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No Loss in the In Vivo Efficacy of Ischemic Preconditioning in Middle-Aged and Old Rabbits

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OBJECTIVES We tested the hypothesis that cardioprotection with ischemic preconditioning (PC) is lost in the aging, or senescent, heart.

BACKGROUND Although infarct size reduction with PC has been documented in virtually all models, a purported exception to this paradigm is the aging heart, the population in which cardioprotection is most relevant. However, no previous studies have assessed the concept of an age-associated loss in the efficacy of PC in an in vivo model of acute myocardial infarction in which definitive hallmarks of cardiovascular aging were demonstrated and a reduction of infarct size, the "gold standard" of PC, served as the primary end point.

METHODS Using the in vivo rabbit model, three cohorts of animals were studied: adult (4 to 6 months old), middle-aged (~2 years old) and old (~4 years old) rabbits. Within each cohort we assessed: 1) infarct size (measured by tetrazolium staining and expressed as percent myocardium at risk) in control and PC groups; and 2) morphologic and functional hallmarks of cardiovascular aging (progressive myocyte hypertrophy, increased myocardial fibrosis and attenuated responsiveness to beta-adrenergic stimulation).

RESULTS In adult animals, infarct size was significantly smaller in the PC group than in the control group ($29 \pm 4\%$ vs. $57 \pm 2\%$; $p < 0.01$). Although middle-aged and old rabbits exhibited all three archetypal indexes of cardiovascular aging, a comparable (~50%) reduction in infarct size with PC was evident in both cohorts.

CONCLUSIONS These data provide the first in vivo evidence that infarct size reduction with PC is not precluded by increased cardiovascular age, per se. (J Am Coll Cardiol 2001;38:1741–7)
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It has been well established that brief episodes of ischemia can protect, or 'precondition', the heart and significantly limit infarct size caused by a subsequent, sustained period of coronary artery occlusion (1). Indeed, cardioprotection with preconditioning (PC) has been documented in virtually all experimental models and, importantly, may also be evident in the clinical setting (1,2). However, one purported exception to this paradigm is the aging heart: evidence obtained from the rat model suggests that the benefits of PC wane with increasing age and are lost in the hearts of senescent animals (3–10).

As the aging cohort is undoubtedly the population in which acute myocardial infarction (MI) is most prevalent and cardioprotection is most relevant (11,12), a loss in efficacy of ischemic PC with increasing age would have profound, but hitherto largely unexplored clinical implications (13–16). However, this concept is based exclusively on studies conducted in isolated buffer-perfused heart preparations that relied primarily on a surrogate index of cardioprotection—namely, the early recovery of left ventricular (LV) function after relief of sustained global ischemia (3–10). No previous studies have addressed the issue of an age-related loss in the efficacy of PC in an in vivo, blood-perfused model of acute MI in which: 1) definitive hallmarks of cardiovascular aging were demonstrated; and 2) a reduction of infarct size, the recognized "gold standard" of PC (1), served as the primary end point.

Using the in vivo rabbit model, we quantified infarct size reduction with PC in adult (4 to 6 months old), middle-aged (24 to 27 months old) and old (42 to 60 months old) animals. We report that, despite conclusive morphologic and functional evidence of cardiovascular aging in the middle-aged and old populations (e.g., myocyte hypertrophy, increased myocardial fibrosis and attenuated response to beta-adrenergic stimulation [17–23]), the efficacy of infarct size reduction with PC is preserved in both middle-aged and old rabbits. Thus, our results provide the first evidence that cardioprotection by ischemic PC is not precluded by increased cardiovascular age, per se, in an in vivo model of acute MI.

METHODS

This study was approved by the Institutional Animal Care and Use Committee of Good Samaritan Hospital and conforms to the "Position of the American Heart Association on Research Animal Use," adopted in November 1984.

Protocol 1: Infarct Size and Morphologic Confirmation of Aging

Surgical preparation. Thirty-eight pathogen-free New Zealand White rabbits were anesthetized with intramuscular injections of ketamine (200 mg) plus xylazine (100 mg),

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Abbreviations and Acronyms

AN	= area of necrosis
ANCOVA	= analysis of covariance
ANOVA	= analysis of variance
AR	= area at risk of infarction
dP/dt_{max}	= peak positive LV dP/dt
LV	= left ventricular
LV dP/dt	= first derivative of LV pressure
MI	= myocardial infarction
NE	= norepinephrine
PC	= preconditioning

given twice before the start of the operation. The rabbits were intubated and ventilated with room air supplemented with 100% oxygen. After cannulating the left jugular vein (for administration of fluids) and the left carotid artery (for measurement of heart rate and arterial pressure), the heart was exposed through a left thoracotomy, and a large marginal branch of the circumflex artery was encircled with a snare for later occlusion/reperfusion. Continuous tracings of arterial pressure were obtained on a chart recorder, and body temperature (monitored using a rectal thermometer) was maintained at 38°C to 39°C. Surgical anesthesia was maintained by intraperitoneal injections of sodium pentobarbital (~50 mg/h) throughout the protocol.

Study design. Three cohorts of rabbits were studied: adult (4 to 6 months old; mean body weight 3.0 ± 0.1 kg; n = 14), middle-aged (24 to 27 months old; weight 4.1 ± 0.2 kg; n = 12) and the oldest commercially available rabbits (42 to 60 months old; weight 4.6 ± 0.1 kg; n = 12). Within each cohort, rabbits were randomized to receive either 5 min of PC ischemia plus 10 min of reflow or a matched 15-min control period (n = 6 to 8 per group). All animals then underwent 30 min of sustained coronary artery occlusion followed by 3 h of reperfusion.

At the end of each experiment, the extents of the area at risk of infarction (AR) and area of necrosis (AN) were determined using routine methods (24). Briefly, the coronary artery was reoccluded, and the AR was delineated by injection of blue pigment through a left atrial catheter. After euthanizing the rabbits under deep anesthesia (300 mg of intravenous xylazine, followed by 10 mEq of potassium chloride into the left atrium), the hearts were rapidly excised, cut into five or six transverse slices and photographed. The slices were then incubated in 1% triphenyltetrazolium chloride (10 min a 37°C) to distinguish necrotic from viable myocardium, rephotographed and stored in 10% neutral buffered formalin.

Analysis. HEMODYNAMIC DATA. The heart rate, mean arterial pressure and rate-pressure product (heart rate × mean arterial pressure) were measured at baseline (before randomization), after the control or PC period (immediately before sustained occlusion), at 25 min of occlusion and at 15 min and 3 h after reperfusion.

RISK REGION AND INFARCT SIZE. Right ventricular tissue was trimmed from each heart slice, and the remaining LV was weighed. Photographic images of the tissue slices were projected and traced at magnifications of ~5× to 10×. The AR and AN in each slice were quantified by computerized planimetry, corrected for tissue weight and summed for each heart. The AR was then expressed as percent total LV weight, and AN was expressed as percent of the AR (24).

MYOCYTE HYPERTROPHY AND MYOCARDIAL FIBROSIS. One LV slice, located midway between the apex and the base, was taken from each heart and processed for paraffin embedding. For assessment of myocyte hypertrophy, cross sections (5 μm thick) were stained with hematoxylin and eosin, viewed in brightfield using a 40× objective lens and displayed on a high-resolution monitor. Myocyte cross-sectional areas in noninfarcted myocardium (25 per heart) were quantified by computerized planimetry (25). Myocardial fibrosis was determined from additional 5-μm cross sections stained with picrosirius red (which stains muscle yellow and collagen red) by a video subtraction method developed in our laboratory (26). Briefly, both a blue-filtered brightfield image and a circularly polarized image were obtained from three noninfarcted regions per heart (20× objective lens; 0.06 mm^2 per region). Using video analysis software, the monochrome brightfield image (in which collagen appears dark and muscle is bright) was subtracted from the circularly polarized image (in which both muscle and collagen appear bright), resulting in a subtracted image composed of bright collagen on a black (i.e., gray scale level of 0) background. A histogram of the brightness of each pixel in the image was generated, and the percent collagen content was calculated (26) as:

$$([\text{pixels with a gray scale level} > 0] / [\text{total number of pixels}] \times 100\%)$$

Protocol 2: Functional Confirmation of Aging

Surgical preparation, study design and analysis. Eight additional rabbits (3 adult, 2 middle-aged and 3 old) were anesthetized and ventilated as described in Protocol 1. In this case, however, a fluid-filled catheter was advanced into the LV cavity through the left carotid artery for measurement (closed chest) of LV pressure and its first derivative, LV dP/dt. After obtaining a baseline measurement of LV contractility, each rabbit received sequential 5-min intravenous infusions of the beta-adrenergic agonist isoproterenol at concentrations of 0.1, 0.2, 0.5 and 1.0 μg/kg body weight per min (27). At the end of each 5-min infusion, at which time hemodynamic variables had stabilized, heart rate and peak positive LV dP/dt (dP/dt_{max}) were assessed and expressed as a percentage of the baseline values for each rabbit.

Statistics. For Protocol 1, all discrete variables (AR/LV, AN/AR, myocyte cross-sectional area and fibrosis) were compared by two-factor analysis of variance (ANOVA), for

Table 1. Hemodynamic Data

			Occlusion	Reperfusion	
	Baseline	**Preocclusion**	**25 min**	**15 min**	**3 h**
Heart rate (beats/min)					
Adult rabbits					
Control	166 ± 4	165 ± 5	167 ± 7	172 ± 7	192 ± 9†
PC	160 ± 9	157 ± 9	170 ± 7	173 ± 8	203 ± 10†
Middle-aged rabbits					
Control	145 ± 10	144 ± 9	153 ± 9	154 ± 9	157 ± 7*
PC	136 ± 6	133 ± 5	139 ± 7*	136 ± 5*	141 ± 9*
Old rabbits					
Control	146 ± 12	154 ± 12	161 ± 7	162 ± 4	168 ± 8†
PC	152 ± 7	154 ± 7	158 ± 9	151 ± 8	155 ± 8*
Mean arterial pressure (mm Hg)					
Adult rabbits					
Control	90 ± 3	86 ± 3	74 ± 3†	70 ± 1†	54 ± 4†
PC	86 ± 3	81 ± 3	71 ± 2†	67 ± 2†	48 ± 3†
Middle-aged rabbits					
Control	81 ± 7	77 ± 7	61 ± 7†	53 ± 8†	48 ± 3†
PC	84 ± 5	73 ± 6	64 ± 4†	60 ± 6†	49 ± 3†
Old rabbits					
Control	84 ± 5	77 ± 7	66 ± 7†	60 ± 8†	46 ± 4†
PC	81 ± 3	72 ± 2	65 ± 2†	62 ± 3†	49 ± 3†
Heart rate × mean arterial pressure (beats/min × mm Hg × 10^3)					
Adult rabbits					
Control	15.0 ± 0.5	14.1 ± 0.5	12.2 ± 0.5†	12.0 ± 0.4†	10.2 ± 0.8†
PC	13.6 ± 0.5	12.5 ± 0.5	12.3 ± 0.5†	11.6 ± 0.4†	9.7 ± 0.4†
Middle-aged rabbits					
Control	11.4 ± 0.6*	10.7 ± 0.5*	9.1 ± 0.5*†	7.8 ± 0.8*†	7.4 ± 0.3*†
PC	11.3 ± 0.7*	9.7 ± 0.8*	8.9 ± 0.7*†	8.0 ± 0.8*†	6.8 ± 0.3*†
Old rabbits					
Control	12.5 ± 1.6*	11.9 ± 1.6*	10.6 ± 1.0	9.6 ± 1.2*	7.6 ± 5*†
PC	12.2 ± 0.4*	10.9 ± 0.2*	10.2 ± 0.6*†	9.3 ± 0.2*†	7.5 ± 0.5*†

For all variables: treatment (control vs. PC): p = NS; time: †$p < 0.05$ versus corresponding baseline value; age: *$p < 0.05$ versus corresponding adult group.
PC = preconditioned.

age and treatment. Within each age group, infarct size was further compared between control and PC animals by analysis of covariance (ANCOVA), incorporating the risk region—the major determinant of infarct size in the rabbit—as the covariate. Hemodynamic variables were compared using three-factor ANOVA, for age, treatment and time, with repeated measures. For Protocol 2, the percent change in heart rate and dP/dt_{max} were compared using two-factor ANOVA, for age and dose of isoproterenol, with repeated measures. Post-hoc pairwise comparisons were made using the Newman-Keuls test. All data are expressed as the mean value ± SEM.

RESULTS

Protocol 1

Hemodynamic data. There were no differences in the heart rate, mean arterial pressure or rate-pressure product between the control and PC rabbits in any age group (Table 1).

Adults exhibited the characteristic temporal hemodynamic changes described for anesthetized rabbits: i.e., heart rate increased, whereas the mean arterial pressure and rate-pressure product decreased during the course of the protocol (24). For all time points, middle-aged and old rabbits displayed the expected trend toward lower values of heart rate and mean arterial pressure (19), as well as a significant reduction in the rate-pressure product, as compared with the adult cohort (Table 1).

Risk region and infarct size. The AR averaged 33% to 37% of the total LV weight in the six study groups (p = NS for control vs. PC groups; p = NS for age) (Fig. 1A).

In the adult cohort, the mean infarct size was, as expected, significantly reduced in PC rabbits versus control rabbits, with AN/AR averaging 29 ± 4% versus 57 ± 2%, respectively ($p < 0.01$) (Fig. 1B). Similar profound cardioprotection was also observed with PC in both the middle-aged and old populations: AN/AR was 20 ± 4% versus 48 ± 3% in middle-aged PC versus control rabbits ($p < 0.01$) and 25 ± 5% versus 50 ± 4% in old PC versus control animals (Fig. 1B). This was confirmed by ANCOVA, incorporating the mass of the risk region as a covariate in

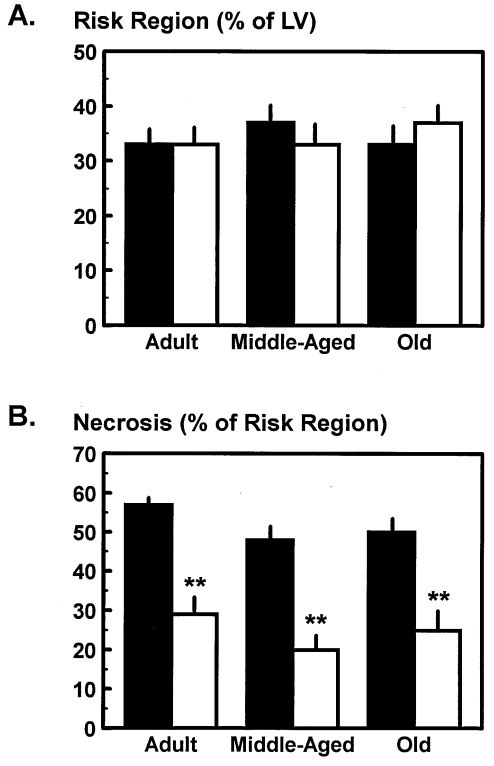

Figure 1. (A) Risk region, expressed as percent total left ventricular (LV) weight, for adult, middle-aged and old rabbits. Results of two-way analysis of variance: $p = 0.79$ for age; $p = 0.94$ for treatment; and $p = 0.40$ for age × treatment. **(B)** Necrosis, expressed as percent risk region, for adult, middle-aged and old rabbits. Results of two-way analysis of variance: $p = 0.05$ for age; $p < 0.01$ for treatment; and $p = 0.90$ for age × treatment. $^{**}p < 0.01$ versus matched control group. **Solid bars** = control groups; **open bars** = PC groups.

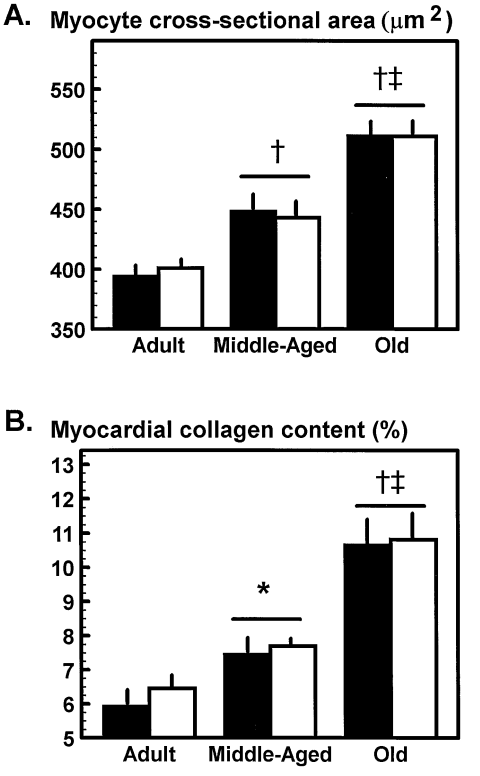

Figure 2. (A) Myocyte cross-sectional area (μm^2) in adult, middle-aged and old rabbit hearts. Results of two-way analysis of variance: $p < 0.01$ for age; $p = 0.75$ for treatment; and $p = 0.98$ for age × treatment. **(B)** Percent collagen content in adult, middle-aged and old rabbit hearts. Results of two-way analysis of variance: $p < 0.01$ for age; $p = 0.41$ for treatment; and $p = 0.97$ for age × treatment. $^{*}p < 0.05$ and †$p < 0.01$ versus adult rabbits; ‡$p < 0.01$ versus middle-aged rabbits. **Solid bars** = control groups; **open bars** = PC groups.

the analysis; for all age groups, infarct mass was significantly reduced in PC rabbits versus age-matched control rabbits ($p < 0.01$ for all ages; data not shown).

Myocyte hypertrophy and myocardial fibrosis. As expected, there were no differences in myocyte size or percent collagen content between control versus PC rabbits in any of the three age groups (Fig. 2A and 2B).

Mean myocyte cross-sectional area for the total adult population was 397 ± 7 μm^2. Both the middle-aged and old cohorts exhibited significant progressive hypertrophy; the myocyte cross-sectional areas for the pooled control and PC groups were 445 ± 11 μm^2 in middle-aged rabbits ($p < 0.01$ vs. adults) and 511 ± 8 μm^2 in old animals ($p < 0.01$ vs. adults and $p < 0.01$ vs. middle-aged rabbits) (Fig. 2A).

Myocardial collagen content in the adult rabbits (pooled control and PC groups) averaged 6.2 ± 0.3%. There was an increase in the percent collagen content with age (Figs. 2B and 3), to a mean value of 7.6 ± 0.3% in middle-aged rabbits ($p < 0.05$ vs. adults) and 10.8 ± 0.5% in old rabbits ($p < 0.01$ vs. adults and $p < 0.01$ vs. middle-aged rabbits) (Fig. 2B).

Protocol 2

Adult rabbits showed a robust and dose-dependent increase in both heart rate and contractility with isoproterenol; at the highest dose of 1.0 μg/kg/min, heart rate and LV dP/dt_{max} increased to 188 ± 5% and 247 ± 14% of baseline, respectively ($p < 0.01$ vs. baseline). The increase in heart rate in response to isoproterenol was similar, for all doses, in both the middle-aged and old cohorts, as compared with the adult cohort ($p = 0.55$ for age; data not shown). In contrast, the isoproterenol-induced increase in dP/dt_{max} was blunted in middle-aged rabbits and abrogated in old rabbits (153 ± 11% and 96 ± 12% of baseline, respectively, with 1.0 μg/kg per min; $p < 0.01$ vs. adults) (Fig. 4).

DISCUSSION

We report that, in rabbits exhibiting definitive hallmarks of cardiovascular aging (i.e., myocyte hypertrophy, myocardial fibrosis and attenuated contractile responsiveness to beta-adrenergic stimulation), ischemic PC significantly limited infarct size, with no loss of efficacy in middle-aged or old rabbits versus adult rabbits. These data provide the first in vivo evidence that cardiovascular aging does not render PC ineffective in protecting the heart against infarction.

Cardiovascular consequences of aging. Aging, per se, even in the absence of concurrent disease, has profound cardiovascular consequences that are consistently observed

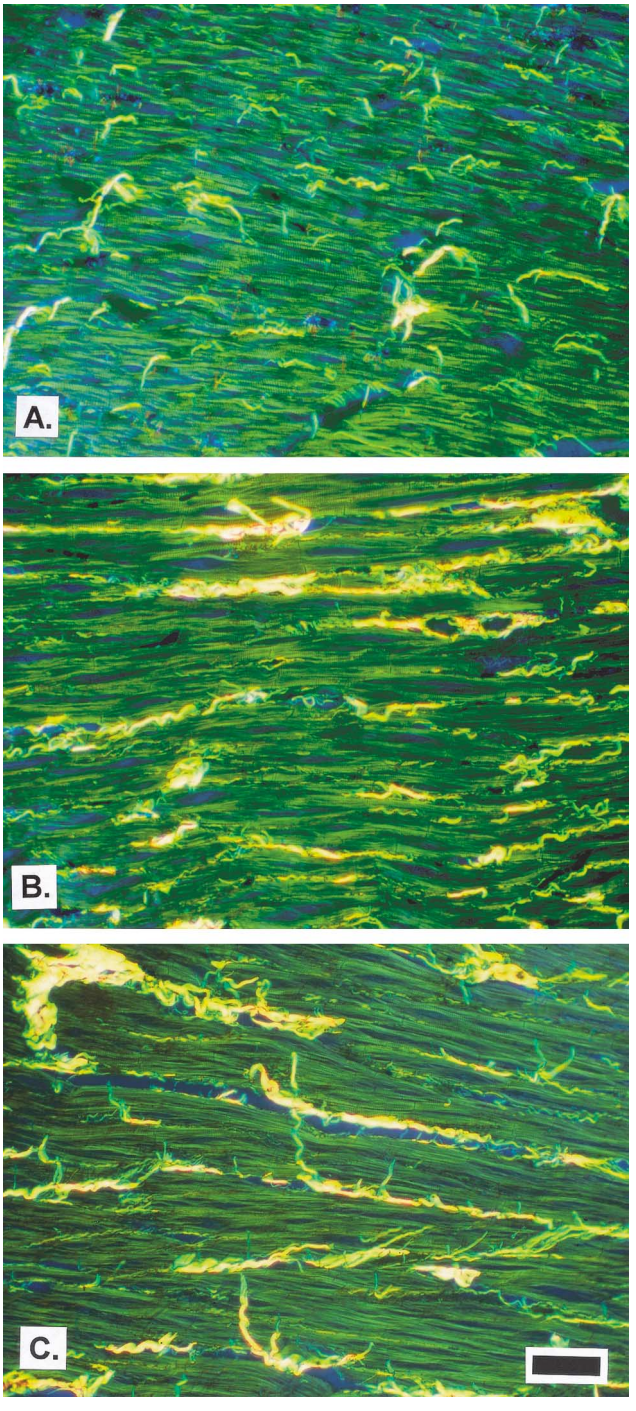

Figure 3. Picrosirius red-stained sections from adult **(A)**, middle-aged **(B)** and old **(C)** rabbit hearts, viewed with circularly polarized light, illustrating the age-related increase in myocardial collagen content. Thick collagen fibers appear **yellow**; thin fibers appear **yellow-green**; and myocytes are **green** and cross striated. Bar = 50 μm.

in experimental models and in humans. Among these, perhaps the best-documented are progressive myocyte hypertrophy, accompanying myocardial fibrosis and marked alterations in G protein-mediated cellular signaling pathways, including a long-appreciated reduction in responsiveness to beta-adrenergic stimulation (17–23).

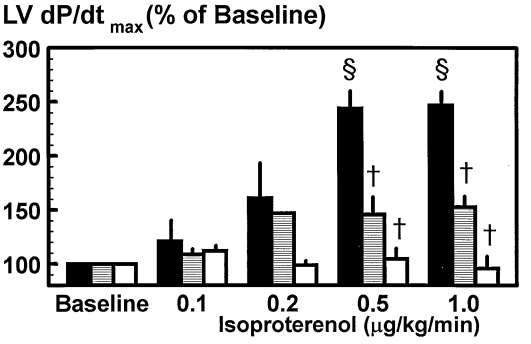

Figure 4. Peak positive LV dP/dt (LV dP/dt_{max}; expressed as a percentage of baseline values) during isoproterenol infusion in adult, middle-aged and old rabbits. Results of two-way analysis of variance: $p < 0.01$ for age; $p < 0.01$ for dose; and $p < 0.01$ for age × dose. †$p < 0.01$ versus adults; §$p < 0.01$ versus baseline. **Solid bars** = adult rabbits; **striped bars** = middle-aged rabbits; **open bars** = old rabbits.

The rabbit has not, historically, been extensively employed in aging studies. Indeed, there has been some dispute as to the maximal life span of the rabbit, with values of both 7 years (28) and 13 years (29) having been reported. For this reason, we considered it imperative to document indexes of cardiovascular aging in our model and, further, to compare our findings with published data on ~2-year-old rats, an accepted model of "senescence" (17). We observed a 1.3-fold increase in myocyte cross-sectional area and a 1.7-fold increase in percent collagen content in ~4-year-old rabbits, as compared with the adult cohort. Despite fundamental differences in tissue fixation, histologic processing and methods of analysis among studies, these data compare favorably with the 1.2- to 2.2-fold increases in myocyte size (area or volume) (18,19) and the 1.2- to 3.3-fold increases in percent collagen content (18) described in 23- to 29-month-old rats. Moreover, our results are consistent with autopsy data from patients who died of causes other than cardiovascular disease, showing a ~1.3-fold increase in myocyte volume between 20 and 75 years of age (20).

With regard to the functional index of cardiovascular aging—beta-adrenergic responsiveness—comparisons among studies are again complicated by methodologic differences, including the use of in vitro rather than in vivo preparations, administration of bolus doses rather than infusions of isoproterenol and, in clinical studies, measurement of noninvasive indexes of LV function rather than the direct assessment of dP/dt. Most previous studies have reported that the isoproterenol-induced increases in both heart rate and LV contractility are blunted, but not abrogated, with increasing age (21–23,30). In contrast, we found that the effect of isoproterenol on dP/dt was *completely abolished* in ~4-year-old rabbits, with no accompanying change in the heart rate response. Although we cannot provide a definitive explanation for the difference between our results and the concomitant but subtotal attenuation of heart rate and contractility seen in other models, this may reflect purported differences among species in adrenergic receptor density, signaling and control (27,30) or the pos-

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sible effects of the ketamine plus xylazine anesthesia employed in our protocol. Nonetheless, the significant myocyte hypertrophy and fibrosis observed with increasing age, together with the complete inability of isoproterenol to elicit an increase in contractility in the ~4-year-old rabbits, provide compelling evidence for cardiovascular aging in our rabbit model.

Age and the efficacy of PC. There is no question that the clinical incidence of coronary artery disease and acute MI is increased with age. In one recent trial, the median age of patients with acute MI was ~62 years to 64 years, with only ~4% of patients being <40 years of age (12). Thus, the aging cohort is precisely the population in which cardioprotection with ischemic PC is most relevant. However, only four clinical studies have focused on whether brief antecedent ischemia (i.e., preinfarct angina) continues to confer protection in the elderly patient with MI. Two studies have concluded that, in patients >60 years old (13) or >64 years old (14), the in-hospital outcome was improved and creatine kinase release was attenuated in cohorts with versus without preinfarct angina, whereas the other two studies found that preinfarct angina had no favorable effect on creatine kinase release, in-hospital outcome and five-year mortality in subsets of patients ≥65 and ≥70 years old (15,16). The reasons for this disparity are unknown, but, as with any clinical protocol seeking to assess the efficacy of ischemic PC, the requisite reliance on indirect enzymatic indexes of myocardial necrosis, as well as possible confounding differences in baseline characteristics (e.g., risk factors, incidence of multivessel disease, history of previous MI, use of anti-anginal drugs) among studies may all play a role.

Seemingly discrepant results have also been obtained in experimental models. Although there are two reports of persistent cardioprotection, irrespective of age, with PC (31,32), questions have been raised regarding the interpretation of these data. Specifically, the studies found that PC limited infarct size in 5.7- to 8-year-old sheep (31) and in isolated hearts harvested from rabbits ≥135 weeks old (32). However, the lengthy life span of both of these species, together with the lack of functional or morphologic evidence of cardiovascular aging in these protocols, makes it unclear as to whether these can truly be considered "old" populations. In contrast, all other experimental studies—all of which have employed the isolated buffer-perfused rat heart—have concluded that the benefits of PC wane in ~9- to 12-month-old rats (3–5,8,10) and are lost in ~1½- to 2-year-old animals (4,6,7,9,10). Interestingly, although cardiovascular indexes of aging were not concomitantly assessed in these later protocols, the progressive loss in efficacy of PC in ~9- to 12-month-old rats appears, on the basis of morphologic studies, to *precede* the age-associated development of myocyte hypertrophy and increased fibrosis in this species (18,19).

Reconciling the data. Our study represents the first evidence that, in an in vivo model of acute MI exhibiting definitive hallmarks of cardiovascular aging, infarct size reduction with PC continues to be evident in middle-aged and old cohorts. How can we reconcile our data with the results obtained in the rat model, all reporting a loss in the efficacy of PC with age?

Two potential explanations warrant consideration. First, the discrepancy may reflect differences in the preparations and end points used. Specifically, all previous studies employing rats used isolated, paced and buffer-perfused hearts, and, perhaps more importantly, only two of these protocols measured infarct size (9,10), whereas all of the other studies relied exclusively on recovery of LV function as the primary end point. Although an early improvement in contractility after relief of sustained ischemia (i.e., attenuation of postischemic "stunning") is typically cited as evidence of protection in studies employing the isolated buffer-perfused heart, it is well recognized that, in contrast to the "gold standard" of infarct size reduction, this does not represent a consistent or reliable index of cardioprotection with ischemic PC (1,33). Moreover, there is evidence that postischemic stunning may be exacerbated in the senescent rat heart (34), thereby raising further questions as to the suitability of this variable as a surrogate end point for PC-induced protection in aging populations. Second, the conflicting results may be due to underlying mechanistic differences between species. For example, there is evidence that, in the rat heart, norepinephrine (NE) is released in response to brief ischemia and may, through stimulation of $alpha_1$-adrenergic receptors, participate in the reduction in infarct size achieved with PC (1,35). Moreover, the loss in efficacy of PC in aging rat hearts has been attributed to an age-associated reduction in cardiac NE release (7). In contrast, NE release after brief ischemia is negligible in rabbit, as well as human, hearts (36,37), and, although exogenous NE can limit infarct size in the myocardium of rabbits, endogenous NE does not appear to be mandatory for PC-induced cardioprotection in this species (1,36). Further prospective studies will be required to establish whether differences in the role of NE (or other as yet unidentified mediators) may be responsible for the different outcomes in the rat versus rabbit model.

Conclusions and future directions. Our results reveal a significant and persistent reduction of infarct size with ischemic PC—irrespective of increasing age—in the in vivo rabbit model of acute MI. Although the cellular mechanisms of PC-induced cardioprotection may differ in adult versus senescent populations—a hitherto unexplored issue that awaits further study—we nonetheless provide the first in vivo evidence that infarct size reduction with PC is not precluded by increased cardiovascular age, per se.

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