LETTERS TO THE EDITOR

A Four-Year-Old Rabbit Cannot Be Considered the Right Model for Investigating Cardiac Senescence

Przyklenk et al. (1) have recently shown that cardioprotection with ischemic preconditioning (PC) is preserved in the senescent heart. The investigators found no differences in infarct size reduction by PC among adult (4 to 6 months), middle aged (~2 years) and old (~4 years) rabbits (1). Reduction of infarct size on “in vivo” rabbits may be considered an appropriate experimental model to study ischemic PC in animals. However, when considered in cardiac aging, serious concerns arise about the experimental model involved in their study. Indeed, animal models are used in aging research to overcome the limitation of studying aging in humans (e.g., the relatively long life span of humans). Because most aspects of aging in rodents are similar to human aging despite their short life span, rats and mice have been used extensively to study the pathophysiology of aging (2).

In contrast, data on the senescent rabbit are not available because of its relative long life span. In fact, the maximum life span potential (MLSP) for rabbits is 13 years (3,4); thus, if we optimistically consider MLSP for humans as 100 years, a 4-year-old rabbit cannot be considered a good model of the aging heart. A 4-year-old rabbit could be compared to a ~30-year-old human and obviously a 6-month-old rabbit to ~4-year-old human. Accordingly, morphologic markers of cardiovascular aging are qualitatively but not quantitatively similar to that observed in well-studied models of aging. Przyklenk et al. (1) showed that mean myocyte cross-sectional area increased from 397 ± 7 μm² in adult to 445 ± 11 μm² in middle aged (+12%) and to 506 ± 10 μm² in old (+27%) rabbits. In addition, the investigators also claimed that myocardial collagen content increased from 6.2 ± 0.3% in adult versus 10.8 ± 0.5% in old rabbit heart. In both cases, these age-related modifications are significantly smaller than that found by Anversa et al. (5), who demonstrated that myocyte cell volume increases up to ~60% from adult to senescent rat hearts while collagen content increases from 7% in adult to 22% in senescent rat hearts. The modifications showed by Przyklenk et al. (1) are approximately half of those expected from a validated model of the aging heart.

Conversely, reduction of ischemic PC mechanism has been well established in a 24-month-old rat model (6–9) that proportionally represents a human being of age 60 (rat MLSP = 3.5 years) (2). Moreover, Przyklenk et al. (1) also showed a slight reduction of ischemic PC efficacy in two-year and three- to five-year versus four- to six-month-old rabbit (~15%). This is in agreement with the concept that pathophysiologic modifications that occur during aging are not “on-off” and that ischemic PC might have a progressive decline with aging. Infarct size progressively increases in the preconditioned rat heart (9) from ~15% in adult animals (3 months), ~25% in middle-aged (12 months) and ~40% in old animals (20 months). Accordingly, as most of the age-related pathophysiologic modifications were observed in the senescent rat and human heart, ischemic PC was restored or preserved by antiaging interventions such as exercise training (10,11). On the basis of this evidence, ischemic PC efficacy should be significantly reduced also in 7- to 8-year-old rabbits that probably represent the 24-month-old rat and 60-year-old human homologues of cardiac senescence.

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REPLY

We thank Dr. Abete and colleagues for their interest in our work (1) and for their query of whether the rabbit is the “right” model to assess the efficacy of ischemic preconditioning (PC) in aging animals.

The rabbit has not been extensively utilized in aging studies. Indeed, there is even controversy as to the maximum life span of the rabbit, with values of 7 years (2,3) versus 13 years (cited by...
Abete et al.) having been reported. This variation in life span is not unique to the rabbit, and it underscores a crucial caveat: life span or age is, in itself, a poor predictor of the aging process (4). Thus, evaluation of established biomarkers of aging (4)—rather than attempts to equate, from maximum life spans, relative ages among species—may represent a more germane approach in addressing this question.

We observed significant myocyte hypertrophy and myocardial fibrosis—the morphologic hallmarks of cardiovascular aging—in four-year-old versus young adult rabbits (1). For example, left ventricular collagen content was 10.8 ± 0.5% (SD 1.8%) versus 6.2 ± 0.3% (SD 1.2%), respectively—a mean 1.7-fold increase (range: 1.2- to 2.5-fold, computed from the SD values) in fibrosis. Abete and colleagues contend that our results are qualitatively, but not quantitatively, similar to those observed in the ~2-year-old rat, an accepted model of senescence. We find, however, that despite methodologic differences among studies, our results fall within the range of data reported for rats (5,6)—including those from Anversa et al. (5), in which collagen volume fraction was 16 ± 4% (mean ± SD) versus 8 ± 2% in 29- versus 4-month-old animals, corresponding to a twofold increase (range: 1.2- to 3.3-fold) in fibrosis. (Of note, the values of 7% and 22% cited by Abete et al. were obtained in the right, rather than the left, ventricle (5)). With regard to hypertrophy, our 1.3-fold increase in myocyte cross-sectional area compares favorably with the 1.4-fold increase reported in 23-month-old versus 7-month-old rats (6), and, interestingly, with human autopsy data (death unrelated to cardiovascular disease) showing, via regression analysis, a ~1.3-fold increase in myocyte volume between 20 and 75 years of age (7).

Finally, the four-year-old rabbits displayed a third, functional increase in myocyte volume between 20 and 75 years of age (7). Interestingly, with human autopsy data (death unrelated to cardiovascular disease) showing, via regression analysis, a ~1.3-fold increase in myocyte cross-sectional area (which compares favorably with the 1.4-fold increase reported in 23-month-old versus 7-month-old rats (6), and, interestingly, with human autopsy data (death unrelated to cardiovascular disease) showing, via regression analysis, a ~1.3-fold increase in myocyte volume between 20 and 75 years of age (7). Abete and colleagues contend that our results are qualitatively, but not quantitatively, similar to those observed in the ~2-year-old rat, an accepted model of senescence. We find, however, that despite methodologic differences among studies, our results fall within the range of data reported for rats (5,6)—including those from Anversa et al. (5), in which collagen volume fraction was 16 ± 4% (mean ± SD) versus 8 ± 2% in 29- versus 4-month-old animals, corresponding to a twofold increase (range: 1.2- to 3.3-fold) in fibrosis. (Of note, the values of 7% and 22% cited by Abete et al. were obtained in the right, rather than the left, ventricle (5)). With regard to hypertrophy, our 1.3-fold increase in myocyte cross-sectional area compares favorably with the 1.4-fold increase reported in 23-month-old versus 7-month-old rats (6), and, interestingly, with human autopsy data (death unrelated to cardiovascular disease) showing, via regression analysis, a ~1.3-fold increase in myocyte volume between 20 and 75 years of age (7).

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Revascularizing Chronic Total Occlusions: What About the Coronary Collaterals and Myocardial Viability Story?

With reference to the study by Suero et al. (1), I wish to make the following comments:

1. Although there was a 10-year survival advantage in patients who had a successful percutaneous coronary intervention (PCI) to a chronic total occlusion (CTO), this study did not look at the relation of such a survival advantage following a successful revascularization to the presence of viability of infarcted myocardium in the 54% with a previous myocardial infarction (MI). This relationship is expected.
2. It may not be correct to state that all CTOs benefit from revascularization. I suspect that the survival advantage in this cohort came mainly from improvement in left ventricular (LV) function following improvement in contractility of viable infarcted myocardial segments (2). In support, there is data from some uncontrolled surgical series to show that improved survival in patients with LV dysfunction correlates with the presence of myocardial viability in several LV segments (3).

This will be the subject of evaluation in the Total Occlusion Study of Canada (TOSCA-2) substudy of the ongoing Occluded Artery Trial (OAT), which follows the previously published TOSCA study (4). Interestingly, this survival advantage occurred although only 10% of patients received a stent. A significant reduction in restenosis following stenting compared with balloon angioplasty of a CTO was reported in the TOSCA study.

3. The role of collaterals in this situation has always been an area both of controversy and interest. This would perhaps be a good opportunity to review the data to see whether the survival advantage reported in this study correlates with the presence of angiographic collaterals, especially as there is now data to show that collateral flow assessed invasively (5) does correlate with viability of...