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ORIGINAL ARTICLE

Accurate and time-saving, two-step intracavernosal injection procedure to diagnose psychological erectile dysfunction

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Abstract

Background: The recognition of the erectile dysfunction pathogenesis is essential to identify the appropriate erectile dysfunction management. As vascular erectile dysfunction could be a manifestation of a systemic arterial damage, the watershed in the erectile dysfunction diagnostic framework is the discrimination between psychological erectile dysfunction and vascular erectile dysfunction. However, reliable tools to directly diagnose psychological erectile dysfunction are currently lacking.

Objective: To identify which parameters could predict psychological erectile dysfunction. Moreover, we suggest a new intracavernosal injection procedure to optimize the erectile dysfunction diagnostic workup.

Materials and methods: A retrospective, real-world analysis was carried out including all men who underwent intracavernosal injection procedure at the Modena Andrology Unit from 2018 to 2021. A first intracavernosal injection procedure with 5 μg of prostaglandin E-1 (PGE-1) was performed. In the absence of a full drug-induced erection (immediate or delayed), an echo-color Doppler penile evaluation after administration of PGE-1 10 μg was conducted, measuring intracavernosal blood flows, to document a possible vascular etiology. Hormonal evaluations were performed.

Results: Out of 179 enrolled patients, 70.4% showed psychological erectile dysfunction, 21.7% vascular erectile dysfunction, and 7.8% hormonal genesis. Multinomial logistic regression analysis identified absence of cardiovascular disease ($p = 0.017$), presence of spontaneous morning erections ($p = 0.018$), and normal penile erections with masturbation ($p = 0.035$) as predictors of psychological erectile dysfunction. Clinically, normal intracavernosal injection test response was detected in 86 patients and abnormal response in 93 subjects. Among the latter, 54 patients experienced a delayed response. The combination of intracavernosal injection test with late penile erections evaluation was able to diagnose psychological erectile dysfunction (sensitivity 97%, specificity 100%), avoiding unnecessary retesting.

Discussion: We propose a two-step intracavernosal injection procedure that allows to recognize psychological erectile dysfunction with a high sensitivity/specificity, saving costs and time, and limiting adverse events. Moreover, the presence of spontaneous

morning erections and valid penile erections after masturbation could guide the diagnostic workup, indirectly identifying those patients deserving of a deeper evaluation of vascular health.

KEYWORDS
erectile dysfunction, ICI, intracavernosal injection, morning erections, unstructured interview

1 | INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain a penile erection sufficient to obtain satisfactory sexual activity.[1] Worldwide, the ED prevalence is very high, affecting up to 25% of men in the general population and 70% in elderly.[2] Not surprisingly, ED represents the first reason that leads the males to seek an andrological consultation.[2]

Many scientific societies developed different guidelines and position statements on the ED management.[3–9] All these recommendations highlight the relevance to achieve an accurate diagnosis of the ED etiology, applying a comprehensive evaluation and targeted physical examination.[6] In this setting, many validated questionnaires for ED evaluation could be applied, with the aim to quantify a subjective symptom (i.e., ED) and, overall, to initiate a conversation with the patient about ED. Indeed, the andrologist works in a delicate context, unravelling intimate and private information, in which psychological implication must be considered in order to avoid obtaining only a superficial evaluation of the disorder.[10,11] In this setting, the main goal of the andrologist is the identification of the ED etiology, distinguishing among psychological, neurologic, hormonal, and vascular forms.[12] In this setting, the most frequent form is expected to be of psychogenic origin. On the other hand, 50%–80% of all cases of organic ED are because of arterial insufficiency of the penile vessels and must be recognized, as the presence of ED could be considered a hallmark of future minor and major cardiovascular events.[13–16] Vascular ED and major cardiovascular events could be considered different manifestations of the same systemic arterial damage that, because of the small diameter of penile arteries, causes sexual dysfunction earlier than other events.[17] While a normal erectile function consists of an adequate arterial inflow and a poor or absent venous outflow, in the presence of impaired cavernosal smooth muscle relaxation or arterial inflow stenosis erection is impaired.[12] The temporal connection between ED vascular forms and major cardiovascular events justifies the need to reach an accurate diagnosis for each man claiming for sexual dysfunction, in order to initiate appropriate diagnostic-therapeutic and preventive procedures.

Specialized tests are required to examine the vascular component of erection, such as intracavernosal injection (ICI) and penile Doppler ultrasound.[18] These tools are dynamic tests, performed by an experienced sonographer in a physician's office or in a hospital setting, providing the injection of vasoactive drugs to examine penile blood flows.[19–21] Although these examinations are objective and reliable, they are used only to rule out a vasculogenic cause, not permitting a comprehensive ED evaluation.[18] Moreover, they are invasive and require skilled personnel, modern equipment, relatively high costs and time, limiting the use of these examinations in many clinical settings. In addition, potential adverse events should be considered, such as priapism, penile pain, and/or general discomfort.[18] Although priapism occurs only in 2%–3% of examinations, its management is very complex and challenging.[22] For this reason, several vasoactive drugs have been tested, such as papaverine, prostaglandin E (PGE)-1, phentolamine, or their combination (TRIMIX - papaverine 4.4 mg, phentolamine 0.15 mg, and PGE-1 1.5 μg in 0.25 ml of physiological solution) to reduce the adverse event risk. PGE-1 is still the vasoactive drug mostly used in ICI examination, and the priapism risk in this context is directly related to the dosages used. Thus, the lowest possible PGE-1 dosage is generally suggested to perform ICI examination.[18] However, using safe PGE-1 doses results in reduced test accuracy, with an increased risk of having to repeat the procedure, thereby increasing costs and potential adverse effects.

Considering the difficulty to reach or rule out a vascular component of ED, together with the high incidence of psychogenic forms, a first discrimination between psychological and organic ED is fundamental to tailor the clinical management.[23,24] Whether some cases are clearly because of psychological causes (i.e., stressful events, selective ED, etc.),[25,26] an accurate tool to measure the psychological distress in sexual dysfunction is still lacking. Thus, we designed this retrospective analysis of real-world data to detect which parameters routinely collected during andrological examination could predict psychogenic ED, focusing on a reliable ICI procedure to increase its accuracy to rule out psychological causes, reducing adverse events and time and cost.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a retrospective clinical trial based on real-world data. The study protocol was approved by the Ethics Committee of "Area Vasta Emilia Nord" (protocol number: AOU0024637/19 of 12/09/2019).

All men consecutively evaluated with ICI procedure at the Andrology Unit of the University of Modena and Reggio Emilia from January 2018 to December 2021 were enrolled. The ICI procedure was proposed to all patients in which history collection did not allow to define a

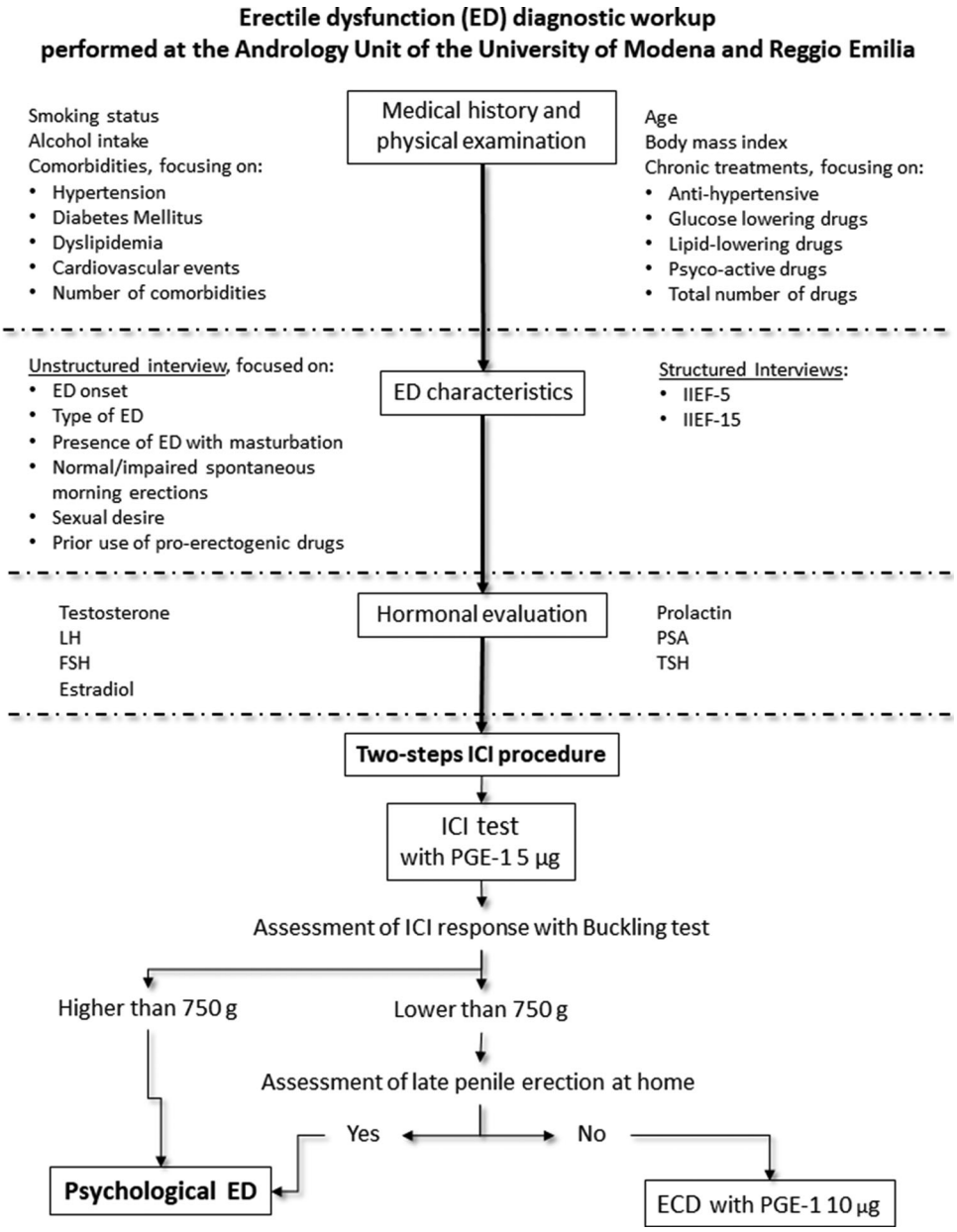

FIGURE 1 Diagnostic protocols routinely applied at Andrology Unit. ECD, echo-color Doppler; ED, erectile dysfunction; FSH, follicle-stimulating hormone; ICI, intracavernosal injection; IIEF, International Index on Erectile Function; LH, luteinizing hormone; PGE-1, prostaglandin E-1; PSA, prostate-specific antigen; TSH, thyroid-stimulating hormone

psychological etiology of the ED, irrespective of age. The standard diagnostic workup and the ICI procedure are described in Figure 1.

2.2 | Data collection

The routine protocol consisted of medical history collection by unstructured interview, including age, smoking status, alcohol intake, number and type of comorbidities, number and type of drugs chronically assumed, and history of cardiovascular disease (Figure 1).[6]

ED was thoroughly investigated considering its onset period, duration, severity, possible situational factors, presence/absence of morning erections, presence/absence of masturbatory ED, and prior use of pro-erectogenic therapies (Figure 1). ED severity was quantified using both the International Index of Erectile Function (IIEF)-5 and the ED domain at IIEF-15.[27]

Considering medical history, an ICI procedure with vasoactive agents was proposed to exclude a vascular ED component. The ICI test was performed following a two-stage procedure. In the first step, the lowest PGE-1 dosage possible (5 µg) was used.[28] This step was performed by MD residents as described previously.[29] In brief, 8–10 min after the injection, the drug-induced erection was assessed using a buckling device (Rigid test, Androline srl, Milan, Italy). A full erection was recorded in case of absent penile buckling when a 1000 g

downward force was slowly applied to the glans, following the erect shaft axis.[30] To assess the gradual nature of the response, patients were divided into four groups according to the buckling test graduation: (I) absent <500 g, (II) mild 500–750 g, (III) moderate 750–1000 g, and (IV) optimal response >1000 g. From a clinical point of view, a normal response was considered when the buckling examination was higher than 750 g.

The second step of the procedure consisted of the echo-color Doppler penile evaluation (ECD) after PGE-1 10 μg injection. This second procedure was performed on a separate day by the same skilled and experienced andrologist for all patients. Before proceeding to the PGE-1 injection, the patient was asked whether the penile erection obtained during the first procedure (ICI test) increased when he left the hospital. The ECD test was then performed when the buckling response to ICI test was lower than 750 g and the patient did not experience any change at home. During ECD, the penile response was evaluated with both buckling test and ultrasound evaluation, measuring the systolic peak and end-diastolic peak velocities at the right and left cavernous arteries of the penis. The systolic peak velocity provides an indirect information about the arterial filling of the corpora cavernosa, while the end-diastolic velocity, about its emptying. Normal responses were considered when systolic peak was higher than 30 mm/s and end-diastolic lower than 5 mm/s. During each step of the ICI procedure, safety was evaluated, reporting cases of priapism and penile pain occurring during and/or after injection.

Hormonal assessment was performed before the ICI procedure, consisting of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, prostate-specific antigen (PSA), prolactin, and thyroid-stimulating hormone (TSH) serum levels, to highlight a possible hormonal cause of the ED.

2.3 | Classification procedures

Vascular ED was defined when a complete erection was not obtained after the entire ICI procedure, with systolic velocity at ECD lower than reference ranges and/or end-diastolic velocity higher than thresholds suggested. Hormonal ED was defined when reduced testosterone serum levels (below 3 ng/ml) were detected, irrespective of the ICI procedure response. A psychological ED form was diagnosed when normal results were obtained from both ICI procedure and hormonal evaluation.

2.4 | Statistical analysis

Data distribution was evaluated by Kolmogorov–Smirnov test. Comparisons of continuous variables among groups were performed by ANOVA univariate and/or Kruskal–Wallis test, according to data distribution. Tukey test was performed for post hoc analyses. Mann–Whitney *U*-test was used when two groups of continuous variables were present. Categorical parameters were compared among groups using Fisher exact test.

The analysis was first performed dividing the cohort of patients into three groups, according to ED etiology, that is, psychological, vascular, and hormonal. Then, the analysis was repeated considering the normal/abnormal response to the first step of ICI procedure. Finally, the analysis was repeated considering the normal/abnormal response to the overall ICI procedure.

In order to predict both psychological ED and normal ICI response, multinomial logistic regression analyses were performed at each step of data analysis. Results from logistic regressions were reported as odds ratio (OR) along with their 95% confidence interval (CI).

All statistical analyses were performed using the "Statistical Package for the Social Science" software for Windows (version 27.0 SPSS Inc., Chicago, IL). Statistical significance was considered for $p < 0.05$.

3 | RESULTS

One hundred seventy-nine patients were enrolled. Table 1 summarizes patients' characteristics. As expected, 70.4% (126 patients) showed a psychological ED. Thus, organic ED was detected in 53 subjects (29.6%), divided in vascular (39 patients, 21.7% of the entire cohort) and hormonal (14 men, 7.8%) forms. Patients with vascular ED showed higher age compared to other groups (Table 1), whereas no differences were detected for body mass index (BMI).

Considering the answers to a validated questionnaire, scores of both IIEF-5 and the ED domain at IIEF-15 were significantly different among groups ($p < 0.001$). At post hoc analysis, lower scores were detected in vascular compared to psychological ED, whereas no differences were detected with hormonal forms (Table 1). Moreover, psychological ED showed lower rate of severe ED and higher rate of mild forms compared to organic groups (Table 1).

Considering the information collected during the unstructured interview, psychological ED was characterized by higher incidence of spontaneous morning erections and normal penile erection with masturbation, compared to organic forms (Table 1). Sexual desire was evaluated both by direct questioning by the clinician during the anamnestic interview and by IIEF-15-related domain (questions 11 and 12). These two methods significantly correlated together (Spearman rho 0.188, $p = 0.013$), suggesting the potential overlap of unstructured and structured interviews. However, sexual desire impairment showed a similar incidence among groups (Table 1).

Cardiovascular diseases were less frequent in psychological ED compared to organic forms, as expected (Table 1). On the contrary, dyslipidemia was more frequent in hormonal compared to both psychological and vascular ED (Table 1). Hypertension and diabetes mellitus rates did not differ among groups (Table 1). Considered all comorbidities together, the comorbidity number and the drug number of drug chronically used did not differ among groups (Table 1).

In order to predict psychological ED, multinomial logistic regression analysis was performed, revealing three relevant variables (Table 2). In details, psychological ED was predicted by the absence of cardiovascular disease ($p = 0.017$), the presence of normal penile erection with masturbation ($p = 0.035$), and the presence of spontaneous morning

TABLE 1 Characteristics of the patients who are compared according to the erectile dysfunction etiology

	Overall ($n = 179$)	Psychological ($n = 126$)	Vascular ($n = 39$)	Hormonal ($n = 14$)	*p*-Value
Age (years)	55.7 ± 11.0	54.0 ± 11.3	60.7 ± 9.2[a]	57.2 ± 9.4	**0.004**
Body mass index (kg/m^2)	29.2 ± 5.2	28.6 ± 4.8	29.7 ± 5.9	32.4 ± 5.6	0.138
Current smoker, *n* (%)	49 (27.2)	39 (31.0)	6 (15.4)	4 (28.6)	0.162
Ex-smoker, *n* (%)	61 (33.9)	40 (31.7)	17 (43.6)	4 (28.6)	0.356
Hypertension, *n* (%)	79 (43.4)	53 (42.1)	20 (51.3)	6 (42.9)	0.596
Diabetes mellitus, *n* (%)	58 (32.2)	36 (28.6)	16 (41.0)	6 (42.9)	0.238
Dyslipidemia, *n* (%)	55 (30.6)	31 (24.6)	14 (35.9)[b]	10 (71.4)[a]	**0.001**
Cardiovascular diseases, *n* (%)	28 (15.6)	14 (11.1)	9 (23.1)[a]	5 (35.7)[a]	**0.020**
Comorbidities number	1.59 ± 1.3	1.5 ± 1.3	1.8 ± 1.3	1.8 ± 1.3	0.258
Chronic treated patients, *n* (%)	131 (72.8)	91 (72.2)	29 (74.4)	11 (78.6)	0.863
Drugs number	2.6 ± 3.0	2.4 ± 2.7	3.4 ± 3.8	2.9 ± 2.9	0.140
IIEF-5 score	10.6 ± 6.1	11.6 ± 6.1	7.3 ± 4.9[a]	10.2 ± 6.2	**0.001**
Erectile domain at IIEF-15	10.7 ± 8.1	11.8 ± 8.3	7.7 ± 6.6[a]	9.3 ± 8.0	**0.015**
Erectile dysfunction at IIEF-15, *n* (%)					**0.007**
Severe	101 (56.1)	61 (50.0)	29 (76.3)[a]	11(78.6)[a]	–
Moderate	26 (14.4)	21 (17.2)	4 (10.5)	1 (7.1)	–
Mild	39 (21.7)	34 (27.9)	4 (10.5)[a]	1 (7.1)[a]	–
Absent	8 (4.4)	6 (4.9)	1 (2.6)	1 (7.1)	–
ED duration (months)	41.7 ± 40.5	39.3 ± 41.0	47.8 ± 37.7	46.8 ± 45.3	0.484
ED duration >2 years, *n* (%)	84 (46.9)	53 (42.1)	23 (59.0)	8 (57.1)	0.132
ED during masturbation, *n* (%)	66 (36.7)	29 (24.0)	30 (78.9)	7 (50.0)	<**0.001**
Impaired morning erections n (%)	58 (32.2)	26 (20.6)	25 (64.1)	7 (50.0)	<**0.001**
Decreased sexual desire, *n* (%)	46 (25.6)	34 (27.0)	7 (17.9)	5 (35.7)	0.355
Total testosterone (ng/ml)	4.8 ± 1.7	5.0 ± 1.4	5.0 ± 2.0[b]	2.2 ± 0.3[a]	<**0.001**
LH (IU/L)	4.4 ± 2.1	4.3 ± 2.2	4.8 ± 2.2	3.9 ± 1.0	0.352
FSH (IU/L)	6.2 ± 5.5	6.1 ± 5.3	6.9 ± 6.9	5.5 ± 2.1	0.717
Estradiol (pg/ml)	24.2 ± 9.0	24.0 ± 8.9	27.5 ± 9.4[b]	18.7 ± 5.5[a]	**0.009**
Prostate-specific antigen (ng/ml)	1.3 ± 1.2	1.3 ± 1.2	1.4 ± 1.5	1.1 ± 0.8	0.752
Prolactin (ng/ml)	11.1 ± 5.1	11.0 ± 5.1	12.2 ± 5.4	8.8 ± 4.0	0.143
TSH (μIU/ml)	2.1 ± 3.9	2.3 ± 4.7	1.6 ± 0.9	2.0 ± 1.0	0.657

Note: Continuous variables are reported as mean ± standard deviation, categorical variables are reported as number (percentage). *p*-Values are obtained by Kruskal–Wallis test.

Abbreviations: ED, erectile dysfunction; FSH, follicle-stimulating hormone; IIEF, International Index on Erectile Function; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

[a]Significantly different from psychological forms at post hoc analyses (Tukey test).

[b]Significantly different from hormonal forms at post hoc analyses (Tukey test).

erections ($p = 0.018$) (Table 2). Interestingly, the ED degree at both IIEF-5 and IIEF-15 was not predictive of the pathogenesis.

Finally, considering hormones, lower testosterone serum levels were detected in hormonal ED, compared to both psychological and vascular ones (Table 1). Accordingly, higher estradiol serum levels were detected in hormonal group compared to other two (Table 1). These differences are expected, as hormonal ED diagnosis is based on hormonal levels. However, interestingly hormones did not help the clinician to highlight the pathogenesis, apart from hormonal forms.

3.1 | ICI procedure

No major procedure-related adverse events, especially priapism and penile pain, were recorded in both ICI and ECD steps of our procedure.

Considering the first step of the procedure (ICI test), insufficient results (<500 g at buckling examination) were obtained in 62 patients (34.4%) and optimal responses (>1000 g) in 69 patients (38.3%). Intermediate results were obtained in 31 (17.2%) and 17 (9.4%) patients, considering 500–750 g and 750–1000 g, respectively. Thus, clinically

TABLE 2 Multinomial logistic regression analysis performed to predict psychological erectile dysfunction

						95% CI	
	B	SE	Wald	*p*-Value	OR	Lower	Upper
Intercept	0.194	1.822	0.011	0.915			
Comorbidities number	−0.218	0.326	0.448	0.503	0.804	0.424	1.524
Drug number	−0.016	0.108	0.022	0.882	0.984	0.797	1.215
ED duration	0.002	0.006	0.096	0.757	1.002	0.990	1.014
IIEF-5	−0.097	0.068	2.031	0.154	0.908	0.794	1.037
ED at IIEF-15	0.030	0.050	0.364	0.546	1.030	0.935	1.136
Smoke	0.686	0.585	1.372	0.241	1.985	0.630	6.255
Ex-smoke	0.137	0.516	0.071	0.790	1.147	0.417	3.152
Alcohol	0.350	0.493	0.502	0.479	1.419	0.539	3.732
No hypertension	−0.194	0.599	0.105	0.746	0.824	0.255	2.663
No diabetes mellitus	−0.059	0.578	0.010	0.918	0.942	0.304	2.926
No dyslipidemia	−0.904	0.625	2.095	0.148	0.405	0.119	1.377
No cardiovascular diseases	−1.557	0.654	5.676	**0.017**	0.211	0.059	0.759
Impaired sexual desire	−0.224	0.520	0.185	0.667	0.800	0.289	2.213
ED with masturbation	1.068	0.508	4.421	**0.035**	2.909	1.075	7.871
No morning erection	1.278	0.539	5.617	**0.018**	3.589	1.248	10.327
Gradual onset of ED	0.796	0.656	1.473	0.225	2.217	0.613	8.023
Constant ED	−0.714	0.544	1.722	0.189	0.489	0.168	1.423

Abbreviations: CI, confidence interval; ED, erectile dysfunction; IIEF, International Index on Erectile Function; OR, odds ratio; SE, standard error.

normal ICI test response (>750 g) was detected in 86 patients and abnormal (<750 g) in 93 subjects.

As expected, patients with normal ICI test were younger and showed higher score at both IIEF-5 and IIEF-15 (Table 3). Severe ED was more frequent in men with impaired compared to normal ICI test ($p < 0.001$). Moreover, patients with normal ICI test showed a lower incidence of both ED with masturbation and impaired spontaneous morning erection, compared to those with altered ICI test (Table 3). Although the number of comorbidities and drugs did not differ between groups, patients with impaired ICI test were more frequently chronically treated, compared to patients with normal response ($p = 0.033$) (Table 3). Finally, hormones did not differ between groups (Table 3), confirming their limited predictive role.

Multinomial logistic regression analysis showed that only the absence of spontaneous morning erection significantly predicted the ICI test results (Table 4).

Considering the second step of our procedure (ECD), 54 patients (49.1%) with abnormal buckling result during ICI test experienced a complete penile erection after leaving the hospital. Thus, an overall number of 123 patients (68.7% of the entire cohort) obtained a complete response to ICI test. This late ICI response was not predicted by any parameter collected (Table S1), suggesting the relevance to evaluate this unpredictable variable. Thus, only three patients (2.4%) with psychological ED did not respond to the entire ICI procedure and required the ECD examination. The combination of ICI test with the evaluation of the late penile erection was able to diagnose psychological ED with high accuracy (sensitivity: 97%, specificity: 100%). In this way, 54 patients not responding to the first step of the procedure were spared from undergoing a new PGE-1 injection with higher dosage.

Patients with a normal result throughout the overall ICI procedure were younger, with higher IIEF-5 and IIEF-15 scores (Table 5). Accordingly, a higher incidence of severe ED was detected in patients with abnormal overall response (Table 5). Moreover, a normal result to ICI procedure was associated to lower rate of both ED at masturbation and impaired spontaneous morning erections (Table 5).

Finally, ECD was performed in 42 patients, with a mean systolic peak velocity of 25.3 ± 10.1 and 24.3 ± 12.4 cm/s (right and left sides, respectively) and an end-diastolic peak of 5.1 ± 2.3 and 4.5 ± 2 cm/s. As expected, ECD parameters were significantly higher in patients with psychological compared to organic ED (Table 6).

4 | DISCUSSION

Here, we demonstrate the importance of focused unstructured interview and of ICI test to diagnose psychological ED. Scientific societies suggest focusing the anamnestic collection on several aspects of ED, such as its onset and severity, whether the problem involves attaining and/or maintaining an erection, situational factors, the presence of spontaneous morning erections, and the presence of ED during masturbation. Here, we confirm that the presence of spontaneous morning erections is the turning point in the differential diagnosis between psychological and organic ED. Moreover, here we propose a two-step ICI procedure that allows recognizing the psychological ED with a high

TABLE 3 Characteristics of the patients who are compared according to normal or abnormal penile response to ICI

	ICI normal response ($n = 86$)	ICI reduced response ($n = 93$)	*p*-Value
Age (years)	53.2 ± 11.6	58.1 ± 10.0	**0.003**
Body mass index (kg/m^2)	28.8 ± 4.6	29.6 ± 5.6	0.448
Current smoker, *n* (%)	29 (33.7)	20 (21.5)	0.067
Ex-smoker, *n* (%)	24 (27.9)	37 (39.8)	0.094
Hypertension, *n* (%)	32 (37.2)	47 (50.5)	0.073
Diabetes mellitus, *n* (%)	23 (26.7)	35 (37.6)	0.120
Dyslipidemia, *n* (%)	22 (25.6)	33 (35.5)	0.151
Cardiovascular diseases, *n* (%)	10 (11.6)	18 (19.4)	0.155
Comorbidities number	1.5 ± 1.3	1.7 ± 1.2	0.224
Chronic treated patients, *n* (%)	57 (66.3)	74 (79.6)	**0.033**
Drugs number	2.3 ± 3.0	2.9 ± 3.0	0.261
IIEF-5 score	12.3 ± 6.2	9.0 ± 5.6	**<0.001**
Erectile domain at IIEF-15	12.7 ± 8.8	8.9 ± 7.0	**0.002**
Erectile dysfunction at IIEF-15, *n* (%)			**<0.001**
Severe	36 (43.4)	65 (71.4)	–
Moderate	17 (20.5)	9 (9.9)	–
Mild	25 (30.1)	14 (15.4)	–
Absent	5 (6.0)	3 (3.3)	–
ED duration (months)	37.7 ± 34.9	45.3 ± 44.8	0.213
ED duration >2 years, *n* (%)	41 (47.7)	43 (46.2)	0.847
ED during masturbation, *n* (%)	46 (51.1)	61 (73.5)	**0.002**
Impaired morning erections, *n* (%)	52 (55.9)	69 (80.2)	**<0.001**
Decreased sexual desire, *n* (%)	21 (24.4)	25 (26.9)	0.706
Total testosterone (ng/ml)	4.7 ± 1.6	4.8 ± 1.8	0.680
LH (IU/L)	4.4 ± 2.1	4.4 ± 2.1	0.988
FSH (IU/L)	5.9 ± 4.4	6.5 ± 6.5	0.535
Estradiol (pg/ml)	23.5 ± 8.0	24.8 ± 9.8	0.368
Prostate-specific antigen (ng/ml)	1.3 ± 1.2	1.3 ± 1.3	0.743
Prolactin (ng/ml)	11.1 ± 5.3	11.0 ± 5.0	0.858
TSH (μIU/ml)	1.9 ± 1.0	2.4 ± 5.4	0.504

Note: Continuous variables are reported as mean ± standard deviation, categorical variables are reported as number (percentage). *p*-Values are obtained by Mann–Whitney *U*-test.

Abbreviations: ED, erectile dysfunction; FSH, follicle-stimulating hormone; ICI, intracavernosal injection; IIEF, International Index on Erectile Function; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

sensitivity (97%) and specificity (100%), limiting cost and time consumption and reducing incidence of adverse events.

The ICI test remains the gold standard approach to diagnose vascular ED. Although ICI accuracy to rule out a vascular etiology is high, it is not able to completely overtake the psychological component of the penile erection, as the patient could experience a variable degree of discomfort during the diagnostic procedure. Because psychological factors could affect the reliability of ICI test, the so-called *retesting* approach has been suggested for overcoming the psychological effect in selected patients.[31,32] Thus, although not reported in current clinical guidelines, the andrologist should consider performing ICI test twice if the normal penile response is not achieved at the first time. Previously, several authors suggested that manual and visual sexual stimulation was applied after vasoactive agent injection to increase the rigidity of erection and if the patient still did not achieve the erection quality at home, a re-dosing should be considered.[33,34] This strategy, aimed at avoiding a second step of vasoactive agent injection is currently applied in clinical practice but it cannot overcome possible psychological issues. Thus, we used a two-step ICI procedure, in which two consecutive diagnostic phases are provided, increasing PGE-1 dosage and evaluating the potential late onset of complete penile erection once the patient exits the hospital. Although this approach requires a two-step

TABLE 4 Multinomial logistic regression analysis performed to predict the response to ICI procedure

						95% CI	
	B	SE	Wald	*p*-Value	Exp(*B*)	Lower	Upper
Intercept	2.616	1.656	2.495	0.114			
Comorbidities number	−0.155	0.297	0.272	0.602	0.856	0.478	1.534
Drug number	−0.079	0.100	0.623	0.430	0.924	0.760	1.124
ED duration	0.006	0.006	0.921	0.337	1.006	0.994	1.017
IIEF-5	−0.064	0.048	1.732	0.188	0.938	0.854	1.032
ED at IIEF-15	−0.037	0.035	1.164	0.281	0.963	0.900	1.031
Smoke	0.633	0.470	1.819	0.177	1.884	0.750	4.730
Ex-smoke	−0.151	0.442	0.117	0.733	0.860	0.361	2.045
Alcohol	−0.365	0.417	0.770	0.380	0.694	0.307	1.570
No hypertension	−0.859	0.516	2.779	0.096	0.423	0.154	1.163
No diabetes mellitus	−0.224	0.515	0.189	0.664	0.800	0.292	2.193
No dyslipidemia	−0.591	0.566	1.089	0.297	0.554	0.183	1.680
No cardiovascular diseases	−1.013	0.630	2.581	0.108	0.363	0.106	1.250
Impaired sexual desire	−0.509	0.447	1.293	0.255	0.601	0.250	1.445
ED with masturbation	−0.099	0.473	0.044	0.835	0.906	0.359	2.289
No morning erection	1.288	0.525	6.019	**0.014**	3.626	1.296	10.148
Gradual onset of ED	0.400	0.458	0.763	0.382	1.493	0.608	3.666
Constant ED	0.641	0.458	1.960	0.162	1.898	0.774	4.654

Abbreviations: CI, confidence interval; ED, erectile dysfunction; ICI, intracavernosal injection; IIEF, International Index on Erectile Function; OR, odds ratio; SE, standard error.

access of the patient to the outpatient clinic, it allows a more reliable, accurate, safe, and cheap diagnostic detection of psychological forms. With this procedure, we are able to quantify the high expected prevalence of psychological ED.[12] Indeed, we detected that psychological ED represents 70% of all cases. Moreover, among organic causes, vascular etiology is recognized in 75.8% of cases, confirming its high prevalence when psychological forms are ruled out.[35] In our cohort, 51% of patients with psychological ED showed normal penile erection after the first step of the procedure, allowing to obtain a quick and safe diagnosis, without continuing with further invasive procedures and time-consuming approaches. Then, 49% of patients with psychological ED did not respond to PGE-1 injection during the lower dose ICI test, but showed a normal penile erection once they left the hospital. Thus, only three patients required the complete ICI procedure to reach the diagnosis of psychological ED. Overall, these data show that when ICI test is first performed with the low PGE-1 dosage, 97.6% of psychological forms is detected, allowing saving time and costs (i.e., medication, tools, time/operator).

The reduction of spontaneous morning erections is one of the symptoms highly suggestive of hypogonadism, together with decreased nocturnal penile tumescence, decreased libido, and reduced testicular volume.[36,37] Thus, the predictive role of some sexual function/dysfunction characteristics in the andrological diagnostic path has already been proposed. However, we demonstrated that this anamnestic parameter collected by unstructured interview is extremely useful also to recognize psychological ED. When predictive logistic models were applied in this study, the anamnestic evaluation remained the strong factor to suspect psychological ED. In particular, ED characteristics with a specific focus on the symptom characteristics in settings other than sexual intercourses, and the presence of spontaneous morning erections could guide the diagnostic ED workup. Even if several questionnaires have been validated so far to grade ED, they are not useful to discriminate among ED etiologies. Although psychological ED showed a lower IIEF-5 and IIEF-15 score compared to both vascular and hormonal forms, these variables did not enter in the predictive model. The main difference between structured and unstructured interviews lies in the possibility for the patient to self-fill in case of validated questionnaires without the need for clinician intervention. This aspect certainly represents an advantage in the andrological field, where the issues addressed are intimate and personal and the patient may experience some degree of embarrassment. For these reasons, obtaining ED characteristics by unstructured interviews requires a fully functioning trustworthy relationship between the clinician and the patient, because this relationship is known to guide decision-making and to influence the therapeutic success in many clinical settings.[38–40] Here, we highlight how a strong clinician–patient relationship provides fundamental information that could help the clinician to unravel the ED diagnostic challenge. This aspect appears even more relevant when considering anthropometrical variables. Although psychological ED is more frequent in younger subjects, the age of the patients did not predict the ED etiology in any of the logistic regressions performed. Similarly, BMI did not enter in predictive models,

TABLE 5 Characteristics of the patients who are compared according to normal or abnormal penile response to ICI, considering the entire ICI procedure

	ICI normal response ($n = 123$)	ICI reduced response ($n = 56$)	p-Value
Age (years)	54.3 ± 10.9	58.8 ± 10.7	**0.011**
Body mass index (kg/m^2)	29.3 ± 5.1	29.1 ± 5.3	0.878
Current smoker, *n* (%)	37 (30.1)	12 (22.1)	0.153
Ex-smoker, *n* (%)	39 (31.7)	22 (39.3)	0.205
Hypertension, *n* (%)	51 (41.5)	28 (50.0)	0.183
Diabetes mellitus, *n* (%)	40 (32.5)	18 (32.1)	0.552
Dyslipidemia, *n* (%)	35 (28.5)	20 (35.7)	0.211
Cardiovascular diseases, *n* (%)	17 (13.8)	11 (19.6)	0.218
Comorbidities number	1.5 ± 1.3	1.7 ± 1.2	0.604
Chronic treated patients, *n* (%)	88 (71.5)	43 (76.6)	
Drugs number	2.5 ± 2.9	3.0 ± 3.3	0.256
IIEF-5 score	11.5 ± 5.9	8.5 ± 6.1	**0.003**
Erectile domain at IIEF-15	11.8 ± 8.3	8.4 ± 7.1	**0.008**
Erectile dysfunction at IIEF-15, *n* (%)			**<0.001**
Severe	61 (51.3)	40 (72.7)*	–
Moderate	21 (17.6)	5 (9.1)	–
Mild	30 (25.2)	9 (16.4)	–
Absent	7 (5.9)	1 (1.8)	–
ED duration (months)	40.5 ± 42.4	44.2 ± 3.62	0.581
ED duration >2 years, *n* (%)	53 (43.1)	31 (55.4)	0.086
ED during masturbation, *n* (%)	32 (27.1)	34 (61.8)	**<0.001**
Impaired morning erections, *n* (%)	28 (22.8)	30 (53.6)	**<0.001**
Decreased sexual desire, *n* (%)	35 (28.5)	11 (19.6)	0.143
Total testosterone (ng/ml)	4.8 ± 1.5	4.8 ± 1.9	0.836
LH (IU/L)	4.3 ± 2.3	4.4 ± 1.9	0.763
FSH (IU/L)	6.2 ± 5.4	6.2 ± 5.9	0.996
Estradiol (pg/ml)	23.8 ± 8.5	25.1 ± 10.1	0.433
Prostate-specific antigen (ng/ml)	1.3 ± 1.1	1.3 ± 1.4	0.750
Prolactin (ng/ml)	10.9 ± 5.0	11.4 ± 5.4	0.551
TSH (μIU/ml)	2.3 ± 4.7	1.7 ± 1.0	0.383

Note: Continuous variables are reported as mean ± standard deviation. Categorical variables are reported as number (percentage). p-Values are obtained by Mann–Whitney U-test.

Abbreviations: ED, erectile dysfunction; FSH, follicle-stimulating hormone; ICI, intracavernosal injection; IIEF, International Index on Erectile Function; LH, luteinizing hormone; TSH. thyroid-stimulating hormone.

confirming that we could not suspect the ED etiology on the basis of physical examination only. Moreover, patients' medical history, number and type of both comorbidities and drugs chronically used did not enter the predictive mathematical model. We observed a lower cardiovascular disease rate in psychological ED, indirectly confirming the previously suggested link between vascular ED and cardiovascular disease.[15]

In conclusion, according to our data, a negative history of cardiovascular disease, the presence of spontaneous morning erections, and ED absence during masturbation represent the crucial anamnestic points to be collected during the andrological evaluation to discriminate between psychological and vascular ED forms. Adding mini-invasive specialized examinations to study the erection vascular component, the proposed two-step ICI procedure is performing very well at diagnosing psychological ED, reserving second-level tests for those patients who really need a deeper evaluation of the penile vascular status. These results should be carefully considered, as we detected a high psychological ED rate in our cohort, which could influence our

TABLE 6 Eco-color Doppler variables comparing patients with psychological ED to patients with other forms of ED

	Psychological ED	Not psychological ED	*p*-Value
Systolic peak (cm/s)			
Right side	32.9 ± 9.1	23.0 ± 9.3	**0.005**
Left side	39.8 ± 9.1	19.4 ± 8.7	**<0.001**
End-diastolic peak (cm/s)			
Right side	3.2 ± 1.6	5.6 ± 2.2	**0.003**
Left side	2.4 ± 2.5	5.2 ± 2.6	**0.005**

Note: Continuous variables are reported as mean ± standard deviation. *p*-Values are obtained by Mann–Whitney *U*-test.
Abbreviation: ED, erectile dysfunction.

conclusions. This incidence could be explained by our clinical practice, in which men with a likely vascular ED (i.e., diabetic ones) were not evaluated with ICI test.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Daniele Santi conceived the study and analyzed the data. Daniele Santi, Giorgia Spaggiari, and Antonio R. M. Granata collected data. Daniele Santi and Giorgia Spaggiari interpreted results and drafted the article. Manuela Simoni and Antonio R. M. Granata revised the article critically for important intellectual content. All authors approved the final version of the manuscript.

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