Effect of Contrast Media on Coronary Vascular Resistance*

Contrast-Induced Coronary Vasodilation

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Study objectives: To determine if the vasodilatory response to the intracoronary injection of ionic and nonionic contrast media in intact pigs is dependent on nitric oxide (NO). The mechanisms responsible for inducing the increase in coronary blood flow in response to the intracoronary injection of contrast media during angiography are still not entirely understood. There is evidence to suggest that the response could be partially mediated by NO.

Participants: We studied 14 anesthetized, open-chested pigs receiving ventilation.

Measurements and results: Changes in coronary blood flow and coronary vascular resistance were measured in response to the coronary artery injection of saline solution (0.5 mol/L, isosmolar with plasma) and three different contrast agents: meglumine sodium ioxaglate (Hexabrix; Mallinckrodt Medical; Point-Claire, Quebec, Canada), a low osmolar ionic contrast agent; iohexol (Omnipaque 300; Sanofi Winthrop; Markham, Ontario, Canada), a nonionic contrast agent; and diatrizoate meglumine 66%, diatrizoate sodium 10% (MD-76; Mallinckrodt Medical), an ionic contrast agent. Measurements were made during three experimental conditions: the coronary artery infusion of (1) saline solution, control; (2) L-nitro-arginine (LNNA; 10⁻³ mol/L and 10⁻² mol/L), a competitive inhibitor of NO synthase; and (3) L-arginine 10⁻¹ mol/L, a substrate for NO synthase. The infusion of LNNA produced an increase in baseline coronary vascular resistance (p < 0.001), but it did not attenuate the vasodilatory response to the infusion of the contrast agents. Both the high and low osmolar ionic and nonionic contrast media caused a decrease in baseline coronary vascular resistance. For all three conditions, MD-76, which has the highest osmolality, produced the greatest decrease in coronary vascular resistance.

Conclusion: The vasodilatory response of the coronary vasculature to contrast agents is directly related to osmolality and is not mediated by NO.

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Key words: coronary blood flow; nitric oxide; pigs

Abbreviations: K(ATP) = adenosine triphosphate-sensitive potassium; L-NAME = N⁵-nitro-L-arginine methyl ester; LNNA = L-nitro-arginine; NO = nitric oxide

The injection of contrast media during coronary angiography produces a variety of hemodynamic and electrophysiologic effects; these include hypotension, a reduction in myocardial contractility, ECG changes, and increased coronary arterial blood flow.¹,² Although the mechanisms responsible for inducing the increase in coronary blood flow are not entirely understood,³ they have variously been attributed to the osmolality, cationic content,⁴ viscosity,⁵ and/or pH⁶ of the injected contrast agent. These physicochemical properties could mediate their effect indirectly through coronary endothelial cells and/or directly on vascular smooth muscle cells.

The role of endothelial nitric oxide (NO) in mediating the vasodilation caused by hyperosmolar solutions has been investigated. However, the results are inconclusive. Ishizaka and Kuo⁷ showed that although the response was endothelium dependent, it was independent of NO. These investigators perfused the abluminal aspect of small coronary arteries in vitro with hyperosmolar glucose or sucrose solutions. The resultant vasodilation was abolished after removal of the endothelium; however, it was not dependent on the release of NO and arachidonic metabolites, or on the activation of adenosine
triphosphate-sensitive potassium (K\text{ATP}) or calcium-sensitive potassium channels in the vascular smooth muscle. The response was attenuated by the intraluminal administration of the K\text{ATP}-channel inhibitor, glibenclamide, suggesting that it is mediated, at least in part, by opening of endothelial K\text{ATP} channels. Vacca et al\(^8\) have also examined the effect of hyperosmolar solutions on coronary blood flow. They infused hyperosmolar saline solution into porcine coronary arteries and showed that the resultant increase in coronary blood flow was not affected by blockade of adrenergic or cholinergic receptors. However, in contrast to the results of Ishizaka and Kuo,\(^7\) the increase in coronary blood flow was abolished by administration of the NO-synthase inhibitor, N\textsuperscript{w}-nitro-L-arginine methyl ester (L-NAME). Recent studies from our laboratory also indicate that increased osmolality is the likely trigger for the contrast-induced vasodilation in the bronchial vasculature (Sasaki et al,\(^9\) and Baile et al\(^10\)). These investigators showed that bronchial arterial injection of ionic and nonionic contrast medium increased bronchial blood flow and the response was partly mediated by NO.

The purpose of this study was to measure changes in coronary blood flow and coronary vascular resistance in response to intracoronary injection of ionic and nonionic contrast media in intact pigs, and to determine whether or not the response was dependent on, or independent of, NO.

### Materials and Methods

All studies were conducted using Canadian guidelines for the use and care of animals. We studied 14 Landrace-cross pigs, weighing from 25 to 35 kg, in the supine position. The pigs were sedated by IM injection of medazolam, 0.5 mg/kg, premedicated with IM ketamine, 500 mg, and anesthetized by IV injection of sodium thiopental, 10 mg/kg. A tracheotomy tube was used for ventilation with 50% oxygen and air, using a tidal volume of 12 to 15 mL/kg/min and respiratory rate of 12 to 14 breaths/min. A tracheotomy tube was used for ventilation with 50% oxygen and air, using a tidal volume of 12 to 15 mL/kg/min and respiratory rate of 12 to 14 breaths/min. Ventilation was adjusted to keep the \(\text{Paco}_2\) between 35 mm Hg and 40 mm Hg, and arterial \(\text{Pao}_2\) > 100 mm Hg. Anesthesia was maintained by using a continuous infusion of ketamine, 15 mg/mL at 0.16 mL/min; and pancuronium bromide, 0.074 mg/min. A catheter was inserted into the left carotid artery for the measurement of systemic arterial BP and to obtain blood samples to measure arterial blood gases. A thermistor-tipped, triple lumen catheter was inserted into the right jugular vein and advanced to the pulmonary artery for the determination of pulmonary arterial pressure and cardiac output using the thermodilution technique.

A second catheter (double lumen) was placed in the superior vena cava for the continuous infusion of the anesthetic, and for the administration of IV fluids and drugs as necessary. All vascular pressures were referenced to the level of the left atrium. After ensuring that the pigs were deeply anesthetized, the chest was opened using a left thoracotomy incision between the fifth and sixth ribs, and 3 to 5 cm H\text{2}O positive end-expiratory pressure was applied. Heparin, 3,000 U, was administered IV, and another 1,000 U was given every 2 h. The left anterior descending coronary artery was carefully exposed, a 2-mm ultrasonic flow probe (Transonic, Ithaca, NY) was placed around it, and mean coronary blood flow was measured continuously. Using fluoroscopy, a 5F cobra catheter was guided into the left main coronary artery via the carotid artery.

**Experimental Protocol:** Vascular pressures (systemic arterial BP, central venous pressure, and pulmonary arterial pressure), coronary blood flow, cardiac output, heart rate, and arterial blood gas tensions were obtained after completion of the surgery, and they were monitored until the pigs were physiologically stable; control measurements were then obtained.

The study consisted of three experimental conditions: (1) control, coronary artery infusion of saline solution; (2) coronary artery infusion of L-nitro-arginine (LNNA), a competitive inhibitor of NO synthase, and (3) coronary artery infusion of L-arginine \(10^{-1}\) mol/L, a substrate for NO synthase. These solutions were infused directly into the left main coronary artery via the cobra catheter at a rate ~1/10 of the coronary flow; during the infusion of each solution, the vasodilatory effect of bolus injections of saline solution and the radiocontrast agents were measured. The first eight pigs that were studied received LNNA \(10^{-2}\) mol/L, and the next six pigs received LNNA \(10^{-3}\) mol/L. The concentration was reduced because the higher concentration caused hemodynamic instability and, consequently, three pigs (not included in the study) died before complete measurements could be made after the infusion of LNNA. The hemodynamic instability was characterized by a sudden, profound fall in cardiac output, a reduction in heart rate, an increase in systemic arterial BP, and a profound decrease in coronary blood flow. Another two pigs that received the high dose of LNNA died after the infusion of L-arginine, but before measurements could be made in response to injection of the four agents (the control and LNNA results from these two pigs were included in the analysis). Complete measurements were obtained for the remaining three pigs in this group and for all six pigs that received the low dose of LNNA.

During the infusion of these solutions, changes in coronary blood flow were measured in response to coronary artery injection of saline solution (0.5 mol/L, isosmolar with plasma), and three different, commonly used contrast agents that were selected to provide a range of ionic properties, osmolalities, and viscosities. The contrast agents were meglumine sodium iodoglate (Hexabrix; Mallinckrodt Medical; Point-Clarke, Quebec, Canada), a low osmolar iodine contrast agent; iohexol (Omnipaque 300; Sanofi Winthrop; Markham, Ontario, Canada), a nonionic contrast agent; and diatrizoate meglumine 66% diatrizoate sodium 10% (MD-76; Mallinckrodt Medical), an ionic contrast agent.

The protocol for injection of the different agents was as follows: the cobra catheter (dead space, 0.7 mL) was loaded with 0.6 mL of one of the agents. The bolus was injected into the left main coronary artery at a rate of 2 mL/min using an infusion pump (time for the infusion of the bolus was ~8 s). Coronary blood flow was recorded 10 s before (baseline), during, and at the peak response to injection of the bolus (from 25 to 30 s). Recording continued until flow had returned to baseline values (~90 s), and the next contrast agent was injected ~3 to 5 min after the previous injection. It took from 45 min to 1 h to complete each experimental condition. Duplicate measurements of the response of coronary blood flow were made for each agent.

Agents were injected in random order.

After the responses to the bolus injections were made during the infusion of saline solution, LNNA was infused into the left main coronary artery for 20 min at a rate 1/10 of the coronary blood flow (~2 mL/min). When the pigs were physiologically stable, hemodynamics and arterial blood gas tensions were recorded, and measurements of coronary artery blood flow were made again in response to a bolus injection of the different...
agents, as described above. Finally, L-arginine was infused into the left main coronary artery at a rate of ~2 mL/min for 20 min. Measurements of hemodynamics and arterial blood gas tensions were repeated, and coronary artery blood flow was recorded in response to the injection of the different agents, as described for control. At the end of the experiment, the pigs were deeply anesthetized and killed by intravascular injection of saturated potassium chloride.

The relative physicochemical properties of saline solution, Hexabrix, Omnipaque 300, and MD-76 were measured. Specifically, we measured density, pH, relative viscosity, and osmolality. Density was measured by weighing, in duplicate, 1 mL of each of the substances. The pH of each agent was measured using a blood gas analyzer (ABL 30 Acid Base Analyzer; Radiometer; Copenhagen, Denmark). The viscosity was measured against water at 37°C using a viscosimeter (model VVR 66044-007; Ostwald; Vancouver, British Columbia, Canada), where the viscosity of water was 1. The osmolality was measured by freezing point depression, using a micro-osmometer (Model 3MO; Advanced Instruments; Norwood, MA). It is possible for a contrast medium to have a high osmolality and low ionic content if the solute does not dissociate. Similarly, ionic content and density, a determinant of viscosity, are not related. Density reflects the concentration and atomic number of the solute.

Data Analysis: To test if a bolus injection of either saline solution, Hexabrix, Omnipaque 300, or MD-76 increased blood flow, baseline and peak coronary blood flow (mL/min) were analyzed using a 1-tailed, paired t test. A two-way analysis of variance (S-PLUS 4; MathSoft; Cambridge, MA) was used to compare changes in baseline coronary blood flow and coronary vascular resistance caused by the infusion of LNNA and L-arginine; coronary vascular resistance was calculated as mean systemic arterial pressure/coronary blood flow. After applying a square root transformation of the data, the absolute and percentage change in coronary vascular resistance were analyzed using a repeated measures analysis of variance (SPSS 7.5; SPSS; Chicago, IL) in which there was one repeating factor and one grouping factor. Density was measured by weighing, in duplicate, 1 mL of each of the substances. The pH of each agent was measured using a blood gas analyzer (ABL 30 Acid Base Analyzer; Radiometer; Copenhagen, Denmark). The viscosity was measured against water at 37°C using a viscosimeter (model VVR 66044-007; Ostwald; Vancouver, British Columbia, Canada), where the viscosity of water was 1. The osmolality was measured by freezing point depression, using a micro-osmometer (Model 3MO; Advanced Instruments; Norwood, MA). It is possible for a contrast medium to have a high osmolality and low ionic content if the solute does not dissociate. Similarly, ionic content and density, a determinant of viscosity, are not related. Density reflects the concentration and atomic number of the solute.

Results

Coronary Blood Flow: For each experimental condition, there were no differences between baseline values of coronary blood flow (mL/min) measured just before the injection of saline solution, Omnipaque 300, Hexabrix, or MD-76, respectively (Table 1). Baseline coronary blood flow before the injection of MD-76 was higher during control than after the infusion of LNNA and L-arginine, but was not different before injection of saline solution, Hexabrix, or Omnipaque 300. Baseline coronary blood flow was not affected by the infusion of LNNA or L-arginine (Table 1).

Coronary Vascular Resistance: Baseline coronary vascular resistance increased on the infusion of LNNA (p < 0.001). After the infusion of L-arginine, baseline coronary vascular resistance was less than it was during the infusion of LNNA (p < 0.02; Table 2), but it remained greater than the control value (p < 0.01). For each experimental condition, there were no differences between baseline values of coronary vascular resistance measured just before the injection of saline solution, Omnipaque 300, Hexabrix, or MD-76, respectively.

Changes in coronary vascular resistance (mean ± SE) are shown in Figure 1. The values shown were obtained before and after the injection of each of the four agents for control, LNNA, and L-arginine periods. In comparison to control, the change in resistance was greater after LNNA for all four agents (p < 0.01). The change in coronary vascular resistance (Fig 1) was variable in response to injection of each of the four agents: the greatest change was observed after injection of MD-76 for all three experimental conditions, and this decrease was greater than that caused by each of the other three agents (p < 0.01). Injection of saline solution caused less of a decrease in resistance than did the other three agents (p < 0.01). During control, the decrease in resistance after Hexabrix was greater than after Omnipaque 300; however, during LNNA infusion, there was no difference in the decrease in resistance between Omnipaque 300 and Hexabrix. There was no difference in coronary artery blood flow or coronary vascular resistance between the pigs.

Table 1—Baseline Coronary Blood Flow (mL/min)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline Solution</th>
<th>Hexabrix</th>
<th>Omnipaque 300</th>
<th>MD-76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 11)</td>
<td>26 ± 6</td>
<td>27 ± 4</td>
<td>26 ± 3</td>
<td>26 ± 5†</td>
</tr>
<tr>
<td>LNNA (n = 11)</td>
<td>23 ± 4</td>
<td>22 ± 4</td>
<td>22 ± 4</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>L-arginine (n = 9)</td>
<td>23 ± 5</td>
<td>23 ± 5</td>
<td>23 ± 4</td>
<td>22 ± 6</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± SD.
†p < 0.001, greater than LNNA and L-arginine.

Table 2—Baseline Coronary Vascular Resistance (mm Hg/mL/min)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline Solution</th>
<th>Hexabrix</th>
<th>Omnipaque 300</th>
<th>MD-76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 11)</td>
<td>3.8 ± 1.2</td>
<td>3.6 ± 0.8</td>
<td>3.7 ± 0.8</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td>LNNA (n = 11)</td>
<td>5.1 ± 0.9†</td>
<td>5.3 ± 1.2†</td>
<td>5.2 ± 1.0†</td>
<td>5.3 ± 1.0†</td>
</tr>
<tr>
<td>L-arginine (n = 9)</td>
<td>4.6 ± 1.1‡</td>
<td>4.6 ± 1.0‡</td>
<td>4.7 ± 0.8‡</td>
<td>4.8 ± 1.1‡</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± SD.
†p < 0.01, greater than control.
‡p < 0.001, greater than control.
§p < 0.02, L-arginine less than LNNA.
that received the high or low dose of LNNA (Table 3). Although L-arginine did not restore coronary vascular resistance to control values, the absolute values of coronary vascular resistance were less ($p < 0.01$) than during LNNA. However, the change in coronary vascular resistance remained higher than during the control period.

**Hemodynamics and Blood Gas Tensions:** There was no difference in values for heart rate or pulmonary arterial pressure for any of the three experimental conditions (Table 4). Arterial BP increased after the infusion of LNNA ($p < 0.001$) and remained higher than control after the infusion of L-Arginine ($p < 0.02$). Cardiac output was less than control after the infusion of LNNA and L-arginine ($p < 0.01$). There was a twofold increase in mean systemic vascular resistance after the infusion of LNNA ($p < 0.01$); this did not return to the control value after the infusion of L-arginine. Hemodynamic parameters were affected more by the higher dose of LNNA ($10^{-2}$ mol/L vs $10^{-3}$ mol/L; Table 4). When compared to their control value, cardiac output was lower and pulmonary arterial and systemic arterial BP were greater ($p < 0.001$) in the pigs that received the high dose of LNNA compared to those that received the low dose. Similarly, when compared to their control value, mean systemic vascular resistance was higher in the pigs that received the high dose of LNNA ($p < 0.05$). Arterial blood gas tensions remained constant throughout the experiment.

**Physicochemical Properties:** The physicochemical properties of each injectate are shown in Table 5.

### Table 3—Hemodynamics and Vascular Resistance: High vs Low Dose of LNNA*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Systemic Arterial BP mm Hg</th>
<th>$P_{pa}$ mm Hg</th>
<th>CO mL/min</th>
<th>CVR mm Hg/mL/min</th>
<th>SVR mm Hg/mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 5)</td>
<td>95 ± 9</td>
<td>18.6 ± 0.9</td>
<td>3,290 ± 760</td>
<td>3.70 ± 0.91</td>
<td>0.029 ± 0.01</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>92 ± 6</td>
<td>17.5 ± 2.5</td>
<td>3,420 ± 820</td>
<td>3.53 ± 0.85</td>
<td>0.027 ± 0.01</td>
</tr>
<tr>
<td>LNNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 5), $10^{-2}$ mol/L</td>
<td>127 ± 9†</td>
<td>20.0 ± 0.8†</td>
<td>1,560 ± 340†</td>
<td>5.35 ± 1.29</td>
<td>0.067 ± 0.01†</td>
</tr>
<tr>
<td>(n = 6), $10^{-3}$ mol/L</td>
<td>101 ± 6</td>
<td>17.5 ± 2.5</td>
<td>2,970 ± 800</td>
<td>4.52 ± 1.08</td>
<td>0.035 ± 0.01</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± SD; values recorded during stable conditions; CO = cardiac output; CVR = coronary vascular resistance; $P_{pa}$ = pulmonary arterial pressure; SVR = systemic vascular resistance.

†$p < 0.001$, different from their control values.
There was a significant correlation between the percentage decrease in coronary vascular resistance and osmolality ($r = 0.99$). There was also a significant correlation between osmolality and pH; however, the range was very small and the correlation was not as close ($r = 0.95$).

**Discussion**

Results from this study show that both high and low osmolar ionic and nonionic contrast media cause an decrease in coronary vascular resistance and increase in coronary artery blood flow (not shown in results; Fig 1; Table 3). The magnitude of the response appears to be related to the osmolality of the contrast agent: the greater the osmolality, the greater the decrease in coronary vascular resistance (Table 5). Although the infusion of the NO synthase inhibitor LNNA caused an increase in baseline coronary vascular resistance (Table 2), it did not attenuate the vasodilatory response to the infusion of the contrast agents, suggesting that unlike the bronchial vasculature, the dilatory response of the coronary vasculature to hyperosmolar stimuli is not mediated by NO. We combined the data for the high- and low-dose LNNA because there was no suggestion of a dose-response relationship between the concentration of LNNA and the magnitude of the radiocontrast-induced vasodilatation. The mean increases in coronary blood flow in response to saline solution, Hexabrix, Omnipaque 300, and MD-76 during the infusion of high-dose LNNA were 4.4, 4.8, 7.6, and 14.9 mL/min, respectively; the increases in response to the same agents during the infusion of the low-dose of LNNA were 1.7, 3.0 5.0 and 14.2 mL/min, respectively. There was no significant difference for any agent; in fact, the change in blood flow tended to be greater during the infusion of high-dose LNNA.

Our results confirm and extend those reported recently by Ishizaka and Kuo, but are in contrast to those of Vacca et al. Ishizaka and Kuo used an in vitro approach to examine the mechanism of the vasodilatory response of the coronary vasculature to hyperosmolar stimuli. They perfused isolated porcine coronary arteries that were between 60 and 100 μm in diameter, and measured the vasodilatory response to changes in the osmolality of the solution applied to the ablumenal surface of the vessels. Although the addition of hyperosmolar solutions of sucrose and glucose caused vascular dilation that was dependent on the presence of an intact vascular endothelium, inhibitors of NO synthase and arachidonic acid metabolism failed to attenuate the response. However, intralumenal (but not ablumenal) administration of potassium chloride or the K(ATP)-channel inhibitor, glibenclamide, significantly attenuated the vasodilation induced by osmolar solutions. Ishizaka and Kuo concluded that the vasodilation was related in some way to the opening of K(ATP) channels in the vascular endothelium, but they could not determine how this happened. Vacca et al studied the effect of intracoronary infusion of hyperosmolar solutions of sucrose and glucose caused vascular dilation that was dependent on the presence of an intact vascular endothelium, inhibitors of NO synthase and arachidonic acid metabolism failed to attenuate the response. However, intralumenal (but not ablumenal) administration of potassium chloride or the K(ATP)-channel inhibitor, glibenclamide, significantly attenuated the vasodilation induced by osmolar solutions. Ishizaka and Kuo concluded that the vasodilation was related in some way to the opening of K(ATP) channels in the vascular endothelium, but they could not determine how this happened. Vacca et al studied the effect of intracoronary infusion of hyperosmolar solutions of sucrose and glucose caused vascular dilation that was dependent on the presence of an intact vascular endothelium, inhibitors of NO synthase and arachidonic acid metabolism failed to attenuate the response. However, intralumenal (but not ablumenal) administration of potassium chloride or the K(ATP)-channel inhibitor, glibenclamide, significantly attenuated the vasodilation induced by osmolar solutions. Ishizaka and Kuo concluded that the vasodilation was related in some way to the opening of K(ATP) channels in the vascular endothelium, but they could not determine how this happened. Vacca et al studied the effect of intracoronary infusion of hyperosmolar solutions of sucrose and glucose caused vascular dilation that was dependent on the presence of an intact vascular endothelium, inhibitors of NO synthase and arachidonic acid metabolism failed to attenuate the response. However, intralumenal (but not ablumenal) administration of potassium chloride or the K(ATP)-channel inhibitor, glibenclamide, significantly attenuated the vasodilation induced by osmolar solutions. Ishizaka and Kuo concluded that the vasodilation was related in some way to the opening of K(ATP) channels in the vascular endothelium, but they could not determine how this happened.

<table>
<thead>
<tr>
<th>injectate</th>
<th>Density, g/mL</th>
<th>pH</th>
<th>Relative Viscosity</th>
<th>Osmolality, osm/kg</th>
<th>CVR, % Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline solution</td>
<td>1</td>
<td>6.5</td>
<td>1</td>
<td>308</td>
<td>30</td>
</tr>
<tr>
<td>Hexabrix</td>
<td>1.380</td>
<td>6.6</td>
<td>9</td>
<td>666</td>
<td>41</td>
</tr>
<tr>
<td>Omnipaque 300</td>
<td>1.392</td>
<td>6.8</td>
<td>10.3</td>
<td>898</td>
<td>74</td>
</tr>
<tr>
<td>MD-76</td>
<td>1.495</td>
<td>6.9</td>
<td>11.5</td>
<td>1,898</td>
<td>141</td>
</tr>
</tbody>
</table>

*Values are presented as No.; see Figure 3 legend for expansion of abbreviations.
the infusion. The increase in coronary blood flow was not affected by blockade of adrenergic or cholinergic receptors. However, in contrast to the results of our present study and those of Ishizaka and Kuo, the coronary vasodilation was abolished by the intracoronary administration of the NO-synthase inhibitor, L-NAME.

In our study, we administered two concentrations of the NO synthase inhibitor, LNNA, directly into the coronary artery; neither concentration produced significant alterations in coronary blood flow, but both resulted in an increase in coronary vascular resistance, systemic arterial BP, and systemic vascular resistance (Table 4). Although the higher dose of LNNA had a greater effect on these variables than the lower dose, the data were combined for comparison with the control values. We attempted to reverse the increase in coronary vascular resistance produced by LNNA by the administration of L-arginine. However, two of the pigs who received the high dose of LNNA developed hemodynamic instability, and it was not possible to stabilize them after the infusion of L-arginine. In addition, three pigs whose data are not included in any of the results died after receiving the high dose of LNNA. It is possible that this hemodynamic instability was due to the formation of platelet thrombi and subsequent coronary vascular occlusion as a result of the inhibition of NO synthase and enhanced platelet adhesiveness (in the pigs that died, coronary blood flow decreased to < 2 mL/min despite a measurable, although reduced, systemic arterial BP).

The discrepancies in results between our study and that of Vacca et al may be related to one or a number of differences between the experimental protocols. These include the age of the pigs, the hyperosmolar agents that were used, and the NO-synthase inhibitors that were used. In our study, the pigs were 25 kg juveniles (3 months old), whereas in the study of Vacca et al, the pigs were 70 kg adults; it is possible that the response of coronary vessels to hyperosmolar stimuli may be different between adult and juvenile pigs. In our study, we infused hypertonic radiocontrast agents, whereas Vacca et al infused hypertonic saline solution. However, we do not think that this is a likely explanation for the observed differences because in a previous study there was a direct correlation between the osmolality of the injectate and changes in bronchial arterial blood flow when hyperosmolar dextrose or contrast agents were injected. Although the percentage increase in coronary blood flow in response to the hyperosmolar injectate was similar in magnitude in both studies, the duration of the response differed. Vacca et al observed that the greater the osmolality, the more prolonged the vascular response. However, we observed that coronary blood flow returned to baseline within ~5 min. Another possible explanation for the different results is the difference in the concentration of the NO-synthase inhibitors (LNNA and L-NAME) that were used. Again, this is an unlikely explanation because we gave two different concentrations of LNNA (one higher and one lower than that given by Vacca et al), and we found no difference in the response to hyperosmolar stimuli with either dose. Vacca et al administered 0.005 mmol/kg of L-NAME, and we gave 0.02 mmol/kg of LNNA to five pigs and 0.002 mmol/kg of LNNA to six pigs. Finally, because we did not test whether acetylcholine-induced vasodilation was completely inhibited by LNNA 10^-3 and LNNA 10^-2, we cannot completely rule out that the release of NO did not partially contribute to the contrast-induced coronary vasodilatation.

**Conclusion**

Although NO is a major determinant of basal coronary vascular tone, the substantial vasodilation, observed in response to the injection of contrast media into the coronary vasculature, appears to be unrelated to the NO-synthase pathway in juvenile pigs. A more likely mechanism is that the vasodilation is related to the opening of K(ATP) channels in the vascular endothelium, as suggested by Ishizaka and Kuo. The opening of these channels could be mediated by the bolus of hyperosmolar solution or by a transient change in the shear stress on the endothelial cells. In a previous study involving the vasodilatory response to radiocontrast agents in the bronchial circulation, we showed that bronchial arterial vasodilatation was most closely related to the osmolality and not to the density of the bolus injectate. Since shear is directly related to density, we concluded that the pertinent stimulus in the bronchial circulation was osmolality; however, in that study, NO-synthase inhibitors attenuated the response considerably, indicating that endothelial release of NO was a mechanism of vasodilatation. If the response in the coronary vessels is due to opening of K(ATP) channels in the vascular endothelium, the vasodilatory response would persist, even in the presence of a dysfunctional endothelial NO-synthase pathway. Whether this would be true in the presence of generalized endothelial dysfunction awaits the determination of the role of other endothelial mechanisms, such as K(ATP) channels.

**References**

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