Upregulation of the Nitric Oxide–cGMP Pathway in Aged Myocardium

To the Editor:

Zieman et al. recently assessed the effect of age on the cardiac NO-cGMP pathway postulating that, since NO promotes ventricular relaxation, a reduction in functional NO activity may explain the increased ventricular diastolic dysfunction associating with normal aging. Perhaps surprisingly, the authors observed that elderly male Wistar rats (22 to 25 months old) showed higher constitutive cardiac NOS activity and cardiac endothelial nitric oxide synthase (eNOS) levels than young adult rats (4 to 7 months). Much of this increased activity appeared to take place in the cardiac endothelium rather than the myocytes. The authors concluded that the age-related impairment of ventricular relaxation is mediated by mechanisms other than NO, and, indeed, increased NO production may act as a failed adaptive mechanism in this pathology. This is in notable contrast to the situation in vascular endothelium where impaired endothelial function seems due to reduced eNOS activity as seen in the aorta of the same rat model.\(^1\)\(^2\)\(^3\) We believe that caution should be exercised in applying the results of this model to human aging. Important differences exist in cardiac structural changes associated with aging between Wistar rats and humans. The aged male Wistar rats in this study showed an almost 50% increase in heart weight over younger rats. Such cardiac hypertrophy in the absence of hypertension is a recognized feature of aging in these animals and is not reproduced in the elderly human male.\(^1\) Zieman et al.\(^1\) offer no explanation of how this species-related cardiomyopathy may have influenced their results. More work examining the effects of cardiac hypertrophy on cardiac NO release is required before these results can be accepted as a consequence of age alone.

We are not aware of any work measuring the change with aging in cardiac NO pathway activity in healthy humans directly. However, because NO production within the coronary circulation accounts for the greater part of endogenous nitrate production, indirect evidence of cardiac NO production can be gained from combined levels of nitrate and nitrite (NO\(_x\)), breakdown products of NO formation, in the plasma.\(^5\) Accordingly, the increased NO production in the myocardium of aged Wistar rats correlates with increased levels of plasma NO\(_x\) in aged animals.\(^2\)\(^3\) Previous work from our laboratory examined plasma NO\(_x\) in healthy human populations without evidence of cardiac disease. In a population of 8 young (18 to 21 years) and 7 older (50 to 62) healthy male adults with matched dietary nitrate/nitrite intakes, we observed that, in contrast to the Wistar rat model, NO\(_x\) levels were significantly lower in the older group (18.8±3.2 \(\mu\)mol/L) than in the young group (22.9±3.9 \(\mu\)mol/L; \(P<0.04\)). Although the interpretation of isolated NO\(_x\) levels is difficult because of confounding factors such as a decline in renal function with age, the influence of this would be to increase rather than reduce levels. Although this is not directly contrary to an increase in regional cardiac NO release, a large reduction in NO release from other beds would have had to occur to account for our results. These data raise doubt as to whether the intriguing findings of Zieman et al.\(^1\) in aged rats are applicable in humans. More work in humans is required to assess the potentially important impact of NO pathway activity on the pathology associated with normal cardiovascular senescence.

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