Editorial Commentary

Arteriosclerosis
Inevitable or Self-Inflicted?

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Over the last 20 years, aortic stiffness has emerged as an important, independent predictor of cardiovascular outcome. Recent data suggest that it may add to existing risk prediction models and improve patient stratification. However, the precise biological pathways and processes underlying aortic stiffening remain unclear. A better understanding of these is an important prerequisite for the rational design of novel antistiffening drugs, which may prove valuable in reducing cardiovascular risk, particularly in those individuals with stiff arteries.

In almost all populations, aortic stiffness is positively correlated with age, and in multiple regression analyses age is invariably the dominant determinant of stiffness.1 Consequently, age-related aortic stiffening (arteriosclerosis) is often considered to be inevitable. The process underlying arteriosclerosis is generally believed to be fatigue fracture of elastic fibers within the arterial wall. As such, age is actually a surrogate for cycle number (ie, number of heart beats), which, together with the level of cyclic stress (pulse pressure), determines the rate of elastic fiber degeneration. To a limited extent, this view has been substantiated by animal studies, and our own recent observations in the Caerphilly Heart Study.2 We found that the heart rate pulse pressure product, integrated over a 20-year follow-up period, was independently correlated with current aortic pulse wave velocity (aPWV). However, this cannot be the whole story, not least because the correlation that we observed was quite modest, and several other lines of evidence strongly suggest that arteriosclerosis is more pathological than inevitable.

More than 20 years ago, Avolio et al3 published a seminal article describing the relationship between age and aPWV in 2 different Chinese populations. They noted that individuals living in a rural province appeared to exhibit much less age-related stiffening than those in an urban setting. They speculated that differences in sodium intake may have been responsible for this effect, and to some extent the findings mirror those reported previously for blood pressure itself. Nevertheless, the observations of Avolio et al3 indicate that, although some degree of biological aging may be inevitable, a substantial proportion of arteriosclerosis is attributed to pathological processes (Figure 1). This may explain why the population variability in aPWV increases significantly with age.

Data published in this issue of Hypertension4 extend the observations of Avolio et al3 into a completely different ethnic population. Lemogoum et al4 assessed aPWV in 2 groups of Cameroonian pygmies, one living a traditional hunter-gatherer existence in a rural setting and one in a more Westernized, semiurban environment. On average, aortic stiffness was ≈20% lower in the rural individuals but did not differ between the semiurban pygmies and other ethnically unrelated individuals in the same environment. Interestingly, wave reflection, as assessed by augmentation index, did not differ significantly among the 3 groups. Although aPWV correlated positively with age in the semiurban dwellers, there was no association in the rural cohort. However, the sample size was very modest, and much smaller than that of Avolio et al,3 so some degree of the age-related stiffening could not be robustly excluded. Nevertheless, the observations of Lemogoum et al4 do appear to substantiate those of Avolio et al,3 although both were cross-sectional, and longitudinal studies in indigenous populations have not been undertaken.

Lemogoum et al4 speculate that their findings concerning aortic stiffness provide evidence that the hunter-gatherer lifestyle of the traditional pygmies is associated with a lower risk of atherosclerosis. However, they overlook the important point made by Avolio et al,3 that it is actually arteriosclerosis and not atherosclerosis that underlies age-related aortic stiffening. Indeed, the 2 processes are pathologically distinct and largely driven by different mechanisms (Figure 2). Moreover, the correlation between atherosclerotic load, assessed at postmortem, and in-life aPWV is very modest.5 More recently, Cecelja et al6 reported no association between aPWV and noncalcified plaque load assessed by ultrasound. Furthermore, atherosclerotic risk factors, other than blood pressure, per se, appear to play a relatively minor role in arterial stiffening, as highlighted by a recent systematic review7 and longitudinal observations.2

If arteriosclerosis is not entirely inevitable, then what might be responsible for the seeming inextricable rise in aPWV in Westernized societies? Blood pressure early on in life would seem an attractive explanation, because this would increase cyclic stress, theoretically accelerating elastic fiber degeneration. Indigenous populations are known to have lower blood pressures, in part because of lower average sodium intake. Data from the Framingham Heart Study suggest that pulse pressure, frequently regarded as a surrogate...
for arterial stiffness, tracks throughout life and that early differences become magnified with aging, the so-called “horse race” effect. Although Avolio et al\(^3\) and Lemogoum et al\(^4\) both attempted to correct or control for blood pressure differences between populations, they did not have longitudinal data and, thus, cannot reliably exclude a blood pressure effect.

A number of other plausible mechanisms underlying atherosclerosis have been postulated, including calcification of the medial components of the arterial wall, inflammation, and cross-linking of elastic fibers. The calcium content of the aortic media increases with age, particularly after the fifth decade, which coincides with acceleration in arteriosclerosis. In animal models, pharmacologically induced calcification leads to an increase in stiffness and pulse pressure, and, in humans, the amount of calcium detected on computed tomography correlates with aPWV in older subjects.\(^8\) Calcium appears to be deposited on or immediately adjacent to elastic fibers, particularly those that have fractured. However, whether fracture/fragmentation occurs first leading to calcification or vice versa is, at present, unclear.

Aortic stiffness correlates with serum markers of inflammation in otherwise healthy individuals, and aPWV is elevated in subjects with chronic inflammatory conditions and can be “normalized” by effective anti-inflammatory therapy.\(^9\)

The mechanisms underlying inflammation-related stiffening are unclear, and factors such as endothelial dysfunction have been postulated, although this seems unlikely in humans. Elastin is subject to cross-linking by advanced glycation end products, with a subsequent reduction in distensibility. These cross-links increase with aging and correlate with aPWV\(^10\) and, thus, may partly underlie arteriosclerosis. Before we can attribute arteriosclerosis to any of these mechanisms, it would be helpful to understand the extent to which they are altered or, indeed, absent in indigenous populations like those studied by Avolio et al\(^3\) and Lemogoum et al.\(^4\) Clearly, further mechanistic studies in ethnic populations will provide important insights in this regard.

Although arteriosclerosis will affect almost all of us, it appears to be the result of an urbanized, Western lifestyle and not simply a consequence of growing older. As such, age-related normal values for aortic stiffness, which have been
promoted by some, appear to be misguided: a 70-year-old ought have roughly the same aPWV as a 17-year old. Although such “healthy aging” remains elusive for most of us, a better understanding of the processes underlying arteriosclerosis may ultimately allow this aim to be achieved. An important first step is the realization that atherosclerosis and arteriosclerosis are different conditions, as Sir George Pickering pointed out 60 years ago, and have different driving forces.

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**References**


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