

EDITORIAL: NEW SCIENTIFIC INFORMATION RELATED TO VARICOCELES

The American Urological Association and American Society of Reproductive Medicine jointly convened Best Policy Practice Groups for Male Infertility and recently stated, "Varicocele repairs may be considered the primary treatment option when a man with a varicocele has suboptimal semen quality and a normal female partner."¹ They considered percutaneous embolization and surgery, and noted that most experts performed inguinal or subinguinal microsurgical repairs to maximize preservation of arterial and lymphatic vessels while reducing the chances of persistence or recurrence. Although these comments represent the considered opinion of 12 experts and 125 consultants from the field of male infertility, anyone familiar with varicoceles knows that discussion of the pathophysiology and management continues to be hotly debated.

Any new scientific information that sheds light onto varicoceles should be welcomed, such as the articles in this issue of *The Journal of Urology*.[®] They are timely and may add new molecular and anatomical information to the varicocele literature. Fujisawa and Ishikawa (page 2363) address the relationship of varicoceles to apoptosis by monitoring soluble Fas concentrations in seminal plasma to study the Fas signaling system in relation to the hypospermatogenesis of varicoceles. Hopps et al (page 2366) characterized the vascular anatomy of the spermatic cord at the subinguinal and inguinal levels, and related this information to microsurgical varicocele repairs.

APOPTOSIS, SPERMATOGENESIS AND VARICOCELES

Spermatogenesis is an ongoing proliferative process that leads to the production of millions of spermatozoa each day. Apoptosis has been recognized as a normal process that may determine the ultimate sperm output, and this process seems to be increased among infertile men with varicoceles. Several studies on laboratory animals and humans have suggested that varicoceles can induce apoptotic pathways because of heat stress,² androgen deprivation³ and accumulation of toxic materials.⁴ In human studies Simsek et al documented increased apoptosis among patients with varicocele.⁵ They reported that the mean percentage of apoptotic cells per total germ cells per high power field was 14.7% for men with varicoceles compared with 2% for controls. In a report on ejaculated sperm up to 10% of the sperm cells in the ejaculate of men with varicoceles were apoptotic compared with 0.1% among fertile controls.⁶ In testis biopsy material from men with varicoceles Hurley et al correlated the number of apoptotic cells in the seminiferous tubules to the cadmium levels.⁷

Fujisawa and Ishikawa investigated a potentially interesting marker for apoptosis among patients with varicocele. Recognizing that the soluble form of Fas (s-Fas) can block Fas dependent apoptosis, they screened seminal plasma of oligospermic men with varicoceles, oligospermic men without varicocele and normal controls for levels of s-Fas and s-Fas L. S-Fas L was undetected in all cases while s-Fas was specifically lower only in those with varicocele. The lower levels of s-Fas were reversed by varicocelectomy.

Although it seems that the Fas/Fas L system is a major regulator of normal spermatogenesis, a recent study suggests that other molecular systems may be operative. For example, testicular histology among men with varicoceles and oligospermia is characterized by maturation arrest at the spermatid stage,⁸ and Fas has been reported to be up-regulated in patients with post-meiotic germ cell arrest.⁹ In addition, cad-

mium is an inducer of the Fas signaling pathway,¹⁰ and there seems to be an increase in tissue and seminal cadmium among men with varicoceles.⁴ In somatic cells the Fas system has been correlated to levels of heat shock protein^{11,12} but among men with varicoceles there seems to be an inconsistent heat shock protein response,¹³ which underscores the heterogeneity of the mechanisms producing hypospermatogenesis with varicoceles. These inconsistencies may explain why only 67% of men tested by Fujisawa and Ishikawa responded to varicocele surgery with an associated increase in s-Fas in seminal plasma.

Despite these data, several questions remain unanswered in this study. What is the source of s-Fas in seminal plasma? Why do s-Fas levels change with varicocele repair? Do the levels of testicular apoptosis reduce following varicocelectomy? Furthermore, there is still some controversy whether Serotoli cells or germ cells express Fas.^{14,15} Nevertheless, the article by Fujisawa and Ishikawa should stimulate future investigations into the mechanisms regulating apoptosis with varicoceles.

ANATOMY OF THE VARICOCELE

A variety of methods are now available for the treatment of varicoceles, including percutaneous embolization, inguinal microsurgery, laparoscopy and microsurgical repairs. Since the article by Hopps et al relates to the subinguinal anatomy, I will evaluate these anatomical findings with regard to varicocele microsurgery.

The early procedures for varicocelectomy were performed for pain, for which Palomo described high ligation of the entire spermatic cord above the internal ring including the internal spermatic artery.¹⁶ In 1955 Tulloch adapted this procedure for the management of infertility,¹⁷ and other clinicians have followed the example of this classic publication by continuing to use varicocelectomy for this purpose. With regard to the high ligation, some clinicians have challenged the basic premise of this procedure because it involved the entire spermatic cord including the artery. However, recently Sun et al used colored Doppler after this surgery and demonstrated persistent blood flow to the testicles,¹⁸ presumably because of arterial flow from the cremasteric and vasal arteries.¹⁹ Furthermore, 2 widely quoted prospective randomized trials on varicocelectomy involved use of high ligation to treat varicoceles.^{20,21} Both studies revealed a statistically significant improvement in sperm density after surgery, and 1 study demonstrated statistically improved pregnancy rates.²⁰ Others noted that there may be recurrent or persistent reflux following high ligation because of retrograde blood flow into the cremasteric veins.²² These failed cases may do well with secondary subinguinal varicocelectomy because Hopps et al documented access to dilated external spermatic veins at the subinguinal level in 92%.

The inguinal approach represents the oldest method for varicocele treatment as described by Ivanissevich and Gregorini.^{23,24} They ligated the internal spermatic veins within the inguinal canal for the management of pain. This technique was adapted and popularized for the treatment of infertility by Dubin and Amelar but there were complications.²⁵ Hydrocele formation ranged between 7% and 39%²⁶ and testicular atrophy occurred in rare cases. Disruption of the arteries at this level is significant because the arterial collaterals are limited below the inguinal region.²⁷ These findings are consistent with those of Hopps et al who noted a

mean of 3.2 lymphatic vessels per cord that needed preservation during the inguinal dissection. Furthermore, Hopps et al noted that 67% and 25% of cases had only 1 solitary artery in the inguinal and subinguinal locations, respectively, which required careful microdissection to avoid injury.

To preserve the arteries and avoid lymphatics, some investigators introduced the use of optical aids during microsurgical varicocelectomies. We introduced the subinguinal microsurgical varicocelectomy with ligation and sclerosis,²⁸ and Goldstein et al modified the microsurgical technique with delivery of the testis in search of scrotal collaterals including the gubernacular veins.²⁹ Followup data by Marmar and Kim indicated virtually no hydrocele formation with the subinguinal technique and a palpable recurrence rate of only 0.8%.³⁰ These results seem comparable to cases involving delivery of the testicle. Although, Hopps et al report that 71% to 79% of their patients had enlarged veins within the gubernaculum they questioned the role of these veins in the pathophysiology of varicocele recurrence. They cite Murray et al who noted scrotal collaterals in 7% of recurrent varicoceles³¹ but these scrotal recurrences were found only in cases managed by percutaneous occlusions.

Hopps et al advocate occlusion of all veins greater than 2.0 mm including the deferential vein. However, most clinicians have avoided ligation of this vein for several reasons. The deferential vein drains into the internal iliac system which has never consistently demonstrated reflux during venography of patients with clinical varicoceles. Furthermore, after varicocelectomy the deferential vein may represent an important source of drainage from the testis. The deferential vein also may be adherent to the deferential artery which is an important source of arterial flow following varicocelectomy. Recently, Amelar cited that the deferential artery may be the only source of flow to the testes after varicocelectomy and particularly cautioned against vasectomy among men who had undergone varicocelectomy because during vas ligation the deferential artery will be ligated, thereby introducing a potential cause of testicular atrophy.³²

During subinguinal dissections Hopps et al note that the internal spermatic arteries were often surrounded by a dense complex of adherent veins. These findings suggest that aggressive dissection of these structures may injure the arteries. In fact, Chan et al reported a 0.9% accidental injury to the testicular arteries during microsurgical varicocelectomy,³³ and Kumar et al actually repaired an artery during microsurgical varicocelectomy when the artery was adherent.³⁴ Therefore, a less aggressive dissection may be warranted and use of sclerosing agents to obliterate venous collaterals adjacent to the artery may be quicker, simpler and less damaging.²⁸

NEW SCIENTIFIC INFORMATION

In clinical practice several situations related to varicoceles have been confusing. For example, there are some men with varicoceles who father children and have normal semen analyses. There are other men who do not improve despite adequate surgical repair of varicoceles. In an attempt to resolve some of these clinical issues, we introduced the concept of the "2nd hit hypothesis."^{35,36} The varicoceles negatively influence spermatogenesis through retrograde blood flow, increased testicular heat and increased interstitial pressure, while the molecular/genetic defects may actually determine the extent of infertility. According to the 2nd hit hypotheses, if molecular/genetic defects are absent, men with varicoceles may be fertile. If the molecular/genetic defects are extensive then these men will not improve after varicocele treatment. If the defects are limited, these men may benefit from the varicocele repair. The challenge for the future will be to identify in advance of surgery patients with these molecular/

genetic markers who will have the best opportunity for improved testicular function following varicocele repair.

Recently, reproductive endocrinologists have been offering in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) as another clinical alternative. However, studies indicate that IVF/ICSI seems no more effective than varicocelectomy, but more expensive than the surgical procedure. In their meta-analysis Penson et al reported that the probability of a live birth after varicocelectomy was 29.7% (with 1% having twins) compared to 25.4% after IVF/ICSI (with a multiple gestation rate of 39%).³⁷ In a separate study Schlegel reported that the cost per delivered baby with IVF/ICSI was \$89,091 compared to \$26,268 after varicocelectomy.³⁸ Thus, varicocele surgery seems desirable for selected varicocele cases.

Although a large body of literature suggests improved semen parameters and fertility following varicocelectomy,³⁹ some investigators have challenged the benefit of these procedures because these are case controlled studies rather than prospective randomized trials. The statistical evaluation of these data is the subject of an ongoing debate. Recently, Evers and Collins reported a meta-analysis including 7 prospective randomized trials that evaluated varicocelectomy and pregnancy outcomes.⁴⁰ They claimed that there was insufficient evidence to conclude that treatment of clinical varicocele improved the likelihood of conception for couples with male infertility. They stated that routinely treating men from subfertile couples was ill advised.

This conclusion is regrettable because the data in the meta-analysis were questionable. Specifically, several patients in the study groups had normal semen analysis. Of the 7 studies 4 included men with subclinical varicoceles. None of the patients was screened for molecular/genetic abnormalities. Two of the studies had questionable data for the outcome of controls, including one with an accumulative pregnancy rate for controls of 47%, and the other had a 24.5% pregnancy rate with counseling of controls that actually included optimization of female reproduction functions. The pregnancy rates for controls among the remaining studies in the meta-analysis ranged between 4.5% and 10%. Finally, the varicocele treatment did not include microsurgical procedures as suggested by the Best Practice Study Groups, and there was limited followup information concerning recurrences with either high ligation or embolization.

CONCLUSIONS

There is a lot to learn about male infertility from the varicocele model. I hope that future studies may consider the molecular testing set forth by Fujisawa and Ishikawa and the anatomical information described by Hopps et al to develop new scientific information related to varicoceles. Perhaps, future investigators will construct prospective randomized trials with more thoughtful entry criteria and surgical considerations. Such investigations will advance the basic fund of knowledge regarding the pathophysiology of varicoceles and the surgical procedures for correction of these lesions.

Joel Marmar
Division of Urology
Robert Wood Johnson Medical School at Camden
Camden, New Jersey

and

Susan Benoff
Fertility Research Laboratories
North Shore-Long Island Jewish Research Institute
Manhasset, New York

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