

Varicocele and infertility: Role of pressure flow dynamics

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Abstract

Varicocele is prevalent in infertile individuals as well as in normal adolescents and adults. It has an increasing trend with growing age. Infertile individuals with varicocele, develop varying degrees of sperm abnormalities that range from mild to severe semen abnormalities, even azoospermia may develop. The main proposed features of these abnormalities are incompetence of one-way valves of the draining veins of testes, that allow backflow of blood into testes. This backflow produces abnormally high intra-testicular pressure and temperature, that has been confirmed by thermography and pressure estimation in various studies. Microsurgical varicocelectomy may reverse the pathologic effects on spermatogenesis in most patients, which points towards the cause and effect relationship of varicocele with testicular damage. We propose that the prolonged effect of gravity might or may not be the initiating factor for varicocele, as in our experience, around 1/4th of hypogonadotropic hypogonadism patients who had no varicocele before treatment, developed varicocele within 3 to 6 mo of treatment with gonadotropins. Occasionally varicocele is produced by "Nutcracker

phenomenon", which is compression of left renal vein between the abdominal aorta and superior mesenteric artery. The deleterious effects of varicocele may develop slowly, causing delayed secondary infertility or rapidly, leading to azoospermia or individual may be spared of damage due to unknown factors that need further research.

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Key words: Varicocele; Scrotal Doppler ultrasonography; Testicular blood flow; Pressure flow dynamics; Testes; Infertility; Oligospermia; Aesthenospermia

Core tip: Varicocele is prevalent in infertile individuals as well as in normal adolescents and adults. It has an increasing trend with growing age. Infertile individuals with varicocele, develop varying degrees of sperm abnormalities. Microsurgical varicocelectomy may reverse the pathologic effects in most patients, which points towards the cause and effect relationship of varicocele with testicular damage. The question as to how some individuals are spared of the deleterious effects of varicocele, needs further research.

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INTRODUCTION

Varicocele is a disorder of the draining veins of testes. Normally these veins have competent valves, which are required to prevent backflow of blood into testes. In individuals with varicocele, these valves become incompetent, leading to reflux/backflow of venous blood into testes^[1-3]. This backflow increases intra-testicular pressure and heat, while decreasing oxygen concentration in testes. These

factors cause testicular injury through inflammatory mediators and production of free radicals^[4]. As a result, testicular function, especially spermatogenesis, is affected which may cause male infertility. The consequences of varicocele are variable in different individuals, some may suffer from infertility whereas others may not^[3,5].

The pathophysiology of varicocele is yet not clear although its association with male infertility is known since 1950^[2]. It is suggested that not a single factor, but various factors are involved in the pathological effect of varicocele. Patient's life style and genetic factors may be among them^[2]. The effects of varicocele are more prominent on the left side, due to higher hydrostatic pressure in the left internal spermatic vein. Also the blood column on the left side, after incompetence of one-way venous valves is longer (40 cm) on the left side. It has been suggested that varicocele is a bilateral disease. In a series of venographies, varicocele was found to be bilateral in 84% cases. Amongst them, collateral venous channels and retroperitoneal venous bypasses were observed in 70% cases on left side and 75% on right side^[6-8].

RESEARCH

A thorough literature search was conducted at the Medline database. The controlled vocabulary of the medical subject headings included varicocele and pressure, varicocele and blood flow, varicocele and hemodynamics, varicocele and Doppler ultrasonography and varicocele and scrotal Doppler ultrasonography (CDUS). The references retrieved were reviewed and relevant references were chosen according to their relevance for the subject. The references list from each reference was further checked to identify relevant references. Only English language articles were selected.

PREVALENCE OF VARICOCELE

World Health Organization has reported that among men with normal sperm quality, 11.7% have varicocele whereas 25.4% individuals with infertility have varicocele^[9]. The prevalence of varicocele in middle school boys has been found to be 16.5%. Its prevalence increases with age, around 10% per decade and reaches 75% at the eighth decade of life^[10,11].

When individuals with varicocele were investigated by CDUS, it was found that 94% had grade 2 and 3 reflux on Doppler study. In individuals without clinical varicocele, 40% were found to have reflux of grade 1 and 2 in their testicular veins^[12].

DIAGNOSTIC IMAGING FOR VARICOCELE

Scrotal CDUS has been used for determining the flow of varicocele veins including their backflow on valsalva maneuver^[12]. If blood flow in a varicocele vein reverses its direction by raised intra-abdominal pressure, it may be considered significant for the diagnosis of varicocele^[13]. In the same study, similar kind of blood flow pattern

was also detected in 54% individuals without varicocele, which invites ambiguity. The backflow pattern has been graded during valsalva maneuver, from Grade 1 (reflux < 2.0 s) to Grade 3 (reflux > 2.0 s)^[14]. The CDUS findings have been proposed to be clinically useful because the maximal reflux velocity and total cross-sectional area of the affected testicular veins can predict the number of internal spermatic veins requiring ligation during microsurgical subinguinal varicocelectomy^[15].

PRESSURE FLOW DYNAMICS OF VARICOCELE

In normal population, testicular veins, like other veins, have low-pressure dynamics with no backflow. It has been proposed that if venous valves are incompetent, high intravenous pressure in the internal spermatic veins may be transmitted to the testes. This happens due to the intra-abdominal destination of these veins. High intra-abdominal pressure, in the absence of proper functioning venous valves, delivers backpressure into the testicular veins^[16]. The reflux of blood in the internal spermatic veins of testes has been found to be similar at all levels of veins irrespective of its branching pattern. However, the velocity of blood in these veins decreases as the number of branches increase closer to the testes^[15]. It has been found that varicocele veins have high hydrostatic pressure that exceeds the pressure in testicular arterial microcirculation, leading to ischemic damage^[6]. It has been reported that animal studies have shown conflicting evidence of both increased as well as decreased testicular blood flow after experimentally induced varicocele^[17]. This is probably due to the fact that animal models do not mimic the human disease process well, at least in its diversity of pathophysiological phenomenon.

In clinical situations, patients, with upper motor neuron lesion and spastic paralysis of the abdominal muscles, develop varicoceles whereas lower motor neuron lesion patients, with flaccid paralysis rarely, develop varicocele^[18]. This can be explained by the phenomenon that spastic paralysis produces high pressure in the abdomen whereas flaccid pressure does not. This study favors the concept of high abdominal pressure as a major cause of varicocele related changes. Hydrostatic pressure in varicocele veins depends on the height of blood column rather than vein diameter^[6]. The taller individuals have higher prevalence and severity of left-sided varicocele and it is probably related to the length of left internal spermatic veins and the consequent increased hydrostatic pressure in them^[19]. During sclerotherapy of internal spermatic veins of varicocele patients, it was observed that most men had absent valves of the internal spermatic veins^[20]. It is the destruction of one-way valves of the veins that allows transfer of pathologic hydrostatic pressure towards testicular venous microcirculatory system. In varicocele, this pressure is around five times higher than normal and exceeds arteriolar pressure, leading to hypoxia. This is also true for right-sided varicocele^[16].

It has been suggested that varicocele is either of “pressure-type” or “shunt-type”. The “pressure type” varicocele is due to valvular incompetence of internal spermatic vein (testicular vein) whereas “shunt type” is caused by the cremasteric vein and/or deferential vein incompetence^[21]. The authors were also of the opinion that spontaneous reflux causes the shunt type varicocele, *i.e.*, the dilatation of medium-sized and large varicocele veins, whereas Valsalva-induced reflux results in “pressure type” or the stop type mechanism, associated with subclinical varicocele^[22,23]. This needs further investigation for better understanding.

“Nutcracker syndrome” is another proposed, though rare explanation for varicocele in many studies. According to this view, varicocele results from compression of left renal vein between the abdominal aorta and superior mesenteric artery that may result in varicocele and left flank pain. This phenomenon has mainly been reported in the pediatric population^[24-26]. Adolescent patients with the nutcracker phenomenon and left varicocele may present with symptoms of hematuria, proteinuria, scrotal discomfort, and flank pain. In 12 such patients, a shunt anastomosis of the proximal part of the spermatic vein and inferior epigastric vein was done and varicocele was treated by ligation of the left spermatic vein. The symptoms disappeared in all the patients. The diameters and peak velocities of left renal vein significantly decreased and left testicular volume significantly increased after surgery^[27].

Experimental anatomic modeling suggests that in varicocele, both testicular as well as epididymal venous outflow is deranged resulting in pathological compensatory hemodynamic changes. Intra-testicular pressure increases, intra-organ vascular integrity is impaired leading to extravasation and testicular venous infarction. There is local arterial hypertension and inter-arterial shunting of the arterial blood. This triggers the mechanism of secondary arterial ischemia of testis and epididymis. The circulatory disorder is pronounced in case of testicular venous outflow blockade which is severe in combined testicular-cremasteric venous block which causes hemodynamic collapse^[28].

Varicocele veins have a higher intravascular pressure compared to other veins and it leads to deterioration in blood flow of testes^[29,30]. It was reported that normal individuals have 59.9 mm. Hg venous pressure on the left spermatic veins which in varicocele patients was higher by 19.7 mm. Hg at rest and 22 mm. Hg during Valsalva's maneuver in varicocele patients^[31]. It has been observed that after transplant nephrectomy varicocele develops in 23.3% male patients^[32].

It has been observed that in normal individuals on Valsalva test, femoral vein caliber increases by 22.6% \pm 5.7%, whereas in patients with varicocele, it rises to 61.1% \pm 10.0%. It has been suggested that the formation of tension chamber in femoral vein may be the cause of ilio-spermatic reflux of varicocele^[33].

In our recent publication, we have reported that hypogonadotropic hypogonadism patients, on presentation,

have small size testes and barely appreciable blood flow with no evidence of varicocele. After treatment with gonadotropins, 23% patients developed varicocele within 3-6 mo of treatment^[34]. We propose that as this change appeared in a short period of time, which is not enough for the gravity effect to take place, it is most likely that the varicocele veins along with incompetent valves were already there but remained undetectable due to poor arterial blood flow, which was insufficient to fill up the veins. This finding of course needs further investigation; however it favors the hypothesis that the prolonged effect of gravity may not be, at least, the initiating factor for the development of varicocele. Similarly, the effect of constipation on varicocele was studied and found that chronic constipation alone, does not cause varicocele, but it can facilitate its effects^[35].

A body of evidences demonstrated that varicocele causes serious damage to testes, which can be successfully improved by microsurgical varicocelectomy, thus proving the cause-effect relationship^[36]. Even in non-obstructed azoospermic patients suffering from varicocele, sperms appeared in ejaculate in 34.6% patients after microsurgical varicocelectomy^[37]. Based on aforementioned evidences, it seems appropriate that varicocele produces harmful effects but what we still don't know is that how some individuals are spared of these effects.

In conclusion, varicocele is a disease that may cause deleterious effects quickly, leading to azoospermia or slowly, causing infertility due to semen abnormalities or the individual may be spared due to various unknown factors that need further research.

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