Loss of Preconditioning by Attenuated Activation of Myocardial ATP-Sensitive Potassium Channels in Elderly Patients Undergoing Coronary Angioplasty

Tsung-Ming Lee, MD; Sheng-Fang Su, PhD; Tsai-Fwu Chou, MD; Yuan-Teh Lee, MD, PhD; Chang-Her Tsai, MD, PhD

Background—The ischemic preconditioning response among elderly patients is known to be lower than in adult patients. Since mitochondrial ATP-sensitive potassium (K\textsubscript{ATP}) channels exert preconditioning effects, we undertook this study to determine whether this attenuated activation of K\textsubscript{ATP} channels influences the reduced responsiveness of elderly patients to ischemic preconditioning.

Methods and Results—Fifty-six patients undergoing angioplasty for a major epicardial coronary artery were randomly allocated to either an ischemic preconditioning group, a nicorandil (an agonist of K\textsubscript{ATP} channels) group, or a glibenclamide (an antagonist of K\textsubscript{ATP} channels) group based on their age: adult groups (n=26; age, 55±5 years; mean age, 45±5 years) and elderly groups (n=30; age, ≥65 years; mean age, 71±3 years). Ischemic preconditioning with a 120-second coronary occlusion significantly lowered the ischemic burden assessed by ST-segment shift, chest pain score, and myocardial lactate extraction ratios in the adult group. This did not occur in the elderly group. The impaired preconditioning responsiveness in the elderly patients was reversed by nicorandil administration or an ischemic period lengthened to 180 seconds. However, nicorandil-induced cardioprotection was abolished by administering glibenclamide in both the adult and elderly groups.

Conclusions—The present study demonstrates that preconditioning significantly enhances the tolerance of the heart to subsequent ischemia in adults but not in senescent patients. Since prolonged ischemia and nicorandil are able to mimic preconditioning and can reverse impaired responsiveness, impaired preconditioning of the aged heart appears to be due to an attenuated activation of K\textsubscript{ATP} channels. (Circulation. 2002;105:334-340.)

Key Words: coronary disease ■ ion channels ■ ischemia ■ reperfusion

Clinical studies have shown that the morbidity and mortality rates after an acute myocardial infarction are higher in the elderly.\textsuperscript{1,2} Even adjustment for age-associated diseases does not explain the higher rate of mortality observed in elderly patients.\textsuperscript{3} With advancing age, anatomic, mechanical, and biochemical alterations have an impact on functional modification of membrane proteins and ion homeostasis and cause senescent hearts to be less tolerant to ischemia than adult hearts;\textsuperscript{4} however, the specific factors for this have not been clearly identified.

Ischemic preconditioning (PC) is a cardioprotective phenomenon in which short periods of myocardial ischemia result in a resistance of the myocardium to a subsequent ischemia.\textsuperscript{5} We have previously demonstrated that PC is mediated, at least in part, by mitochondrial ATP-sensitive potassium (K\textsubscript{ATP}) channels.\textsuperscript{6} The opening of these channels may be important in PC because inhibition of K\textsubscript{ATP} channels with glibenclamide abolishes the cardioprotective effects of PC in both experimental and clinical studies.\textsuperscript{6,7} The use of agents (nicorandil) to open this channel may mimic a physiological response that acts to attenuate ischemic injury.\textsuperscript{8} Coronary angioplasty is a useful model for clinical study of PC because it permits adjustment of ischemic time and measurement of metabolic responses to coronary occlusion.\textsuperscript{9} Data concerning the aged effect on PC are controversial.\textsuperscript{10–12} The conflicting evidence can largely be attributed to the use of different species. Few reports are available about whether PC in humans undergoing angioplasty is affected by aging. Thus, this study investigates whether a loss of PC is observed in elderly patients undergoing angioplasty and whether the reduced effects of PC are caused by the attenuated activation of K\textsubscript{ATP} channels through the use of nicorandil, a specific agonist of mitochondrial K\textsubscript{ATP} channels, and glibenclamide, a blocker of K\textsubscript{ATP} channels.
activate mitochondrial KATP channels without the interference of a nitrate effect. To determine the potential role of KATP channels in preconditioning, prolonged ischemia with a coronary occlusion of either 120 seconds or 180 seconds, with a successful balloon angioplasty resulting in residual stenosis <30%. No patient had a history of diabetes mellitus, which would confound the effect of sulfonylurea drugs. Medications, including calcium channels and β-adrenergic blockers, were withheld for 24 hours before the procedure. Any patients who had taken nitroglycerin within 4 hours before catheterization were excluded from this study. A total of 56 consecutive patients were randomly allocated to 1 of 9 groups according to age: adult groups (≥55 years old; range, 35 to 55 years; mean age, 45 ± 5 years) and elderly groups (≥65 years old; range, 65 to 78 years; mean age, 71 ± 2.3 years) (Figure). Nicorandil was intravenously administered 5 minutes before the first balloon inflation at a dose of 80 μg/kg, which has been shown to specifically activate mitochondrial KATP channels without the interference of a nitrate effect. To determine the potential role of KATP channels in preconditioning, prolonged ischemia with a coronary occlusion of 180 seconds was assessed. The study was approved by the National Taiwan University Hospital Review Board, and all subjects provided written informed consent before participation.

Methods

Study Population

The study was conducted prospectively. All patients fulfilled the entry criteria: (1) history of chronic stable angina pectoris ≥3 months and a positive stress test for myocardial ischemia; (2) no history on the ECG of previous myocardial infarction or pathologic Q waves or bundle-branch blocks, which could interfere with the interpretation of ST-segment changes; (3) no angiographically visible collateral blood at baseline; (4) a single proximal or mid-epicardial coronary artery lesion between 70% to 90% reduction of lumen diameter; and (5) tolerance of 2 ischemic durations of either 120 seconds or 180 seconds, with a successful balloon angioplasty resulting in residual stenosis <30%. No patient had a history of diabetes mellitus, which would confound the effect of sulfonylurea drugs. Medications, including calcium channels and β-adrenergic blockers, were withheld for 24 hours before the procedure. Any patients who had taken nitroglycerin within 4 hours of catheterization were excluded from this study. A total of 56 consecutive patients were randomly allocated to 1 of 9 groups according to age: adult groups (≥55 years old; range, 35 to 55 years; mean age, 45 ± 5 years) and elderly groups (≥65 years old; range, 65 to 78 years; mean age, 71 ± 2.3 years) (Figure). Nicorandil was intravenously administered 5 minutes before the first balloon inflation at a dose of 80 μg/kg, which has been shown to specifically activate mitochondrial KATP channels without the interference of a nitrate effect. To determine the potential role of KATP channels in preconditioning, prolonged ischemia with a coronary occlusion of 180 seconds was assessed. The study was approved by the National Taiwan University Hospital Review Board, and all subjects provided written informed consent before participation.

Study Protocol

Catheterization Procedures

Diagnostic left heart catheterization and angiography were performed from a femoral approach, as previously described. After completion of diagnostic catheterization, a 6F Judkins guiding catheter was advanced to the ostium of the left or right coronary artery. To assess collateral flow during coronary occlusion, a 0.014-inch Doppler wire (FloWire, Cardiometrics, Inc) was introduced, and the wire tip was positioned such that a characteristic and stable flow velocity waveform was obtained. Collateral blood flow was defined as retrograde or persistent antegrade flow during balloon occlusion, as previously described. The distal segment of the guide wire was placed 2 to 3 cm beyond the balloon catheter tip. The external end of the guide wire was connected to the chest lead by a sterile alligator clamp to record the intracoronary ECG. Multiple pairs of perpendicular views (90°) of the left and right coronary arteries were obtained. Quantitative measurements of coronary artery dimensions were made with the use of a computer-based edge enhancement technique (DCI System, Philips, Inc), as previously described. For each lesion, the view showing the most severe degree of stenosis was used for analysis. Blood pressure and heart rate were continuously monitored during the procedure. Patients were not sedated.

Angioplasty Procedure

After angiographic collateral assessment and intracoronary ECG monitoring, either nicorandil or the same volume of normal saline was administered through the guiding catheter. After a 5-minute drug-free period, the lesion was crossed with a balloon. After the balloon was positioned across the lesion, the patients underwent a 3-minute balloon inflation followed by one 2-minute or two 2-minute balloon inflations separated by 5-minute intervals of reperfusion, with the Doppler guide wire remaining across the lesion at the same site for each successive recording. During the reperfusion intervals, the angioplasty balloons were withdrawn from the stenotic site and the guide wire was left at the same position. Because balloon pressure is a determinant of cardiac pain during coronary angioplasty, identical balloon pressure was maintained during the first and second inflations in each patient, with inflation pressures ranging from 6.0 to 10.0 atm.

Assessment of Myocardial Ischemia

The intracoronary ECG was recorded on-line at a paper speed of 25 mm/s during the two balloon inflations and at selected times after deflation. Calibration was performed at the beginning of the proce-
dure (1 mV = 5 mm). At all time points, the ST-segment shift was measured 80 ms after the J point on a minimum of three complexes. ST-segment elevation was evaluated in a blinded manner by two observers who viewed the ECGs in random order without knowledge of which patient was being presented. Differences in interpretation were resolved by consensus. Changes in ST-segment levels recorded between the control and at the ends of the first inflation and the second inflation were compared to evaluate the severity of myocardial ischemia.

To confirm myocardial ischemia during balloon inflations, selective catheterization of the great cardiac vein was successfully attempted. Simultaneous samples of the aortic root and the great cardiac vein were obtained for measurements of lactate contents. The myocardial lactate extraction ratio (MLR) was calculated by the following formula: \( \frac{(L_{AO} - L_{CV})}{(L_{AO})} \times 100 \), where \( L_{AO} \) and \( L_{CV} \) represent plasma lactate concentrations in the aortic root and in the great cardiac vein, respectively. To determine the confounding roles of glucose and insulin in PC, sinus blood samples, reflecting local concentrations for glucose and insulin concentrations, were assayed. For comparisons, peripheral venous blood for measuring glucose and insulin concentrations was also sampled before glibenclamide was administered.

Before coronary angioplasty, patients were informed that they might have chest pain during balloon inflations. Immediately before termination of balloon inflation, patients were asked to quantify the intensity of cardiac pain by using a visual-analog scale on a scale of 0, from no pain (0) to the most severe pain (10).

**Statistics**

Continuous variables are expressed as mean±SD. Patients were analyzed by means of ANOVA among the groups. A 2-way repeated-measures ANOVA was used to search for possible effects of nicorandil and glibenclamide on the measurements of intracoronary ECG and lactate and, if an F value was found to be significant, a 2-tailed Student’s t test for paired observation with Bonferroni correction was used to test differences. The interaction term of nicorandil and glibenclamide effects was incorporated into the model. Visual analog scales were analyzed by means of the Wilcoxon signed rank test. \( \chi^2 \) analysis was used for categoric variables and Fisher’s exact test was used for patient numbers <5. Probability values are 2-tailed, and a value of \( P<0.05 \) is considered statistically significant.

**Results**

The clinical features of the patients are outlined in Table 1. There were no significant differences among the groups regarding sex or the frequency of cardiovascular risk factors. Coronary stenosis was similarly reduced among the groups (Table 2). Glucose concentrations were fairly stable throughout the study. Insulin concentrations were significantly increased in patients administered with glibenclamide. The balloon pressure used was similar (data not shown). No myocardial injury was reflected in any patients after angioplasty as assessed by ECG.

**Hemodynamics**

No significant changes were seen in mean blood pressure and heart rate among the 9 groups at baseline and after the first and second angioplasty (data not shown). Rate-pressure product, an index of oxygen consumption, was comparable among the 9 groups (Table 2).

The quantitative variables for the assessment of the collateral circulation obtained during the first and second balloon inflations indicated the presence of low-grade collaterals and did not differ among the study groups.

**Myocardial Ischemia**

**Cardiac Pain**

Before each inflation, all patients were asymptomatic. In the adult preconditioning group, chest pain during the second inflation was significantly smaller than during the first inflation, indicating effective PC. In contrast, the chest pain score at the first inflation was significantly smaller in the nicorandil-treated group versus the preconditioning group at the first inflation. Although patients in the preconditioning and nicorandil-treated groups had less anginal severity at the second inflation, cardiac pain was significantly higher in patients pretreated with glibenclamide (Table 3).

However, in the elderly preconditioning group, with a coronary occlusion of 120 seconds, the severity of chest pain was similar at the first and second inflations, in contrast to the adult preconditioning group. With a longer 180-second ischemic period, chest pain at the second inflation was significantly higher in the adult preconditioning group versus the preconditioning group at the first inflation. Although patients in the preconditioning and nicorandil-treated groups had less anginal severity at the second inflation, cardiac pain was significantly higher in patients pretreated with glibenclamide (Table 3).

TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Adult Group</th>
<th></th>
<th></th>
<th>Elderly Group</th>
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<td></td>
<td>PC</td>
<td>NC</td>
<td>Glib</td>
<td>Glib+NC</td>
<td>PC</td>
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<td>Age, y</td>
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<td>46±5</td>
<td>41±7</td>
<td>45±5</td>
<td>72±4</td>
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<td>Male/female</td>
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<td>6/2</td>
<td>4/2</td>
<td>4/1</td>
<td>5/2</td>
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<tr>
<td>CAD risk factor</td>
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<tr>
<td>Hypertension, %</td>
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<td>5 (63)</td>
<td>4 (67)</td>
<td>3 (60)</td>
<td>5 (71)</td>
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<td>Smoking, %</td>
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<td>4 (50)</td>
<td>4 (67)</td>
<td>4 (80)</td>
<td>4 (57)</td>
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<td>Tchol, mg/dL</td>
<td>218±30</td>
<td>230±33</td>
<td>221±56</td>
<td>242±22</td>
<td>235±37</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>265±52</td>
<td>241±68</td>
<td>248±36</td>
<td>264±50</td>
<td>242±60</td>
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<tr>
<td>Vessel disease</td>
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<td></td>
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<tr>
<td>LAD</td>
<td>4</td>
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<td>LCX</td>
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<td>RCA</td>
<td>1</td>
<td>2</td>
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<td>0</td>
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</table>

Glib indicates glibenclamide; PC, preconditioning; NC, nicorandil; LAD, left anterior descending artery; LCX, left circumflex artery; CAD, coronary artery disease; Tchol, total cholesterol; TG, triglycerides; and RCA, right coronary artery.

Values are mean±SD or number (%). An adult or elderly group was defined as patient age ≤55 or ≥65 years old.
TABLE 3. Myocardial Ischemia Evaluated by Subjective Cardiac Pain, Values of ST-Segment Shift, and MLR Throughout the Study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adult Group</th>
<th>Elderly Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC</td>
<td>NC</td>
</tr>
<tr>
<td>Cardiac pain</td>
<td>6.0 ± 0.8</td>
<td>3.4 ± 0.7†</td>
</tr>
<tr>
<td>ST-segment shift, mV</td>
<td>2.3 ± 0.5*</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>1.10 ± 0.31</td>
<td>0.51 ± 0.06†</td>
</tr>
<tr>
<td></td>
<td>0.43 ± 0.08*</td>
<td>0.48 ± 0.07</td>
</tr>
<tr>
<td>MLR, %</td>
<td>20 ± 15</td>
<td>13 ± 25</td>
</tr>
<tr>
<td></td>
<td>−98 ± 40‡</td>
<td>−0.2 ± 18‡</td>
</tr>
<tr>
<td></td>
<td>−25 ± 29*</td>
<td>−0.2 ± 26</td>
</tr>
</tbody>
</table>

PC indicates preconditioning; NC, nicorandil; Glib, glibenclamide. Values are mean ± SD. An ST-segment shift was defined as the differences in ST-segment levels between baseline and end of the first inflation and the second inflation. *P<0.05 compared with data from inflation 1; †P<0.05 compared with PC group at the same time classified by age; ‡P<0.05 compared with baseline.

provided similar effects in both elderly and adult patients. In the nicorandil-treated patients in combination with either preconditioning or nicorandil, cardiac pain severity at the end of the second inflation was similar to that at the first inflation, indicating that nicorandil abolished the cardioprotective effects.

**Intracoronary ECG**

Before each inflation, there was no ST-segment shift in the intracoronary ECG. In the adult preconditioning group, the mean ST-segment shift at the second balloon inflation was less than observed at the first inflation (1.10 ± 0.31 versus 0.43 ± 0.08 mV at the second inflation, P=0.0007), whereas in the elderly preconditioned patients, the shift was similar at the first and second inflations (Table 3). In the elderly patients with a longer 180-second ischemic period, the changes in the ST-segment shift were less at the second inflation compared with those at the first inflation. In the nicorandil-treated patients, the changes of ST-
Lactate Measurements

The respective baseline values were positive and similar, indicating the absence of significant lactate production in the preangioplasty state. MLR was more negative in the preconditioning group than in the adult preconditioning group at the end of the second inflation (P < 0.01), indicating less lactate production from ischemic myocardium in the latter group. In the elderly group, during prolonged ischemia with 120-second occlusion, lactate production from the great cardiac vein was significantly higher versus the group with a 120-second ischemia (1.1 ± 0.2 in 120-second ischemia versus 1.6 ± 0.3 mmol/L, P < 0.006) at the end of the first inflation. The benefits of metabolic features were abolished after administering glibenclamide in both adult and elderly groups.

Discussion

This study showed that the beneficial effects of PC on ischemic tolerance were seen in adults but not in senescent hearts. To the best of our knowledge, this is the first report revealing that a loss of PC in aged patients undergoing angioplasty was inadequate activation for KATP channels during myocardial ischemia, which can be reversed by either prolonged ischemic duration or exogenous agonists of KATP channels. These results suggest that the impaired PC response was associated with some defects in signal transduction of activation of KATP channels with aging.

The observation that aged hearts have a reduced PC confirms previous findings,11,12 showing that PC was not effective in the aged myocardium. Since activation of mitochondrial KATP channels is a common effector for triggering PC,8 we suggest that attenuated activation of KATP channels plays an important role in impaired PC. This notion is supported by the following observations: (1) A 120-second occlusion was effective in reducing ST-segment levels only in adult patients but not in elderly patients. Prolonged ischemia with a 180-second balloon inflation was effective in the elderly patients. A longer period of occlusion caused higher lactate accumulation in the great cardiac vein. Landry et al18 have shown that lactate directly activates KATP channels in humans, although a negative result was shown in rat myocardium.19

The conflicting results could be due to differences between species. (2) The impairment of PC in the aged heart was not observed when the KATP channel agonist nicorandil was used. Nicorandil is a specific agonist of mitochondrial KATP channels.8 In the elderly groups, the ST-segment shifts and chest pain scores noted at the first inflation in nicorandil-treated patients were indistinguishable from those observed at the second inflation in the group with prolonged ischemia, suggesting that the degree of protection afforded by nicorandil was comparable to that afforded by prior exposure to ischemia. (3) The effect of nicorandil on PC was abolished by pretreatment with glibenclamide, confirming the predominant role of KATP channels in this phenomenon.

Aging and KATP Channels

The mechanisms by which aging affects PC remain undefined. However, several factors can be excluded: (1) Hemodynamics and collateral circulation: Aging did not exert any hemodynamic effects, nor was it associated with an increase in myocardial collateral blood flow. (2) Differences in ischemic burden: The severity of the ischemic burden is of concern because of the difference in activation of KATP channels in a graded pattern. Except for patients in the group with a 180-second ischemia, our protocol provided similar ischemic burdens in both adult and elderly patients, as documented by parameters of myocardial ischemia. Thus, the inadequate stimulation of KATP channels to trigger PC in the aged hearts was not due to different ischemic severities. (3) Differences in insulin concentrations: Although glibenclamide stimulates insulin secretion as shown in this study, the increased insulin levels cannot be a confounding factor of PC. Increased insulin levels have been shown to enhance PC.20 Thus, if glibenclamide had induced PC by increasing insulin levels, we should have obtained fewer ECG changes and less pain in glibenclamide-treated patients at the end of the first inflation.

The diminished responses in elderly patients are not due to nonspecific impairment of PC because their responses to prolonged ischemia and an exogenous agonist, nicorandil, were preserved. There may be some mechanisms related to the elevated threshold for inducing PC in aged hearts. First, it is possible that the number or affinity of KATP channels in the myocardium decreases with aging. No data are available regarding changes in myocardial KATP channels with aging or their functional consequences. Single-channel recordings have shown that the open probability and the density of KATP channels of rat skeletal muscle fibers are reduced by aging.21 An age-dependent increase of oxygen free radicals has been proposed as one of the mechanisms responsible for an attenuated response of KATP channels.21 Oxygen free radicals may react with various thio-containing proteins, including channel proteins, from the reduced to the oxidized form. Mitochondrial KATP channels, formed by assembly of Kir6.1 and the sulfonylurea receptors, contains thio groups.22 L-Cysteine, a sulf-hydril group—reducing agent, restored the open probability of KATP channels of aged rats.23 Besides, aged hearts have been shown to be intrinsically more susceptible to oxidant damage associated with ischemia-reperfusion.24 Thus, age-related oxidant damage, especially during stressful conditions, such as myocardial ischemia, could be a functional disadvantage in the activation of KATP channels.
Second, aged hearts are inferior to adult hearts in translating the signals to the biochemical steps necessary for inducing PC. Many agonists have been shown to trigger the opening of KATP channels, including catecholamines, adenosine, and heat shock proteins.24 Norepinephrine has been proposed as a mediator of triggering PC. Norepinephrine release in response to PC is reduced in the senescent rat heart, and an exogenous administration of norepinephrine is able to restore PC.11 Cai et al25 have shown reduced adenosine receptors and G-protein coupling in rat ventricular myocardium during aging. Exogenous adenosine has been shown to enhance PC in the aged hearts.26 In addition, Nitta et al27 suggested that the greater vulnerability of aged hearts to ischemia may be due to impaired production of heat shock protein 70. Finally, a failure of protein kinase C translocation,28 a common pathway for activating KATP channels, may contribute to attenuated activation of KATP channels in aged hearts. Thus, insufficient activation of an endogenous mechanism allowing for maximal cardioprotection may explain why the aging heart is more sensitive to ischemia. However, with multiple regulatory mechanisms contributing to the activation of KATP channels, an alteration in one mechanism could be compensated for a change in another to maintain near normality of activation. Thus, in the in vivo approach, it would be difficult to distinguish whether different responses to PC in the elderly versus adult patients were due to differences in KATP channel sensitivity per se or its mediators. Either way, there is an age-related decline in activation of KATP channels, which may contribute to impaired cardiac protection by PC in elderly patients.

**Clinical Implications**

Previous studies have shown that coronary artery disease in elderly patients is associated with a high mortality rate, implying an impaired PC responsiveness.29 Whether this age-related impaired PC responsiveness is associated with a more severe coronary atherosclerosis is unclear. In this study, we selected a homogeneous group of patients with similar stenosis of a major epicardial artery. Thus, the absence of cardioprotection in elderly patients may not be related to a more extensive coronary artery disease but to an attenuated activation of PC. The possible loss of PC in the aging heart might account in part for the higher mortality rate from acute coronary syndrome observed in elderly patients. The lack of PC can be reversed by pharmacological preconditioning with nicorandil in elderly patients who underwent coronary angioplasty, coronary artery bypass surgery, and valvular surgery to limit the detrimental effects of myocardial ischemia. This is especially so in high-risk patients, including those with severely depressed left ventricular function, left main coronary artery disease, and unstable angina. However, more clinical studies are necessary to confirm this finding.

**Conclusions**

The present study demonstrates that PC significantly enhances the tolerance of the heart to subsequent ischemia in adults but not in senescent patients, as assessed by clinical, ECG, and metabolic evidence. Since prolonged ischemia and exogenous KATP channel agonists (nicorandil) are able to mimic PC in both adult and senescent hearts, the impaired PC response of the aged heart appears not to be due to a defect in the downstream signal pathways per se but to an impaired initial activation of KATP channels.

**Acknowledgments**

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