**Brief Definitive Communication**

**Glibenclamide, a Putative ATP-Sensitive K⁺ Channel Blocker, Inhibits Coronary Autoregulation in Anesthetized Dogs**

Takahiro Narishige, Kensuke Egashira, Yutaka Akatsuka, Yousuke Katsuda, Kohtaro Numaguchi, Makoto Sakata, Akira Takeshita

We tested the hypothesis that ATP-sensitive K⁺ channels are involved in the mechanism mediating coronary autoregulation in open-chest dogs. We perfused the left anterior descending coronary artery with arterial blood from an extracorporeal circuit and measured steady-state coronary blood flow (CBF) with stepwise changes in coronary perfusion pressure (CPP) between 50 and 150 mm Hg during an intracoronary infusion of vehicle or glibenclamide (a putative blocker of ATP-sensitive K⁺ channels). CBF was relatively stable over CPP between 50 and 110 mm Hg during vehicle infusion, indicating the presence of autoregulation at the CPP range. During glibenclamide infusion (10 μg · min⁻¹ · kg⁻¹), CBF progressively decreased with reduction in CPP below 110 mm Hg, whereas the CPP-CBF relation at CPP above 110 mm Hg was not altered by glibenclamide. The autoregulation index [1−(ΔF/P)/(ΔP/P)], where F indicates CBF and P indicates CPP] was greater than 0 over the CPP range between 50 and 100 mm Hg during vehicle infusion and was less than 0 during glibenclamide infusion. Glibenclamide did not alter systemic arterial pressure, heart rate, left ventricular pressure, and changes in regional myocardial oxygen consumption associated with changes in CPP. In the absence of glibenclamide, the CPP-CBF relation was reproducible in the repeated studies for time control. These results suggest that ATP-sensitive K⁺ channels play an important role in mediating coronary autoregulation at the lower range of CPP in the blood-perfused dog heart. (Circ Res. 1993;73:771-776.)

**KEY WORDS** • coronary autoregulation • glibenclamide • ATP-sensitive K⁺ channels

Coronary autoregulation is characterized by the intrinsic ability of the coronary circulation to maintain a relatively stable blood flow supply in the face of changes in perfusion pressure over a wide range.¹⁻⁴ It has been postulated that coronary autoregulation may be linked to local myocardial metabolism.¹⁻⁴ For a mediator of local metabolic control of coronary blood flow (CBF), adenosine has been postulated.¹⁻⁴ However, it appears that adenosine does not play an important role in coronary autoregulation, since adenosine deaminase or adenosine receptor antagonists that blunted coronary reactive hyperemia had no effects on coronary autoregulation.⁵,⁶

Recent studies have suggested that changes in myocardial oxygen and carbon dioxide tensions may mediate coronary autoregulation.⁶⁻⁹ It has been shown that there is a good correlation between myocardial oxygen tension and basal coronary vascular conductance¹⁻² and that coronary venous oxygen tension strongly and inversely correlates with the degree of coronary autoregulation.⁶⁻⁷ However, it is not understood whether coronary autoregulation is mediated directly by changes in tissue oxygen tension or by some mediating factors, such as ATP-sensitive K⁺ channels (Kₐ ATP channels) that may be altered by changes in tissue oxygen tension.

Recently, several studies have suggested that Kₐ ATP channels may be importantly involved in the control of CBF.¹⁰⁻¹⁴ Daut et al¹¹ have shown that hypoxic or ischemic vasodilation of the coronary artery is prevented by glibenclamide (a putative blocker of Kₐ ATP channels). Komaru et al¹² also have demonstrated that coronary epicardial microvascular dilation associated with proximal coronary artery stenosis is abolished by the topical superfusion of glibenclamide. However, they did not examine the autoregulation of CBF with changes in coronary perfusion pressure (CPP) before and after intracoronary administration of glibenclamide. It is possible that reduced myocardial oxygen tension following reduction in CPP activates Kₐ ATP channels of vascular smooth muscle cell directly or indirectly through changes in metabolic substance(s). In the present study, we aimed to determine if Kₐ ATP channels were involved in the mechanism mediating coronary autoregulation. For this purpose, we examined the effects of glibenclamide on the steady-state CPP-CBF relation in the anesthetized blood-perfused dog heart.

**Materials and Methods**

**Animal Preparation**

Adult mongrel dogs (16 to 23 kg) of either sex were anesthetized with an intravenous administration of so-
dium pentobarbital (25 mg/kg) and ventilated with a positive-pressure respirator. In each animal, arterial pH, PO₂, and PCO₂ were maintained within the physiological range (pH, 7.30 to 7.50; PO₂, 80 to 110 mm Hg; PCO₂, 25 to 45 mm Hg). Supplemental oxygen was given if needed. Sodium bicarbonate solution was administered intravenously to correct metabolic acidosis if present. A left thoracotomy was performed, and the heart was suspended in a pericardial cradle. A heating pad was used to regulate the body temperature of the animals.

A proximal segment of the left anterior descending coronary artery was cannulated with a 2.5-mm polyethylene cannula and perfused with blood through an extracorporeal circuit from the left carotid artery. Heparin (250 U/kg by bolus followed by 100 U/kg per hour) and indomethacin (3 mg/kg) were administrated intravenously to prevent blood coagulation and platelet aggregation. Blood from the carotid artery was delivered to a reservoir 50 mL in volume by a digital roller pump (Masterflex 7524-10, Cole-Parmer Instrument Co, Chicago, Ill). Blood in the reservoir was filtered and drained into the left anterior descending coronary artery. CPP at the tip of the cannula was measured through an inner tube that was connected to a Statham strain gauge manometer (model P23Db), and CPP was kept at a given level over a wide range of CBF by carefully controlling pump speed. By use of a heat exchanger, the temperature of blood in the reservoir was maintained at approximately 37°C. A cannulating-type electromagnetic flow probe was placed in the external circuit between the reservoir and the cannula, and blood flow to the left anterior descending coronary artery was measured by connecting the flow probe to a flowmeter (model MVF-2000, Nihon-Kohden Inc, Tokyo, Japan). A 3F catheter-tipped pressure transducer (model PC 350, Millar Instruments, Houston, Tex) was inserted into the left ventricular (LV) cavity through the left atrial appendage for the measurement of LV pressure. The positive first derivative of LV pressure (LV dP/dt) was obtained by electronic differentiation. These hemodynamic variables were continuously monitored using a polygraph system (Nihon-Kohden) and recorded on a multichannel recorder.

Myocardial oxygen consumption (MVO₂) of the myocardium perfused by the left anterior descending coronary artery was determined in some animals. The great cardiac vein was punctured, and a miniature tube was advanced into the anterior interventricular vein for venous blood sampling. It is reported that venous drainage to the great cardiac vein comes exclusively from the left anterior descending coronary artery.①5 Arterial blood was sampled from the cannula inserted into the left anterior descending coronary artery. Oxygen saturation of arterial and venous blood samples was measured by a calibrated oxygen analyzer (Unistat Oximeter, American Optical, Buffalo, NY). The hemoglobin content in venous blood was measured. MVO₂ was calculated by the following formula: MVO₂ (mL/min)=CBF (mL/min)×0.0136×Hb (g/dL) [Sao₂ (%) − Svor (%)]/100, where Hb is hemoglobin, and SaO₂ and SvO₂ indicate oxygen saturation of coronary arterial and venous blood, respectively.

Glibenclamide (Sigma Chemical Co, St Louis, Mo) was dissolved in 4% glucose solution containing 0.01N NaOH and was infused into the extracorporeal circuit at a dose of 10 μg·min⁻¹·kg⁻¹. In a preliminary study, we examined the effect of glibenclamide at this dose on coronary vasodilation evoked with the K₆₅₄ channel opener pinacidil (n=5). The percent increases in CBF by intracoronary pinacidil at 10, 30, and 100 μg/min (90±11%, 117±28%, and 366±50%, respectively) were significantly attenuated during simultaneous infusion of glibenclamide (11±8%, 13±4%, and 128±32%, respectively). Glibenclamide also reduced the peak to baseline CBF ratio of reactive hyperemia after a 20-second coronary occlusion from 5.4±1.0 to 3.2±1.0 but did not change the increase in CBF evoked by acetylcholine at 3 μg (154±40% and 148±29%).

Experimental Protocol

Protocol 1. Eleven dogs were used in this protocol. The steady-state CPP-CBF relation was obtained before (vehicle infusion) and after intracoronary infusion of glibenclamide at a dose of 10 μg·min⁻¹·kg⁻¹, whereas heart rate, aortic pressure, LV pressure, LV dP/dt, and CBF in the left anterior descending artery were measured. After the animals were stabilized for 30 minutes at CPP of 100 mm Hg, which was nearly equal to the mean arterial pressure in each animal, vehicle solution (1 mL/min) was infused into the extracorporeal circuit and thus into the left anterior descending coronary artery. Two minutes after the beginning of vehicle infusion, CPP was increased or decreased in a stepwise fashion by 10 mm Hg increments from 100 to 150 mm Hg or from 100 to 50 mm Hg, respectively. The order of the increase or decrease in CPP was randomized. CBF was allowed to stabilize at least for 2 minutes before CPP was changed to the next level. After the hemodynamics were allowed to stabilize for 30 minutes at CPP of 100 mm Hg, glibenclamide (1 mL/min) was continuously infused into the extracorporeal circuit, and the steady-state CPP-CBF relation was obtained during glibenclamide infusion in the same way as during vehicle infusion.

In 6 of the 11 dogs, steady-state arterial and coronary venous blood were sampled simultaneously at CPP of 130, 100, and 70 mm Hg. MVO₂ was determined at each level of CPP during vehicle and glibenclamide infusion. In 5 dogs, the left circumflex coronary artery blood flow was also measured using an electromagnetic flow probe.

Protocol 2. Four dogs were used in this protocol. To examine the possibility of the time-related change in autoregulation, we determined the CPP-CBF relation twice in a 30-minute interval, while aortic pressure, heart rate, LV pressure, and LV dP/dt were continuously monitored and recorded.

Quantification of Autoregulation

The degree of autoregulation was quantified by calculating the closed-loop gain of the system, i.e., an autoregulation index, as described by Norris et al: autoregulation index=1−(ΔF/F)/(ΔP/P), where F is the steady-state CBF at a given CPP (P) and ΔF is the change in CBF resulting from a 10 mm Hg change in CPP (ΔP). With this approach, unity indicates perfect autoregulation, the values between 0 and 1 indicate the presence of autoregulation, and values of <0 indicate the absence of autoregulation.
Statistical Analysis

Only the dogs that showed autoregulation of CBF during vehicle infusion (autoregulation index of >0.2 by reducing CPP from 100 to 70 mL/min) were enrolled in the study with glibenclamide. The dog preparations that had basal CBF values of ≥60 or ≤15 mL/min were excluded from analysis.

Values are expressed as mean±SEM. When the CPP-CBF relation and the CPP–autoregulation index relation were compared before and after glibenclamide, analysis of variance (ANOVA) for repeated measures was used. If ANOVA showed a significant difference, paired t tests were used for comparisons of CBF or autoregulation index values at a given CPP before and after glibenclamide. When changes in hemodynamic variables were compared at a given CPP, paired t tests were used.

Results

Fig 1 shows the effect of glibenclamide (10 μg·min⁻¹·kg⁻¹) on the CBF-CPP relation for the CPP range between 50 and 150 mm Hg in 11 dogs. During vehicle infusion, CBF was relatively stable at CPP values ranging from 50 to 110 mm Hg. The autoregulation index within this CPP range was greater than 0, indicating the presence of autoregulation. In contrast, the autoregulation index was <0 at CPP of ≥120 mm Hg, indicating the absence of autoregulation at higher CPP values.

During glibenclamide infusion, CBF linearly decreased with the decrease in CPP from 100 to 50 mm Hg, whereas the CPP-CBF relation at the CPP range from 100 to 150 mm Hg was not altered by glibenclamide. There was a significant difference in the CPP-CBF relation during vehicle and glibenclamide infusion (P<.01 by ANOVA). CBF values at CPP of 50, 70, 60, and 50 mm Hg during glibenclamide infusion were significantly smaller (P<.01) than those during vehicle infusion, indicating that the CPP-CBF relation at the lower CPP range was shifted downward by glibenclamide. There was also a significant difference in the CPP–autoregulation index relation during vehicle and glibenclamide infusion (P<.01 by ANOVA). The autoregulation indexes at CPP of ≤100 mm Hg were <0 during glibenclamide infusion.

The Table summarizes the hemodynamic variables at CPP of 70, 100, and 130 mm Hg during vehicle and glibenclamide infusion. Glibenclamide did not alter hemodynamic variables such as mean arterial pressure, heart rate, LV end-diastolic pressure, and positive peak LV dp/dt. During vehicle infusion, CBF, coronary venous oxygen saturation, and calculated MVO₂ were relatively constant. CBF and coronary venous oxygen saturation values at CPP of 100 mm Hg during glibenclamide infusion did not significantly differ from those during vehicle infusion. The increase in CPP from 100 to 130 mm Hg did not alter CBF and coronary venous oxygen saturation, whereas the decrease in CPP from 100 to 70 mm Hg caused a greater decrease in CBF and coronary venous oxygen saturation during glibenclamide than during vehicle infusion (P<.01). Calculated myocardial MVO₂ at CPP of 70, 100, and 130 mm Hg did not significantly differ during vehicle and glibenclamide infusion. In addition, there was no detectable change in the left circumflex CBF at CPP of 70, 100, and 130 mm Hg during vehicle and glibenclamide infusion.

Fig 2 shows the results of the time-control experiment in another group of four dogs in which the steady-state CPP-CBF relation was determined twice during vehicle infusion. The CPP-CBF relation and the autoregulation indexes at each CPP were comparable between the first and second experiment.

Discussion

The major finding of this study is that glibenclamide, a putative blocker of K<sub>ATP</sub> channels, abolished coronary autoregulation in the in situ blood-perfused canine heart, in which coronary autoregulation was present during vehicle infusion at CPP of ≤110 mm Hg. This finding suggests that K<sub>ATP</sub> channels play an impor-
Hemodynamic Variables at Coronary Perfusion Pressure of 70, 100, and 130 mm Hg During Vehicle and Glibenclamide Infusion

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<tr>
<td>Mean AoP, mm Hg</td>
<td>11 109±5</td>
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<td>HR, bpm</td>
<td>11 123±3</td>
<td>122±4</td>
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<td>LVEDP, mm Hg</td>
<td>11 2±1</td>
<td>2±1</td>
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<td>+ Peak dP/dt, mm Hg/s</td>
<td>11 2750±440</td>
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<td>CBF of LAD, ml/min</td>
<td>11 27±4</td>
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<td>CBF of LCx, ml/min</td>
<td>5 42±3</td>
<td>41±3</td>
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<td>Svo₂, %</td>
<td>6 44±3</td>
<td>45±7</td>
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<td>MVO₂, ml/min</td>
<td>6 2.7±0.3</td>
<td>2.9±0.3</td>
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<td>CBF/MVO₂</td>
<td>6 10.7±1.6</td>
<td>10.6±1.5</td>
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CPP indicates coronary perfusion pressure; AoP, aortic pressure; HR, heart rate; bpm, beats per minute; LVEDP, left ventricular end-diastolic pressure; + peak dP/dt, peak positive first derivative of left ventricular pressure; CBF, coronary blood flow; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; Svo₂, oxygen saturation of coronary venous blood; and MVO₂, myocardial oxygen consumption. Values are mean±SEM. *P<.01 vs corresponding value during vehicle infusion.

CPP-CBF relation after vehicle infusion. We showed previously that coronary vasodilation evoked by pinacidil at 5 μg/kg was comparable to that in the peak reactive hyperemic response after coronary occlusion for 20 seconds in dogs, which has been shown to produce maximal coronary vasodilatation. Glibenclamide at this dose significantly shifted downward the steady-state CPP-CBF relation at the lower CPP range, and the autoregulation index at that CPP range became <0 during glibenclamide infusion, indicating that coronary autoregulation was abolished by glibenclamide. These results strongly suggest that KATP channels play an important role in mediating autoregulation in the in situ blood-perfused dog heart.

We need to consider the possibility that the change in the steady-state CPP-CBF relation after glibenclamide might have been caused by a non-specific mechanism, such as changes in systemic or coronary hemodynamics, or in the myocardial metabolic state. In particular, it has been suggested that there is a strong inverse correlation between coronary venous oxygen tension and coronary autoregulation. However, blood flow of the left circumflex coronary artery did not change with decreases in CPP (Table).

The main purpose of this study was to determine if glibenclamide influenced coronary autoregulation in the in situ blood-perfused dog heart. Glibenclamide at the dose used in this study (10 μg·min⁻¹·kg⁻¹) prevented coronary vasodilation evoked with intracoronary infusion of pinacidil, a KATP channel opener. We showed previously that coronary vasodilation evoked by pinacidil at 5 μg/kg was comparable to that in the peak reactive hyperemic response after coronary occlusion for 20 seconds in dogs, which has been shown to produce maximal coronary vasodilatation. Glibenclamide at this dose significantly shifted downward the steady-state CPP-CBF relation at the lower CPP range, and the autoregulation index at that CPP range became <0 during glibenclamide infusion, indicating that coronary autoregulation was abolished by glibenclamide. These results strongly suggest that KATP channels play an important role in mediating autoregulation in the in situ blood-perfused dog heart.

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Venous oxygen saturation decreased but did not increase (Table), which suggests that the loss of autoregulation during glibenclamide infusion did not result from the increase in venous oxygen tension. It has been shown that venous carbon dioxide tension may also affect autoregulation.\textsuperscript{8,9} We did not measure carbon dioxide tension, but the influence of venous carbon dioxide tension on autoregulation is reportedly small at venous oxygen tension of >20 mm Hg.\textsuperscript{8} It also is shown that the increase in baseline coronary vascular resistance or the decrease in baseline CBF augments the degree of autoregulation even with no change in MVO\textsubscript{2}.\textsuperscript{1,4,7} However, baseline coronary vascular resistance or CBF at CPP of 100 mm Hg did not significantly differ during glibenclamide and vehicle infusion (Table). Furthermore, changes in MVO\textsubscript{2} associated with changes in CPP were similar during infusions of glibenclamide and vehicle (Table). Thus, it is unlikely that changes in the steady-state CPP-CBF relation during glibenclamide resulted from these nonspecific mechanisms. We also performed the time-control study with vehicle infusion. The CPP-CBF relations in the time-control study were comparable for the entire range of perfusion pressure (Fig 2).

Komaru et al\textsuperscript{12} demonstrated that dilation of epicardial microvessels associated with reduction in CPP was abolished by topical superfusion of glibenclamide in dogs. Our results extended the observation by Komaru et al by demonstrating that autoregulation of CBF at the lower CPP range was abolished by intracoronary infusion of glibenclamide. It is important to measure CBF in order to examine the magnitude of autoregulation, since different segments of the vascular tree or arteries in different layers of the myocardium may be recruited during autoregulation.\textsuperscript{1-4,24} These results suggest that the autoregulatory mechanism in the coronary vasculature is closely linked to K\textsubscript{ATP} channels of the microvascular smooth muscle cell. It appears that K\textsubscript{ATP} channels open as CPP decreases so that vasorelaxation and a subsequent increase in CBF ensue.

The mechanisms by which the decrease in CPP facilitates the opening of K\textsubscript{ATP} channels are not known and were not explored in the present study. It is known that K\textsubscript{ATP} channels open when intracellular ATP concentration falls in myocardial and vascular smooth muscle cells.\textsuperscript{11,13,14,25,26} However, it appears unlikely that a fall of ATP concentration was related to oxygen consumption of the vascular smooth muscle cell per se, since it has been shown that basal oxygen consumption of vascular smooth muscle is quite low and is not influenced even in hypoxia.\textsuperscript{27} Nichols and Lederer\textsuperscript{12} have recently suggested the possibility that the decrease in tissue oxygen concentration in the myocardium may be a signal that is transmitted to the vascular smooth muscle cell and regulates generation of ATP and thus opening of K\textsubscript{ATP} channels in vascular smooth muscle cells. The latter suggestion is interesting in view of the previous finding that coronary autoregulation is coupled strongly to tissue oxygen tension rather than MVO\textsubscript{2}.\textsuperscript{7} It is plausible that glibenclamide abolished coronary autoregulation by preventing the opening of K\textsubscript{ATP} channels as myocardial oxygen tension fell with decreases in CPP and CBF. It is also possible that other tissue factors may modulate the degree of coronary autoregulation, because K\textsubscript{ATP} channel activity is modified by tissue concentrations of ADP, lactate, and extracellular cations.\textsuperscript{28,29}

We may consider the role of adenosine in mediating coronary autoregulation, since previous studies have shown that adenosine-induced coronary vasodilation is mediated in part by K\textsubscript{ATP} channels.\textsuperscript{10,11} However, it has been shown that adenosine deaminase did not influence coronary autoregulation.\textsuperscript{5} Hanley et al\textsuperscript{10} have shown that the interstitial adenosine level (measured by the epicardial dial technique) did not change with decreases in CPP at the range of autoregulation. Thus, it appears that adenosine plays little role in coronary autoregulation.

Previous studies have demonstrated that coronary autoregulation occurs over the range of CPP of 60–80 to 120–150 mm Hg in anesthetized dogs,\textsuperscript{1,18,20,30} Our dogs showed autoregulation at the range of CPP between 50 and 110 mm Hg (Fig 1). Thus, the upper limit of the autoregulatory range was somewhat lower than that reported in some previous studies. Nevertheless, our findings clearly indicate that autoregulation was present.
in our dogs during vehicle infusion, which was abolished by glibenclamide.

Glibenclamide at 10 $\mu g \cdot min^{-1} \cdot kg^{-1}$ caused a small but insignificant decrease in CBF at CPP of 100 mm Hg (Table). This result is somewhat different from that in our previous study, which showed a significant decrease in basal CBF by glibenclamide at 5 $\mu g \cdot min^{-1} \cdot kg^{-1}$. The reasons for the difference are not known but might have been related to the difference in basal coronary artery tones. We have observed that the vasoconstricting effect of glibenclamide is greater in the vasodilated or ischemic preparation (authors’ unpublished observations). In the present study, only the dogs that showed autoregulation of CBF during vehicle infusion were used for the study with glibenclamide.

In summary, glibenclamide abolished coronary autoregulation over the lower CPP range in the blood-perfused in situ dog heart. These results suggest that $K_{ATP}$ channels may play an important role in the mechanism mediating coronary autoregulation in dogs. Further studies are needed to determine the cellular mechanisms by which $K_{ATP}$ channels mediate coronary autoregulation.

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References

Glibenclamide, a putative ATP-sensitive K+ channel blocker, inhibits coronary autoregulation in anesthetized dogs.
T Narishige, K Egashira, Y Akatsuka, Y Katsuda, K Numaguchi, M Sakata and A Takeshita

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