Why do veins stiffen with advancing age?

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Veins, like the large arteries (8, 16, 21), stiffen with increasing age (6, 11–12, 14, 18, 20). From a cardiovascular control perspective, venous capacitance, which relates the magnitude of the total contained volume of the vasculature to the pressure (i.e., the volume at a given internal pressure), is vitally important to long-term blood pressure regulation. In animal models, this is measured quantitatively by coupling blood volume to mean circulatory filling pressure, a concept described in the 1950s by Arthur Guyton (9). Approximately 70% of the total blood volume is contained in the low-pressure venous system, which can be viewed as a voluminous reservoir. Both the capacitance and the compliance of the veins are very large relative to that of the arteries, such that overall vascular capacitance is largely dependent on the structure and function of veins (7). Modest vеноconstriction can drastically reduce the amount of blood stored within the veins and redistribute this blood to the high-pressure arterial side of the circulation, increasing effective blood volume (4). This central redistribution of blood volume may be an important characteristic of the hemodynamic alterations noted in hypertension (4). Overall, the regulation of the venous system is critical to the maintenance of cardiovascular control; consequently, there is a strong need to examine factors such as aging that alter this system.

In humans, vein “stiffness” is often assessed as limb venous compliance. Compliance is the slope of the volume-pressure relationship. This relationship is pressure dependent and nonlinear (15). As such, it is critical to quantify compliance over a range of pressures. Valuable information on limb venous compliance in both health and disease has been obtained in humans using the relatively simple and noninvasive technique of venous occlusion plethysmography (10). More recently, high-resolution ultrasound has been used to assess single-vein compliance (3, 19). To ascertain the relative importance of venous smooth muscle tone on cardiovascular function, both techniques have been coupled with acute perturbations such as non-baroreflex-mediated sympathoexcitatory maneuvers (e.g., the cold pressor test and handgrip exercise) and endothelium-independent decreases in smooth muscle tone (e.g., sublingual nitroglycerin). What is most surprising is that these very powerful perturbations often have little to any effect on measured limb venous compliance (10, 13, 20). Before concluding that alterations in smooth muscle tone have no role at all on limb venous compliance in humans, it is important to note that lower body negative pressure (LBNP) has been shown to acutely reduce venous compliance in men (5–6, 13). LBNP transiently causes a reduction in central blood volume, thereby unloading the baroreceptors, which elicits sympathoexcitation. Importantly, reductions in venous compliance during LBNP were noted in both young (5, 13) and older men (5), suggesting that acute increases in venous smooth muscle tone can alter venous compliance. What we do not know is whether chronic increases in venous smooth muscle tone contribute to the age-related decline in venous compliance.

In this issue of the Journal of Applied Physiology, Sielatycki and colleagues (17) examined this pertinent question in their well-designed study. In this investigation, calf venous compliance was assessed in young (27 ± 1 yr old) and older (67 ± 2 yr old) men both before and during acute systemic β-and α-adrenergic blockade, achieved by intravenous infusion of propranolol and phentolamine. The predominant receptor causing reflex constriction of the veins is the α2-receptor (15). Before adrenergic blockade, and similar to previous reports (6, 11, 12, 14, 18, 20), older men had reduced venous compliance compared with young men. Adrenergic blockade did not alter venous compliance in either young or older men, such that the age-related reduction in venous compliance persisted during adrenergic blockade in the older subjects. Venous capacitance, estimated by the point at which the compliance relation shifted from a rapid filling response to a slower increase in volume after cuff pressure was applied, was also reduced in the older group both before and during adrenergic blockade. Importantly, the percentage of blockade was similar between young and older men. Thus this study strongly suggests that increased smooth muscle tone, as a result of increased sympathetic/adrenergic influences in older men, does not contribute to the age-associated reduction in venous compliance. It is important to note that venous smooth muscle tone is not controlled exclusively by adrenergic input. In fact, various factors aside from the sympathetic nervous system, such as endothelin (4) and myogenic tone (1), are known to affect venous function and may play a role in regulating venous capacitance and compliance. Indeed, the authors suggest that other functional factors or aging-induced structural changes to the venous wall appear to be responsible for the age-related reduction in venous compliance in healthy men.

Structurally, young healthy veins consist of three distinct media layers: a thin internal layer of smooth muscle cells, a thick middle layer consisting of bundles of smooth muscle cells separated by collagen and elastic fibers, and an external transitional layer in which the limits between media and adventitia are not often clearly defined (2). Aged veins display subintimal fibrous thickening, fibrosis of the three media layers, a decrease in elastic tissue, increased collagen cross-linking, and hyperplasia of the smooth muscle cells (2). In addition, it is well-established that in the arterial system aging is likewise associated with increases in large-artery stiffness and therefore reductions in arterial compliance (8, 16, 21). While the underlying cellular and molecular mechanisms responsible for age-related decreases in arterial compliance are incompletely understood, they are generally believed to result from structural changes, such as increased collagen cross-linking, fragmentation and thinning of elastin, and increases in fibronectin, as well as...
functional abnormalities including increases in vascular smooth muscle tone and endothelial dysfunction (8, 16, 21). Regardless of the specific underlying cause, the age-related reduction in arterial compliance, similar to the impact of decreased venous compliance, may impair cardiovascular control and reduce the ability of the vasculature to buffer hemodynamic stresses.

The study presented in this issue by Sielatycki et al. (17) represents an important advance for furthering our understanding of venous compliance and its contribution to cardiovascular control mechanisms in both health and disease. However, the present contribution is not without inherent limitations. The conclusions must be limited to whole limb venous compliance in healthy men. The splanchnic circulation receives ~25% of cardiac output and contains ~20% of total blood volume (7) and, along with the cutaneous circulation, is the most compliant and largest blood reservoir in the body. These characteristics, coupled with the fact that the neural control of the cutaneous circulation is primarily controlled by core body temperature, suggest that venoconstriction and mobilization of blood may be especially important in the splanchnic circulation (7). Due to methodological challenges, this vascular bed has not been studied in detail in humans, and there is a clear need for future studies directed at this compartment of the venous system.

In individuals with established hypertension, there is a clear increase in vascular resistance; however, there is also a noted reduction in venous capacitance (4). This decrease in capacitance is most evident in the veins, particularly those in the splanchnic region. There are data from animals suggesting that the reduction in venous capacitance redistributes circulating blood centrally and contributes to the development of hypertension (4). However, the role of reduced capacitance in the pathophysiology of human hypertension is less clear. While the older subjects who participated in the highlighted study by Sielatycki and colleagues (17) were not hypertensive, they did have a statistically significant elevated resting blood pressure compared with the young control subjects. As such, it is possible that the age-related reduction in venous capacitance may contribute to the increases in blood pressure that commonly occur with advancing age. While we still do not know the precise mechanisms underlying why the veins stiffen with advancing age, it appears that adrenergic influences on smooth muscle tone are not a contributing factor.

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REFERENCES