Effect of ATP-Sensitive Potassium Channel Inhibition on Coronary Metabolic Vasodilation in Humans

H.M. Omar Farouque, Stephen G. Worthley, Ian T. Meredith

Objective—Experimental evidence indicates that ATP-sensitive potassium (K<sub>ATP</sub>) channels regulate coronary blood flow (CBF). However, their contribution to human coronary metabolic vasodilation is unknown.

Methods and Results—Seventeen patients (12 male, age 58±10 years) were studied. Coronary hemodynamics were assessed before and after K<sub>ATP</sub> channel inhibition with subselective intracoronary glibenclamide infused at 40 µg/min in an angiographically smooth coronary artery after successful percutaneous coronary intervention to another vessel. Metabolic vasodilation was induced by 2 minutes of rapid right ventricular pacing. Coronary blood velocity was measured with a Doppler guidewire and CBF calculated. The time course of hyperemia was recorded for 2 minutes after pacing, and hyperemic volume was estimated from the area under the flow-versus-time curve (AUC). Compared with vehicle infusion (0.9% saline), glibenclamide reduced resting CBF by 9% (P=0.04) and increased resting coronary vascular resistance (CVR) by 15% (P=0.03). Glibenclamide reduced pacing-induced peak CBF (50.8±6.8 versus 42.0±5.4 mL/min, P=0.001), peak CBF corrected for baseline flow (25.1±4.6 versus 17.6±3.1 mL/min, P=0.01), and increased minimum CVR (2.6±0.3 versus 3.1±0.3 mm Hg/mL per minute, P=0.002). Compared with vehicle, glibenclamide reduced total AUC at 2 minutes (3535±397 versus 3027±326 mL, P=0.001).

Conclusions—Vascular K<sub>ATP</sub> channels appear to be involved in functional coronary hyperemia after metabolic stimulation.


Key Words: blood flow ■ ion channels ■ sulfonylurea ■ vasoconstriction ■ coronary circulation

The increase in coronary blood flow (CBF) associated with increased myocardial metabolism is commonly referred to as metabolic vasodilation. Several vasodilator substances produced by the myocardium or from the vascular endothelium have been proposed as mediators of metabolic vasodilation including adenosine, nitric oxide, vasodilator prostanoids, potassium and hydrogen ions, and carbon dioxide. Despite a growth in knowledge on the factors that mediate metabolic vasodilation, a precise understanding of this complex phenomenon is still elusive.

Over the past decade, attention has focused on the contribution of the metabolically regulated ATP-sensitive potassium (K<sub>ATP</sub>) ion channel to the control of coronary vascular tone. These channels are found in the vasculature and may provide a link between cellular metabolism and vascular tone through its effect on membrane potential. Studies in animals suggest that vascular K<sub>ATP</sub> channels are involved in the regulation of resting CBF, reactive coronary hyperemia, and metabolic coronary vasodilation. We have recently demonstrated a role for K<sub>ATP</sub> channels in the regulation of resting blood flow in the human coronary circulation. However, the importance of K<sub>ATP</sub> channels in mediating metabolic coronary vasodilation in humans has not previously been assessed. Accordingly, we sought to determine the contribution of K<sub>ATP</sub> channels to pacing-induced metabolic coronary vasodilation in humans.

Methods

Seventeen patients undergoing elective percutaneous coronary intervention for single-vessel coronary artery disease were studied and their clinical characteristics are displayed in Table 1. Subjects had at least 1 angiographically smooth or mildly stenosed (<20% diameter stenosis) major epicardial coronary artery that had not been previously instrumented. Coronary flow studies were performed in vessels fulfilling these criteria after successful percutaneous intervention to an unrelated stenotic coronary artery. Patients with unstable angina, significant valvular heart disease, left ventricular ejection fraction <50%, and renal or hepatic disease were excluded. Thirteen patients (age 57±10 years, 10 male) received intracoronary glibenclamide and 4 patients (age 62±8 years, 2 male) participated in reproducibility experiments. The study was approved by the Southern Health Human Research Ethics Committee, and written informed consent was obtained before cardiac catheterization.

Intracoronary Doppler Flow Study and Metabolic Vasodilation

Intracoronary Doppler flow velocimetry was performed as described previously using a 0.014-inch Doppler guidewire (FloWire; CardioMetrics, EndoSonics). The study vessel was the left anterior descending coronary artery in 8 patients, circumflex coronary artery in 8 patients, and the right coronary artery in 1 patient. Coronary metabolic vasodilation was achieved by rapid right ventricular pacing, and hyperemic volume was estimated from the area under the flow-versus-time curve (AUC). Compared with vehicle infusion (0.9% saline), glibenclamide reduced baseline CBF by 9% (P=0.04) and increased resting coronary vascular resistance (CVR) by 15% (P=0.03). Glibenclamide reduced pacing-induced peak CBF (50.8±6.8 versus 42.0±5.4 mL/min, P=0.001), peak CBF corrected for baseline flow (25.1±4.6 versus 17.6±3.1 mL/min, P=0.01), and increased minimum CVR (2.6±0.3 versus 3.1±0.3 mm Hg/mL per minute, P=0.002). Compared with vehicle, glibenclamide reduced total AUC at 2 minutes (3535±397 versus 3027±326 mL, P=0.001).
Experimental Protocol

The study design is outlined in Figure 1. Vasoactive medication was discontinued at least 12 hours before the procedure. All patients received oral doses of aspirin (300 mg) and clopidogrel (300 mg) before percutaneous coronary intervention, and studies were conducted in a quiet environment with the lights dimmed. Coronary flow velocity was allowed to return to a stable baseline between vehicle and glibenclamide infusions. Systemic venous blood samples were taken before and after glibenclamide infusion for measurement of plasma glucose, insulin, and C-peptide. Reproducibility of the pacing protocol was assessed in 4 subjects who underwent 2 separate periods of ventricular pacing but received vehicle infusion only.

Statistical Analysis

Clinical characteristics are expressed as mean±SD. Other values are reported as mean±SEM. Hemodynamic and biochemical data were analyzed using the 2-tailed paired Student t test. Paired data that did not conform to a normal distribution were analyzed using the Wilcoxon signed-rank test. Two-way repeated measures analysis of variance was used to analyze pacing-induced changes in CBF from baseline before and during glibenclamide. During both saline and glibenclamide infusions, pacing-related hemodynamic parameters were compared with the resting state immediately before initiation of pacing. Peak hyperemic CBF (peak CBF) and hyperemic volume induced by pacing (AUC) were corrected for changes in baseline flow immediately before pacing by subtracting the latter value. P<0.05 was considered statistically significant.

Results

Pacing Reproducibility

Four subjects underwent 2 periods of pacing to assess reproducibility of the pacing protocol. Pacing induced reproducible hyperemic responses (Table I, available online at http://atvb.ahajournals.org).

Effect of Glibenclamide on Resting Coronary Tone

Intraprocedural glibenclamide infusion at 40 μg/min was not associated with changes in heart rate (69±3 versus 68±3 bpm, P=NS), mean arterial pressure (109±5 versus 108±5 mm Hg, P=NS), or rate-pressure product (9808±665 versus 9898±658 bpm×mm Hg, P=NS) compared with vehicle infusion. A small vasoconstrictor effect was noted with a 4% reduction in conduit coronary artery diameter compared with baseline (2.23±0.09 versus 2.15±0.09 mm; P=0.04; Figure 2). Glibenclamide did not significantly alter resting CBF velocity (22.8±2.4 versus 21.9±2.5 cm/second; P=0.20; Figure 2). Compared with vehicle, glibenclamide reduced resting CBF by 9% (P=0.035; Figure 2) and increased coronary vascular resistance by 15% (P=0.028; Figure 2).

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Total Group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Systemic hypertension</td>
</tr>
<tr>
<td>Family history of IHD</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>N of risk factors per patient*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.

IHD indicates ischemic heart disease; LDL, low-density lipoprotein.

*Indicates the 5 mentioned risk factors, obesity (body mass index >30kg/m²), and age >60 years.

Clinical drug and glibenclamide infusion. A small vasoconstrictor effect was noted with a 4% reduction in conduit coronary artery diameter compared with baseline (2.23±0.09 versus 2.15±0.09 mm; P=0.04; Figure 2). Glibenclamide did not significantly alter resting CBF velocity (22.8±2.4 versus 21.9±2.5 cm/second; P=0.20; Figure 2). Compared with vehicle, glibenclamide reduced resting CBF by 9% (P=0.035; Figure 2) and increased coronary vascular resistance by 15% (P=0.028; Figure 2).
Effect of Glibenclamide on Pacing-Induced Hyperemia

Rapid ventricular pacing during vehicle infusion did not alter coronary artery diameter measured at 2 minutes after cessation of pacing compared with baseline (2.23±0.09 to 2.23±0.10 mm). However, pacing during glibenclamide infusion resulted in a trend to epicardial vasoconstriction (2.15±0.09 to 2.09±0.09 mm, \( P=0.05 \)). Glibenclamide also resulted in a trend to reduction of peak CBF velocity compared with vehicle (42.8±4.4 versus 40.6±4.2 cm/sec; \( P=0.12 \)). Pacing increased CBF by 100% during vehicle infusion, from 25.4±3.8 to 50.8±6.8 mL/min. Notably, glibenclamide attenuated the increase in CBF induced by pacing to 74% from 24.2±3.6 to 42.0±5.4 mL/min (\( P=0.03 \); analysis of variance; Figure II, available online at http://atvb.ahajournals.org). Peak CBF was 17% less during glibenclamide infusion compared with vehicle infusion (\( P=0.001 \); Table 2). Compared with vehicle infusion, the functional hyperemic volume induced by pacing at 2 minutes was reduced by glibenclamide (3535±397 versus 3027±326 mL; \( P=0.001 \), Table 2). When corrected for changes in baseline coronary flow before the initiation of pacing, the differences in peak CBF and hyperemic volume remained significant (Table 2). Coronary vascular resistance decreased by 49% from 5.2±2.6 to 2.6±0.3 mm Hg/mL per minute during pacing with vehicle (\( P<0.001 \)). During glibenclamide infusion, the reduction in CVR was attenuated to a 43% decrease, from 5.5±0.7 to 3.1±0.3 mm Hg/mL per minute. Minimum CVR after pacing was 19% greater with glibenclamide (\( P=0.002 \); Table 2). Mean heart rate, arterial pressure, and rate-pressure product were similar during each of the pacing runs (Table 2).

Humoral Parameters

There were no changes in plasma glucose levels before and after glibenclamide infusion (5.6±0.4 versus 5.6±0.4 mmol/L; \( P=\text{NS} \)). However, there was an increase in plasma insulin concentrations from 10.3±6.1 to 16.4±3.9 mU/L (\( P=0.06 \)). C-peptide levels were also increased from 0.9±1.0 to 1.1±0.1 nmol/L (\( P=0.04 \)), indicating that the increase in insulin during the study was related to pancreatic insulin secretion.

Discussion

In this study, we confirm that coronary vascular K<sub>ATP</sub> channel inhibition produces an increase in basal coronary vascular tone in angiographically smooth coronary arteries of patients with coronary atherosclerosis. Importantly, we demonstrate for the first time to our knowledge that coronary vascular K<sub>ATP</sub> channel inhibition with glibenclamide results in attenuation of the coronary vasodilation induced by pacing.

**TABLE 2. Effect of Pacing on Systemic and Coronary Hemodynamic Parameters**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Glibenclamide</th>
<th>( P )</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>151±1</td>
<td>151±1</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>108±5</td>
<td>110±5</td>
<td>NS</td>
</tr>
<tr>
<td>Rate-pressure product (bpm · mm Hg)</td>
<td>16658±992</td>
<td>16934±976</td>
<td>NS</td>
</tr>
<tr>
<td>Peak CBF (mL/min)</td>
<td>50.8±6.8</td>
<td>42.0±5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔPeak CBF (mL/min)</td>
<td>25.1±4.6</td>
<td>17.6±3.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Minimum CVR (mm Hg/mL per min)</td>
<td>2.6±0.3</td>
<td>3.1±0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>AUC (mL)</td>
<td>3535±397</td>
<td>3027±326</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔAUC (mL)</td>
<td>834±223</td>
<td>418±154</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ΔPeak CBF was calculated by subtracting baseline flow from peak CBF to account for differences in baseline CBF. AUC indicates area under the flow–time curve over 2 minutes and is a reflection of the hyperemic volume induced by pacing. ΔAUC refers to the hyperemic volume corrected for baseline flow. \( P \) values refer to paired comparisons of the listed variables between vehicle (saline) and glibenclamide infusions.
tachycardia in humans. This was evident as a modest reduction of peak CBF and in the hyperemic volume after rapid cardiac pacing during glibenclamide infusion. These findings imply that K\textsubscript{ATP} channels contribute not only to resting coronary tone but also to metabolic vasodilation in the human coronary circulation.

**K\textsubscript{ATP} Channels and Resting Coronary Tone**

ATP-sensitive potassium channels are involved in mediating basal coronary vascular tone in animals. In vivo studies in the canine and porcine coronary circulations indicate that K\textsubscript{ATP} channel blockade with glibenclamide reduces basal CBF by 7% to 52% \cite{1-4,11-13,18}. The large variation in the magnitude of reduction in CBF documented in these studies is probably related to differences in the experimental model used and the dose and method of administration of glibenclamide. Our findings of a significant 9% reduction in resting CBF and a 15% increase in CVR are consistent with the body of published literature from nonhuman species and humans \cite{7}.

**K\textsubscript{ATP} Channels and Coronary Metabolic Vasodilatation**

Rapid cardiac pacing has been used to study metabolic coronary vasodilation, avoiding the confounding effects of catecholamine and autonomic influences associated with exercise. Katsuda et al demonstrated that coronary vascular K\textsubscript{ATP} channel blockade reduced pacing hyperemia by 21% in conscious dogs and 8% in anesthetized dogs \cite{5}, with estimated intracoronary glibenclamide concentrations of 2 to 8 μmol/L and 2 to 12 μmol/L, respectively. Our findings in humans with comparable estimated glibenclamide levels are consistent with these data. However, other studies using pacing in the presence and absence of adrenoceptor agonists have not supported a role for K\textsubscript{ATP} channels in these processes \cite{14,19}.

Although the evidence implicating K\textsubscript{ATP} channels in the regulation of resting CBF is convincing, this is not the case for exercise-induced coronary metabolic vasodilatation. Studies in conscious chronically instrumented dogs indicate that glibenclamide does not attenuate the exercise-induced increase in CBF. However, peak CBF at each level of exercise was reduced compared with corresponding measurements during vehicle infusion.

Bache et al have examined the interplay between K\textsubscript{ATP} channels and other vasodilator systems including adenosine and nitric oxide by simultaneously blocking the effects of these mediators in the canine coronary circulation. They postulated that preservation of exercise related flow-reserve after K\textsubscript{ATP} channel inhibition alone might be caused by a greater dependence on alternative vasodilator pathways. The collective blockade of K\textsubscript{ATP} channels, adenosine receptors, and nitric oxide synthesis resulted in minimal exercise-induced coronary metabolic vasodilatation. However, data from the laboratory of Feigl et al using a similar canine model have been at variance with these findings. The reason for these discrepancies may be related to methodological differences such as the use of intracoronary versus intravenous glibenclamide. Taken together, these studies suggest that K\textsubscript{ATP} channels are not essential elements of the coronary vascular response to exercise in the normal porcine or canine heart.

The activity of K\textsubscript{ATP} channels in vascular tissue may be different in disease states. The role of coronary vascular K\textsubscript{ATP} channels has been studied in canine hearts with pressure-overload hypertrophy. In this model, K\textsubscript{ATP} channel blockade significantly blunted the exercise-induced increase in CBF, unlike the situation in normal hearts. A similar situation exists in the maintenance of basal coronary tone among hypertensive rats with hypertrophied hearts \cite{15}. Although our findings in the coronary circulation of patients with atherosclerosis differ from the observations in healthy animal hearts, they are compatible with results of studies performed in diseased hearts. Furthermore, K\textsubscript{ATP} channels contribute to coronary vasodilation during reactive hyperemia and when coronary artery pressure decreases. Therefore, activation of K\textsubscript{ATP} channels may be of particular importance in maintaining myocardial perfusion in patients with coronary stenoses and ischemia.

**Role of Other Vasoactive Pathways in Humans**

In the current study, K\textsubscript{ATP} channel inhibition reduced coronary metabolic vasodilation by a modest degree, implying that other mechanisms also contribute to metabolic vasodilation. Previous studies have examined the role of nitric oxide in metabolic coronary vasodilation, with most of these reports demonstrating that epicardial flow-mediated dilation is nitric oxide dependent \cite{24,25-26}. However, microvascular vasodilation in response to pacing may not be dependent on nitric oxide \cite{23}. Data from our laboratory have also emphasized a role for vasodilator prostanooids in the regulation of metabolic vasodilatation \cite{8}.

Adenosine has been proposed as an important endogenous mediator of metabolic coronary vasodilation. However, published studies in humans have not provided convincing evidence for this theory. Adenosine receptor blockade with methylxanthines did not alter pacing-induced coronary flow-velocity in patients with nonstenotic coronary arteries, although volumetric flow was not calculated in this study. In another study, coronary venous adenosine levels did not increase with cardiac pacing in subjects without risk factors and angiographically smooth coronary arteries, implying that endogenous adenosine does not contribute to coronary vasodilation in this setting. Edlund et al, using coronary sinus thermodilution, showed a reduction in exercise-induced coronary hyperaemia with intravenous theophylline. However, their conclusion that adenosine contributes to metabolic vasodilatation has been disputed by others. Soluble factors such as bradykinin, endothelin, and endothelium-derived hyperpolarizing factor may also be involved. It is evident that multiple elements including chemical and physical factors play a role; however, further study is required to correlate their contribution and interactions to this complex process.

**Methodological Considerations**

We observed a small increase in plasma insulin and C-peptide levels in keeping with the known insulinotropic action of sulfonylureas produced by pancreatic K\textsubscript{ATP} channel inhibition. Insulin is known to possess vasodilator properties, which in theory may offset the vasoconstrictor effect observed during glibenclamide infusion. However, it is unlikely that the small
changes in insulin would have had a significant impact as its vasoactive effects are delayed in onset and occur at higher concentrations than the low physiological levels observed during this study.\textsuperscript{32}

Ethical considerations preclude the study of subjects without coronary pathology, thus subjects enrolled for this study had atherosclerotic coronary disease. As such they are likely to have had impairment in endothelium-dependent vasodilatation, as suggested by the lack of epicardial coronary dilatation with pacing during vehicle infusion. It is possible that a functional endothelium may have offset the vasoconstrictor response to \(K_{\text{ATP}}\) channel inhibition, and that our results may not be applicable in healthy patients with normal coronary arteries.

The magnitude of contribution by \(K_{\text{ATP}}\) channels to metabolic vasodilation may have been underestimated in this study because of submaximal metabolic vasodilation. Moreover, a higher dose or longer glibenclamide infusion may have resulted in greater vascular \(K_{\text{ATP}}\) channel inhibition.\textsuperscript{33} The fact that a slightly greater reduction in basal CBF was noted in our previous study is consistent with this notion.\textsuperscript{7} Study subjects were premedicated with low-dose oral aspirin (300 mg) before catheterization; however, this is unlikely to have induced changes in CBF. Oral aspirin doses as high as 650 mg do not appear to alter resting CBF or pacing-induced hyperemia in patients with coronary disease.\textsuperscript{34} Coronary vascular effects of prostanoïd inhibition are seen with aspirin doses in the anti-inflammatory dose range.\textsuperscript{8}

The precise mechanisms leading to activation of vascular \(K_{\text{ATP}}\) channels during increased metabolic demand could not be determined from this study. Although adenosine has been proposed as a mediator of metabolic vasodilation that may act through \(K_{\text{ATP}}\) channels, this may not be the case in the human circulation.\textsuperscript{7,28,35} Indeed \(K_{\text{ATP}}\) channels can be activated by many different stimuli including altered cyclic nucleotide levels, certain ions, pH levels, and other endogenous vasoactive substances.\textsuperscript{19} It is conceivable that these stimuli may play a role in activating \(K_{\text{ATP}}\) channels during increased metabolic vasodilation.

**Clinical Implications**

Activation of \(K_{\text{ATP}}\) channels may provide an important compensatory mechanism to maintain myocardial perfusion in the presence of coronary artery stenoses. In this regard, potassium channel openers have an important role in the management of patients with ischemic heart disease. The antianginal efficacy of drugs in this class is related to coronary vasodilation produced by the activation of coronary vascular \(K_{\text{ATP}}\) channels. The potential efficacy of this class of drugs has been borne out by the results of the randomized IONA study, which indicate improved cardiovascular outcomes for patients with chronic stable angina treated with the \(K_{\text{ATP}}\) channel opener, nicorandil.\textsuperscript{36}

In summary, we have demonstrated that \(K_{\text{ATP}}\) channels are involved in the regulation of resting CBF and metabolic coronary vasodilation in the human coronary circulation of patients with atherosclerosis. This was evidenced by a reduction in basal CBF and pacing-induced hyperemia after intracoronary infusion of the \(K_{\text{ATP}}\) channel inhibitor, glibenclamide. Our findings suggest that \(K_{\text{ATP}}\) channels are active in the human coronary circulation and underscore the importance of ion channels in the maintenance of vascular tone.

**Acknowledgments**

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**References**

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Coronary Blood Flow (ml/min)

Rest Pacing

$P = 0.03$
On-Line Figure Legend

I. The time-course of hyperemia after the cessation of pacing is displayed in this figure from an individual patient. Compared to vehicle infusion ( ), glibenclamide ( ) reduced the hyperemic flow response after pacing. The area under the flow-time curve (AUC) was calculated over a 120 second time period.

II. The effect of vehicle and glibenclamide infusions on pacing-induced coronary blood flow. Coronary blood flow during vehicle infusion is indicated by the solid line, and glibenclamide infusion by the dashed line. Data are mean ± SEM. *P<0.05 (ANOVA).
I

![Graph showing coronary blood flow over time](image)
TABLE I. PACING REPRODUCIBILITY

<table>
<thead>
<tr>
<th></th>
<th>Pacing Run #1</th>
<th>Pacing Run #2</th>
</tr>
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<tbody>
<tr>
<td>Peak CBF (mL/min)</td>
<td>47.0 ± 11.8</td>
<td>45.9 ± 12.8</td>
</tr>
<tr>
<td>Minimum CVR (mmHg/mL/min)</td>
<td>2.8 ± 0.8</td>
<td>3.8 ± 0.9</td>
</tr>
<tr>
<td>Hyperemic volume at 2 minutes (mL)</td>
<td>4478 ± 1272</td>
<td>4377 ± 1347</td>
</tr>
<tr>
<td>Rate-pressure product (bpm • mmHg)</td>
<td>15410 ± 1112</td>
<td>15746 ± 1123</td>
</tr>
</tbody>
</table>

There were no statistically significant differences in coronary hemodynamic variables or rate-pressure product between the two pacing runs.