VARICOCELE INDUCED HYPOXIA AND MALE INFERTILITY

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Abstract

Objective: to evaluate the possibility of altered gas content or pH as a cause of spermatogenic depression in infertile males with varicocele.

Setting: Department of Dermatology, and Venreology, Urology and Clinical pathology, Benha Faculty of Medicine and department of Radiology Zagazig Faculty of Medicine.

Patients and intervention: Twenty four infertile males with left sided varicocele were included. Cases were subjected to history, clinical examination and two semen analysis. Po2,Pco2, pH and BE were determined in blood samples obtained from internal spermatic vein and the antecubital vein

Results and conclusion: The study revealed presence of hypoxia in the internal spermatic vein compared to peripheral circulation. No correlation between the duration of infertility and associated varicocele. No correlation between sperm count and oxygen tension or saturation but rather with blood pH and Co2 tension on the other hand sperm motility and percent of abnormal forms were affected with decreased oxygen tension and saturation

Introduction:

Varicocele was first described by Ambroise Pare in 1550 (1), and has been implicated as a reversible common cause of male subfertility for almost half a century (2), mainly on the basis of three observations. The incidence of varicocele has been noted to be higher in the male partners of infertile couples than that in the general population (40% and 15% respectively) (1,3), the presence of varicocele is in some males associated with abnormalities in semen analysis (4,5,6) and testicular histology (7,8,9), and varicocelectomy has been noted to result in improvement in semen quality (10,11,12,13) and pregnancy rates (14,15,16,17).

Varicocele results from retrograde flow of venous blood from the renal vein down the internal spermatic vein into the circulation of both testes. To accommodate this increased volume of blood, the veins of the testes become varicosed. The mechanism by which varicocele exerts its deleterious effect on spermatogenesis and/or semen quality still remains unknown (18). Several theories have been suggested, elevation of testicular temperature, reflux of renal and adrenal venous blood with toxic, metabolic or endocrine substances into the internal spermatic vein, and stasis of venous blood with decreased oxygen tension result in semineferous epithelium hypoxia (4,18,19,20,21,22).

Measurements of the blood gases and pH were obtained in the internal spermatic vein and peripheral venous blood (antecubital fossa vein) simultaneously collected during high ligation in infertile men with varicocele in an attempt to evaluate the possibility of altered gas content or pH as a cause of spermatogenesis depression.

Patients and Methods:

Twenty-four infertile males with a left-sided varicocele, ages between 24 and 45 (mean 32.83 ±7.12) with duration of infertility ranging from 2 to 15 years (mean 6 ±3.75) were included in this study. A complete medical history and physical and genital examinations were performed. None of the subjects reported previous episodes of cryptorchidism, orchitis, hydrocele, testicular trauma or torsion, or had undergone surgery of the urogenital tract. Patients who received treatment such as hormonal therapy or other medication for infertility were excluded. Additionally, there was no evidence of a female factor contributing to the couple's infertility, including ovulatory dysfunctions, pelvic pathology, or tubal disease.

The diagnosis of varicocele was based on physical examination in the erect and supine positions using Valsalva's maneuver, graded into: small (grade I) palpable Valsalva's impulse in the pampiniform plexus without dilatation; medium (grade II) palpable dilatation of the pampiniform plexus; and large (grade III) visible distension of the scrotal veins when standing (23). This was confirmed by gray scale real time, duplex and color Doppler scrotal ultrasonography.

Gray scale sonographic & color Doppler examinations were performed using Aloka SSD-2000 ultrasound machine with a 7.5 MHz linear transducer. In all patients, the pampiniform plexuses were evaluated in a longitudinal and transverse scans performed cranial and slight lateral to the head of the epididymis on each side. After localization of the spermatic cord, the patient was instructed to perform Valsalva maneuver while the examiner observes the change in the blood flow signals due to reversed flow. Comparison with the opposite side was always done. When findings were equivocal, examination of the pampiniform plexuses was done with the patient standing. On gray scale sonography, varicocele was diagnosed when the caliber of the veins in the pampiniform plexus is greater than 2 mm at rest and increases when the patient stands upright or performs a Valsalva maneuver. On color Doppler sonography, varicocele was diagnosed when there was retrograde blood flow at the very start of the Valsalva maneuver.

At least two semen analyses within three months interval were performed for each patient before surgery. Semen samples were collected by masturbation after a period of sexual abstinence of at least 4 days, and the semen was examined immediately after collection according to the standard WHO procedures (24). Volume, pH, consistency, and appearance of the ejaculate were determined. Motility was assessed in a wet drop preparation and designated as grade I (rapid linear progressive motility), II (sluggish), III (immotile)[23]. Sperm concentration was determined using a haemocytometer. Analysis of the morphological characteristics and pus cells were performed in a stained smear.

Internal spermatic vein ligation was performed under general anesthesia with the patient in 30^0 feet down position, and receiving optimum oxygenation. The inguinal approach was used to identify the internal spermatic vein above the internal *inguinal* ring. The vein was cannulated for a distance of 4 cm in the direction of the testes in order to collect 8 cc blood sample, and another specimen of peripheral blood was collected from the antecubital vein simultaneously. PO2, PCO2, SO2, pH, and BE were determined within minutes of collection using the Radiometer ABLS PH and blood gas analysing system,Copenhagen,Denmark.

Statistical analysis of the results was done using standard PC software "Microstat version 2.0" employing a logistic t test for comparison between two independent means and correlation coefficient (r) for relationship of different variables using Pearson's method.

Results:

The results of this study are presented in tables 1-3 and figure 1. A tabular report of the mean and standard deviation values of pH, PO2, PCO2, SO2, and B.E. of the internal spermatic venous blood and that of the peripheral blood (antecubital arm vein) and the statistical comparison between them are shown in table (1) and fig (1).

A highly significant decrease in PO2 and SO2 (*mean values 41.75 ± 7.32* and 54.83± 8.43, P<0.001) between the internal spermatic venous blood and the peripheral (antecubital arm) venous blood, respectively.

Correlation study between the pH, and blood gases and the different semen parameters are found in table (3). No significant correlation was found between the duration of infertility (associated varicocele) and PH or blood gases determinations in the internal spermatic vein (table 3). A noteworthy finding is the correlation between the total sperm count and both the pH (p<0.001, r= 0.80) and PCO2 (P<0.01,r=-0.70) content of internal spermatic venous blood. On the other hand, there is a significant correlation between the sperm motility and pH (p<0.05, r=0.52), PO2 and SO2 (p<0.01, r=0.68 and 0.71 respectively). Likewise a significant correlation between the percentage of abnormal form and PO2 (p<0.05, r= -0.53), PCO2 (p<0.05, r=0.42), SO2 (p<0.05,r=-0.50), and BE (p<0.05, r= -0.52). A correlation between pus cells and pH (p<0.05, r=0.60), and PCO2 (p<0.05,r=-0.53) were also found, table (3).

Table (1): Mean and standard deviation (SD) values of PH, PO2, PCO2, SO2, and B.E. and the statistical comparison between the internal spermatic venous blood and peripheral(antecubital arm) venous blood.

ariable	t. sperm. vein Mean + SD	eriph. arm vein Mean + SD	"t" Paired	P	Significance
PH	7.31 + 0.02	7.36 + 0.04	5.6544	<.000009	Highly sign.
PO2	41.75 + 7.32	54.83 + 8.43	4.8207	<.000073	Highly sign.
PCO2	42.75 + 5.74	39.75 + 3.04	-2.3814	<.025907	Sign.
SO2	61.17 + 6.03	71.08 + 6.32	4.7501	<.000087	Highly sign.
B.E.	-7.08 + 1.74	-5.50 + 1.41	3.9249	<.000678	Highly sign.

pH: pH of blood at patient temperature. PO2: Oxygen tension in blood at patient temperature.
PCO2: Carbon dioxide tension in blood at patient temperature.
SO2: Oxygen saturation of hemoglobin in blood. BE: Base excess.

Table (2): The mean and standard deviation (SD) of semen parameters.

Variable	Mean + SD	Semen parameter	Mean + SD
(Years)	32.83 + 7.12	Sperm count/ml	16.75 + 3.31
ation of infertility	6 + 3.75	Total sperm count	46.58 + 16.34
tinence (days)	4.67 + 0.64	Motility (percent)	45 + 10.43
ume (ml)	2.75 + 0.77	Percent abnormal forms	44.17 + 11.20
uefaction time	25.83 + 3.50	Pus cells/HPF	3.96 + 2.68

Table (3): Correlation between different parameters of blood gases analysis of internal spermatic vein and semen parameters.

Variable	PH		PO2		PCO2		SO2		BE	
	r	P	r	p	r	p	r	p	r	p
ation of infertility	0.14	0.05	.05	0.05	-0.0	0.05	.11	0.05	.16	0.05
rm count	0.80	0.01	.38	0.05	-0.70	0.01	.35	0.05	.57	0.01
Motility	0.52	0.05	.68	0.01	-0.36	0.05	.71	0.01	.65	0.05
bnormal forms	-0.38	0.05	0.53	0.05	0.42	0.05	0.50	0.05	0.52	0.05
cells/HPF	0.60	0.05	.05	0.05	-0.53	0.05	.01	0.05	.31	0.05

r= Correlation coefficient, p<0.01 Highly significant,
p<0.05 Significant, p>0.05 Insignificant.

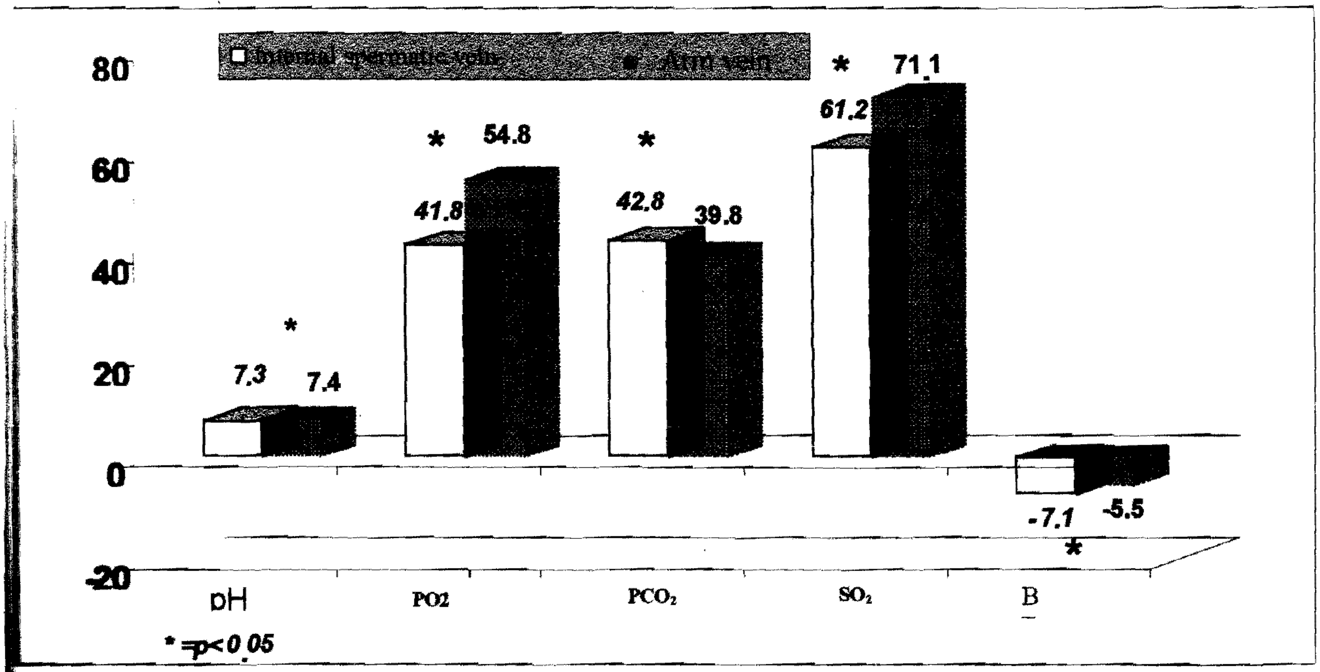

Fig (1) Mean values of pH & blood gases in internal spermatic vein & peripheral venous blood (arm).

Discussion

Idiopathic varicocele was first described in ancient times and various modes of treatment have been attempted. The pathophysiology of this common condition remains unclear, and no theory fully explains either its cause or the physiological alterations by which varicocele induces infertility.

Abnormalities of the scrotal thermoregulatory mechanism have been studied by Zorgnotti and Macloed (4) and they found a significantly high intrascrotal temperature (0.6-0.8° C) in infertile subjects with varicocele than in control group. Retrograde flow of adrenal or renal metabolites such as catecholamines or prostaglandins have also been investigated and agreed upon by Ito et al (19) and Takihara et al (20) as one of the theories. Leydig cell dysfunction related either to disturbance of the scrotal temperature-regulatory system or to testicular tissue hypoxia secondary to venous blood stasis, was examined and accepted by Rodrigues-Rigau et al (8). The theory of varicocele induced stasis of blood with decreased oxygen tension with resultant poor tissue oxygenation (hypoxia) was denied by Donohue and Brown in 1969. They observed that varicocele may not be decreasing the oxygen tension in the venous plexus of the testes, but may in effect be increasing it. They further questioned whether increasing oxygen tension can be in itself deleterious?

This initiated this study and on the contrary to the conclusion of Donohue and Brown, it revealed a significant decrease in oxygen tension and saturation (hypoxia) and increase in carbon dioxide in the internal spermatic vein in comparison to the peripheral venous blood.