Novel Evidence-Based Classification of Cavernous Venous Occlusive Disease

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Purpose: The primary aim of our study was to determine whether an evidence-based rationale could categorize cavernous venous occlusive disease into mild, moderate and severe erectile dysfunction.

Materials and Methods: A total of 863 patients underwent color duplex Doppler ultrasound from January 2010 to June 2013 performed by a single urologist. We identified a cohort of 75 patients (8.7%) with a diagnosis of cavernous venous occlusive disease based on a unilateral resistive index less than 0.9, and right and left peak systolic velocity 35 cm per second or less after visual sexual stimulation. At a median followup of 13 months patients were evaluated for treatment efficacy.

Results: A total of 75 patients with a median age of 60 years (range 19 to 83) and a mean body mass index of 26.3 kg/m^2 (range 19.0 to 39.3) satisfied the criteria of cavernous venous occlusive disease. When substratified into tertiles, resistive index cutoffs were obtained, including mild cavernous venous occlusive disease—81.6 to 94.0, moderate disease—72.6 to 81.5 and severe disease—59.5 to 72.5. Using these 3 groups the phosphodiesterase type 5-inhibitor failure rate ($p = 0.017$) and SHIM (Sexual Health Inventory for Men) score categories (1 to 10 vs 11 to 20, $p = 0.030$) were statistically significantly different for mild, moderate and severe cavernous venous occlusive disease. Treatment satisfaction was also statistically significantly different. Penile prosthetic placement was a more common outcome among patients with erectile dysfunction and more severe cavernous venous occlusive disease.

Conclusions: Our retrospective analysis supports a correlation between the phosphodiesterase type 5 inhibitor failure rate, SHIM score and the rate of surgical intervention using resistive index values. Our data further suggest that an evidence-based classification of cavernous venous occlusive disease by color Doppler ultrasound is possible and can triage patients to penile prosthetic placement.

Key Words: penis; impotence, vasculogenic; ultrasonography, Doppler, color; phosphodiesterase 5 inhibitors; treatment failure

Abbreviations and Acronyms

BMI = body mass index
CDDU = color Doppler duplex ultrasound
CVOD = cavernous venous occlusive disease
ED = erectile dysfunction
EDV = end diastolic velocity
ICI = intracavernous injection
IPP = inflatable penile prosthesis
PDE-5 = phosphodiesterase type 5
PSV = peak systolic velocity
RI = resistive index
VS = visual sexual stimulation

Accepted for publication April 27, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by an internal institutional grant.

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Erectile dysfunction is a chronic disorder that demonstrates increasing prevalence with age.[1] It can be defined as inability to attain or maintain erection for satisfactory sexual intercourse.[2] The etiology of ED can be classified into psychogenic, neurogenic, hormonal and/or vasculogenic causes.[2] Vasculogenic ED accounts for 60% to 80% of all cases and can be

0022-5347/16/1964-1223/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2016.04.089
Vol. 196, 1223-1227, October 2016
Printed in U.S.A.

further subclassified into arterial insufficiency, CVOD or a combination of the 2 conditions.[3]

CDDU analysis coupled with ICI of a penile vasoactive agent (alprostadil, papaverine and phentolamine) is clinically useful when the distinction of vasculogenic ED cannot be made by history and physical examination alone. CVOD can be defined as inability to maintain adequate erection despite appropriate arterial inflows. Corporeal smooth muscle is the principal factor in trapping blood in the corporeal sinusoids, preventing leakage out of the penis. Alterations in the fibroelastic microstructure, cavernous smooth muscle and endothelium allow blood to escape the penis, thereby causing sexual dysfunction.[4]

CVOD can be defined based on Doppler metrics such as EDV, PSV and RI. Sikka et al defined CVOD as adequate arterial inflow with a semirigid erection, given an EDV greater than 6 cm per second.[5] They categorized partial venous leak as PSV greater than 30 cm per second and EDV as 3 to 6 cm per second with RI between 0.6 and 0.8. They also defined complete venous leak as PSV greater than 30 cm per second and EDV greater than 6 with RI less than 0.6. Unfortunately, this classification lacks clinical corroboration to patient symptomatology, ie does complete vs partial venous leak manifest differently in patients? In fact, to date the categorization of venous leak in terms of severity has not been verified clinically in evidence-based fashion.

Therefore, the primary aim of our study was to provide a novel evidence-based classification of venous leak as mild, moderate and severe, and substantiate this classification clinically.

MATERIALS AND METHODS

A total of 863 patients underwent in-office testing with intracavernous pharmacological erection augmented by VS and analysis by CDDU using a M-Turbo® with a 10 MHz probe from January 2010 to June 2013 as performed by a single urologist (GAB). All patients in whom PDE-5 inhibitor therapy previously failed or who presented with penile curvature or desired to determine the etiology of ED were considered for CDDU.

The technique of penile CDDU has been reviewed previously.[6] Universally, it involves intracavernous injection of a vasoactive pharmacological agent augmented by visual sexual stimulation with Doppler ultrasound guidance. Our protocol is to administer 10 mcg alprostadil to all men younger than 70 years and 20 mcg to all men 70 years old or older. Every patient underwent post-injection Doppler examination at 5 to 10 minutes and post-VS measurements. The Doppler parameters recorded included preVS and post-VS PSV, EDV, RI and erection hardness score (1 to 4).

Of these 863 patients a cohort of 75 (8.7%) with a diagnosis of venous leak based on unilateral RI less than 0.9, and right and left post-VS PSV greater than 35 cm per second were identified. We chose to implement the strictest criteria for inclusion (PSV greater than 35 cm per second in the right and left cavernous arteries), resulting in 75 patients and likely resulting in less than 10% of patients presenting for CDDU analysis to be included in study. However, this exclusivity allowed us to truly examine the subset of patients with genuine CVOD without arterial inflow bias. By choosing more strict arterial parameters (PSV 35 cm per second or greater) than Sikka et al[5] we eliminated a category of cases that they defined as partial arterial, that is when PSV is between 25 and 30 cm per second. Thus, the conclusion that we drew about venous insufficiency was based on a group of men with unequivocally excellent cavernous inflow.

Demographic information, such as age, age at ED onset, BMI, history of ED, history of prostate surgery (radical prostatectomy vs endourological procedure), medical comorbidities (hypertension, diabetes, heart disease, smoking, hyperlipidemia and tobacco abuse), Peyronie's disease, SHIM score, PDE-5 inhibitor failure rates and various Doppler parameters, were recorded for each patient. Patients were excluded from analysis if they had a history of significant penile trauma resulting in penile fracture and prior penile surgery (IPP, penile plication, incision and grafting, iatrogenic shunt formation, etc).

PDE-5 inhibitors, a PDE-5 inhibitor with VenoSeal™, ICI and IPP were offered as treatment. At a median followup of 13 months treatment satisfaction was recorded for each patient. A total of 14 patients did not return after initial CDDU and, thus, they were removed from treatment efficacy analysis.

Numerical variables were summarized as the sample median and range, and categorical variables were summarized as the number and percentage. Average RI values, defined as the average of left and right RI, were divided into 3 categories based on the 33.3rd and 66.7th percentiles. The Fisher exact test or the Wilcoxon rank sum test was used for single variable comparisons of demographics and clinical characteristics among the different groups of patients. The Spearman correlation test was used to evaluate association between average RI values as a numerical measure and SHIM scores. No adjustment for multiple testing was done in these exploratory analyses. The association between satisfactory treatment in 4 levels and the severity of CVOD was assessed by the Spearman rank order test and the Cochran-Armitage test. Since Peyronie's disease also seems to affect treatment options, the distribution of Peyronie's disease by CVOD severity was also examined to check whether confounding factors might have been introduced. All tests were 2-sided with $p < 0.05$ considered significant. Statistical analyses were performed with SAS®, version 9.2 and R (https://www.r-project.org/).

RESULTS

The cohort had a median age of 60 years (range 19 to 83) and a mean BMI of 26.3 kg/m^2 (range 19.0 to 39.3). Arteriogenic risk factors were not well represented, including hypertension in 54.7% of patients, diabetes in 12.0%, heart disease in 10.7%,