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The Varicocele-Pathophysiology Based on Clinical and Experimental Studies

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Introduction

Description of idiopathic varicocele was seen even in ancient times and various modes of treatment have been attempted. In 1952, after performing a varicocelectomy in a patient with azoospermia, Tulloch reported improvement in the sperm count to 27 million/ml, and patient's wife became pregnant one year after the operation[1]. Since then this condition has come to be considered an important cause of male infertility in Europe and the U.S.A. In Japan, varicocele has begun to received clinical attention only recently.

Many points concerning this common condition still remain unclear, and no theory fully explains either its cause or the mechanism by which varicocele induces infertility. When a varicocele is present and the chief complaint is male infertility, the pregnancy rate after surgery is reported to be higher than other types of therapy. Thus, the authors generally perform high ligation as the treatment of choice for varicocele. This article reviews the authors' investigations into the pathophysiology of varicocele, together with the surgical treatment. A discussion of the relevant literature follows.

I. Incidence

The incidence of varicocele in healthy males is reported to be about 15% (8-23%)[3], with the affected side being the left in 70-100% of cases, the right in 0-9% of cases, and both sides in 0-23% of cases[2-4]. The incidence of varicocele rises suddenly at 10-14 years and is 16.2% in males aged 10-19 years. There also have been recent reports of testicular atrophy and infertility prevention by the surgical treatment of varicoceles in children[3,5].

Varicocele generally is believed to be an important factor in about 40% (21-41%) of infertile males visiting andrology clinics[2-4]

II. Etiology of Varicocele

Varicoceles are either primary or secondary. Compression or obstruction of the internal spermatic veins due to pelvic tumors produces secondary varicocele. However, most varicoceles, and particularly those associated with infertility, are of the primary type.

Hypotheses concerning the etiology of primary varicocele involve (1) abnormalities of the valves of the internal spermatic veins[6] and (2) the "nutcracker phenomenon"[7]. Venous valve defects alone cannot explain

the difference in the incidence of varicocele between the right and left sides, and valvular incompetence probably is secondary to internal spermatic vein dilation[8]. Thus, the "nutcracker phenomenon" appears more credible at present. This theory maintains that the left renal vein becomes trapped and compressed between the abdominal aorta and the superior mesenteric artery. The phenomenon is believed by some authors to include not only renal vein compression involving the superior mesenteric artery (proximal type), but also a distal type in which the common iliac artery compresses the left common iliac vein. We have examined the relationship between the renal vein and the internal spermatic vein by venography performed from the ligation site during high ligation procedures. Apparent compression of the renal vein was observed frequently in patients with varicocele (Fig. 1). There were some cases in which dilation of the internal spermatic vein was observed but the contrast medium flowed smoothly into the inferior vein cava without remaining in the renal vein (pumping mechanism disorder), and other cases in which the renal vein flow was poor, the renal vein was dilated, and significant retention or backflow of the contrast medium was observed, suggesting renal vein compression.

Some authors have attributed varicocele to the degeneration of the cremaster muscle and spermatic cord muscular membrane or to phlebosclerosis of the pampiniform plexus. However, these hypotheses generally can be ruled out because varicoceles do not necessarily develop after spermatic cord capsule resection during herniorrhaphy.

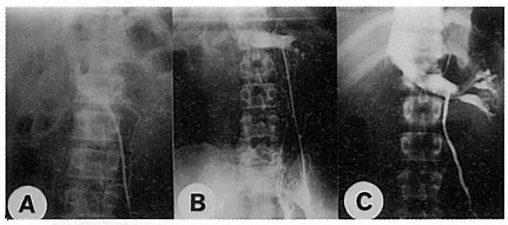

Fig. 1 Venography of the left internal spermatic vein.
A: Dilation of the internal spermatic vein is present, but the contrast medium flows smoothly into the inferior vena cava through the left renal vein.
B, C: Unlike in Fig. A, the contrast medium remains in the renal veins. Its reflux into the intrarenal venous system and development of collateral pathways are seen.

III. Disorders of Spermatogenesis due to Varicocele

Opinions still vary widely as to whether varicocele uniformly affect spermatogenesis. Nilsson et al.[9] suggested that they do not, presenting the following reasons: (1)The high incidence of varicocele in patients with infertility is due to unnecessary referrals and the preponderance of patients with the disease, (2)Since about 10% of all males have varicocele, coincident abnormal spermatogenesis would be expected, and (3)They observed neither improvement in semen analysis nor an increase in pregnancy rate after varicoceletomy. In fact, seminal abnormalities are not necessarily observed in all males with varicocele. It has been stated that abnormal spermatogenesis occurs in about one of every 5 patients with a varicocele[4], and that no semen abnormalities were observed in 14% of infertile outpatients with this condition. In addition, fertile males with varicocele have been reported to comprise 26.3% of those requesting vasectomy[10].

The other side of this argument is that a fall in relative sperm motility compared to the sperm count has been observed in men with varicocele and a normal sperm count, and that the pregnancy rate in the spouses of men within a given range of sperm counts who received high ligation was significantly higher than in a corresponding idiopathic infertility group. A slight deterioration of semen analysis or even early endocrinologic testicular failure has been reported in a fertile varicocele group compared to a normal control group[11]. Therefore, investigations should be based on the working hypothesis that abnormal spermatogenesis can occur due to varicocele.

It has been shown that although varicocele usually is left-sided only, the other testis also is affected and fertility tends to be reduced. Many reports have stated that bilateral tes-

ticular biopsy reveals disorders of both testicles, although no clear right-left difference in severity is seen[12-14]. Dubin et al.[12] observed that a right-left difference occurred in only 10% of cases, while Hirokawa et al.[15] found that the damage tended to be more severe on the side with the varicocele only in cases where the seminiferous tubules showed abnormal spermatogenesis. However, more recent reports have supported the existence of more severe damage occurring on the side with the varicocele[16-19]. The presence or absence of difference between the right and left testicles seems to be important in light of the results obtained by the authors[18]. During high ligation of lift-sided varicoceles in patients with a chief complaint of infertility, bilateral testicular biopsies were performed and the DNA content of the testicular tissues was measured by flow cytometry (FCM). At the same time, the germinal cell maturity was assessed using Johnsen's score, and a Yamaguchi University Orchiometer[16] was used to measure the testicular volumes.

Varicoceles were classified into grades I to III, from small to large size. The left testis volume was found to be smaller than the right testis with all grades of varicocele, and the right-left volume difference was found to be larger in grades II and III (Table 1A). The left testis volume in patients with grade II and III varicoceles was smaller than that of a normal control group, and a significant difference also was seen between grades I and III. On the other hand, the right testis volume was lower than the normal control group only in grade III, and a difference in volume was seen between grades I and III (Table 1B).

Johnsen's mean score often is used as an index of germinal cell maturity. It showed no significant difference between the right and left testicles in patients with grade I and II varicoceles, while significantly lower values were observed in the left testicles with grade III. Compared to the normal control group, significantly lower values were found only in the left testicles with grade II and in both testicles with grade III (Table 2).

The percentage of haploid cells (%1C), which indicates the spermatid ratio, was significantly lower in the left testicle of patients with all grades of varicocele compared to the control group, and no clear difference was observed between the different grades of varicocele. The right testicles in patients with grade I and III varicoceles showed slightly lower %1C values than the normal controls (Table 3). The percentage of tetrapolid cells, which mainly indicates the primary spermatocyte ratio, showed a right-left difference in all grades of varicoceles and tended to be heigher in patients with small varicoceles. This may be due to maturation arrest of germinal cells and stagnation of cells in small varicoceles. In summary, disorders of spermatogenesis were observed in

Table 1.A Testis volume

		Testicular size (ml)		
		Rt	Lt	dif.(Rt − Lt)
		Mean ± SE	Mean ± SE	Mean ± SE
Normal		19.6 ± 1.12 (5)	20.2 ± 0.73 (5)	0.60 ± 0.60
	Rt − Lt	NS		
Varicocele	Grade I	17.5 ± 1.30 (14)	16.3 ± 1.23 (14)	1.93 ± 0.46
	Rt − Lt	$p < 0.01$		
	Grade II	18.0 ± 1.10 (14)	15.6 ± 0.92 (14)	3.14 ± 0.72
	Rt − Lt	$p < 0.01$		
	Grade III	14.8 ± 1.02 (16)	12.7 ± 1.11 (16)	2.75 ± 0.54
	Rt − Lt	$p < 0.01$		

( ) : Number of cases

Table 1.B Testis volume

Rt testicular size				Lt testicular size			
Normal	Varicocele			Normal	Varicocele		
	Grade I	Grade II	Grade III		Grade I	Grade II	Grade III
⟨—NS—⟩	⟨—NS—⟩	⟨—p < 0.05—⟩		⟨—NS—⟩	⟨—NS—⟩	⟨—p < 0.10—⟩	
⟨——— NS ———⟩				⟨———p < 0.05———⟩			
⟨———p < 0.05———⟩				⟨———p < 0.01———⟩			
⟨———p < 0.10———⟩				⟨———p < 0.01———⟩			

Table 2 Testis score count

	Johnsen's mean score	
	Right testis	Left testis
Control	9.44 ± 0.09[a] (5)	9.44 ± 0.09 (5)
Varicocele		
Grade I	8.58 ± 0.10 (12)	8.37 ± 0.17 (12)
Grade II	8.59 ± 0.16 (9)	7.97 ± 0.49* (9)
Grade III	7.93 ± 0.35** (13)	7.27 ± 0.52$^{*}_{\#}$** (13)

a : Data are expressed as mean ± SE
( ) : Number of cases
* : $p < 0.05$ vs control
** : $p < 0.01$ vs control
\# : $p < 0.05$ Rt − Lt

both testicles, tended to be more severe on the affected side than the contralateral side, and tended to be more severe with larger varicoceles.

However in most studies of varicocele, the subjects have been infertile, while the clinical impression is that all men with varicocele are not necessarily infertile. Therefore, whether or not there is a strict cause-and-effect relationship between varicocele and male infertility needs further animal experimentation. To study the effect of a unilateral varicocele on bilateral spermatogenesis in an animal model, we investigated the changes in spermatogenesis in rats with surgically induced varicoceles (Fig. 2). The testicular weight, flow cytometric DNA analysis, and the mean seminiferous tubular diameter (MSTD) were used as the criteria for evaluation[19].

We found that in rats with varicoceles, the testicular weight, the percentage of haploid cells (Fig. 3), and the MSTD decreased in both testicles in contrast to sham-operated

Table 3 %Haploid cell (%1C) of testis tissues

	%1C	
	Right testis	Left testis
Control	59.0 ± 1.6[a] (5)	59.0 ± 1.6 (5)
Varicocele		
Grade I	43.9 ± 5.0* (12)	39.0 ± 4.5#* (12)
Grade II	52.9 ± 3.2 (11)	40.5 ± 5.8#* (9)
Grade III	45.1 ± 5.8* (12)	41.2 ± 5.5#* (12)

a : Data are expressed as mean ± SE
( ) : Number of cases
* : $p < 0.05$ vs control
** : $p < 0.01$ vs control
# : $p < 0.01$ Rt − Lt

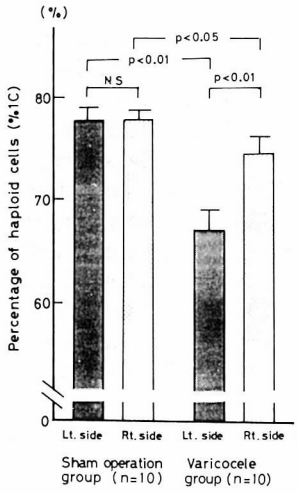

Fig. 3 Percentage of haploid cells in the testes of each group (mean ± SE).

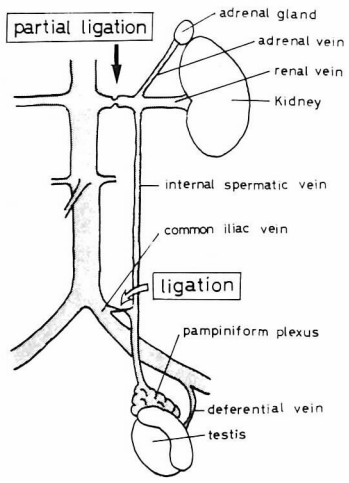

Fig. 2 Diagram of the procedure for inducing left-sided varicocele in rats.

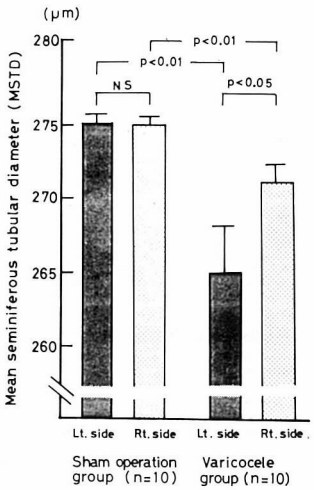

Fig. 4 Mean seminiferous tubular diameter in each group (mean ± SE.)

rats, and the decrease was greater on the left side (Fig. 4). These results suggested that a unilateral varicocele may impair spermatogenesis in both testicles, with the impairment being greater on the ipsilateral side. Our observations based of flow cytometric DNA analysis in human and animal studies confirmed the detrimental effect of a unilateral varicocele on both testicles[18,19].

Ⅳ. Mechanisms of the Impairment of Spermatogenesis by Varicocele

Various causes have been suggested for the effects on spermatogenisis that are apparently associated with varicocele, but none has been proven (Table 4). Among these hypotheses, the most plausible seem to be the testicular temperature elevation hypothesis and the toxic sustance reflux hypothesis.

The temperature hypothesis, which maintains that varicoceles raise the testicular temperature, is a longstanding idea. Testicular temperature elevation is known to have an adverse effect on spermatogenesis[20-24]. It has been reported that the normal scrotal temperature is lower than the rectal temperature, that the temperature difference between the rectum and the scrotum is smaller in men with varicoceles, and that the intrascrotal temperatures drops after surgery for varicocele. Also, the intrascrotal temperatures are higher in men with varicoceles than in normal individuals, and the temperature is 0.3℃ higher on the affected side than the healthy side, particularly in the standing position[20]. Whether or not temperature alone can induce infertility in patients with varicocele cannot be established easily. We also have reported that the scrotal temperature rises in varicocele in studies using deep testicular temperature measurements[21-23]. Moreover, the clinical application of thermography has revealed that spermatogenesis tends to be maintained in patients with varicocele but without elevation of the right testicular temperature[24].

We determined the deep testicular regional temperatures in patients with varicocele, in-

Table 4 Mechanism of spermatogenic function disorder due to varicocele

Testis temperature elevation
Reflux of harmful substances into the testicles
Retention of testis metabolic products
Hypoxia or hyperoxia of the testis
Decrease in testis blood flow
Seminiferous tubule occlusion by venous dilation
Leydig cell function abnormality
Epididymal function abnormality

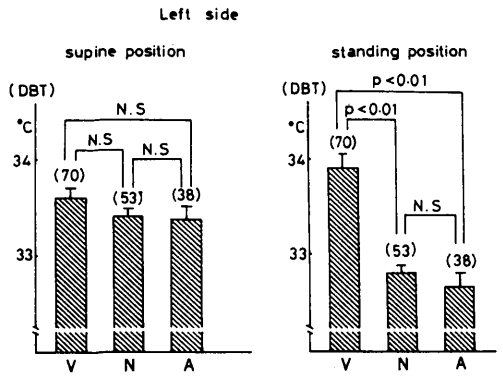

Fig. 5 Left deep testicular regional temperature (supine position versus standing position).
V. Varicocele group
N: No varicocele group
A: After operation goup

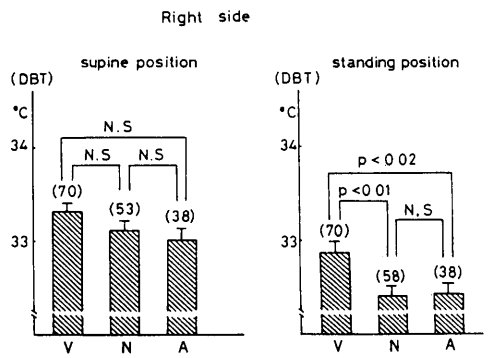

Fig. 6 Right deep testicular regional temperature (supine position versus standing position).
V. Varicocele goup
N: No varicocele group
A: After operation group

fertile patients without varicocele, and postvaricocelectomy patients[14-16]. No difference was observed in deep testicular regional temperatures in the supine position, but higher temperatures were observed in the right and left testicles of the varicocele group in the standing position (Figs. 5 and 6). The temperature was highest and the temperature elevation from the supine to the standing position was largest on the left side of patients with large varicoceles (Fig.7).

Many researchers have examined the hypothesis which maintains that a high concentration of metabolic byproducts from the kidneys and adrenal glands reach the testicles and have an adverse effect on testicular function, due to backflow into the internal spermatic vein from the renal vein and also due to venous recirculation to the opposite testis. It has been reported that catecholamine levels in the internal spermatic venous blood of patients with varicoceles are higher than in controls[25,26]. However, cortisol and renin levels were found not to differ in later studies[25,27]. Attention also has been paid to the hypothesis that prostaglandin (PG) E and F formed in the kidneys reflux into the testicles and impair spermatogenesis[28-30]. Our finding that phospholipase A_2 levels in semen drop significantly after varicocelectomy may be consistent with this theory. We cannulated the internal spermatic vein during high ligation for varicocele and collected blood with the cannula tip directed toward the kidneys. We simultaneously collected peripheral venous blood and measured PGE and PGF levels in both samples. Higher

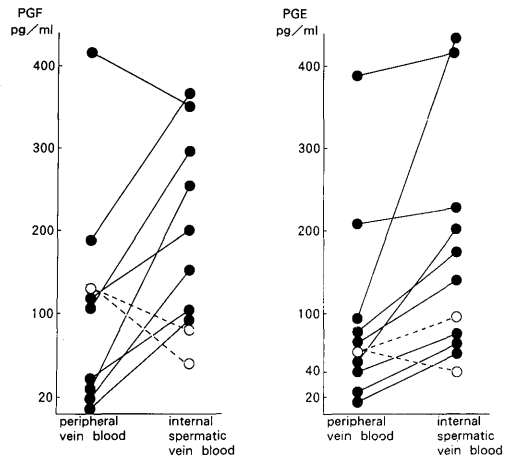

Fig. 8 PGE and PGF levels in peripheral blood and internal spermatic venous blood of patients with varicocele.
○------○: Control goup
●——●: Varicocele goup

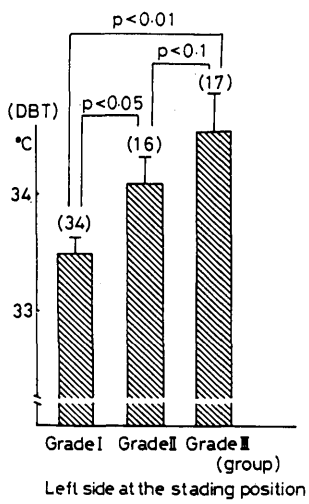

Fig. 7 Correlation between deep testicular regional temperature and grade of varicocele in the standing position.

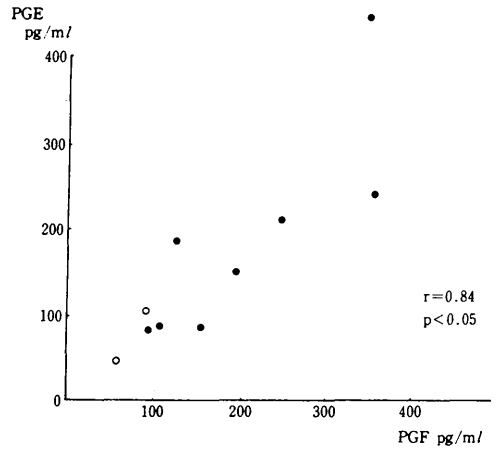

Fig. 9 Correlation between the PGE and PGF levels in internal spermatic venous blood in patients with varicocele.
○: Control goup
●: Varicocele goup

levels of PGE and PGF were observed in the internal spermatic vein blood than in the peripheral blood (Fig.8). Moreover, a significant correlation between PGE and PGF levels in internal spermatic venous blood existed, further supporting the PG backflow hypothesis (Fig.9). Abnormalities of blood flow due to vasoconstriction induced by PG and inhibition of the action of LH by PGF acting on LH receptors in the testicles may be the mechanisms of action of disorders of spermatogenesis in varicocele[31]. Moreover, in vitro animal experiments performed by the authors have revealed a close relationship between epididymal contractility and PG[32]. Therefore, the posibility exists that sperm transportation and maturation in the epididymis also may be affected by PG backflow in varicocele.

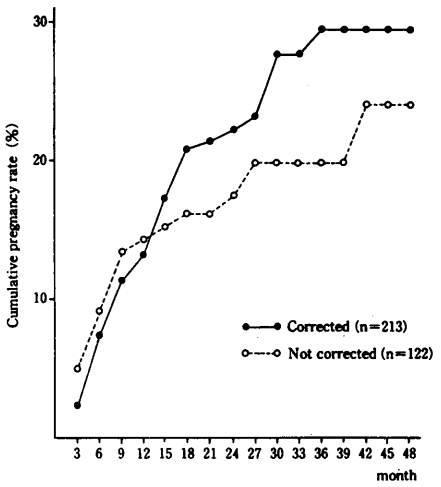

Fig. 10 Cumulative pregnancy rate in partners of men with varicoceles (comparison between treated and untreated goups).

V. Treatment Results

The results of treatment of varicocele vary widely, and this has made it difficult to define the clinical significance of this disease. The ratio of improvement in the semen analysis and pregnancy rate of patients' partners after surgical treatment has been reported to range from 53-92% and 20-55%, respectively[1-4,33,35]. These figures cannot be accepted unconditionally in view of the spontaneous variations which can occur in semen analysis, as well as difference in the method of measurement, assessment, and preoperative severity. Surgical treatment (high ligation or embolization) was performed in 335 patients with varicocele and infertility in a multicenter research study in Japan involving the following institutions: Kawasaki Medical University, Tokyo Medical and Dental University, Yokohama City University, Chiba University, Toho University, and Yamaguchi University. Siginificant improvement was observed in semen analysis, particularly in the sperm concentration and sperm motility. The pregnancy rate was 23.5% in the treated group and 18.0% in the untreated group. The cumulative pregnancy rate tended to rise in the treated goup 18 to 24 months after surgery (Fig.10). The pregnancy rate was significantly higher in treated group members with sperm concentrations of 10×10^6 -40×10^6/ml and a sperm motility below 20%.

Conclusions

The investigation of spermatogenesis in patients with varicoceles based on flow cytometric DNA analysis in human and animal studies has confirmed a detrimental effect of a unilateral varicocele, on both testicles, with the impairment being greater on the ipsilateral side.

Mechanisms leading to impairment of spermatogenesis by varicocele was investigated and showed us the following suggestions. Among the hypotheses, the two most plausible seem to be the testicular temperature elevation hypothesis and the toxic substance reflux hypothesis.

By the use of the deep testicular regional temperature measurement revealed that the temperature was highest and the temperature elevation from the supine to the standing position was largest on the left side of patients with large varicoceles. The measurement of spermatic vein blood prostaglandins revealed that higher levels of PGE and PGF were observed in the internal spermatic vein blood than in the peripheral blood.

Moreover, a significant correlation between PGE and PGF levels in internal

spermatic venous blood existed also supporting the PG backfow hypothesis, implicating that the possibility exists that sperm transportation and maturation in the epididymis may also be affected by PG backflow in varicocele.

The clinical results of varicocele opration at five multicenters and Yamaguchi series showed definitively that varicocele patients benifit from varicocelectomy.

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