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Letters

Deceleration of Age-Related Aortic Stiffening in a Population With High Longevity Rates

The IKARIA Study

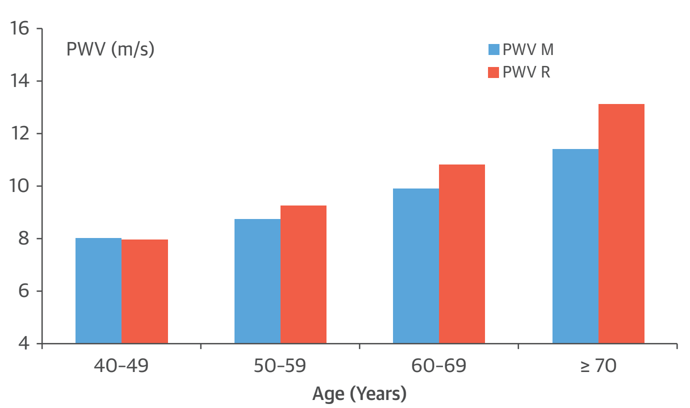
Ikaria is among the 5 places in the world with the highest rates of longevity (1). Aortic stiffness, assessed by aortic pulse wave velocity (PWV), is an independent predictor of cardiovascular and all-cause mortality (2).

We evaluated aortic stiffness in 138 healthy inhabitants of Ikaria Island and investigated whether there is a differentiation between the measured and reference PWV. The population was divided into 4 age groups, each per decade: 40 to 49 years ($n = 29$); 50 to 59 years ($n = 39$); 60 to 69 years ($n = 31$); and ≥70 years ($n = 39$). Aortic stiffness was assessed by measuring carotid-femoral (aortic) PWV. Participants were nondiabetic, free from overt cardiovascular disease, and under no treatment for hypertension or dyslipidemia, corresponding to the European Reference Value Population for PWV (3). We calculated PWV using the formula $PWV = 0.8(x_{direct})/\Delta t$ (3). Reference values were calculated by regression equations for PWV according to blood pressure (BP) category (optimal BP: $PWV = 0.000 \times age + 0.83 \times 10^{-3} \times age^2 + 5.55$, normal BP: $PWV = 0.000 \times age + 0.99 \times 10^{-3} \times age^2 + 5.69$, high normal BP: $PWV = 0.000 \times age + 1.05 \times 10^{-3} \times age^2 + 5.91$, grade I hypertension: $PWV = 0.000 \times age + 1.18 \times 10^{-3} \times age^2 + 6.17$, grade II/III hypertension: $PWV = 0.044 \times age + 0.85 \times 10^{-3} \times age^2 + 5.73$) (3). The difference between the reference and measured PWV in each age group was studied with the paired Student *t* test.

The percentage of current smokers was reduced with advancing age decade (16% vs. 17% vs. 7% vs. 7%, respectively; $p < 0.01$). Systolic BP showed a gradual increase from younger to older inhabitants (from 131.1 ± 11.7 mm Hg to 136.7 ± 14.1 mm Hg to 142.9 ± 17.1 mm Hg to 152.1 ± 21.8 mm Hg, respectively; $p < 0.01$). Interestingly, no difference was observed in the values of diastolic BP across the age groups (from 81.7 ± 6.5 mm Hg to 83.9 ± 10.1 mm Hg to 80.8 ± 7.7 mm Hg to 81.7 ± 11.6 mm Hg, respectively; p = not significant). Regarding the metabolic profile, low-density lipoprotein cholesterol levels were significantly lower in the elderly group 4 compared with group 1, but no significant difference was observed between all other group comparisons (from 145.9 ± 35.1 mg/dl to 136.9 ± 35.4 mg/dl to 133.9 ± 42.5 mg/dl to 120.6 ± 35.5 mg/dl, respectively). Importantly, values of high-density lipoprotein cholesterol were similar among all groups (from 46.6 ± 10.4 mg/dl to 47.1 ± 9.7 mg/dl to 48.6 ± 8.8 mg/dl to 44.6 ± 11.3 mg/dl; p = NS), implying a constant favorable high-density lipoprotein cholesterol profile across all age groups. Plasma glucose levels did not significantly change among groups.

PWV showed a gradual increase from the fourth decade of life to the elderly ($p = 0.05$ for the comparison between groups 1 and 2; $p < 0.01$ for the comparison between all other groups). No difference between the measured and reference values was observed in subjects between 40 and 49 years old (7.98 ± 0.96 m/s vs. 7.92 ± 0.69 m/s, respectively; p = NS), but after the fifth decade of life, measured PWV was consistently and significantly lower than the reference values in all age groups (group 2: 8.71 ± 1.22 m/s vs. 9.22 ± 0.80 m/s; $p < 0.01$; group 3: 9.87 ± 1.17 m/s vs. 10.78 ± 0.92 m/s;

FIGURE 1 **Difference Between the Measured and Reference Values of Carotid-Femoral PWV in the Inhabitants of Ikaria Island**



Difference between the measured (M) and reference (R) values of carotid-femoral pulse wave velocity (PWV) across the advancing age decade in the inhabitants of Ikaria Island. After the fifth decade of life, until the very elderly, the measured PWV was consistently and significantly lower compared to its reference value.

$p < 0.001$; and group 4: 11.53 ± 2.22 m/s vs. 13.17 ± 1.54 m/s; $p < 0.001$) (**Figure 1**). In multivariate regression analysis, PWV was independently related to age group ($b = 0.61$; $p < 0.001$), mean BP ($b = 0.29$; $p = 0.001$), heart rate ($b = 0.23$; $p = 0.006$), and creatinine ($b = 0.19$; $p = 0.01$); (R^2 of the model: 0.59).

In the present study, we assessed aortic stiffness in a population with high rates of longevity. Aortic stiffness increases gradually with age; however, at >50 years of age, aortic stiffening seems to be decelerated because the measured PWV was significantly lower than reference values. This finding may be attributed to either a favorable hemodynamic pattern (progressive increase in systolic BP with age, but stable diastolic BP at older ages—an excessive decrease of diastolic BP hampers coronary flow) or to beneficial genetic and metabolic backgrounds that are implicated in the process of both longevity and aortic stiffness. The favorable lipid profile and the relatively low percentage of smokers among the elderly may have contributed to the results (4). Moreover, previous results from the IKARIA study showed a favorable effect of physical activity on endothelial function, which may be related to attenuated aortic stiffening (1). Hereditary aspects of aortic elasticity may also play a role given the evidence that paternal longevity is associated with decreased PWV in offspring (5).

The cross-sectional nature of our study does not allow for conclusions regarding causality, and selection bias may have interfered. Whether this privilege of aortic mechanics can also be extended to the younger generations living in the particular island is a hypothesis that needs further investigation. Finally, aortic imaging modalities that provide structural information could have enhanced our results.

Whether aortic stiffness retains its established predictive value with increasing age is an intriguing issue, with most studies attesting to an incremental predictive ability even at older ages. Given the adverse prognostic impact of aortic stiffening on cardiovascular and total mortality, the present findings may imply a possible link between longevity and aortic stiffness.

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Clinical Relevance of Exaggerated Exercise Blood Pressure

Exercise stress testing is routinely used to assess cardiovascular risk, and measurement of blood pressure (BP) during the test is a standard component of patient monitoring (1). Irrespective of whether BP is considered normal at rest (in-clinic BP <140/90 mm Hg), some individuals may experience abnormal (hypotensive or hypertensive) BP responses during exercise testing. Our recent meta-analyses demonstrated that abnormal BP responses carry significant risk for future cardiovascular events and mortality, independent of resting BP and other cardiovascular risk factors (2,3). Although exercise hypotension is a sign of significant cardiovascular pathology, it is possible that some of the cardiovascular risk associated with exercise hypertension (exaggerated exercise blood pressure [EEBP]) relates to underlying (masked) hypertension (4) gone unnoticed with clinic BP screening, or to future development of overt hypertension detectable with in-clinic BP screening. A pooled summary of studies assessing the relationship between EEBP and incident hypertension has never been undertaken, and is an important step with respect to determining whether EEBP has utility for early identification of people at heightened cardiovascular risk. Therefore, we sought to conduct a systematic review and meta-analysis to determine