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Original Article

Color Doppler ultrasound imaging in varicoceles: Is the difference in venous diameter encountered during Valsalva predictive of palpable varicocele grade?

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Abstract *Objective:* The clinical grading system for varicoceles is subjective and dependent on clinician experience. Color Doppler ultrasound (US) has not been standardized in the diagnosis of varicoceles. We aimed to determine if US measurement of varicocele could be predictive of World Health Organization (WHO) varicocele grade.
Methods: Men who presented for either scrotal pain or infertility to a tertiary men's health clinic underwent physical examination, and varicoceles were graded following WHO criteria (0=subclinical, 1, 2, 3). US was used to measure largest venous diameter in the pampiniform plexus bilaterally at rest and during Valsalva maneuver. Receiver operator characteristic curve analysis was used to determine if resting diameter, diameter during Valsalva, or change in diameter between at rest and during Valsalva provided the highest sensitivity and specificity for determining clinical grade. Threshold values for diameter were determined from these receiver operator characteristic curves.
Results: A total of 102 men (50 with clinical varicocele and 52 with subclinical varicocele) were included. Diameter at rest was the best ultrasonographic discriminator between subclinical and clinical varicoceles (area under the curve [AUC]=0.67) with a diameter threshold of 3.0 mm (sensitivity 79%, specificity 42%). Diameter during Valsalva had the greatest AUC for determining clinical Grades 1 versus 2 (AUC=0.57) with diameter threshold of 5.7 mm (sensitivity 71%, specificity 33%). For differentiating between Grades 2 and 3, diameter at rest had the greatest AUC of 0.65 with a threshold of 3.6 mm (sensitivity 71%, specificity 58%).

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Conclusion: Our results corroborate other studies that have shown a weak correlation between US and clinical grading. The use of diameter during Valsalva was less predictive than diameter at rest and was only clinically significant in differentiating between Grade 1 and 2 varicocele. A standardized method for determining clinically relevant varicoceles on US would allow for improved patient counseling and clinical decision-making.

1. Introduction

A varicocele is an abnormal dilation of the scrotal venous pampiniform plexus caused by reflux of venous blood flow in the internal spermatic vein [1]. The condition is estimated to be present in 15%–20% of all males, and is associated with infertility in 20%–40% of cases [1]. While the American Urological Association and the American Society of Reproductive Medicine currently classify varicoceles as a clinical diagnosis made on physical exam, use of ultrasound (US) has shown growing utility as a diagnostic tool that may, in some cases, have higher sensitivity and specificity than palpation alone [2,3]. The European Association of Urology (EAU) recommends US for confirmation of varicoceles after diagnosis by initial physical exam [4].

Grading of varicoceles by physical exam is based on criteria established by the World Health Organization (WHO), which ranges from "0" for absence of varicocele on physical exam to "3" for a varicocele visible through the scrotal skin [5,6]. Despite the frequent use of US for varicocele diagnosis, there is no standardized method of correlating US findings with the WHO grading scale [7]. Although straight-forward, in practice varicocele grading can be challenging for inexperienced providers. Additionally, significant intra-observer variability exists for physical exam grading of varicoceles [8]. US evaluation of varicoceles may provide the opportunity to establish a reliable and objective measurement independent of observer bias. However, it is unknown whether US can be used as an accurate predictor of varicocele grade. In this study, we sought to determine if US could discriminate between (1) subclinical and clinical varicoceles, (2) between Grade 1 and Grade 2 varicoceles, and (3) between Grade 2 and Grade 3 varicoceles.

2. Patients and methods

Institutional review board approval (H-29159) was obtained for this study. A retrospective review was conducted of men presenting to a tertiary men's health clinic from January 2009 to December 2017 for evaluation of fertility or scrotal pain. Men who were found to have varicoceles during evaluation were included in our study. Men were excluded who had another possible etiology for infertility or scrotal pain, including undescended testis, inguinal hernia, hydrocele, genitourinary trauma, infection, scrotal mass, history of scrotal surgery, and inflammation. All men received both a physical exam and a US as part of their work-ups. This yielded a total of 102 men, 50 with clinical varicocele and 52 with subclinical varicocele (detected by US but not by physical exam). The mean age of individuals was 34 years old with a range from 15 years to 57 years old (Table 1).

Physical examination was conducted by an experienced infertility specialist in a warm private room to facilitate relaxation of the scrotal skin. Individuals were examined by palpation and inspection in a standing position with and without Valsalva maneuver; classification of varicocele size and grade was made in accordance with WHO criteria. US was conducted in the supine position by an experienced genitourinary US technician with a high frequency linear probe. To minimize bias, the technician was blinded to the previous physical exam results. The largest venous diameter in the pampiniform plexus was measured bilaterally both at rest and during Valsalva.

Unpaired *t*-test was used to compare right- to left-sided venous diameters. Analysis of variance was used to evaluate if the US-derived mean maximum venous diameter for each clinical grade was statistically different. This was conducted separately for right- and left-sided varicoceles and for measurements at rest and during Valsalva (Tables 2 and 3). As left-sided varicocele is more common and

Table 1 Patient demographics (n=102).

Characteristic	Value
Age, year	
Mean±SD	34±7
Range	15–57
Reason for presentation, *n*	
Pain	8
Infertility	94
BMI, kg/m^2	
Mean±SD	30.4±9.1
Range	19.3–88.0
Left testicle clinical grade, *n*	
0	52
1	12
2	31
3	7
Right testicle clinical grade[a], *n*	
0	52
1	19
2	25
3	1

BMI, body mass index; SD, standard deviation.
[a] Five right side testicles were not graded by physical exam.

Table 2 Comparison of left scrotal ultrasound diameter measurements (mm) at rest and during Valsalva between different varicocele grades.

Clinical grade	At rest		During Valsalva		Difference between means
	Mean±SD	Range	Mean±SD	Range	
Grade 0 (n=52)	3.12±0.98	0–5.2	4.46±1.52	2.2–10.3	1.34
Grade 1 (n=12)	3.71±0.88	2.4–5.6	4.86±1.42	3.4–7.5	1.15
Grade 2 (n=31)	3.89±1.56	1.3–7.6	4.84±2.62	0–14.2	0.94
Grade 3 (n=7)	4.60±1.74	2.7–8.1	4.96±1.97	2.7–8.8	0.36
Total (n=102)	3.52±1.30	0–8.1	4.65±1.92	0–14.2	1.13
p-Value	0.004		0.776		

SD, standard deviation; n, number of patients per group as determined by physical exam grading.

Table 3 Comparison of right scrotal ultrasound diameter measurements (mm) at rest and during Valsalva between different varicocele grades.

Clinical grade	At rest		During Valsalva		Difference between means
	Mean±SD	Range	Mean±SD	Range	
Grade 0 (n=52)	3.04±1.18	0–6.2	4.14±1.21	2.1–6.9	1.1
Grade 1 (n=19)	2.98±1.07	0–5.3	4.20±1.17	2.4–6.0	1.22
Grade 2 (n=20)	3.39±0.92	1.4–4.8	4.14±0.99	2.2–5.6	0.75
Grade 3 (n=11)	3.75±1.41	2.2–6.7	3.95±1.64	2.1–8.1	0.5
Total (n=102)	3.18±1.15	0–6.7	4.13±1.20	2.1–8.1	0.95
p-Value	0.202		0.961		

SD, standard deviation; n, number of patients per group as determined by physical exam grading.

clinically significant, receiver operator characteristic (ROC) curve analysis was used on left-side varicocele data to determine if resting diameter, diameter during Valsalva, or change in diameter between rest and Valsalva provided the highest sensitivity and specificity for determining clinical grade with US. Threshold values for diameter were determined from these ROC curves. Statistical analyses were performed using R Statistical Software (version 1.2.5001; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 102 men underwent a scrotal US due to concern for scrotal pain or infertility (Table 1). Varicocele diameters measured by US at rest, during Valsalva, and the difference between these values are presented in Figs. 1 and 2. There was a difference between US varicocele sizes by WHO grade for left-sided varicoceles at rest (p=0.004; Table 2). However, there was no difference in US varicocele size by WHO grade for right-sided varicoceles and for left-sided varicocele during Valsalva (p>0.05; Tables 2 and 3).

To determine if US could discriminate between (1) subclinical and clinical varicoceles, (2) between Grade 1 and Grade 2 varicoceles, and (3) between Grade 2 and Grade 3 varicoceles, ROC curves were constructed with left-sided maximum venous diameter at rest, during Valsalva, and the difference between the diameters at rest and during Valsalva (Fig. 3). The measurement type (Valsalva, rest, or difference) with the greatest AUC for each ROC curve was noted. The higher the AUC, the better the ability of that test to discriminate between different clinical grades. Diameter at rest was the best ultrasonographic discriminator between subclinical and clinical varicoceles (AUC=0.67; Table 4) with a diameter threshold of 3.0 mm (sensitivity 79%, specificity 42%). Diameter during Valsalva had the greatest AUC for determining clinical Grades 1 versus 2 (AUC=0.57; Table 4) with diameter threshold of 5.7 mm (sensitivity 71%, specificity 33%). For differentiating between Grades 2 and 3, diameter at rest had the greatest

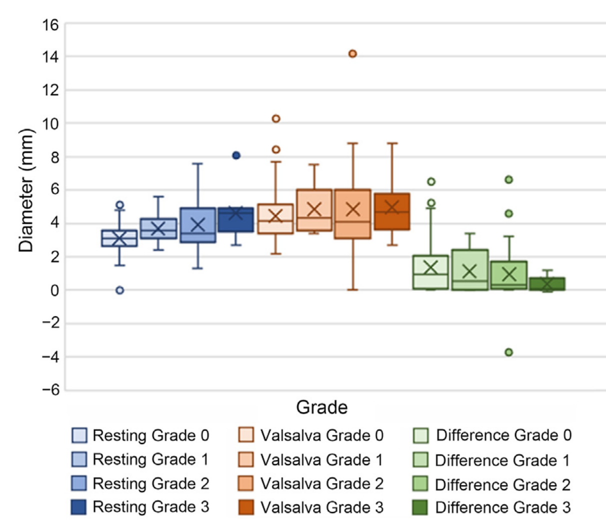

Figure 1 Left testicle ultrasound maximum venous diameter at rest, during Valsalva, and the difference between the two.

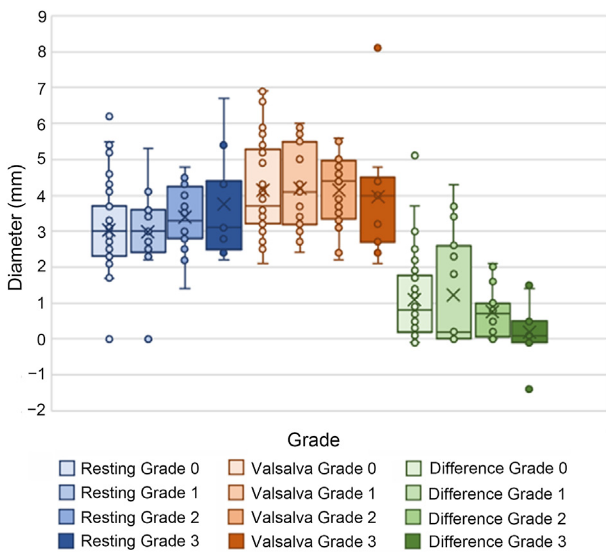

Figure 2 Right testicle ultrasound maximum venous diameter at rest, during Valsalva, and the difference between the two.

AUC of 0.65 with a threshold of 3.6 mm (sensitivity 71%, specificity 58%; Table 4).

4. Discussion

The accurate diagnosis and detection of varicocele has important implications in the management of male fertility. A study of over 9000 men by the WHO has shown that varicocele is more than two times more likely to be found in men with abnormal as compared to normal semen parameters [9]. Varicocele has been linked to decreased testicular volume and impaired sperm quality [9]. A varicocele repair, wherein the internal spermatic vein is surgically ligated or radiologically embolized, can be an effective means of enhancing semen parameters and improving fertility potential [10,11]. Several studies have shown that men with Grade 3 varicoceles have greater improvements in semen parameters than men with Grade 1 and Grade 2 varicoceles after varicocele repair [12–14]. Given that varicocele grade plays a role in the success of varicocele repair, it is important to establish consistent and accurate varicocele grading techniques [15–18].

Our retrospective study of 102 patients with subclinical or clinical varicoceles aimed to determine if a correlation could be established between the WHO physical exam-based varicocele grade and the maximum venous diameter of the pampiniform plexus measured by US. Our results indicated that there is only a modest correlation between US and clinical grading. The diameter of the largest vein measured at rest was best able to predict the difference between subclinical and clinical varicocele (at a 3.0 mm cut-off) and between Grade 2 and Grade 3 varicoceles (at a 3.6 mm cut-off). However, the specificity of this cut-off was low. Even so, this is well in line with most commonly considered threshold for diagnosis of varicocele by US of 3 mm [7]. The diameter of the largest vein during Valsalva was best able to predict the difference between Grade 1 and Grade 2 varicoceles (at a 5.7 mm cut-off), but again had low sensitivity and specificity at 71% and 33%. The difference between the diameter at rest and the diameter during Valsalva, which some have argued corresponds to

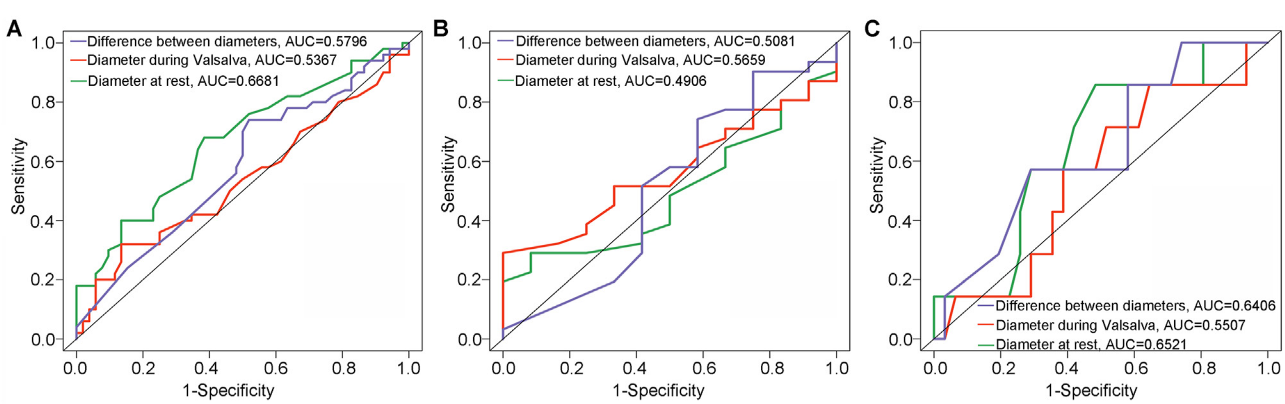

Figure 3 Receiver operator characteristic curves of the abilities of sonographic measurements to differentiate between clinical classifications. (A) Subclinical *vs.* clinical varicocele; (B) Grade 1 *vs.* Grade 2 varicocele; (C) Grade 2 *vs.* Grade 3 varicocele. AUC, area under the curve.

Table 4 Cut-off values of venous diameter to distinguish between clinical grades of varicocele.

Varicocele WHO grade (physical exam)	Best Measurement	Cut-off value (mm)	Sensitivity (%)	Specificity (%)	AUC
0 *vs.* 1–3	Diameter at rest	3.0	79	42	0.67
1 *vs.* 2	Diameter during Valsalva	5.7	71	33	0.57
2 *vs.* 3	Diameter at rest	3.6	71	58	0.65

WHO, World Health Organization; AUC, area under the curve.

the amount of venous reflux, interestingly did not prove to be useful in correlating US with clinical grade [19]. Given the poor sensitivity and specificity demonstrated in the AUC curves, our results suggested that US is likely not a suitable tool for establishing or verifying the clinical grade of a varicocele.

Analysis of variance conducted on our sample showed that for left sided varicoceles at rest, mean venous diameters were significantly different between clinical grades ($p=0.004$). During Valsalva, neither left- ($p=0.202$) nor right-sided ($p=0.961$) varicoceles showed significantly different venous widths between clinical grades. These findings further underscored the fact that US measurements provide a poor correlation to grading by physical exam. In our study, right-sided varicocele showed less variation in venous diameter overall, making it more difficult to characterize by US. This is expected given the anatomical differences between right- and left-sided testicular drainage. The angle between the left testicular vein and the renal vein, failure of the valve between the testicular and renal veins, and the possibility of the left internal spermatic vein being compressed between the superior mesenteric artery and the aorta in "Nutcracker" syndrome all make left sided varicocele far more common (representing 80%—90% of varicoceles overall) [20]. Although we observed a trend of increasing maximum venous diameter with increasing clinical grade, there was still substantial overlap of diameters within each grade (Figs. 1—2).

Our findings are similar to data reported by Caskurlu et al. [21] where the maximum venous diameter was compared between infertile individuals with and without clinical varicocele and no significant difference in venous diameter between groups was found. Cina et al. [22] studied scrotal venous diameters in healthy subjects (men with normal semen analyses, no palpable varicocele on clinical exam, and no prior scrotal US) and interestingly found a high degree of overlap in diameters identified in these individuals and diameters reported in others studies to be indicative of varicocele. Hoekstra and Witt [23] examined 156 testicles by US and palpation and found that the internal spermatic vein became palpable at 3.0—3.5 mm. Metin et al. [24] reported that varicoceles with a maximum venous diameter between 3 mm and 4 mm were palpable in 50% of cases. Cina et al. [22] provided an interesting perspective on these previously reported palpation thresholds by showing that individuals with normal semen analysis had scrotal vein reflux 53% of the time and had scrotal venous diameters up to 3.70—3.88 mm without any evidence of palpable varicocele. This underscores the need for caution when searching for absolute measurement cut-offs that can be applied to establish clinical grade.

Two prior studies using US to establish varicocele grade have presented results that conflict with our findings. Pilatz et al. [25] studied 129 men with clinical varicocele and 88 men without clinical varicocele to determine if US venous diameters could predict the presence or absence of a clinical varicocele. They found that a cut-off of 2.45 mm in relaxed supine position had 84% sensitivity and 81% sensitivity to differentiate between testicular units with and without clinical varicocele. They also identified a cut-off of 2.95 mm with Valsalva that had an 84% sensitivity and 84% specificity to differentiate between testicular units with and without clinical varicocele. This differed from our aim of correlating venous US widths with specific WHO clinical grades, which may have allowed them to establish higher sensitivity and specificity cut-offs than seen in our study. They also found it was not possible to reliably differentiate between normal pampiniform plexus and subclinical varicocele with US measurements, which agreed with previous reports that there was a wide range of venous diameters found among healthy men without varicocele.

Karami et al. [26] also used US to measure venous width of varicoceles, and similar to our study, sought to find cut-off points that would differentiate between WHO clinical varicocele grades. They stated that they measured venous width at four discrete points: the inguinal canal, and the head, body, and tail of the epididymis. In contrast to our study, they found the most sensitive and specific cut-off points using venous width measurement at the level of the epididymal head in the upright position with Valsalva maneuver. Our study used US measurements conducted in the supine position, making it difficult to compare the studies. Although the authors achieved fairly high sensitivity and specificity with their results, their method of measuring venous diameter at just the epididymal head is unconventional by current guidelines, which advocate for measuring the largest vein irrespective of location [7]. Furthermore, given that the scrotal veins lie superior to the epididymis, it is anatomically difficult to theorize how scrotal veins could be measured at different sites along the epididymis. For these reasons, the generalizability of this study may be limited.

Limitations of our study include the modest population size, which was heavily weighted towards subclinical varicoceles (52/102), and the retrospective nature of our work. Subclinical varicoceles may ultimately be less important to accurately grade and characterize given the uncertain nature of their effect on fertility. Nonetheless, our study provides an important counterargument to recent work suggesting that US can reliably predict the clinical grade of varicocele.

5. Conclusion

Our results support growing evidence that wide variations exist between varicocele size on US and physical exam. We show that although some correlation exists between grading by physical exam and measured varicocele size on US, US measurements are not sufficiently sensitive and specific to serve as a standalone measure of varicocele severity. US may be best employed for cases in which the varicocele grade by physical exam is equivocal. Even so, future work with larger cohort sizes will be needed to establish exactly what US criteria should be used as there is currently a lack of agreement on whether venous diameters can establish clinical grade at all, and if so, what cut-off should be used. A standardized method for determining clinically relevant varicoceles by US would allow for improved patient counseling and clinical decision-making regarding varicocele repair to improve fertility parameters.

As our work suggests, given the variability of scrotal venous diameters and their relatively poor correlation with WHO varicocele grade, such a standardized US technique may not ultimately be achievable. WHO clinical grade as determined by physical exam remains the gold standard to diagnose varicocele.

Author contributions

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Data analysis: Kelly Lehner, Catherine Ingram, Utsav Bansal, Larry I. Lipshultz.
Drafting of manuscript: Kelly Lehner, Catherine Ingram, Utsav Bansal.
*Critical revision of manuscrip*t: Kelly Lehner, Catherine Ingram, Utsav Bansal, Collen Baca, Adithya Balasubramanian, Nannan Thirumavalavan, Jason M. Scovell, Saneal Rajanahally, Matthew Pollard, Larry I. Lipshultz.
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Conflicts of interest

The authors declare no conflict of interest.

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