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## INVITED REVIEW

Male Fertility

# Diagnosis of clinical and subclinical varicocele: how has it evolved?

Ruth E Belay, Gene Omar Huang, Jim Ken-Chie Shen, Edmund Yuey Kun Ko

In this review, we examine the evolution and application of various diagnostic modalities for varicoceles starting with venography, scintigraphy, and thermography and their role in the evaluation of a varicocele patient. Some of these methods have been supplanted by less invasive and more easily performed diagnostic modalities, especially ultrasound and Doppler examination of the scrotum. Advances in ultrasound and magnetic resonance imaging hold the potential to expand the role of imaging beyond that of visual confirmation and characterization of varicoceles. The ability to identify the early indicators of testicular dysfunction based on imaging findings may have implications for the management of varicoceles in the future.

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## INTRODUCTION

Varicocele, defined by the dilatation of the venous pampiniform plexus, occurs secondary to retrograde flow via the spermatic vein due to incompetent or absent valves.<sup>1</sup> The prevalence of varicocele is estimated at 15%–20% for healthy men, with 35%–40% affected among men seeking infertility treatment.<sup>2</sup> Physical examination has long represented the foundation for diagnosing varicoceles. The introduction of radiographic diagnostic studies has allowed for improved detection and further characterization of varicoceles. However, improved detection has generated a subset of subclinical varicoceles which are identified radiographically, but not appreciated on physical examination. Management of these subclinical varicoceles is controversial and, consequently, both the American Society of Reproductive Medicine (ASRM) and American Urological Association (AUA) have recommended against routine radiographic screening with ancillary imaging on patients without a palpable abnormality.<sup>3,4</sup> In this review, we will discuss the various modalities utilized in varicocele detection and how they have evolved.

## PHYSICAL EXAMINATION

Evaluation for varicocele requires proper room setup, environment, and systematic examination. A warm and comfortable environment for the patient is ideal to allow for relaxed scrotal skin. Cold temperatures and patient distress can result in tightening of the scrotum and preclude identification of a varicocele. It is the authors' preference to first perform examination in the standing position, both without and with Valsalva maneuvers. Subsequent examination is then repeated in the supine position to evaluate for decompression of the dilated veins. In addition to palpating for pampiniform plexus dilatation, testicular size and consistency should be noted. Grading of varicoceles (**Table 1**) is based on criteria published by Dubin and Amelar.<sup>5</sup>

The physical examination for varicocele is limited by its subjective nature in addition to patient body habitus. A study involving

experienced andrologists and clinicians identified a significant inter- and intra-observer variability in the grading of varicoceles and estimation of testicular size.<sup>6</sup> A significant inter-observer error of 16% was found in estimating testicular size, and varicocele grading was inconsistent. In this study, of six clinicians who examined the same patient twice, only two obtained the same results on repeat examination. Compared to venography, physical examination was determined to have a sensitivity of 71% and a specificity of 69%.<sup>7</sup> Ultrasound was found to be superior to Prader orchidometers with regards to testicular size estimation.<sup>8</sup> However, even ultrasound has been found to suffer from significant inter-institutional variability.<sup>9</sup> Despite these limitations, physical examination still represents the gold standard for diagnosing clinically significant varicoceles, which have the clearest indications for repair.<sup>3,4</sup>

## IMAGING MODALITIES

### Venography

Early reports of retrograde spermatic venography for varicocele were primarily diagnostic in nature and shed light on the mechanism of valvular incompetence or absence.<sup>1</sup> Percutaneous access is typically achieved through the right femoral or internal jugular vein, followed by advancement of a catheter to the spermatic vein and retrograde contrast administration (**Figure 1**).<sup>2</sup> Venography is generally considered the most sensitive test, as nearly 100% of individuals with clinically palpable varicocele demonstrate spermatic vein reflux.<sup>1</sup>

However, because of its invasive nature and potential for false-positives,<sup>10</sup> contemporary use primarily involves concurrent therapeutic intervention with embolization.<sup>11</sup> A retrospective review of salvage varicocele embolization after failed surgical ligation therapy highlighted the importance of venography in identifying persistent collateral veins, specifically at the retroperitoneal or inguinal level.<sup>12</sup>

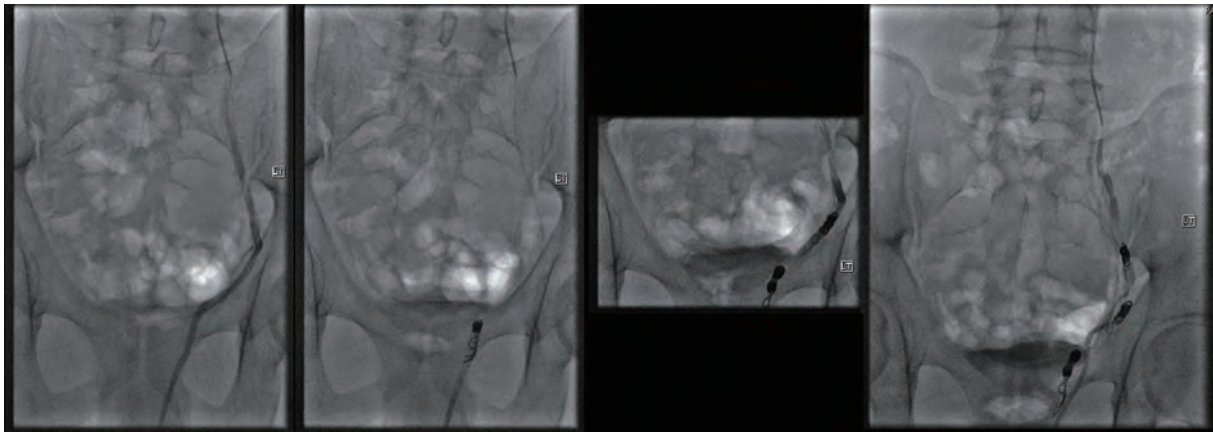


Figure 1: Venography and embolization of a left-sided grade 3 varicocele.

Table 1: Dubin and Amelar varicocele grading system

Grade	Description
1	Palpable only with the patient standing and performing a concurrent Valsalva maneuver
2	Palpable with the patient standing, without a Valsalva maneuver
3	Visible through the scrotal skin and palpable with the patient standing

### Thermography and scintigraphy

Historically, scrotal thermography and scintigraphy were developed as noninvasive alternatives to venography. Thermography is a technique using a flexible film containing heat sensitive liquid crystals, which detects changes in scrotal temperature. Identification of varicoceles was based on the finding of hyperthermia over the region of the pampiniform plexus or testis.<sup>13</sup> A more contemporary pilot study evaluating diagnostic criteria defined the presence of varicocele in patients with pampiniform plexus temperature of  $\geq 34^{\circ}\text{C}$  or a difference in temperature of  $\geq 0.5^{\circ}\text{C}$  between the left and right pampiniform plexus.<sup>20</sup> However, other intratesticular pathologies, such as testicular cancer or infection/inflammation, can also result in ipsilateral hyperthermia, thereby decreasing the diagnostic specificity for identifying varicoceles.<sup>14</sup>

Labeled blood-pool scintigraphy detects varicoceles by demonstrating pooling of tracer on static images and reflux of tracer on dynamic images.<sup>15</sup> Unlike thermography, which can only identify the presence of varicocele, scintigraphy can evaluate and quantify the degree of spermatic vein reflux.<sup>16,17</sup> Improved detection of subclinical varicoceles with thermography and scintigraphy has been reported;<sup>16,18</sup> however, the variability in technique<sup>7,19</sup> and lack of standard diagnostic criteria make widespread practice impractical.<sup>20</sup> Both thermography and scintigraphy, however, would be supplanted by the increasing availability and capability of ultrasound imaging.

### Ultrasound

Scrotal ultrasound is currently the most established and widely used modality for the study of varicoceles. With the use of high-frequency ultrasound probes and the advent of Doppler technology, scrotal ultrasound has become increasingly easy to perform. It can provide high-resolution images and characterize vascular flow within the testes as well as adjacent structures. Given its high sensitivity and specificity (97% and 94% when compared to venography<sup>7</sup>), noninvasive nature, and relative ease of performance, scrotal ultrasound with Doppler examination has become the study of choice in evaluating scrotal and testicular pathology.<sup>21</sup>

Ultrasound examination of the scrotum is performed with the patient in the supine position. The scrotum is supported with a rolled towel and warmed ultrasound gel is placed on the scrotum. The examination is best performed with high-frequency linear array transducers, usually  $>7.5$  MHz. The examiner should have a low threshold to undertake further study of the varicocele with the patient upright and/or with a Valsalva maneuver.<sup>21,22</sup> The characteristic ultrasound appearance of a varicocele is that of “multiple, anechoic, serpiginous, tubular structures,” near the superior and lateral aspects of the testis (Figures 2 and 3).<sup>22</sup> Color, power, or spectral Doppler ultrasound with settings optimized for low flow velocities is commonly used to aid in the diagnosis of varicoceles.<sup>23</sup> Typical Doppler findings include venous flow at rest with intermittent or continuous flow reversal with Valsalva. Multiple grading systems exist for the purpose of classifying the dynamic sonographic findings of varicocele. The Sarteschi and Dubin classifications as shown in Tables 2 and 3 are among the most commonly used.<sup>33,34</sup> A scoring system published by Chiou *et al.* (Table 4) further improved the sensitivity and specificity of ultrasound in identifying clinically palpable varicoceles.<sup>25</sup>

While the general ultrasound appearance of varicoceles is agreed-upon, there are no standardized criteria regarding the extent of venous dilation or reflux that must be present to meet the definition of a varicocele. In a series of 217 men with clinical and subclinical varicoceles, venous diameter of  $>2.95$  mm during Valsalva was associated with sensitivity and specificity of 84% each for clinical varicocele.<sup>35</sup> In general, clinicians agree that clinically relevant varicoceles are more than 2.5–3 mm in diameter.<sup>24</sup> A scoring system including color Doppler ultrasound findings of vein dilation and flow reversal demonstrated a sensitivity of 93% and a specificity of 85% when compared to physical examination in a series of 127 testes.<sup>25</sup> The use of a Doppler stethoscope to detect spermatic vein reflux with a 9 MHz pencil probe has also been described.<sup>36</sup> Unfortunately, a series studying 118 patients without clinically palpable varicoceles found that Valsalva-induced reflux occurred on the left in 83% and right in 53%, dampening enthusiasm for the Doppler stethoscope’s continued use.<sup>40</sup>

Until recently, ultrasound evaluation of testicular parenchyma has been relatively simple. Gray-scale ultrasonography can provide a rough estimation of echotexture, calculate testicular volume, and identify parenchymal calcifications or tumors. Doppler ultrasound can provide information about parenchymal flow on a macrovascular level. However, the level of detail afforded by these studies is insufficient to detect varicocele-induced damage to the testicular parenchyma. More recent advances including real-time elastography

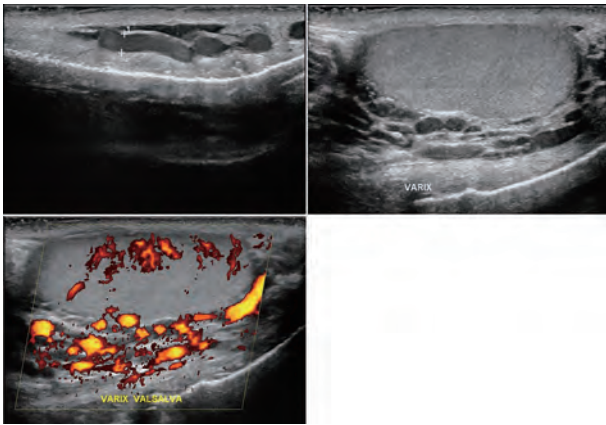


Figure 2: Typical ultrasound appearance of a left-sided grade 3 varicocele.

Table 2: Sarteschi classification

Grade	Description
1	Venous reflux at the emergence of the scrotal vein only during the Valsalva maneuver; hypertrophy of the venous wall without stasis
2	Supratesticular reflux only during the Valsalva maneuver; venous stasis without varicosities
3	Peritesticular reflux during the Valsalva maneuver; overt varicocele with early stage varices of the cremasteric vein
4	Spontaneous basal reflux that increases during the Valsalva maneuver, possible testicular hypotrophy, overt varicocele, and varicosities in the pampiniform plexus
5	Spontaneous basal reflux that does not increase during the Valsalva maneuver, testicular hypotrophy, overt varicocele, and varicosities in the pampiniform plexus

Table 3: Dubin classification

Grade	Description
0	Moderate, transient venous reflux during Valsalva maneuver (physiologic findings)
1	Persistent venous reflux that ends before the Valsalva maneuver is completed
2	Persistent venous reflux throughout the entire Valsalva maneuver
3	Venous reflux that is present under basal conditions and does not change during the Valsalva maneuver

Table 4: Chiou *et al.* scoring system

	Score
Maximum vein diameter (mm)	
<2.5	0
2.5–2.9	1
3.0–3.9	2
≥4.0	3
Plexus/sum of diameter of veins	
No plexus identified	0
Plexus (+) with sum diameter <3 mm	1
Plexus (+) with sum diameter 3–5.9 mm	2
Plexus (+) with sum diameter ≥6 mm	3
Change of flow velocity on Valsalva maneuver	
<2 cm s <sup>-1</sup> or duration <1 s	0
2–4.9	1
5–9.9	2
≥10	3
Total score	0–9

Total score of ≥4 defined as varicocele

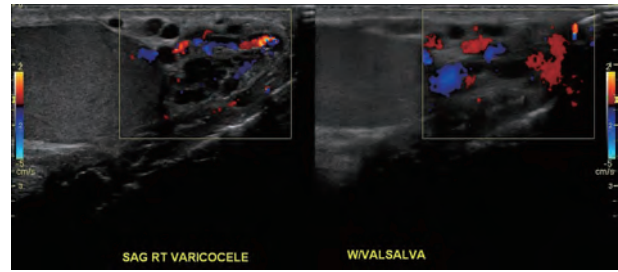


Figure 3: Typical ultrasound appearance of a right-sided grade 3 varicocele.

and contrast-enhanced ultrasonography have demonstrated the potential to correlate the presence of varicoceles to sonographic findings of testicular parenchymal damage and microvascular perfusion defects. Elastography involves postprocessing techniques to quantify testicular tissue stiffness based on measured strain. Contrast-enhanced ultrasound requires intravenous injection of micro-bubbles and allows for superior visualization of both micro- and macro-vasculature.<sup>23</sup> Findings such as increased tissue stiffness or loss of microvessel density may suggest early signs of testicular dysfunction. Although still investigational, these technologies may prove to be clinically useful in determining patients that may benefit from varicocele repair based on imaging findings.

**Computerized tomography (CT)**

Within the scope of varicocele evaluation, cross-sectional imaging is generally reserved for delineation of retroperitoneal anatomy. Approximately, 85%–90% of clinically significant varicoceles are palpated on the left.<sup>37</sup> However, a series evaluating 286 infertile men with physical examination, thermography, Doppler sonography, and venography found that inclusion of subclinical varicoceles resulted in 80.7% rate of bilateral disease, suggesting that infertility resulting from varicocele is often from a bilateral process.<sup>38</sup> The predisposition of left-sided palpable varicoceles is hypothesized to be a result of increased hydrostatic pressures generated by the perpendicular insertion of the left spermatic vein into the renal vein when compared to the oblique insertion of the right spermatic vein into the vena cava.<sup>26</sup> For this reason, classic teaching advises retroperitoneal imaging to rule out renal and retroperitoneal tumors in cases of isolated right-sided varicocele or acute onset of unilateral varicocele in an older patient. However, the overall yield is low, as only 2%–3% of renal tumors present as symptomatic varicoceles.<sup>27</sup>

The feasibility of varicocele evaluation using CT imaging has been reported but is impractical due to its significant radiation exposure.<sup>28</sup> Although lower dosed CT protocols are currently weighed against conventional protocols,<sup>29</sup> the low-cost and widespread availability of ultrasound still makes it the preferred initial imaging modality. The increasing resolution of CT imaging, however, has made it an excellent adjunctive modality to study retroperitoneal anatomy. Among a cohort of men identified with a retro-aortic left renal vein on CT imaging, 77% were found to have varicoceles on scrotal ultrasound, which supports the hypothesis of increased hydrostatic pressures resulting in higher incidence of left-sided varicoceles.<sup>30</sup> At this time, the role of CT imaging is minimal in diagnosis of varicocele and reserved for clinical scenarios where a retroperitoneal process or malignancy is suspected.

**Magnetic resonance imaging (MRI)**

Though not common in the literature, there have been some published studies regarding the use of magnetic resonance imaging (MRI) for the diagnosis and imaging of varicoceles. Proposed benefits of MRI in



comparison to other existing imaging modalities include most notably, lack of operator dependency, and highly detailed delineation of the retroperitoneal anatomy. When a retroperitoneal cause of varicocele is suspected, MRI may play a role in confirming and further evaluating this cause. In particular, MR angiography has been proposed to study varicoceles secondary to nutcracker syndrome.<sup>31</sup>

Current areas of research include the use of MRI to evaluate the sequelae of varicoceles, providing important prognostic information to be weighed in considering management options. Diffusion-weighted MRI of the testes was evaluated in a cross-sectional study of 25 subjects with clinically apparent varicoceles and 25 healthy control subjects. Apparent diffusion coefficient (ADC) values were significantly lower in patients with varicocele compared to healthy controls. Based on ADC values, the series demonstrated 90% sensitivity and 96% specificity for the diagnosis of these varicoceles while potentially providing the ability to detect fibrosis of the testicular parenchyma.<sup>32</sup>

## CONCLUSIONS

The introduction of radiographic modalities has vastly improved the ability to detect or confirm the presence of varicoceles. The use of imaging in varicocele has the potential to evolve if early signs of testicular dysfunction can be identified to assist in selection of patients for varicocele repair. Thermography and scintigraphy are of increasingly historic significance while venography and cross-sectional imaging still offer additional information in complex varicocele cases. Ultrasound has emerged as the de facto adjunct to clinical examination due to its inexpensive, widespread, and noninvasive characteristics. The most recent AUA and ASRM guidelines do not recommend the routine use of scrotal ultrasound to diagnose varicoceles. Instead, the role of scrotal ultrasound is reserved for situations in which physical examination is inconclusive, such as patients with large body habitus or thick scrotal skin precluding accurate examination.<sup>3,4</sup> On the contrary, the European Association of Urology (EAU) recommends confirmation by color Duplex ultrasound after the diagnosis of varicocele is made by clinical examination.<sup>39</sup> The widespread use of scrotal ultrasound, however, has resulted in increased detection of subclinical varicoceles. The question of whether subclinical varicoceles should be repaired is discussed elsewhere in this issue.

## AUTHORS CONTRIBUTIONS

All authors had equal contribution to the conception, research, writing of, and review/approval of the manuscript.

## COMPETING INTERESTS

None of the authors declared competing financial interests.

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