Post-stenotic coronary blood flow at rest is not altered by therapeutic doses of the oral anti-diabetic drug glibenclamide in patients with coronary artery disease

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Objective: To investigate whether blood flow in normal and post-stenotic coronary arteries is altered by therapeutic doses of the sulfonylurea agent glibenclamide.

Patients: 12 patients with a high grade stenosis of the left anterior descending coronary artery (n = 10) or left circumflex coronary artery (n = 2), and an angiographically normal corresponding left circumflex artery or left anterior descending artery, respectively.

Design: Two Doppler ultrasound wires were positioned in the “normal” and post-stenotic artery for simultaneous measurements of coronary blood flow velocity under baseline conditions and after intravenous glibenclamide, 0.05 mg/kg body weight. Local coronary blood flow was calculated from the average peak velocity and the cross sectional area derived from quantitative coronary angiographic analysis. Coronary flow reserve was determined after intracoronary injection of 30 µg adenosine and 12 µg papaverine.

Results: One hour after glibenclamide, serum insulin increased from (mean (SD)) 7.4 (2.0) to 44.8 (25.5) mU/l (p < 0.005), and C peptide from 1.4 (0.4) to 3.4 (1.2) ng/l (p = 0.005). In normal coronary arteries coronary flow reserve was 2.6 (0.4) after adenosine and 3.0 (0.4) after papaverine, while in post-stenotic arterial segments it was 1.2 (0.3) after adenosine (p = 0.005) and 1.3 (0.3) after papaverine (p = 0.005). There was no significant difference after glibenclamide. In non-stenotic arteries, average peak velocity (18.8 (5.2) cm/s) and calculated coronary blood flow (23.8 (10.7) ml/min) were not altered by glibenclamide (18.3 (5.2) cm/s and 22.8 (10.4) ml/min, respectively). In post-stenotic arteries, baseline average peak velocity was 13.3 (4.9) ml/min and coronary blood flow was 9.1 (3.0) ml/min, without significant change after glibenclamide (13.3 (5.2) cm/s, 9.0 (3.2) ml/min).

Conclusions: Glibenclamide, 0.05 mg/kg intravenously, is effective in increasing serum insulin, suggesting a KATP channel blocking effect in pancreatic β cells. It does not compromise coronary blood flow and vasodilation in response to adenosine and papaverine in post-stenotic and angiographically normal coronary arteries at rest.

Cardiovascular mortality in diabetic patients on sulfonylurea drugs may be increased in comparison with those on insulin treatment. In comparison with insulin treated patients, an increased mortality has recently been reported in patients on sulfonylurea drug treatment undergoing primary angioplasty for acute myocardial infarction. It is suggested that opening of the cardiac KATP channels is involved in the phenomenon of ischaemic preconditioning, in which a notable reduction in infarct size occurs if the myocardium has been pretreated with brief episodes of ischaemia followed by reperfusion. The increased mortality during treatment with sulfonylurea agents has mainly been attributed to inhibition of “preconditioning-like” effects, resulting in a reduced cardioprotective potential.

In human patients, however, this has not yet been proven. Theoretically, the blockade of coronary KATP channels by sulfonylurea drugs may increase in comparison with those on insulin treatment. In comparison with insulin treated patients, an increased mortality has recently been reported in patients on sulfonylurea drug treatment undergoing primary angioplasty for acute myocardial infarction.
Our aim in the present study was to investigate the effects of therapeutic doses of glibenclamide on coronary blood flow in patients with coronary artery disease. We hypothesised that a therapeutic dose of glibenclamide could alter post-stenotic coronary blood flow or vasodilatation in response to adenosine. We studied the influence of glibenclamide on coronary flow in angiographically normal coronary arteries and arteries with a high grade stenosis using intracoronary Doppler flow measurements and quantitative coronary angiography.

METHODS

Written informed consent was obtained from all the patients 24 hours before they were included in the study. The study protocol was approved by the local institutional ethics review board.

Patient selection

We studied 12 patients (mean (SD) age, 54 (6) years; six female, six male) with a high grade stenosis (> 90% diameter stenosis) of the left anterior descending coronary artery or the left circumflex artery (or a major branch). After diagnostic coronary angiography the patients were scheduled for angioplasty because of significant ST segment depression or terminal T wave inversion during or after bicycle testing (four patients), objective signs of ischaemia on myocardial scintigraphy (five patients), or reproducible symptoms of angina during exercise testing (seven patients).

Patients were included in the study if there was a high grade stenosis of the left anterior descending coronary artery (10 patients) with an angiographically normal left circumflex coronary artery, or a high grade stenosis of the left circumflex artery (two patients) with a “normal” left anterior descending artery.

Exclusion criteria were unstable angina, acute myocardial infarction (less than four weeks before), atrial fibrillation, second or third degree atioventricular block, left or right bundle branch block, valvar heart disease, cardiomyopathy, chronic renal failure (serum creatinine > 177 µmol/l), a history of allergic reactions to sulfonylurea agents or sulfonamides, previous treatment with sulfonylureas, and oral anticoagulation treatment.

All cardiovascular drugs, including β receptor blockers, calcium antagonists, long acting nitrates, and angiotensin converting enzyme inhibitors, were withheld 24 hours before the procedure. Where there were anginal symptoms, patients were treated with short acting nitrates.

Coronary angiography and quantitative diameter measurements

Cardiac catheterisation was performed routinely by the Judkins technique with 7 or 8 French catheters through a femoral sheath (contrast agent: iopromide, Ultravist-370, Schering AG, Berlin, Germany). Quantitative measurements of the coronary artery diameters and left ventricular ejection fraction were obtained from digitised cineangiograms, using the coronary angiography analysis system II (Pie Medical, Maastricht, Netherlands). Details of this edge detection based method have been published previously.11 No intracoronary gliceryl trinitrate was given, as this might interfere with the measured vessel diameters and blood flow velocities. The percentage diameter stenosis and the average lumen diameters in two orthogonal projections 5 mm distal to the tip of the Doppler wire were measured, using the guiding catheter as a scaling device along with a user defined reference lumen diameter of an angiographically normal coronary artery segment.

Intracoronary Doppler flow velocity measurements

Intracoronary Doppler flow profiles were obtained using a 0.014 inch (0.36 mm) flexible Doppler guide wire (12 MHz, FloWire, Cardiometrics Inc, Mountain View, California, USA).
Doppler flow profiles were obtained, biplane coronary angiography was done in two orthogonal projections. Vessel diameters were measured 5 mm distal to the tip of the wire. Vessel cross sectional area (CSA) and coronary blood flow (CBF) were calculated as follows: $CSA = 0.25 \times D_{\text{av}} \times D_{\text{av}} \times \pi$, where $D_{\text{av}}$ is mean vessel diameter in right anterior oblique and left anterior oblique projections; and $CBF = CSA \times 0.5 \times$ average peak flow velocity.

**Measurements of serum insulin, C peptide, and blood glucose**

Before the catheterisation procedure and one hour after infusion of glibenclamide (0.05 mg/kg body weight), serum samples were obtained for analysis of insulin and C peptide. The samples were analysed by immunometric assay and competitive immunoassay (Immulite Insulin/Immulite C Peptide, Immulite Analyser, DPC Diagnostic Products Corp, Los Angeles, California, USA). The central 95% reference range for insulin was 6–27 mU/l, and for C peptide, 0.3–1.3 nmol/l.

Blood glucose was measured by bedside testing (Glucometer Elite 3906, Bayer Diagnostics, Munich, Germany) directly before the infusion of glibenclamide and then at 30 minute intervals.

**Drugs**

The following drugs were used during the catheterisation procedure:
- glibenclamide (HB 419) (lyophilisate for parental use), a gift from Hoechst AG, Frankfurt, Germany; the drug was dissolved in 15 ml sterile 0.9% NaCl directly before infusion
- papaverine (Paveron, Linden, Heuchelheim, Germany)
- adenosine (Adrekar, Sanofi Winthrop, Munich, Germany).

**Experimental protocol**

Four hours before the procedure, an intravenous infusion of 5% glucose at a rate of 60 ml/h was initiated and continued for 24 hours. After insertion of the femoral sheath catheter and intrarterial administration of 140 IU heparin/kg body weight, biplane coronary angiography of the left coronary artery was performed for selection of optimal fluoroscopic projections. Under fluoroscopic control, one Doppler wire was placed in the left anterior descending coronary artery and a second was placed in the left circumflex coronary artery. In the coronary artery with the high grade stenosis, the wire was placed distal to the stenosis. After recording the baseline Doppler indices (three independent measurements over a period of three minutes) in both coronary arteries, coronary angiography was done in two orthogonal projections. Thereafter, coronary flow reserve was measured after an intracoronary injection of 30 μg adenosine and 12 mg papaverine.

After a second recording of baseline Doppler flow profiles (three measurements) with subsequent angiography, glibenclamide 0.05 mg/kg body weight was given intravenously over a period of 15 minutes. Thereafter, measurements of Doppler indices (three independent measurements) with subsequent coronary angiography were repeated, followed by recording of coronary flow reserve after adenosine and papaverine and a further recording of Doppler flow profiles with subsequent coronary angiography.

**Statistical analysis**

Values are given as mean (SD). For comparison of serum insulin and C peptide concentrations before and after glibenclamide, a paired Student’s $t$ test was used. Doppler measurements and haemodynamic and angiographic measurements at different time points were compared by analysis of variance for repeated measurements. Correlation between the grade of stenosis and coronary flow reserve was determined by the Spearman correlation coefficient. A probability value of $p < 0.05$ was considered significant.

**RESULTS**

**Patient characteristics**

Twelve patients (mean (SD) age 54 (6) years) were included in the study. Ten patients had a high grade stenosis of the left anterior descending coronary artery and two had a high grade stenosis of the left circumflex coronary artery. Cineventriculographic analysis showed wall motion abnormalities in the corresponding myocardial territory in five patients (moderate hypokiniesia in three, severe hypokinesia in two). No patient had a history of myocardial infarction. The ECG did not show Q waves in the corresponding leads. Demographic, clinical, and angiographic data on the patients are shown in table 1.

None of the patients was diabetic and therefore none had ever been on treatment with sulfonylurea drugs.

**Stability of the measured variables**

The mean standard deviation of three independent measurements of the average peak velocity (over a three minute period at baseline) was 2.1 cm/s (range 0.6–4.1 cm/s). Before measurements of coronary flow reserve, recording of the Doppler profile in the post-stenotic artery revealed an average peak velocity of 13.4 (4.8) cm/s. After determination of coronary flow reserve in the post-stenotic artery, baseline average peak velocity was 13.3 (4.9) cm/s (NS v the first baseline recording). In the normal coronary arteries, average peak velocity before and after measurements of coronary flow reserve was also unchanged, at 18.7 (5.2) cm/s and 18.8 (5.2) cm/s, respectively. No intracoronary glyceryl trinitrate was given during the protocol. Stability patterns were similar after administration of glibenclamide.

Determination of vessel diameters before and after measurements of coronary flow using quantitative coronary angiography showed minimal variation in the measured variables—

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**Table 1** Clinical and angiographic characteristics of the 12 patients with coronary artery disease

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>12</th>
<th>Female/male</th>
<th>6/6</th>
<th>Age (years)</th>
<th>54 (6)</th>
</tr>
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**Angiographic characteristics**

| Ejection fraction | 56 (9)% |
| Diameter stenosis (10 LAD, 2 LCx) | 94 (5)% |
| Additional stenosis of the right coronary artery | 4 |

**Cardiovascular risk factors**

| Systemic hypertension | 8 |
| Hypercholesterolaemia | 7 |
| History of cigarette smoking or current smoker | 5 |
| Diabetes mellitus | 0 |
| Obesity | 8 |
| Family history of cardiovascular diseases | 6 |

Values are mean (SD).

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery.

**Table 2** Coronary flow reserve (CFR) after 30 μg adenosine and 12 mg papaverine at baseline and after 0.05 mg/kg glibenclamide

<table>
<thead>
<tr>
<th>Poststenotic coronary artery</th>
<th>Angiographically normal artery</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>After glibenclamide</td>
</tr>
<tr>
<td>CFR&lt;sub&gt;adenosine&lt;/sub&gt;</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>CFR&lt;sub&gt;papaverine&lt;/sub&gt;</td>
<td>1.3 (0.3)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
for example, the mean cross sectional area was 2.4 (0.7) mm$^2$, as calculated from the first angiographic image before flow reserve measurements, and 2.4 (0.6) mm$^2$ in the second image after determination of coronary flow reserve.

Coronary flow reserve after adenosine and papaverine

Coronary flow reserve after intracoronary administration of 30 µg adenosine was 1.2 (0.3) in the post-stenotic segment, while in the angiographically normal arteries it was significantly higher, at 2.6 (0.4) (p < 0.005). After administration of glibenclamide, mean coronary flow reserve did not change, remaining at 1.2 (0.2) in the post-stenotic segment and 2.6 (0.3) in the normal coronary artery (table 2). Adenosine induced coronary vasodilatation was not significantly altered after glibenclamide. Coronary flow reserve after administration of 12 mg papaverine tended to be higher than after adenosine induced hyperaemia. Coronary flow reserve determined by papaverine did not change before and after glibenclamide (table 2). There was a significant negative correlation between the degree of maximum diameter stenosis and coronary flow reserve after both adenosine and papaverine (Spearman correlation coefficients, $-0.7711$ for adenosine (p < 0.05) and $-0.8840$ for papaverine (p < 0.005)). Adenosine and papaverine cause coronary vasodilatation by different mechanisms, papaverine having a direct relaxing effect on vascular smooth muscle cells. Because of this, the coronary flow reserve was always higher after papaverine than after adenosine.

Doppler profiles, vessel diameters, and coronary angiography

An original Doppler profile, with its typical diastolic increase in flow, is shown in fig 2. In the post-stenotic artery average peak velocity and vessel size were smaller than in the normal coronary artery (table 3). Calculated cross sectional area of the post-stenotic artery was 58% of that in the “normal” coronary artery, as the measurements were performed in the arterial segment distal to the vessel narrowing. In neither the post-stenotic coronary artery nor the normal coronary artery was there a significant change in average peak velocity, cross sectional area, or calculated quantitative coronary blood flow before or after glibenclamide. Heart rate and systemic blood pressure did not change. Serum insulin and C peptide concentrations are shown in fig 3.
pressure remained constant during the experimental procedure and no significant changes were observed after administration of glibenclamide (table 3).

**Serum insulin, C peptide, and blood glucose**

Serum insulin increased significantly one hour after administration of glibenclamide, 0.05 mg/kg body weight (p < 0.005) (fig 3). C peptide concentrations also increased significantly over the same time period (fig 3). There was only a slight decrease in blood glucose during the procedure (fig 4), as 5% glucose was given continuously intravenously. Blood glucose concentrations were monitored for 24 hours. No patient had clinical symptoms of hypoglycaemia during follow up.

**DISCUSSION**

The main results of this invasive study in patients with coronary artery disease were as follows:

- coronary blood flow before and after administration of 0.05 mg/kg glibenclamide was not significantly different in post-stenotic and angiographically normal coronary arteries
- intravenous glibenclamide at a dose of 0.05 mg/kg body weight increased serum insulin and C peptide concentrations significantly
- the amount of coronary vasodilatation induced by adenosine and papaverine was not significantly different before and after administration of glibenclamide

**Coronary flow and KATP channels in animal studies**

Recent studies on different animal models have provided a large body of knowledge about the mechanisms responsible for the regulation of coronary blood flow in different conditions, such as hypoxia, ischaemia, coronary autoregulation, and increased metabolic demand.

First described by Daut and colleagues in 1990, hypoxic coronary vasodilatation is mediated by opening of the vascular K<sub>ATP</sub> channels in the isolated saline perfused guinea pig heart. Apart from the myogenic and flow induced vascular control of basal coronary tone, it has been suggested that K<sub>ATP</sub> channels and adenosine in determining coronary tone during the different phases of hypoxia. In dogs, adenosine receptor blockade and nitric oxide synthase inhibition do not impair the normal increase in coronary flow during hypoxia. However, following blockade of the K<sub>ATP</sub> channel system, both adenosine and nitric oxide seemed to contribute to the exercise induced increase in blood flow. Other studies have shown that the regulation of coronary tone during metabolic stimulation, pacing, and exercise depends mainly on nitric oxide and not on K<sub>ATP</sub> channel activation.

In the present study, coronary blood flow in the angiographically normal coronary artery can be compared with investigations on basal coronary tone in animal studies. However, a simple transfer of animal models to a clinical situation in humans is not feasible. Several animal studies have been performed on isolated hearts perfused with saline at constant pressure. In such studies, the role of the K<sub>ATP</sub> channel in the coronary circulation might not be completely comparable because of perfusion pulsatility, the effects of the type of perfusion medium, denervation of the heart, and alterations of neurohumoral interactions. As recently shown in a dog model, glibenclamide lowered regional coronary flow under basal conditions, but with higher perfusion pulsatility no reduction in regional coronary flow was observed during glibenclamide administration.

Post-stenotic coronary flow in human patients represents a situation of impaired oxygen supply, but might be best described as a chronic adaptation to a reduced perfusion pressure. In a closed chest model in dogs, coronary autoregulation (defined as the ability to maintain constant flow under conditions of changing perfusion pressure) was not affected by glibenclamide in a range between 60–100 mm Hg. Animal models of pure hypoxia and increased metabolic stimulation differ from the clinical setting of chronic coronary stenosis with respect to the regulation of coronary flow.

**Vascular K<sub>ATP</sub> channels in humans**

Despite intense animal research, the role of vascular K<sub>ATP</sub> channels in the human coronary circulation is still under debate. The forearm vasodilator response to diazoxide (a K<sub>ATP</sub> channel opener)—as measured by venous occlusion plethysmography in healthy volunteers—was inhibited by glibenclamide. It was concluded that therapeutic concentrations of glibenclamide result in a significant blockade of vascular K<sub>ATP</sub> channels in humans. Similarly, the vasodilator response to ischaemia in the forearm was reduced by glibenclamide. However, there is only limited information about the role of K<sub>ATP</sub> channels in the human coronary circulation. In a combined angiographic and intracoronary Doppler study, post-stenotic blood flow was increased after intracoronary application of niconardil, a K<sub>ATP</sub> channel opener with additional effects similar to those of nitrates.

In the present study, the influence of a therapeutic dose of glibenclamide on coronary flow was investigated in patients with coronary artery disease. Measurements of serum insulin and C peptide concentrations after administration of glibenclamide revealed a pronounced effect on insulin release, suggesting an inhibitory effect on pancreatic K<sub>ATP</sub> channel, which results in enhanced exocytic insulin release—as expected from the pharmakokinetic data on glibenclamide. Concentrations of sulfonylurea required to block vascular K<sub>ATP</sub> channels may be greater than those effective at the pancreatic β cells. Therapeutic doses of glibenclamide possibly inhibit a fraction of K<sub>ATP</sub> channels in coronary smooth muscle cells and might impair hypoxic coronary vasodilatation, as suggested by the apparent dissociation constants of glibenclamide at vascular and pancreatic K<sub>ATP</sub> channels in guinea pigs. Our present study suggests that coronary basal tone in angiographically normal coronary arteries, post-stenotic coronary flow at rest, and the hyperemic response to adenosine are not significantly altered after therapeutic doses of glibenclamide.

![Figure 4 Blood glucose concentrations directly before administration of glibenclamide and during follow up. Values are means, error bars = SD.](http://heart.bmj.com/)
Coronary flow assessed by Doppler flow profiles and quantitative angiography

Determination of coronary flow characteristics using intracoronary Doppler measurements of coronary flow velocity in combination with quantitative angiographic analysis is a well established method of investigating coronary blood flow in vivo. Validation studies have shown a high correlation in experimental animal studies between the flow velocity and coronary blood flow velocity, which are used to estimate the true coronary flow velocity. The estimated mean flow velocity was calculated as 0.5 x average peak velocity by assuming a time averaged parabolic velocity profile across the vessel. Using a combination of Doppler flow measurements and cross sectional intravascular ultrasound imaging, other groups have suggested a better correlation with a calculated mean flow velocity of 0.47 x average peak velocity. Assessment of coronary flow reserve from average peak velocity after papaverine and adenosine is a well established method, but it might underestimate the hyperemic response, as changes of vessel diameters are not taken into account by this method.

Sulfonylurea drugs and coronary artery disease

The potential risk of sulfonylurea drug treatment in diabetic patients with coronary artery disease is still under debate. In a prospective trial in 3867 newly diagnosed diabetic patients, there was no difference in the clinical outcome after 10 years between sulfonylurea treatment and insulin treatment. On the other hand, some clinical studies have suggested that there is an increased cardiac mortality in patients on sulfonylurea drug treatment. Alternatives to sulfonylurea drugs should be considered care-fully.

Conclusions

Alternatives to sulfonylurea drugs should be considered carefully in the treatment of diabetic patients with coronary artery disease, despite there being no deterioration in coronary flow at rest under the influence of glibenclamide in this population.

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REFERENCES

Localised cardiac tamponade caused by intrapericardial haematoma: a rare cause of ascites presenting 10 years after open heart surgery

A 59 year old man underwent quadruple coronary artery bypass grafting in 1989. Ten years later he was admitted to hospital as an emergency with a two week history of increased abdominal swelling, lethargy, breathlessness and ankle swelling. Examination revealed a sinus tachycardia, raised jugular venous pressure, pronounced abdominal ascites, and pitting oedema of the ankles. He was normotensive with normal heart sounds and no significant murmurs. His lung fields were clear. Transthoracic echocardiography revealed moderate left ventricular systolic impairment and localised right ventricular tamponade. Computed tomography confirmed significant compression of the right ventricle by a pericardial mass which contained some central calcification. No communication with the cardiac chambers or extrinsic structures could be identified. At surgery the mass was successfully excised. Histological analysis revealed an organised, partly calcified haematoma. Cardiac tamponade after surgery most often occurs within the first postoperative week or two and generally presents acutely with haemodynamic compromise. Intrapericardial organised haematoma, causing localised compression of the cardiac chambers late after open heart surgery, is unusual.

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Transcatheter closure of coronary artery to pulmonary artery fistula using covered stents

A 40 year old normotensive, diabetic man presented to the emergency department in congestive heart failure. He had been diagnosed elsewhere with dilated cardiomyopathy. The ECG revealed T wave inversion in precordial leads, and echocardiography showed dilated left ventricle (LV) with global hypokinesia and severe LV dysfunction. Tc-sestamibi resting myocardial perfusion study revealed reduced tracer concentration in the anterior wall and septum and viable myocardium in these areas. A subsequent coronary angiogram showed multiple coronary fistulas from the septal branches of the left anterior descending coronary artery (LAD) draining into the pulmonary artery (below left). A 3 × 19 mm Jostent coronary stent graft was deployed in the LAD to occlude the septal arteries feeding the fistulas. As the post deployment angiogram (below centre) showed residual fistulas from the septal branches distal to the stent, another 3 × 12 mm Jostent was deployed in the distal part of the first stent occluding the septals causing residual fistulas. The final angiogram showed good antegrade flow in the LAD with obliteration of fistulas (below right).

Coronary fistulas most commonly originate from the right coronary artery and the majority are asymptomatic. The related problems that occur usually are myocardial ischaemia and angina (the result of a “coronary steal”), congestive heart failure, bacterial endocarditis, cardiac arrhythmia or rupture of an aneurysmal fistula. Current treatment options include surgical ligation and coil embolisation. Recently covered stents have been successfully employed for the closure of coronary fistulas.

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