

Varicocele-induced infertility: Newer insights into its pathophysiology

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ABSTRACT

The association between varicoceles and male infertility has been known since the 1950s; however, the pathophysiology of the process remains uncertain. The primary proposed hypotheses involve hyperthermia, venous pressure, testicular blood flow, hormonal imbalance, toxic substances, and reactive oxygen species. It is difficult to identify a single or dominant factor, and it is likely that many of these factors contribute to the infertile phenotype seen in clinical practice. Moreover, patient lifestyle and genetic factors likely affect patient susceptibilities to the varicocele insult. While the current studies have weaknesses, they provide building blocks for futures studies into the pathophysiology of the varicocele.

Key words: Varicocele, reactive oxygen species, hot temperature

INTRODUCTION

The term varicocele was originally coined by British surgeon T.B. Curling in 1843 to describe the pathologic dilation of veins of the spermatic cord.^[1] The earliest descriptions of treatment for varicoceles come from the Roman encyclopedist Celsus, who practiced from 25-35 AD. While early varicocelectomy was performed for pain or cosmetic improvement, it was not until 1952 that the association between varicocele and infertility was recognized. T.S. Tulloch published a case report of a man with testicular biopsy-proven maturation arrest in whom sperm count improved after varicocelectomy.^[2] Other reports of similar findings soon followed, thus shifting the focus of varicoceles from pain to subfertility.^[1] Today

approximately 37,000 varicocelectomies are performed annually in the U.S.^[3]

Varicoceles develop from a reversal of blood flow within the internal spermatic and cremasteric veins.^[4] There are three main anatomic explanations for the origins of varicoceles.^[5] The first theory emphasizes the fact that the drainage of the testicular veins differs between the right and left. While the right enters directly into the inferior vena cava at an oblique angle, the left joins the left renal vein at a right angle. This difference is thought to result in increased hydrostatic pressure on the left resulting in dilation of the pampiniform plexus. The second theory postulates that an absence of competent valves leads to varicoceles. In fact, in a study of 659 men with varicoceles, 73% were found to have absent venous valves when assessed by contrast venography.^[6] The final theory suggests that compression of the renal vein between the aorta and superior mesenteric artery increases the hydrostatic pressure in the testicular vein via a “nutcracker” effect.^[5]

Epidemiologic studies suggest that approximately 15% of all men in the general population have a clinical varicocele. In contrast, between 19–41% of men evaluated for infertility are found to have varicoceles.^[5] Interestingly, the rate of varicocele is increased in men with secondary infertility to approximately 70%, suggesting that varicoceles may cause a progressive decline in fertility potential.^[7] Most commonly, varicoceles arise sometime after puberty as demonstrated by a study which found no varicoceles in boys six to nine years of age, with increasing numbers in boys aged 10-14 years.^[8] There is also evidence for a genetic component to

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Access this article online

Quick Response Code: 	Website: www.indianjurol.com
	DOI: 10.4103/0970-1591.78428

the disease as clinical varicoceles are found in higher rates in first-degree relatives (i.e. brothers, fathers) of patients with varicoceles compared to fertile controls.^[9,10]

In clinical practice, most reports show persistent abnormality of sperm count, motility, or morphology.^[4,5,11] The “stress pattern,” which consists of elongated, tapered sperm head and amorphous cells, is commonly, though not consistently, attributed to varicocele patients.^[12] Even using the current “strict” morphology criteria, men with varicoceles are found to have a lower number of morphologically normal sperm.^[13] In the rat model, varicoceles were found to increase germ cell apoptosis which may contribute to oligospermia.^[14]

That some men with a clinical varicocele are infertile despite normal semen morphology and concentrations caused some investigators to study if sperm function was compromised in the varicocele patient. Many studies have focused on the acrosome reaction during zona pellucida binding.^[15,16] Indeed, investigators showed that 45% of infertile men with a varicocele had an abnormal acrosome reaction, which could be normalized for many of these men after varicocelectomy.^[15]

Many investigators have reported that treatment of varicocele improves semen parameters, pregnancy rates, and intrauterine insemination pregnancy and birth rates.^[17-19] However, there is controversy regarding the efficacy of varicocelectomy in the management of infertility. Much of the uncertainty with regards to treatment likely stems from the heterogeneity of the entity itself. Varicoceles exist in different sizes with grading based on ultrasonographic and physical examination characteristics. Within these grades, there are ranges of semen abnormalities. Moreover, while some men with infertility have varicoceles and abnormal semen parameters, men with normal fertility and normal semen can also harbor the identical spermatic cord pathology. Given the clinical variation, it is perhaps not surprising that there is some uncertainty as to the efficacy of repair. While some systematic reviews of available literature suggested no benefit of varicocelectomy, other reviews do suggest efficacy of surgical repair.^[20-23] The main difference in results involves inclusion criteria of the studies analyzed in the meta-analyses. The reviews suggesting benefit to varicocelectomy are limited to studies of men with clinical varicoceles with abnormal semen parameters—the men most often offered varicocelectomy today.^[22,23]

In addition to the debate surrounding the clinical benefit of varicocelectomy, another controversial aspect of the varicocele regards its pathophysiology. The primary proposed hypotheses involve hyperthermia, venous pressure, testicular blood flow, hormonal imbalance, toxic substances, and reactive oxygen species.^[4,5,11,24,25] It is difficult to identify a single or dominant factor, and it is likely that many of these etiological causes contribute to the infertile phenotype

seen in clinical practice. Our current understanding of the pathophysiology of the varicocele is built upon both human data as well as animal models. While the current studies may have inherent weaknesses, they do provide building blocks for futures studies into the pathophysiology of the varicocele.

PROPOSED MECHANISMS

Hyperthermia

Scrotal temperature is maintained a few degrees below body core temperature in order to optimize the environment for normal testicular function by the countercurrent heat exchange system first postulated by Dahl and Herrick in 1959.^[26] The inflowing arterial blood from the testicular artery is cooled in the spermatic cord by returning venous blood in the pampiniform plexus. A dilation of the venous plexus would then disrupt the efficiency of this system. The explanation for why a left-sided varicocele affects the function of the contralateral testis is unclear, but any unilateral pathology may be transmitted via the collateral drainage that exists between the testes.^[11,27]

From experiments involving induced cryptorchidism or testicular hyperthermia as a means of contraception as well as data from recreational wet heat exposure, it is apparent that testicular heating impairs semen parameters.^[28-30] There is conflicting data in humans, however, as to the effects on scrotal temperature of a varicocele. Several reports found no difference in scrotal temperature between infertile men with and without varicocele.^[31,32] In contrast, Shiraishi and colleagues found abnormal scrotal temperature regulation of men with varicoceles compared to normal men.^[33] In addition, Goldstein and Eid found that infertile men with varicoceles had higher scrotal surface temperatures compared to control subjects.^[34] The conflicts in studies may be due in part to the fact that the scrotal temperature is known to vary widely with changes in body position and activity over a 24-h period.^[35]

Just as there are conflicting reports of preoperative temperature regulation, postoperative findings of scrotal temperatures also vary. While some studies show a restoration of normal thermoregulation after varicocelectomy, others found no difference in scrotal temperatures despite improvements in semen parameters.^[36,37]

Goldstein and Eid also measured intratesticular temperatures using a 29G needle inserted directly into testicular tissue and found significant elevations in temperatures in varicocele patients compared to controls.^[34] Animal studies have also investigated intratesticular temperature changes caused by varicocele. Saypol *et al.*, used both a dog and rat model to show that surgical impairment of testicular venous blood flow either by partial occlusion of the renal vein or ligation of the testicular vein led to increases in bilateral

intratesticular temperatures.^[38] Other investigators also showed that such testicular thermal derangements caused by induced varicoceles could be reversed following varicocele repair in both the rat and rabbit model.^[39,40] Animal models must be viewed with some skepticism, as the acute surgical induction of a varicocele does not mirror the chronic process that exists in man.

Cryptorchidism, both congenital and experimental, provides a more chronic model of testicular hyperthermia and may provide a more accurate representation of the putative varicocele temperature insult. In an experiment meant to explore the utility in male contraception, adult volunteers had an artificial cryptorchid state created by wearing an athletic supporter during the day to hold the testes in the inguinal canal.^[28,41] After several months, the investigators found sperm concentration, motility and morphology all diminished. Within 12 months of discontinuation of the protocol, the men's semen parameters returned to baseline. It is interesting to note that histological changes of both germ cells and seminiferous tubules obtained from testis biopsies are similar between men with varicocele or cryptorchidism.^[42,43]

The mechanism for how heat affects spermatogenesis remains speculative. There is evidence that heat may affect androgen production which can have deleterious effects on the maintenance of sperm production.^[33] Rajfer *et al.*, showed that experimentally induced varicocele can lead to impairment of 17,20-desmolase and 17 α -hydroxylase enzymes of the steroid biosynthetic pathway.^[44] In addition, some data also suggests that scrotal hyperthermia increases the rate of germ cell apoptosis.^[45] Investigators have explored several candidate genes that may regulate this process including cold-inducible RNA binding protein (Cirp), whose levels are reduced with testicular hyperthermia (e.g. as occurs as with cryptorchidism or hot baths) as well as heat shock proteins whose levels are induced by hyperthermia.^[46,47]

Venous pressure

Another likely pathway by which a varicocele impairs testicular function regards venous pressure. While increased venous pressure could plausibly limit arterial inflow in an effort to maintain normal intratesticular pressures, the experimental evidence of such mechanisms is conflicted.^[48,49] Sweeney used a hamster testis model to measure intratesticular vascular pressure and found that subtunical testicular capillaries were sensitive to increase in venous pressure.^[49] With such derangement of intracapillary pressures, the hydrostatic and oncotic pressures that regulate the osmotic regulation of metabolic products could be compromised.

Another consequence of increased venous pressure involves delayed vascular drainage. Radioisotope and retrograde

venography studies have demonstrated delayed vascular washout in men with varicoceles.^[22,50,51] Such venous stasis likely contributes to thermal regulatory defects and accumulation of toxins thought to play a role in the pathophysiology of varicocele.

As mentioned above, another possible consequence of altered venous blood flow due to varicoceles involves derangements in testicular blood flow. Using the dog model, studies showed that testicular blood flow increased after surgically induced varicoceles after only three months and returned to normal after repair.^[38] Similar studies in the rat model showed increased testicular blood after only one month.^[38,39,52] Investigators have postulated that such an increase in testicular blood flow could overwhelm the testicular countercurrent thermal exchange system leading to testicular hyperthermia.^[38]

In contrast, other studies have showed decreased testicular blood flow in the rat model of varicocele when measured up to four weeks postoperatively.^[53] A similar decrease in blood flow was found in the primate model at five months postoperatively but gradually returned to normal over a two-year period.^[54] Human studies have not shown such differences in blood flow.^[5]

Hormonal imbalance

Several studies have suggested that infertile patients with varicoceles have lower serum testosterone concentrations, leading to the hypothesis that varicoceles may alter Leydig cell function. Animal models of varicocele have demonstrated reduced serum testosterone levels in dogs and decreased intratesticular testosterone levels in rats.^[55,56] Moreover, Rajfer noted decreased levels of 17,20-desmolase and 17 α -hydroxylase in a rat model of varicocele, suggesting that testosterone synthesis itself may be compromised.^[44]

While some reports have suggested that serum testosterone levels are lower in men with varicoceles, other reports have questioned such claims.^[57,58] Certain groups have attempted to identify specific men with varicoceles most at risk for low testosterone levels, such as men over 30.^[59] In 1992, the results of a World Health Organization (WHO) multi-center study of varicoceles concluded that men over the age of 30 with a varicocele had lower serum testosterone levels compared to men under 30 with a varicocele.^[59] As such a pattern is not seen in men without varicoceles, the WHO concluded that a varicocele represents a progressive lesion with a time-dependent effect on Leydig cell function.

The true androgen-mediated affect of the varicocele, however, may relate more to the intratesticular testosterone concentration rather than serum level. Rajfer and colleagues noted a decrease in intratesticular testosterone in the rat varicocele model, while no effect was noted on serum androgen levels.^[44] Indeed, intratesticular levels of

testosterone are higher than serum levels.^[60] The androgen receptor may also play an important role in the impairment in spermatogenesis caused by a varicocele.^[4] Defects in the androgen-mediated pathway may make a man more sensitive to alterations in the intratesticular hormonal milieu compromised by a varicocele.^[4,25]

Despite lower serum testosterone levels in men with varicoceles, the androgen levels of men with varicoceles do remain within most laboratories' normal values.^[57,61] Investigators have suggested that Leydig cell hyperplasia may compensate for individual Leydig cell impairment.^[62] Others have suggested that Leydig cell numbers are decreased as well as demonstrating histologic changes in cell morphology with a varicocele.^[25] Some studies have also looked to the pituitary response to gonadotropin-releasing hormone as a more sensitive test of Leydig cell function, arguing that men with a larger release of LH or FSH in response to GnRH are more likely to show clinical improvement after varicocelectomy.^[63]

The effect of varicoceles on Sertoli cell function has also been assessed. Changes in serum inhibin B levels are controversial, with contrasting findings of both elevated and reduced levels in several studies.^[64,65] However, one group reported impaired expression of Sertoli cell E-cadherin and alpha-catenin proteins in men with varicoceles, postulating a compromise in the blood-testis barrier.^[66]

Controversy also exists as to whether varicocelectomy can reverse such endocrinopathies with some investigators suggesting an improvement of hormonal derangements, while others failed to show any difference between pre and postoperative values.^[5,67,68]

Toxic substances

Studies have implicated both intrinsic and extrinsic substances as possible culprits in the pathophysiology of varicocele. An accumulation of endogenous substances from the renal or adrenal circulation have been posited to impair testicular function. Indeed, venography in men with varicoceles demonstrates an increase in venous reflux in men with varicoceles, which may contribute to an accumulation of metabolic products from the renal or adrenal venous circulation.^[69,70] Some investigators have postulated that higher concentrations of catecholamines from the adrenal circulation could lead to testicular vasoconstriction and thus impaired testicular blood flow; however, the lack of any other adrenal products found in abnormal concentrations in the varicocele testis argues against such a hypothesis.^[71,72]

A well-studied exogenous toxic agent known to affect spermatogenesis relates to smoking.^[4] Cigarette exposure negatively impacts semen parameters in men.^[73] Similarly, in rat varicocele models, nicotine exposure impaired spermatogenesis.^[74] Cadmium has also recently garnered increased attention as a possible explanatory agent in the

pathophysiology of varicocele. Cadmium workers and cigarette smokers are known to have increased serum levels of cadmium. Interestingly, men with varicoceles may have seminal cadmium levels as high as those from smokers.^[75]

Cadmium exposure and its accumulation are known to impair spermatogenesis, sperm function and lead to impaired reproductive potential in men.^[76] Oral administration of cadmium to rats led to impaired sperm count and motility as well as germ cell apoptosis and Leydig cell dysfunction.^[25,77] Investigators have found evidence that cadmium levels predict impaired testicular function in men with varicoceles and can help predict responsiveness to varicocelectomy.^[25,78]

Evidence suggests, furthermore, that genetics influence murine susceptibility to testicular damage by cadmium. Differential expression of the zinc transporter ZIP8 apparently fuels this difference, which may provide a biologic explanation as to why varicocele affects men differently.^[79]

Reactive oxygen species

Production of reactive oxygen species (ROS) is necessary for normal sperm function via intracellular signal transduction where it facilitates capacitation, the acrosome reaction, and attachment to the oocyte.^[80,81] While a balance normally exists in the seminal plasma between ROS production and removal, pathologic conditions can lead to an excess production of ROS.^[82,83] Such an accumulation of ROS can result in peroxidation of sperm membrane lipids, altering sperm morphology and motility.^[82,84] Indeed, there is an inverse relationship between semen ROS and sperm motility.^[85]

While most studies show that seminal ROS levels are higher in men with varicoceles than controls, others have questioned the association between varicoceles and ROS levels.^[86-88] Experimental evidence shows that the administration of oral antioxidants (i.e. glutathione, carnitine) can improve semen parameters in men with varicoceles, suggesting the importance of ROS in the varicocele's pathophysiology.^[89-91]

Similar to other proposed mechanisms, the damaging effects of hypoxia may be exacerbated by cofactors within individual patients. Genetic and lifestyle factors may predispose patients to more severe damage from a varicocele. For example, patients with deletions in the antioxidant glutathione S-transferase M1 enzyme display elevated levels of 8-hydroxy-2'-deoxyguanosine in their sperm DNA, have deletions in mitochondria DNA, and have impaired sperm motility.^[92] Genotypes of the glutathione S-transferase enzyme have also been shown to predict clinical benefit from varicocelectomy.^[93] In addition, alterations in sperm membrane fatty acid composition associated with varicoceles may also increase susceptibility to ROS-induced damage.^[94] Cigarette smoking may also exacerbate oxidative sperm damage.^[95]

CONCLUSIONS

There is evidence that many factors are responsible for the pathology of varicoceles' apparent deleterious effect in clinical practice. While experiments and observations in humans and animals have increased our understanding of possible mechanisms of the varicocele's testicular insult, more work remains. It is also important to note the emerging evidence that lifestyle and genetic factors play a role in predicting which patients will manifest a clinical phenotype as a result of a varicocele and who will benefit from surgical repair.

REFERENCES

- Noske HD, Weidner W. Varicocele--a historical perspective. *World J Urol* 1999;17:151-7.
- Tulloch WS. A consideration of sterility factors in light of subsequent pregnancies. *Edinburgh Med J* 1952;59:29-34.
- Meacham RB, Joyce GF, Wise M, Kparker A, Niederberger C. Male infertility. *J Urol* 2007;177:2058-66.
- Marmar JL. The pathophysiology of varicoceles in the light of current molecular and genetic information. *Hum Reprod Update* 2001;7:461-72.
- Naughton CK, Nangia AK, Agarwal A. Pathophysiology of varicoceles in male infertility. *Hum Reprod Update* 2001;7:473-81.
- Braedel HU, Steffens J, Ziegler M, Polsky MS, Platt ML. A possible ontogenic etiology for idiopathic left varicocele. *J Urol* 1994;151:62-6.
- Witt MA, Lipshultz LI. Varicocele: a progressive or static lesion? *Urology* 1993;42:541-3.
- Oster J. Varicocele in children and adolescents. An investigation of the incidence among Danish school children. *Scand J Urol Nephrol* 1971;5:27-32.
- Raman JD, Walmsley K, Goldstein M. Inheritance of varicoceles. *Urology* 2005;65:1186-89.
- Mokhtari G, Pourreza F, Falahatkar S, Kamran AN, Jamali M. Comparison of prevalence of varicocele in first-degree relatives of patients with varicocele and male kidney donors. *Urology* 2008;71:666-8.
- Schoor RA, Elhanbly SM, Niederberger C. The pathophysiology of varicocele-associated male infertility. *Curr Urol Rep* 2001;2:432-6.
- MacLeod J. Seminal cytology in the presence of varicocele. *Fertil Steril* 1965;16:735-57.
- Kruger TF, Menkveld R, Stander FS, Lombard CJ, Van der Merwe JP, van Zyl JA, *et al*. Sperm morphologic features as a prognostic factor in in vitro fertilization. *Fertil Steril* 1986;46:1118-23.
- Barqawi A, Caruso A, Meacham RB. Experimental varicocele induces testicular germ cell apoptosis in the rat. *J Urol* 2004;171:501-03.
- Glazier DB, Marmar JL, Diamond SM, Gibbs M, Corson SL. A modified acrosome induction test. *Arch Androl* 2000;44:59-64.
- Fuse H, Iwasaki M, Mizuno I, Ikehara-Kawauchi Y. Evaluation of acrosome reactivity using the Acrobeads test in varicocele patients: findings before and after treatment. *Arch Androl* 2003;49:1-6.
- Marks JL, McMahon R, Lipshultz LI. Predictive parameters of successful varicocele repair. *J Urol* 1986;136:609-12.
- Daitch JA, Bedaiwy MA, Pasqualotto EB, Hendin BN, Hallak J, Falcone T, *et al*. Varicolectomy improves intrauterine insemination success rates in men with varicocele. *J Urol* 2001;165:1510-13.
- Zheng YQ, Gao X, Li ZJ, Yu YL, Zhang ZG, Li W. Efficacy of bilateral and left varicolectomy in infertile men with left clinical and right subclinical varicoceles: a comparative study. *Urology* 2009;73:1236-40.
- Evers JL, Collins JA. Assessment of efficacy of varicocele repair for male subfertility: a systematic review. *Lancet* 2003;361:1849-52.
- Evers JH, Collins J, Clarke J. Surgery or embolisation for varicoceles in subfertile men. *Cochrane Database Syst Rev* 2009:CD000479.
- Marmar JL, Agarwal A, Prabakaran S, Agarwal R, Short RA, Benoff S, *et al*. Reassessing the value of varicolectomy as a treatment for male subfertility with a new meta-analysis. *Fertil Steril* 2007;88:639-48.
- Agarwal A, Deepinder F, Cocuzza M, Agarwal R, Short RA, Sabanegh E, *et al*. Efficacy of varicolectomy in improving semen parameters: new meta-analytical approach. *Urology* 2007;70:532-8.
- Benoff S, Gilbert BR. Varicocele and male infertility: part I. Preface. *Hum Reprod Update* 2001;7:47-54.
- Benoff S, Marmar JL, Hurley IR. Molecular and other predictors for infertility in patients with varicoceles. *Front Biosci* 2009;14:3641-72.
- Dahl EV, Herrick JF. A vascular mechanism for maintaining testicular temperature by counter-current exchange. *Surg Gynecol Obstet* 1959;108:697-705.
- Turner TT, Caplis LA, Brown KJ. Vascular anatomy of experimentally induced left varicocele in the rat. *Lab Anim Sci* 1996;46:206-10.
- Mieusset R, Bujan L, Mansat A, Pontonnier F, Grandjean H. Effects of artificial cryptorchidism on sperm morphology. *Fertil Steril* 1987;47:150-55.
- Liu YX. Temperature control of spermatogenesis and prospect of male contraception. *Front Biosci (Schol Ed)* 2010;2:730-55.
- Shefi S, Tarapore PE, Walsh TJ, Croughan M, Turek PJ. Wet heat exposure: a potentially reversible cause of low semen quality in infertile men. *Int Braz J Urol* 2007;33:50-56.
- Lund L, Nielsen KT. Varicocele testis and testicular temperature. *Br J Urol* 1996;78:113-15.
- Mieusset R, Bujan L, Mondinat C, Mansat A, Pontonnier F, Grandjean H. Association of scrotal hyperthermia with impaired spermatogenesis in infertile men. *Fertil Steril* 1987;48:1006-11.
- Shiraishi K, Takihara H, Matsuyama H. Elevated scrotal temperature, but not varicocele grade, reflects testicular oxidative stress-mediated apoptosis. *World J Urol*; 2009.
- Goldstein M, Eid JF. Elevation of intratesticular and scrotal skin surface temperature in men with varicocele. *J Urol* 1989;142:743-45.
- Hjollund NH, Storgaard L, Ernst E, Bonde JP, Olsen J. Impact of diurnal scrotal temperature on semen quality. *Reprod Toxicol* 2002;16:215-21.
- Lerchl A, Keck C, Spiteri-Grech J, Nieschlag E. Diurnal variations in scrotal temperature of normal men and patients with varicocele before and after treatment. *Int J Androl* 1993;16:195-200.
- Wright EJ, Young GP, Goldstein M. Reduction in testicular temperature after varicolectomy in infertile men. *Urology* 1997;50:257-59.
- Saypol DC, Howards SS, Turner TT, Miller ED Jr. Influence of surgically induced varicocele on testicular blood flow, temperature, and histology in adult rats and dogs. *J Clin Invest* Jul 1981;68:39-45.
- Green KF, Turner TT, Howards SS. Varicocele: reversal of the testicular blood flow and temperature effects by varicocele repair. *J Urol* 1984;131:1208-11.
- Sofikitis N, Miyagawa I. Effects of surgical repair of experimental left varicocele on testicular temperature, spermatogenesis, sperm maturation, endocrine function, and fertility in rabbits. *Arch Androl* 1992;29:163-75.
- Mieusset R, Grandjean H, Mansat A, Pontonnier F. Inhibiting effect of artificial cryptorchidism on spermatogenesis. *Fertil Steril* 1985;43:589-94.
- Morgentaler A, Stahl BC, Yin Y. Testis and temperature: an historical, clinical, and research perspective. *J Androl* 1999;20:189-95.
- Yin Y, Hawkins KL, DeWolf WC, Morgentaler A. Heat stress causes testicular germ cell apoptosis in adult mice. *J Androl* 1997;18:159-65.
- Rajfer J, Turner TT, Rivera F, Howards SS, Sikka SC. Inhibition of testicular testosterone biosynthesis following experimental varicocele in rats. *Biol Reprod* 1987;36:933-7.
- Wang C, Cui YG, Wang XH, Jia Y, Sinha Hikim A, Lue YH, *et al*. transient scrotal hyperthermia and levonorgestrel enhance testosterone-induced spermatogenesis suppression in men through increased germ cell

- apoptosis. *J Clin Endocrinol Metab* 2007;92:3292-304.
46. Ogi S, Tanji N, Iseda T, Yokoyama M. Expression of heat shock proteins in developing and degenerating rat testes. *Arch Androl* 1999;43:163-71.
 47. Nishiyama H, Danno S, Kaneko Y, Itoh K, Yokoi H, Fukumoto M, *et al.* Decreased expression of cold-inducible RNA-binding protein (CIRP) in male germ cells at elevated temperature. *Am J Pathol* 1998;152:289-96.
 48. Sweeney TE, Rozum JS, Gore RW. Alteration of testicular microvascular pressures during venous pressure elevation. *Am J Physiol* 1995;269:37-45.
 49. Sweeney TE, Rozum JS, Desjardins C, Gore RW. Microvascular pressure distribution in the hamster testis. *Am J Physiol* 1991;260:1581-89.
 50. Mali WP, Arndt JW, Coolsaet BL, Kremer J, Oei HY. Haemodynamic aspects of left-sided varicocele and its association with so-called right-sided varicocele. *Int J Androl* 1984;7:297-308.
 51. Comhaire F, Simons M, Kunnen M, Vermeulen L. Testicular arterial perfusion in varicocele: the role of rapid sequence scintigraphy with technetium in varicocele evaluation. *J Urol* 1983;130:923-26.
 52. Green KF, Turner TT, Howards SS. Effects of varicocele after unilateral orchiectomy and sympathectomy. *J Urol* 1985;134:378-83.
 53. Hsu HS, Chang LS, Chen MT, Wei YH. Decreased blood flow and defective energy metabolism in the varicocele-bearing testicles of rats. *Eur Urol* 1994;25:71-5.
 54. Harrison RM, Lewis RW, Roberts JA. Pathophysiology of varicocele in nonhuman primates: long-term seminal and testicular changes. *Fertil Steril* 1986;46:500-10.
 55. Ghosh PK, York JP. Changes in testicular testosterone and acid and alkaline phosphatase activity in testis and accessory sex organs after induction of varicocele in Noble rats. *J Surg Res* 1994;56:271-76.
 56. Shafik A, Wali MA, Abdel Aziz YE, el-Kateb S, el-Sharkawy AG, Olfat E, *et al.* Experimental model of varicocele. *Eur Urol* 1989;16:298-303.
 57. Younes AK. Low plasma testosterone in varicocele patients with impotence and male infertility. *Arch Androl* 2000;45:187-95.
 58. Pirke KM, Vogt HJ, Sintermann R, Spyra B. Testosterone in peripheral plasma, spermatic vein and in testicular tissue under basal conditions and after HCG-stimulation in patients with varicocele. *Andrologia* 1983;15:637-41.
 59. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. *Fertil Steril* 1992;57:1289-93.
 60. Jarow JP, Chen H, Rosner TW, Trentacoste S, Zirkin BR. Assessment of the androgen environment within the human testis: minimally invasive method to obtain intratesticular fluid. *J Androl* 2001;22:640-45.
 61. Gat Y, Gornish M, Belenky A, Bachar GN. Elevation of serum testosterone and free testosterone after embolization of the internal spermatic vein for the treatment of varicocele in infertile men. *Hum Reprod* 2004;19:2303-06.
 62. Sirvent JJ, Bernat R, Navarro MA, Rodriguez Tolra J, Guspi R, Bosch R. Leydig cell in idiopathic varicocele. *Eur Urol* 1990;17:257-61.
 63. Hudson RW, McKay DE. The gonadotropin response of men with varicoceles to gonadotropin-releasing hormone. *Fertil Steril* 1980;33:427-32.
 64. Pierik FH, Abdesselam SA, Vreeburg JT, Dohle GR, De Jong FH, Weber RF. Increased serum inhibin B levels after varicocele treatment. *Clin Endocrinol (Oxf)* 2001;54:775-80.
 65. Mormandi E, Levalle O, Ballerini MG, Hermes R, Calandra RS, Campo S. Serum levels of dimeric and monomeric inhibins and the degree of seminal alteration in infertile men with varicocele. *Andrologia* 2003;35:106-11.
 66. Koksall IT, Ishak Y, Usta M, Danisman A, Guntekin E, Bassorgun IC, *et al.* Varicocele-induced testicular dysfunction may be associated with disruption of blood-testis barrier. *Arch Androl* 2007;53:43-48.
 67. Segenreich E, Shmueli H, Singer R, Servadio C. Andrological parameters in patients with varicocele and fertility disorders treated by high ligation of the left spermatic vein. *Int J Fertil* 1986;31:200-03.
 68. Su LM, Goldstein M, Schlegel PN. The effect of varicocelectomy on serum testosterone levels in infertile men with varicoceles. *J Urol* 1995;154:1752-55.
 69. Comhaire F, Kunnen M. Selective retrograde venography of the internal spermatic vein: a conclusive approach to the diagnosis of varicocele. *Andrologia* 1976;8:11-24.
 70. Comhaire F, Kunnen M, Nahoum C. Radiological anatomy of the internal spermatic vein(s) in 200 retrograde venograms. *Int J Androl* 1981;4:379-87.
 71. Comhaire F, Vermeulen A. Varicocele sterility: cortisol and catecholamines. *Fertil Steril* 1974;25:88-95.
 72. Steeno O, Koumans J, De Moor P. Adrenal cortical hormones in the spermatic vein of 95 patients with left varicocele. *Andrologia* 1976;8:101-04.
 73. Vine MF, Tse CK, Hu P, Truong KY. Cigarette smoking and semen quality. *Fertil Steril* 1996;65:835-42.
 74. Peng BC, Tomashefsky P, Nagler HM. The cofactor effect: varicocele and infertility. *Fertil Steril* 1990;54:143-8.
 75. Chia SE, Xu B, Ong CN, Tsakok FM, Lee ST. Effect of cadmium and cigarette smoking on human semen quality. *Int J Fertil Menopausal Stud* 1994;39:292-98.
 76. Benoff S, Hauser R, Marmar JL, Hurley IR, Napolitano B, Centola GM. Cadmium concentrations in blood and seminal plasma: correlations with sperm number and motility in three male populations (infertility patients, artificial insemination donors, and unselected volunteers). *Mol Med* 2009;15:248-62.
 77. Benoff S, Auburn K, Marmar JL, Hurley IR. Link between low-dose environmentally relevant cadmium exposures and asthenozoospermia in a rat model. *Fertil Steril* 2008;89:73-79.
 78. Benoff SH, Millan C, Hurley IR, Napolitano B, Marmar JL. Bilateral increased apoptosis and bilateral accumulation of cadmium in infertile men with left varicocele. *Hum Reprod* 2004;19:616-27.
 79. Dalton TP, He L, Wang B, Miller ML, Jin L, Stringer KF, *et al.* Identification of mouse SLC39A8 as the transporter responsible for cadmium-induced toxicity in the testis. *Proc Natl Acad Sci U S A* 2005;102:3401-6.
 80. de Lamirande E, Gagnon C. Capacitation-associated production of superoxide anion by human spermatozoa. *Free Radic Biol Med* 1995;18:487-95.
 81. de Lamirande E, Lamothe G. Reactive oxygen-induced reactive oxygen formation during human sperm capacitation. *Free Radic Biol Med* 2009;46:502-10.
 82. Aitken RJ, Clarkson JS. Cellular basis of defective sperm function and its association with the genesis of reactive oxygen species by human spermatozoa. *J Reprod Fertil* 1987;81:459-69.
 83. de Lamirande E, Gagnon C. Impact of reactive oxygen species on spermatozoa: a balancing act between beneficial and detrimental effects. *Hum Reprod* 1995;10:15-21.
 84. Alvarez JG, Touchstone JC, Blasco L, Storey BT. Spontaneous lipid peroxidation and production of hydrogen peroxide and superoxide in human spermatozoa. Superoxide dismutase as major enzyme protectant against oxygen toxicity. *J Androl* 1987;8:338-48.
 85. de Lamirande E, Gagnon C. Reactive oxygen species and human spermatozoa. I. Effects on the motility of intact spermatozoa and on sperm axonemes. *J Androl* 1992;13:368-78.
 86. Mazzilli F, Rossi T, Marchesini M, Ronconi C, Dondero F. Superoxide anion in human semen related to seminal parameters and clinical aspects. *Fertil Steril* 1994;62:862-68.
 87. Weese DL, Peaster ML, Himsel KK, Leach GE, Lad PM, Zimmern PE. Stimulated reactive oxygen species generation in the spermatozoa of infertile men. *J Urol* 1993;149:64-7.
 88. Cocuzza M, Athayde KS, Agarwal A, Pagani R, Sikka SC, Lucon AM, *et al.* Impact of clinical varicocele and testis size on seminal reactive oxygen species levels in a fertile population: a prospective controlled study. *Fertil Steril* 2008;90:1103-1108.

89. Lenzi A, Culasso F, Gandini L, Lombardo F, Dondero F. Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. *Hum Reprod* 1993;8:1657-62.
90. Tripodi L, Tripodi A, Mammi C, Pulle C, Cremonesi F. Pharmacological action and therapeutic effects of glutathione on hypokinetic spermatozoa for enzymatic-dependent pathologies and correlated genetic aspects. *Clin Exp Obstet Gynecol* 2003;30:130-6.
91. Cavallini G, Ferraretti AP, Gianaroli L, Biagiotti G, Vitali G. Cinnocicam and L-carnitine/acetyl-L-carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. *J Androl* 2004;25:761-70.
92. Chen SS, Chang LS, Chen HW, Wei YH. Polymorphisms of glutathione S-transferase M1 and male infertility in Taiwanese patients with varicocele. *Hum Reprod* 2002;17:718-25.
93. Okubo K, Nagahama K, Kamoto T, Okuno H, Ogawa O, Nishiyama H. GSTT1 and GSTM1 polymorphisms are associated with improvement in seminal findings after varicocelectomy. *Fertil Steril* 2005;83:1579-80.
94. Lenzi A, Picardo M, Gandini L, Dondero F. Lipids of the sperm plasma membrane: from polyunsaturated fatty acids considered as markers of sperm function to possible scavenger therapy. *Hum Reprod Update* 1996;2:246-56.
95. Saleh RA, Agarwal A, Sharma RK, Nelson DR, Thomas AJ Jr. Effect of cigarette smoking on levels of seminal oxidative stress in infertile men: a prospective study. *Fertil Steril* 2002;78:491-9.

How to cite this article: Eisenberg ML, Lipshultz LI. Varicocele-induced infertility: Newer insights into its pathophysiology. *Indian J Urol* 2011;27:58-64.

Source of Support: Nil, **Conflict of Interest:** None declared.

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