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Mysteries, Facts, and Fiction in Varicocele Pathophysiology and Treatment

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Abstract

Development of varicocele in the human has been associated with reduced male reproductive potential. Induction of left experimental varicoceles in the rat, rabbit, and monkey results in a bilateral detrimental effect on testicular endocrine and exocrine function. This review discusses mechanisms mediating the consequences of varicocele on male reproductive potential, indications for the treatment of varicocele, and techniques for varicocelectomy and reviews the difficulties in the interpretation of studies evaluating the effect of varicocele reversal on semen parameters and male reproductive potential.

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1. Introduction

Varicocele, a vascular abnormality of the testicular venous drainage system is manifested by a mass of abnormally dilated, tortuous veins of the pampiniform and/or the cremasteric venous plexus. Varicocele represents the most common cause of primary and secondary infertility in men [1]. Although the prevalence of a clinical varicocele in the male general population is approximately 15%, it has been implicated as a factor responsible for infertility in 35% of infertile men [2,3] and in 81% of men with secondary infertility [4]. Furthermore, it has been demonstrated that clinical varicocele is diagnosed in 11.7% of infertile men with normal semen analysis and 25.4% of infertile men with abnormal semen analysis [5].

2. Etiology of varicocele

The cause for the high incidence of unilateral varicocele on the left side is that the left testicular vein (LTV) runs vertically when the man is standing up and inserts into the left renal vein at a right angle [6]. The right testicular vein, in contrast, runs tangentially to insert into the inferior vena cava. This results in less flow turbulence and back pressure in the right testicular vein and consequently leads to a lower incidence of venous dilation in the right spermatic cord. In addition, incompetent or absent venous valves in the spermatic veins, which have been documented in previous studies [7,8], may be an important contributing factor in the development of varicocele, since man's upright posture may cause an increase in LTV pressure when the valves are incompetent, thus leading to venous distension and dilatation. We have demonstrated the absence of valves within the LTV at the pelvic or lumbar level in 33% and 37% of patients, respectively [9].

Vascular contractions of the LTV caused by catecholamines from the left adrenal gland and drained into the left renal vein via the left adrenal vein and then into the LTV have been proposed as a another factor for the development of left varicocele [10]. Such contractions of the LTV may increase the pressure in the LTV and might cause retrograde blood flow in the LTV. However, these supposed

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contractions of the LTV have never been demonstrated on venography and, therefore, this remains a hypothesis.

In a few cases, compression of the left renal vein between the superior mesenteric artery and the aorta (the nutcracker phenomenon) increases intravenous pressure in the left renal vein and the LTV, leading to dilation of the LTV and establishment of varicocele [6]. Finally, on rare occasions, renal or retroperitoneal tumors exerting pressure on the LTV or on the renal vein may lead to varicocele development.

3. Pathophysiology of varicocele

3.1. Effects of left varicocele on the ipsilateral testis

The pathophysiologic mechanism responsible for the detrimental effects of a left varicocele on the ipsilateral testicular function has not really been elucidated [11–17]. However, several theories have been proposed.

3.1.1. The theory of an increased testicular temperature

Varicoceles are thought to induce their noxious effect by elevating scrotal temperature via reflux of warm abdominal blood through incompetent valves of the spermatic veins [18–20] and there is good evidence to support this theory.

The elevated intrascrotal temperature results in reductions in testosterone synthesis by Leydig cells and reduced Sertoli cell secretory function [21]. In fact, Rajfer and coworkers [22] have demonstrated a decrease in intratesticular testosterone content in varicocelized rats attributable to a functional defect in testicular 17,20-desmolase. In addition, varicocele ligation has been demonstrated to be associated with reductions in intrascrotal temperature in infertile men [23]. Similarly, the induction of left varicocele in rats [24,25], in rabbits [26,27], and in nonhuman primates [28] resulted in a significant elevation of testicular temperature. Surgical repair of experimentally induced varicoceles in the rat model [29] and in the rabbit model [26] significantly reduced testicular temperatures.

The increases in left testicular temperature in varicocelized rats have been shown to result in a decrease in intratesticular testosterone content [22,24] and in varicocelized rabbits have been considered to result in Sertoli cell secretory dysfunction [26]. Similarly, in a subpopulation of men with varicocele, a cause-and-effect mechanism has been established between Leydig cell secretory dysfunction and varicocele [30].

3.1.2. The theory of insufficiency of the hypothalamo-pituitary-gonadal axis

The observation that the serum levels and spermatic vein levels of luteinizing hormone, follicle-stimulating hormone, and testosterone do not vary predictably from normal in the majority of patients with varicocele has resulted in the hypothesis that the hypothalamo-pituitary-gonadal axis is not affected by a varicocele [31]. In contrast, Hudson and coworkers [32] described an excessive gonadotropin response to gonadotropin-releasing hormone (GnRH) stimulation in a group of infertile men with varicocele. Furthermore, they found that following varicocele ligation, only individuals who demonstrated a normalization of their gonadotropin response to GnRH stimulation improved their sperm concentration. Thus it may be speculated that there is a certain subpopulation of men with varicoceles who demonstrate an imbalance in the sensitivity of hypothalamo-pituitary-testicular axis.

3.1.3. The theory of retrograde flow of adrenal or renal metabolites down the left spermatic vein

Javert and Clark [33] suggested that retrograde blood flow occurs in men with varicoceles. Mazo and colleagues [34] provided initial evidence for a functional interrelationship between adrenals and testes in the pathogenesis of infertility in men with a left varicocele. Cohen and coworkers [35] suggested that in patients with varicoceles, a retrograde flow of adrenal catecholamines through the testicular vein results in damage to spermatogenesis. Ito and coworkers [36] reported that reflux of renal venous blood down the spermatic vein resulted in elevated concentrations of prostaglandin E and prostaglandin F in spermatic venous blood in varicocele patients, which may impair spermatogenesis by various mechanisms. The same group found no increase in spermatic vein cortisol concentrations and, therefore, they hypothesized that adrenal metabolites do not reflux but renal metabolites do. On the other hand, renin concentrations might be expected to be elevated if renal vein blood was refluxing down the LTV to any significant degree, yet Lindholmer and et al. [37] found no difference in renin concentrations in peripheral blood and LTV blood in men with varicocele.

The literature does not allow the unequivocal acceptance of the theory that retrograde blood flow through the LTV is an important aspect of varicocele. For instance, Sofikitis and Miyagawa [38] have shown that left adrenalectomy in varicocelized rats does not inhibit the development of varicocele-related physiologic changes in the testis, suggesting that retrograde flow of adrenal metabolites via the LTV cannot be important in varicocele pathophysiology. Furthermore, studies in an experimental rabbit varicocele model confirmed the varicocele-related alterations that have been established in the human [26,27]. However, in the rabbit, the LTV does not drain into the renal vein but into the left lumbotesticular trunk, which collects blood mainly from the retroperitoneal wall. This is strong evidence that the role of adrenal or renal metabolites in the development of testicular damage in the varicocelized rabbit is disputable.

3.1.4. The theory of testicular hypoxia and alterations in the testicular extracellular fluid dynamics: Is there a metabolic defect in the varicocelized testis?

Studies in experimental varicocele models in the rat have documented that vascular endothelial growth factor expression is associated with angiogenesis in the varicocelized testis, and this suggests that varicocele can lead to tissue hypoxia and induce angiogenesis [39]. Hsu and