilation. To test the hypothesis that oxygen-derived free radicals are responsible for the impaired microvascular response to increases in MVO2 during prolonged hyperglycemia, a dobutamine and RAP protocol described in protocol 2 was performed.

After completion of the protocols, the dogs were killed with an overdose of anesthetic followed by saturated potassium chloride (10 ml), and the heart was fixed for later determination of myocardial perfusion and calculation of MVO2.

Statistical Analysis

Microvessels (<100 μm) were included in the analysis if they met two a priori-determined criteria: 1) the nitroprusside response was >20%; and 2) the vessel regained tone within 15% of baseline after washout of nitroprusside. One vessel from the normal group and two vessels from the HG group were excluded, because the response to nitroprusside was <20%. Three of the normal, none of the HG, two of the SQ29,548-treated diabetic, and one of the SOD-treated diabetic vessels were excluded because of a failure to regain tone after nitroprusside washout.

All values are presented as means ± SE. One-way analysis of variance was used to evaluate the changes in hemodynamic variables, blood gases, blood glucose, and MVO2 among the experimental preparations and in diameters among the studied vessels. Student-Newman-Keuls post hoc testing was performed where appropriate. A P < 0.05 was considered statistically significant.

RESULTS

Endothelial Function Protocol (Protocol 1)

Serum electrolytes, BUN, Cr, blood gases, and hemodynamics for both the normal and prolonged hyperglycemia animals studied under protocol 1 were not significantly different between the groups and were within the range of normal (data not shown). Microvascular diameters at baseline were not different between the groups (normal, 97 ± 10 μm; HG, 111 ± 12 μm). During suffusion of acetylcholine (1, 10, and 100 μM) the arterioles in normal animals dilated significantly more than those in diabetic animals (Fig. 1A). During suffusion of nitroprusside (1, 10, and 100 μM) the arterioles dilated to a similar degree in both groups (Fig. 1B).

Metabolic Stress Protocols (Protocols 2–4)

Baseline microvascular diameters were similar among the groups (Normal, 60 ± 3 μm; HG, 70 ± 5 μm; SQ29,548-treated HG, 66 ± 5 μm; SQ29,548-treated
Hemodynamics, glucose, pH, and blood gases for protocols 2–4

Table 1. Hemodynamics, glucose, pH, and blood gases for protocols 2–4

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 10)</th>
<th>HG (n = 7)</th>
<th>HG + SQ (n = 5)</th>
<th>N + SQ (n = 4)</th>
<th>HG + SOD (n = 5)</th>
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<tr>
<td>HR (beats/min)</td>
<td>124 ± 11</td>
<td>130 ± 11</td>
<td>138 ± 11</td>
<td>155 ± 15</td>
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<td>136 ± 16</td>
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<td>MAP (mmHg)</td>
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<td>Glucose (mg/dl)</td>
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<td>33 ± 1</td>
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<td>pO2 (mmHg)</td>
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<td>93 ± 3</td>
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<td>DOB (m)</td>
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<td>177 ± 11</td>
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<td>MAP (mmHg)</td>
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<td>Glucose (mg/dl)</td>
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<td>pO2 (mmHg)</td>
<td>142 ± 20</td>
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<td>114 ± 24</td>
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<td><strong>DOB + RAP</strong></td>
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<tr>
<td>HR (beats/min)</td>
<td>273 ± 9</td>
<td>277 ± 14</td>
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<td>298 ± 1</td>
<td>269 ± 17</td>
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<td>MAP (mmHg)</td>
<td>84 ± 3</td>
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<td>84 ± 4</td>
<td>88 ± 10</td>
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<td>Glucose (mg/dl)</td>
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<td>378 ± 44*</td>
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<td>pCO2 (mmHg)</td>
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<td>34 ± 1</td>
<td>36 ± 6</td>
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<td>pO2 (mmHg)</td>
<td>120 ± 21</td>
<td>115 ± 10</td>
<td>105 ± 13</td>
<td>79 ± 2</td>
<td>93 ± 9</td>
<td>85 ± 10</td>
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DOB, dobutamine; DOB + RAP, DOB and rapid atrial pacing; HG, hyperglycemia group; HG + SQ: SQ29,548-treated HG group; HG + SOD, SOD, superoxide dismutase (SOD)-treated HG group; HR, heart rate (beats/min); MAP, mean atrial pressure (mmHg); N + SQ: SQ29,548-treated normal (N) group; N + SOD: SOD-treated N group. Units: glucose, mg/dl; pCO2 and pO2, mmHg. *P < 0.05 vs. Normal.
Myocardial perfusion and arteriovenous oxygen content difference

Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 10)</th>
<th>HG (n = 5)</th>
<th>HG + SQ (n = 5)</th>
<th>N + SQ (n = 4)</th>
<th>HG + SOD (n = 5)</th>
<th>N + SOD (n = 5)</th>
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<tr>
<td>Myocardial perfusion</td>
<td>121 ± 16</td>
<td>127 ± 23</td>
<td>150 ± 26</td>
<td>141 ± 17</td>
<td>104 ± 31</td>
<td>128 ± 30</td>
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<tr>
<td>avO2D</td>
<td>10 ± 1</td>
<td>12 ± 1</td>
<td>10 ± 1</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
<td>13 ± 1</td>
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<tr>
<td>DOB</td>
<td></td>
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<tr>
<td>Myocardial perfusion</td>
<td>248 ± 21</td>
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<td>226 ± 32</td>
<td>266 ± 34</td>
<td>255 ± 57</td>
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<td>avO2D</td>
<td>9 ± 1</td>
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<td>13 ± 2</td>
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<tr>
<td>Myocardial perfusion</td>
<td>376 ± 56</td>
<td>297 ± 48</td>
<td>379 ± 73</td>
<td>368 ± 54</td>
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Groups are as listed in Table 1. avO2D, arteriovenous oxygen content difference (ml/l). Myocardial perfusion, ml · min⁻¹ · 100 g⁻¹.

MVO₂ was significantly greater than at baseline in every group (P < 0.05, Fig. 2).

Microvascular Diameters

Responses to increases in MVO₂ in normal and HG dogs: Protocol 2. In normal animals, coronary microvascular diameters progressively increased with increasing MVO₂ (Fig. 3). In animals with prolonged hyperglycemia, during dobutamine infusion, coronary arteriolar dilation was similar to that seen in normal animals. During dobutamine and RAP, coronary arterioles in normal animals (treated or untreated with SQ29,548 or SOD) dilated significantly compared with both baseline and dobutamine measurements. However, during dobutamine and RAP, coronary arterioles from diabetic animals did not dilate further (Fig. 3), despite a further rise in MVO₂ similar to that seen in normal animals.

Effect of SQ29,548 treatment in diabetes: protocol 3. After treatment with SQ29,548, baseline diameters did not change [HG + SQ, -2 ± 3; N + SQ, -5 ± 10%, P = not significant (NS)]. In these animals, during dobutamine, coronary arterioles dilated to a similar degree to those from normal and untreated diabetic animals. During combined dobutamine and RAP, however, coronary arterioles from SQ29,548-treated diabetic and normal animals dilated similarly and significantly more than arterioles from untreated diabetic dogs (Fig. 3).

Effect of SOD treatment in diabetes: protocol 4. After treatment with topical SOD, baseline diameters did not change (HG + SOD, -4 ± 1; N + SOD, -6 ± 6%, P = NS). In these dogs, coronary arterioles dilated to a similar degree to those from normal and untreated HG animals (Fig. 3) during dobutamine. With dobutamine and RAP, however, coronary arterioles from HG animals treated with topical SOD dilated similarly to those from normal animals but significantly more than those from untreated HG animals (Fig. 3). During dobutamine and RAP, arteriolar dilation was similar in SQ29,548- and SOD-treated HG dogs.

DISCUSSION

There are three major findings in this study. First, in vivo coronary arteriolar responses to increases in MVO₂ are impaired in dogs with prolonged hyperglycemia. Second, our study importantly showed that blockade of endoperoxide receptors with SQ29,548 prevents

![Fig. 2. Graph showing myocardial oxygen consumption (MVO₂) during the protocol in the 6 groups of dogs. Normal (N), n = 10; HG, n = 7; SQ29,548-treated HG (HG + SQ), n = 5; SQ29,548-treated N (N + SQ), n = 4; superoxide dismutase (SOD)-treated HG (HG + SOD), n = 5; SOD-treated N (N + SOD), n = 5; DOB, dobutamine; DOB + RAP, DOB with rapid atrial pacing.]

![Fig. 3. Graph showing coronary microvascular response (% change from baseline diameter) in all groups throughout the protocol. In normal dogs, regardless of pretreatment, there was an increase in diameter during increases in MVO₂. At the lower level of stimulation (DOB), the responses among all groups were not different. During DOB + RAP, dilatation in the HG group was impaired compared with the normal and the treatment groups (P < 0.05). There were no differences in the responses to DOB + RAP among the N and the 2 treated groups of HG dogs or treated N groups (P = NS). Groups and numbers of animals are as in Fig. 2.]

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this impaired dilation to marked metabolic stimulation, suggesting a role for thromboxane A₂ and/or prostaglandin H₂. Third, we showed restoration of dilator function during prolonged hyperglycemia with topical administration of superoxide dismutase, indicating that the superoxide anion plays a role in this impaired response. Thus, in dogs with prolonged hyperglycemia, dilation of coronary arterioles is impaired in response to endothelium-dependent vasodilators and during increases in MVO₂. Coronary dilation during increases in MVO₂ in hyperglycemic dogs may be restored with either blockade of endoperoxide receptors or with scavengers.

Endothelium-Dependent Vasodilation in Diabetes

Endothelium-dependent vasodilation has been shown to be impaired in diabetic animals (26, 32) in vitro. Our data clearly demonstrate that coronary arteriolar dilation to acetylcholine is impaired in in vivo with exposure to prolonged hyperglycemia (Fig. 1A). However, impaired dilation during hyperglycemia is selective for endothelium-mediated dilation, because dilatory responses were similar to normal animals during administration of the endothelium-independent vasodilator nitroprusside (Fig. 1B). Several mechanisms for endothelial dysfunction have been proposed (26), not all of which directly involve nitric oxide. There may be increased release of an endothelium-derived constricting factor (EDCF), most likely a prostanoid. Additionally, oxygen-derived free radical production is increased in diabetes, which may have two effects. First, nitric oxide may be destroyed by superoxide anion. Second, the presence of free radicals may alter the metabolism of arachidonic acid through the cyclooxygenase pathway to favor production of vasoconstricting, rather than vasodilatory, prostanoids.

Our failure to observe a difference in baseline diameter after pretreatment with SOD or SQ29,548 was unexpected. However, this result is consistent with that of Tesfamariam and colleagues (30, 32), who noted enhanced thromboxane production only during stimulation with acetylcholine. The measurements of thromboxane were not abnormal in basal states but were elevated in diabetes or hyperglycemia during stimulated states. This suggests that the diabetic milieu lowers the threshold for stimulation-induced elevation in endoperoxides.

Mechanism of Coronary Vasodilation During Increases in MVO₂ in Normal Animals

Coronary arterioles are responsible for closely coupling coronary blood flow and MVO₂ (14), although the exact mechanism of this coupling remains unclear. Because coronary blood flow can increase five- to six-fold from baseline (20), the primary means by which oxygen delivery to the myocardium may be increased during increased demand is via coronary dilation. Microvascular dilation during increased MVO₂ is heterogeneous according to vessel size (14), with the greatest magnitude of dilation being inversely related to baseline coronary diameter. Adenosine has received the most attention as a potential mediator of metabolic vasodilation, but its role has been seriously questioned (13, 14).

Jones et al. (13) have recently reported that nitric oxide participates in coronary microvascular dilation during increased metabolic demand with rapid atrial pacing. In addition, our laboratory demonstrated that coronary microvascular dilation during increases in MVO₂ with a dobutamine and pacing protocol is virtually abolished by nitric oxide synthase inhibition (9). In contrast to the findings of Jones et al. and Embrey et al. (9), some investigations have shown that increases in coronary flow due to increased metabolic demand are due to ATP-sensitive potassium channels and not to a nitric oxide-mediated pathway. In a study by Narishige et al. (23), using anesthetized open-chest dogs and a model of metabolic stimulation (β₂-adrenergic receptor stimulation), found that glibenclamide prevented increases in coronary blood flow associated with increases in MVO₂. Their results using either isoproterenol or denopamine demonstrated a role for K₁ ATP in mediating increases in coronary blood flow during increases in oxygen consumption. In similar preparations in awake exercising dogs, others have not reproduced these findings (3, 6, 7).

Role of Endoperoxides and Free Radicals in Impaired Microvascular Dilation During Increased MVO₂

Because, in this experimental preparation, blockade of prostaglandin H₂/thromboxane A₂ receptor or scavenging oxygen radicals has little or no effect on the baseline diameters, this excludes a nonspecific vasodilatory response to these agents alone. Instead, only after endothelial stimulation (i.e., with increases in MVO₂) do these agents produce measurable effects on coronary reactivity. Thus these antagonists appear to protect the intrinsic vasodilatory mechanisms to increases in MVO₂ in the face of diabetes mellitus.

Our data support the concept that release of an EDCF and/or (see next paragraph) free radicals participate in impaired metabolic dilation during hyperglycemia. Interestingly, reversal of either of these mechanisms permits normal vasodilation to increasing metabolic demand.

There are two possible explanations for either thromboxane A₂/prostaglandin H₂ receptor blockade or superoxide scavenging to restore normal dilator function of arterioles during increased MVO₂. First, there may be coexistent pathways for superoxide production and for endoperoxide production in the diabetic state. If both pathways are required to achieve inhibition of endothelium-mediated dilation, inhibition of either would allow for normal dilation to occur. The second possibility is that superoxide production and endoperoxide production are sequentially linked (15).

Clinical Implications

This study provides insight into potential mechanisms for the observed decreased exercise tolerance in
diabetic patients. Our study provides direct evidence that endoperoxides and oxygen-derived free radicals play a role in impaired coronary microvascular dilation during increases in \( \text{MV˙O}_2 \). Pharmacological use of antioxidants such as vitamins C and E (27) or cyclooxygenase inhibitors such as aspirin or indomethacin may improve exercise tolerance and decrease the propensity for ischemia in diabetic patients. In summary, this study provides evidence that vasoconstrictor eicosanoids and oxygen-derived free radicals mediate impaired coronary arteriolar dilation during increased myocardial oxygen consumption during prolonged hyperglycemia.

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