Article

Right varicocele and hypoxia, crucial factors in male infertility: fluid mechanics analysis of the impaired testicular drainage system

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Abstract

Varicocele is considered a predominantly unilateral left-sided disease. However, since male fertility is preserved with only one healthy testis, infertility perforce represents bilateral testicular dysfunction. It was hypothesized that: (i) right varicocele cannot be diagnosed by palpation and therefore has not been treated in the past by the traditional treatment, and (ii) right varicocele causes impaired oxygen supply in the right testicular microcirculation, leading to germ cell degeneration. This study performed venographies of both right and left internal spermatic veins during the treatment of 840 infertile men with varicocele and analysed the results using tools of fluid mechanics. Histopathology of the right testis revealed stagnation of blood flow and degenerative changes attributed to lack of adequate oxygenation in all testicular cell types. Right varicocele was found in the vast majority of the patients. We found that due to the destruction of one-way valves, pathologic hydrostatic pressure is produced in the testicular venous microcirculatory system about five times higher than normal, exceeding arteriolar pressure. The pressure gradient between the arterioles and venules in the testicular tissue is therefore reversed, leading to persistent hypoxia. Right varicocele, although undetected, is prevalent in fertile men with varicocele, hence only bilateral occlusion of the internal spermatic veins, including the associated bypasses, eliminating the pathologic hydrostatic pressure will lead to resumption of arterial blood flow in the testicular microcirculation.

Keywords: andrology, hypoxia, male infertility, varicocele

Introduction

Varicocele is a leading cause of male infertility (Gorelick and Goldstein, 1993; Matthews et al., 1998; Gat et al., 2004a; Agarwal, 2006), whereas genetic defects or chemotherapy explain a minor proportion of the cases (Agarwal and Said 2004; Paduch et al., 2005). It represents impairment of the testicular venous drainage systems, where the one-way valves in the main drainage vessels are gradually destroyed over time and become incompetent, or are defective from birth. It is considered a predominantly unilateral (left-sided) disease. Its pathophysiology has not been clearly delineated and the treatments offered generally do not seem to be effective (Evers and Collins, 2004). The medical literature is replete with articles demonstrating inconsistent and even contradictory results, which have led some clinicians to dissociate varicocele
from male infertility. Since male fertility is preserved with only one healthy testis, oligoteratoasthenozospermia (OTA) or azoospermia represent bilateral testicular dysfunction. This poses an enigma to clinicians: how can left-sided varicocele cause bilateral testicular dysfunction? Using ultrasonography, combined with ultrasonography and confirmed by venography, it has been shown that varicocele can be identified in over 80% of infertile men and that 84% are bilateral (Gat et al., 2004b).

Varicocele causes a progressive deterioration over time in semen quality and testicular function, ranging from OTA to azoospermia (Gorelick and Goldstein, 1993; Matthews et al., 1998; Gat et al., 2005a). The benefits of unilateral varicocele repair (surgical, venographic or laparoscopic) to sperm concentration, motility, and morphology have been questioned (Evers and Collins, 2004). Adequate treatment by bilateral occlusion of the internal spermatic veins, including the associated network of venous bypasses and retroperitoneal collaterals, can be achieved by two methods: (i) percutaneous transvenous occlusion (embolization) (Kunnen and Comhaire, 1992; Gat et al., 2004a), and (ii) bilateral microsurgery of the impaired testicular venous drainage system (Matthews et al., 1998; Pasqualotto et al., 2003). Bilateral treatment led to the resumption of sperm production (with subsequent pregnancy in the female partner), even in previously azoospermic men (Matthews et al., 1998; Pasqualotto et al., 2003; Gat et al., 2004a) and to elevation of serum testosterone and free testosterone (Comhaire and Vermeulen, 1975; Su et al., 1995; Gat et al., 2004a; Gat and Gornish, 2006).

In the light of the above, the prevalence and significance of right varicocele were investigated by venographies and fluid mechanics analysis. The reason why right varicocele cannot be clinically detected was also investigated. This lack of detection leads to partial treatment in about 80% of infertile men, causing clinicians to dissociate varicocele from male infertility.

Materials and methods

Patients

Eight hundred and forty infertile men, clinically suspected of suffering from varicocele, were evaluated by thermography and venography. Ten men, not from the venography group, who had verified right and left varicocele diagnosed by ultrasonography and thermography, underwent right testicular biopsy during fertility work-up.

Contact thermography

Contact thermography was performed with flexible liquid crystal thermo strip (FertiPro, Bremen, Belgium), as previously described (Gat et al., 2005b).

Gat–Goren technique for detection, measurements and treatment

Venographies were performed according to the Gat–Goren technique, as previously described (Gat et al., 2003). In brief (for the right side), the guiding catheter, advanced from the right common femoral vein through an intravascular 6.5F sheath, is positioned in the left renal vein, over the vertebral bodies. For the right internal spermatic vein (ISV), a ‘shepherd’s crook’-shaped catheter is positioned in the inferior vena cava (IVC), above the orifice of the right renal vein. Through this catheter, the 3F superselective catheter enters the orifice of the ISV directly.

Manual injections with a tilt-table fluoroscopic system can demonstrate partially or intermittently competent valves, traces of incompetent or destroyed valves, collaterals and venous bypasses (Siegel et al., 2006). Measurements taken included the length of the right spermatic vein, its vertical length, distances between incompetent valves and bypass classification, including retroperitoneal collaterals associated with the disease. The back-flow upon Valsalva’s manoeuvre when the catheter’s tip was at the upper orifice of the right spermatic vein was also studied.

Testicular histopathology

Testicular histopathology was performed on Epon-embedded testicular tissue samples from men with varicocele from the collection with approval of the Medical College of Ohio Internal Review Board. One-micrometre semi-thin sections were cut with a LKB ultramicrotome. The sections were stained with 1% toluidine blue. A Nikon Ophitphot light microscope (Nikon, Japan) was used for examination of the tissue samples for photomicrography at variable magnifications. The patients who underwent testicular biopsy were not the same patients studied in the angiography.

Results

In the course of venography performed for diagnosis and treatment of varicocele on 840 patients, incompetent valves allowing reflux were demonstrated in the right ISV in 725 patients (86%). In 549 of these patients (76%), retroperitoneal venous collaterals and bypasses were associated with the right ISV. However, only in 52% of cases did these bypasses cause pathologic hydrostatic pressure. In 36 patients (5%), the right ISV drained into the right renal vein. In 21 patients (3%), the right ISV drained into the right renal vein and into the IVC, and in 668 patients (92%), the right ISV inserted only into the IVC (Figure 1; Table 1).

While reflux is clearly demonstrated on venographic catheterization of the ISV by injection of contrast material, a standard Valsalva manoeuvre performed by the patient always failed to produce reflux in the right ISV unless it joined the right renal vein directly (in about 8% of the cases) (Table 1). It is notable that back-flow was not produced in right varicocele despite the lack of competent valves in the right ISV. This data clearly demonstrated that right varicocele could not be detected by conventional means. This lack of clinical detection causes partial treatment in about 80% of infertile men and leads clinicians to dissociate varicocele from male infertility. Furthermore, it was observed that the lower the valve is in the ISV, the more likely it is to be destroyed due to hydrostatic pressure overload.

Since reflux is considered the prime proof of venous valve incompetence, it seems a contradiction that in the absence of reflux there is abnormal venous drainage. The average vertical
**Figure 1.** Right varicocele with associated network of bypasses and retroperitoneal collaterals. The right internal spermatic vein (ISV) inserts into the inferior vena cava (IVC). One-way valves are absent. The venous bypasses lack valves. Back-flow (reflux) is seen during fluoroscopy as contrast material flows freely downstream from point IVC towards the testes. IVC = inferior vena cava; ISV = internal spermatic vein.

**Table 1.** Numbers and incidence of right varicocele, bypasses and demonstration of back-flow on Valsalva’s manoeuvre during venography.

<table>
<thead>
<tr>
<th></th>
<th>Number (%)</th>
<th>Back-flow on Valsalva manoeuvre (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total venographies</td>
<td>840</td>
<td></td>
</tr>
<tr>
<td>Right varicocele</td>
<td>725 (86)</td>
<td>57 (8)*</td>
</tr>
<tr>
<td>Bypasses and collaterals</td>
<td>549 (76)*</td>
<td></td>
</tr>
<tr>
<td>Bypasses causing pathological hydrostatic pressure</td>
<td>374 (52)*</td>
<td></td>
</tr>
<tr>
<td>ISV inserted to IVC only</td>
<td>668 (92)*</td>
<td>0*</td>
</tr>
<tr>
<td>ISV inserted to right renal vein only</td>
<td>36 (5)*</td>
<td>36*</td>
</tr>
<tr>
<td>ISV inserted to right renal vein and IVC</td>
<td>21 (3)*</td>
<td>21*</td>
</tr>
</tbody>
</table>

ISV = internal spermatic vein; IVC = inferior vena cava.

*Percentage of right varicocele cases.
height of the blood column produced in the abnormal right ISV valves was 35 cm. This means that the hydrostatic pressure exerted on the venous drainage system was about 27 mmHg (equation 1). Note that the estimated intravascular pressure in the arteriolar microcirculation is about 18–20 mmHg (Ganong, 1999). Based on these measurements and the calculated hydrostatic pressures, it was found that there is reversal in the pressure gradient between the arteriolar and the venular systems in the testicular tissue in varicocele: the venular pressure exceeds arteriolar pressure. Hence, there is an abnormal supply of arterial oxygenated blood into the testicular tissue that leads to hypoxia in the sperm production site. This has potentially serious implications concerning the deterioration of spermatogenesis, and, therefore, demands detailed explanation.

Histopathology of the right testis in varicocele showed stagnation of blood flow in the microcirculatory system, evidenced by the clotted blood blocking the entire lumen of the arterioles and venules in the interstitial space around the seminiferous tubules (Figure 2a). Histopathology also demonstrated hypoxic–ischaemic degenerative changes leading to germ cell destruction, formation of numerous vacuoles in the spermatogenic compartment and exfoliation of immature spermatozoa as well as depletion of Leydig cells (Figure 2b). The interstitial space becomes filled with fibroblasts and collagen (Figure 2b), further reducing the oxygen diffusion from the capillaries in the interstitial space to the seminiferous tubules.

Discussion

Both the cause and diagnosis of varicocele disease are related to the nature of the blood flow in the spermatic veins. It is therefore useful to present the relevant aspects of fluid mechanics that could explain why right varicocele cannot be easily clinically detected. Varicocele is caused by gravitational forces, which oppose the valve-assisted upwards flow in the internal spermatic veins. These forces can be expressed in terms of the hydrostatic pressure difference, $P$, in the form:

$$P = \rho gh$$  

(equation 1; Streeter, 1971)

derived from Pascal’s and Newton’s laws, where $\rho$ is the liquid density (g/cm$^3$), $g$ is the gravitational acceleration (981 cm/s$^2$) and $h$ is the vertical distance (cm) below a reference point.

Figure 2a. Light micrograph of the right testicular biopsy of a patient with varicocele. Note degeneration of germ cells indicated by numerous vacuoles in the seminiferous tubules. Microcirculatory vessels are occluded with blood (arrows). Some areas of the intertubular space are depleted of Leydig cells. Note the partial mechanical occlusion of the arteriole lumen by clotted blood indicating an abnormal oxygen supply. Original magnification (×200). ST = seminiferous tubules.

Figure 2b. Light micrograph of a right testicular biopsy from another patient with varicocele. Note the ischaemic degenerative changes revealed as fibrotic seminiferous tubules (arrows) and fibrosis of the arterioles (arrow heads). Non-fibrotic seminiferous tubules show thick basement membrane. The interstitial area is filled with a variety of cells and collagen. Note the increased distance between the arteriole and seminiferous tubules and fibrotic changes in arteriole wall and basement membrane. Original magnification (×200).
\( P \) is independent of the shape or size of the liquid column above the reference point. It varies only with vertical height and exists independently of motion in the liquid. If all the valves in each of the spermatic veins are incompetent, the hydrostatic pressure on the pampiniformis plexus relative to the corresponding upper junction (the renal vein or the IVC), can reach 30 mmHg in the left and 27 mmHg in the right ISV. The flow of fluid through a vessel, like any tubular flow, is possible only if there is a negative pressure-gradient in the direction of the flow.

Retrograde flow into the ISV in left varicocele occurs during a Valsalva manoeuvre-induced compression of the renal vein. The slight reduction in volume then results in a pressure rise in the renal vein, which is sufficient to cause back-flow in the left ISV. On the right side, in 92% of the cases, the ISV drains into the IVC, which in the resting state has an average pressure of 0 mmHg, (−5 mmHg up to +5 mmHg), whereas the average pressures of the spermatic veins are 10–12 mmHg (Ganong, 1999). In order to produce back-flow from the IVC to the ISV, the patient has to elevate the pressure in the IVC above 10–12 mmHg, plus pressure to overcome the viscous friction \( P_f \), which can be calculated using the Poiseuille equation:

\[
P_f = \frac{128 \mu L}{\pi D^4} Q, \quad \text{(equation 2; Streeter, 1971)}
\]

where \( \mu \) is the fluid viscosity, \( L \) and \( D \) are the tube length and diameter respectively and \( Q \) is the flow rate. The parametric group in the brackets represents the viscous resistance to flow in a blood vessel.

By employing equations 1 and 2, it can be deduced that in order to produce back-flow in the right ISV, the pressure in IVC would have to be elevated over 18–20 mmHg. This means that the pressure in the IVC will exceed the pressure of most of the interconnected veins to the IVC and blood will flow back from the IVC towards the peripheral venous system, instead of flowing to the heart. From a physiological point of view, the pressure in the IVC must remain the lowest pressure in the venous system in order to maintain continuous venous blood flow to the heart. Otherwise, reversal of flow in the IVC would cause fainting. So, the pressure in the IVC can never be higher than the pressures of tributary connected veins. For this reason, there is no back-flow in the right ISV via the IVC under physiological conditions.

In order to substantiate the theoretical understanding, this prediction was tested during venographies. Whereas reflux was clearly demonstrated by injection of contrast material into internal spermatic veins with incompetent or destroyed valves, a Valsalva manoeuvre performed by the patient always failed to produce reflux from the IVC to the right ISV. This suggests that detrimental hydrostatic pressure exists even in the absence of reflux.

Since back-flow into the ISV from the IVC cannot be produced on the right, no palpable enlargement of the veins is present. This clearly demonstrates that right varicocele cannot be detected by conventional means. Thus, the appropriate screening tool is contact thermography of the testis. It detects the rise in temperature due to the effect of decreased convective heat transfer from the testes caused by the stagnation of blood in the right ISV. When combined with ultrasonography, it yields the highest sensitivity and accuracy in the diagnosis of bilateral varicocele (Comhaire et al., 1976; Gat et al., 2004b).

The findings from venography combined with the fluid mechanics analysis prove that in the majority of infertile men suffering from varicocele the right side is also affected (86%) but cannot be easily detected. It also shows that associated retroperitoneal bypasses and collateral veins, which are more frequent on the right side than on the left side (75% compared with 70%), have the same detrimental effect as in the main vessel (ISV), since the pressure does not depend on the vessel’s diameter. They exert the same pathologic hydrostatic pressures that reverse the pressure gradient between the arteriolar and the venular systems in the testicular microcirculation, as proved by equation 1.

Histopathological analysis of the right testis in patients with varicocele, described above, leads to the conclusion that there is abnormal blood flow in the testicular microcirculation leading to two catastrophic phenomena: (i) metabolites and waste material do not flow normally out of the testis; (ii) the supply of oxygen and nutrient materials in arteriolar blood do not flow normally into it. Microscopic examination of the expression of these continuous ischaemic events is germ cell destruction, formation of numerous vacuoles in the spermatogenic compartment, exfoliation of immature spermatids, depletion of Leydig cells, thickening of the basement membrane and sclerosis/fibrosis in the vessel (Chakraborty et al., 1985; Aitken et al., 2003; Ozgur et al., 2003).

The oxygen supply to these tissues is further decreased due to the lowering of the diffusion rate, as a result of sclerosis and fibrosis in the wall of the arterioles, the endothelial cells and thickening of the basement membrane (Figure 2b). This increases the distance that the oxygen molecule has to diffuse from the vessel lumen to the seminiferous tubules and changes the diffusion properties of the materials. The diffusion rate, \( F_{o_2} \), can be calculated following Fick’s law:

\[
F_{o_2} \approx DA \frac{(P1–P2)}{S}
\]

where \( D \) is the diffusion coefficient, \( A \) is the contact area, \( P1–P2 \) is the pressure difference and \( S \) is the distance (White, 1986).

This process is progressive, and may explain why varicocele disease affects male infertility over time (Gorelick and Goldstein 1993; Gat et al., 2005b).

The vast majority of past patients described in the literature were treated by ligation of the spermatic vein on only the left side and the bypasses were ignored. This partial treatment has yielded limited, inconsistent and even conflicting results, which in turn, has misled some clinicians to disconnect varicocele from infertility. The disconnection of male infertility from varicocele disease explains why most infertile men are not examined for varicocele (Evers and Collins, 2003; Evers and Collins, 2004).

The conclusion by Evers and Collins in their meta-analyses...
(Evers and Collins, 2003, 2004) that the treatment of varicoceles is not effective, prudentially supports our findings that right varicocele is a crucial factor in causing male infertility. Since right varicocele has been ignored and thus left untreated, the standard, unilateral, i.e. partial, treatment of left varicocele for male infertility is not effective. In light of these findings, the proper interpretation and conclusion of the two comprehensive meta-analyses of Evers and Collins (2003, 2004) should be that inadequate treatment techniques for varicocele (left high ligation) indeed do not improve fertility in affected males. Based on these data and fluid dynamics analysis, it is likely that acknowledgement of the bilateral nature and the hypoxic effect of varicocele disease would lead to adequate treatment.

Based on our findings, varicocele is a bilateral vascular disease. The right side is affected in 86% of infertile men with varicocele. The disease is associated with a complex network of bypasses and retroperitoneal collaterals. In 92% of the patients, no reflux occurs to the right spermatic vein, even by Valsalva manoeuvre, and therefore right varicocele cannot be detected by palpation. Pathological hydrostatic pressure exists in the right internal spermatic veins, causing hypoxia in the seminiferous tubules, Sertoli and Leydig cells, and exists regardless of the presence of back-flow, depending only on the vertical height of the right ISV, and its venous bypasses.

Thermography, based on heat conductivity, is the best screening tool for detecting right varicocele. Ultrasonography is less sensitive than thermography but these combined tools yield the best results. Percutaneous transvenous occlusion (embolization) or bilateral microsurgery of the entire impaired testicular venous drainage system can effectively eliminate the increased hydrostatic pressure. This permits the return of normal supply of oxygenated arterial blood flow and nutrient material into the testicular microcirculation and the sperm production site.

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