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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 μm^2 in adult to 445 ± 11 μm^2 in middle aged (+12%) and to 506 ± 10 μm^2 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), to ~25% in middle-aged (12 months) and to ~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-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