Erectile dysfunction and its relationship with cardiovascular risk factors and disease

Eshiobo Irekpita, MBBS, FWACS, *Taofik A. Salami,* MBBS, FMCP.

ABSTRACT

تعتبر عملية انتصاب القضيب عملية هديرولوكية مركبة، وللجهاز القلبي الوعائي (CVS) دورا مركزياً بها. إن توقف وظيفة الانتصاب (ED) وعدم القدرة على تحقيق الانتصاب أو الحفاظ على القضيب منتصباً بشكل كافي للممارسة الجنسية المُرضية، كان يعود في السابق وبشكل جزئي إلى التقدم في العمر. ويتزامن ذلك مع أمراض محددة وعادات نمط الحياة مع أسباب– تؤثر على العلاقة، ومن بينها داء السكري، ارتفاع ضغط الدم، اضطراب الدهون في الدم، التدخين، وتضيق التصلب العصيدي، وقد تسبب هذه الأمراض الإصابة بمرض الشريان التاجي (CAD) وتوقف وظيفة الانتصاب (ED) مبكراً نتيجة لصغر حجم الشريان الفرجي. يجب تقييم حالة الرجال الذين يعانون من توقف وظيفة الانتصاب (ED) من ناحية عوامل خطر كإصابة الجهاز القلبي الوعائي، حيث يكون هنالك دليل على أن توقف الانتصاب بسبب مرض الشريان التاجي (CAD). يجب أن تكون معالجة الرجال الذين يعانون من مرض الشريان التاجي (CAD) وتوقف وظيفة الانتصاب المصاحبة بشكل مفرد، كما يجب أن يخضعوا للعلاج الثنائي من قبل الطبيب المعالج وأخصائي المسالك البولية.

Penile erection is a complex hydraulic process, in which the cardiovascular system (CVS) plays a central role. Erectile dysfunction (ED) is the inability to achieve, and/or maintain penile erection sufficient for satisfactory sexual intercourse, and was previously regarded as part of aging. It is associated with certain diseases and life style habits with a cause-effect relationship, including diabetes mellitus, hypertension, dyslipidemia, and cigarette smoking. Through atherosclerotic narrowing, these diseases may cause coronary artery disease (CAD) and ED, with ED featuring earlier due to the small size of the pudendal artery. The common denominator in ED and CAD is endothelial dysfunction. Men presenting with ED should be evaluated for CVS risk factors, as there is mounting evidence that ED is a sentinel event for CAD. The treatment of men with CAD and concomitant ED should be individualized, and undertaken jointly by the managing physician and urologist.

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From the Departments of Surgery (Irekpita), and Medicine (Salami), Ambrose Alli University, Ekpoma, Nigeria.

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Address correspondence and reprint request to: Dr. Eshiobo Irekpeta, Department of Surgery, Ambrose Alli University, Ekpoma, Edo State, Nigeria. E-mail: tatsalami@yahoo.com

Erectile dysfunction (ED) is the inability to achieve, and/or maintain penile erection sufficient for satisfactory sexual intercourse.[1] Before the 1980's, it was considered an inevitable part of the aging process for which there was no treatment, and was therefore rarely discussed. In Pommervile's[2] words "20 years ago ED did not exist as a diagnostic term. Its former name, impotence, carried a heavy connotation - an impotent man was powerless, worthless, less than a man. Impotence was seldom discussed in the medical literature, and even less discussed in the locker rooms, or the bedrooms of nations." This perception has changed remarkably, and ED is now a subject of intense research, with the result that more men are now effectively treated, and have returned to normal sexual life. The last century was remarkable in terms of research into ED, with profound discoveries associating it with certain diseases with a cause-effect relationship.[3] This has translated into the development of simple effective treatment modalities, and improvement in the quality of life of the affected men.

There was a remarkable increase in the medical understanding of erectile function and dysfunction in the area of incidence, prevalence, etiology, as well as, risk factors for ED,[4] though a unifying definition is currently unavailable.[5,6] Shaeer et al[7] in their study of the prevalence of ED in diverse nationalities, representing a wide range of cultural, religious, racial, and socio-

economic backgrounds concluded that, prevalence rates from various countries are difficult to compare because of variable definition, and age range. They recorded a prevalence rate of 57.4% in Nigeria, 63.6% in Egypt, and 80.8% in Pakistan among primary health care seekers. These include men with cardiovascular (CV) diseases, and other risk factors.

Penile erection is a complex hydraulic process,[8] that is initiated and controlled by the nervous systems with profound physiological responses from, and consequences on the cardiovascular system (CVS). The contribution from the CVS to the phenomenon of penile erection is well documented by El-Sakka and Lue,[9] in their review of the physiology of penile erection. From a holistic perspective, penile erection and sexual intercourse, which may follow, place a recognizable level of demand on the CVS. The relationship between ED and the CVS is double edged, and both are currently known to have the same risk factors.[10] This article aims to examine this relationship and its implication for the treatment of men who have ED, on cardiovascular risk factors and disease.

Anatomy, neurophysiology, and mechanism of penile erection. The human penis is made up of a paired corpus cavernosa located dorsally, and a ventrally located corpus spongiosum.[11] The erectile tissue proper is located in the corpora cavernosa, and is surrounded by a tough tunica albuginea. The cavernosa is made up of sinusoids with smooth muscle wall, lined by endothelium similar to those found in the blood vessels.[12] The helicine arteries, the terminal branches of the cavernosa artery empty into these sinusoids, and the blood collect into veins which course beneath the tunica before piercing it. The penis has both autonomic and somatic nerve supply, the latter subserving the penile skin, while the former serves the erectile tissue. The parasympathetic fibers, which supply the penis arise from the Onuf's nucleus (S2-S4),[13] and courses behind the rectum[14] to form the pelvic plexus from which post ganglionic fibers pass posterolateral to the prostate to reach the cavernosa. The sympathetic supply originates from T10-L2, and the fibers course behind the peritoneum to the area of the aortic bifurcation where they form the superior hypogastric plexus (presacral).[15] Fibers from the superior hypogastric plexus joins those of the parasympathetic to form the inferior hypogastric plexus. The fibers reach the corpora through the same pathway as the parasympathetic nerves.

The neurotransmitters traditionally associated with the sympathetic and parasympathetic systems are respectively, the catecholamines and acetylcholine. The events which lead to penile erection are not completely accounted for by these neurotransmitter substances. Currently, the substance which acts as a neurotransmitter in the process of penile erection is considered a non-adrenergic, non-cholinergic one, and is now known to be nitric oxide (NO).[16] The nerve fibers that secrete NO are thought to accompany the parasympathetic fibers to the genito-urinary tract.[17] Other neurotransmitters secreted within the cavernosa and vessels includes vaso-active intestinal peptide (VIP), and several prostaglandins. Nitric oxide is also secreted by the endothelial lining of the corpora cavernosa. The receptors for these neurotransmitters are located in the tissues of the lower genito-urinary tract. The process of penile erection occurs through several mechanisms and is classified as follows;[18] a) central: central stimulus emanates from thought, sight, and smell related to sexual intercourse. The impulses generated in the process pass down the spinal cord from the higher centers to the pelvic parasympathetic processes. b) reflexogenic: this originates from the stimulation (tactile) of the dorsal nerve of the penis. The impulses generated pass through the efferent pathway to the Onuf nucleus. The efferent pathway is parasympathetic and causes penile erection, but this is however, modifiable by the higher centers located in the medial pre-optic area and para-ventricular nucleus. c) nocturnal penile tumescence: this penile erection which takes place during rapid eye movement sleep. It is presently considered to play an important role in keeping the erectile tissue perfused.

Penile erection occurs when central, reflexogenic, or nocturnal penile tumescence (NPT) stimulus leads to the release of NO, and acetylcholine from the parasympathetic endings in the erectile tissue. Nitric oxide diffuses directly into the cell,[19] and modulates the activities of adenylate cyclase, which in turn increases the synthesis and release of cyclic guanosyl monophosphate (cGMP). Guanosyl monophosphate activates protein kinase G, leading to the decrease in calcium influx into the cell, which in turn causes activation of myokinase, and thus relaxation of the smooth muscle cell, a key step in the erectile processes.[16] The influx of blood into the sinusoidal spaces, as a result of smooth muscle relaxation, leads to penile engorgement and rigidity, and this is sustained by the NO produced by the endothelial lining of the cavernosa as a result of sheer stress of rapid blood influx.[20] This engorgement compresses the veins against the tough tunica, thereby impeding venous outflow in the presence of increased arterial inflow. The role and contribution of this venous occlusion to the penile rigidity is unclear.

Penile detumescence is not a direct reversal of this process, but is rather brought about by sympathetic activation. Catecholamines released during orgasm and ejaculation cause contraction of the sinusoidal smooth muscles, which lead to reduced arterial inflow and opening of the venous channels. Venous outflow

increases in the presence of reduced arterial inflow with a resultant penile flaccidity. Catecholamines activate phosphodiesterase 5, which in turn speeds up the destruction of NO, the non adrenergic non cholinergic (NANC) neurotransmitter responsible for penile tumescence.

Vascular changes associated with cardiovascular risk factors and erectile dysfunction. Arteries are classified into 3 types based on size:[21] a) large or elastic arteries typical of which are, the aorta innominate, subclavian, and iliac arteries b) medium size arteries, examples of which are, coronary and renal arteries. These are also referred to as distributing arteries c) small arteries usually less than 2 mm in diameter, and course for most of the time through the substance of tissue and organs, for instance, the pudendal and cavernosal arteries. The artery, independent of its classification, has 3 layers namely, the intima, media, and adventitia. The intima is made up of endothelial lining, which rest on a basement membrane, while the media consists mainly of vascular smooth muscle cells, which are constantly under tonic control mostly by the endothelium,[22] in order to maintain blood flow according to tissue, organ, and regional requirements. The intima endothelium has diverse physiological endowment and capacity, to control the events that take place in the intima and media.[23] Changes in the endothelium intimately affect the physiological functions of the blood vessel, and indirectly the tissue, organ, or region sub-served by the vessel. Various neurotransmitters such as NO and various prostaglandin are elaborated by the endothelium, while expressing a large number of receptors for circulating hormones, local mediators, and vasoactive factors released from blood cells.[24] Endothelium can also sense local changes in pressure and flow, and respond appropriately resulting in vasodilatation and constriction, to enable the vessel to respond to changes in the local milieu. The effect of the endothelial activity however, is vasodilatation.

Nitric oxide is responsible, similar to the lower genito-urinary tract for the basal-endothelium-dependent dilator tone.[25,26] It inhibits cytochrome C oxidase, reduces oxygen consumption by the vasculature, and modifies adhesiveness of endothelial cells for circulating white cells. These are in addition to its traditional role of activating guanylate cyclase, the mechanism by which penile erection is produced. The secretion of NO is stimulated by sheer stress on the endothelium, and stimulation by acetylcholine, bradykinin, and substance P.[27] The diminished NO mediated dilatation has been implicated in hypertension, diabetes mellitus, cigarette smoking, and hypercholesterolemia, all of which are referred to as causes, or risk factors for erectile dysfunction.[28]

Atherosclerosis is the common pathway, by which these factors produce their deleterious effects on both the CVS and the penile erectile tissues, with NO playing a central role.[29] The earliest manifestation of atherosclerosis is a decrease in bioavailability of NO in response to pharmacological, or hemodynamic stimulus, either due to increased breakdown, or decreased production.[24] Endothelial dysfunction results from inhibition of dimethylarginine dimethyl amino hydrolase, which catalyses the hydrolysis of asymmetric dimethyl arginine, an inhibitor of endothelial nitric oxide synthase (NOS). There is uncoupling of endothelial NOS leading to oxidative stress in the endothelium, and the formation of peroxy nitrites, oxidation of pro-inflammatory nuclear factor kappa B, the latter leading to cellular inflammation.[30] These life style abnormalities are called cardiovascular risk factors, because when complicated by atherosclerosis, the coronary artery is often involved with subsequent development of coronary artery disease. Erectile dysfunction may precede coronary artery disease,[31] because of the difference in the size of the coronary, and pudendal arteries that supply the heart and cavernous tissues, (small artery theory).[32] The effect of treatment of atherosclerosis with statins on ED is presently controversial with varied opinion, as to whether or not, statins precipitate ED.[33]

Cardiovascular risk factors and erectile dysfunction. Diabetes mellitus (DM). Men with diabetes mellitus are more likely to have erectile dysfunction, and erectile dysfunction is currently suggested as an observable marker of diabetes mellitus.[34] The erectile dysfunction in DM, is both neurological and vasculogenic, the former due to autonomic neuropathy,[35] and the latter, as a result of atherosclerosis. Both are common complications of the disease. The naturopathic and vascular changes also affect the heart through cardiovascular autonomic neuropathy, and atherosclerosis of the coronary artery. Abdominal adiposity and obesity are associated with increase cardiovascular morbidity in DM, while lipid profiles and endothelial inflammation are also significantly higher.[36] Meng et al[37] in their work showed, that higher glucose level induces apoptosis in endothelial cells, while Di Filippo et al[38] also concluded that in DM, the incidence of CVS disease is higher, due to the established risk factors such as obesity, dyslipidemia, hypertension, and atherosclerosis as a result of increased inflammation. These factors lead to increased production of free radicals, impaired NO metabolism, and increase movement of lipids into the media, a sine qua non for early, and diffuse atherosclerosis. Through the latter, erectile, cerebral, and cardiovascular function may be impaired. Over two-thirds of male patients with DM develop ED.[39]

Hypertension. Systemic hypertension is the most common non-communicable disease in Nigeria, and hypertension and diabetes often co-exits.[40] Essien et al[41] in 2007 observed that the mean venous glucose level is higher in hypertensive adult Nigerians, than their normotensive counter parts. Recent studies suggest that approximately 67-68% of men with hypertension have some degree of erectile dysfunction.[42] There is however, a controversy as to whether hypertension per se, or its treatment, induces erectile dysfunction in these men.[43] Atherosclerosis induced by hypertension is due to endothelial damage by the sheer stress of elevated blood pressure. This damage induces inflammatory changes, impairment of NO metabolism, and increase movement of lipids into the media, a pre-requisite for atherosclerosis. The angiotensin 1 (AT1) produced in the renin-angiotensin system leads to super oxide formation, which further worsens the endothelial damage. From this perspective, it may be deduced that hypertension can solely be responsible for erectile dysfunction. Modebe[44] in Nigeria reported ED in 8% of the 227 untreated hypertensives, and 61% in the treated group. The conclusion here is that treatment, rather than the hypertension itself may significantly contribute to the development of ED. Shiri et al[45] in their study, aimed at investigating the effect of cardiovascular diseases, and the concomitant medication use on erectile function concluded, that the risk of ED was higher in men suffering from treated hypertension and heart disease, than in those with the untreated condition. The use of calcium channel blockers, angiotensin II antagonist, non selective B blockers, and diuretics increase the risk of developing ED. Erectile dysfunction was however, not associated with the use of organic nitrates, angiotensin-converting enzymes (ACE) inhibitors, selective B blockers, and serum lipid lowering drugs.

The ongoing telmisartan alone, and in combination with ramipril global endpoint trial/telmisartan randomized assessment study in ACE-intolerant subjects with cardiovascular disease (ONTARGET/TRANCEND)[46] study shows on the contrary, that calcium channel blockers tend to have a significant adverse effect on erectile function, while treatment with beta blockers, diuretics, ACE inhibitors, AT1 antagonist and alpha antagonists, do not. Treatment with ACE inhibitors and AT1 antagonist, or a combination of both, is suggested to improve erectile function in cardiovascular high-risk patients.

Dyslipidemia and cigarette smoking. Nicotine remains the most commonly mentioned toxin from cigarette smoke, but others exist. These toxins cause endothelial inflammation, which causes abnormality of NO metabolism, and increase in movement of lipids into the muscular media, with subsequent formation of atherosclerosis. Dyslipidemia is associated with changes in endothelium dependent vasodilation in the peripheral vessels, such as the coronary, and pudendal arteries. Modified low-density lipo-protein appears to inhibit NO synthesis, or speed up its destruction, possibly by enhancing super oxide anion.[47] Lipo-proteins enter into the arteries by way of the process of transcytosis, and in the presence of endothelial inflammation and hyper-lipoproteinemia, there is increased entrance into the media and intima.[48] This reduces NO dependent vasodilating effect, and consequently leads to atherosclerosis. Dyslipidemia is a feature of various cardiovascular diseases and risk factors,[49] all of which have the potential for causing erectile dysfunction.

Congestive cardiac failure (CCF). Various cardiovascular disorders cause CCF, and these include hypertension, congenital, and acquired valvular heart defects and cardiomyopathy. Ukoh and Okorofuo[50] in their study, observed hyperlipemia in 3 groups of patients in Nigeria: 1) hypertensives with or without heart disease, 2) patients with ischemic heart disease, and 3) those with hypertensive cardiomyopathy. From this, it is clear that diseases that cause congestive cardiac failure may be associated with factors, which cause atherosclerosis, and by extension produce erectile dysfunction. Congestive cardiac failure is associated with peripheral venous stasis, decreased venous return, decreased stroke volume, and cardiac output, a prerequisite for physical inactivity. Most patients with chronic cardiovascular disease experience decreased libido, and frequency of sexual activity as well as ED.[51] Up to 75% of patients with heart failure reported ED.[52] The treatment of heart failure with drugs such as diuretics, beta receptor blockers, and digoxin may worsen ED due to medication side effect,[53] which may in turn lead to non-compliance.

Coronary artery diseases (CAD). Approximately one-quarter of all deaths among men, and one-fifth of all deaths among women in Britain are due to ischemic heart disease.[54] In England and Wales, 30% of all deaths among men, and 22% among women are the result of ischemic heart disease.[55] Through atherosclerotic narrowing of the coronary artery, cardiovascular risk factors may cause angina or myocardial infarction, depending on the extent of severity. Coronary artery disease and erectile dysfunction have endothelial dysfunction as a common denominator, but ED may precede CAD by several years. Bansal et al[56] in their work indicated that, 56% of an ED population have asymptomatic myocardial ischemia, 75% of men with CAD have symptoms of ED, and 91% of their ED population have cardiovascular risks. There is now mounting evidence that erectile dysfunction is an early predictor of CAD. Men presenting with ED with no

other cardiovascular symptoms provide an opportunity for the treating physician to evaluate for asymptomatic CAD, and to reduce CAD risk factors.[57] Currently, erectile dysfunction is considered a sentinel event for coronary artery disease, as both have their origin from endothelial dysfunction,[58] and it is advised that men presenting with ED without other symptoms, offer an opportunity for the evaluation for cardiovascular risk factors, and asymptomatic CAD.[49] Herschorn[58] in his work on cardiovascular safety of phosphodiesterase 5 inhibitors said that "in general, sexual activity has an effect similar to mild-moderate exercise in increasing heart rate, blood pressure, cardiac output, and respiratory rate. The degree of change in these physiologic parameters however, is greater than expected because of a disproportionate increase in sympathetic activation. The absolute risk of sexual activity triggering a myocardial infarction (MI) is low. Men with CAD, or previous MI have a 10-fold higher risk, which means that during sexual intercourse, the probability of such a man having MI is 20/million/hour. Traditionally, CAD is treated with nitrates, which dilate the coronary arterial bed. The active factor in the nitrates is NO, which is responsible for endothelium dependent vasodilatation, and the neurotransmitter responsible for penile erection. The treatment of ED was recently revolutionized by the introduction of phosphodiesterase 5 inhibitors, which are targeted at reducing the break down of NO.[19] Their actions are therefore, similar, to those of the nitrates used for the treatment of CAD, and they may actually act in synergy.

There are varied opinions as to whether these drugs should be used together in patients who have coronary artery disease, and concomitant erectile dysfunction. Parker et al[59] insisted in their work that though contraindicated, there are situations when a patient who has recently taken a phosphodiesterase 5 inhibitor might need intravenous nitroglycerin treatment. They however, cautioned, that this should be with close monitoring of the blood pressure, and heart rate in men with stable CAD. In the study by Webb et al,[60] however, when sublingual nitroglycerin was administered, there was a 4-fold decrease in systolic blood pressure in patients on sildenafil treatment. Sildenafil potentiated the hypotensive effect of glyceryl trinitrate. They concluded that sildenafil is an absolute contradiction in patients using organic nitrates. Velasquez et al[61] also stressed this in their case report, and review of the literature. Their reported adverse cardiac events associated to sildenafil medication side effects, included MI, angina, ventricular tachycardia, and death.

In conclusion, the CVS is central to the phenomenon of penile erection, and sexual intercourse that follows, places a recognizable burden on the heart.[62] Patients who have cardiovascular risk factors should be questioned on ED, as self-reporting is not reliable as a result of embarrassment, and ignorance on the part of the patient. The treatment of the cardiovascular risk factors, CAD, and heart failure may precipitate, or exacerbate ED, and this may be responsible for non-compliance by some men, in order to maintain potency.[63] The treatment of these men should jointly be undertaken by the physician and urologist, in order to achieve optimal results, and maximize their quality of life. Men with cardiovascular risk factors and disease should be stratified according to cardiac risk, and be advised accordingly with respect to the simultaneous, and indiscriminate use of phosphodiesterase 5 inhibitors, and nitrates. They should be properly informed of the implication of treatment for ED, and in the face of overt or covert CAD. The use of phosphodiesterase 5 inhibitors and nitrates in men with ED and CAD calls for caution, individualization, and joint consultation between the managing physician and urologist.

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