Varicoceles

Varicocelectomies have been performed in clinical practice for more than 50 years, and over time there have been several significant advances in surgical techniques and molecular/genetic studies to explain the pathophysiology. In this issue of The Journal Schwentner et al (page 1049) address surgical modification of the subinguinal microsurgical varicocelectomy and Lee et al (page 1045) present a molecular investigation of the veins that were acquired from patients undergoing varicocelectomy or hernia surgery. Both of these articles are timely and deserve further discussion.

The Best Practices Group of the American Urological Association noted that most experts perform inguinal or subinguinal varicocelectomies with optical magnification,[1] and Schwentner et al referred to these procedures as the gold standard. Marmar et al were the first to describe the subinguinal microsurgical varicocelectomy, and they preserved the testicular artery, minimized morbidity, reduced recurrence and eliminated hydrocele formation.[2] They observed lymphatic vessels on the outer cremasteric fascia, and within the spermatic cord when the fascia was opened and retracted laterally. In the original experience with 71 patients they reported recurrence in 4 patients (5.6%), of which 2 were palpable and 2 were only audible. There were no clinical hydroceles. In a subsequent report by the same group, 466 patients had 606 subinguinal microsurgical varicocelectomies,[3] and there were 10 patients with a recurrence (2.1%), of which 5 were palpable and 5 were only audible. The palpable recurrence rate was only 0.82% per unit. There was only 1 clinical hydrocele on a patient who had prior inguinal surgery.

Schwentner et al performed 50 subinguinal microsurgical varicocelectomies and injected isosulfan blue preoperatively into half of these men to identify the lymphatic during the surgery. The recurrence rate was 4.0% of all patients. After 1 year there were no postoperative hydroceles in the stained group compared to 4 hydroceles (16%) in the unstained group. The hydroceles were all detected by ultrasonography rather than by palpation. It was unclear whether these lesions were clinically meaningful because they were managed by puncture rather than open surgery, which is usually the procedure of choice for significant lesions. Since the incidence of recurrence and clinically significant hydroceles is reported to be low in larger series of subinguinal microsurgical variocelectomies,[2–4] the need for lymphatic staining may not be necessary with greater experience. However, the lymphatic staining technique proposed by Schwentner et al may help microsurgeons gain early experience with identification of the spermatic cord lymphatic vessels.

Lee et al presented a molecular study of 8 men with visible grade III varicoceles treated with varicocelectomy, and 6 controls treated with hernia surgery. They examined sections of the internal spermatic veins for hypoxia-inducible factor-1α. Since most investigators agree that varicoceles are associated with retrograde blood flow into the internal spermatic veins, Lee et al hypothesized that this marker was a measure of stasis and hypoxia. They reported a 7-fold increase of this marker in the veins of each of the patients with varicocele, and concluded that hypoxia may be a cause of hypospermatogenesis, serving as a stimulus for vascular endothelial growth factor and angiogenesis. Although these data were limited, they provide encouragement for further studies on molecular markers in the veins of patients with varicocele because of their proximity to testis tissue. The expectation was that this approach may lead to a greater understanding of the pathophysiology of these lesions and aid in the development of innovative treatment plans. For example, one such study reported increased nitric oxide in the dilated spermatic veins of adolescents with palpable varicoceles.[5] After identification of similar molecular markers in testis tissue, others administered melatonin as a potent free radical scavenger of nitric oxide.[6] At this point several investigators have proposed a variety of medical therapies for specific abnormal processes related to spermatogenesis that have been identified by abnormal markers in the testis tissue. A full discussion of this topic is beyond the scope of this editorial, but we will summarize some of our recent work that is pertinent to the topic.

In our laboratory we used testis tissue to study molecular/genetic markers. First we developed a minimally invasive technique for a percutaneous testis biopsy with ultrasonic control.[7] In the past this tissue was used for histology alone, but we have studied 17 molecular/genetic markers related to spermatogenesis and apoptosis within testis tissue. Our findings may explain some of the clinical diversity among patients with varicocele.[8] Some men with varicoceles are fertile and they seemingly do not demonstrate any molecular/genetic defects within the testis tissue, others with limited defects improve after varicocelectomy, whereas others with extensive defects may not improve after surgery. Some markers may be used to predict the outcome of varicocelectomy. When testis tissue demonstrated increased tissue cadmium and microdeletions of the L-type, voltage dependent calcium channel, the positive predictive values were 86.4% and 92.8%, respectively, for a less than 50% increase in sperm density after varicocelectomy.

It seems that the time has come to be more selective regarding varicocelectomies for infertile men. Ultrasonically controlled testis biopsies may be acquired early in the evaluation to study specific markers associated with abnormal processes, and to help develop specific medical therapies and/or propose surgery for those men with a realistic chance of improvement. Although the acquisition of internal spermatic veins requires surgery, testis tissue may be obtained safely in an office setting. Nevertheless, the work of Lee et al

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points the way toward the era of molecular/genetic investigations on relevant tissue of infertile men.

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REFERENCES

1. Jarow, J. P., Sharlip, I. D., Belker, A. M., Lipshultz, L., Sigman, M., Thomas, A. J. et al: Best practice policies for male infertility. J Urol, **167:** 213, 2002
2. Marmar, J. L., DeBenedictis, T. J. and Praiss, D. E.: The management of varicoceles by microdissection of the spermatic cord at the external inguinal ring. Fertil Steril, **43:** 583, 1985
3. Marmar, J. L. and Kim, Y.: Subinguinal microsurgical varicocelectomy: a technical critique and statistical analysis of semen and pregnancy data. J Urol, **152:** 1127, 1994
4. Goldstein, M., Gilbert, B. R., Dicker, A. P., Dwosh, J. and Gnecco, C.: Microsurgical inguinal varicocelectomy with delivery of the testis: an artery and lymphatic sparing technique. J Urol, **148:** 1808, 1992
5. Romeo, C., Ientile, R., Santoro, G., Impellizzeri, P., Turiaco, N., Impala, P. et al: Nitric oxide production is increased in the spermatic veins of adolescents with left idiopathic varicocele. J Pediatr Surg, **36:** 389, 2001
6. Semercioz, A., Onur, R., Orgas, S, and Orhan, I.: Effects of melatonin on testicular tissue nitric oxide level and antioxidant enzyme activities in experimentally induced left varicocele. Neuro Endocrinol Lett, **24:** 86, 2003
7. Marmar, J. L. and Benoff, S.: The safety of ultrasonically guided testis aspiration biopsies and efficacy of use to predict varicocelectomy outcome. Hum Reprod, **20:** 2279, 2005
8. Rosenthal, J., Marmar, J. L., and Benoff, S.: The incidence of molecular/genetic markers in testis tissue from severely and mildly oligospermic men with varicoceles and infertility. Fertil Steril, **84:** S55, 2005