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Reversal of benign prostate hyperplasia by selective occlusion of impaired venous drainage in the male reproductive system: novel mechanism, new treatment

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Summary

The prostate is an androgen-regulated exocrine gland producing over 30% of the noncellular components of the semen and promoting optimal conditions for survival and motility of sperm in the vagina. Benign prostate hyperplasia (BPH) is the most common benign neoplasm in men. Its aetiology is not clear, and therefore, current medical treatments are directed towards the symptoms. Though testosterone is known to be the promoter of prostate cell proliferation, no causal relation between serum testosterone levels and BPH has been found. In this study, we propose a novel and tested pathophysiological mechanism for the evolution of BPH and suggest a tested and effective treatment. We found that in all BPH patients, the one-way valves in the vertically oriented internal spermatic veins are destroyed (clinically manifested as varicocele), causing elevated hydrostatic pressure, some 6-fold greater than normal, in the venous drainage of the male reproductive system. The elevated pressure propagates to all interconnected vessels leading to a unique biological phenomenon: venous blood flows retrograde from the higher pressure in the testicular venous drainage system to the low pressure in the prostatic drainage system directly to the prostate (*law of communicating vessels*). We have found that free testosterone levels in this blood are markedly elevated, with a concentration of some 130-fold above serum level. Consequently, the prostate is exposed to: (i) increased venous pressure that causes *hypertrophy*; (ii) elevated concentration of free testosterone causing *hyperplasia*. We have treated 28 BPH patients using a technique that restores normal pressure in the venous drainage in the male reproductive system. The back-pressure and the back-flow of blood from the testicular to the prostate drainage system were eliminated and, consequently, a rapid reduction in prostate volume and a regression of prostate symptoms took place.

Introduction

Benign prostatic hyperplasia (BPH) is a major disease among ageing men (Walsh, 2002). It is the most common benign neoplasm, affecting almost 75% of men during the seventh decade of life (Wei *et al.*, 2005). Prevalence of BPH increases with patient age and according to autopsy studies 86% of men have BPH by the ninth decade of their lives (Bostwick *et al.*, 1992). Researchers have been puzzled by the following paradox: while testosterone is known to promote prostate cell proliferation (Feldman & Feldman, 2001), relatively low levels of serum testosterone are found in patients with BPH (Lagiou *et al.*, 1997; Roberts *et al.*, 2004). Moreover, anti-androgen treatments have a limited or transient effect on BPH; while the circulating androgen in the serum reduces to *castrated levels*, intraprostatic androgen and dihydrotestosterone (DHT) levels remain persistently high and the activities of

androgen receptors (AR) remain elevated (Page *et al.*, 2006). Hence, it is unclear whether BPH is related to *serum testosterone* or attributable to other factor(s). We will present in this study a detailed description of the causes of BPH and a treatment that leads to its reversal, at least partially. We show that the disease is caused by a failure of venous drainage in the male reproductive system. For the benefit of the reader, we shall first review briefly the main points in our discussion.

The prostate is an androgen-regulated exocrine gland in the male reproductive system; the gland produces an essential part of the fluid in the ejaculate that provides an optimal environment and 'working conditions' for the activity and the survival of the sperm within the 'hostile' conditions prevalent in the vagina. The testes are the production site of two products: sperm and free testosterone (FT). The testes receive oxygen and nutrients from the testicular arteries and drain the waste products and the FT via the internal spermatic veins (ISVs). Epidemiological studies in castrated males strongly support the key role of the testes in the pathogenesis of BPH (Chatterjee, 2003; Labrie *et al.*, 2005).

Testosterone, in its free form (unbound to proteins) diffuses into prostate cells and is known to be the promoter of prostate cell proliferation (Feldman & Feldman, 2001). It is mainly produced by the testes, and under normal conditions, reaches the systemic blood through the testicular venous drainage system (i.e., through the ISV) (Fig. 1). It eventually reaches the prostate via the prostate artery after it has passed through the venous and arterial

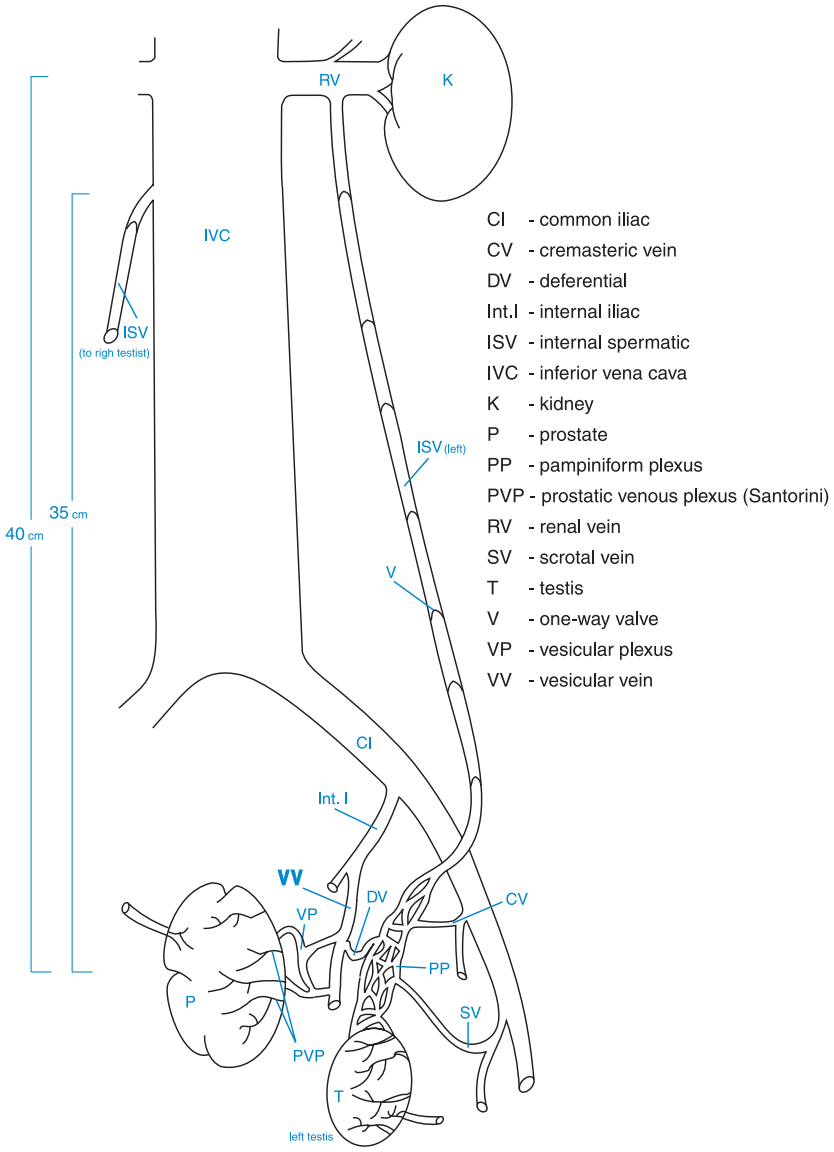

Fig. 1 Schematic description (left side only) of the anatomy of the testicular and the prostatic venous drainage systems. Both sides are not symmetrical in respect of the fluid mechanics aspects of the system and there is a difference in the vertical lengths of right and left internal spermatic veins (ISVs). The testes and the prostate share a common drainage venous flow: vesicular vein internal iliac, common iliac and ultimately the inferior vena cava. As there are no one-way valves between the testicular and prostatic drainage systems, free communication is possible if the hydrostatic pressure increases in the testicular side.

circulation, where it undergoes marked dilution and more than 98% of it binds to albumin and sex-hormone-binding globulin (SHBG) in which form it is not able to diffuse into the prostatic cells. Upon entering the prostatic cell cytoplasm, 90% of the FT is converted irreversibly by the 5α-reductase enzymes, to DHT - a more potent hormone - which has an obligatory role in the development of BPH. DHT has a more than 5-fold higher affinity for the AR than does FT (Geller, 1992; Chatterjee, 2003).

The one-way valves in the ISV facilitate venous blood flow upwards against the gravity, since there is no active pump in the vertical testicular drainage. Several studies have demonstrated that the destruction of one-way valves is a bilateral vascular disease (Gat *et al.*, 2003, 2004a), with a prevalence that increases with age (Canales *et al.*, 2005); reaching over 75% at the age of 70 (Levinger *et al.*, 2007). Without competent one-way valves the ISVs cease to function as drainage systems and become passive vessels. Each ISV then contains a vertical blood column that produces elevated hydrostatic pressure in the testicular venous drainage system. Note that the pressure in this system depends only on the height of the vertical blood column and not on the diameter of the blood vessel (Streeter, 1971; Gat *et al.*, 2005). This pathologically elevated hydrostatic pressure causes persistent hypoxia in the testicular microcirculation, leading to deterioration in spermatogenesis (Gat *et al.*, 2006) followed by a reduction in the testosterone production (Comhaire & Vermeulen, 1975; Gat *et al.*, 2004c). Each ISV is associated with a network of small bypasses and retroperitoneal collaterals (Comhaire *et al.*, 1981), and each of these, when vertically oriented, results in similar pathological hydrostatic pressure in the pampiniform plexus (PP) (White, 1986; Gat *et al.*, 2005). Hence, effective treatment of varicocele must include the occlusion of the ISVs on both sides and of all the associated vertical venous bypasses and the retroperitoneal collaterals by microsurgery or by super-selective retrograde venography (Gat *et al.*, 2005). The technique for percutaneous transvenous varicocele treatment was originally developed by Kunnen & Comhaire (1992) for the treatment of varicocele in male infertility and recently has been modified and further perfected specifically for the treatment of the impaired venous drainage apparatus in the male reproductive system (Gat *et al.*, 2006).

We will show that BPH is a consequence of the destruction of the one-way valves in the ISVs. The mechanisms leading to BPH are explained below in some detail.

Flow in the testicular and prostate venous drainage systems

Normally, as seen in (Fig. 1), the prostatic venous drainage flows in part through the prostatic venous plexus (PVP), the vesicular vein (VV), the internal iliac vein (II), the common iliac vein (CI), and ultimately to the inferior vena cava (IVC). The testes are drained mainly via the ISVs with some contribution by three other vessels; the deferential vein system (DV), the scrotal vein system, and the cremasteric vein. The blood in the DV flows to the VV, to the CI and ultimately to the IVC. Note that both the testicular and the prostatic drainage systems share a common space, the VV, which (from hydraulic point of view) is a connecting vessel between these two drainage systems and the intravascular pressures in these vessels are subject to the principle of 'communicating vessels', a direct derivative of *Bernoulli's* law of *energy conservation in fluids dynamics*. Under normal conditions the one-way valves have two main functions: (i) to facilitate the flow of venous blood upwards against gravity; and (ii) to divide the vertical ISV into 6–8 separate compartments, limiting the hydrostatic pressure on each valve to 6 mmHg. However, when the one-way valves are destroyed, two adverse hydraulic phenomena take place in the testicular venous drainage system, creating new, abnormal conditions in the testicular-prostate drainage systems: (i) Loss of the mechanism that propels the venous blood upwards against gravity, namely, the ISVs cease to function as drainage systems in the erect or sitting positions; and (ii) with the loss of the valves, the entire ISV becomes a single blood filled compartment that exerts an elevated hydrostatic pressure in the testicular drainage system. The pressure can be estimated according to the number of the valves that were destroyed which is found to be 6- to 8-fold the normal pressure. Consequently, the testicular venous drainage is shunted to existing alternative venous routes all of which then experience elevated pressure (*communicating vessels*). Consequently, the increased pressure propagates along all inter-connected vessels. Testicular blood flows now along the pressure gradient from high to low, namely, from the testicular drainage system to the prostate drainage system, carrying undiluted and unbound high concentrations of FT, bypassing the systemic blood circulation and flowing directly to the prostate.

Proposed mechanisms for the development of BPH

Based on the above, we hypothesise that BPH develops as a consequence of the progressive, age-dependent failure of the one-way valves in the ISVs. Two parallel processes lead to BPH:

1 Hypertrophy: A *mechanical* effect of congestion and enlargement of the prostate occurs as the pathological hydrostatic pressure in the testicular drainage systems is transmitted to the prostate via the testicular-prostate drainage systems.

2 Hyperplasia: A *biological* process of accelerated prostate cell proliferation resulting from the extremely high concentration of free testosterone reaching directly from the testes to the prostate (via the '*back-door*', in contrast to the normal pathway via the systemic circulation and the prostatic artery).

Proposed treatment for BPH

Derived from the above explanation, it is clear that, to be effective, a proposed treatment would need to eliminate the pathological hydrostatic pressure in the testicular venous drainage system. Such treatment can be performed by microsurgery or by super-selective venography and sclerotherapy of the impaired internal spermatic veins bilaterally, including the network of venous bypasses and retroperitoneal collaterals associated the impaired ISVs. This treatment prevents the pressure gradient between the two drainage systems and eliminates the back-pressure and the back-flow from the testes directly to the prostate. The normal physiological environment of the prostate gland would be restored, with normal venous pressures and a normal supply of FT through the prostate artery.

Patients and methods

In order to substantiate our assertions we conducted the following studies:

Study 1: In 245 cases, while performing venographies on patients with varicocele, we measured the height of the vertical blood columns in the ISVs (in order to estimate the venous hydrostatic pressure).

Study 2: In 12 infertile men with varicocele, during the above procedure, we tested the concentration of total testosterone and FT in 21 blood samples taken from the lower part of the left and the right ISVs along with peripheral blood testosterone and FT levels.

Study 3: The study was done on a series of 28 men, 41–77 years of age. These patients suffered at least 2 years from BPH (as diagnosed by urologists) with signs and symptoms of an enlarged prostate, associated with lower urinary track symptoms. Symptoms included a sensation of not fully emptying the bladder after finishing urination, a higher urination frequency, an urgency to urinate, 'stopping and starting' the urinary stream during urination, a weak urinary stream, and nocturia of at least once per night. Among all symptoms, nocturia was the main complaint cited by the patients as affecting the quality of life. Patients who suffered from either chronic prostatitis or chronic urinary tract infection were not included in the study. In order to prevent as much as possible inter-examiners and inter-instrumental errors, and to limit the examiner's bias, trans-abdominal ultrasonography for the measurement of prostate volume was performed intermittently by three highly experienced ultrasonographers, with the two US instruments (Philips HD 11 XE and ATL, HDI - 3500). One of the radiologists was not aware of the purpose of this clinical study and the other two were not exposed to the findings. Each patient was examined at least four times during the follow-up study in order to follow the changes in volume after the treatment of the impaired venous drainage system. Prostate-specific antigen (PSA) was measured before the treatment. Bilateral varicocele was diagnosed in all the patients by colour flow Doppler ultrasound and contact thermography. Thermography, was performed using a flexible liquid crystal thermostrip Varicoscreen® (FertiPro, Beemen, Belgium), which is considered most accurate and sensitive for detection of subclinical and bilateral varicocele (Trum *et al.*, 1996; Gat *et al.*, 2004b). Treatments were performed by percutaneous super-selective venography and sclerotherapy of the entire complex network of internal spermatic veins including all associated venous bypasses and retroperitoneal collaterals (Gat *et al.*, 2005).

Follow up was done at least 6 months from the starting of the treatment. After treatment, the patients did not use any drug or 'over-the-counter' preparation related to prostate treatment. Prostate volume and PSA were examined every 4–6 weeks and patients reported their lower urinary tract symptoms. Among these, nocturia was recorded in order to examine if there was relief of this symptom and whether it correlated with reduction of prostate enlargement.

The study was carried out with the approval of the hospital ethics committee, according to the principles of the Declaration of Helsinki. All patients assigned a written informed consent to participate in the study prior to the procedure. The treatments were performed by a highly experienced interventional radiologist in a digital fluoroscopic suite equipped with a 45/90 degree tilt table (Gat *et al.*, 2003, 2004a).

Study 4: We examined the back-flow from the testicular drainage system (PP) to the prostate via the prostate drainage system. In conjunction with the varicocele treatment procedure, contrast material was injected into the lower third of the impaired venous drainage system of the right side, exerting gentle pressure to simulate the hydrostatic pressure on the testicular drainage system in the erect posture.

Results

Study 1: The average distance between competent one-way valves in the ISVs is 6–8 cm; the average vertical height of the blood column in the right ISV is ~35 cm and in the left one is ~40 cm. The hydrostatic pressure

in the vein is calculated from $P = \rho \times g \times h$ (Streeter, 1971), where ρ the density of the liquid (gr cm^{-3}), g the gravitational acceleration (981 cm s^{-2}), and h the vertical height of the blood column (cm); leading to some 27 mmHg on the right and some 31 mmHg on the left drainage system. These pressures are elevated some 6–8 times above normal.

Study 2: We found an average concentration of the total testosterone in the lower part of each ISV (adjacent to the DV) to be 2084 nmol l^{-1}; in comparison to 21.33 nmol l^{-1} in the serum. The unbound, free testosterone was found to be 3632 pmol l^{-1}; in comparison to 27.33 pmol l^{-1} in the serum. Hence, the concentration of the total testosterone is nearly 100-fold higher (see also Jarwo, 2001; Walsh, 2002) and that of the free testosterone is some 133-fold higher than the normal values in the serum.

Study 3: Before treatment, the average parameters of all patients were as follows: prostate volume 56 ml (ranging from 28 to 122); PSA 3.5 ng ml^{-1} (ranging from 0.4 to 13); nocturia 3.57 times a night (ranging from 1 to 7). Following the treatment, the prostate volume decreased to an average of 36.9 ml (ranging from 22–93); PSA decreased to 3.2 ng ml^{-1} (ranging from 0.3–8.9); nocturia decreased to an average of 0.96 (range 0–2) (see Table 1). The results after treatment represent a period of 6 months interval from the treatment.

Study 4: On retrograde venography of the PP, after a delay of about 10 s, a contrast material 'blush', of the prostate gland capsular region, was observed (Fig. 3). Both are clearly seen in the image. This image demonstrates that in the testicular venous drainage system, in the absence of competent one-way valves, when the hydrostatic pressure is elevated (in the erect man's posture) venous blood from the testicular drainage (high pressure) can flow directly to the prostate (low pressure) as was expected according to a straightforward application of physical principles.

Statistics

The data were analysed using paired-comparison *t*-test (repeated measure analysis). Prostate volume significantly reduced after treatment, with value $P < 0.0001$ ($t = 8.95$, $n = 27$). PSA value slightly decreased after treatment, however, not significantly with $P = 0.1117$ ($t = -1.65$, $n = 26$,). Nocturia was significantly reduced after treatment, with $P < 0.0001$ ($t = -9.93$, $n = 26$), as seen in Table 1.

Table 1 Prostate volume PSA and nocturia before and after the treatment of 28 patients with BPH

Variables	Before treatment	After treatment	*P*-value
Prostate volume	56.00 ± 4.12	36.93 ± 3.10	<0.0001
PSA	3.56 ± 0.63	3.27 ± 0.45	0.1117
Nocturia	3.56 ± 0.63	0.96 ± 0.14	<0.0001

PSA, prostate-specific antigen; BPH, benign prostate hyperplasia.

Discussion

Physical deterioration of the one-way valves in the ISV

Normally lacking an active pump in the testicular venous drainage system, the one-way valves function as a unique hydraulic system that raises the venous blood upwards, stepwise, against gravity while preventing downward flow. The valves do not open and close in a synchronous way (as they do in the lower limbs), but are activated by intermittent pressure fluctuations produced by the action of nearby muscles and abdominal structures. Under these conditions, some of the valves are closed while others, above them, are open. Hence, the average hydrostatic pressure exerted on lower valves is higher than the average calculated physiological hydrostatic pressure exerted on each valve, which is ~4–6 mmHg (see above and Figs 1 and 2a). This is also the approximate hydrostatic pressure at the testicular and the prostate venous drainage systems under normal conditions.

This pressure P can be calculated using the equation for calculation of the hydrostatic pressure (a derivative of Pascal and Newton's principles):

$$P = \rho \times g \times h$$

P is independent of the shape or diameter of the liquid column and of any motion in the liquid but only on its height (h). For a normal compartment height of 6–8 mm (see Figs 1 and 2a), the physiological average pressure on a valve, is ~4–6 mmHg. This pressure is also the approximate hydrostatic pressure at the testicular and the prostate venous drainage systems under normal conditions.

As each valve opens and closes at least 100 000 times a year (~2–3‰ of the number of heart beats), the valves are exposed repeatedly to an excessive load exerted on their elastic collagen tissue, leading to their *progressive* physical deterioration, culminating eventually in their complete destruction. The vertical height of the blood column in the right ISV is ~35 cm and in the left one is ~40 cm. When all the valves in each of the ISVs are incompetent, the hydrostatic pressure at the drainage system relative to the corresponding insertion of the ISV is over 30 mmHg on the left side and 27 mmHg on the right side. Recent studies showed that the incidence of this phenomenon increases with age (Canales *et al.*, 2005), reaching over 75% at the age of 70 (Levinger *et al.*, 2007).

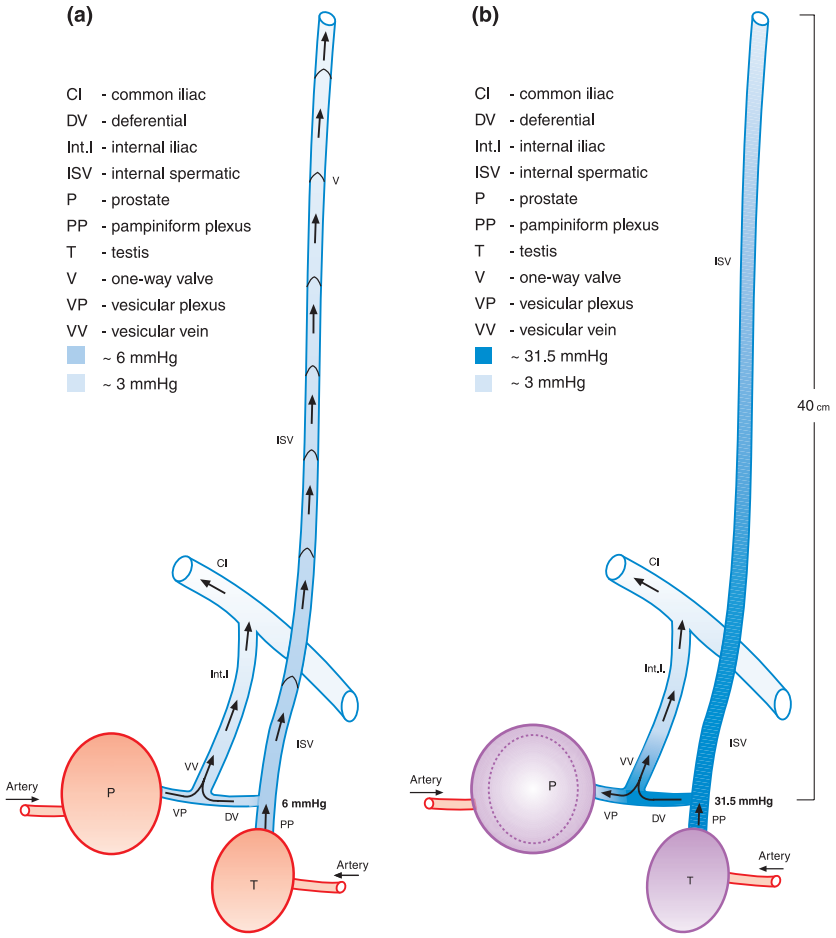

Fig. 2 (a) Schematic description of the blood flow in medial part of the left testicular venous drainage system in healthy males. The pressure gradient is along the direction of blood flow, as indicated by the arrows. Drainage from testes joins the drainage from the prostate and both continue to the internal iliac vein (Int. I), the common iliac (CI), and finally to the inferior vena cava (IVC). Note that none of these vessels have one-way valves.

Fig. 2 (b) Schematic description of the blood flow in the medial part of the left testicular venous drainage system in males with varicocele disease. The pressure gradient is indicated by color density gradient. The destruction of valves in the left internal spermatic vein (ISV) results in a 40-cm vertical blood column, exerting a high hydrostatic pressure on the venous drainage system of testes. Venous blood flows along 'negative gradient' of the pressure from the testicular drainage system to the vesicular vein (VV), the vesicular plexus (VP), and finally the prostatic venous plexus (PVP or the 'Santorini plexus') and the prostate. The prostate is now exposed to (i) an increased hydrostatic pressure, and (ii) to an elevated free testosterone.

Effect of elevated pressure in the testicular venous drainage system on the entire reproductive system

When the valves are destroyed, venous blood in the ISVs cannot flow upwards. The drainage from the testes is diverted into three other channels with elevated pressure. One of these, the DV, which drains the testes, creates hydraulic connection with the PVP, which drains the prostate via the VV. The VV, being the connecting vessel between the two systems, is a common space shared by the testicular and the prostate drainage systems. On the side of the prostatic drainage system, there is physiological pressure; however, on the side of the testicular drainage systems the pressure is substantially higher. Venous blood from the testicular side will flow retrograde into the prostate venous drainage (via the VV and the PVP), reaching the prostate (study 4 & Fig. 3) at elevated hydrostatic pressure with elevated concentration of FT.

It should be noted that in quadruped animals, the venous drainage of the reproductive system is horizontal and therefore does not need one-way valves. Studies on animal models have shown that by an artificial increase of the intra-abdominal pressure in a canine model, radio-opaque contrast material can be transferred from the DV directly to the prostate (Pierrepoint *et al.*, 1975; Dhabuwala *et al.*, 1978). These comparative anatomical data further confirm and support the clear, hydraulic effects that we expected in our study regarding the connection between the testicular and prostate drainage systems that the fluid dynamics of both systems obey the principle of 'communicating vessels', where any change in the pressure of one system causes immediate changes in the pressure and in the flow directions in the other connected system to the point that the fluid dynamic equilibrium is conserved (Bernoulli's principle).

Two parallel effects then occur in the prostate, a rapid mechanical effect – hypertrophy; and a slower, biological process – hyperplasia.

Hypertrophy occurs as a result of elevated venous back-pressure, causing congestion and mechanical enlargement of the gland. It can be recognised by studying its effect on the lower segment of the ISVs and the PP, which dilate until they can be easily palpated (varicocele). The volume of the ISVs, and in particular that of

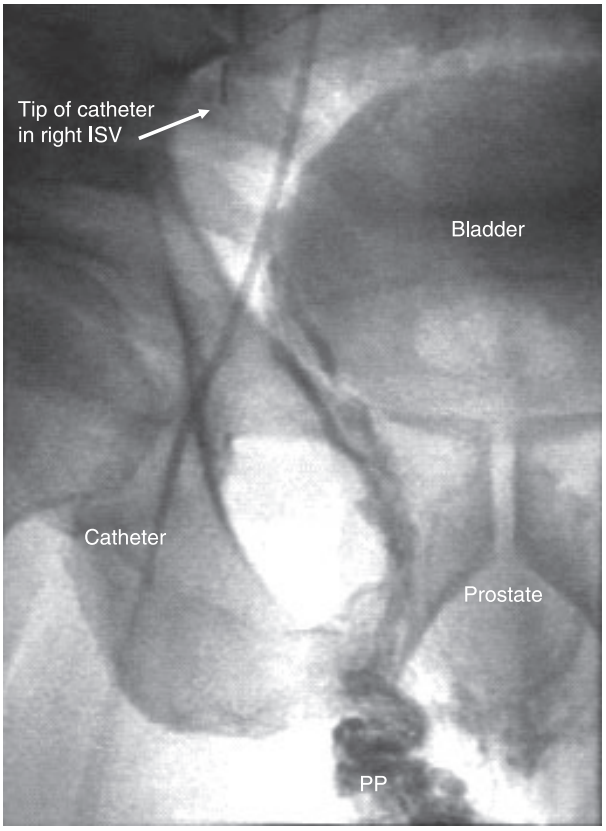

Fig. 3 Venographic demonstration of prostate gland and relationship to testicular venous system using intravenous contrast material in a patient with varicocele. Retrograde flow seen from tip of catheter, placed in lower internal spermatic vein (ISV). Hydrostatic pressure in the testicular venous drainage system is higher than in prostate drainage system, and back-pressure and back-flow propagate to prostate venous drainage system and directly into prostate. Blood flow from pampiniformis plexus (PP, in testicular system) to the prostate is shown. Note that back-pressure exerted on prostate via PP is substantially higher than physiological pressure, leading to prostate hypertrophy, while the venous blood, rich in free testosterone, leads to prostate hyperplasia.

the PP, can increase by 3- to 9-fold under the elevated pressure (Wishahi, 1992). The prostate, exposed to that elevated pressure and composed of elastic tissue, enlarges in response to the increasing pressure in a similar manner; leading to hypertrophy of the prostate.

Hyperplasia, the biological process, can be explained as follows: Under normal conditions, FT reaches the prostate gland via the prostatic artery, after travelling through the general circulation system (nearly 150-cm long). Over this long route, the testosterone dilutes by 70- to 100-fold (Jarwo *et al.*, 2001; Walsh, 2002) and binds to SHBG. Only a small fraction of the testosterone, <2%, remains free (Feldman & Feldman, 2001). However, when the valves are destroyed, the blood that arrives directly from the testes to the prostate via the 'back-door', travels only 10–15 cm, thus carrying high levels of FT - 133 times the normal serum concentration [Study 2], and thus promotes accelerated prostatic cell proliferation. The result is a change in the normal proliferation/apoptosis balance of prostatic cells (Chatterjee, 2003), leading to *hyperplasia* of the prostate. Of course, the persistent accelerated proliferation of prostate cells does not stop at the level of hyperplasia in BPH and may progress with time, in uncontrolled process, to neoplasia.

Reversal of BPH after the treatment

When restoration of normal hydrostatic pressure in the testicular venous drainage system is achieved, there is no pressure gradient between the two systems, hence, back-pressure and back-flow from the testes to the prostate are eliminated. Blood from both drainage systems, meeting at the VV, now jointly flow towards the internal iliac vein (II), the CI, and ultimately to the IVC. At that stage, the effects of back-pressure and back-flow do not exist anymore:

1 The intraprostatic pressure returns to normal, congestion regresses and the volume of the gland decreases rapidly within weeks.
2 Androgen now arrives only via the prostatic artery and the concentration of the FT arriving at the prostate is physiological: <1% of the one before the treatment. This correction can be considered as *super-selective intraprostatic androgen deprivation therapy*. The proliferation/apoptosis ratio (Chatterjee, 2003) returns to normal, and prostatic cells are no longer under the influence of pathological proliferative stimuli. The prostate returns gradually towards the normal 'steady state', which depends also on its elastic property.

The enlarged prostate has two adverse mechanical effects on the urinary system: (i) it reduces the bladder volume reservoir leading to frequency of urination; and (ii) by exerting pressure on the urethra it narrows its diameter, causing weak stream and limiting bladder emptying. When the urethral diameter is reduced by 50%, urine flow is only approximately 7% of the normal stream $[(1/2)^4]$ (Hagen-Poiseuille equation).

The proposed treatment reduces prostate enlargement mostly attributable to reduction of intraprostatic pressure, resulting in a general decrease in prostate volume homogeneously in all dimensions; however, it leaves the gland intact.

Conclusions

Benign prostate hyperplasia develops due to an impairment of the testicular venous drainage system in the erect posture of the human. Based on our fluid-mechanics

analysis of the venous drainage in the reproductive system, and the results of the developed treatment, the following statements can be made:

1 Benign prostate hypertrophy is caused by increased hydrostatic pressure in the prostate drainage system, while benign prostate hyperplasia is caused by an excessively high concentration of free testosterone; both arriving from the testes to the prostate by pathological back-pressure and back-flow through the testicular and the prostate drainage systems.
2 Eliminating the pathological hydrostatic pressure in the testicular venous drainage system by occlusion of the impaired ISVs, including all the associated venous bypasses and retroperitoneal collaterals by super-selective transvenous sclerotherapy or by microsurgery, eliminates the venous back-pressure and the back-flow of blood to the prostate. This reduces its exposure to elevated free testosterone. This initially reduces benign prostate hypertrophy, and subsequently, at least partially, reverses benign prostate *hyp*erplasia.
3 We recommend that patients with BPH be examined for bilateral varicocele and be treated according to the suggested treatment**.**
4 Under the pathophysiological conditions we describe, free testosterone flows to the prostate via the 'back-door' (venous drainage system) in concentrations of two orders of magnitude above serum level. Hence, the normal physiological relation between serum levels of androgen and intraprostatic androgen levels is severed. Therefore, serum levels of androgen in these patients do not reflect the true biologic drama that takes place in the prostatic tissue and especially in the prostate cells where their 'command chamber' may 'go crazy' under such huge abnormal activation by FT.

Using this understanding of the found pathophysiologic mechanism, we can begin to explain the development of prostate cancer and some of its interesting and enigmatic biological phenomena, such as: persistently elevated intraprostatic androgen concentrations and elevated androgen receptor activity, even with castrated levels of *serum testosterone* during anti-androgen therapy (Mostaghel *et al.*, 2007); why castration-resistant prostate cancer develops (androgen-independent prostate cancer) (Chen *et al.*, 2004; Isaacs & Isaacs, 2004); why prostate cancer is one of the slowest among cancer diseases where most patients with localised prostate cancer, under active surveillance, remain stable or show non-clinically significant progression, which precludes the necessity for radical treatment (Klotz, 2005); the biological paradox that, on the one hand, lower serum testosterone levels are found in patients with prostate cancer (Morgentaler *et al.*, 1996); and with more aggressive disease (Hoffman *et al.*, 2000); but, on the other hand, testosterone replacement therapy that doubles serum testosterone levels does not increase intraprostatic testosterone and does not have negative effect on prostate tissue (Marks *et al.*, 2006).

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