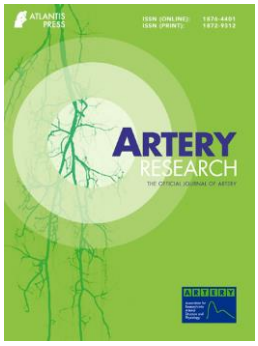

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Gender differences in arterial structure and function. Are men really from Mars and women from Venus?

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KEYWORDS
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Abstract Gender difference of cardiovascular disease is one of the most investigated and still unsolved items. Finding an answer to this, may have important implications for understanding the differences between men and women in atherosclerosis and possibly lead to the development of gender-specific treatment for cardiovascular disease.

Introduction

Gender difference of cardiovascular disease is one of the most investigated and still unsolved items. Cardiovascular disease seems to happen later on in life in women and it has been suggested that estrogen might have a cardioprotective effect, however this question is still matter of debate. Also, it has been suggested that a gender difference is present for stroke and peripheral arterial disease but it seems to be more prominent for incident coronary heart disease.[1] This might suggest that gender differences in cardiovascular disease may differ according to vascular site, as supported by previous autopsy studies.[2]

In this brief review, arterial structural and functional patterns of several vascular territories in men and women are discussed.

Arterial structure

Several techniques can be used to study the structure of the arteries. Radiographic images were primarily used to investigate the presence and the extension of arterial calcification.[3] In the last decennia the use of ultrasound has become one of the most used methods to investigate the presence and the progression of (sub)-clinical atherosclerotic alterations.[4,5] By ultrasound it is possible to assess artery diameter, the number and the degree of plaque at several sites but also it is possible to visualize and measure the intima–media thickness (IMT), one of the first atherosclerotic alterations of the vessel walls. The preferential site to perform these latter measurements is the carotid artery because of the easy performance of the exam and the strong association between carotid atherosclerosis and

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incident cardiovascular diseases. With relatively new techniques, as the measurement of arterial calcium by electron beam tomography, it is possible to assess coronary atherosclerosis.[6] Since it is possible to investigate the arterial structure at different sites, possible questions are: is there a difference between genders and are the differences site-specific? Autopsy studies have shown a clear increase in aortic surface area with age.[7] Changes of aortic diameter and left ventricular mass have also been investigated within the Generation R Study, a prospective cohort study from fetal life until young adulthood performed in Rotterdam, The Netherlands. In 1001 healthy children, from early fetal life onward it was investigated whether left cardiac structures track were associated with fetal growth and blood flow characteristics until the age of 2 years. It was found that the mean aortic root diameter and left ventricular mass were higher in boys than in girls at the age of 1.5, 6 and 24 months.[8] A recent study, performed within the framework of the Rotterdam study, a prospective, ongoing population-based study, has investigated the gender differences of the vascular tree.[9] In subjects participating the third phase of the study non-invasive measurements of atherosclerosis were obtained. The median coronary calcium score, mean carotid IMT and carotid plaque score were higher in men than in women in all age categories. The findings of this study showed that gender difference in the coronary vessels was larger than in the other vascular beds; moreover, the observed gender difference in atherosclerosis of the coronary arteries was particularly high in younger participants but still present in the oldest old. For mean ankle arm index (AAI), and median aortic calcification the pattern was more heterogeneous, with less differences between genders. The age-adjusted male: female odds ratios for having a calcium score above 1000 in the two lowest age tertiles were 6.9 (95% confidence interval (CI): 3.4, 13.9) and 7.4 (95% CI: 4.3, 12.7), showing that the men had a substantially higher degree of coronary calcification than the women. This difference appeared to be more moderate in older age (subjects in the highest tertile of age), in this case, the odds ratio declined to 2.7 (95% CI: 1.8, 4.0). Analyses were repeated after adjustment for conventional cardiovascular risk factors and additionally for C-reactive protein level, hormone replacement therapy, and use of cardiac medication. In this case, estimates were only slightly changed. Furthermore, also after exclusion of subjects with a history of cardiovascular disease (myocardial infarction, stroke, heart failure, angina pectoris, and peripheral artery disease), the patterns did not materially change.

Arterial function

The assessment of arterial stiffness is increasingly used in the clinical assessment of patients and several techniques can be used to investigate large artery stiffness. The most used are the measure of the arterial distensibility by ultrasound, or the study of the augmentation index (AIx) and the measurement of the pulse wave velocity (PWV) by tonometry. This latter is generally accepted as the most simple, non-invasive, robust, and reproducible method to determine arterial stiffness.[10] A major reason for measuring arterial stiffness and wave reflections in clinical practice comes from the demonstration that arterial stiffness has an independent predictive value for cardiovascular events.[11,12]

Within the framework of the Anglo-Cardiff Collaborative Trial, a study including in 4001 healthy normotensive individuals, aged 18–90 years, measurements of arterial functional properties were performed.[13] As previously reported,[14] at all ages, central AIx was higher in female subjects. As suggested by the authors, one of the possible explanations for this finding might be the shorter average height of women, and, hence, a closer proximity between the heart and sites of wave reflection. However, the results did not change after adjustment for height suggesting a gender difference in wave reflection. On the other hand, gender had no effect on large artery stiffness; no difference was found between men and women in either aortic or brachial PWV, suggesting that gender might not directly influence either central or peripheral arterial stiffening in healthy normotensive individuals. Peripheral systolic blood pressure increased progressively with age, whereas peripheral diastolic blood pressure increased until approximately 50 years, declining thereafter, resulting in a widening of peripheral pulse pressure. Also in this case a gender difference was observed, and the widening of peripheral pulse pressure was significantly more prominent in women than men. Central systolic blood pressure increased more with age than did peripheral systolic blood pressure, and again, the increase in central systolic blood pressure was more prominent in women than in men. Within the framework of the Rotterdam study, a higher mean aortic PWV levels in men when compared with women was reported.[15] The difference although not large persisted in the elderly until the age of 80 years. Above that age, no difference between men and women was observed. Aortic PWV increased with age, although relations of PWV with systolic blood pressure and pulse pressure were non-linear, flattening off at higher levels.

Considerations

The differences in arterial structure and function between genders do not seem to be completely explained by differences in cardiovascular risk factors. To explain the differential gender effects across vascular sites, we should search for risk factors that have different effects on atherosclerosis in men and women but also have varying effects on atherosclerosis in different vascular beds. Although risk factors as diabetes mellitus, high density lipoprotein cholesterol, and triglycerides have been found to have a more robust effect among women,[16] cardiovascular risk factors are considered to be generally the same for both genders. Moreover, risk factors for atherosclerosis in different vascular beds are the same as those that predispose to disease in each individual vascular bed.[17,18] However, the impact of risk factors may vary according to vascular site; it is known that smoking and diabetes mellitus have a stronger impact on peripheral arterial disease when compared with the other risk factors.[19] Furthermore, although the risk factors are generally the same, differences in vascular anatomy, leading to regional disturbances

of blood flow, and local changes in the arterial wall that affect interaction with blood components may still cause differences between the vascular sites.

It has been hypothesized that oestrogens may have a protective effect on the arteries. This hypothesis is supported by several studies. Recent studies have demonstrated that androgens have a complex affect on the vessels wall, and that the expression of the androgen receptor on cells involved in atherosclerosis is gender-dependent.[20,21] An effect of androgens on macrophage foam cell formation, one of the early events in atherosclerosis has been demonstrated. In vitro studies have shown that the exposure to dehydrotestosterone produced a dose-dependent androgen receptor-mediated increase in cholesteryl esters accumulation in monocyte-derived macrophages.[22,23]

Not much is known about risk factors for atherosclerosis that simultaneously differ between men and women and between vascular sites. Finding these factors may have important implications for understanding the differences between men and women in atherosclerosis and possibly lead to the development of gender-specific treatment for cardiovascular disease.

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