Arterial Stiffening and Atheroma Formation
- Two Features of Inevitable Aging-associated Phenomena -

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INTRODUCTION

Cardiac and cerebrovascular diseases, as well as malignant disease, are an important cause of mortality in Japan. Epidemiological data have clarified several conventional risk factors for atherosclerotic disorders such as coronary artery disease and ischemic stroke; these factors include hypertension, diabetes, dyslipidemia and obesity. Aging, although an inevitable physiological phenomenon experienced by virtually all living creatures, is also known to enhance vascular remodeling and dysfunction, leading to athrogenesis. Not only the prevalence of atherosclerotic disease, but also that of heart failure may increase with advancing years. The presence of heart failure will shorten both life and activity of daily living (ADL), and between one and four million people are thought to be suffering from heart failure in Japan. Coronary atherosclerosis is also one of the underlying causes of heart failure, a worldwide endemic. Indeed, “man is as old as his arteries”, an observation pointed out by Sir William Osler about 100 years ago. We therefore have to deal with aging as an ADL-restricting risk factor for cardiovascular disease, where possible. Here I give a brief overview of aging-phenotype related arterial changes: namely, arteriosclerosis and atheromatous lesion formation.

Arteriosclerosis — stiffening of the arteries

The aging process increases the stiffness of arteries, a process called arteriosclerosis. Although this word resembles “atherosclerosis”, arteriosclerosis (arterial stiffening) is one of the two components of atherosclerosis. The other component is atherosclerosis, in which fatty streak formation is an early pathological finding. In 1904, the pathologist Felix Marchand recognized that fatty degeneration of the vessels is consistently associated with vessel stiffening, and therefore introduced the term “atherosclerosis” to indicate this combination [1], where the Greek “athero” means gruel or porridge, and “sclerosis” means hardening [2]. Recent studies have demonstrated, in agreement with this observation, that individuals who have a high degree of arteriosclerosis have a higher probability of having increased endovascular atherothrombotic burden. Nevertheless, we should be aware that discrepancies between the extent of arterial sclerosis and that of atherosclerosis may often be present.

Although nowadays evaluation of the extent of arteriosclerosis is commonly performed even as part of general health screening, until recently the other component of atherosclerosis, namely atheroma formation and subsequent luminal narrowing, has received much more attention than arteriosclerosis. There may be several reasons for this. First, life-threatening vascular disorders, such as myocardial infarction and stroke, may be evoked, most of the time, by a combination of atheromatous plaque formation and accompanying intraluminal thrombus. Second, narrowing and/or occlusion of the middle to large arteries, such as the carotid artery, aorta and intracranial arteries, can be readily visualized by ultrasonography,
computed tomography and magnetic resonance imaging. Third, technically it has been relatively difficult to assess the extent of arterial stiffness; for example, one might have to insert a transducer catheter into the aorta and other arteries to measure the pulse wave velocity.

On the other hand, recent technologic advancement has enabled us to estimate arterial stiffness more easily than before. It is known that pulse wave velocity is faster in stiffened arteries. Therefore, theoretically, we can estimate the extent of arterial stiffness by measuring the velocity of arterial pressure pulse waveform between certain two points. Measurement of the pulse wave velocity between the brachial artery and the ankle is performed in many institutions in Japan and is reported as the “baPWV” value [3]. Cardio-ankle vascular index (CAVI) may also used as a parameter that reflects arterial stiffness [4]. CAVI may be superior to baPWV because it is less dependent on blood pressure [5].

**Arteriosclerosis is also an undesirable component of atherosclerosis**

Histologically, arterial stiffening is characterized by the medial calcification of the aortic wall and the destruction of elastic fibers [6]. Why is arterial stiffening an undesirable phenotype? The pulsatile blood flow provided by the heart is considered to be, in its true form, harmful for the peripheral organs. This is because high pressure may burst a vessel, while low pressure may not provide a constant supply of nutrients. The arterial conduit, when elasticity is sufficiently preserved, helps to dampen this pulsatile waveform and to keep the pressure more constant (Figure 1). A stiffened aorta is less effective at dampening, and blood flow in the coronary arteries, the amount of which is greater in the diastolic than the systolic phase, is also reduced. In addition, arterial stiffening increases the pulse wave velocity; therefore, the reflected wave will return to the point of origin before the aortic valve closes, which leads to an elevation of systolic intra-arterial pressure without a concomitant increase in the blood flow supplying peripheral organs (Figure 2).

![Figure 2 Early reflection of the pulse wave will increase arterial pressure, but reduce effective blood flow.](image)

In addition, as the pathologist Felix Marchand noted, arteriosclerosis is frequently associated with atherothrombotic luminal narrowing, and arterial stiffening is, no wonder, associated with future cardiovascular mortality [7]. In addition to enhanced atheromatous plaque formation, elevated heart rate [8], and isolated systolic dysfunction [9,10] may be prevalent in individuals with increased arterial stiffening, a feature that may also explain the observed association between arteriosclerosis and increased cardiovascular mortality.

**Factors facilitating arterial stiffening**

Although arterial stiffening is an aging-associated phenomenon (Figure 3), several other factors are known to enhance arterial stiffness. These factors include hypertension [11], glucose intolerance [12], and cigarette smoking [13]. It has been proposed that values of baPWV or CAVI can be utilized to determine so-called ‘vascular age’. In this sense, it can be said that smoking, as well as hypertension, will speed up the process of aging. Several recent studies have shown that elevated serum uric acid levels may also be associated with increased pulse wave velocity [14-16]. We showed that less than 20% of men had increased arterial stiffness when serum uric acid level was 5.2 mg/dL or lower, whereas more than 40% of men had increased arterial stiffness when serum uric acid level
Atherososis and arteriosclerosis

Figure 3 Mean baPWV values plotted according to age in individuals who underwent general health screening.

Atherosis and atheroma formation: the other undesirable component of atherosclerosis

Atherosis, which is characterized by fatty streak formation and subsequent atheromatous plaque formation [17], is the other feature of atherosclerosis. Experimental and histologic data have demonstrated that atheromatous plaque formation is a complex process, comprising vascular endothelial injury, infiltration of immune-inflammatory cells (monocytes/macrophages and activated T lymphocytes), and subsequent release of cytokines from these cells [17]. The finding that elevated levels of C-reactive protein, a commonly-used marker of inflammatory response, represent a risk factor for coronary artery disease, is now widely accepted [18], although there remains debate over whether this acute-phase protein plays a causal role in the pathogenesis of atherosclerosis [19].

When the extent of luminal narrowing evoked by atheromatous plaque formation and accompanying intraluminal thrombus exceeds a certain degree, the symptoms of tissue ischemia occur. For coronary ischemia, the signs and/or symptoms may not be apparent if the percentage of luminal narrowing is less than 75%. In this sense, when a patient has apparent angina-associated symptoms, most commonly exercise-induced chest symptoms, the atherogenic process might have already gone beyond its early phase.

One may wish to detect atheromatous plaque formation, if present, while it is in its early phase. Evaluation of the carotid artery by ultrasonography may help us to visualize asymptomatic and early-phase atherosclerosis localized in the carotid artery wall. Of note, the presence of carotid atherosclerosis is associated with not only cerebrovascular events [20] but also ischemic heart disease [21,22].

The prevalence of atheromatous plaque formation increases with age

Essentially, the risk factors for carotid plaque are the same as those for coronary artery disease; among these factors, hypertension may have the strongest association [23,24]. Advancing age is, no wonder, also a risk factor for carotid atherosclerosis. In a set of individuals who underwent general health screening, we can see that the prevalence of carotid plaque apparently increases with age for both genders (Figure 4). It can be observed that, in men older than 75 years, carotid plaque was found in more than 70% of individuals. In this sense, atheromatous plaque formation in the carotid artery, and presumably also in the coronary artery, can said to be an inevitable aging-related phenomenon, just as arteriosclerosis.

Figure 4 Prevalence of carotid plaque in individuals who underwent general health screening.

Controlling the development of aging-associated atherosclerosis

Although arteriosclerosis and atheromatous plaque formation are virtually inevitable aging-associated phenomena, cardiovascular events and stroke, when they occur, may lead to a fatal outcome or a marked reduction in ADL; therefore, it is desirable to control the process of atherogenesis and vascular stiffening.
What can we do to achieve this?

The recognition of dyslipidemia as a major modifiable risk factor has introduced the possibilities of both treatment and prevention [25]. Anti-dyslipidemic therapy has created new opportunities for intervention, especially since the advent of statins. Nevertheless, lifestyle modification, such as cessation of smoking, exercise training [26] and controlling body weight to avoid extreme obesity [27], is undoubtedly important issue that everybody who would like to live a healthy life and reach a vigorous old age should always keep in mind. In addition, routine health check-ups may help to keep us informed about the status of our atherosclerotic condition.

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