



Associations of Self-Reported Erectile Function with Non-Invasive Measurements of Endothelial Function: A Preliminary Study

Jong Kyou Kwon^{1,*}, Joo Yong Lee¹, Hae Do Jung¹, Cheol Kyu Oh³, Young Deuk Choi¹, Kang Su Cho²

¹Department of Urology, Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, ²Department of Urology, Gangnam Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, Seoul, ³Department of Urology, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Purpose: To evaluate the association of self-reported erectile function and endothelial function using the EndoPAT device.

Materials and Methods: We prospectively enrolled 76 men (age ≥ 40 years) after obtaining a complete medical history and a self-reported questionnaire (International Index of Erectile Function-5 [IIEF-5], SEP Q2, Q3). Endothelial function was non-invasively measured with an EndoPAT 2000, recorded as the reactive hyperemia index (RHI), and analyzed according to the patients' baseline characteristics.

Results: The mean patient age and IIEF-5 score were 62.50 ± 8.56 years and 11.20 ± 6.36 , respectively. In comparing the RHI according to erectile dysfunction (ED) risk factors, the RHI was significantly lower in older subjects ($p=0.004$). There was no difference in the RHI according to age, body mass index, waist circumference, obesity, smoking habit, or other comorbidities. When the subjects were divided into four groups according to the severity of ED, no statistical differences in the RHI value were found among the groups. There was no difference in IIEF-5 according to the RHI when categorized according to the normal cutoff value or quartile ranges. The second subdomain of IIEF-5 (erection firmness) was significantly correlated with the RHI value ($R=0.309$, $p=0.007$); however, this was not the case with the other IIEF-5 subdomains. Self-assessment showed a tendency toward a negative correlation with the RHI value ($R=-0.202$, $p=0.080$).

Conclusions: The role of endothelial function measurement by the EndoPAT in the evaluation and management of ED patients remains inconclusive. However, further studies are needed to validate the role of endothelial function measurement, by the EndoPAT or any other device.

Key Words: Endothelium; Erectile dysfunction; Plethysmography

INTRODUCTION

Endothelial function is known to be impaired in patients

with chronic pathologic conditions, including coronary artery disease, diabetes mellitus, hypertension, obesity, renal failure, impaired lipid profiles, and erectile dysfunction.

Received: Jul 8, 2015; Revised: Jul 27, 2015; Accepted: Aug 3, 2015

Correspondence to: Kang Su Cho

Department of Urology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.

Tel: +82-2-2019-3471, Fax: +82-2-3462-8887, E-mail: kscho99@yuhs.ac

*Current affiliation: Severance Checkup, Yonsei Health System, Yonsei University College of Medicine, Seoul, Korea

Copyright © 2015 Korean Society for Sexual Medicine and Andrology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

tion (ED) [1-6]. Endothelial dysfunction is of critical importance as an early predictor of these vascular diseases [7-9]. The risk factors for cardiovascular disease (CVD) and ED are frequently similar, and ED is believed to be a major sign and independent predictor of future cardiovascular events in patients with CVD [10-12].

The assessment of endothelial function is relevant for the etiological evaluation and follow-up of patients with sexual dysfunction. The pulse in the arteries of the fingers or the flow-mediated dilatation (FMD) of the brachial artery by manipulation of blood flow can be used to evaluate endothelial function. Theoretically, FMD is thought to be related to an increase in the shear stress experienced by the vessels and the release of nitric oxide [13]. This technique has been widely used as a tool for assessing endothelial dysfunction. However, the results are operator-dependent, and this measurement does not reflect systemic hemodynamic changes because FMD is measured only in one arm [14]. More recent studies have described the efficacy of peripheral artery tonometry (PAT) for assessing the endothelial function of peripheral vessels [14,15]. The EndoPAT apparatus (EndoPAT 2000; Itamar Medical Ltd., Caesarea, Israel) was devised to overcome these problems, allowing the non-invasive measurement of vaso-reactivity without the disadvantages of conventional measuring methods. The EndoPAT plethysmographically measures changes of vascular pressure in the finger by detecting arterial pulsation, and translates the signal into PAT.

Since endothelial dysfunction is well-known to be a causative factor of ED, the measurement of endothelial function with EndoPAT could be used as a tool for assessing individual erectile function in various clinical conditions. Moreover, characterizing the pathophysiology and relationship between PAT and erectile dysfunction could potentially have a significant impact on patients. While much effort has been directed towards the evaluation of endothelial dysfunction in relation to CVD, data on the use of PAT to evaluate the role of endothelial function in ED are scarce. The aim of this study was to evaluate the association of EndoPAT scores with self-reported erectile function according to the International Index of Erectile Function-5 (IIEF-5) questionnaire in an outpatient urology clinic.

MATERIALS AND METHODS

The Institutional Review Board of Severance Hospital (Seoul, Korea) approved the study protocol. From October 2014 to March 2015, we prospectively enrolled subjects who provided written informed consent to participate in this study after receiving detailed information about the study. The inclusion criteria were men over 40 years of age who visited our outpatient urology clinic for counseling about a urologic problem, such as lower urinary tract symptoms or erectile dysfunction. Patients with comorbidities such as a history of pelvic surgery, uncontrolled diabetes mellitus, hypertension, urinary tract infection, malignancy, or any neurologic disease that could affect erectile function were excluded. A total of 76 patients were enrolled in the study.

All patients underwent a complete medical history (including an assessment of their history of diabetes mellitus, hypertension, coronary artery obstructive disease, and smoking status), physical examination (height, weight, body mass index, waist circumference, and systolic/diastolic blood pressure), urinalysis, and completed the IIEF-5 and Sexual Encounter Profile (SEP) Q2 and Q3 questionnaires. Endothelial function was non-invasively measured with an EndoPAT 2000 device according to the manufacturer's specifications. All tests were performed in a specific isolated location that was quiet and kept at room temperature, and all subjects had fasted for at least three hours before the measurements were collected. Plethysmographic probes were placed on the index finger of each hand, and a blood pressure cuff was placed and inflated on one arm for five minutes to provoke a brief episode of ischemia. Release of the cuff led to an endothelium-dependent dilation of the downstream vascular bed from a surge of blood flow. Measurements were obtained continuously during the five-minute baseline period, cuff occlusion, and after cuff deflation. All data were automatically recorded, and the post-occlusion to pre-occlusion ratio of the PAT signal was defined as the reactive hyperemia index (RHI) and analyzed according to the patients' baseline characteristics using the accompanying EndoPAT software. An RHI value of less than 1.67 implies impaired endothelial function [14]. Analyses were conducted after categorizing the RHI and other risk factors as binary out-

comes and establishing correlations between the parameters.

All data were analyzed using IBM SPSS ver. 20.0.0.2 (IBM Co., Armonk, NY, USA). Statistical analyses of continuous variables were conducted using the Student's t-test, one-way analysis of variance (ANOVA), the Mann-Whitney U-test, or the Kruskal-Wallis test. Pearson's correlation analysis was used to investigate relationships between the variables. Two-sided tests were applied, and $p < 0.05$ were considered to indicate statistical significance.

RESULTS

The mean patient age was 62.50 ± 8.56 years, and the mean patient IIEF-5 score was 11.20 ± 6.36 . The clinical characteristics of the patients and details of their responses to the questionnaires assessing ED symptoms are shown in

Table 1. Characteristics of the study population

Variable	Value
No. of patient	76
Age (yr)	62.50 ± 8.56
Height (cm)	167.93 ± 7.62
Weight (kg)	68.41 ± 11.57
BMI (kg/m^2)	24.30 ± 4.17
Waist circumference (cm)	89.09 ± 9.22
SBP (mmHg)	127.21 ± 15.90
DBP (mmHg)	78.46 ± 11.85
Medical history	
CAOD	4 (5.3)
Hypertension	39 (51.3)
Diabetes mellitus	16 (21.1)
Dyslipidemia	28 (36.8)
Smoking history	56 (73.7)
Ex-smoker	44 (57.9)
Current smoker	12 (15.8)
Non-smoker	20 (26.3)
Marital status	
Not married	1 (1.3)
Married	69 (90.9)
Divorced	3 (3.9)
Bereaved	3 (3.9)

Values are presented as number only, mean \pm standard deviation, or number (%).

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, CAOD: coronary artery obstructive disease.

Table 1, 2.

When the RHI was compared according to ED risk factors, it was found that the RHI was significantly lower in older subjects (1.48 ± 0.38 in subjects ≥ 63 years of age vs. 1.79 ± 0.50 in subjects < 63 years of age, $p = 0.004$). No significant differences in RHI were found according to age, body mass index, waist circumference, obesity, smoking habits, or other comorbidities (Table 3).

Relationships between the RHI and IIEF-5 scores were tested (Fig. 1). When subjects were divided into four groups according to the severity of ED based on their total IIEF-5 scores, no statistically significant differences in the RHI were found ($p = 0.542$ by ANOVA). No significant differences were found in IIEF-5 scores according to RHI when the RHI was categorized according to the normal cutoff value ($p = 0.342$ by the Student's t-test) or quartile ranges ($p = 0.476$ by ANOVA). No statistically significant differences in the RHI were found according to the penetration success rate (SEP Q2) or the intercourse success rate (SEP Q3) (data not shown).

In the correlation analyses between the RHI and each of the IIEF-5 subdomains (Fig. 2), the second subdomain of

Table 2. Results of the IIEF-5 and SEP Q2 and Q3 questionnaires

IIEF-5 sum	11.20 ± 6.36
IIEF-5 Q1 (erection confidence)	2.45 ± 1.02
IIEF-5 Q2 (erection firmness)	2.12 ± 1.46
IIEF-5 Q3 (maintenance frequency)	2.00 ± 1.40
IIEF-5 Q4 (maintenance ability)	2.03 ± 1.56
IIEF-5 Q5 (intercourse satisfaction)	2.61 ± 1.78
Severity of ED	
Complete ED (IIEF-5 ≤ 9)	28 (36.8)
Moderate ED ($10 \leq \text{IIEF-5} \leq 13$)	20 (26.3)
Mild ED ($14 \leq \text{IIEF-5} \leq 17$)	15 (19.7)
Normal (IIEF-5 ≥ 18)	13 (17.1)
Self-assessment	
1 (normal)	15 (19.7)
2 (mild ED)	29 (38.2)
3 (moderate ED)	22 (28.9)
4 (complete ED)	10 (13.2)
SEP2 answered as "yes"	52 (68.4)
SEP3 answered as "yes"	29 (38.2)

Values are presented as mean \pm standard deviation or number (%).

IIEF-5: International Index of Erectile Function-5, SEP: Sexual Encounter Profile, ED: erectile dysfunction.

Table 3. Comparison of the RHI according to erectile dysfunction risk factors

Variable	Number	RHI value	p-value
Age (yr)			0.004 ^b
< 63	41	1.79±0.50	
≥ 63	35	1.48±0.38	
BMI (kg/m ²)			0.166 ^b
< 25	51	1.59±0.39	
≥ 25	25	1.77±0.59	
WC (cm)			0.487 ^b
< 90	47	1.62±0.46	
≥ 90	29	1.70±0.49	
Obesity ^a			0.507 ^b
No	38	1.61±0.40	
Yes	38	1.68±0.54	
Smoking			0.699 ^c
Non-smoker	20	1.71±0.45	
Ex-smoker	44	1.64±0.52	
Current smoker	12	1.56±0.32	
Diabetes mellitus			0.158 ^d
No	16	1.68±0.49	
Yes	60	1.52±0.35	
Hypertension			0.825 ^b
No	37	1.64±0.49	
Yes	39	1.66±0.45	
Dyslipidemia			0.645 ^b
No	48	1.67±0.51	
Yes	28	1.62±0.39	

Values are presented as number only or mean±standard deviation.

RHI: reactive hyperemia index, BMI: body mass index, WC: waist circumference.

^aBMI≥25 kg/m², or WC≥90 cm, ^bStudent's t-test, ^cKruskal-Wallis test, ^dMann-Whitney U-test.

IIEF-5 (erection firmness) was found to be significantly correlated with the RHI ($R=0.309$, $p=0.007$). However, no statistically significant correlations were found between the RHI and other IIEF-5 subdomains. Self-assessment scores showed a marginally significant tendency to be negatively correlated with RHI ($R=-0.202$, $p=0.080$).

DISCUSSION

EndoPAT is a promising non-invasive technique for measuring peripheral vasodilation response, which has been associated with both endothelial dysfunction and CVD [16,17]. Subclinical and systemic inflammatory changes due to atherosclerosis result in endothelial dys-

function in both large and small blood vessels, and play a critical role in cardiovascular and peripheral vascular disease [18]. Specific changes in penile vasculature (*i.e.*, decreased diameter of the cavernosal arteries along with a high proportion of endothelial content in the penile vascular bed) can be used as a sensitive indicator of systemic vascular conditions [10]. Specifically, abnormal responses to hyperemic environments measured using PAT have been found to be significantly correlated with coronary microvascular endothelial dysfunction, as measured by coronary angiography [14]. As a non-invasive modality for evaluating both the current and future risks of CVD, the usefulness of PAT has been well documented in many publications, and it is a clinically relevant test when considering treatment plans for patients at risk for CVD. Marked endothelial dysfunction has been shown in patients with vasculogenic ED in comparison to non-ED patients with similar risk factors [19], and endothelial dysfunction may be an early manifestation of ED. Furthermore, since vasculogenic ED is also known as a herald of impending systemic CVD, the relationship between ED and CVD may be important for the potential early detection of cardiovascular risk in ED patients.

The presence of a close relationship between endothelial dysfunction and ED has become clear, especially because endothelial dysfunction has been increasingly reported to be associated with vasculogenic ED. Recently, advances in diagnostic technology have greatly improved the capability to identify the pathophysiologic profile of a vascular condition. One such advance, the EndoPAT 2000 device, permits the accurate detection and quantification of endothelial function through a PAT measurement. Occlusion of the brachial artery induces endothelium-mediated changes in the vascular tone, reflecting a downstream hyperemic response [20]. These findings are compared to concurrent non-endothelium-dependent changes in vascular tone from measurements on the contralateral arm, which are used to correct for the systemic hemodynamic changes resulting from alteration of the autonomic nervous system. Computerized calculations made using the EndoPAT software can provide the researcher with information about the change in pulse volume in response to local ischemia and the accompanying reperfusion as reflected by the RHI, and about arterial stiff-

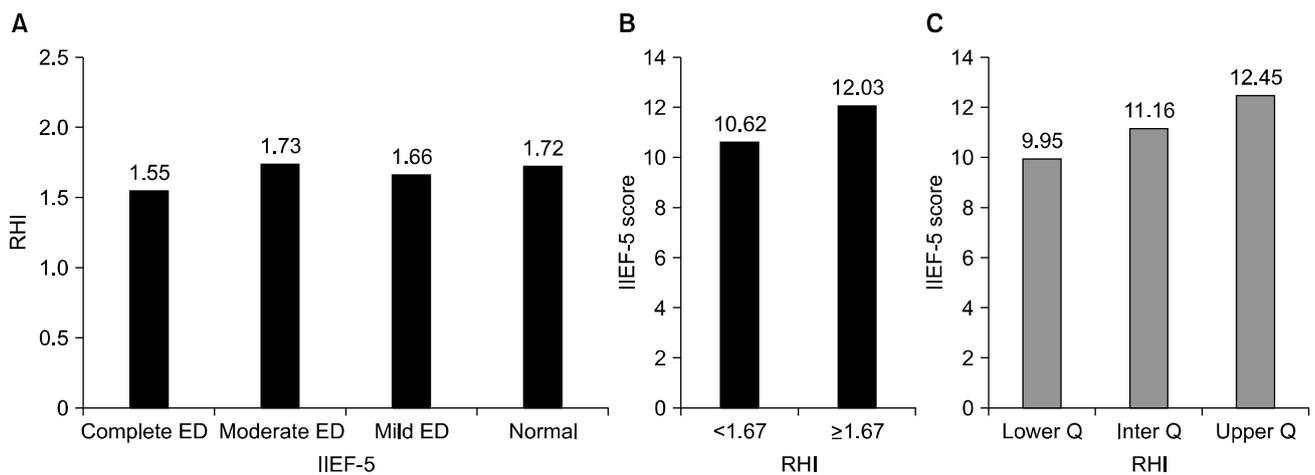


Fig. 1. Relationships between the reactive hyperemia index (RHI) and International Index of Erectile Function-5 (IIEF-5) scores. (A) No statistically significant differences were observed in the RHI when subjects were divided into four groups according to the severity of erectile dysfunction based on their total IIEF-5 scores ($p=0.542$ by ANOVA). (B) No significant differences in IIEF-5 scores were observed according to the RHI when categorized with respect to the normal cutoff value ($p=0.342$ by the Student's *t*-test). (C) No statistically significant differences in IIEF-5 scores were observed according to the RHI when categorized according to quartile ranges ($p=0.476$ by ANOVA). ANOVA: analysis of variance, Q: quartile, ED: erectile dysfunction.

ness as defined by the augmentation index. The test is simple and easy to perform, requiring only two finger probes and a blood pressure cuff, and does not have the disadvantage of operator dependency. The RHI, a measure of endothelial function, is known to be rather stable over time, whereas the augmentation index is known to have substantial intra-individual variability, limiting its value for clinical assessments [21]. With this in mind, we used the RHI to analyze relationships among PAT metrics and risk factors.

In this study, we failed to show a significant difference in the RHI according to either categorical risk factors or the severity of ED. Our correlation analysis revealed that only the IIEF-5 Q2 was positively correlated with the RHI. Likewise, other subdomains, including self-assessment, showed poor correlations. Our results are very similar to those reported by Aversa et al [22]; in a small study of 70 patients, they found no statistically significant differences in PAT scores between ED and non-ED groups. Interestingly, Vardi et al [23] measured the baseline blood flow in both the forearm and the penis, and calculated the corresponding vascular resistance values for patients without significant systemic vasculopathy using venocclusive plethysmography at both the forearm and the penile levels. They found that the baseline blood flow of the forearm was sim-

ilar between the ED and non-ED groups, but that the blood flow of the penis was significantly lower, with significantly higher penile vascular resistance observed among patients with ED. This result suggested that penile, but not forearm, endothelial function is significantly altered in patients with ED in comparison to those without ED. Seager et al [15] also reported similar results, finding a lack of predictive correlations between PAT and color Doppler ultrasound parameters in men with ED. Several possible explanations could exist for these results. The PAT signal can be altered by some comorbidities involving systemic vascular disorders, such as hypertension, diabetes mellitus, hyperlipidemia, and other risk factors for CVD, yielding a low or abnormal RHI value compared to that observed in a healthy population [13]. Since the PAT measurement has primarily been validated in CVD patients, the threshold value for identifying endothelial dysfunction indicative of ED might be different from the appropriate cutoff value in the context of CVD. More studies are warranted to identify a valid threshold value specific for endothelial dysfunction in ED.

Several confounding factors were present in the present study that may have contributed to the absence of correlation between EndoPAT scores and ED. First, the patients enrolled in this study were for the most part older men

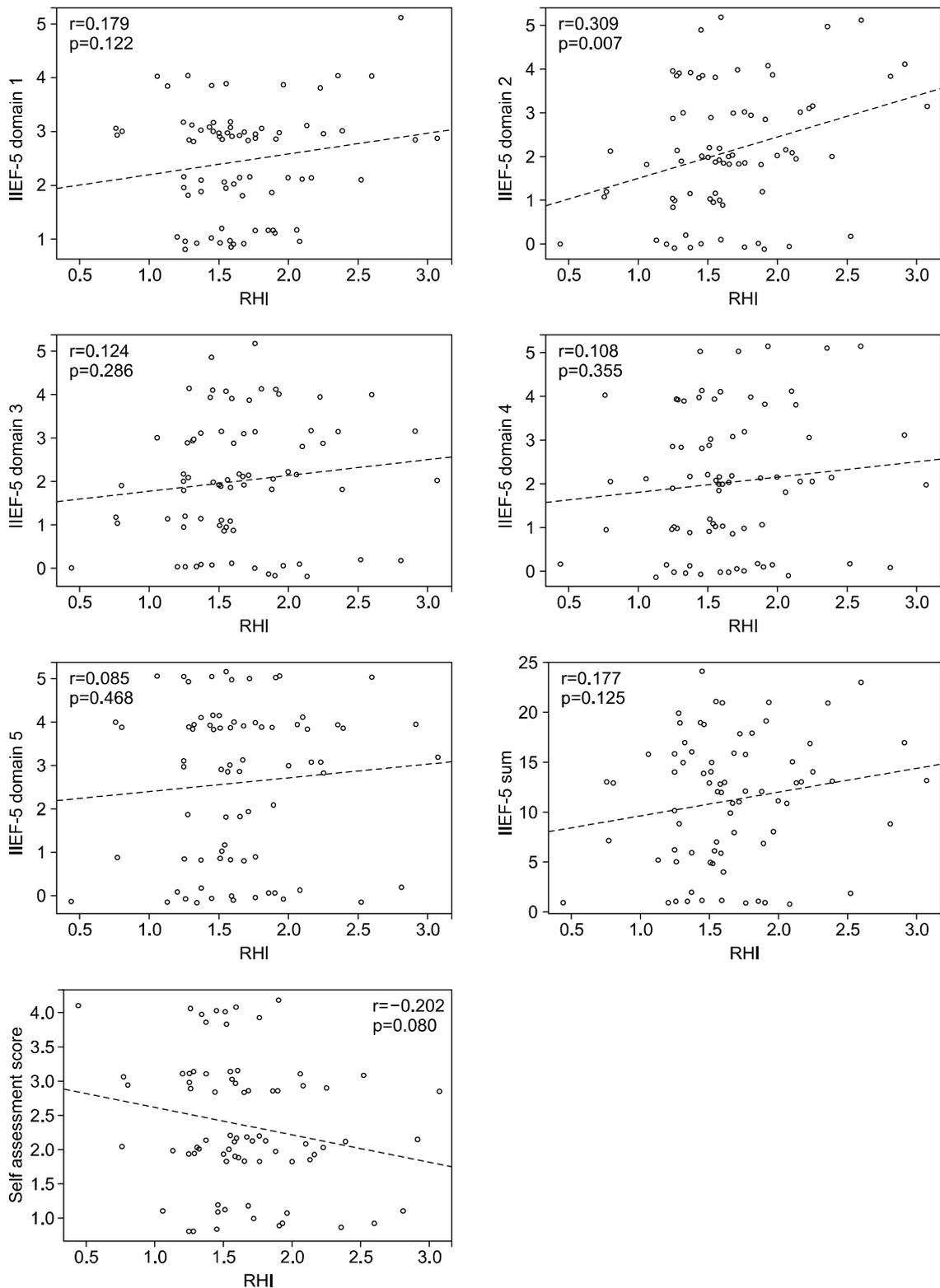


Fig. 2. Correlations between the reactive hyperemia index (RHI) and the International Index of Erectile Function-5 (IIEF-5) subdomains. The second subdomain of the IIEF-5 (erection firmness) was significantly correlated with the RHI ($R=0.309$, $p=0.007$). However, no statistically significant correlations were found between RHI values and other IIEF-5 subdomains. Self-assessment scores showed a marginally significant tendency to be negatively correlated with the RHI ($R=-0.202$, $p=0.080$).

(mean age, 62.50 ± 8.56 years) who may have had problems with sexual activity. In our study population, 90.9% of subjects reported that they were married, but their mean overall IIEF-5 score was 11.20 ± 6.36 . Approximately 60% of participants were diagnosed with complete to moderate ED. Second, our study cohort was potentially heterogeneous in ways that could have affected our findings. We did not classify patients into subgroups according to comorbidities and smoking history, but several studies have documented improvements in endothelial dysfunction as a result of prolonged pharmacological interventions or lifestyle modifications such as smoking cessation and dietary changes [24-27]. Third, no other ED risk factors were evaluated in the present study. We did not measure serum testosterone levels or perform Doppler ultrasound imaging, which could have been helpful in distinguishing vasculogenic and non-vasculogenic ED.

The present study is the first report on the relationship between EndoPAT scores and ED conducted in a real clinical setting in a Korean population. The clinical usefulness of EndoPAT in the evaluation and management of ED appears unclear. Nevertheless, the results of this preliminary study indicate that more precise and well-designed studies are needed to evaluate the relationship between endothelial function and ED.

CONCLUSIONS

In this study, endothelial function, as measured by EndoPAT, was not associated with erectile function as reflected by overall IIEF-5 scores, but did show a significant correlation with scores in the IIEF-5 erection firmness subdomain. No consensus exists regarding whether endothelial function as measured by EndoPAT should play a role in the management of ED patients. However, further studies are needed to validate the role of endothelial function measurements, by EndoPAT or any other device, in the evaluation and management of ED patients.

ACKNOWLEDGEMENTS

This study was supported by a new faculty research seed money grant from the Yonsei University College of Medicine (2014-32-0030).

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Bolad I, Delafontaine P. Endothelial dysfunction: its role in hypertensive coronary disease. *Curr Opin Cardiol* 2005;20:270-4.
2. Vanhoutte PM. Endothelial dysfunction: the first step toward coronary atherosclerosis. *Circ J* 2009;73:595-601.
3. Hartge MM, Unger T, Kintscher U. The endothelium and vascular inflammation in diabetes. *Diab Vasc Dis Res* 2007;4:84-8.
4. Meyers MR, Gokce N. Endothelial dysfunction in obesity: etiological role in atherosclerosis. *Curr Opin Endocrinol Diabetes Obes* 2007;14:365-9.
5. Kawano H, Motoyama T, Hirai N, Kugiyama K, Yasue H, Ogawa H. Endothelial dysfunction in hypercholesterolemia is improved by L-arginine administration: possible role of oxidative stress. *Atherosclerosis* 2002;161:375-80.
6. Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. *Lancet* 1985;1:181-4.
7. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Münzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* 2001;104:2673-8.
8. Karatzi K, Papamichael C, Karatzis E, Papaioannou TG, Vaidonikola PT, Lekakis J, et al. Acute smoking induces endothelial dysfunction in healthy smokers. Is this reversible by red wine's antioxidant constituents? *J Am Coll Nutr* 2007;26:10-5.
9. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;101:1899-906.
10. Vlachopoulos C, Ioakeimidis N, Terentes-Printzios D, Stefanadis C. The triad: erectile dysfunction-endothelial dysfunction-cardiovascular disease. *Curr Pharm Des* 2008;14:3700-14.
11. Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005;294:2996-3002.
12. Kloner RA. Erectile dysfunction as a predictor of cardiovascular disease. *Int J Impot Res* 2008;20:460-5.
13. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnell RP, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J* 2003;146:168-74.
14. Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr, Kuvin JT, Lerman A. Noninvasive identification of patients with

- early coronary atherosclerosis by assessment of digital reactive hyperemia. *J Am Coll Cardiol* 2004;44:2137-41.
15. Seager CM, Li J, Shoskes DA. Lack of predictive correlation between peripheral arterial tone and colour flow Doppler parameters in men with erectile dysfunction. *BJU Int* 2013; 112:E186-90.
 16. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J* 2010;31:1142-8.
 17. Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Menzoian JO, Vita JA. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. *Circulation* 2002;105:1567-72.
 18. Vlachopoulos C, Rokkas K, Ioakeimidis N, Stefanadis C. Inflammation, metabolic syndrome, erectile dysfunction, and coronary artery disease: common links. *Eur Urol* 2007;52: 1590-600.
 19. Yavuzgil O, Altay B, Zoghi M, Gürgün C, Kayıkçıoğlu M, Kültürsay H. Endothelial function in patients with vasculogenic erectile dysfunction. *Int J Cardiol* 2005;103:19-26.
 20. Billups KL, Bank AJ, Padma-Nathan H, Katz S, Williams R. Erectile dysfunction is a marker for cardiovascular disease: results of the minority health institute expert advisory panel. *J Sex Med* 2005;2:40-50; discussion 50-2.
 21. Moerland M, Kales AJ, Schrier L, van Dongen MG, Bradnock D, Burggraaf J. Evaluation of the EndoPAT as a Tool to Assess Endothelial Function. *Int J Vasc Med* 2012; 2012:904141.
 22. Aversa A, Francomano D, Bruzziches R, Pili M, Natali M, Spera G, et al. The application of digital pulse amplitude tonometry to the diagnostic investigation of endothelial dysfunction in men with erectile dysfunction. *Andrologia* 2011; 43:9-15.
 23. Vardi Y, Dayan L, Apple B, Gruenwald I, Ofer Y, Jacob G. Penile and systemic endothelial function in men with and without erectile dysfunction. *Eur Urol* 2009;55:979-85.
 24. Fisher ND, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens* 2003;21:2281-6.
 25. Barringer TA, Hatcher L, Sasser HC. Potential benefits on impairment of endothelial function after a high-fat meal of 4 weeks of flavonoid supplementation. *Evid Based Complement Alternat Med* 2011;2011:796958.
 26. Aversa A, Vitale C, Volterrani M, Fabbri A, Spera G, Fini M, et al. Chronic administration of Sildenafil improves markers of endothelial function in men with type 2 diabetes. *Diabet Med* 2008;25:37-44.
 27. Yeo TW, Lampah DA, Gitawati R, Tjitra E, Kenangalem E, McNeil YR, et al. Recovery of endothelial function in severe falciparum malaria: relationship with improvement in plasma L-arginine and blood lactate concentrations. *J Infect Dis* 2008;198:602-8.