Ischemic preconditioning during coronary angioplasty is preserved in elderly patients

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Aging; Coronary angioplasty; Ischemic preconditioning.

Background. **To establish whether the adaptation to ischemia observed in humans during percutaneous transluminal coronary angioplasty (PTCA) after repeated balloon inflations, i.e. a clinical correlate of ischemic preconditioning, is preserved in elderly patients.**

Methods. **We studied 53 consecutive patients undergoing successful angioplasty for an isolated stenosis of a major epicardial coronary artery. On the basis of age, patients were separated into terciles: patients in the lower and middle terciles were grouped together (Group 1, adult patients, n = 24, mean age 50 – 6 years) and compared with those in the upper tercile (Group 2, elderly patients, n = 29, mean age 68 – 3 years). Intracoronary electrocardiogram was obtained at the end of the first two balloon inflations. Collateral recruitment during repeated balloon inflations was assessed by using an intracoronary Doppler guide wire (23 patients) or by using an intracoronary pressure guide wire (30 patients).**

Results. **In Group 1, ST-segment changes during the second inflation were significantly less than those at the end of the first inflation (6 – 3 vs 13 – 5 mm, p < 0.001). Similarly, in Group 2, ST-segment changes during the second inflation were significantly less than those at the end of the first inflation (6 – 4 vs 13 – 6 mm, p < 0.001). In both groups, collateral recruitment did not change from the first inflation to the second inflation (p = 0.1).**

Conclusions. **Our study confirms that adaptation to ischemia during repeated balloon inflations in the setting of PTCA is independent of collateral recruitment and, therefore, is mainly due to ischemic preconditioning. More importantly, our study indicates that ischemic preconditioning is preserved in elderly patients.**

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Introduction

Ischemic preconditioning, a powerful form of myocardial protection from irreversible ischemic injury, has been shown in all animal species investigated[1-4] and, recently, in isolated human myocytes[5] and atrial trabeculae[6]. There is now evidence indicating that ischemic preconditioning occurs also in humans in the setting of percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass surgery, pre-infarction angina and exercise-induced ischemia[7]. Experimental studies, however, suggest that the cardioprotective effect of preconditioning might be lost in the aging heart[8,9]. Age-related reduction of the cardiac protective effect of ischemic preconditioning might help explain why age is an independent predictor of mortality rate in patients with acute myocardial infarction[10]. It is worth noting that, in a recent study, Abete et al.[11] found that the protective effect of pre-infarction angina was attenuated in the elderly. Indeed, the odds ratio for in-hospital adverse events in patients with pre-infarction angina compared with those without was remarkably low in patients < 65 years old (0.13) and sensibly higher and no longer significant in patients 65 years old (0.63). The authors speculated that the attenuation of the protective effect of pre-infarction angina in elderly patients was due to the attenuation of the protective effect of ischemic preconditioning[11]. However, the mechanisms responsible for the beneficial effects of pre-infarction angina are multiple, including ischemic preconditioning, collateral recruitment and earlier reperfusion[12].

Thus, the present study was aimed at establishing whether metabolic adaptation to

ischemia operates also in elderly patients, during repeated coronary balloon occlusions in the setting of elective successful PTCA. Indeed, in this clinical model the role played by ischemic preconditioning in determining adaptation to ischemia can be assessed more directly than in the clinical model of pre-infarction angina[7].

Methods

Patient population. On the basis of age, 53 consecutive patients, who underwent successful uncomplicated elective PTCA for an isolated obstructive lesion (internal diameter reduction comprised 50 to 90% on the basis of the use of the quantitative cardiovascular software program ACA, Philips, DCI, Best, The Netherlands)[13] in the proximal two thirds of a major epicardial coronary artery, were separated into terciles: 9 patients were in the lower tercile (from 38 to 48 years), 15 patients in the middle tercile (from 49 to 59 years) and 29 patients in the upper tercile (from 60 to 70 years). For statistical analysis, patients in the lower and middle terciles were grouped together (Group 1, adult patients, n = 24) and compared to those in the upper tercile (Group 2, elderly patients, n = 29). Patients with stenoses > 90% were not included in the study, in order to avoid pre-inflation ischemia due to obstruction from the guide wire across the lesion, which would prolong the ischemic time of the first inflation compared with the second[14]. All patients fulfilled the entry criteria of: 1) history of chronic stable angina pectoris lasting 3 months, 2) no history of previous myocardial infarction nor pathologic Q waves on the electrocardiogram (ECG), 3) no angiographic evidence of coronary collateral vessels (grade 0, according to Rentrop s classification)[15], and 4) right dominant coronary circulation. No patient had evidence of left ventricular hypertrophy or of wall motion abnormalities on the echocardiogram or conduction defects on the ECG that could have interfered with the interpretation of ST-segment changes. All patients had normal hepatic and renal function, and fasting blood glucose levels. Beta-adrenergic blocking agents were withdrawn 5 days before the study. All patients were on oral aspirin (100 mg od), diltiazem (60 mg tid) and isosorbide dinitrate (40 mg bid) for 48 hours before PTCA. All patients received the morning dose of treatment prior to PTCA, which was performed within the next 4 hours. No patient had angina in the last 24 hours before the study. No patient received sublingual or intravenous nitrates in the last 24 hours before the study or throughout the study. Patients were not pre-medicated with diazepam or other sedatives. All patients gave written informed consent for participation in the study, which was approved by the Institutional Ethics Committee.

Study protocol. PTCA of the stenosed artery was performed within 5 days of the diagnostic coronary angiography, by a standard technique using the right femoral approach, as previously described[16]. Briefly, after heparinization (10 000 IU i.v.) and placement of the guiding catheter through an 8-F femoral sheath in the right femoral artery and performance of baseline angiography, the guide wire was placed across the lesion in the distal segment of the stenosed artery. The balloon catheter was then placed within the stenosis and the balloon was inflated for 2 min. After balloon deflation and withdrawal proximal to the lesion, with the guide wire still across the lesion, a recovery period of 5 min was allowed to reestablish baseline hemodynamic and ECG conditions. A second balloon inflation for 2 min was then performed. In each individual patient, balloon pressure during the first and second inflation was identical. After the first two inflations, PTCA was completed on the basis of the specific needs of individual patients.

Assessment of myocardial ischemia. Standard surface 12-lead and intracoronary ECGs derived from the angioplasty guide wire were continuously monitored and simultaneously recorded (Mingograph 7, Siemens, Solna, Sweden) at a paper speed of 25 mm/s throughout the study. The ECGs were analyzed by a cardiologist who had no knowledge of the study protocol. At baseline (with just the guide wire across the lesion) and at the end of the first two inflations, ST-segment shift was measured 80 ms after the J point. The severity of myocardial ischemia was expressed as: 1) the summation of the absolute values of ST-segment elevation or depression from baseline, on surface ECG, from all 12 leads; and 2) the absolute values of ST-segment elevation or depression from baseline on intracoronary ECG. ST-segment shifts were expressed in millimeters (1 mm = 0.1 mV).

Assessment of cardiac pain. At the beginning of each PTCA procedure, patients were informed that they might develop chest pain. At the end of the first two balloon inflations, the intensity of cardiac pain was assessed by using a visual analog scale[17]. Patients were asked to put a mark on a 100-mm scale marked from no symptoms (0) to severe symptoms (100). For each inflation, the severity of cardiac pain divided by the absolute values of ST-segment shifts on intracoronary ECG at the end of the inflation was also obtained as an index of pain severity normalized for the degree of myocardial ischemia.

Intracoronary Doppler flow velocity and pressure measurements. In the first consecutive 23 patients (11 patients in Group 1, and 12 patients in Group 2), a 5-F femoral sheath was also inserted in the left femoral artery. A 5-F Judkins femoral catheter was advanced through the left femoral sheath into the ostium of the contralateral coronary artery for guidance of a 0.014-in. (0.036 cm) Doppler-tipped guide wire (FloWire, Cardiometrics, Mountain View, CA, USA). After placement of the angioplasty guiding catheter into the ostium of the coronary artery to be dilated, a 0.014-in Doppler-tipped intracoronary guide wire (FloWire and FloMap,

Cardiometrics) was advanced through the 5-F Judkins catheter into the medium tract of the contralateral vessel (right or left anterior descending coronary artery) and positioned until an optimal and stable Doppler signal, not in the proximity of a side branch, was obtained. Blood flow velocity was calculated as previously described[18]. Average peak velocity in the contralateral artery was measured before and at the end of the first two inflations. Collateral recruitment was expressed as the changes in average peak velocity in the contralateral coronary artery during the first and second balloon inflations.

In the remaining 30 patients (13 patients in Group 1, and 17 patients in Group 2), PTCA was performed by using a 0.014-in fiberoptic pressure monitoring guide wire (Pressureguide, Radi Medical, Uppsala, Sweden)[19]. After placement of the angioplasty guiding catheter into the ostium of the coronary artery to be dilated, the pressure guide wire was set at zero, calibrated, advanced through the guiding catheter and placed across the lesion in the distal segment of the stenosed artery. The intracoronary pressure-derived collateral flow index, which expresses collateral flow relative to normal flow through the patent vessel, was determined by simultaneous measurements of mean aortic pressure (P_{Ao}, mmHg, via the angioplasty guiding catheter) and the distal coronary artery pressure during balloon occlusion (coronary wedge pressure, P_w, mmHg, via the pressure guide wire). Central venous pressure (CVP, mmHg) was measured in the right atrium through a 5-F NIH catheter advanced through a right femoral vein sheath. Collateral flow index was calculated as (P_w - CVP) divided by (P_{Ao} - CVP)[19] and determined at the end of the first two inflations.

Statistical analysis. Two-factor repeated measures ANOVA with repeated measures on one factor was used to compare ischemic ECG, average peak velocity and collateral flow index changes during balloon inflations in adult (Group 1) and elderly (Group 2) patients. When significant differences were detected, pairwise comparisons were made using the ScheffØ F test. Comparisons of the remaining continuous or discrete variables between the two groups were performed using an unpaired Student s t test or a χ^2 test, respectively. Visual analog scales were analyzed using the Wilcoxon signed rank test or the Mann-Whitney U test as appropriate. Correlations between changes in average peak velocity or in collateral flow index from the first to the second inflation and changes in ST-segment shift were assessed by univariate linear regression analysis. Data are expressed as mean – 1 SD; values of $p < 0.05$ were considered statistically significant.

Results

The two groups of patients did not differ in clinical, anatomic or hemodynamic features (Table I). In both groups, the values of systolic arterial pressure and heart rate were similar before and at the end of the first two inflations (Table I).

PTCA was successfully performed in all 53 patients (residual stenosis < 30%) (Table I). The mean balloon pressure and the recovery period between the two balloon inflations were similar in Group 1 and Group 2 (5.3 – 1.5 vs 5.6 – 1.2 atm, p = 0.5, and 337 – 44 vs 331 – 45 s, p = 0.6, respectively).

Table I. Clinical, anatomic and hemodynamic features in the two groups of patients.

	Group 1 (n=24)	Group 2 (n=29)	p
Age (years)	50 – 6	68 – 3	0.001
Sex (M/F)	20/4	22/7	0.7
Vessel disease (%)			
LAD	70	52	
LCx	17	24	0.4
RCA	13	24	
Degree of stenosis (%)			
Before PTCA	87 – 8	88 – 10	0.7
After PTCA	20 – 10*	19 – 12*	0.8
Heart rate (b/min)			
Baseline 1	72 – 11	74 – 16	0.7
Inflation 1	72 – 11	74 – 14	0.5
Baseline 2	72 – 11	73 – 15	0.7
Inflation 2	71 – 11	73 – 14	0.6
Systolic arterial pressure (mmHg)			
Baseline 1	136 – 22	134 – 22	0.8
Inflation 1	132 – 17	131 – 16	0.9
Baseline 2	135 – 15	136 – 23	0.8
Inflation 2	131 – 13	133 – 16	0.7

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery. * $p < 0.001$ vs stenosis before PTCA.

Myocardial ischemia. The values of ST-segment shift from baseline at the end of the first two inflations are reported in table II and figure 1. In Group 1, the mean ST-segment shift at the end of the second balloon inflation was significantly less than that at the end of the first inflation on both the surface ECG (7 – 4 vs 11 – 4 mm, $p < 0.001$) and the intracoronary ECG (6 – 3 vs 13 – 5 mm, $p < 0.001$). Similarly, in Group 2, the mean ST-segment shift at the end of the second balloon inflation was significantly less than that at the end of the first inflation on both the surface ECG (5 – 3 vs 9 – 4 mm, $p < 0.001$) and the intracoronary ECG (6 – 4 vs 13 – 6 mm, $p < 0.001$). Of note, there was no significant difference between the two groups of patients in the degree of ST-segment shift at the end of the first and the second inflation on either surface ($p = 0.1$ and $p = 0.08$, respectively) or intracoronary ECG (both $p = 0.9$).

Cardiac pain. In Group 1, the severity of cardiac pain at the end of the second inflation was less than that at the end of the first inflation (24 – 17 vs 48 – 23 mm, $p < 0.001$). Similarly, in Group 2, the severity of cardiac pain at the end of the second inflation was less than that at the end of the first inflation (26 – 15 vs 47 – 19 mm, $p < 0.001$) (Table II, Fig. 1). Of note, there was no significant difference between the two groups of patients in cardiac pain severity at the end of the first ($p = 0.9$) and the second ($p = 0.6$) inflation. In both groups, the severity of cardiac pain normalized for the absolute values of ST-segment shift on the intracoronary ECG did not significantly change from the first to the second in-

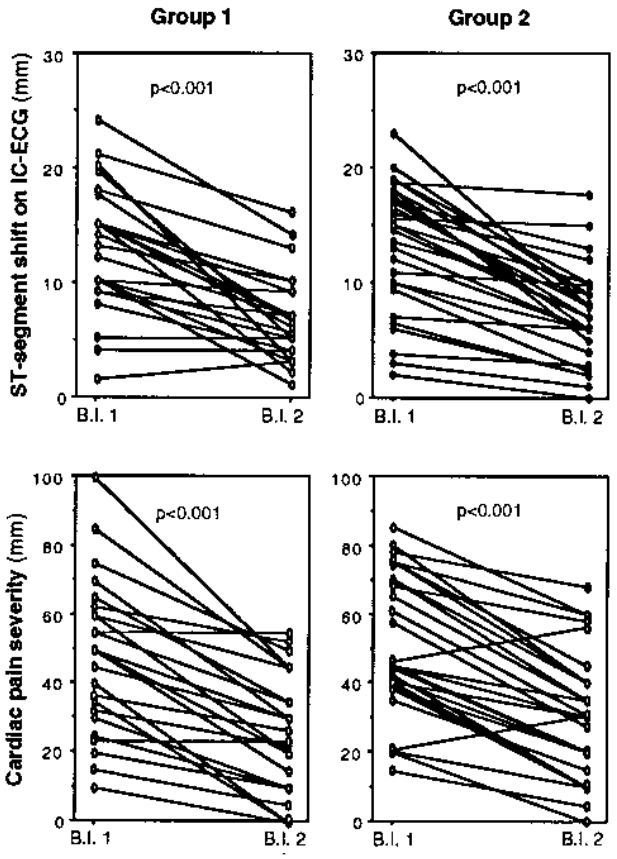

Figure 1. *Individual values of ST-segment shifts on the intracoronary electrocardiogram (IC-ECG) and of cardiac pain severity at the end of the first and second balloon inflations (B.I.) in the two groups of patients. In both groups, ST-segment changes and cardiac pain severity at the end of the second balloon inflation were significantly less than those at the end of the first inflation.*

Table II. Values of ST-segment shift, cardiac pain, average peak velocity and collateral flow index in the two groups of patients.

	Group 1 (n=24)	Group 2 (n=29)	p
ST-segment shift on S-ECG (mm)			
Inflation 1	11 – 4	9 – 4	0.1
Inflation 2	7 – 4*	5 – 3*	0.08
ST-segment shift on IC-ECG (mm)			
Inflation 1	13 – 5	13 – 6	0.9
Inflation 2	6 – 3*	6 – 4*	0.9
Pain severity (mm)			
Inflation 1	48 – 23	47 – 19	0.9
Inflation 2	24 – 17*	26 – 15*	0.6
Pain severity/ST on IC-ECG			
Inflation 1	5.1 – 4.6	5.6 – 6.7	0.7
Inflation 2	4.1 – 3.4	5.2 – 3.9	0.4
Average peak velocity (cm/s)			
Baseline 1	21 – 11	22 – 14	0.8
Inflation 1	25 – 12*	26 – 14*	0.8
Baseline 2	21 – 11	22 – 14	0.9
Inflation 2	25 – 12*	26 – 14*	0.8
Collateral flow index			
Inflation 1	0.16 – 0.10	0.16 – 0.10	1.0
Inflation 2	0.16 – 0.11	0.16 – 0.09	0.9

Values of average peak velocity in the contralateral coronary artery refer to the first 23 patients (11 in Group 1 and 12 in Group 2); values of collateral flow index refer to the remaining 30 patients (13 in Group 1 and 17 in Group 2). IC-ECG = intracoronary electrocardiogram; S-ECG = surface 12-lead electrocardiogram. * $p < 0.001$ vs inflation 1 value.

flation (from 5.1 – 4.6 to 4.1 – 3.4, p = 0.1, and from 5.6 – 6.7 to 5.2 – 3.9, p = 0.4, respectively) and was similar between groups at the end of the first (p = 0.7) and the second inflation (p = 0.4) (Table II).

Collateral recruitment. The values of average peak velocity in the contralateral artery in the first 23 patients and those of collateral flow index in the remaining 30 patients are reported in table II. In both groups, average peak velocity in the contralateral coronary artery significantly increased from baseline to the end of the first inflation (from 21 – 11 to 25 – 12 cm/s, p < 0.001, and from 22 – 14 to 26 – 14 cm/s, p < 0.001, respectively), but it did not show a further increase during the second inflation (25 – 12 and 26 – 14 cm/s, respectively; p = 0.9 and p = 0.1 vs the first inflation). Of note, there was no significant difference between the two groups of patients in average peak velocity at the end of the first (p = 0.8) and the second inflation (p = 0.8). Similarly, in both groups, collateral flow index did not change from the first to the second inflation (from 0.16 – 0.10 to 0.16 – 0.11, p = 0.1, and from 0.16 – 0.10 to 0.16 – 0.09, p = 0.1, respectively) and was similar between the two groups at the end of the first (p = 1.0) and the second inflation (p = 0.9). Finally, in both groups, changes in average peak velocity (r = 0.02, p = 0.9, and r = 0.3, p = 0.4, respectively) or in collateral flow index (r = 0.2, p = 0.5, and r = 0.1, p = 0.7, respectively) from the first to the second inflation did not correlate with those in ST-segment shift on intracoronary ECG.

Discussion

Our results, in agreement with those of previous studies based on the same clinical model[16,20-23], confirm that in patients with poorly grown coronary collaterals at angiography adaptation to ischemia during repeated balloon inflations in the setting of PTCA is independent of collateral recruitment and, therefore, is mainly due to ischemic preconditioning. More importantly, our study indicates that in this clinical model ischemic preconditioning is preserved in elderly patients.

Ischemic preconditioning response in elderly patients. With advancing age there are anatomic, mechanical, ultrastructural, and biochemical alterations that compromise the adaptive response of the heart[24]. In particular, a number of experimental studies have shown that the aging heart exhibits reduction of adrenergic responsiveness[25], alteration of coronary microcirculation[26], impairment of calcium transport[27], and of excitation-contraction coupling[28]. Aging hearts are also more vulnerable to global ischemia[29] and protected cardioplegic arrest[30]. Taken together these experimental findings may at least partially explain why patient age is a powerful independent predictor of a poor clinical outcome following acute myocardial infarction[10], coronary artery bypass surgery[31] or PTCA[32]. More recently, it has been suggested that the greater vulnerability of elderly patients to the ischemic insult might be related also to the lack or attenuation of an endogenous mechanism of myocardial adaptation to ischemia, i.e. ischemic preconditioning[11]. Indeed, in isolated and perfused rat hearts, Abete et al.[8] demonstrated that ischemic preconditioning reduces postischemic dysfunction in adult but not in senescent hearts, findings consistent with those of Tani et al.[9] in a similar experimental model. These findings, however, were not confirmed in other experimental models. For instance, Burns et al.[33] found that the degree of the cardioprotective effect of preconditioning, as measured by a reduction in infarct size, was similar in senescent and young adult ovine hearts. Similarly, McCully et al.[34] found that adenosine enhancement of cardioprotection afforded by ischemic preconditioning, resulting in a reduction of infarct size and enhancement of postischemic functional recovery, was preserved in senescent isolated rabbit hearts. These contrasting findings indicate that the effect of aging on ischemic preconditioning might differ remarkably in different experimental models and in different species. Therefore, we addressed this problem in humans. Our results indicate that the progressive myocardial adaptation to ischemia observed during repeated balloon occlusions, an experimentally validated clinical model of ischemic preconditioning[35], is not affected by aging. Indeed, the reductions of ECG ischemic changes and of cardiac pain severity during the second balloon inflation were similar in adult and elderly patients. Of note, in both groups, the severity of cardiac pain normalized for the severity of myocardial ischemia did not change from the first to the second inflation and was similar between groups at the end of both first and second inflations. These findings indicate that the lessening of anginal pain during the second inflation was entirely predicted by the lessening of myocardial ischemia independently of patient age. Finally, as the mean age of elderly patients enrolled in the present study was 68 years, we cannot rule out that the protective effect of ischemic preconditioning is attenuated or even lost in older patients. This hypothesis is supported by a recent study showing that the warm-up effect on exercise, another clinical correlate of preconditioning, is lost in a cohort of patients of mean age 76 years[36].

Role of collateral recruitment. The major limitation with the PTCA model of ischemic preconditioning is the possibility that the adaptation to ischemia observed following repeated coronary balloon occlusions might be due to progressive collateral recruitment, rather than to a metabolic myocardial adaptation. In this study, we assessed collateral recruitment by using two different methods, i.e. intracoronary Doppler and pressure wires. Changes in blood flow velocity in the contralateral coronary artery during balloon occlusion by using a

Doppler guide wire, in the absence of significant changes in arterial pressure or heart rate, as was the case in our study at the end of both inflations, represent a reliable quantitative index of collateral perfusion during PTCA[37]. Similarly, pressure-derived collateral flow index, which allows us to measure collateral flow as a percentage of antegrade flow through the patent vessel, is a well accepted quantitative index of collateral perfusion[19].

We found that coronary blood flow velocity increased at the end of the first inflation but did not increase further at the end of the second inflation. Similarly, collateral flow index did not increase from the first to the second inflation. These findings, therefore, suggest that in patients with poorly grown coronary collaterals at angiography, the adaptation to ischemia during repeated coronary balloon occlusions is not due to progressive collateral recruitment, but rather to ischemic preconditioning. They confirm our previous results[22,23] and are in agreement with those of Kyriakidis et al.[38] and Sakata et al.[39]. At variance with these results, in patients with poorly grown coronary collaterals, Billinger et al.[40] have recently shown a significant relationship between ECG ischemic changes and pressure-derived collateral flow index during repeated balloon occlusions. However, they measured ST-segment shifts only 1 min after the beginning of balloon inflations, a period insufficient for the achievement of the full evolution of ST-segment shift, and adjusted ST-segment amplitude with QRS amplitude, an index of myocardial ischemia which remains to be validated in the experimental setting of repeated balloon inflations. Finally, further analysis showed that collateral recruitment accounted for 30% only of the observed variation in ECG ischemic changes, thus implying an important role for ischemic preconditioning in the adaptation to ischemia during PTCA.

It is worth noting that in both adult and elderly patients and at the end of both first and second balloon inflations, collateral flow accounted for about 15% of the normal flow through the patent vessel. This suggests that the capability of the senescent myocardium to recruit collaterals is preserved; impaired collateral recruitment is, therefore, unlikely to account for the attenuation of the protective effect of pre-infarction angina in elderly patients[11].

Conclusions and clinical implications. Our findings indicate that both ischemic preconditioning and collateral recruitment during repeated balloon inflations in the setting of PTCA are well preserved in elderly patients. Therefore, our results indicate that the attenuation of the beneficial effects of pre-infarction angina in elderly patients[11] is unlikely to be due to loss of ischemic preconditioning or collateral recruitment. It might be due, theoretically, to loss of earlier reperfusion, which is one of the mechanisms proposed to explain the better prognosis of patients with pre-infarction angina[41]. It is worth noting that the mean age of elderly patients enrolled in the present study was 68 years, thus further investigations are warranted to establish whether the preconditioning response during PTCA is preserved also in octogenarian patients. Finally, our findings suggest that preconditioning-mimetic drugs may confer additional cardioprotection to standard medical treatments in elderly patients. This is of clinical relevance in an increasingly aged patient population.

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