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Authors

Clavijo, Raul I
Miner, Martin M
Rajfer, Jacob

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Erectile Dysfunction and Essential Hypertension: The Same Aging-related Disorder?

Raul I. Clavijo, MD,[1] Martin M. Miner, MD,[2,3] Jacob Rajfer, MD[1]
[1]Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Department of Family Medicine and Department of Urology, Warren Alpert Medical School, Brown University, Providence, RI; [3]Men's Health Center, The Miriam Hospital, Providence, RI

An erection is a mechanical event dependent primarily on corporeal vascular dynamics wherein arterial inflow and storage of blood within the corpora is greater than the egress of blood from the corpora. The most common cause of erectile dysfunction (ED) is the inability of the corporal tissue to store the blood within the corporal sinusoids once inflow into the corpora begins. This failure to store is primarily due to a corporal smooth muscle dysfunction and, in most men, is most likely an aging-related occurrence. Because the corporal smooth muscle is embryologically and physiologically indistinguishable from the smooth muscle within our arterial system, the authors hypothesize that the aging-related dysfunction that occurs within the penis also occurs within the arterial system, and that this smooth muscle dysfunction within the arterial media is most likely the cause of what is called essential hypertension. This panvascular smooth muscle myopathy could explain why hypertension is the most common comorbidity associated with ED and appears to indicate that both ED and essential hypertension are the same disorder, albeit in two different organ systems.

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KEY WORDS

Erection • Endothelium • Smooth muscle • Hypertension

Almost all men recognize at some time in their lives that their erectile function begins to change. For most men, the ability to attain and maintain an erection during the teenage years is second nature. However, by the time men hit the fourth and fifth decade of life, many have recognized that their erectile function has changed, and the ability to maintain an erection during sex has diminished; the refractory period, the time in between erectile events, begins to increase. Although men in their teenage years and young adult lives are able to have multiple erectile events at will, this ability begins to fade as aging sets in. Because the ability to maintain an erection is directly related to the function of

the corporal smooth muscle, this increase in the refractory period is a clinical sign that the smooth muscle of the corpora is likely becoming dysfunctional. This review highlights what we know about the corporal smooth muscle cell and demonstrates that what occurs to the corporal smooth muscle cell also occurs to its embryologic sibling, the smooth muscle cell within the media of the peripheral vascular system. As a result of this relationship, changes in the function of the penis can reflect changes in the vascular system.

The Role of Nitric Oxide in Erectile Dysfunction

The physiologic events necessary for erection to occur are well known. As a result of some form of sexual stimulus, the cavernosal nerves synthesize and release nitric oxide (NO) from its nerve terminals onto the smooth muscle cells of both the corpora cavernosa and the penile arterial system.[1-3] This neuronally derived NO, via its second messenger—cyclic guanosine monophosphate—causes relaxation of the smooth muscle cells within the media of the penile arterial vessels (which leads to arterial vasodilatation and an increase in blood flow to the penis), and the smooth muscle cells within the cavernosal bodies (which opens the cavernosal sinusoids to provide a place to store the increase in penile blood flow).

Endothelial dysfunction (EnD) is considered a systemic pathologic state of the vascular endothelium in which there is an imbalance between vasodilating and vasoconstricting modulators produced by the endothelium.[4] This imbalance is believed to be due primarily to a reduction in the bioavailability of endothelial-derived NO.[5] The association between EnD and erectile dysfunction (ED), in the setting of the extensively studied association of EnD with cardiovascular diseases,[6,7] has led many investigators to hypothesize that EnD is the main cause of ED.[8,9] However, we have recently reviewed the data to show that there is very little solid scientific evidence to support earlier contentions that NO from the endothelium of either the vascular system or the corporal sinusoids is operative in this process.[10] Similarly, although it was initially claimed that the maintenance of an erection was due to the release of NO from the endothelium, recent follow-up experiments have now shown that this part of the erectile response is likely due to neuronal NO and not endothelial-derived NO.[11]

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The Role of Smooth Muscle Dysfunction in ED

As the body ages, the tissues that contain smooth muscle (eg, bladder, peripheral vascular system, and penis) display a progressive loss of the parenchymal smooth muscle cells, which are replaced by collagen fibers.[12-14] The loss of smooth muscle cells in the penis means that the remaining smooth muscle mass may not function as well as it did previously and, from a physiologic point of view, may not be able to relax and store blood as well as it did with its full complement of smooth muscle cells. A man needs to lose approximately 15% of corporal smooth muscle mass before leakage of blood occurs from the penis.[15] Because this programmed cell loss (apoptosis) with aging is thought to be a genetically determined event, the recognition of an increase in the refractory period or the inability to maintain an erection will occur at a different age for each individual. This explains why the majority of men, regardless of age, have evidence of venous leakage or cavernosal veno-occlusive dysfunction (CVOD) when evaluated with sophisticated testing for complaints of ED.[16-18] However, because the ability to attain and then maintain an erection is the result of a dynamic balance between inflow and outflow of blood within the cavernosal bodies, a man experiencing an increase in his refractory period may not complain of ED unless (1) the venous outflow, which is dependent on the amount of corporal smooth muscle apoptosis, reaches the critical stage in which the arterial inflow is insufficient to compensate for the progressive increase in venous leakage; or (2) the inflow becomes so restricted that it is incapable of overcoming the amount of venous leakage that is already present. Clinical evidence indirectly supporting these two scenarios can be seen when men age < 50 years are evaluated for a complaint of ED.[17,19] In men who have none of the risk factors for arterial disease (eg, hypertension, diabetes, metabolic syndrome), an issue with the

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arterial system of the penis is rarely identified as the primary cause of ED.[20] However, if the vascular system is the cause of ED in these young patients, it is usually CVOD or venous leakage and not arterial disease that is the culprit.[16,19] If men develop any of the risk factors for vascular disease that can affect the arterial tree, the evaluation of the vascular system of their penis at the time they present with a complaint of ED usually will identify defective arterial inflow as well as venous leakage.[17,21]

The Penis and the Peripheral Vascular System

The penis should be considered as a specialized vascular organ and an extension of the vascular system. Therefore, it follows that any defect or disorder that affects the vascular system should also affect the penis and vice versa. As such, if the majority of patients with ED have a loss of corporal smooth muscle cells due to a progressive, genetically predetermined, aging-related apoptosis within the cavernosal tissue, it follows that these patients should also demonstrate the same aging-related smooth muscle loss within their peripheral vascular systems.[22] In the peripheral arterial system, the apoptotic process within the arterial media leads to a condition called arteriosclerosis; that is, arterial stiffness, in which the ability of the media of the artery to relax is compromised. These stiffer arteries are known to cause an increase in peripheral vascular resistance, and patients may then present with hypertension.[23-25] Such panvascular smooth muscle apoptosis may explain why hypertension is the most common medical condition associated with ED.[26] In fact, Bansal[27] first suggested that ED, specifically early-onset aging-related ED, and essential hypertension are the same disorder, albeit in two different tissues. Clinical data to support this theory emanate from the study in which arterial stiffness alone (arteriosclerosis) was found in patients with ED who did not have any additional vascular risk factors.[20]

Furthermore, animal data to support this theory come from a study that assessed the natural history of ED associated with hypertension in a well-established rat model of genetic hypertension. These data demonstrated that fibrotic remodeling from rats genetically prone to hypertension are detectable at an earlier time point in the erectile compared with aortic tissue, pointing to a possible role for ED as an early warning sign for hypertension in this animal model.[28] Using the same rat model, one group looked at the ultrastructure of penile cavernous tissue in these and normotensive rats. They found that the small arteries of the penis in these hypertensive animals underwent structural changes, such as medial thickening, lumen narrowing, and increase of vascular resistance, suggesting that hypertension might affect the ultrastructure of the penis. They also noted smooth muscle cells in the penis that were in the early stage of apoptosis.[29] One may conclude from these observations that the initial disruption in many men at risk of developing ED is cavernosal smooth muscle loss and associated remodeling of supporting structures. These changes may begin at an early age and lead to venous leakage, the earliest signal of a man's inability to sustain erections. In other men, this venous leakage may not become clinically recognized until the patient enters middle age or senescence, which is the time when disorders such as hypertension and diabetes impact arterial inflow to the penis. When arterial inflow to the penis is unable to compensate for the already ongoing venous outflow, the imbalance leads to symptomatic ED.

ED and Essential Hypertension: The Same Disorder in Different Tissues?

Because we believe that ED and essential hypertension are the same disorder, how does this explain the multitude of studies that indicate that ED and coronary artery disease (CAD) are related?[30,31] We know that approximately 40% of men who present with ED are shown to have occult cardiovascular disease,[32,33] with the severity of ED correlating positively with both the degree of occult ischemic heart disease and the extent of coronary atherosclerosis.[30,34] In addition, it has been shown that ED precedes the onset of symptomatic CAD by a mean of approximately 3 years in patients with both ED and documented CAD,[35,36] and men with ED appear to carry a 23% increased risk of cardiovascular death.[37] The one unifying concept that can explain all these events is the aging-related vascular smooth muscle cell apoptosis that occurs within the entire vascular tree. In the penis, this smooth muscle loss will cause CVOD, which, at its initial stage, begins to affect the refractory period. With time, this progresses to symptomatic venous

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leakage (difficulty maintaining the erection). In the peripheral vascular system, this dysfunction leads to an increase in peripheral vascular resistance and patients may present with hypertension. If the hypertension goes unrecognized and untreated, EnD may ensue.[38] Once this occurs within the peripheral vascular system, arterial flow is impacted, which may then exacerbate whatever CVOD is present and cause these patients to present with symptomatic ED. In fact, in men with ED but no cardiovascular risk factors, the presence of ED alone has failed to predict a cardiovascular death.[36] At present, it is not recommended that every patient with hypertension be evaluated to rule out CAD, and it appears that this recommendation should also be applicable to patients who have ED but none of the vascular risk factors. In fact, the Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease reported a similar recommendation.[39]

Conclusions

The initiation and/or maintenance of the erectile response seem more dependent on the integrity of the smooth muscle within the corpora and the penile vasculature rather than on the function of its endothelium. Hypertension essentially describes a vascular system that has difficulty with vasodilatation and is dependent on the ability of the smooth muscle within its media to function normally; it is the most common disorder seen in patients with ED. Because the smooth muscle within the media of the peripheral vascular system is both embryologically and physiologically similar to that of the cavernosal smooth muscle, logic dictates that preprogrammed genetic events affecting the penile vasculature also impact the peripheral vasculature, and gives credence to the theory that aging-related ED and essential hypertension are probably the same disorder, albeit in two different tissues. This suggests that men with ED should be screened primarily for hypertension rather than CAD, especially those men without other vascular risk factors. ■

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MAIN POINTS

- The most common cause of erectile dysfunction (ED) is the inability of the corporal tissue to store the blood within the corporal sinusoids once inflow into the corpora begins.
- This failure to store is primarily due to a corporal smooth muscle dysfunction and is likely an aging-related occurrence.
- Corporal smooth muscle is embryologically and physiologically indistinguishable from the smooth muscle within our arterial system; therefore, the aging-related dysfunction that occurs within the penis also occurs within the arterial system, and is most likely the cause of essential hypertension.
- This panvascular smooth muscle myopathy could explain why hypertension is the most common comorbidity associated with ED and appears to indicate that both ED and essential hypertension are the same disorder.

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