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Penile Doppler Ultrasound Predicting Cardiovascular Disease in Men with Erectile Dysfunction

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Abstract Cardiovascular disease is a major cause of morbidity and mortality in the USA. Traditional risk factors such as obesity, physical inactivity, and diet are used to screen for cardiovascular disease. However, these risk factors miss a significant population who are at risk for future cardiac events. Erectile dysfunction (ED) has many associated conditions in common with cardiovascular disease and has been shown to be an independent risk factor for cardiovascular. Measurements made on penile Doppler ultrasound (PDU), such as cavernosal artery peak systolic velocity (PSV), cavernosal artery intima-medial thickness, and the finding of cavernosal artery calcification, are indicators of generalized vascular disease. Thus, elements of PDU can identify men at higher risk for cardiovascular disease. This review outlines the proper technique for PDU and the literature supporting the use of PDU to predict cardiovascular disease in men with erectile dysfunction.

Keywords Cardiovascular disease · Erectile dysfunction · Penile Doppler ultrasound · Risk

Introduction

Cardiovascular disease is the leading cause of death for both men and women in the USA. In fact, 600,000 deaths per year in the USA are attributable to ischemic heart disease [1]. Current screening methods, which assess traditional risk factors such as diabetes mellitus type II (DM2), obesity, diet, and physical inactivity, only capture about half of those at high risk for developing cardiovascular disease and fail to identify seemingly healthy young men who have a 17 % risk of developing cardiovascular disease [2, 3•]. Early identification and treatment of metabolic factors (e.g., hypertension, dyslipidemia, hyperglycemia) can delay and possibly prevent the development of cardiovascular disease [4, 5]. Thus, finding new predictors of cardiovascular disease risk may significantly decrease this burden and improve overall health.

Erectile dysfunction (ED) is defined by the persistent inability to attain or maintain an erection sufficient for intercourse and is estimated to affect 18 million men in the USA from age 20 and beyond [6]. Arteriogenic ED represents a subtype of ED caused by penile arterial insufficiency and can represent an early manifestation of generalized vascular disease with risk factors paralleling those of cardiovascular disease. Multiple cross-sectional studies have identified a direct correlation between metabolic syndrome, DM type 2, elevated waist-to-hip ratio, and HTN with ED severity as defined by the International Index of Erectile Function (IIEF) score [7, 8]. Multiple mechanisms may overlap between the disease processes, including endothelial dysfunction related to reduced testosterone stimulation of nitric oxide (NO) expression [9], atherosclerosis-mediated smooth muscle atrophy and fibrosis [10], hyperglycemia-induced NO inactivation [11], and increased production of oxygen-derived free radicals through activation of protein kinase C [12]. Reduced vascular NO levels in turn have been implicated in increased adherence of leukocytes and platelets and impaired vasodilation [13, 14]. Because the penile arteries measure 1–2 mm compared with the size of the coronary arteries (3–4 mm), clinically significant atherosclerosis and endothelial dysfunction may lead to earlier manifestation of disease in erectile tissue. Therefore,

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the physician evaluating ED has a unique opportunity to diagnosis vascular impairment at a time when lifestyle changes and possible medical intervention have the potential to change morbidity and mortality of cardiovascular disease.

Penile Doppler ultrasound (PDU) utilizing color and spectral Doppler is commonly used in the diagnostic workup of a patient with erectile dysfunction (ED). PDU assesses the quality of arterial blood flow and sufficiency of veno-occlusive mechanisms, both necessary for an adequate erection. Penile vasculature assessed during penile Doppler ultrasound can indicate cardiovascular disease and allow identification of men who are at the high risk of developing cardiovascular disease. This review analyzes the role of penile ultrasonography in predicting cardiovascular disease. We will also focus on the ultrasound technique necessary to detect arteriogenic disease and identify clinically relevant findings that would identify patients who would benefit from a detailed cardiologic evaluation.

Ultrasound Technique

Penile ultrasound is best performed with a high-frequency linear array transducer with an ultrasound frequency of 7.5–18 MHz which allows for high-resolution images of the penis and internal vascular structures (Table 1). Color and spectral Doppler are essential elements of penile ultrasonography in addition to B-mode ultrasound. Innovative new technologies including sonoelastography have the potential for changing the way we diagnose diseases of the phallus and follow their resolution.

Survey Scan

Routine scanning during penile ultrasound should include both transverse and longitudinal views of the penis by placing the transducer probe on the dorsal or ventral aspect of the penis. The technique presented here uses a dorsal approach, which is easier for the flaccid phallus. However, the ventral approach, often with placement of legs in the lithotomy position, is often better with a fully erect phallus as well as being able to visualize the proximal corpora cavernosa. The goal is to visualize the cross-sectional view of the two corpora cavernosa dorsally and the corpus spongiosum ventrally along the length of the penis from the base of the penile shaft to the glans penis.

The corpora cavernosa appear dorsally, as two homogeneously hypoechoic circular structures, each surrounded by a thin (usually less than 2 mm) hyperechoic layer representing the tunica albuginea that envelops the corpora. The corpus spongiosum is a ventrally located circular structure with homogeneous echotexture, usually more echogenic than the corpora cavernosa [15]. It is best visualized by placing the ultrasound transducer probe on the ventral aspect of the penis; however, the urethra is easily compressible so minimal pressure should be maintained while scanning. For routine anatomic scanning of the flaccid penis with ultrasound, all three corpora can be sufficiently viewed from a single dorsal approach to the penile shaft. A survey scan is first performed prior to obtaining static images at the proximal (base), mid-portion and distal (tip) portions of the corpora cavernosal bodies for documentation. The value of the survey scan cannot be over stated. The initial survey scan is essential to evaluate for plaques, intracavernosal lesions and urethral pathology as well as evaluation of the dorsal penile vessels.

Table 1 Penile ultrasound technique

Penile ultrasound technique
1 Patient in supine or lithotomy position
Survey scan
2 Identify and measure the corpora cavernosa, spongiosum, urethra
3 Save images at proximal, mid-portion, and distal cavernosa. Identify and measure any calcified plaques or variable tissue echogenicity.
Doppler
4 Identify cavernosal arteries
5 Measure arterial diameter, PSV, EDV, RI
6 Inject vasoactive agent
7 Serial measurements of arterial diameter, PSV, EDV, RI

PSV peak systolic velocity, *EDV* end diastolic velocity, *RI* resistive index ((PSV−EDV)/PSV

Penile Doppler Ultrasound

PDU utilizing both color and spectral Doppler modalities has been a vital part of the assessment of patients with ED. PDU allows for a baseline evaluation of the functional anatomy as well as providing a real-time assessment of the dynamic changes experienced in response to the dosing of vasoactive medications.

An important consideration when performing PDU is the angle of incidence. Velocity of blood flow is measured by the magnitude of shift in sound-wave frequency, known as the Doppler shift, detected by the ultrasound transducer when encountering active blood flow. Of the factors that affect the Doppler shift (e.g., frequency of the ultrasound beam, speed of sound in soft tissue, and velocity of the moving reflectors such as blood in a vessel), the sonographer only controls the angle between the ultrasound beam and vector of blood flow. As the angle of incidence approaches 90°, the Doppler shift approaches 0, artificially decreasing the calculated velocity of blood flow. Therefore, the ideal angle of incidence is between 0 and 60° for accurate measurement of blood flow velocity (Fig. 1).

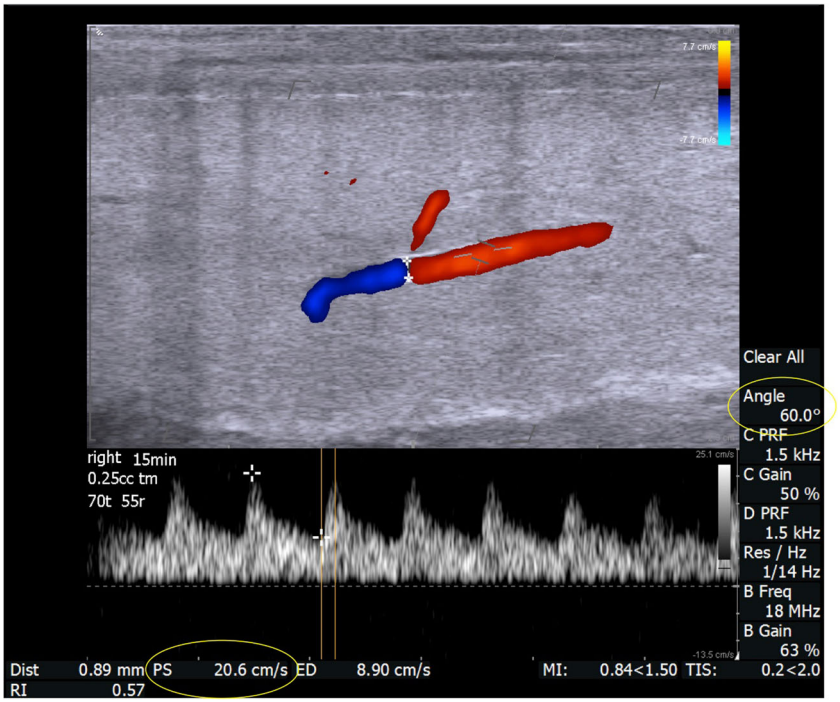

Fig. 1 The electronic cursor is lined up with the right cavernosal artery in this patient 15 min after injection of 0.25 ml of TriMix. The angle of incidence is 60°, the PSV is 20.6 cm/s and the diameter of the artery is 0.89 mm. The caliper should be approximately 75 % of the inner diameter of the artery being interrogated as it is here

PDU is mostly directed toward the cavernosal arteries. The cavernosal arteries are visualized within the corpora cavernosa, and the depth of these arteries can be easily defined within the corpora during transverse scanning to ensure a comprehensively represented assessment of diameter at different points along its course. Color Doppler examination of the penis should be performed in both transverse and longitudinal planes of view. Using the transverse views as a guide to cavernosal artery depth, turning the transducer probe 90° then provides longitudinal views of each corpus cavernosum separately, allowing for identification of the cavernosal arteries in longitudinal section. The diameter of the cavernosal artery should be measured on each side. Measurements of vessel diameter to assess the peak systolic flow velocity (PSV) as well as end-diastolic flow velocity (EDV) allow for the assessment of a vascular resistive index (RI). The diameter of the cavernosal artery ranges from 0.2 to 1.0 mm in a flaccid penis [16, 17]. PSV varies at different points along the length of the cavernosal artery, typically with higher velocities occur more proximally [18]. Hence, assessment of the PSV and EDV is usually recorded at the junction of the proximal one third and the distal two thirds of the exposed penile shaft. In the flaccid state, cavernosal artery PSV normally measures 5–15 cm/s, at baseline. This should be assessed and compared to the pharmacostimulated state [19, 20].

The intracavernosal injection should then be given. At regimented serial time points following the injection of vasoactive medication, cavernosal artery dimensions and flow velocities should be recorded to assess the response to pharmacologic stimulation. After prepping the lateral aspect of the penile shaft with an alcohol or povidone-iodine prep pad, a finely measured volume of a vasoactive agent should be injected into one corpus cavernosum (in the distal two thirds of the penile shaft) using a 29- or 30-gauge 1/2″ needle. Pressure should be held on the injection site for 1 to 2 min to prevent hematoma formation. The amount to inject is patient specific. For example, a patient presenting with no erections after a radical prostatectomy that had had normal erections prior to his procedure would be given a very low dose (i.e., 0.05 ml) of our standard TriMix (Papaverine 30 mg/ml; Phentolamine 2 mg/ml; PGE-1 10 mcg/ml). A patient, however, with significant cardiovascular disease with no erections would be given a much higher dose to begin with (i.e., 0.2 ml or greater).

Vasoactive agents used for pharmacologic stimulation of erection include prostaglandin E1, papaverine, or trimix (combination of prostaglandin E1, papaverine, and phentolamine) [21]. As with every medication administration, the expiration date of the medication should be reviewed, patient allergies should be evaluated, and the dose administered together with the lot number of the medication should be documented. Informed consent should be obtained after the patient is counseled about the possible off label use of the medications used, known risk for developing a low-flow priapism and appropriate follow-up if this were to arise [22]. For patients given a vasoactive agent and develop low-flow priapism, aspiration, irrigation, and injection of intracorporal phenylephrine are usually successful to reverse the priapism state. Corporal aspiration alone can be successful in the setting of pharmacologically induced priapism in the absence of confounding factors (e.g., concomitant use of

phosphdiesterase inhibitors, sickle cell disease, etc.) following diagnostic duplex penile ultrasonography. In cases of diagnostic PDU with intracavernosal pharmacostimulation where a resistive index of 1.0 or greater is achieved, immediate treatment or prolonged observation to achieve detumescence is recommended because of the high specificity of absent diastolic flow for priapism [23].

Role of Penile Ultrasound in Predicting Cardiovascular Disease

PSV is the most accurate measure of arterial disease as the cause of ED. The average PSV after intracavernosal injection of vasoactive agents in healthy volunteers without ED ranges from 35 to 47 cm/s, with a PSV of 35 cm/s or greater signifying arterial sufficiency following pharmacostimulation [24–29]. Primary criteria for arteriogenic ED include a PSV less than 25 cm/s, cavernosal artery dilation less than 75 %, acceleration time >110 ms. In cases of equivocal PSV measurements, particularly when PSV is between 25 and 35 cm/s, other parameters can be useful such as asymmetry of greater than 10 cm/s in PSV comparing the two cavernosal arteries, focal stenosis of the cavernosal artery, and cavernosal-spongiosal flow reversal [30].

In cases where arterial function and venous leak may be coexistent processes, indeterminate results may be yielded on PDU and a mixed vascular cause of ED may be assumed. However, venous competence cannot be accurately assessed in a patient with arterial insufficiency.

Predicting Cardiovascular Risk

B-Mode

While penile ultrasound provides an assessment of penile function and erectile dysfunction, many individual elements can portend cardiovascular risk. Presence of calcifications involving the cavernosal artery on the B-mode survey scan can give clues to endothelial dysfunction, arterial insufficiency, and underlying atherosclerotic disease [31]. Peripheral artery calcifications generally develop with age and can decrease the vessel wall elasticity and compliance predisposing to atherosclerosis and decreased perfusion. In a retrospective review of 1500 men with either Peyronie's disease and/or ED who had penile sonography, 22 % were found to have intracavernosal artery calcification with a statistically significant increase in the prevalence of calcifications in men with cardiovascular risk factors, including smoking, hypertension, hyperlipidemia, and diabetes ($p<0.05$) [32].

As axial resolution of ultrasound probes improve, assessment of the artery wall thickness and plaque burden have emerged as new morphological parameter for detecting atherosclerosis. Carotid artery intima-media thickness (IMT) has been demonstrated as an independent predictor of stroke and cardiovascular disease [33]. Men with ED have also been shown to have demonstrable plaque burden and larger IMT measurements (>0.3 mm) than men without ED [34, 35]. Using ROC curve analysis, Caretta et al. [35] found a better sensitivity and specificity for IMT >0.3 mm (sensitivity=84 % and specificity=87.5 %) than PSV for predicting the presence of carotid and femoral vasculopathy. In addition, men with cavernosal artery alterations in this study had a higher number of cardiovascular risk factors ($p<0.05$).

Doppler Ultrasound

Penile Doppler ultrasound is the gold standard for diagnosing arteriogenic ED through its quantitative and qualitative assessment of overall penile blood flow and ability to assess cavernosal arterial patency. This is exemplified in a prospective study of 49 men with predominantly arteriogenic ED with no prior cardiac evaluation underwent PDU prior to undergoing stress echocardiography. Twenty percent of subjects had abnormalities on stress echocardiography, including severe cardiac wall motion abnormalities, as compared to a reported 2–3 % incidence in the general population. Using univariate and multivariate analysis, cavernosal artery insufficiency as defined by PSV<30 cm/s remained a significant predictor of an abnormal stress echocardiogram [36]. Although historically, the spectral Doppler indices were assessed in the erect state, Corona et al. [37] showed that the PDU can also be performed in a flacid phallus. Using a cutoff of 13 cm/s for PSV was predictive of a PSV obtained in the erect phallus of <25 and <35 cm/s with an accuray of 89 and 82 %. In a subset of 20 patients with uncomplicated type 2 diabetes mellitus who underwent additional adenosine stress myocardial perfusion scintigraphy (SPECT), a threshold of <13 cm/s was predictive of impaired coronary flow reserve with an accuracy of 80 % ($p<0.05$).

Longitudinal studies have also demonstrated the predictive ability of an incomplete response to vasodilatory medications administered during PDU. This was demonstrated in a 2011 study by Rastrelli et al. [38•] who showed in a sample of 1687 men longitudinally evaluated for sexual dysfunction with penile color Doppler ultrasound. Of the 1687 men studied, 37 (2.2 %) demonstrated no response to intracavernosal injection therapy. The non-responders were more likely to have higher prevalence of hypogonadismal symptoms, higher rates of diabetes and metabolic syndrome, and a higher incidence of major cardiac event (hazard ratio 2.745, $p<0.05$).

Conclusion

Cardiovascular disease is a major cause of morbidity and mortality in the USA, yet traditional risk factors can miss a

significant population at risk for cardiac events. A number of recent studies have suggested that arteriogenic erectile dysfunction may be a nontraditional risk factor for cardiovascular disease and such diagnosis may provide a window of opportunity during which intervention can prevent or mitigate the development of cardiavascular disease [39–51]. The evaluation of ED on penile ultrasound provides a thorough overview of penile vascular health and gives a snapshot of overall vascular status. Many findings on penile ultrasound are found independent of traditional risk factors for cardiovascular disease and can identify men at risk for cardiovascular disease who can benefit the most from early intervention. Erectile dysfunction is often a re-entry point for men into health care after years of neglect. Penile Doppler ultrasound is an important diagnostic tool that not only documents penile vascular function but also has the potential for reducing the devastation of cardiovascular disease by providing early diagnosis and treatment.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Nikhil Gupta, Dr. Amin Herati, and Dr. Bruce R. Gilbert each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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