Coronary Vascular Responsiveness to Adenosine Is Impaired Additively by Blockade of Nitric Oxide Synthesis and a Sulfonylurea

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Objectives. We sought to define effects of glibenclamide, a sulfonylurea known to block ATP-dependent potassium (K\textsubscript{ATP}) channels, and N\textsuperscript{\textbullet}-nitro-L-arginine methyl ester (L-NAME), an L-arginine analog known to block nitric oxide (NO) synthesis, on coronary vascular responsiveness to adenosine.

Background. The role of adenosine in coronary flow regulation becomes increasingly important when K\textsubscript{ATP} channel function or NO synthesis is impaired. Both variables are potentially altered in patients with coronary artery disease taking a sulfonylurea.

Methods. Dose-response curves relating coronary conductance to plasma adenosine concentration were obtained by using intra-coronary infusions of adenosine (10 to 1,000 µg/min) in chronically instrumented dogs.

Results. ED\textsubscript{50}, the plasma concentration of adenosine needed to produce 50% of the maximal increase in conductance under baseline conditions, increased threefold after either 1 or 10 mg/kg of L-NAME. ED\textsubscript{50} also increased in response to glibenclamide in a dose-related fashion (5.7-fold increase per 1 mg/kg body weight of glibenclamide). Effects of combined blockade of K\textsubscript{ATP} channels and NO synthesis were additive, with increases in ED\textsubscript{50} as high as 15-fold. Both L-NAME and glibenclamide increased systemic pressure and reduced coronary conductance, confirming the roles of NO and K\textsubscript{ATP} channels in regulating coronary and systemic vascular tone under rest conditions as well as during stress.

Conclusions. Coronary vascular responsiveness to adenosine is blunted in vivo by both L-NAME and glibenclamide. Effects of the sulfonylurea and blockade of NO synthesis are additive and can limit coronary vasodilation as well as other responses involving K\textsubscript{ATP} channels and NO.

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It is now established that nitric oxide (NO) and ATP-dependent potassium (K\textsubscript{ATP}) channels play important roles in coronary flow regulation. NO exerts a tonic vasodilating effect on conduit and resistance vessels in humans (1,2) and experimental animals (3–5). Blockade of NO synthesis with L-arginine analogs blunts reactive hyperemia (6,7) and can limit flow increases during exercise in the presence of a coronary stenosis (7). Likewise, blockade of K\textsubscript{ATP} channels (glyburide) can reduce rest coronary flow (8–10), diminish flow increases during reactive hyperemia (11,12) and limit flow responses to exercise (10). At the highest rates of administration studied in intact animals, glibenclamide can reduce rest flow sufficiently to induce myocardial ischemia (13).

Adenosine, the prototypic agent used to produce maximal coronary vasodilation, assumes increasing importance when K\textsubscript{ATP} channel function or NO synthesis is impaired. When K\textsubscript{ATP} channels are blocked with a sulfonylurea such as glibenclamide, endogenously produced adenosine plays a pivotal role in maintaining rest flow in the presence of coronary stenoses and in effecting coronary vasodilation during a stress such as exercise (14). Because vasodilator responses to adenosine are partly mediated by endothelial release of NO (15), it is also possible that coronary vascular responses to adenosine are blunted in the presence of endothelial dysfunction. However, existing studies of effects of blockade of NO synthesis on responses to adenosine (16–18) have given variable results.

Clinical interest in administration of sulfonylureas relates primarily to the use of these agents in the treatment of non-insulin–dependent diabetes mellitus. Engler and Yellon (19) have suggested that K\textsubscript{ATP} channel blockade, by adversely affecting myocardial preconditioning responses to ischemia, could have contributed to the increased cardiovascular mortality reported in patients treated with tolbutamide in the University Group Diabetes Program study. Although effects of sulfonylureas on coronary vasodilator responses are also of interest, experimental studies of the coronary circulation have employed doses of these agents that are at least an order of magnitude larger than those used clinically. In addition, coronary vasoregulation is likely to be affected by the endothelial dysfunction occurring in both diabetes and coronary artery
Abbreviations and Acronyms

- ANCOVA = one-way analysis of covariance
- CI = confidence interval
- ED50 = the plasma concentration of adenosine needed to produce 50% of the maximal increase in conductance under baseline conditions
- KATP = ATP-dependent potassium
- LAD = left anterior descending coronary artery
- LCx = left circumflex coronary artery
- L-NAME = N\textsuperscript{-}nitro-\textit{l}-arginine methyl ester
- L-NMMA = N\textsuperscript{-}nitro-methyl\textit{l}-arginine
- NO = nitric oxide

Disease. Endothelial dysfunction could potentially accentuate coronary vascular effects of K\textsubscript{ATP} channel blockade by blunting alternative vasodilating mechanisms, that is, endothelial production of NO.

The present study was undertaken to determine whether, and to what degree, coronary vascular responsiveness to adenosine is altered by blockade of NO synthesis and K\textsubscript{ATP} channels, both singly and in combination. Effects of glibenclamide and N\textsuperscript{-}nitro-\textit{l}-arginine methyl ester (L-NAME), an \textit{l}-arginine analog known to block NO synthesis, were examined in vivo in chronically instrumented dogs, thereby avoiding effects of anesthesia or thoracotomy, or both. To simulate the clinical situation, glibenclamide was administered systemically rather than by intracoronary infusion, and in smaller doses than previously employed experimentally. The lower dose levels also avoided possible effects of glibenclamide unrelated to K\textsubscript{ATP} channels (20).

Methods

Studies were performed in male or female mongrel dogs by using procedures and protocols concordant with the Position of the American Heart Association on Research Animal Use.

Experimental preparation. Nineteen male or female dogs weighing 23 to 44 kg were fitted with instruments after an overnight fast and the usual period of on-site conditioning. After premedication with Innovar-Vet (fentanyl, 0.4 mg/ml, and droperidol, 20 mg/ml, 1 ml intramuscularly), anesthesia was induced with sodium thiopental (20 mg/kg body weight intravenously) or methohexital (11 mg/kg). After intubation and institution of mechanical ventilation, a surgical plane of anesthesia was maintained with a gas mixture of nitrous oxide (40%) and halothane (1% to 2%). A left thoracotomy was performed under sterile conditions and plastic catheters were placed into the descending aorta and left atrium. A Konigsberg micromanometer was inserted into the left ventricle through the left ventricular apex. The proximal portion of the left circumflex coronary artery (LCx, n = 15) or left anterior descending coronary artery (LAD, n = 4) was fitted with a Transonic Systems transit time ultrasound flow probe (model 3RB on the LCx, model 2SB on the LAD) and a hydraulic occluder. A 22-gauge angiocatheter connected to small-bore tubing was inserted into the artery distal to the flow probe. Bipolar pacing leads were sewn onto the left atrial appendage. Potential collateral flow through epicardial vessels was limited by ligating visible anastomoses between branches of the LCx and LAD. Catheters and wires were exteriorized through the chest wall and placed in an external jacket. The chest was closed and the pneumothorax evacuated. Keflin (30 to 35 mg/kg intravenously or intramuscularly twice daily) was administered for 1 to 3 days postoperatively, and narcotic analgesia (Buprenex, 0.01 to 0.02 mg/kg subcutaneously every 8 to 12 h) was given as needed for postoperative discomfort. Catheters were flushed with saline solution and filled with heparin every 1 to 2 days (10,000 U/ml for the LCx catheter and 1,000 U/ml for other catheters). Aspirin (325 mg orally) was given daily beginning on postoperative day 3. The dogs were allowed to recover for ≥7 days before studies were initiated.

Study procedure. The dogs were studied while lightly sedated with Innovar-Vet and resting in a sling to which they had previously been acclimated. Catheters used for pressure measurement were connected to strain gauge transducers (Viggo-Spectramed P23XL), with the zero reference level taken at midchest. The strain gauges and the left ventricular micromanometer were connected to transducer preamplifiers (model 1147, Gould, Inc.). Ultrasound flow probes were connected to a Transonic Systems model T-206 meter; the zero flow levels were established by momentary coronary artery occlusion.

Dose-response relations for adenosine were obtained by infusing adenosine dissolved in isotonic saline solution into the LCx (or LAD) and measuring steady state LCx (or LAD) flows at infusion rates of 10, 30, 60, 100, 300, 600 and 1,000 μg/min; infusion volumes were between 0.1 and 1.0 ml/min. Glibenclamide (Sigma Chemical) was prepared by dissolving 1.0 mg/kg in ~0.2 ml of dimethyl sulfoxide and 50 ml of normal saline solution containing 3 mEq of sodium bicarbonate. L-NAME was dissolved in isotonic saline solution.

Studies were performed on two separate days in 10 dogs. On one day adenosine dose-response relations were obtained under baseline conditions and after 0.3 and an additional 0.7 mg/kg of glibenclamide given intravenously. On the other day, dose-response relations were obtained under baseline conditions, after 1 mg/kg of L-NAME given into the left atrium, and after 0.3 and an additional 0.7 mg/kg of glibenclamide. Atrial pacing at 120 beats/min was used on both days. Blood glucose levels were monitored periodically; in four dogs, an intravenous infusion of 5% dextrose in water was initiated to ensure that glucose levels remained above 3.3 μmol/liter. In two dogs studied with graded intracoronary infusions of acetylcholine (1 to 20 μg/min), L-NAME reduced peak coronary flow responses by 66% and 68%, respectively. In the final three dogs studied, plasma samples were obtained after each glibenclamide dose (on the day L-NAME was not given) for high performance liquid chromatography measurements of glibenclamide levels (National Medical Services, Inc.).

To evaluate responses to a larger dose of L-NAME, adenosine dose-response relations were obtained in nine additional dogs (all with LCx catheters) under baseline conditions and
of the form: \( f(x) \)

Adenosine dose-response data were fitted to a sigmoid model to L-NAME and glibenclamide were therefore evaluated from tables and logarithmic values for ED\(_{50}\) on the two study days both L-NAME and glibenclamide, baseline hemodynamic variables were compared by paired \( t \) tests and their reproducibility was estimated separately. Responses to L-NAME were evaluated by comparing values before and after administration of L-NAME with the use of paired \( t \) tests. Responses to glibenclamide were evaluated separately on the two study days, by using linear regression; on days when L-NAME was not given, only the baseline values for that day were used in calculating the responses to glibenclamide.

In dogs given only L-NAME, hemodynamic data and logarithmic values for ED\(_{50}\) before and after L-NAME were compared by paired \( t \) tests. All statistical tests were two-tailed, with \( p < 0.05 \) considered statistically significant. The software package used for data analysis was SYSTAT, version 5.03.

### Results

**Responses to glibenclamide and L-NAME.** Baseline values of arterial pH, pCO\(_2\), pO\(_2\) and hemoglobin averaged 7.36 ± 0.01, 37 ± 1.5 mm Hg, 88 ± 2.3 mm Hg and 11.4 ± 0.7 g/dl, respectively. Values for log (ED\(_{50}\)) hemodynamic variables and blood glucose are shown in Table 1. Plasma glibenclamide concentrations averaged 1.54 \( \mu \)mol/liter (range 1.40 to 1.70) after 0.3 mg/kg and 6.14 \( \mu \)mol/liter (range 4.86 to 6.88) after the total dose of 1.0 mg/kg.

Adenosine dose-response curves from individual dogs are shown in Figures 1 (day of study with glibenclamide alone) and 2 (day of study with L-NAME and glibenclamide). Logarithmic values of ED\(_{50}\) are shown as a function of glibenclamide dose in Figure 3. Results of ANCOVA indicated that L-NAME (1.0 mg/kg) significantly increased log (ED\(_{50}\)) from 0.79 ± 0.09 to 1.26 ± 0.09 (adjusted mean ± SEM, \( p = 0.005 \)). This represents a threefold increase in the ED\(_{50}\) plasma concentration of adenosine, from 6.17 \( \mu \)mol/liter (95% confidence interval (CI) 3.88 to 9.77) to 18.2 \( \mu \)mol/liter (95% CI 11.4 to 29.0). The log (ED\(_{50}\)) response to glibenclamide was similar on

### Table 1. Log(ED\(_{50}\)), Hemodynamic and Blood Glucose Values Before and After Glibenclamide and L-NAME in 10 Dogs

<table>
<thead>
<tr>
<th></th>
<th>Log(ED(_{50})) (( \mu )mol/liter)</th>
<th>Aortic Pressure (mm Hg)</th>
<th>Coronary Flow (ml/min)</th>
<th>Coronary Conductance Index (ml/min per mm Hg)</th>
<th>Peak Left Ventricular ( dP/dt^* ) (mm Hg/s)</th>
<th>Blood Glucose† (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study day 1</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.54 ± 0.15</td>
<td>95 ± 3.7</td>
<td>44 ± 6.4</td>
<td>0.47 ± 0.06</td>
<td>2,015 ± 143</td>
<td>7.9 ± 1.1</td>
</tr>
<tr>
<td>GB, 0.3 mg/kg</td>
<td>0.72 ± 0.15</td>
<td>100 ± 3.6</td>
<td>41 ± 5.6</td>
<td>0.42 ± 0.06</td>
<td>1,953 ± 106</td>
<td>6.5 ± 0.7</td>
</tr>
<tr>
<td>GB, 1.0 mg/kg</td>
<td>1.22 ± 0.09</td>
<td>102 ± 4.0</td>
<td>37 ± 5.2</td>
<td>0.36 ± 0.05</td>
<td>1,983 ± 71</td>
<td>5.1 ± 0.4</td>
</tr>
<tr>
<td><strong>Study day 2</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.49 ± 0.18</td>
<td>91 ± 3.3</td>
<td>48 ± 7.0</td>
<td>0.53 ± 0.07</td>
<td>1,792 ± 191</td>
<td>5.8 ± 0.3</td>
</tr>
<tr>
<td>L-NAME</td>
<td>0.86 ± 0.21</td>
<td>109 ± 4.7</td>
<td>48 ± 7.4</td>
<td>0.45 ± 0.07</td>
<td>1,900 ± 158</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>GB, 0.3 mg/kg</td>
<td>1.16 ± 0.20</td>
<td>113 ± 4.3</td>
<td>48 ± 7.4</td>
<td>0.43 ± 0.07</td>
<td>1,815 ± 117</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>GB, 1.0 mg/kg</td>
<td>1.68 ± 0.23</td>
<td>109 ± 4.1</td>
<td>47 ± 6.9</td>
<td>0.44 ± 0.06</td>
<td>1,786 ± 113</td>
<td>5.1 ± 0.4</td>
</tr>
</tbody>
</table>

* \( n = 8 \), † \( n = 9 \). Values are mean ± SEM. \( dP/dt^* \) = first derivative of left ventricular pressure; ED\(_{50}\) = the plasma concentration of adenosine needed to produce 50% of the maximal increase in conductance under baseline conditions; GB = glibenclamide; L-NAME = N\(^\text{\*}\)-nitro-L arginine methyl ester.
both study days, that is, with and without L-NAME (Figure 3). The regression coefficient for glibenclamide dose was 0.76 ± 0.11 (p < 0.0001), indicating a 5.7-fold increase in ED\textsubscript{50} per 1 mg/kg of glibenclamide (95% CI 3.3 to 10.0). Thus, ED\textsubscript{50} was increased 15-fold by the combination of L-NAME and glibenclamide.

Aortic pressure increased in response to L-NAME (18 ± 3.1 mm Hg, p = 0.0003), and to glibenclamide when the sulfonylurea was given in the absence of L-NAME (6.8 ± 2.8 mm Hg per 1.0 mg/kg of glibenclamide, p < 0.0001). However, when glibenclamide was given after L-NAME, aortic pressure did not change further. Coronary conductance showed a similar but directionally opposite pattern, decreasing in response to L-NAME (0.53 ± 0.07 to 0.45 ± 0.07 ml/min per mm Hg, p < 0.03) and to glibenclamide in the absence of L-NAME (−0.097 ± 0.017 ml/min per mm Hg per 1.0 mg/kg of glibenclamide, p < 0.0001), but not changing further when glibenclamide was given after L-NAME. Coronary flow decreased in response to glibenclamide alone (−6.92 ± 1.47 ml/min per 1.0 mg/kg of glibenclamide, p < 0.0001), but it was unchanged by L-NAME or glibenclamide after L-NAME.

Response to larger dose of L-NAME. Baseline values of arterial pH, pCO\textsubscript{2}, pO\textsubscript{2}, and hemoglobin in dogs given 10 mg/kg of L-NAME averaged 7.39 ± 0.01, 33 ± 1.9 mm Hg, 84 ± 2.3 mm Hg and 10.2 ± 0.5 g/dL, respectively. After L-NAME, the dose-response relation relating LCx conductance to plasma adenosine concentration shifted to the right in each case, with log (ED\textsubscript{50}) increasing from 0.56 ± 0.16 to 1.06 ± 0.22 (p = 0.005) (Fig. 4). This represents a 3.2-fold increase in ED\textsubscript{50} from 3.64 μmol/liter (95% CI 1.59 to 8.34) to 11.5 μmol/liter (95% CI 3.62 to 36.6), and is similar to that observed after 1 mg/kg of L-NAME. Peak values of coronary conductance did not change systematically (1.15 ± 0.06 vs. 1.13 ± 0.04 ml/min per mm Hg, p = 0.79). L-NAME increased mean aortic pressure by 20 ± 6 mm Hg (105 ± 4.2 to 125 ± 4.1 mm Hg, p < 0.01) and decreased LCx conductance by 19 ± 3.1% (0.37 ± 0.04 to 0.30 ± 0.04 ml/min per mm Hg, p < 0.05). These responses were also similar to those after 1 mg/kg of L-NAME.

Discussion

The present study demonstrates that coronary vascular responsiveness to adenosine is impaired by both L-NAME and glibenclamide and that effects of the two agents are additive. The physiologic relevance of the findings is supported by their occurrence in an in vivo setting in which mechanisms that could potentially counteract effects of sulfonylureas or blockade of NO synthesis, or both, remained available.
K_{\text{ATP}} channel–adenosine interactions and effects of glibenclamide. The reductions in coronary vascular responsiveness to adenosine after glibenclamide in this study are similar in direction but smaller in magnitude than those reported by groups that administered larger doses of glibenclamide systematically. Belloni and Hintze (23) found that 2.0 mg/kg of glibenclamide produced a 10-fold increase in the ED_{50} for changes in coronary conductance produced by intravenous adenosine in chronically instrumented dogs with muscarinic and beta-adrenergic receptors blocked pharmacologically. Clayton et al. (12) reported that increments in coronary flow in response to intracoronary adenosine in open chest dogs were blunted to a still greater degree after 3 mg/kg of glibenclamide. Taken together, these reports and the present study indicate that glibenclamide blunts adenosine-induced coronary vasodilation in a dose-dependent manner over a wide range of sulfonylurea concentrations.

Although plasma or serum glibenclamide levels have not been reported in previous in vivo studies of coronary vascular responses, the larger systemic doses employed in previous studies must have resulted in higher blood levels than in the present study. Perfusate concentrations of glibenclamide in most studies of isolated hearts, arteries or myocytes have also exceeded the plasma or serum levels reported in man, often by one to two orders of magnitude. Although comparisons with levels achieved in patients involve a variety of factors that cannot be assessed fully, our glibenclamide values after administration of 0.3 mg/kg may be of interest in relation to those reported in diabetic patients, whose daily doses of glibenclamide can be as high as 20 mg. After a single oral dose of 2.5 mg of glibenclamide, Ikegami et al. (25) found serum levels to average 0.28 μmol/liter (138 ng/ml), with individual patients showing levels as high as 0.47 μmol/liter. After 5 mg, other investigators (26–31) observed average levels of 0.28 to 0.73 μmol/liter. Coppack et al. (32) reported values averaging 0.31, 0.50 and 0.88 μmol/liter, respectively, after single 5-, 10- and 20-mg doses. Information about steady state levels in patients is limited and includes rather wide variability. In patients taking 2.5 to 25 mg of glibenclamide daily, Sartor et al. (28) reported a poor correlation between prescribed dose and serum levels measured just before the usual daily dose. Individual levels varied from 0 to 1.52 μmol/liter and averaged 0.48 μmol/liter. Huupponen et al. (33) also found a wide range of values in patients taking 10 ± 5 (mean ± SD) mg daily.

Comparisons with studies employing continuous intracoronary infusion of glibenclamide in intact animals are more difficult because of uncertainty about first-pass extraction of the sulfonylurea and increasing plasma levels with time. Rest coronary flow in intact animals is decreased regularly by an intracoronary dose of 50 μg/kg per min (9,10,14). This dose also alters responses to exercise in the absence as well as the presence of coronary stenosis (10). Intracoronary infusions of glibenclamide sufficient to produce coronary artery concentrations of 55 to 80 μmol/liter (27,000 to 39,000 ng/ml) compromise rest flow to the point of ischemia (13).

The mechanism of interaction between adenosine and K_{\text{ATP}} channels remains incompletely understood, particularly under conditions in which intracellular ATP levels are normal (23,24). Data from Song et al. (20) confirm that K_{\text{ATP}} channel behavior is affected by levels of glibenclamide similar to those in the present study, that is, 1 μmol/liter of glibenclamide abolished the outward K^+ current activated by pinacidil, a K_{\text{ATP}} channel opener, in guinea pig atrial myocytes. The study of Song et al. also indicates that the higher concentrations of glibenclamide employed in several previous studies can have effects that are not specific to K_{\text{ATP}} channels; that is, 30 μmol/liter of glibenclamide blocked K^+ current activated by a muscarinic agonist and a guanosine triphosphate analog as well as adenosine.

**Effects of l-arginine analogs.** Although coronary vascular effects of NO were first appreciated in conduit arteries, NO is now known to dilate coronary resistance as well as epicardial vessels in both experimental animals (3–7) and humans (1,2). Jones et al. (34) reported that L-NAME constricts small arteries and arterioles >100 μm, and Kuo et al. (35) demonstrated that L-NMMA, another l-arginine analog, abolishes flow-related vasodilation in porcine arterioles. In addition, as discussed by Smith and Canty (6) and Duncker and Bache (7), several studies have shown that l-arginine analogs blunt one or more aspects of the reactive hyperemia response after transient coronary occlusion.

The present data demonstrate that L-NAME reduces coronary vascular responsiveness to adenosine by itself, and accentuates glibenclamide-induced reductions in adenosine responsiveness. These findings may relate to observations, recently summarized by Smits et al. (15), indicating that vasodilator responses to adenosine are mediated in part by endothelial release of NO. The present findings are also compatible with the finding of Rubanyi and Vanhoutte (36) that adenosine-induced relaxation in canine coronary artery rings is reduced when endothelium is removed, and with studies (37,38) indicating the presence of A_2 purinoceptors on endothelium as well as vascular smooth muscle. Sensitivity to adenosine could be affected by any change in adenosine uptake by endothelial cells or erythrocytes induced by l-NAME (or glibenclamide). A further possibility suggested by Kontos and Wei (39) is that arginine analogs directly influence the function of K_{\text{ATP}} channels. In any event, the present data indicate that adenosine-related effects of l-NAME are maximal at a dose of 1 mg/kg, which is an order of magnitude less than that used in many earlier studies.

Our l-NAME data also clarify previously reported responses to adenosine. Parent et al. (16) found that Nω-nitro-l-arginine attenuated flow responses to bolus intracoronary administration of 100 ng/kg of adenosine in chronically instrumented dogs, whereas Canty and Schwartz (17) did not observe a reduction in steady state mean flow during an intracoronary infusion of 500 μg/min of adenosine after l-NAME. Similarly, Gurevicius et al. (18) found that l-NAME and l-NMMA did not reduce the canine flow response to intracoronary adenosine, 800 μg/min, in open chest dogs. The adenosine dose in the study of Parent et al. is comparable to
the lower doses used in the present study, which also were responsive to blockade of NO synthesis. The adenosine doses in the studies of Canty and Schwartz and Gurevicius et al. are at the higher end of the present adenosine dose range. Effects of reduced endothelial production of NO on vasodilator responses to adenosine bear on the clinical use of acetylcholine/adenosine flow ratios to identify abnormalities in coronary endothelial function (40). These measurements presume that maximal coronary vasodilation to adenosine is not affected by endothelial dysfunction and can be used as a reference to identify a reduced response to receptor-mediated stimulation of NO production. The present data emphasize the importance of using sufficiently large doses of intracoronary adenosine to ensure that maximal vasodilatation is reached. Adenosine is typically infused at rates calculated to achieve final blood concentrations of 10^{-6}, 10^{-5} and 10^{-4} mol/liter (0.267, 2.67 and 26.7 μg/ml) (40). Because these calculations are based on estimated rest values of coronary flow, and flow normally can increase 4- to 5-fold in response to adenosine, actual concentrations are proportionately lower. The use of sufficient infusion rates to demonstrate that a maximal vasodilating effect has been achieved seems advisable, particularly when endothelium-mediated vasodilator mechanisms may be compromised.

Clinical implications. The systematic reductions in coronary conductance observed in response to L-NNAME and glibenclamide confirm that NO and K_{ATP} channels each play a significant role in maintaining coronary vasodilator tone, even under rest conditions. Endogenous adenosine production becomes particularly important in maintaining rest coronary flow in the presence of coronary stenosis and in effecting coronary vasodilation during periods of increased myocardial oxygen demand (14). The additive impairment in adenosine-related vasodilation caused by blockade of NO synthesis and sulfonamide administration is therefore most likely to be relevant to patients with coronary artery disease and impaired endothelial function given a sulfonamide. A glibenclamide-related accentuation of impaired coronary vasodilation would be expected to be dose dependent and of greatest concern during situations potentially leading to demand-induced ischemia. To our knowledge, however, direct assessments of coronary vascular responses to sulfonamides in patients with coronary artery disease are not yet available.

References

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