Poor Response to Alprostadil ICI Test is Associated with Arteriogenic Erectile Dysfunction and Higher Risk of Major Adverse Cardiovascular Events

Giulia Rastrelli, MD,* Giovanni Corona, MD, PhD,*† Matteo Monami, MD,‡ Cecilia Melani, MD,§ Daniela Balzi, MD,§ Alessandra Sforza, MD,† Gianni Forti, MD,* Edoardo Mannucci, MD,‡ and Mario Maggi, MD*

*Sexual Medicine and Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy; †Endocrinology Unit, Azienda Usl di Bologna, Maggiore-Bellaria Hospital, Bologna, Italy; ‡Diabetes Section Geriatric Unit, Department of Critical Care, University of Florence, Florence, Italy; §Epidemiological Unit, Azienda Sanitaria Locale 10, Florence Italy

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ABSRACT

Introduction. Intracavernous alprostadil injection (ICI) test has been considered useless in assessing the vascular status of subjects with erectile dysfunction (ED).

Aim. To analyze the clinical correlates of ICI test in patients with ED and to verify the value of this test in predicting major adverse cardiovascular events (MACE).

Methods. A consecutive series of 2,396 men (mean age 55.9 ± 11.9 years) attending our outpatient clinic for sexual dysfunction was retrospectively studied. A subset of this sample (N = 1,687) was enrolled in a longitudinal study.

Main Outcome Measures. Several clinical, biochemical, and instrumental (penile color Doppler ultrasound; PCDU) factors were evaluated. All patients underwent an ICI test, and responses were recorded on a four-point scale ranging from 1 = no response to 4 = full erection.

Results. Among the patients studied, 16.4%, 41.2%, 40.2% and 2.2% showed grade 4, 3, 2, and 1 ICI test response, respectively. After adjusting for confounders, subjects with grade 1 ICI test response showed reduced perceived sleep-related, masturbation-related, and sexual-related erections when compared with the rest of the sample. In addition, a worse response to ICI test was associated with a higher prevalence of hypogonadism-related symptoms and signs along with lower testosterone levels. The prevalence of both diabetes mellitus and metabolic syndrome was inversely related to ICI test response. Accordingly, dynamic and basal peak systolic velocity (PSV), as well as acceleration at PCDU, decreased as a function of ICI test response. In the longitudinal study, after adjusting for confounders, grade 1 response was independently associated with a higher incidence of MACE (hazard ratio = 2.745 [1.200–6.277]; $P < 0.05$). These data were confirmed even when only subjects with normal PSV (>25 cm/s) were considered.

Conclusions. Our results demonstrate that poor ICI test response is associated with several metabolic disturbances and higher incidence of MACE. We strongly recommend performing ICI test with alprostadil in all ED subjects.

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Key Words. Intracavernous Alprostadil Injection Test; Erectile Dysfunction; Penile Doppler Ultrasound; Cardiovascular Diseases

Corona and Rastrelli equally contributed to the paper.

Introduction

Penile erection is a neurovascular event resulting from the interaction of biological, intrapsychic, and relational factors [1].

Recently, erectile dysfunction (ED) has been regarded as an early surrogate marker of forthcoming cardiovascular (CV) events, as the two conditions have a common underlying vascular pathology. We therefore introduced the oxymoron concept that impotent subjects are indeed "lucky" [2] because ED offers an invaluable opportunity to screen for associated CV morbidities. Detecting arteriogenic ED could result in a potential decrease of forthcoming major adverse CV events (MACE), with beneficial effects not only in sexually related quality of life (QoL) but also in health-related QoL and overall life expectancy. The penile color Doppler ultrasound (PCDU) is nowadays considered the gold standard for the diagnosis of arteriogenic ED [3]. The most widely used parameter to predict adequacy of penile circulation is cavernous peak systolic velocity (PSV, cm/s) measured 5–20 minutes after an intracavernous injection (ICI) of a vasodilating agent, such as alprostadil [3]. The evaluation of penile flow could be used, in patients with ED, to stratify CV risk. We have shown that a dynamic PSV below 25 cm/s is associated with a relevant increase of CV risk [4]: the risk of MACE increases by 5% for each 5 cm/s decrement of dynamic PSV. However, the elevated cost and the limited reproducibility of PCDU, together with its lack of standardization, prevent many clinicians from using it routinely [5]. The European Association of Urology (EAU, [6]) and the American Urological Associations Guidelines ([7]) for ED state that PCDU is not recommended in routine practice but can be helpful whenever information regarding vascular supply is needed as, for example, in the choice of surgical treatment [8]. The guidelines of the British Society for Sexual Medicine are in line with this point of view [9].

More than 20 years ago, it was suggested that a positive response to ICI of a vasodilating agent, such as alprostadil, could rule out a vascular pathology, therefore indicating other pathogenetic causes [10,11]. Since that time, ICI testing with alprostadil has become a minimally invasive, easy to perform diagnostic procedure for characterizing ED in the office setting. ICI testing has been used as an aid in differentiating the origin of ED as vasculogenic, neurogenic, or psychogenic [10,11]. A positive response, especially at low doses, is considered indicative of neurogenic or psychogenic ED. If partial tumescence occurs, mild to moderate arterial or venous disease may be present, and an erection after alprostadil injection that is not sustained may be indicative of venous dysfunction. While a good response to an ICI test rules out venous leakage, a failed erectile response to the test may not be completely representative of the patient's erectile status [12]. The drug can be used alone (simply monitoring for erectile response after ICI) or prior to other testing (e.g., penile angiography, or, more often, PCDU). However, its popularity has substantially decreased in the era of phosphodiesterase type 5 (PDE5) inhibitors [13], since it is hardly reproducible, largely depending on the degree of complete cavernous smooth muscle relaxation [14,15]. Today, revised EAU guidelines indicate that "intracavernous injection test provides limited information about the vascular state" [16] and the International Society of Sexual Medicine considers the testing obsolete [17].

Aim

The aim of this study is to retrospectively analyze the clinical correlates of alprostadil testing in a large series of patients consulting for ED and to verify the real value of this simple diagnostic test in predicting MACE.

Methods

Cross-Sectional Study

A consecutive series of 2,396 heterosexual male patients attending the Outpatient Clinic for sexual dysfunction for the first time was retrospectively studied. The sociodemographic and clinical characteristics of the sample are summarized in Table 1. All patients enrolled underwent the usual diagnostic protocol applied to newly referred subjects at the Andrology Outpatient Clinic. All the data provided were collected as part of the routine clinical procedure. An informed consent for the study was obtained from all patients. Patients were interviewed prior to the beginning of any treatment, and before any specific diagnostic procedures, using the Structured Interview on Erectile Dysfunction (SIEDY, 1). This is a 13-item structured interview made up of three scales, which identify and quantify components concurring with ED. Scale 1 deals with organic disorders and consists of question nos. 4, 13, and 15, concerning medical history, morning/nocturnal erection, and ejaculate volume, respectively. Scale 2 deals with