Enhanced contribution of NO to exercise-induced coronary responses after α-adrenergic receptor blockade

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Takamura, Masayuki, Robert Parent, and Michel Lavalée. Enhanced contribution of NO to exercise-induced coronary responses after α-adrenergic receptor blockade. Am J Physiol Heart Circ Physiol 282: H508–H515, 2002.—We hypothesized that nitric oxide (NO), in addition to β-adrenergic effects, may contribute to exercise-induced coronary responses after α-adrenergic receptor blockade. Data were analyzed as relationships between coronary sinus (CS) O2 saturation (CS O2sat) or coronary blood flow (CBF) and myocardial O2 consumption (MVO2). As MVO2 increased, CS O2sat fell more (P < 0.05) after Nω-nitro-L-arginine methyl ester (L-NAME; slope = −2.9 ± 0.4 × 10−2 %saturation·μl O2·min−1·g−1) than before (slope = −2.1 ± 0.3 × 10−2 %saturation·μl O2·min−1·g−1). The slope of CBF versus MVO2 was not altered. After blockade of α-adrenergic receptors alone (phenotamine), CS O2sat fell to decrease as MVO2 increased (slope = −0.1 ± 0.5 × 10−2 %saturation·μl O2·min−1·g−1). L-NAME given after phenotamine led to substantial decreases in CS O2sat (P < 0.01) as MVO2 increased (slope = −2.1 ± 0.4 × 10−2 percent saturation·μl O2·min−1·g−1). CBF responses to exercise were smaller (P < 0.01) after phenotamine + L-NAME (slope = 6.1 ± 0.1 × 10−3 ml/μl O2) than after phenotamine alone (slope = 6.9 ± 0.2 × 10−3 ml/μl O2). Thus a significant portion of exercise-induced coronary responses after α-adrenergic receptor blockade involves NO formation.

METHODS

During exercise, the balance between coronary blood flow (CBF) and myocardial oxygen consumption (MVO2) is finely tuned through local metabolic feedback mechanisms (6), over which α-adrenergic constriction and feedforward β-adrenergic dilation are superimposed (7). Together, these factors lead to a relative mismatch between myocardial perfusion and metabolic demand displayed as a decrease in coronary sinus (CS) blood O2 levels in the face of increases in MVO2 (2, 9–11, 19). Nitric oxide (NO) production, which is increased during exercise (3, 23), has been considered as a factor that contributes to maintain the equilibrium between myocardial O2 supply and demand. While NO production plays a major role in the dilation of large epicardial conductance arteries during exercise (27), its contribution to vasomotor responses of resistance coronary vessels has been reported to be minimal (1, 3, 25). In fact, arginine analogues had only a limited influence on the slope of the relationship between CS O2 tension and MVO2, an index of the match between coronary perfusion and MVO2 (1, 3, 25). Conceivably, the loss of NO formation may trigger compensatory mechanisms, which can impair a further decrease in CS O2 tension (13, 14). The possibility that adenosine production becomes more important after the blockade of NO formation has been recently ruled out (25).

On the basis of our earlier studies (15, 20) showing that coronary β-adrenergic dilation of resistance coronary vessels in conscious dogs involves NO formation, we hypothesized that exercise performed after α-adrenergic receptor blockade may involve a greater contribution of NO triggered directly through enhanced β-adrenergic receptor activation or indirectly through hemodynamic effects of α-adrenergic receptor blockade. The contribution of NO formation was assessed as differences of the slopes of relationships between CS O2 saturation levels or CBF and MVO2 after α-adrenergic blockade alone and after the combined blockade of α-adrenergic receptors and NO formation in exercising dogs.

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after 1 ml of blood was collected in lightly heparinized syringes and sealed after sampling.

Dogs ran successively for 3 min at 3 miles/h (0% grade), 4 miles/h (5% grade), and 6 miles/h (10% grade). Blood samples were obtained 2.5–3.0 min after the beginning of each step under steady-state conditions. One hour after the first run, 1.5 mg/kg of phentolamine was administered intravenously, and the dogs were immediately placed on the treadmill to perform the exercise protocol. Adequacy of α-adrenergic blockade was demonstrated in preliminary experiments (n = 5). Mean arterial pressure (MAP) responses (24 ± 1 from 93 ± 5 mmHg) caused by 3.0 μg/kg iv phenylephrine (Sabex; Boucherville, Quebec, Canada) were blunted (P < 0.01) after phentolamine (−2 ± 1 from 93 ± 4 mmHg).

On different days, the exercise protocol was performed after Nω-nitro-L-arginine methyl ester (l-NNAME; 10 mg/kg iv) was given over 10 min. Adequacy of NO formation blockade with this dose of l-NNAME has been demonstrated earlier (21) and confirmed in preliminary experiments (n = 5) by smaller (P < 0.01) acetylcholine chloride-induced (3 μg/kg iv) CBF increases after l-NNAME (67 ± 15 from 61 ± 7 ml/min) than before (121 ± 13 from 61 ± 7 ml/min).

The exercise protocol was repeated at least 48 h later after combined administration of phentolamine + l-NNAME or propranolol (1.0 mg/kg iv) + phentolamine. All drugs except for phenylephrine were obtained from Sigma (St. Louis, MO). Except for one animal, in which the l-NNAME alone protocol could not be completed, all other experiments were carried out in the same eight dogs.

Data analysis. Data are reported as means ± SE and statistical significance was reached when P < 0.05 in all cases. An analysis of variance for repeated measurements was used for simultaneous overall comparisons of baseline hemodynamic variables under the five experimental conditions (28). Post hoc comparisons were made with the Newman-Keuls test to isolate contrasts of interest. Overall responses to exercise before and after l-NNAME were compared using a two-way analysis of variance for repeated measurements. A similar approach was used to simultaneously compare phentolamine alone versus phentolamine + l-NNAME and propranolol + phentolamine. Data for CBF and CS O2 saturation were reported as relationships centered on corresponding mean MVO2 levels for each exercise level. A one-way analysis of variance was first performed to determine if the dependent variable was altered during exercise and a two-way analysis of variance was used to compare the effects of the various treatments. A linear regression analysis was then performed for each animal after each drug, followed by an analysis of variance for repeated measurements on slopes or a paired Student’s t-test when only two experimental conditions were compared. Because CS O2 saturation failed to decrease as MVO2 increased after phentolamine alone (one-way analysis of variance), a relationship between CS O2 saturation and MVO2 could not be demonstrated (slope not different from 0). Therefore, control or treatments were considered statistically different from phentolamine when the slopes differed from zero.

All experimental procedures were approved by an ethical committee on animal care and performed in accordance with Guide to the Care and Use of Experimental Animals (Canadian Council on Animal Care, Publication No. 0-919087-18-3, Ottawa, Ontario, Canada, 1993).

RESULTS

Baseline hemodynamics. Baseline hemodynamic variables for all experimental groups are reported in Table 1. Except for the expected increases (P < 0.01) in left ventricular pressure (LVP) and MAP and decreases (P < 0.01) in heart rate, l-NNAME had no other significant effects. A similar response pattern was observed when l-NNAME + phentolamine was compared with phentolamine alone. Propranolol + phentolamine caused no further hemodynamic effects compared with phentolamine alone, except for a significant decrease (P < 0.01) in the LV first derivative of pressure development over time (dP/dt), as reported in Table 1.

Blockade of NO formation. As reported in Fig. 1, LVP and MAP were higher (P < 0.01) and LV dP/dt was lower (P < 0.01) throughout exercise in dogs treated with l-NNAME. Heart rate, aortic blood O2 saturation, and Hb levels did not significantly differ before and after l-NNAME. The graded exercise protocol led to the expected increases (P < 0.01) in CBF as MVO2 augmented (Fig. 2). Mean CBF levels achieved during exercise did not statistically differ before and after l-NNAME. The slopes of the relationships between CBF and MVO2 did not

Table 1. Baseline hemodynamic variables before and after l-NNAME and after phentolamine alone or combined with l-NNAME or propranolol

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Control (n = 8)</th>
<th>l-NNAME (n = 7)</th>
<th>Phentolamine (n = 8)</th>
<th>Phentolamine + l-NNAME (n = 8)</th>
<th>Propranolol + Phentolamine (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVP, mmHg</td>
<td>132 ± 3</td>
<td>159 ± 6†</td>
<td>119 ± 4</td>
<td>140 ± 6*</td>
<td>111 ± 3</td>
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<tr>
<td>LV dP/dt, mmHg/s</td>
<td>3,804 ± 162</td>
<td>3,577 ± 189</td>
<td>4,199 ± 230</td>
<td>3,878 ± 247</td>
<td>3,037 ± 152†</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>102 ± 3</td>
<td>127 ± 6†</td>
<td>86 ± 3</td>
<td>116 ± 5*</td>
<td>89 ± 2</td>
</tr>
<tr>
<td>CBF, ml·min⁻¹·g⁻¹</td>
<td>1.05 ± 0.09</td>
<td>1.11 ± 0.16</td>
<td>0.99 ± 0.09</td>
<td>1.05 ± 0.12</td>
<td>1.02 ± 0.11</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>99 ± 5</td>
<td>83 ± 4†</td>
<td>116 ± 6</td>
<td>94 ± 3†</td>
<td>107 ± 4</td>
</tr>
<tr>
<td>MVO2, μl·O2·min⁻¹·g⁻¹</td>
<td>149 ± 13</td>
<td>156 ± 22</td>
<td>133 ± 14</td>
<td>145 ± 15</td>
<td>137 ± 13</td>
</tr>
<tr>
<td>CS saturation, %</td>
<td>16.1 ± 0.8</td>
<td>16.4 ± 1.2</td>
<td>14.5 ± 0.7</td>
<td>15.0 ± 0.7</td>
<td>15.2 ± 1.3</td>
</tr>
<tr>
<td>Ao saturation, %</td>
<td>97.2 ± 0.4</td>
<td>97.0 ± 0.5</td>
<td>96.5 ± 0.2</td>
<td>96.9 ± 0.3</td>
<td>96.9 ± 0.5</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>13.1 ± 0.3</td>
<td>13.0 ± 0.3</td>
<td>12.1 ± 0.3</td>
<td>12.6 ± 0.3</td>
<td>12.5 ± 0.4</td>
</tr>
</tbody>
</table>

*Values are means ± SE are reported; n = no. of dogs. Post hoc comparisons were made between control and Nω-nitro-L-arginine methyl ester (l-NNAME) and between phentolamine alone and phentolamine + l-NNAME or propranolol + phentolamine. LVP, left ventricular pressure; LV dP/dt, first derivative of LVP over time; MAP, mean arterial pressure; CBF, coronary blood flow; HR, heart rate; MVO2, myocardial oxygen consumption; CS, coronary sinus; Ao, aorta; Hb, hemoglobin concentration. °P < 0.01 vs. control; †P < 0.01 vs. phentolamine alone.
Fig. 1. Means ± SE left ventricular pressure (LVP), first derivative of LVP over time (LV dP/dt), mean arterial pressure (MAP), heart rate, aortic blood O2 saturation, and hemoglobin (Hb) before and after Nω-nitro-i-arginine methyl ester (L-NAME). Variables are reported at control (standing) and at each step of a graded exercise protocol in the same seven dogs. †P < 0.01, different from control.

differ before (5.0 ± 0.1 × 10⁻³ ml/μl O₂) and after L-NAME (4.9 ± 0.2 × 10⁻³ ml/μl O₂). CS O₂ saturation fell significantly (P < 0.01) as MVO₂ increased under control conditions and after L-NAME. Overall, mean CS O₂ saturation levels did not significantly differ during exercise performed before and after L-NAME. However, the slope of the relationships between CS O₂ saturation levels and MVO₂ was steeper (P < 0.05) after L-NAME (−2.9 ± 0.4 × 10⁻² %saturation·μl O₂·min⁻¹·g⁻¹) than before (−2.1 ± 0.3 × 10⁻² %saturation·μl O₂·min⁻¹·g⁻¹). Thus, for any given increase in MVO₂, CS O₂ saturation fell more after L-NAME, consistent with a greater mismatch between myocardial O₂ demand and supply.

**Blockade of α-adrenergic receptors.** Coronary responses involving metabolic and β-adrenergic dilation (after phentolamine) and metabolic dilation alone (after propranolol + phentolamine) were compared to demonstrate the involvement of β-adrenergic influences after α-adrenergic receptor blockade.

Phentolamine prevented the fall (P < 0.01) in CS O₂ saturation observed under control exercise and resulted in higher (P < 0.05) mean CBF levels, as reported in Fig. 3. Further blockade of β-adrenergic receptors with propranolol resulted in a substantial fall (P < 0.01) in CS O₂ saturation levels during exercise. As expected, increases in CBF throughout exercise were smaller (P < 0.01) after the combined blockade of α- and β-adrenergic receptors than after α-adrenergic receptor blockade alone.

After phentolamine + propranolol, CS O₂ saturation fell significantly (P < 0.01) as MVO₂ increased (slope = −5.3 ± 1.0 × 10⁻² %saturation·μl O₂·min⁻¹·g⁻¹). In contrast, CS O₂ saturation failed to decrease throughout exercise performed after phentolamine alone (slope = −0.1 ± 0.5 × 10⁻² %saturation·μl O₂·min⁻¹·g⁻¹) (Fig. 3). Consistent with these findings, the slope of the relationship between CBF and MVO₂ was steeper (P < 0.01) after phentolamine (6.9 ± 0.2 × 10⁻³ ml/μl O₂) than after propranolol + phentolamine (5.0 ± 0.2 × 10⁻³ ml/μl O₂) or under control conditions (4.9 ± 0.1 × 10⁻³ ml/μl O₂). Thus lifting α-adrenergic constriction led to a better match between cardiac metabolic demand and O₂ delivery as MVO₂ increased during exercise. After α-adrenergic receptor blockade, β-adrenergic receptor activation was an important determinant of coronary dilator responses.
Combined blockade of α-adrenergic receptors and NO formation. L-NAME + phentolamine lead to augmented LVP (P < 0.05) and MAP (P < 0.01) levels throughout exercise compared with phentolamine alone but did not influence other hemodynamic variables as reported in Fig. 4. After the combined administration of propranolol + phentolamine, LVP (P < 0.05), LV dP/dt (P < 0.01), and heart rate (P < 0.01) remained lower than after phentolamine alone.

Exercise performed after phentolamine + L-NAME resulted in substantial decreases (P < 0.01) in CS O₂ saturation levels, not displayed after phentolamine alone (Fig. 3). Propranolol + phentolamine also led to significant decreases (P < 0.01) in CS O₂ saturation.

A significant (P < 0.01) relationship between CS O₂ saturation levels and MV O₂ was found after phentolamine + L-NAME (slope = −2.1 ± 0.4 × 10⁻² %saturation · μl O₂ · min⁻¹ · g⁻¹) but not after phentolamine alone, as indicated earlier. Thus, for any given increase in MV O₂, CS O₂ saturation fell more (P < 0.01) after phentolamine + L-NAME than after phentolamine alone, consistent with the involvement of NO in coronary dilation displayed after α-adrenergic receptor blockade. NO accounted for ~45% of the differences in slopes between phentolamine alone and phentolamine + propranolol.

The slope of the relationship between CBF and MV O₂ after phentolamine (6.9 ± 0.2 × 10⁻³ ml/μl O₂) was decreased (P < 0.01) by the addition of L-NAME (6.1 ± 0.1 × 10⁻³ ml/μl O₂). Thus, for any given increase in MV O₂, CBF increased less (P < 0.01) after phentolamine + L-NAME than after phentolamine alone, consistent with the involvement of NO formation to the dilation of coronary resistance vessels after α-adrenergic receptor blockade.

The steeper (P < 0.01) slope of the relationship between CBF and MV O₂ after phentolamine + L-NAME (6.1 ± 0.1 × 10⁻³ ml/μl O₂) than under control conditions (4.9 ± 0.1 × 10⁻³ ml/μl O₂) is indicative of α-adrenergic vasoconstriction. Changes in the slope of the relationship between CS O₂ saturation and MV O₂ caused by phentolamine + L-NAME (−2.1 ± 0.4 × 10⁻² %saturation · μl O₂ · min⁻¹ · g⁻¹) from control condi-
DISCUSSION

The present study highlights the significant contribution of NO to exercise-induced coronary dilation after α-adrenergic receptor blockade. We have relied on a strategy allowing, by pharmacological means, to exclude α-adrenergic constriction and to specifically examine dilator mechanisms contributing to exercise-induced coronary responses thereafter. Our data demonstrate that NO, in addition to β-adrenergic effects, is pivotal in causing coronary dilation during exercise performed under α-adrenergic receptor blockade. Together, these mechanisms help to ensure a closer match between myocardial O2 demand and supply.

One important limitation should be kept in mind when considering the present data. By lifting the inhibitory activity of α-adrenergic receptors on noradrenaline release, phentolamine will cause an exaggerated β-adrenergic activation. Consequently, experiments conducted under α-adrenergic blockage cannot allow a direct quantitative assessment of β-adrenergic-induced coronary dilation taking place during normal exercise although under normal conditions, interstitial norepinephrine levels are well above the threshold for causing coronary β-adrenergic dilation (8).

During exercise, the level of CBF is determined through several mechanisms, including local vasodilator effects coupled to increases in cardiac metabolism over which are superimposed α-adrenergic constriction and β-adrenergic dilation (7). Acting in concert, these factors are responsible for determining the subtle equilibrium between O2 demand and supply reflected by the relationship between CS O2 levels and MVO2. Under normal exercise conditions, a relative mismatch exists between O2 demand and supply displayed as a reduction of coronary venous O2 levels in the face of increases in MVO2 (2, 7, 9–11, 19). Local feedback mechanisms coupled to cardiac metabolism are considered to be the major determinants of CBF (6). The error signal generated through this process cannot, however, completely ensure an adequate match between myocardial perfusion and metabolic demand. Coronary venous O2 tension has been reported to fall as MVO2 was increased by pacing-induced tachycardia + paired-pulse stimulation (16). A similar phenomenon occurs during exercise performed only under local metabolic control (after α- and β-adrenergic blockade), i.e., CS O2 level declines as MVO2 increases (7).
Our data concerning the effects of blockade of NO formation (without prior blockade of \(\alpha\)-adrenergic receptors) on the relationship between coronary venous blood \(O_2\) saturation and \(\dot{MV}_O_2\) during exercise slightly differed from earlier studies. Altman et al. (1) and Tune et al. (25) reported that blockade of NO formation caused a parallel shift in the relationships between CS blood \(P_O_2\) and \(\dot{MV}_O_2\), consistent with a slight contribution of NO of similar magnitude under baseline condition and during exercise. Bernstein et al. (3) also reported a parallel shift in the relationship between CS blood \(P_O_2\) and \(\dot{MV}_O_2\), although limited to the lower levels of \(\dot{MV}_O_2\) during exercise. Interestingly, none of these studies observed that blockade of NO formation caused a significant reduction of CBF as \(\dot{MV}_O_2\) increased during exercise. Thus NO was not essential for the coronary dilation during exercise. In that respect, our data are consistent with these earlier studies because the slopes of relationships between CBF and \(\dot{MV}_O_2\) were similar before and after L-NAME. In contrast, the slope of the relationship between CS \(O_2\) saturation and \(\dot{MV}_O_2\) was slightly steeper after L-NAME than before in our study. This suggests that NO may help to better match CBF to cardiac metabolic demand at higher levels of \(\dot{MV}_O_2\). In this connection, it is of interest to note that nitrite and nitrate production across the coronary bed has been reported to increase at the highest exercise intensities (3, 23). Given the limited consequences of the blockade of NO formation on the match between myocardial \(O_2\) demand and CBF reported by us and by others, we have to acknowledge that NO could only play a limited role during exercise under normal conditions. This conclusion ignores other important effects of NO, which uncouples mitochondrial oxidative phosphorylation and alters substrate utilization by the heart (24). By targeting these mechanisms, the blockade of NO formation could have conceivably modified the relationship between myocardial perfusion and cardiac metabolism.

Several earlier studies (2, 7, 9–11, 19) have demonstrated that \(\alpha\)-adrenergic influences limit CBF during exercise by showing higher CS \(O_2\) levels at any given level of \(\dot{MV}_O_2\) after pharmacological blockade of these receptors. Therefore, \(\alpha\)-adrenergic constriction competes with metabolically induced coronary dilation and limits coronary perfusion (17).

In this context, \(\beta\)-adrenergic dilation during exercise may serve to add to local metabolic feedback and limit the consequences of \(\alpha\)-adrenergic constriction on the match between coronary perfusion and \(\dot{MV}_O_2\). Miyashiro and Feigl (16) first provided evidence supporting the existence of feedforward \(\beta\)-adrenergic dilation in the coronary circulation. They showed that norepinephrine administration after \(\alpha\)-adrenergic blockade, which unmasks \(\beta\)-adrenergic effects, caused significant coronary dilation and prevented the fall in CS \(O_2\) levels. During exercise, a similar phenomenon takes place. Feedforward \(\beta\)-adrenergic dilation can be demonstrated on the basis of an altered relationship between CS \(O_2\) levels and \(\dot{MV}_O_2\). As \(\dot{MV}_O_2\) increased during exercise, CS \(O_2\) levels were disproportionately higher when \(\beta\)-adrenergic effects and local metabolic feedback intervened, i.e., after phenolamine, than when local metabolic feedback alone accounted for coronary dilation, i.e., after propranolol + phenolamine (7). Our data agree with those of Gorman et al. (7), who demonstrated the contribution of feedforward \(\beta\)-adrenergic dilation to coronary responses caused by exercise in dogs. On the basis of a quantitative model allowing calculations of interstitial norepinephrine concentration during exercise, they estimated the contribution of feedforward \(\beta\)-adrenergic dilation to overall CBF response to exercise to be \(\sim 25\%\) (8). This phenomenon allows for a better match between CBF and cardiac metabolism during exercise. The relative contribution of feedforward \(\beta\)-adrenergic activation to coronary dilation may show substantial interspecies differences. In contrast to dogs, swine display minimal \(\alpha\)-adrenergic constriction during exercise, thereby allowing the contribution of feedforward \(\beta\)-adrenergic dilation to exercise-induced coronary responses to become more apparent, as demonstrated by Duncker et al. (5).

In the present study, we measured CS \(O_2\) saturation levels as an index of the match between myocardial \(O_2\) supply and demand, whereas Gorman et al. (7) used CS \(O_2\) tension as an index of tissue \(O_2\) level to achieve the same objective. In the present study, the shifts of the slopes of the relationships between CS \(O_2\) saturation and \(\dot{MV}_O_2\) caused by phenolamine and phenolamine + propranolol were qualitatively similar to those reported by Gorman et al. (7). In fact, absolute values of slopes in both studies were very close under the various experimental conditions. This indicates that the slope of the relationship between \(O_2\) tension and saturation was close to unity over the narrow range of \(O_2\) levels measured in CS blood. Therefore, the potential bias created by measuring \(O_2\) saturation levels in the present experiments could only have been limited.

As \(\dot{MV}_O_2\) increased during exercise, CS \(O_2\) saturation fell after phenolamine + L-NAME but did not after phenolamine alone. Consequently, the relationship between CS \(O_2\) saturation and \(\dot{MV}_O_2\) had a negative slope after phenolamine + L-NAME but not after phenolamine alone. In this situation, the slope of the relationship between CBF and \(\dot{MV}_O_2\) was steeper after phenolamine alone than after L-NAME + phenolamine, i.e., for any given increase in \(\dot{MV}_O_2\) during exercise, CBF increased more after phenolamine alone than after L-NAME + phenolamine. Thus NO formation played a significant role in exercise-induced coronary dilation after \(\alpha\)-adrenergic receptor blockade. NO helped to maintain a better match between myocardial perfusion and cardiac metabolic demand. The contribution of NO became more important as exercise intensity increased because the differences in CS \(O_2\) saturation between phenolamine alone and phenolamine + L-NAME widened as \(\dot{MV}_O_2\) increased.

Our data indicate that after \(\alpha\)-adrenergic receptor blockade, NO was an important determinant of the balance between myocardial \(O_2\) supply and demand. This raises an important question. What is the mech-
anism triggering NO formation after α-adrenergic receptor blockade? A receptor-operated process involving β-adrenergic receptors may trigger NO formation, as suggested by our earlier studies (15, 20). It is also possible that augmented NO production may be a consequence of hemodynamic conditions created by the blockade of α-adrenergic receptors, in particular a flow-dependent phenomenon caused by elevated CBF after phentolamine. If β-adrenergic activation directly triggered NO formation, L-NAME should have produced a substantial portionate increases in CBF along with increases of to-and-fro flow oscillation after α-adrenergic blockade, which may act as the trigger for NO formation. NO formation after α-adrenergic receptor blockade was pivotal in maintaining a better match between cardiac metabolic demand and O2 supply.

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