Mechanisms of Decreased Vascular Function With Aging

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Atherosclerosis of the coronary, cerebral, or peripheral circulation, the single leading cause of morbidity and mortality in most countries, develops with aging. Therefore, advanced age is one of the primary risk factors for the presence of atherosclerotic cardiovascular disease. Abnormalities in the regulatory functions of the vascular endothelium, commonly referred to as “endothelial dysfunction,” are among the earliest detectable stages in the process of atherosclerosis. For example, patients with traditional risk factors, eg, hypertension, hypercholesterolemia, smoking, diabetes mellitus, and obesity, but without overt evidence of atherosclerosis, have demonstrable endothelial dysfunction. In turn, this abnormality contributes to the premature development and to the progression of the atherosclerotic process.

All of those aforementioned conditions are also associated with advanced age, thus leading to an important question: are there mechanisms that result in vascular degeneration and disease with aging that are independent of known or traditional risk factors? The answer seems to be yes, based on the results of earlier studies that have shown the presence of endothelial dysfunction and other vascular abnormalities in older subjects, even when controlling for risk factors. It is important to note that not all studies have controlled for all risk factors. Moreover, even when the known traditional risk factors are accounted for, other so-called novel risk factors may still be more prevalent among older patients and may help to contribute to any reported vascular abnormality, hence the difficulty in establishing the independent contribution of aging to atherosclerosis.

What are the mechanisms that may lead to progressive worsening of vascular function and structure with aging above and beyond those conditions known to be associated with atherosclerosis? Previous studies, in both animal models and humans, have shown that aging is associated with a gradual decline of NO activity in the vessel wall. Increased formation of reactive oxygen species, alteration in the expression and/or activity of endothelial NO synthase (eNOS), and decrease in NO bioavailability have all been suggested as potential mechanisms underlying the impaired endothelium-dependent vasodilator responses that occur with aging. These findings are relevant because it is known that decreased NO activity leads to changes that herald the development of atherosclerosis and conditions associated with premature development of atherosclerosis (eg, diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, etc) are also characterized by impaired NO activity.

In this issue of Hypertension, Nicholson et al report another mechanism of abnormal vascular function associated with aging, namely, impaired prostacyclin (PGI2)-mediated vasodilation. The authors observed that local infusion of PGI2 into the brachial artery resulted in diminished vasodilation of the regional forearm vasculature in older subjects when compared with younger controls. Certain methodologic aspects of this study that may affect the interpretation of its results are worth considering. In particular, older subjects had higher blood pressure (an average of 6 mm Hg higher for systolic and 8 mm Hg higher for diastolic blood pressure) and higher plasma cholesterol (an average of 27 mg/dL). These differences did not reach statistical significance (likely because of the small sample size), and no correlation was found between the response to PGI2 and either blood pressure or plasma cholesterol. Nevertheless, they cast doubts with regard to an independent effect of aging on the response to prostanooids.

It must also be noted that PGI2 has a well-described direct relaxing effect on the vascular smooth muscle, which is mediated primarily by its cell-surface PGI2 receptor. Activation of cell-surface PGI2 receptors that are enriched on vascular smooth muscle cells and platelets results in G protein–mediated activation of adenylate cyclase and formation of cAMP that ultimately leads to phosphorylation of protein kinase A, reduction of intracellular calcium, and smooth muscle cell relaxation (Figure). Recent data suggest that the effect of PGI2 may also be mediated via intracellular peroxisome proliferator-activated receptor-β/δ, but the role of this pathway in the regulation of vascular tone is not known. Historically, cAMP-mediated PGI2 pathway and cGMP-mediated NO pathway, in addition to less well-characterized endothelium-derived hyperpolarizing factor, are considered the main vasodilator signaling cascades that regulate vascular tone (Figure). Increasing evidence suggests that significant cross-talk between the NO and PGI2 pathways exists at multiple levels involving NO regulation of cyclooxygenase (COX) expression and prostaglandin synthesis and release. Molecular mechanisms underlying cross-talk between NO and COX enzymes, as well as their net effects, appear to differ significantly depending on the cell type and still remain to be fully elucidated.

In the study of Nicholson et al, the results obtained during NO inhibition with L-arginine analogs indicate the presence of NO-mediated response to PGI2. However, although interactions between prostanooids and eNOS gene expression have been reported, evidence of a direct and acute increase in eNOS activity in response to PGI2 administration has not
been clearly established. This should be the subject of future investigations to further advance our understanding of the effects of vasodilator prostanoids in the vasculature. Of note, the results of the study by Nicholson et al\(^2\) show that the non–NO-mediated response to PGI\(_2\) is not impaired in older subjects. Hence, at least in the context of this study, PGI\(_2\) seems to have behaved much like other endothelium- and NO-dependent vasodilators, eg, acetylcholine, for which impaired vasodilator response with aging has been described previously. In fact, that the response to PGI\(_2\) during NO inhibition was similar between older and younger subjects appears to indicate that the vascular smooth muscle response to this vascular prostanoid is preserved with aging. What follows is that the reported impaired response to PGI\(_2\) may be just another manifestation of impairment of the NO system that occurs with aging.

Previous studies investigating the relationship between COX-derived prostanoids and endothelial function have focused on the effect of COX inhibition on vascular resistance and on the response to endothelium-dependent vasodilators. Thus, eg, aspirin was shown to have a vasoconstrictor effect on baseline vascular tone and an augmenting effect on the

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Figure. Endothelial NO and prostaglandin vasodilator pathways. Endothelial agonists, eg, acetylcholine (Ach), substance P (subs P), and bradykinin (BK), bind to their respective transmembrane receptors leading to the formation of phosphoinositol (PPI) and elevated intracellular calcium (Ca\(^{++}\)). Increased Ca\(^{++}\) levels activate eNOS. Shear stress activates eNOS via increased intracellular Ca\(^{++}\) and activated protein kinases (PKs). Isoproterenol and PGI\(_2\) act on their receptors to increase cAMP concentrations and to activate eNOS through a mechanism that does not involve PPI (direct activation of eNOS after PGI\(_2\) binding has not been yet demonstrated in endothelial cells, but the results of Nicholson et al\(^2\) support this hypothesis). Activated eNOS forms NO using the amino acid L-arginine as a substrate, with the formation of L-citrulline as a side product. NO diffuses freely from the endothelial cells to the underlying vascular smooth muscle, where it activates soluble guanylyl cyclase (sGC) that converts GTP to cGMP. Increase in cGMP results in relaxation of smooth muscle cells and consequent vasodilation. Also in the endothelial cell, elevated intracellular Ca\(^{++}\) and PKs activate phospholipase A\(_2\) (PLA\(_2\)). Activated PLA\(_2\) liberates arachidonic acid (AA) from membrane-bound phospholipids, which is then available for metabolism by COX. Prostaglandin H\(_2\) (PGH\(_2\)) is generated via the peroxidase activity on COX; its further transformation depends on the cell type and enzymes that are present. Endothelial cells express prostacyclin synthase (PGIS), resulting in predominant PGI\(_2\) formation, whereas platelets express thromboxane synthase (TXS), leading to the synthesis of thromboxane A\(_2\) (TXA\(_2\)). Other prostaglandins, eg, prostaglandin E\(_2\) (PGE\(_2\)), prostaglandin D\(_2\) (PGD\(_2\)), and prostaglandin F\(_{2\alpha}\) (PGF\(_{2\alpha}\)), are also formed. PGI\(_2\) acts on its receptors on the smooth muscle cells linked to activation of adenylyl cyclase (AC), leading to conversion of ATP to cAMP. Increase in cAMP levels causes smooth muscle relaxation and consequent vasodilation.
response to acetylcholine, both in the coronary and in the peripheral circulations. These results suggest that, in humans, vasodilator prostanoids, eg, PGI₂, contribute to the maintenance of basal vascular tone, whereas vasoconstrictor products of COX limit endothelium-dependent vasodilation. This may explain the well-demonstrated beneficial effect of aspirin in patients with coronary artery disease. Increased production of vasoconstrictor prostanoids has been suggested to occur with aging based on the results with COX inhibition by indomethacin that potentiated the vasodilator effects of acetylcholine in elderly patients. Additional basic mechanistic studies may reveal relative contributions of the PGI₂ pathway and COX-mediated vasoconstriction in aging vessels. Because COX produces both vasodilator (eg, PGI₂) and vasoconstrictor (eg, thromboxane A2) prostanoids, an impaired response to PGI₂ with aging may lead to an imbalance in the COX derivatives. In fact, studies have shown upregulation of endothelial COXs and enzymes of prostaglandin-endoperoxidase catabolism with enhanced generation of vasoconstrictive prostanoids during the aging process.

The findings reported by Nicholson et al² point to abnormalities in vascular behavior that may contribute to the age-related changes that precede the clinical manifestations of vascular complications. Importantly, these abnormalities are expressed both at the level of conductance vessels that develop atherosclerosis (eg, coronary, carotid, and lower extremity arteries) and at the small vasculature responsible for systemic vascular resistance, and they participate in the development and perpetuation of hypertension and its complications. Further investigation leading to a better understanding of the mechanisms underpinning the role of COX products, their inhibition, and the resulting changes to the regulation of vascular biology is necessary. This may shed some light into the ongoing controversy between selective and nonselective COX inhibition and the potential for untoward effects on cardiovascular outcomes.

The implications of a study associating aging with vascular abnormalities are important given the paucity of information about the mechanisms that contribute to vessel senescence beyond those involved in other (better known) processes. We currently have drugs to effectively treat hypertension, dyslipidemia, and diabetes mellitus, and we know of the salutary effects of lifestyle modifications to correct smoking habit, weight gain, and lack of exercise. However, we have no effective means to alter the process of vascular degeneration that occurs with aging. Until those mechanisms are better defined and understood, the medical community will be left without therapeutic tools to arrest a naturally occurring process of decay in vascular health that ultimately accounts for most deaths in developed societies.

Disclosures

None.

References

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