




## ORIGINAL ARTICLE

# Paying the price for standing tall: Fluid mechanics of prostate pathology

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**Abstract**

**Background:** Age-dependent increase in the incidence of benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are both related to cell proliferation and survival controlled by intraprostatic free testosterone (FT) concentration. Paradoxically, BPH and PCa occur as circulating testosterone levels decrease, so any possible relationship between testosterone levels and development of BPH and PCa remains obscure.

**Results:** In BPH the enlarging prostate is exposed to high testosterone levels arriving directly from the testes at concentrations about hundredfold higher than systemic FT. This occurs because venous blood from the testes is diverted into the prostate due to the elevated hydrostatic pressure of blood in the internal spermatic veins (ISVs). Elevated pressure is caused by the destruction of one-way valves (clinically detected as varicocele), a unique phenomenon related to human erect posture. While standing, human males are ISVs vertically oriented, resulting in high intraluminal hydrostatic pressures—a phenomenon not found in quadrupeds. In this communication, we demonstrate the fluid mechanics' phenomena at the basis of varicocele leading to prostate pathology.

**Conclusions:** So far, varicocele has been studied mostly for its etiologic role in male infertility and, thus, for its effects on the testes. It is becoming clear that varicocele is a major etiologic factor in BPH and likely also in PCa. Restoring normal testicular venous pressure by treatment of the abnormal ISV's in varicocele has been shown to avert the flow from the prostate with the effect of reducing prostate volume, alleviating symptoms of BPH, and increasing concentrations of circulating FT.

**KEYWORDS**

benign prostate hyperplasia, human erect posture, testicular venous pressure, varicocele, varicocele occlusion

**Abbreviations:** BPH, benign prostatic hyperplasia; CV, cremasteric vein; DV, deferential vein; FT, free testosterone; IL, internal iliac vein; ISV, internal spermatic vein; ISVs, internal spermatic veins; IVC, inferior vena cava; OWV, one-way valve; PCa, prostate cancer; PVP, prostatic venous plexus; SAN, Santorini plexus; SV, scrotal vein; VP, vesicular plexus; VV, vesicular vein.

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## 1 | INTRODUCTION

Benign prostate hyperplasia (BPH) and prostate cancer (PCa) are among the most common ailments of older men,<sup>1</sup> both linked to the alteration of prostatic cell proliferation rate and survival.<sup>2</sup> In 1941, Huggins and Hodges<sup>3</sup> reported that testosterone regulates prostate cell proliferation. Exposure to high concentrations of testosterone maintains prostate cell proliferation and survival leading to BPH and, subsequently, malignancy.<sup>3</sup>

Since the Huggins-Hodges discovery, many have sought to understand the development of BPH and PCa and resolve the paradoxical observation that with advancing age, the level of testosterone in the peripheral blood decreases while the incidence of BPH and PCa increases.<sup>4</sup> Also, paradoxically, given their discovery, is the observation that lower serum testosterone levels correlate with more advanced and more aggressive PCa.<sup>5</sup> Extensive studies of the mechanism of testosterone action have failed to advance sufficiently the understanding of BPH and PCa pathogenesis; studies of the association of the prostate disease with other possible causes have similarly failed to solve the aforementioned paradox.<sup>4</sup> Nonetheless, treatment for BPH and PCa continues to be based largely on anti-androgen drugs resulting in partial and transient effects.

Based on the clinical insight into the pathogenesis of male infertility, we have focused on the effects of bipedalism on age-dependent changes in venous blood flow in the male pelvis.<sup>4</sup> These effects lead to the unique pathology found in men. Due to their erect posture, hydrostatic pressure in the internal spermatic (testicular) veins (ISVs) is elevated in comparison with quadrupeds whose ISVs are oriented horizontally. In time, the elevated venous pressure in these veins in humans causes mechanical failure and destruction of one-way valves (OWVs) within the vertically oriented ISVs. This increases the hydrostatic pressure in the testicular venous drainage and elevates the pressure in the communicating vessels of the prostate venous drainage to the level exceeding the pressure in the veins leaving the prostate and reversing venous flow into the prostate. Parenthetically, the horizontally oriented ISVs of quadrupeds do not need and do not have OWVs.

The disappearance of OWVs in the ISVs with the concomitant elevation of hydrostatic pressure dilates the testicular veins, including those of the pampiniform plexus, the clinical entity called varicocele. As a result, intratesticular venular pressure can rise to exceed the perfusion pressures in the testicular arterial system. This remarkable reversal of the normal pressure gradient across the testicular tissue prevents the normal flow of oxygen and nutrients to the testes—explaining why varicocele has been long understood as a major factor in etiology of male infertility.<sup>6-8</sup> We have shown that varicocele pathologically redirects venous blood flow into the prostate.<sup>4</sup> The diverted venous blood from the testes carries undiluted free testosterone (FT) directly into the prostate. Under these circumstances, instead of receiving their normal supply of testosterone from systemic blood through prostatic arteries, prostate cells receive a high concentration of testosterone directly from the testes through the diverted testicular venous efflux. This situation led us to predict that under the pathophysiologic conditions of absent venous

valves in the ISVs, the high testosterone levels arriving to the prostate will result in BPH and other pathology.<sup>9</sup>

Indeed, recent direct measurements demonstrate that testosterone (and dihydrotestosterone) “accumulate in the hyperplastic prostate tissue.”<sup>10</sup> We assert that the reason is precisely the exposure of the prostate to supraphysiological testosterone levels arriving directly from the testes via the testicular-prostatic drainage. At the same time, by reducing the normal supply of nutrients and oxygen to the testes, varicocele leads to the reduction of testicular testosterone output (as measured in peripheral blood). Thus, the same pathophysiologic mechanism increases the amount of testosterone directed towards the prostate even as it reduces overall testosterone production by the testes.<sup>11</sup>

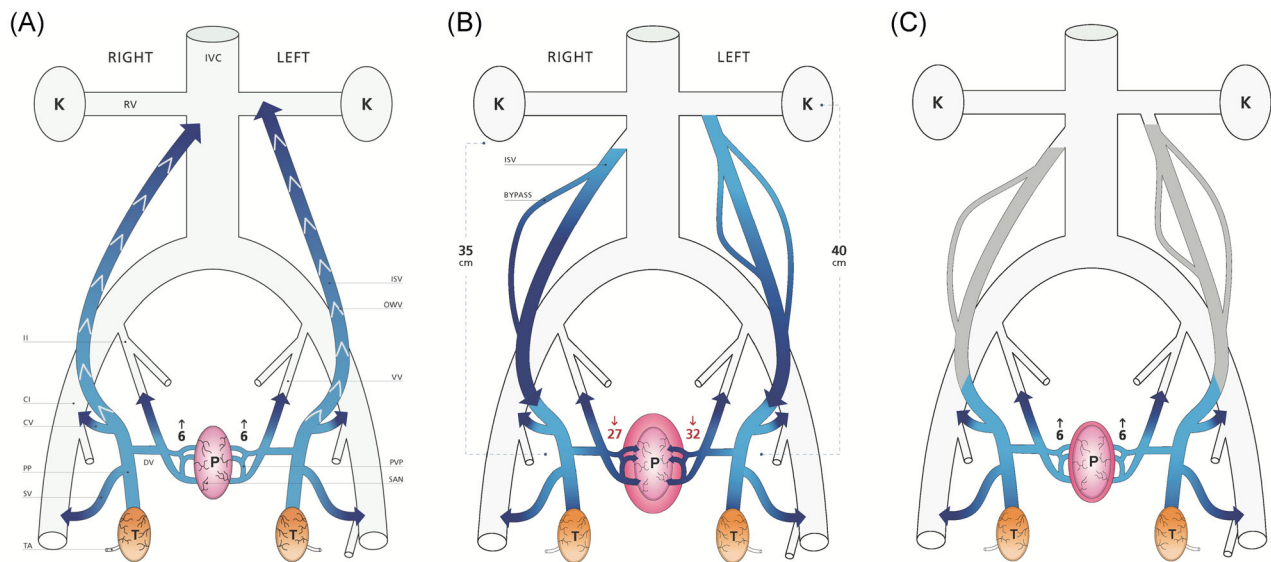
Occluding the malfunctioning ISVs in patients with varicocele restores normal hemodynamics of the prostate.<sup>6</sup> Significantly, of the 206 patients treated for BPH by our own technique, 81.5% experienced significant symptom relief and reduction of prostate volume.<sup>12</sup> With the results we have achieved by eliminating the elevated pressures, we demonstrate the important role of fluid mechanics in BPH. In this communication, we present a detailed analysis of the physical forces involved.

## 2 | CIRCULATORY SYSTEM OF HUMAN TESTES AND PROSTATE

Unlike in mammalian quadrupeds, gonadal veins of male *Homo sapiens* contain OWVs. These valves promote the flow of venous blood against gravity towards the heart and prevent the downward flow of venous blood towards the testes from the veins of upper abdominal organs such as kidneys and adrenal glands. In addition, the valves divide the vertical columns of blood within ISVs into six to eight segments reducing the hydrostatic pressure of the vertically oriented testicular veins to shorter segments between adjacent valves (Figure 1A). Together with ISVs, the cremasteric veins (CVs), scrotal veins (SVs), and deferential veins (DVs) also drain a portion of the testicular venous efflux (Figure 1A). Using venography, we regularly observe the three latter veins with diameters approximately only one quarter as large as the usual diameter of ISV. According to the Hagen-Poiseuille principle,<sup>13</sup> which states that the difference in the rate of flow between two vessels is related to the fourth power of the ratio of vessel diameters,<sup>1</sup> under normal conditions, the combined contribution of the three veins represents only a small fraction of the capacity of the entire venous drainage system.

The lower extremities veins also contain OWVs. However, the deep veins of the lower extremities are found within the muscles of the calf and thigh. During movement, muscle contractions compress the veins and act to pump the venous blood with the valves promoting upwards flow as they open and close in synchrony.<sup>14,15</sup>

<sup>1</sup> $Q_2/Q_1 = k(d_2/d_1)^4$ . Here  $Q_{1,2}$  are flow rates before and after expansion and  $d_{1,2}$  are diameters before and after expansion, respectively. The fourth-power dependence shows that even a small increase in vein diameter will strongly increase the blood flow rate.



**FIGURE 1** Schematic presentation of the anatomy and venous blood flow in normal and pathological testicular and prostatic venous drainage systems. A, Under normal conditions, most venous blood from the testes drains into the internal spermatic veins (ISVs) where one-way valves assist in lifting it towards the heart. From the prostate, venous blood is driven by the upwards pressure gradient of 6 mm Hg in the venous plexus/Santorini plexus of the prostate to the vena cava (where the pressure is  $-5$  mm Hg). B, Destruction of one-way valves in ISVs reverses downwards the direction of the hydrostatic pressure in the right ISV up to 27 mm Hg and up to 32 mm Hg in the left ISV. This produces the pressure gradient from the deferential vein (DV) in the direction of the prostatic venous plexus (PVP) partially diverting the free-testosterone rich testicular venous efflux via DV to PVP and Santorini plexus directly into the prostate. C, Occlusion of the faulty ISVs and their newly formed collaterals (indicated by the gray areas) eliminates the pathological venous overpressure and restores normal pressure relationships within the testes/prostate venous system and reestablishes normal pressures within the venous drainage system. CI, common iliac vein; CV, cremasteric vein; DV, deferential vein; II, internal iliac vein; ISV, internal spermatic vein; IVC, internal vena cava; K, kidney; OWV, one-way valve; P, prostate; PP, pampiniform plexus; PVP, prostatic venous plexus; RV, renal vein; SAN, Santorini plexus; SV, scrotal vein; T, testis; VP, vesicular plexus; VV, vesicular vein [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

However, the mechanism of lifting venous blood leaving the testes differs from the mechanism in legs because the ISVs are located along the posterior wall of the abdominal cavity where they are not surrounded by muscles. Intra-abdominal pressure changes are not coordinated; hence, venous blood flows upwards when the pressure in the lower segments demarcated by adjacent valves is higher than in the higher segments.<sup>15</sup> If intravenous pressure in a segment is higher than in the segment above it, the OWV opens and blood moves into the higher segment. When intravascular pressure in a segment decreases, the valve closes so that blood that has advanced upwards cannot flow back. Thus, blood progresses upwards without direct active pumping against gravity. Importantly, opening and closing of OWVs is asynchronous, exerted by intermittent changes of an intra-abdominal pressure difference between two adjacent valves.

### 3 | WHY DO OWVs IN ISVs DETERIORATE AND MALFUNCTION?

If several valves in an ISV transiently open at the same time, hydrostatic pressure on the closed valve below becomes proportionally more elevated.<sup>15</sup> As a result, elastic properties and valve

margins are put under stress and gradually deteriorate, first in the lower valves that can experience the highest pressures when multiple valves happen to open simultaneously, and later in the higher ones; this process is well documented by venography.<sup>6</sup> Mechanical deterioration and eventual disappearance of the OWVs<sup>6,16</sup> results eventually in a single continuous vertical column of blood on average 32 to 35 cm high in the right ISV and 40 to 45 cm high in the left ISV corresponding to the combined pressure within the six to eight previously separate segments (Figure 1A,B). The result is a sixfold to eightfold hydrostatic pressure increase in the testicular venous system.

Even before the age of thirty, deterioration of OWVs in ISVs can be diagnosed in nearly 20% of males.<sup>7</sup> The phenomenon, clinically detected as varicocele, is the major cause of male infertility.<sup>17,18</sup> Damage to the valves progresses with age and the incidence increases at a rate of nearly 15% per decade; by the end of the seventh decade, its prevalence is above 75%.<sup>19</sup> Significantly, in taller men valves deteriorate more rapidly because their ISVs are longer and the distance between two adjacent valves is larger; this leads to more rapid wear and tear of each valve. Upon destruction of OWVs, in taller men hydrostatic pressure in ISVs is higher than the hydrostatic pressure in ISVs of shorter man<sup>20</sup> (Figure 1B).

## 4 | WHAT HAPPENS IN TESTICULAR VENOUS DRAINAGE IN ABSENCE OF FUNCTIONING VALVES?

The left ISV is 40 to 45 cm long and is compartmentalized to seven or eight interval segments, each 5 to 6 cm long. According to Pascal's law,<sup>13</sup> hydrostatic pressure  $P$  is the product of the specific gravity of the fluid and the height of the column.<sup>2</sup> With specific gravity of blood of 1.03 g/mL, for a 1-cm column, we calculate the  $P_{1\text{cm}} = 0.78$  mm Hg (103 Pa). Hence, for a 6-cm segment the pressure on the valve will be  $P_{6\text{cm}} \sim 4.7$  mm Hg (480 Pa). In the absence of functioning valves, the blood column is continuous, 40 to 45 cm long. Under these conditions and in upright posture, the calculated pressure in the left ISV can reach up to 31.2 mm Hg (3.2 kPa) to 35.1 mm Hg (3.6 kPa), that is, six to eight times above normal pressure. Similarly, in the vertical height of the oblique right ISV, the pressure can reach 27 mm Hg to 30 mm Hg, five to six times normal value (Figure 1B).

Recently, Rahman et al<sup>21</sup> measured blood pressure within the ISV in patients undergoing microsurgical varicocelectomy.<sup>21</sup> In the "maximum dilated ISV (A)" (presumably the left ISV), they measured the pressure  $15.93 \pm 6.34$  mm Hg (range, 16–46 mm Hg). Upon the Valsalva maneuver, these values increased to  $31.03 \pm 12.63$  mm Hg (range, 17–61 mm Hg). The measurements were taken during surgery under spinal anesthesia, and the authors do not report in which exact positions patients were at that time of measurements. Nonetheless, these direct measurements are within the range of values we propose based on straightforward principles of fluid dynamics. It is particularly intriguing that the mean value of 31 mm Hg measured under the Valsalva maneuver in "ISV A" is identical to the value we calculated for the 40-cm long vertical ISV.

Destruction of OWVs raises the hydrostatic pressure within testicular venous drainage to the extent that it exceeds the pressure within local arteries preventing the proper exchange of oxygen and metabolites. This causes persistent hypoxia in the testes leading to impaired sperm production and infertility.<sup>6</sup> Physiological response to hypoxia stimulates the evolution of venographically detectable networks of minute vertically oriented venous bypasses associated with ISVs.<sup>6</sup> Initially, their diameters are on the scale of micrometers enabling movement of venous blood by capillary force upwards. The function of these bypasses is to maintain testicular venous drainage under the circumstances when the main drainage by ISVs fails after the destruction of the OWVs.

The capillary force involved is described by the Young-Laplace equation.<sup>13</sup> The height to which blood is raised by a capillary force depends on the surface tension of the fluid and diameter of the vessel. Capillary force is unique in that it can move fluids upwards against gravity without the requirement for external energy or external force.<sup>3</sup> When ISVs cease functioning as testicular drainage,

<sup>2</sup> $P = \rho \times h$ . Here,  $P$  is the hydrostatic pressure,  $\rho$  specific gravity of the fluid, and  $h$  the height of the fluid column.

<sup>3</sup>Pressure difference along the surface of the capillary wall,  $\Delta P$ , is proportional to the surface tension of the fluid,  $\gamma$ , and inversely proportional to the radii of the vessels,  $r_1$  and  $r_2$ .  $\Delta P = \gamma \times [1/r_1 + 1/r_2]$ . When by approximation  $r_1 = r_2$ , as it occurs in blood vessels, then

new capillary bypasses arise in association with and along with ISVs. Our analysis of venographic studies indicates that diameters of these capillaries are of the order of tens of micrometers rarely reaching the width of 1 mm. We hypothesize that the capillary networks provide the alternative mechanism of testicular venous drainage necessary for sperm production, a clear evolutionary advantage. With time, this important function of capillaries is lost as their diameters widen under the increased hydrostatic pressure. Consequently, the capillary force promoting upward flow vanishes (footnote 3). At the advanced stage of pathology, hydrostatic pressure within these veins is the same as in ISVs (as hydrostatic pressure does not depend on the diameter of the vessel or motion of the fluid, but only on the height of the vertical fluid column; footnote 2).

## 5 | WHAT HAPPENS WITHIN TESTES DUE TO ABNORMAL VENOUS HYDROSTATIC PRESSURES?

Arterial pressure drives oxygenated, nutrient-rich blood to testicular tissue. For a normal function, this pressure must be higher than the pressure on the drainage side of the circuit. When the OWVs in the testicular venous system fail, venous pressure exceeds the pressure in the arteries (Figure 1B). Consequently, the normal flow of oxygenated blood is not maintained resulting in persistent hypoxia at the sites of spermatogenesis and testosterone production.<sup>6</sup> This, in turn, reduces sperm count, motility, and quality. Later, testosterone production is affected, too, reducing its concentration in peripheral blood.<sup>21-23</sup>

## 6 | ADVENTITIOUS VENOUS DRAINAGE ROUTES

Without OWVs, ISVs fail as the main testicular drainage, but the interconnected venous drainage system also includes smaller horizontal DV, SVs, and CVs. The DV drains the testes into the vesicular vein (VV) through which it communicates with Santorini venous plexus and prostatic venous plexus (PVP) that drain the prostate (Figure 1). DV and PVP drain into the VV and further into the internal iliac (II) vein and into the inferior vena cava (IVC). However, pressure in the valve-less ISVs—up to eightfold above normal<sup>6,7</sup>—increases the pressure by the same factor in all the interconnected horizontally oriented vessels, according to the Bernoulli principle (see below). Ordinarily, the Santorini plexus (SAN) and PVP (draining the prostate) and DV (draining the testes) meet in the VV where they direct both the testicular and prostatic venous blood upwards to the II vein, the IVC and to the heart. Under the abnormal conditions brought about by the destruction of the OWVs, the prostatic venous drainage system is exposed to the eightfold pressure elevation in the ISVs.

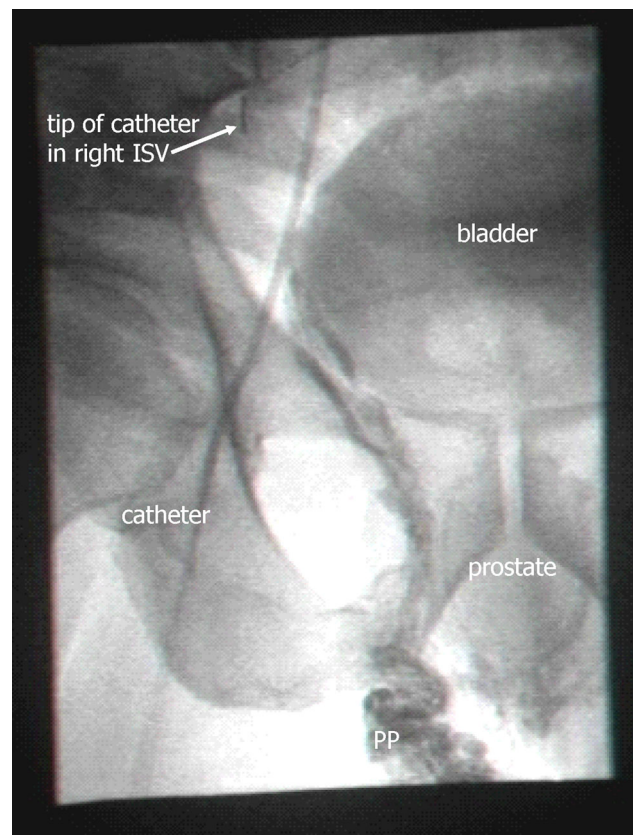
$\Delta P = 2 \gamma / r$ , allowing the assessment of the height blood can reach by capillary force to assist the existing alternative testicular venous drainage system (*v. infra*), at least partially and transiently.

This creates a pressure gradient that diverts a portion of testicular venous blood directly into the prostate—a radical and consequential change of flow direction.

The abnormally high intravenous pressure expands the diameters of interconnected CVs, SVs, and DVs to accommodate the increase in flow. The increase is governed by the Hagen-Poiseuille principle (footnote 1) demonstrating that even a rather small increase in vein diameter will strongly increase the blood flow rate. The result is that the small changes in the diameter of DV, SV, and CV can compensate for the lost upward pumping capacity of normal ISVs.

Under these conditions, veins draining the testicular region are under hydrostatic pressure nearly six times (on the right side) to eight times (on the left side) above normal levels. Pressure in the largely horizontal DV can reach 30 to 36 mm Hg,<sup>6</sup> whereas the normal, physiologic pressure in the SAN is about 5 to 6 mm Hg (Figure 1B). These conditions create the abnormal pressure gradient at the meeting point of the DV and the SAN according to Bernoulli principle<sup>13</sup> of communicating vessels, a derivative of the law of conservation of fluid energy.<sup>4</sup> According to this principle, the steady-state hydrostatic pressure in two drainage systems (eg, ISV and SAN) connected by a horizontal tube (eg, DV) is identical. Hence, any pressure change in testicular veins will change the pressure and flow direction in the communicating venous system of the prostate. As a result of the pressure gradient, the flow from the high-pressure testicular DVs is now directed not only, as usual, to VV and ultimately to IVC, but is also diverted towards the low-pressure prostatic SAN; the back-pressure from DV to PVP results in retrograde flow from the testes via the PVP and SAN to the prostate. This is a unique pathophysiological phenomenon of an organ receiving its key regulating molecule via its venous drainage (Figure 2).

It has been known that dogs<sup>24</sup> and nonhuman primates<sup>25</sup> develop BPH. Interestingly, in dogs “the DV was found to open variably, but always into the prostatic venous system... [allowing] the possible transfer of large concentrations of androgens into the prostatic circulation ... No valves were demonstrated in any of these vessels.”<sup>26</sup> Thus, it appears that the absence of OWVs results in the elevated hydrostatic pressure in the testicular drainage system every time the dog sits. However, all the differences between dogs and men, including shorter canine lifespan, can play a role in prostate pathology. Nonhuman primates have been studied for the role of varicocele in male infertility,<sup>27</sup> but natural prostate pathophysiology has received less attention so far. While these primate relatives of ours do exhibit occasional bipedalism, it is neither their dominant mode of locomotion<sup>28</sup> nor is their posture erect to the same extent as in humans. In general, nonhuman primates have a shorter lifespan than humans and pathological changes in the prostate occur earlier than in humans (who generally develop the in the sixth decade or later) indicating possible differences in prostate



**FIGURE 2** Venographic visualization of the prostate and its relationship to testicular venous system. Intravenous contrast material was introduced into the lower part of the ISV of the patient with bilaterally destroyed one-way ISV valves. Following the destruction of one-way valves within internal spermatic veins, hydrostatic pressure in the testicular venous drainage is higher than in prostate venous drainage resulting in testicular venous backflow into the prostate along the pressure gradient from pampiniform plexus via the deferential vein and Santorini's plexus. This is visualized by the contrast material “blush” to the prostate capsular region. In this case, the contrast blush can be considered to represent the abnormal venous blood flow from the testes in the absence of one-way valves; it contains free testosterone at concentrations hundredfold above that in arterial blood that arrives to the prostate by prostatic artery. (Reproduced from Gat et al<sup>11</sup> with permission.)

pathogenesis. Thus, the pathogenesis of BPH and PCa in nonhuman primates remains to be elucidated.

## 7 | FLOW OF FREE TESTOSTERONE

FT is the only hormone regulating and controlling the prostate; it controls cell division, differentiation, maintenance, and survival.<sup>23</sup> FT exits from testes in high concentration, flows through the veins upwards to the heart and returns to the prostate by arteries. Along this route, more than 150 cm long, FT is diluted in the total volume of blood approximately hundredfold.<sup>22,29,30</sup> In addition, in the general circulation some 98% to 99.5% of FT is inactivated by binding to the sex-hormone binding globulin.<sup>22</sup> As a consequence, under normal

<sup>4</sup>The sum of the pressure energy,  $P_e$ , the potential (head) energy of the vertical column of the liquid,  $goh$ , and the kinetic energy,  $\rho V^2/2$ , is constant,  $C: P_e + goh + \rho V^2/2 = C$  (where  $V$  stands for fluid velocity and  $\rho$  for fluid density).

conditions, active FT reaches the prostate by arterial supply in a concentration three orders of magnitude lower (1:1000) than the active androgen leaving its production site in the testes. Under the conditions of retrograde venous flow due to varicocele, we measured the concentration of FT above the meeting point of ISVs and DV; we found that FT arrives to the prostate at concentrations more than one hundred times above the concentration supplied normally by the prostatic artery.<sup>11</sup> Therefore, normal prostate control by FT is disrupted and ceases to function.

Recently, Pejčić et al<sup>10</sup> measured testosterone levels in prostate tissue obtained by biopsy and quantified it by mass spectrometry. In samples collected from men suffering from BPH, they correlated testosterone amounts in a gram of tissue with the total prostate volume. They found that the higher the prostate volume, the higher the testosterone amount in a gram of tissue. On average, the amount of testosterone in the unit mass of the hyperplastic prostate was double compared with normal tissue; while the increase may not seem dramatic, one must keep in mind that prostate converts testosterone into dihydrotestosterone functioning as a testosterone "sink." Indeed, the amount of dihydrotestosterone in BPH was four-fold higher than in the normal prostate.<sup>10</sup> These results, together with earlier evidence<sup>31,32</sup> and our own data,<sup>4</sup> are fully in line with the argument for the role of varicocele in the redirection of venous flow from the testes directly into the prostate.

Even with any decrease in testicular testosterone output as a result of aging and/or varicocele, the effective concentration of testosterone flowing into the prostate remains one hundred times above that in the systemic circulation. For example, a 50% reduction in testosterone production and its concomitant decrease in serum can manifest themselves in a diminished sense of wellness and decreased libido.<sup>33</sup> Yet, the active FT, which continues to flood the prostate under these circumstances, still remains some 50 to 60 times above normal serum concentration.<sup>11</sup> The likely direct effects of these conditions are accelerated prostate cell proliferation causing BPH and increased likelihood of PCa<sup>3,4</sup> (not eliminating the possibility of other contributing factors as well). This conception of the disease process necessitates the question: Can we correct the underlying mechanical failure due to the erect posture and arrest or even reverse the resulting prostate pathology?

## 8 | RESTORING NORMAL HYDROSTATIC PRESSURES IN TESTICULAR-PROSTATIC VENOUS DRAINAGE

If the pressure between testicular and prostatic drainage systems is equalized, FT will cease to flow into the prostate via venous drainage. This can be accomplished by occluding each impaired vertically oriented large and small (capillary) vein in the testicular venous drainage which exerts high hydrostatic pressure when OWVs in the ISVs are destroyed. We accomplish this by our own procedure employing interventional radiology, venography, and sclerotherapy of the vertical testicular venous network (the Gat-Goren Procedure<sup>9,11,12</sup>,

Figures 1C and 2). This can be achieved by microsurgery as well. Occlusion of all pertinent veins normalizes the pressure at the lower part of the testicular drainage system and eliminates the abnormal pressure gradient between the testes and the prostate. This restores the normal direction of testicular efflux away from the prostate (Figure 1C). Now FT arrives to the prostate normally by prostatic artery only and in normal, physiological concentrations. The result is a gradual reduction of hyperplastic prostate volume, improvement of BPH symptoms<sup>11</sup> and, we assert, elimination of localized PCa cells in the early stage of development.<sup>4</sup> It is plausible that applied early enough, the procedure could prevent BPH and reduce the incidence of PCa. Thus, BPH can be viewed as the consequence of the mechanical failure of the valves in ISVs. Occlusion of varicose ISVs is the mechanical antidote to the problem, mechanical treatment of a mechanical cause.

## 9 | CONCLUSIONS

1. The reasons for the age-dependent increase in the levels of testosterone in the prostate can be understood from the fluid mechanics analysis of the reversal of blood flow from testicles to the prostate.
2. Failure of the OWVs in ISVs, the major conduit of venous blood from the testes, increases hydrostatic pressure in the testicular drainage system, reduces the supply of oxygenated blood to testicular tissue, and leads to male infertility and decreased testosterone production. The same hydrostatic feature diverts venous blood from the testes directly to the prostate. As this blood takes to the prostate undiluted testosterone (rather than hundredfold lower concentration normally supplied by arterial blood), it stimulates prostate cell proliferation leading to prostate enlargement and possibly cancer.
3. Testosterone levels in peripheral blood do not reflect testosterone levels in the prostate and are not related to prostate pathology.
4. Preventing the flow of undiluted FT from the testes directly to the prostate can arrest and reverse, if performed early, the development of BPH, and, possibly, localized PCa. This is accomplished by occluding all vertically oriented malfunctioning veins of the testicular venous drainage bilaterally.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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## REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. *CA Cancer J Clin*. 2010;60(5):277-300.
2. Banerjee PP, Banerjee S, Brown TR, Zirkin BR. Androgen action in prostate function and disease. *Am J Clin Exp Urol*. 2018;6(2):62-77.

3. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.* 1941; 1(4):293-297.
4. Gat Y, Joshua S, Gornish M. Prostate cancer: a newly discovered route for testosterone to reach the prostate. Treatment by super-selective intra-prostatic androgen deprivation. *Andrologia.* 2009;41(5): 305-315.
5. Regis L, Planas J, Celma A, de Torres IM, Ferrer R, Morote J. Behavior of total and free serum testosterone as a predictor for the risk of prostate cancer and its aggressiveness. *Actas Urol Esp.* 2015;39(9):573-581.
6. Gat Y, Zuckerman Z, Chakraborty J, Gornish M. Varicocele, hypoxia and male infertility. Fluid mechanics analysis of the impaired testicular venous drainage system. *Hum Reprod.* 2005; 20(9):2614-2619.
7. Gat Y, Gornish M. Technical Investigations Including Imaging Procedure Colour Flow Doppler and Thermography for the Detection of Reflux in Varicocele. In: Schill W-B, Comhaire B, Hargreave TB, eds. *Andrology for the Clinician.* 1st ed. Berlin, Germany: Springer; 2006: 447-453.
8. Alsaikhan B, Alrabeeah K, Delouya G, Zini A. Epidemiology of varicocele. *Asian J Androl.* 2016;18(2):179-181.
9. Goren M, Gat Y. Varicocele is the root cause of BPH: destruction of the valves in the spermatic veins produces elevated pressure which diverts undiluted testosterone directly from the testes to the prostate. *Andrologia.* 2018;50(5):e12992.
10. Pejčić T, Tosti T, Tešić Ž, et al. Testosterone and dihydrotestosterone levels in the transition zone correlate with prostate volume. *Prostate.* 2017;77(10):1082-1092.
11. Gat Y, Gornish M, Heiblum M, Joshua S. Reversal of benign prostate hyperplasia by selective occlusion of impaired venous drainage in the male reproductive system: novel mechanism, new treatment. *Andrologia.* 2008;40(5):273-281.
12. Gat Y, Goren M. Benign prostatic hyperplasia: long-term follow-up of prostate volume reduction after sclerotherapy of the internal spermatic veins. *Andrologia.* 2018;50(2):e12870.
13. Streeter VL. *Fluid Mechanics.* 5th ed. New York, NY: McGraw-Hill; 1971:241-246. 130-140, 241-246.
14. Black CM. Anatomy and physiology of the lower-extremity deep and superficial veins. *Tech Vasc Interv Radiol.* 2014;17(2):68-73.
15. Ariane M, Wen W, Vigolo D, et al. Modelling and simulation of flow and agglomeration in deep veins valves using discrete multi physics. *Comput Biol Med.* 2017;89:96-103.
16. Chopard RP, Biazotto W, Speranzini MM, Antonopoulos I, Lucas GA. Morphology, distribution and types of valves in the adult male's testicular veins. *Bull Assoc Anat.* 1992;76(232):25-28. 1992.
17. Soifer E, Weiss D, Marom G, Einav S. The effect of pathologic venous valve on neighboring valves: fluid-structure interactions modeling. *Med Biol Eng Comput.* 2017;55(6):991-999.
18. Gat Y, Bachar GN, Everaert K, Levinger U, Gornish M. Induction of spermatogenesis in azoospermic men after internal spermatic veins embolization for the treatment of varicocele. *Hum Reprod.* 2005;20(4): 1013-1017.
19. Levinger U, Gornish M, Gat Y, Bachar GN. Is varicocele prevalence increasing with age? *Andrologia.* 2007;39(3):77-80.
20. Zuccolo L, Harris R, Gunnell D, et al. Height and prostate cancer risk: a large nested case-control study ( ProtecT) and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2008;17(9):2325-2336.
21. Ur Rehman K, Qureshi AB, Numan A, et al. Pressure flow pattern of varicocele veins and its correlation with testicular blood flow and semen parameters. *Andrologia.* 2018;50(2), <https://doi.org/10.1111/and.12856>
22. Feldman BJ, Feldman D. The development of androgen independent prostate cancer. *Nat Rev Cancer.* 2001;1(1):1-45.
23. Tanrikut C, Goldstein M, Rosoff JS, Lee RK, Nelson CJ, Mulhall JP. Varicocele as a risk factor for androgen deficiency and effect of repair. *BJU Int.* 2011;108(9):1480-1484.
24. Smith J. Canine prostatic disease: a review of anatomy, pathology, diagnosis, and treatment. *Theriogenology.* 2008;70:375-383.
25. Steiner MS, Couch RC, Raghov S, Stauffer D. The chimpanzee as a model of human benign prostatic hyperplasia. *J Urol.* 1999;162(4):1454-1461.
26. Dhabuwala CB, Pierrepoint CG. Venous drainage and functional control of the canine prostate gland. *J. Endocr.* 1977;75:105-108.
27. Harrison RM, Lewis RW, Roberts JA. Pathophysiology of varicocele in nonhuman primates: long-term seminal and testicular changes. *Fertil Steril.* 1986;46(3):500-510.
28. Druelle F, Aerts P, Berillon G. The origin of bipedality as the result of a developmental by-product: The case study of the olive baboon (*Papio anubis*). *J Hum Evol.* 2017;113:155-161.
29. Jarow JP, Chen H, Rosner TW, Trentacoste S, Zirkin BR. Assessment of the androgen environment within the human testis: minimally invasive method to obtain intratesticular fluid. *J Androl.* 2001;22(4):640-645.
30. Walsh PC. *Campbell's Urology.* 8th ed. Philadelphia, PA: Saunders; 2002:1245-1249.
31. Page ST, Lin DW, Mostaghel EA, et al. Persistent intraprostatic androgen concentrations after medical castration in healthy men. *J Clin Endocrinol Metab.* 2006;91(10):3850-3856.
32. Mostaghel EA, Page ST, Lin DW, et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. *Cancer Res.* 2007;67(10):5033-5041.
33. Rizk PJ, Kohn TP, Pastuszak AW, Khera M. Testosterone therapy improves erectile function and libido in hypogonadal men. *Curr Opin Urol.* 2017;27(6):511-515.

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