

The Interplay of Aging, Aortic Stiffness and Blood Viscosity in Atherogenesis

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ABSTRACT

Normal aortic compliance allows cardiac output to be distributed throughout the cardiac cycle, resulting in lower peak blood velocity. Loss of compliance with aging, hypertension, and possibly other risk factors for atherosclerosis increases peak blood velocity, creating eddy currents in areas of changing vascular geometry, as well as creating adverse patterns of diastolic flow. In the resulting areas of low flow, increased blood viscosity creates the potential for thrombosis. Occlusive thrombi may cause death; parietal or mural thrombi may organize to form atherosclerotic plaques.

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Key words: Aging; Atherosclerosis; Aortic Stiffness; Compliance; Blood viscosity; Risk factor

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INTRODUCTION

Aging is inevitable and with aging there is the progressive loss of the ability to maintain homeostasis, which is subsequently reflected in cellular dysfunction and if not corrected will lead to our demise. Our cardiovascular system clearly plays a leading role in this process. One result of the loss of homeostasis in the cardiovascular system is thrombosis and development of atherosclerotic plaques. Increased aortic stiffness is generally recognized to be an early step in the development of atherosclerotic cardiovascular, including cerebrovascular, disease, the leading cause of deaths worldwide^[1]. According to the 2013 guidelines issued by the European Society of Hypertension and the European Society of Cardiology, determining pulse wave velocity, the “gold standard” surrogate marker for aortic stiffness, should be considered in any clinical evaluation of a hypertensive patient^[2]. By setting the stage for thrombosis and atherogenesis, progressive aortic stiffening is an important factor in aging, which will ultimately limit lifespan. This editorial will present pertinent evidence for a central role for progressive aortic stiffening in affecting an individual’s lifespan, and propose how aortic stiffening and increased blood viscosity will interact as variables, contributing to atherosclerosis. Major risk factors for accelerated atherogenesis which are associated with increased aortic stiffness include age, gender, dyslipidemia, hypertension^[2], cigarette smoking^[3] and diabetes mellitus^[4]. All major risk factors for atherogenesis are associated with increased blood viscosity^[5]. Because all of these risk factors accelerate the development of morphologically similar lesions, we favor an atherogenic process which explains the increased risk associated with all major risk factors, not just hypercholesterolemia and intimal lipid accumulation (Figure 1).

INCREASED AORTIC STIFFNESS IS A CONSEQUENCE OF AGING

It is estimated that homeothermic mammals have an allotment of

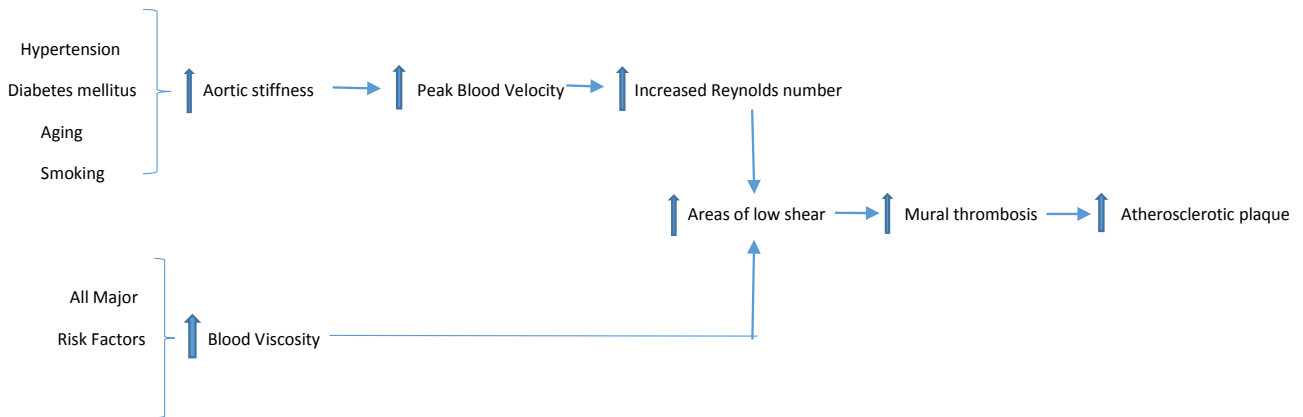


Figure 1 The pathways by which increased arterial stiffness and increased blood viscosity accelerate atherogenesis. All risk factors create larger areas of low shear, which increase the likelihood for development of mural or parietal thrombi, which, upon organization, develop into atherosclerotic plaques.

approximately 1×10^9 heartbeats in a lifetime^[6]. Thus, the mighty whale, with a resting heart rate of 30 to 35 beats per minute, has a life expectancy of roughly 30 years, but the rat, with a heart rate of 370 beats per minute, is expected to live only 3 to 3.5 years. Theoretically, it is unlikely that pump failure alone is solely responsible in limiting lifespan in aging individuals. Gerstenblith *et al.* have proposed that cardiac contractile function is maintained with aging, at least in humans^[7]. Alternatively, the inverse relationship between heart rate and life span suggests that a higher heart rate can cause material or structural fatigue, which will enhance severe failure more quickly. The importance of aortic stiffening in aging and cardiovascular disease is seen in a disease of premature aging, Hutchinson-Gilford progeria syndrome. Patients die at an average age of thirteen, and ninety percent of deaths are due to myocardial infarction and stroke, even though their serum cholesterol, LDL, HDL and C-reactive protein levels are similar to age-matched controls^[8]. In one study, progeria patients with an average age of seven had the aortic stiffness expected in a 60-69 year old^[9]. Those data suggest an important role for aortic stiffening in cardiovascular disease and longevity. The material which fails, causing progressive aortic stiffening, is probably the structural protein elastin. Turnover of elastin is essentially minimal, and synthesis of this molecule ceases at the end of puberty. Indeed, the intimal and medial layers of arteries in patients with Hutchinson Gilford Progeria syndrome are often fibrotic and stiff probably relating to breaks in elastin fibers and the depletion of smooth muscle cells. This is particularly evident at aortic branches and areas immediately distal to atherosclerotic plaques^[10]. Accelerated loss of aortic compliance is a possible explanation for the U-shaped dose response curve for the benefits of exercise. Increased cardiovascular mortality has been previously reported in association with strenuous exercise^[11,12]. Although there are no data on the fatiguing properties of elastin, extrapolation from natural rubber may be enlightening. With cyclical 10% stretch, similar to that experienced by our aorta and proximal large diameter arteries in our youth, rubber has been shown to fracture after 8×10^8 cycles. At 3% stretch, fracture is expected after 3×10^9 cycles. After the fracturing of elastin, our aortic wall stress is manifested by the interplay with collagen molecules^[13].

INCREASED AORTIC STIFFNESS CREATES THE HEMODYNAMIC MILIEU FOR ATHEROGENESIS

In a perfectly stiff aorta, blood flow would only occur during systole.

Aortic capacitance allows our cardiac output to be distributed over the entire cardiac cycle. If cardiac output remains constant, conservation of mass dictates that increasing aortic stiffness requires a subsequent increase in peak systolic blood velocity. Thus, aortic capacitance serves to cause a slower, more even, and constant blood flow, i.e., the “windkessel” function^[14,15]. The increased blood velocity caused by increased aortic stiffness increases Reynolds number, which indicates the likelihood of developing flow separation in areas of changing vascular geometry. In these areas of flow separation, a sluggish blood flow state can arise. This produces an increased residence time for blood to interact with the vascular wall, particularly at “stagnation points.” The principle is the same as in the development of eddy currents around a stationary rock in a rapidly flowing stream (Figures 2, 3).

The adverse effect of vascular stiffness on blood flow was demonstrated by Ku and Giddens using a glass model of the carotid bifurcation^[16]. They found that following prolonged pulsatile flow through the use of their developed model that debris accumulated against the outer wall of the carotid sinus because there was insufficient flow to disperse it. Their observation suggests that increased arterial stiffness creates a “residence time” for blood longer

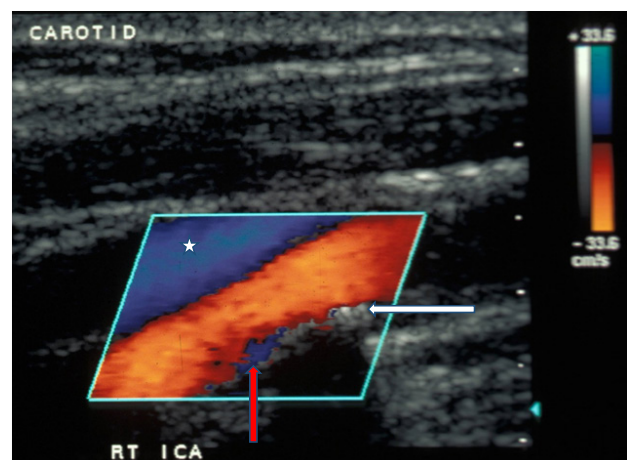


Figure 2 Color ultrasound of internal carotid (bottom vessel, red in color) and internal jugular (top vessel, white star). Direction and velocity of blood flow can be estimated from color scale in upper right. White arrow points to an atherosclerotic plaque. As blood approaches atherosclerotic plaque, blood increases in velocity, changing from dark red to yellow-orange in color. Red arrow points to an area of slow retrograde flow on the distal aspect of the plaque. Figure courtesy of Dr. Robert S. Perret.

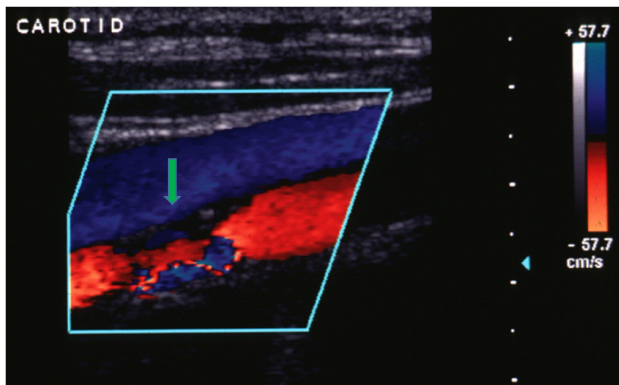


Figure 3 Color ultrasound of internal carotid artery (red) and internal jugular vein (blue). Direction and velocity of flow can be estimated using color scale in upper right. Partially obstructing atherosclerotic plaque or thrombus is present on the wall adjacent to the jugular vein (green arrow). The opposite wall also contains areas with retrograde slow flow (blue) immediately adjacent to and intermingled with small areas of very high velocity antegrade flow (punctate bright yellow and orange areas). Figure courtesy of Dr. Robert S. Perret.

than one cardiac cycle, perhaps even of indefinite duration, a situation promoting thrombus formation. As noted by the 19th century German pathologist Virchow, stasis of blood leads to thrombosis^[17]. Areas of stasis are predisposed to thrombosis because of the accumulation of activated clotting factors, decreased influx of antifibrinolytic molecules, and decreased flow-mediated expression of anti-platelet molecules such as nitric oxide and prostacyclin by the endothelium. Thrombi in arteries tend to remain localized to a single vessel wall because the rapid flow effect against the opposing vessel wall prevents thrombus formation. Thus, the formed thrombi are referred to as parietal or mural thrombi.

ATHEROSCLEROTIC PLAQUES ARE ORGANIZED MURAL THROMBI

The location of the debris accumulation in the previously described bifurcation model coincides with the pathological location of carotid atherosclerotic plaques *in vivo*^[18,19]. Duguid showed in the 20th century that atherosclerotic plaques are organized mural thrombi^[20]. The parietal location of arterial thrombi explains why atherosclerotic plaques are eccentric, not circumferential (Figure 4). In contrast, the slower uniform flow in veins allows thrombi to become occlusive, as seen in deep vein thrombosis.

In the process of organization, blood vessels grow into a thrombus, exudate, or necrotic tissue. Neovascularization allows the influx of fibroblasts which synthesize collagen, resulting in fibrosis or scarring. Duguid's hypothesis is supported by the high prevalence of atherosclerotic plaques in Dacron arteriovenous shunts used for dialysis access^[21] (Figure 5).

These shunts create a hemodynamic environment in which blood flow is so rapid that it creates a palpable thrill. Because of the inanimate nature of these shunts, there is a very limited ability to respond to injury. Further, they lack a tunica media as a source for smooth muscle migration into the intima. Migration of smooth muscle in response to intimal injury is a tenet of previous atherogenesis theory. Instead, thrombi are colonized by circulating stem cells which initiate the organization process and undergoing differentiation can result in the formation of an atherosclerotic plaque^[22] (Figure 6).



Figure 4 H&E stain of a muscular artery with organizing non-occlusive thrombus. The lumen is indicated by a black star. Note the eccentric or parietal location of the thrombus. The process of organization transforms the thrombus into an atherosclerotic plaque. Hematoxylin and eosin, 100x.

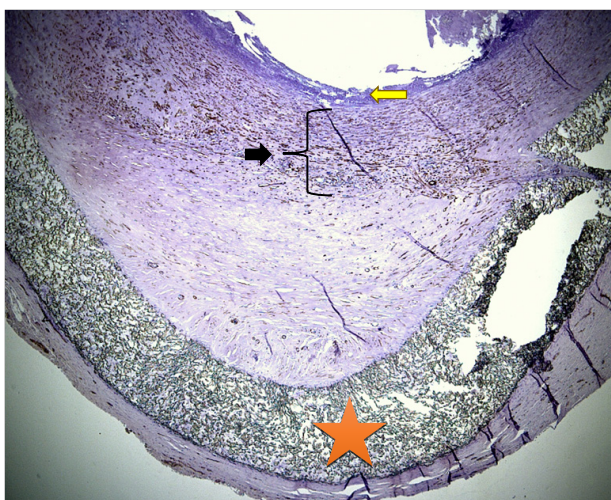


Figure 5 Low power photomicrograph of atherosclerotic plaque in a Dacron graft (star). The section has been stained for smooth muscle actin (brown-staining cells). A layer (enclosed by black bracket) rich in smooth muscle cells (numerous brown cells) is present near the lumen. On the surface of the plaque is a thin layer of fibrin (yellow arrow). Hematoxylin counterstain, 40x.

In addition, the presence of atherosclerotic plaques in synthetic arteriovenous shunts shows that atherogenesis is not a process which begins in youth with fatty streaks and progresses over decades.

The partial obstruction created by an atherosclerotic plaque creates an even more adverse hemodynamic situation distally. A partial obstruction produces an increase in blood velocity across the obstruction, which will foster the development of new areas of flow separation distally. The increased blood velocity will

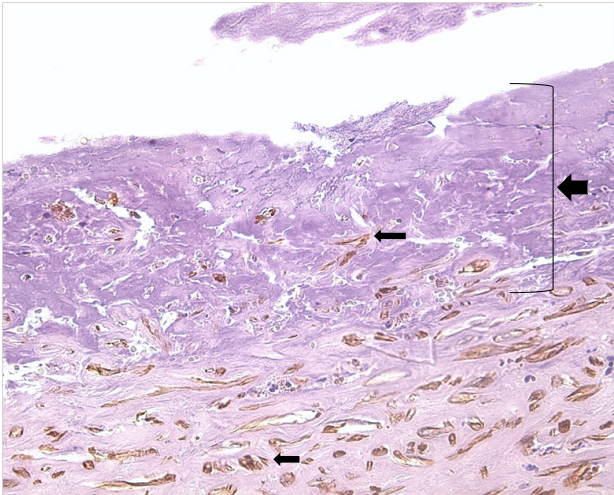


Figure 6 High power photomicrograph of an atherosclerotic plaque in a Dacron graft stained for smooth muscle actin. Small arrows point to two representative positive cells. At top is a fibrin-rich layer (enclosed by brackets) containing scattered positive cells. Beneath that is a layer containing numerous smooth muscle actin positive cells. (Hematoxylin counterstain, 400x).

also increase shear-mediated platelet activation, increasing the likelihood for thrombosis distal to the plaque. These phenomena result in the formation of new plaques with a propensity for superimposed thrombosis, so-called “vulnerable” plaques. These adverse hemodynamics result in the formation of plaques which are more likely to become symptomatic in spite of a lesser degree of obstruction compared to the initial proximal plaque. Thus, “vulnerable” plaques are a consequence of adverse hemodynamics, not inflammation^[23]. The thin fibrous cap and increased lipid content of these plaques may simply be due to interruption of the organization process by a superimposed thrombosis.

In addition to increasing peak blood velocity, increased aortic stiffness changes the patterns of aortic blood flow in ways which could encourage atherogenesis. Normal aortic compliance permits retrograde blood flow in the distal aorta during diastole. This constant blood flow throughout the cardiac cycle limits the residence time required for mural thrombus formation. Increasing aortic stiffness with aging decreases the prevalence of diastolic retrograde aortic flow in the lower thoracic aorta beginning at age 23 in one study. By age 37, retrograde flow was absent^[24]. The loss of retrograde flow with aging in the distal thoracic aorta correlates with the increasing prevalence of atherosclerotic plaques in the abdominal aorta. In the Pathobiological Determinants of Atherosclerosis in Youth Study, 0.1% of the abdominal aortic surface area was covered by atherosclerotic plaque in black males aged 15 to 19. By age 30 to 34, 7.6% of the surface area was covered by atherosclerotic plaque^[25]. Atherosclerotic plaques are composed of large amounts of collagen, which further contributes to aortic stiffening.

Aging and increased aortic stiffness increase diastolic retrograde flow in the descending aorta^[26]. This increased retrograde aortic flow augments diastolic flow in the carotid system. In the carotid arterial circulation antegrade flow occurs throughout the cardiac cycle. Conceivably, if this augmented diastolic flow was rapid enough, then an area of flow separation could persist throughout the entire cardiac cycle, as suggested by the results using the Ku and Giddens’ glass model. However, the major significance of increased retrograde flow in the descending aorta is probably augmented diastolic flow in the coronary arteries. The great majority of flow in the coronary arteries occurs in diastole because of systolic contraction. The augmented

coronary flow caused by retrograde flow in the descending aorta could increase Reynolds number and cause areas of flow separation. The meager systolic flow in the coronary circulation increases the likelihood of a residence time longer than a cardiac cycle. The concave surface of the heart causes the coronary circulation to be adverse from a hemodynamic standpoint when compared to a long straight vessel.

INCREASED BLOOD VISCOSITY CREATES LARGER AREAS OF SLOWER FLOW

Increased aortic stiffness is a non-specific effector by which several risk factors accelerate atherogenesis. The second non-specific effector is increased blood viscosity. Blood is a non-Newtonian fluid, meaning that its viscosity is inversely related to flow. Like ketchup, blood becomes “thicker” or more viscous the slower it flows. Thus, in the areas of flow separation created by increased aortic stiffening, a situation of decreased flow can evolve which can lead to increased viscosity, further slowing blood flow, and further increasing viscosity, i.e. a vicious cycle.

One of the principal causes of the non-Newtonian behavior of blood is erythrocyte aggregation. Erythrocytes are kept apart by their electronegative surface charge, and are able to approach each other only to within 7.9 nm of their glycocalyxes^[27]. Low-density lipoprotein and fibrinogen, by virtue of their large diameter, are able to span the minimum intercellular distance between two erythrocytes and foster erythrocyte aggregation. In this way, these molecules accentuate the non-Newtonian property of blood, creating larger areas of slower blood flow in areas of low shear or slow blood flow^[28]. High-density lipoprotein competes with LDL for erythrocyte binding. Because of its smaller particle diameter, it antagonizes erythrocyte aggregation and decreases blood viscosity. Erythrocyte aggregates are weak, and easily disrupted by blood flow. LDL and fibrinogen increase the yield strength of erythrocyte aggregates, i.e. the stress or force needed to permanently deform them^[29,30]. This will allow erythrocyte aggregations to enlarge, leading to larger areas of stasis, triggering thrombus formation, a process recently reviewed by Wagner *et al.*^[31]. Thus, a hemorheologic abnormality, increased blood viscosity, interacts with a hemodynamic one, increased peak blood velocity, as factors or variables contributing to the development or progression of atherogenesis.

We have presented evidence, calling attention to anatomic and physiological factors contributing to the formation and progression of atherogenesis that can and most certainly play a role in creating a situation for thrombus formation. We believe and hope that future researchers will make a concerted effort to acknowledge this process and to address these parameters or variables and their potential role in the development and progression of atherogenesis. Encompassing these factors, future therapeutic interventions may be developed to aid in stabilizing existing cardiovascular disease with the ultimate goal to lower the existing rates of morbidity and mortality, currently found in this disease.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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