The following is the abstract of the article discussed in the following letter:

**Powell, J. T., R. J. Turner, M. Sian, R. Debasso, and T. Länne.**


Aortic stiffness is a predictor of cardiovascular mortality. The mechanical properties of the arterial wall depend on the connective tissue framework, with variation in fibrillin-1 and collagen I genes being associated with aortic stiffness and/or pulse pressure elevation. The aim of this study was to investigate whether variation in fibrillin-1 genotype was associated with aortic stiffness in men. The mechanical properties of the abdominal aorta of 79 healthy men (range 28–81 yr) were investigated by ultrasoundographic phase-locked echo tracking. Fibrillin-1 genotype, characterized by the variable tandem repeat in intron 28, and collagen type I alpha 1 genotype characterized by the 2,064 G\(\text{G/T}\) polymorphism, were determined by using DNA from peripheral blood cells. Three common fibrillin-1 genotypes, 2-2, 2-3, and 2-4, were observed in 50 (64%), 10 (13%), and 11 (14%) of the men, respectively. Those of 2-3 genotype had higher pressure strain elastic modulus and aortic stiffness compared with men of 2-2 or 2-4 genotype \((P = 0.005)\). Pulse pressure also was increased in the 2-3 genotype \((P = 0.04)\). There was no significant association between type 1 collagen genotype and aortic stiffness in this cohort. In conclusion, the fibrillin-1 2-3 genotype in men was associated with increased aortic stiffness and pulse pressure, indicative of an increased risk for cardiovascular disease.

**Influence of fibrillin-1 genotype on aortic stiffness in men: a note of caution**

*To the Editor:* Powell et al. \((4)\) have described a positive association between a fibrillin-1 (FBN-1) genotype \([\text{variable nucleotide of tandem repeat (VNTR) in intron 28}]\) and aortic stiffness in first degree relatives of patients with aortic abdominal aneurysms \((n = 79)\). From these data, the authors suggest that the FBN-1 gene is involved in aortic stiffness in men aged 55 yr \((\text{predominantly older men, range 40–59 yr})\). Recently, we investigated the same VNTR in FBN-1, in a much larger cohort \((n = 742)\) of apparently healthy individuals aged 16–83 yr and included both male and female subjects. Despite using this large and adequately powered population \([\text{at least 97\% power, to detect } >3\% \text{ difference in pulse wave velocity (PWV) between the genotypes}]\), we were unable to demonstrate any relationship between the FBN-1 genotype and aortic PWV or augmentation index \((\text{AIx})\) \((\text{Fig. 1, A and B})\) \((5)\), both established predictors of outcome as reported by Powell et al. Obviously, in our study, we used PWV and not the pressure strain elastic modulus and stiffness \((\beta)\) indexes used by Powell et al. as measures of aortic stiffness. However, only PWV has been shown to be an independent predictor of cardiovascular mortality \((1, 2, 3)\), and PWV should be seen as the gold standard if the results are really to be used for cardiovascular risk prediction. In addition, we did not find any difference in pulse pressure between the genotypes as suggested by Powell et al.’s study that used only men. Furthermore, we have carried out a separate subgroup analysis to look specifically at older men \((>50 \text{ yr})\), but we failed to find any relationship between the VNTR and aortic PWV. We also did not find any significant gender differences between the three main genotypes \((2-2, 2-3, 2-4)\). Our negative result is perhaps not surprising given that the VNTR in question is intronic, and to date, no functional effects of these common variants have been reported. Structural proteins, including fibrillin-1 have an important role in arterial wall properties; however, the findings of Powell et al. should be interpreted with caution, until replicated in a much larger cohort of subjects, across a wide age range and including both men and women.

**REFERENCES**


**REPLY**

*To the Editor:* We are pleased to learn of the interest that Dr. Yasmin and coworkers show in our work. We investigated the stiffness of the abdominal aorta in 79 men \((\text{predominantly middle-aged men, range 40–59 yr})\) and found a higher stiffness in those of 2-3 genotype compared with other genotypes \((2-2\) and 2-4 genotype: \(P < 0.005\) \((10)\)). This is in contrast to the findings of Yasmin et al., who did not find any correlation between aortic PWV or AIx and fibrillin-1 genotype. In our study, the stiffness of the abdominal aorta was measured by an echo-tracking technique at an anatomically defined local segment of the arterial tree, whereas Yasmin et al. determined aortic PWV over a length of the arterial tree, which includes the common carotid artery, thoracic and abdominal aorta, iliac artery, and part of the femoral artery. This might to some extent explain the divergent results because the elastic behavior of these segments is quantitatively differentiated \((3)\), which

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**Fig. 1.** Relationship between fibrillin-1 genotype and aortic pulse wave velocity \((\text{PWV}; A)\) or augmentation index \((\text{AIx}; B)\) are shown. Values are means \(\pm\) SE.
means that the two modes of assessing arterial stiffness lead to different results. There seem to be a more marked age-related increase in aortic stiffness when measured locally in the abdominal aorta than with PWV, at least in healthy men (6, 11). Furthermore, the fibrillin-1 rich elastic fibers seem to have an impact on arterial stiffness in the abdominal aorta but not in the carotid artery, as shown in patients with genetically defect fibrillin-1 as in Marfan syndrome (2). Thus local stiffness of the abdominal aorta might be a more sensitive marker than aortic PWV regarding the effect of fibrillin-1 genotype on aortic wall properties. The impact of locally determined abdominal aortic stiffness on cardiovascular outcome, however, has not been established so far, in contrast to aortic PWV that is an independent predictor of cardiovascular mortality (1, 4). Because PWV is derived from a longer segment of the central arterial tree, it might be argued that this might have a larger impact on cardiac load. The male cohort in our study was selected by being first-degree relatives of patients with abdominal aortic aneurysms, and a genetic bias in our sample is possible although we excluded all with aortic dilatation. But a comparison with a healthy cohort without relatives affected by aneurysmal disease show similar stiffness values (De Basso R, Arlbrandt A, Sandgren T, Ryden Ahlgren Å, and Länne T, unpublished observations).

Arterial stiffness is an important determinant for systolic pressure and pulse pressure. We found a significant, but rather weak association with fibrillin-1 2-3 genotype ($P = 0.04$) that might have been due to chance in our relatively small sample. However, in earlier studies on middle-aged to old healthy men, men with coronary artery disease, and men who had abdominal aortic aneurysms, the investigated cohorts have been larger, and the association more firm (5, 7–9). This is in contrast to the findings by Yasmin et al., who did not find any significant association. We agree with Dr. Yasmin and coworkers that more studies including a wider age range, larger cohorts, and both genders are needed to determine the importance of fibrillin-1 in the regulation of arterial wall properties as well as cardiovascular morbidity and mortality.

REFERENCES


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