Effects of $K_{\text{ATP}}$ channel blockade by glibenclamide on the warm-up phenomenon

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Aims

The increased tolerance to myocardial ischaemia observed during the second of two sequential exercise tests, i.e. the warm-up phenomenon, has been proposed as a clinical model of ischaemic preconditioning. As ATP-sensitive $K^+$ channels appear to be a mediator of ischaemic preconditioning in both experimental and clinical studies, the aim of this study was to investigate the role of $K_{\text{ATP}}$ channels in the warm-up phenomenon.

Methods and Results

Twenty-six patients with coronary artery disease were randomized to receive 10 mg oral glibenclamide, a selective ATP-sensitive $K^+$ channel blocker, or placebo. Sixty minutes after glibenclamide or placebo administration, patients were given an infusion of 10% dextrose (8 ml . min$^{-1}$) to correct glucose plasma levels or, respectively, an infusion of saline at the same infusion rate. Thirty minutes after the beginning of the infusions, both patient groups underwent two consecutive treadmill exercise tests, with a recovery period of 15 min to re-establish baseline conditions. Before exercise tests, blood glucose levels were similar in placebo and glibenclamide groups (96 ± 10 vs 105 ± 22 mg . 100 ml$^{-1}$, $P=\text{ns}$). After placebo administration, rate-pressure product at 1.5 mm ST-segment depression significantly increased during the second exercise test compared to the first (220 ± 41 vs 186 ± 29 beats . min$^{-1}$ . mmHg . 10$^2$, $P<0.01$), but it did not change after glibenclamide (191 ± 34 vs 187 ± 42 beats . min$^{-1}$ . mmHg . 10$^2$, $P=\text{ns}$), with a significant drug-test interaction ($P=0.0091$, at two-way ANOVA).

Conclusions

Glibenclamide, at a dose previously shown to abolish ischaemic preconditioning during coronary angioplasty, prevents the increase of ischaemic threshold observed during the second of two sequential exercise tests. These findings confirm that ischaemic preconditioning plays a key role in the warm-up phenomenon and that in this setting is, at least partially, mediated by activation of ATP-sensitive $K^+$ channels.

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Key Words: Glibenclamide, ischaemic preconditioning, $K_{\text{ATP}}$ channel, warm-up phenomenon.

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Introduction

The warm-up phenomenon usually refers to increased tolerance to myocardial ischaemia during the second of two sequential exercise tests[^1^-^5]. Although this phenomenon was described in anginal patients more than 50 years ago[^6], its underlying mechanisms remain poorly known. It has been shown that the warm-up phenomenon is due, at least in part, to a mechanism similar to that involved in limiting experimental infarct size following a brief ischaemic episode, i.e. ischaemic preconditioning[^2^-^5,^7]. This hypothesis is supported by the observation that myocardial oxygen consumption is reduced during the second of two sequential exercise tests, suggesting increased metabolic efficiency, a feature of preconditioning[^2]. Furthermore, the time course of the warm-up phenomenon is consistent with that of ischaemic preconditioning, as it lasts no longer than 60–90 min[^3,^4]. The mechanisms of ischaemic preconditioning are multiple and not fully established. In particular, ATP-sensitive $K^+$ ($K_{\text{ATP}}$) channels have been shown to play an important role in mediating ischaemic preconditioning in experimental studies[^8,^9], isolated human myocardium[^10,^11], and in the clinical setting of coronary
angioplasty\textsuperscript{[12,13]}. Thus, in order to establish the role played by \( K_{ATP} \) channels in the warm-up phenomenon, we assessed the effects of glibenclamide, a selective \( K_{ATP} \) channel blocker, in patients with stable angina and documented coronary artery disease, undergoing two sequential treadmill exercise tests.

### Methods

#### Patients

Twenty-six patients (24 men and two women; aged from 36 to 71 years, mean 60 years) with chronic stable angina pectoris (symptom duration ranging from 4 to 42 months) and documented coronary artery disease (internal diameter reduction \( >70\% \) of at least one major branch) participated in this study. All patients had reproducible positive exercise tests for myocardial ischaemia (horizontal or downsloping ST-segment depression \( \geq 2\,0 \text{ mm} \)). Coronary angiography demonstrated one-vessel disease in six patients, two-vessel disease in 15 and three-vessel disease in five patients. All patients were normotensive, in sinus rhythm and without evidence of previous myocardial infarction, heart failure, cardiomyopathy or valvular disease. No patient had evidence of left ventricular hypertrophy or conduction defects which could interfere with the interpretation of ST-segment changes. All patients had normal hepatic and renal function and fasting blood glucose levels. Nitrate preparations other than sublingual nitroglycerin and calcium entry blocking agents were withdrawn 4 days before the study and beta-blocking agents 5 days before. Only sublingual nitroglycerin was used during the latter period and a minimum of 12 h were allowed to elapse before testing was begun if this drug was used. All patients gave written informed consent for participation in the study, which was approved by the Ethics Committee.

#### Study protocol

In this single blind study, patients were randomly allocated to two groups. One group consisted of 13 patients (12 men; age range 36–71 years, mean 61 years) who received 10 mg of oral glibenclamide; the other group consisted of 13 patients (12 men; age range 47 to 70 years, mean 60 years) who received placebo. Sixty minutes after glibenclamide or placebo administration a continuous infusion of 10\% dextrose or saline (8 ml \( \text{min}^{-1} \)), respectively, was started. Thirty minutes after the beginning of the infusion, both patient groups underwent two consecutive treadmill exercise tests. This time interval was chosen as it has previously been demonstrated in human volunteers that the peak plasma levels of glibenclamide are achieved between 60 and 120 min after the oral administration of glibenclamide\textsuperscript{[14]}.

### Exercise test

All patients underwent two consecutive, computer-assisted treadmill exercise tests, using the Bruce protocol, with a recovery period of 15 min between the tests to re-establish baseline electrocardiographic conditions. All exercise tests were performed between 0900h and 1200h and the laboratory temperature was kept at 20–24 °C. A standard 12-lead electrocardiogram and arterial blood pressure (cuff sphygmomanometer) were obtained in the standing position at baseline, at 1-min intervals during exercise, at peak exercise, and each minute up to 15 min after exercise, as well as at 1·5 mm ST-segment depression, at the onset of angina, and when it was clinically indicated. Three electrocardiographic leads were continuously monitored before, during and after exercise, and up-to-date averaged QRS complexes of all electrocardiographic leads were continuously displayed on the screen. The level of the ST-segment, 0·06 s after the J point, was calculated after signal averaging by means of a computer-assisted system (CASE Marquette 12) in all 12 leads. The calculated values were printed out, along with the heart rate, against time in trend format. This provided measurement of the ST-segment level with an accuracy of 0·1 mm.

Criteria for interrupting the test were: (1) ST-segment depression \( \geq 3 \text{ mm} \), (2) maximal age-related heart rate, (3) severe chest pain, (4) physical exhaustion; and (5) the occurrence of other harmful conditions such as hypotension, severe arrhythmia, and dyspnoea. Myocardial ischaemia was diagnosed when a horizontal or downsloping ST-segment depression of 1·5 mm at 0·06 s from the J point was observed in at least one lead. The electrocardiographic strips of all tests were evaluated independently in a blind fashion by two cardiologists; in case of disagreement, the matter was resolved by consensus.

The following parameters were measured: resting heart rate and blood pressure; heart rate, blood pressure and rate-blood pressure product (heart rate \( \times \) systolic blood pressure) at the onset of 1·5 mm ST-segment depression and at peak exercise; maximal ST-segment depression; exercise duration, in seconds; time, in seconds, to the onset of 1·5 mm ST-segment depression; time to the recovery of ST-segment depression, in seconds; and time to pain onset, in seconds.

Venous blood samples for the measurement of blood glucose levels, using a routine glucose oxidase method, were obtained at baseline, 60 min after the administration of glibenclamide or placebo, and before the first exercise test.

### Statistical analysis

Two-factor analysis of variance (ANOVA) with repeated measures on one factor was used to compare haemodynamic and electrocardiographic data during the two sequential exercise tests in patients receiving glibenclamide or placebo. When significant differences
were detected, pairwise comparisons were made using the Scheflé F test. Time to 1·5 mm ST-segment depression and to pain onset were analysed using the Wilcoxon signed rank test or the Mann–Whitney U test as appropriate, because these data did not fit to a normal distribution. Comparisons of the remaining continuous or discrete variables between the two groups were performed using an unpaired Student’s t or a Chi-square test, respectively. Data are expressed as mean values ± 1 SD; P values < 0·05 were considered significant.

### Results

Clinical and anatomical features were similar in the two groups of patients and are presented in Table 1. In glibenclamide-treated patients, blood glucose levels 60 min following glibenclamide administration decreased from 93 ± 11 to 62 ± 10 mg. 100 ml⁻¹ (P < 0·05). However, after 10% dextrose infusion, before the exercise test, levels increased to 105 ± 22 mg. 100 ml⁻¹ (P = ns, compared with the baseline values). In placebo-treated patients, the blood glucose level before the exercise test (96 ± 10 mg. 100 ml⁻¹) was similar to that found in glibenclamide-treated patients (P = ns) (Table 1).

All patients achieved 1·5 mm ST-segment depression during the two exercise tests. The exercise test was interrupted because of severe chest pain in the presence of >1·5 mm ST-segment depression in six (46%) placebo-treated and seven (54%) glibenclamide-treated patients (P = ns) during the first test and, respectively, in five (38%) and seven (54%) patients (P = ns) during the second test. The test was interrupted in the remaining patients because of physical exhaustion in the presence of >1·5 mm ST-segment depression, without statistical differences between groups (P = ns). The main results of the two exercise tests performed after placebo or glibenclamide administration are summarized in Table 2.

### Effects of glibenclamide on the ischaemic threshold

The values of resting heart rate and rate-pressure product in patients on placebo were similar to those in patients on glibenclamide during both the first and second exercise tests (Table 2).

After placebo administration, heart rate and rate-pressure product at 1·5 mm ST-segment depression significantly increased during the second exercise test compared to the first (135 ± 16 vs 120 ± 5 beats . min⁻¹, P < 0·01, and 220 ± 41 vs 186 ± 29 beats . min⁻¹, mmHg . 10², P < 0·01, respectively), but they did not change after glibenclamide (122 ± 11 vs 119 ± 8 beats . min⁻¹, P = ns, and 191 ± 34 vs 187 ± 42 beats . min⁻¹, mmHg . 10², P = ns, respectively), with significant drug-test interactions (P = 0·039 and P = 0·009, respectively, at two-way ANOVA) (Table 2 and Fig. 1).

Of note, the rate-pressure product at 1·5 mm ST-segment depression increased by more than 10% in 10 (77%) patients after placebo and in four (31%) after glibenclamide (P < 0·05).

### Effects of glibenclamide on exercise tolerance

After both placebo and glibenclamide administrations, time to 1·5 mm ST-segment depression during the second exercise test was greater than that during the first test (439 ± 148 vs 331 ± 136 s, P < 0·01; and 407 ± 69 vs 323 ± 119 s, P < 0·01, respectively), as was exercise duration (504 ± 159 vs 412 ± 165 s, P < 0·01; and 470 ± 70 vs 399 ± 106 s, P < 0·05, respectively) (Table 2 and Fig. 1). Time to 1·5 mm ST-segment depression during the second test increased by more than 10% compared to that during the first test in 12 (92%) patients after placebo and in eight (62%) after glibenclamide (P = ns).

After placebo administration, six patients had anginal pain during the first exercise test and five during the second test; after glibenclamide administration,

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Table 1  Clinical and anatomic features in the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glibenclamide</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 7</td>
<td>61 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>Male/female</td>
<td>12/1</td>
<td>12/1</td>
<td>ns</td>
</tr>
<tr>
<td>Vessel disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one-vessel</td>
<td>23</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>two-vessel</td>
<td>62</td>
<td>54</td>
<td>ns</td>
</tr>
<tr>
<td>three-vessel</td>
<td>15</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Symptom duration (%)</td>
<td>13 ± 10</td>
<td>14 ± 9</td>
<td>ns</td>
</tr>
<tr>
<td>Blood glucose levels (mg. 100 ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>98 ± 11</td>
<td>93 ± 11</td>
<td>ns</td>
</tr>
<tr>
<td>60 min after treatment</td>
<td>99 ± 9</td>
<td>62 ± 10*</td>
<td>&lt;0·05</td>
</tr>
<tr>
<td>prior to exercise tests</td>
<td>96 ± 10</td>
<td>105 ± 22</td>
<td>ns</td>
</tr>
</tbody>
</table>

*=P<0·05 vs values at baseline and prior to exercise tests.
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Table 2  Results of the exercise stress tests in the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glibenclamide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test 1</td>
<td>Test 2</td>
</tr>
<tr>
<td>Baseline values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats . min$^{-1}$)</td>
<td>77 ± 11</td>
<td>78 ± 9</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>134 ± 18</td>
<td>125 ± 12</td>
</tr>
<tr>
<td>RPP (beats . min$^{-1}$ . mmHg . 10$^{-3}$)</td>
<td>99 ± 19</td>
<td>97 ± 15</td>
</tr>
<tr>
<td>Values at 1·5 mm ST depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats . min$^{-1}$)</td>
<td>120 ± 5</td>
<td>* 135 ± 16</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>154 ± 22</td>
<td>† 163 ± 26</td>
</tr>
<tr>
<td>RPP (beats . min$^{-1}$ . mmHg . 10$^{-3}$)</td>
<td>186 ± 29</td>
<td>* 220 ± 41</td>
</tr>
<tr>
<td>Time (s) (median values)</td>
<td>331 ± 136</td>
<td>* 439 ± 148</td>
</tr>
<tr>
<td>(326)</td>
<td>(480)</td>
<td>(291)</td>
</tr>
<tr>
<td>Time to pain onset (s)</td>
<td>337 ± 181</td>
<td>* 431 ± 179</td>
</tr>
<tr>
<td>(median values)</td>
<td>(326)</td>
<td>(417)</td>
</tr>
<tr>
<td>Values at peak exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats . min$^{-1}$)</td>
<td>125 ± 8</td>
<td>* 142 ± 14</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>160 ± 26</td>
<td>167 ± 30</td>
</tr>
<tr>
<td>RPP (beats . min$^{-1}$ . mmHg . 10$^{-3}$)</td>
<td>201 ± 36</td>
<td>* 237 ± 48</td>
</tr>
<tr>
<td>Duration of exercise (s)</td>
<td>412 ± 165</td>
<td>* 304 ± 159</td>
</tr>
<tr>
<td>ST depression (mm)</td>
<td>2·4 ± 0·8</td>
<td>2·1 ± 0·6</td>
</tr>
<tr>
<td>ST recovery (s)</td>
<td>496 ± 222</td>
<td>† 380 ± 132</td>
</tr>
</tbody>
</table>

Time to pain onset refers to the six placebo-treated and seven glibenclamide-treated patients with angina during the first exercise test. BP=blood pressure; RPP=rate-pressure product.

*P<0·01, test 1 vs test 2; †P<0·05, test 1 vs test 2; §P<0·05 (at two-way ANOVA), glibenclamide vs placebo; †P<0·01 (at two-way ANOVA), glibenclamide vs placebo.

seven patients had anginal pain during the first and the second exercise test (P=ns). After both placebo and glibenclamide administrations, time to pain onset significantly increased during the second exercise test compared to the first (431 ± 179 vs 337 ± 181 s, P<0·01; and 383 ± 115 vs 324 ± 150 s, P<0·05).

**Discussion**

This single-blind, placebo-controlled, randomized study, carried out in patients with stable angina who received glibenclamide, a selective $K_{ATP}$ channel blocker, or placebo, immediately before two consecutive exercise tests, shows: (1) a loss of improvement of the ischaemic threshold during the second exercise test after glibenclamide, compared to placebo, with a significant drug-test interaction for both heart rate and rate-pressure product at 1·5 mm ST-segment depression; (2) an improvement of exercise tolerance during the second exercise test, following both glibenclamide and placebo, without a significant drug-test interaction for parameters reflecting exercise tolerance. Thus, our findings indicate that $K_{ATP}$ channels play a role in the component of the warm-up phenomenon related to ischaemic preconditioning.

The mechanisms of the warm-up phenomenon still remain poorly understood. Williams et al.[1] and Okazaki et al.[2] have demonstrated in patients with a single stenosis of the left anterior descending coronary artery that great cardiac vein flow is similar during the first and second stress tests, thus suggesting that the warm-up phenomenon is not due to an increase in total myocardial blood flow.

Interestingly, Okazaki et al.[2] found that the warm-up phenomenon was associated with a reduction of myocardial oxygen consumption, thus suggesting that the warm-up phenomenon might be caused by a mechanism similar to that involved in limiting experimental infarct size following a brief ischaemic episode, i.e. ischaemic preconditioning. Of note, the time course of this phenomenon is consistent with that of ischaemic preconditioning, as it lasts no longer than 60–90 min[3,4]. Indeed, in patients with stable angina undergoing three consecutive exercise tests, we previously found that the warm-up phenomenon observed within minutes of a first exercise test is due to adaptation to ischaemia, whereas that observed 2 h after the second exercise test is due to a training effect caused by peripheral mechanisms[3]. Our study shows that glibenclamide, at a dose previously shown to be able to prevent ischaemic preconditioning during coronary angioplasty[12], abolishes the improvement of ischaemic threshold during the second exercise test, compared to placebo, thus indicating that $K_{ATP}$ channels are involved in the setting of exercise-induced ischaemia. In particular, these findings seem to confirm that at least one component of the warm-up phenomenon is due to ischaemic preconditioning[5–7] and indicate that $K_{ATP}$ channels are involved in such a component. These data are consistent with experimental[8,9], in vitro human[10,11] and clinical studies[12,13], showing a key role for $K_{ATP}$ channels in ischaemic preconditioning.
The inability to prevent the improvement of exercise tolerance by glibenclamide is in agreement with the notion that the mechanisms of the warm-up phenomenon are multiple and also include a training effect. It is well established that while, on the one hand, the rate-pressure product at 1.5 mm ST-segment depression represents a reliable, non-invasive index of myocardial oxygen consumption at the ischaemic threshold, which can be improved by ischaemic preconditioning, on the other, time to 1.5 mm ST-segment depression and to pain onset are global indexes of exercise tolerance, which can be improved by ischaemic preconditioning and, more importantly, by the training effect. The latter, in turn, is unlikely to be affected by glibenclamide, thus explaining why K\textsubscript{ATP} channel blockade failed to significantly affect these global indexes of exercise tolerance. These considerations may explain, at least in part, the apparent conflicting results between our study and that of Correa and Schaefer, who showed that glibenclamide has no significant negative effect on indexes of demand ischaemia. In fact, they did not assess the ischaemic threshold, but only end-points reflecting exercise tolerance, which are influenced by the peripheral response, and the rate-pressure product at maximal ST-segment depression, which is likely to be influenced by the subjective attitude of both the physician and the patient.

The chain of events responsible for ischaemic preconditioning and the mechanisms by which K\textsubscript{ATP} channels produce their cardioprotective actions are only partially understood and cannot be deduced by the results of the present study. It is known that a variety of G protein-coupled receptors (e.g. adenosine A\textsubscript{1}, a\textsubscript{1}-adrenergic, muscarinic, bradykinin receptors) results in the activation of protein kinase C. This, in turn, leads to the translocation of protein kinase C from the cytoplasm to the sarclemma, where it phosphorylates a substrate protein, possibly the K\textsubscript{ATP} channel, which confers resistance to ischaemia. In this regard, we have previously shown that adenosine receptor blockade by bamiphylline failed to prevent the warm-up phenomenon, thus suggesting that either purinergic receptors are not involved in such a form of adaptation to ischaemia or, in agreement with experimental evidence, the selective blockade of one pathway only, i.e. that triggered by stimulation of adenosine receptors, might be insufficient to prevent preconditioning in this clinical setting. Of note, the present study, showing that glibenclamide is able to prevent the warm-up component related to ischaemic preconditioning, supports the hypothesis that K\textsubscript{ATP} channels might be the end-effector of the preconditioning phenomenon.

**Limitations of the study**

This study has some limitations. First, as high doses of intracoronary glibenclamide have been demonstrated to decrease coronary blood flow and to interfere with hypoxic and ischaemic vasodilation by blockade of K\textsubscript{ATP} channels in vascular smooth muscle, we cannot rule out that glibenclamide prevented the improvement in the ischaemic threshold during the second exercise test through reduction of ischaemic vasodilation or an unfavourable transmural redistribution of coronary blood flow. However, if this were the case, we should have seen more severe ischaemic changes in glibenclamide-treated patients during the first exercise test. Instead, the ischaemic threshold and exercise tolerance during the first exercise test were similar in glibenclamide- and placebo-treated patients. Second, it cannot be discounted that the improvement in the ischaemic threshold during the second exercise test might have been due to collateral recruitment. However, as glibenclamide is unlikely to affect collateral...
circulation\(^\text{[9]}\), its ability to fully prevent an improvement in the ischaemic threshold during the second exercise test strongly suggests that it is mainly mediated by ischaemic preconditioning.

Another limitation of this study is the use of a single-blind design. However, the selection of objective electrocardiographic end-points, i.e. heart rate and rate-pressure product at 1:5 mm ST-segment depression, and the analysis of the results blind to treatment should substantially overcome the drawbacks of the single-blind design.

Finally, in our study we did not utilize sampling from the coronary sinus for the measurement of biochemical markers of ischaemia. However, it might be difficult to justify the utilization of ‘invasive’ parameters, when ‘non-invasive’ parameters provide similar informations.

Conclusions and clinical implications

Our findings support the notion that the warm-up phenomenon is due to multiple components, one of which is ischaemic preconditioning. They also show that K\(_{\text{ATP}}\) channels play an important role in such a phenomenon.

The results of our study may have some clinical implications. In fact, the demonstration that glibenclamide prevents ischaemic preconditioning during exercise-induced ischaemia, similar to what has been previously found in human atrial tissue\(^\text{[10,11]}\) and during coronary angioplasty\(^\text{[12]}\), may help explain mortality excess from cardiovascular causes observed in diabetic patients on sulfonylureas in the UGDP\(^\text{[23]}\) and BARI\(^\text{[24]}\) trials and the worse outcome of patients who are on sulfonylureas at the time of acute myocardial infarction\(^\text{[25]}\). These findings suggest that the treatment of diabetes in some high-risk coronary patients should be shifted from sulfonylureas to insulin, as recently proposed\(^\text{[26]}\). However, since in our study we assessed the effects of a single dose of glibenclamide in non-diabetic patients (similar to the maximal dose used per day in diabetic patients), we cannot extrapolate our results to the effects of chronic treatment with sulfonylureas, as the responsiveness of K\(_{\text{ATP}}\) channels during chronic treatment with glibenclamide may, in theory, change. Nonetheless, Cleveland et al\(^\text{[11]}\) have shown that human atrial myocardium from diabetic patients exposed to long-term hypoglycaemic agents cannot be functionally protected by a preceding transient simulated ischaemic preconditioning stimulus.

Finally, the evidence that K\(_{\text{ATP}}\) channels are involved in exercise-induced ischaemia as well as in other clinical settings\(^\text{[12,13]}\) supports the use of K\(_{\text{ATP}}\) channel openers as cardioprotective agents in man.

References


