Changes in Wave Reflection With Advancing Age in Normal Subjects

To the Editor:

From their study of a small selected group (521 of 2640 persons) within the Framingham cohort, Mitchell et al conclude that increased central aortic stiffness rather than wave reflection is responsible for the increase in pulse pressure with advancing age in healthy men and women. The authors state that changes in wave reflection with advancing age are consistent with the hypothesis that a marked increase in elastic artery pulse wave velocity (PWV) with little change in muscular artery PWV leads to impedance matching between central aorta and proximal muscular arteries, which reduces proximal wave reflection and shifts reflecting sites distally. This view runs counter to classic studies that say the characteristic feature of the pressure pulse waveform with aging is attributable to early wave reflection resulting from increased elastic artery PWV and shifts of reflecting sites closer to (not further from) the heart.2

Mitchell’s calculation of reflection wave transit time (RWTT) was based on identification of an inflection point (or foot of the reflected wave) on the rising limb of the carotid pressure wave. RWTT duration (129 SD 28 ms) was consistently lower than time to the end of systole (312 to 320 ms). Yet the authors acknowledged in young adults the “reflected pressure wave arriving centrally during diastole,” that is, more than 300 ms after the foot and some 200 ms and 6 standard deviations after their calculated RWTT! Were there no young adults in this study? The average value of RWTT found by Mitchell et al (129 ms) was considerably higher than the mean of 102 to 116 ms found by us in a normal cohort.3 Also, in their study, there was no change in RWTT from the mid-50s to the mid-60s, then RWTT decreased in males but increased in females. In most older subjects (>60 years), especially females (because they are shorter), there is no visible reflected wave foot or inflection point on the pressure waveform, because the forward wave and the reflected wave blend (merge) together. We have pointed out the problems in identification of the reflected wave onset2,3 and in calculation of augmentation, which depends on pressure at this point in time. Mitchell’s calculations of augmentation index, forward and reflected pressure wave amplitudes, and averaged distance to reflection site are based on inflection point identification, and hence are suspect. The consistency of their calculations (with unprecedented correlation coefficients between 0.968 to 0.999) denote similarity in identification but not necessarily accuracy in identifying features of the reflected wave. We have been unable to achieve such consistency.

Mitchell et al conclude that the major aging change in arteries is a consequence of increased aortic stiffness with wave reflection unchanged or decreased. We agree with the former statement but not the latter. Apparent decrease in wave reflection with age was not seen by Mitchell in men, and shown only for women >60-years-old, and statistical significance was not apparent over the full age range studied (authors’ Figure 3).1 Conclusions are at odds not only with Kelly’s detailed study in 1000 normal subjects but with the older sphygmographic studies of Marey, Mahomed, Broadbent, and Mackenzie and clinical teachings of Osler, all of which showed that aging in humans is characterized by increased amplitude of the secondary systolic pressure wave, which we now recognize as caused by exaggerated early wave reflection from the lower body.2,3

Response

We thank Drs O’Rourke and Nichols for their thoughtful critique of our study.1 They take issue with identification of timing of wave reflection using tonometry and with the conclusion that wave reflection remains unchanged or decreases with age. We acknowledge the lack of consensus regarding the best technique for measuring reflected wave transit time. However, our studies were analyzed blinded to age and sex, and the analyses were highly reproducible.

Drs O’Rourke and Nichols compare our results with Kelly et al, who reported carotid tonometry results in 181 men and 226 women, including hypertensive subjects and smokers.2 We reported on a healthy reference sample selected from 2640 middle-aged and elderly individuals. We suspect that later wave reflection and lower augmentation index (at comparable age) in our sample is attributable to selection of healthier participants, although differences in analytical techniques may have contributed. Rather than analyze individual high-fidelity waveforms,
they ensemble-averaged waveforms from decade groups of participants into a single “age-decade wave,” which was analyzed to obtain “mean” waveform characteristics. This averaging process may have obscured waveform landmarks. They also did not calibrate their waveforms (results are presented in units of mV, which are roughly equivalent to mm Hg), which may explain higher values for forward wave amplitude in their study.

With these differences in mind, it is useful to compare the 2 studies (Figure). Both studies found a modest increase in augmentation index before the age of 60 years. However, after the age of 60 years, augmentation index was unchanged (Kelly) or fell (Mitchell), whereas forward (primary) wave amplitude increased substantially in both studies. Kelly also found that timing of wave reflection was unchanged from age 40 to 70 years (102 ms) and then increased (106 ms) in the 71+ age group. Because carotid-femoral pulse wave velocity increases substantially throughout this age range, their data also suggest that the effective distance to reflecting sites increased in the elderly.

Kelly’s pioneering study demonstrated that reflected waves arrive earlier and central augmentation increases markedly with advancing age prior to the age of 40 years, which is an age range when pulse pressure increases modestly. However, both studies show that after age 60 changes in primary wave amplitude predominate at a time when systolic and pulse pressure and cardiovascular risk increase dramatically. Therefore, our interpretation of both data sets is “that increases in central aortic stiffness and forward wave amplitude, rather than reflected wave amplitude, are the primary mechanism for increased central and peripheral systolic and pulse pressure with advancing age in healthy adults.”

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