believe that it is important for urologists to know that the test is no longer available on the market.

Respectfully,
R. Casella
Department of Urology
University Hospital Basel,
Switzerland


RE: CONTRAST ENHANCED COLOR DOPPLER ENDORECTAL SONOGRAPHY OF THE PROSTATE: EFFICIENCY FOR DETECTING PERIPHERAL ZONE TUMORS AND ROLE FOR BIOPSY PROCEDURE

C. Roy, X. Bay, H. Lang, C. Saussine and D. Jacqmin


To the Editor. This is only the second study published reporting the use of contrast enhanced color Doppler targeted prostate biopsy.1 This study could have served as a validity study to test the reproducibility of the earlier results using this new imaging modality. While there were similarities in the biopsy and imaging techniques used in the 2 studies, the patient populations were somewhat different.

The earlier study involved 230 consecutive asymptomatic screening volunteers who participated in the Tyrolean prostate specific antigen (PSA) screening program, with a PSA of more than 1.25 ng/ml and a free-to-total PSA of less than 18% being indications for biopsy. Digital rectal examination (DRE) was not part of the screening process. This study investigated 85 patients with indications for biopsy of either PSA more than 4 ng/ml and/or abnormal DRE. It is noteworthy that 74.1% of patients (63 of 85) had abnormal PSA and DRE, and the 75 patients (88.2%) with abnormal PSA had a mean PSA of 18.2 ± 15 ng/ml (range 4.2 to 35). It appears that this group of patients constituted a nonconsecutive case findings cohort with more clinically apparent disease, and was not representative of the screening population investigated in the study by Frauscher et al. This impression is further reflected by the high cancer detection rate (63.5%, or 54 of 85 patients) and the unusually high positive predictive value of a gray scale ultrasound in detecting cancer in the hypoechoic nodules (50%, or 48 of 96 targeted biopsies of hypoechoic cores). I believe that the patient selection limited the clinical relevance of this report in current urological practice, as this study essentially investigated this new imaging modality in a group of patients who might harbor clinically apparent disease given the high percentage of abnormalities on DRE and PSA.

The authors analyzed the results of biopsy by cores, while omitting the analysis by case. While it is more meaningful to analyze statistically the results by cores in evaluating a new biopsy technique, it is useful to analyze the results by case to see if there is a consistent advantage of targeted biopsy over systemic random biopsy in this group of patients. To this end, it would be worthwhile to analyze separately the results of the 8-core peripheral zone biopsy compared to the yields of targeted biopsy in individual patients. By doing so, additional yields of targeted biopsy compared to systemic random biopsy might be apparent.

The low sensitivity and specificity of transrectal ultrasonography as a diagnostic test and in lesion targeted biopsy has made way for the introduction and popularity of sextant biopsy during the last decade. However, the high false-negative rate of this biopsy technique has fueled the search for a better imaging modality, such as in the current study, for a more effective image guided prostate biopsy. Other imaging modalities being explored in the early diagnosis and staging of prostate cancer include magnetic resonance imaging and, more recently, spectroscopy.2 A study by our department involving 24 consecutive subjects with at least 1 negative previous transrectal ultrasound guided biopsy has demonstrated improvement in the sensitivity of conventional endorectal magnetic resonance imaging from 57.1% to 100% with the addition of PROSE spectroscopy (GE Medical Systems, Milwaukee, Wisconsin).3 With more research in this direction, and with the possible future development of a robotic or computerized biopsy device replacing the current manual biopsy technique, improvement in the detection rate of organ confined prostate cancer can be anticipated.

Respectfully,
John Shyi Peng Yuen
Department of Urology
Singapore General Hospital
Singapore, 169868 Singapore


RE: COMPLEXED PROSTATE SPECIFIC ANTIGEN IMPROVES SPECIFICITY FOR PROSTATE CANCER DETECTION: RESULTS OF A PROSPECTIVE MULTICENTER CLINICAL TRIAL


To the Editor. The authors of this study compared total (t) prostate specific antigen (PSA) and complexed (c) PSA as initial screening tests and concluded that cPSA is a better initial screening test because of better specificity. This was a prospective study that enrolled patients on the basis of “established practices.” These “established practices” were not defined, but are widely known to be tPSA greater than 4 (or 2.5 at certain centers) or a suspicious digital rectal examination (DRE). Thus, the patients who were enrolled were selected for tPSA level, and cPSA was subsequently measured (selection on tPSA). Thus, the tests were conducted serially rather than in parallel. If 2 tests are done serially (tPSA followed by cPSA), then together they will perform better compared to only 1 test performed alone (tPSA only). The effect of selection on tPSA can be seen in table 3 in the article, where the difference in the AUC for tPSA and cPSA is highest in the tPSA 2 to 4 range. This difference might be due to the fact that the patients with tPSA 2 to 4 underwent biopsy because of a suspicious DRE, and, thus, were at greater risk for cancer. This greater risk for cancer has translated into better detection by cPSA.

To compare 2 tests as initial screening tests, they need to be done in parallel in a study population that has not been selected based on either test. The methodology of this study might be biased toward detecting a difference when, in fact, no difference actually exists. If a difference does exist, then it has been masked by the methodology and analysis. The only conclusion that can be drawn from this study is that cPSA has a slightly better specificity in patients who already have increased tPSA levels (greater than 4). For PSA levels less than 4 no definite conclusions can be drawn because the entry criteria were not standardized. The conclusion that cPSA is a better initial screening test...
test than tPSA is not supported by the study methodology, analysis or results.

Respectfully,
Amit Gupta and Claus Roehrborn
Department of Urology
University of Texas Southwestern Medical Center
and
Corinne Aragaki
Department of Epidemiology
University of Texas-Houston School of Public Health
Dallas, Texas

Reply by Authors. First, we would like to thank our colleagues for their comments. They point out a condition that has plagued researchers and government regulatory agencies since the approval for marketing of the first truth distal test, namely how to investigate the behavior of isotypes of an assay when the assay is in clinical use. We stated in the article, “Subjects were enrolled into this study when recommended for prostate biopsy by the physician according to established practices. . . .” Our colleagues claim that those established practices “were not defined, but are widely known to be tPSA greater than 4 (or 2.5 at certain centers). . . .” We agree that we did not specify what practices were followed. Men could have been recommended to undergo biopsy on the basis of a chemical test (such as PSA), family history, DRE result, clinical symptoms or other criteria that the individual physician deemed appropriate. Regardless of how they achieved enrollment status, it was at that point that a blood sample was obtained for analysis. We would like to indicate that 50% of the men enrolled had total PSA values less than 4.0 ng/ml (table 3 in article) and 75% had total PSA values less than 6.4 ng/ml. We also addressed the issue of DRE and its effect on the ROC curves. We found no difference in performance of tPSA between cohorts determined by DRE result.

We clearly state in the article that our intent was to establish equivalent value ranges for tPSA and cPSA and to investigate the clinical use of the assays in those ranges. The methodology for obtaining the data was consistent with this intent within the confines of clinical practice. We stand by our conclusions. We would challenge researchers to consider criteria for future PSA studies where populations that can be assessed without knowledge of chemical result can be identified.

DOI: 10.1097/01.ju.0000125275.03382.0a

RE: RECONSTRUCTION OF THE HYPOSPADIC HOODED PREPUCE

G. Erdenetsetseg and P. A. Dewan

To the Editor. Erdenetsetseg and Dewan reviewed the outcome of a series of patients who had undergone foreskin reconstruction, and concluded that the procedure is successful and can be combined with a range of distal repairs. Moreover, in contrast to another recent report,1 they did not notice an increase in the complication rate due to foreskin reconstruction. As mentioned by the authors, foreskin reconstruction was first described in Italy.2 In this country circumcision has not been well accepted for cultural reasons, and foreskin reconstruction has been standard practice in many institutions for a long while. Erdenetsetseg and Dewan focused their discussion on the low morbidity associated with foreskin reconstruction. We would like to add 2 more considerations. First, according to a task force of the American Academy of Pediatrics, no evidence supports the idea that circumcision would decrease the risk of urinary tract infections, sexually transmitted diseases or penile cancer.4 Therefore, circumcision does not carry any medical benefit. Second, according to Mureau et al, circumcision is a major reason that makes children who undergo hypospadias surgery aware of their congenital malformation.

Erdenetsetseg and Dewan indicate the importance of careful patient selection. They limited reconstruction to cases of distal hypospadias and only when an easy manual approximation of the foreskin in the midline was possible. So far our selection criteria have been similar but we think that these criteria are likely to need reconsideration in the near future. The widespread use of the Snodgrass technique has widely decreased the need to use the prepucce for urethroplasty in proximal cases,5 and Podestà et al have already proposed a modified technique for a foreskin reconstruction in combination with a Mollard-Monfort urethroplasty in cases of proximal hypospadias.

Respectfully,
M. Castagnetti, M. Cinador and E. De Grazia
Pediatric Surgery Unit
“Istituto Materno Infantile”
Via G. Giusti 3
90144 Palermo, Italy


Reply by Authors. Castagnetti et al are to be congratulated for their results with foreskin reconstruction, and we thank them for their kind reflection on our results. The motivation for presenting our study was to highlight an approach that allows a greater guarantee to the parents that a successful outcome will occur, namely manual apposition of the ventral prepuce in the clinic, which allows potential tissue tension. Also, the chance of dehiscence can be shared with the parents.

Castagnetti et al have suggested a change in the exclusion criteria. It would be important for any change in the selection criteria to be closely monitored to ensure that the results continue to be satisfactory. In the meantime foreskin reconstruction can be considered as a cosmetic option in a significant proportion of boys with distal hypospadias, with a better chance of success than has often been published.

DOI: 10.1097/01.ju.0000125275.03382.0a
To the Editor. I read this article with great interest and would like to call attention to a couple of points made. First, the fact that there were ischemic changes in 6 patients is unacceptable. Currently, there are no tissue or reconstructive techniques available for reconstruction of the glans or lost corporeal bodies. Tissue expanders can be used to generate new penile skin and buccal grafts can be used for urethral replacement but new sources of corporeal or glandular tissue are currently unavailable. At the recent American Academy of Pediatrics meeting in New Orleans Husmann, from the Mayo Clinic, and Gearhart reported on 9 patients, of whom there was loss of the hemiglans, distal corpora and penile urethra in 3, loss of bilateral glans, distal corpora and distal penile urethra in 2, partial or complete loss of 1 hemiglans and penile urethra in 2, complete loss of 1 hemiglans, 1 corporal body, 1 urethral plate and the entire penile shaft in 1, and loss of a hemiglans in 1. There were also ischemic changes with true loss of tissue, and Hammouda never fully describes these changes.

My second point is that it is fine that Hammouda disagreed concerning the fact that I thought the complications of complete primary repair are more difficult. However, I would bring his attention to the aforementioned study and see whether he still disagrees that complete penile disassembly is not without worries.1 Also, he offers no scientific evidence as to why he disagrees or any studies to support his position.

In all the articles that Hammouda cited I find no reports of loss of the corpora, glans or urethral plate in any series of patients with the Cantwell-Ransley repair. As mentioned by Hanna in an accompanying editorial comment, this procedure is not for the occasional surgeon because there is a steep learning curve. Clearly, the aforementioned findings in 9 patients have caused us to take even greater care when we resect the urethral plate from the corporeal bodies, leaving it intact for the last centimeter of the attachment to the corporeal and glandular tissue (modified Cantwell-Ransley).2, 3 The complications in this report are not minor, and with the diminutive nature of the penis in exstrophy any loss of tissue can be catastrophic.

Respectfully,
John P. Gearhart
Pediatric Urology
Johns Hopkins University School of Medicine
Baltimore, Maryland 21287-2101

Reply by Author. I am pleased by this letter but a careful reading of my article carries the answer to the points raised, so the reply and references will be from my study. Ischemic changes in the form of sloughing off of half the hemiglans were reported in 2 of the first 10 cases (2 of 42). Six other patients with epispadias were operated on after submission of this article. Two early cases out of 48 (4.2%) are not a major complication. Catastrophic complications such as loss of penile shaft, corpora, penile urethra, 1 hemiglans or overlying skin have been reported after complete penile disassembly2 but they were not reported in our study. I am confident that results will be fine if the surgical tips of the procedure described previously and in the article are adhered to a steep learning curve is mandatory not only for epispadias repair, but for all types of reconstructive urological pediatric procedures.

I still disagree that disassembly is not without worries. My scientific support for that is referred to in many series in addition to mine.4-6

Leaving an intact urethral plate for the last centimeter of the attachment to the corporeal and glandular tissue is a good procedure but not the best.2 Preservation of the urethral mesentery may be helpful.


DOI: 10.1097/01.ju.0000125193.32043.62

RE: AIR EMBOLISM FROM PNEUMOPYELOGRAPHY
J. Varvarakis, L. -M. Su and T. H. S. Hsu


To the Editor. I read this case report on air embolism from pneumopyelography with great interest. I, too, encountered the problem of near fatal air embolism following pneumopyelography and before needle penetration during percutaneous nephrolithotomy.1

As an anesthesiologist, I want to bring certain facts to the attention of practicing urologists. The authors did not mention the type of anesthesia administered and whether nitrous oxide was used while performing pneumopyelography. The size of the air bubbles increases rapidly within a few seconds in the presence of nitrous oxide.2

The prone position increases the risk of air embolism as the operating site is at a higher level than the right side of the heart.3 The saline injected immediately following pneumopyelography to distend the collecting system and the large amount of irrigating fluid used under pressure during surgery further aggravate the risk by producing the pressure gradient for pylovenous backflow.

I disagree with the authors’ advice to use a smaller amount of air for pneumopyelography. Injection of no amount of air is safe in the presence of nitrous oxide, with the patient in the prone position, during an operation where large amounts of irrigating fluid are used. I recommend the use of carbon dioxide instead of air if pneumopyelography is essential peroperatively. Since the standard textbooks on urology do not mention this dangerous and sometimes fatal complication of pneumopyelography, urologists are not aware of the risks involved and tend toward liberal and repeated use of air, which is freely available.

Respectfully,
N. Usha
1149, Sector 24-B
Chandigarh, India 160023


DOI: 10.1097/01.ju.0000124046.90808.b8

RE: 1-STEP REMOVAL OF ENCRUSTED RETAINED URETERAL STENTS
R. Bukhapatnam, J. Seigne and M. Heial


To the Editor. We read this article with great interest, and wish to discuss certain facts indicated in the study. The problem of retained heavily encrusted ureteral stents is often due to a combination of multiple factors such as certain inherent risk factors in the patient and the problem of patient compliance. Such cases often lead us to reconsider whether the stent is a friend or an enemy. We believe that in such heavily encrusted ureteral stents (incrustation width 6 mm or greater) the retrograde passage of a guidewire/open-ended ureteral catheter is seldom possible unless the incrustation width is minimized before retrograde manipulation via 1 to 2 sessions of extracorporeal shock wave lithotripsy.

Respectfully,
J. Varkarakis, L.-M. Su and T. H. S. Hsu


To the Editor. I read this case report on air embolism from pneumopyelography with great interest. I, too, encountered the problem of near fatal air embolism following pneumopyelography and before needle penetration during percutaneous nephrolithotomy.1

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Respectfully,
N. Usha
1149, Sector 24-B
Chandigarh, India 160023


DOI: 10.1097/01.ju.0000124046.90808.b8
It is surprising regarding how the authors were able to manipulate a guidewire/open-ended ureteral catheter/ureteroscope in all 10 patients across such a heavy thick ureteral incrustation greater than 6 mm, since it would have necessitated an extra 5 Fr to 6 Fr ureteral caliber (total caliber 12 Fr) adjacent to the encrusted catheter, unless of course the incrustation width was less than 3 to 6 mm (in which case they were not heavily encrusted) or the ureters were already dilated to 10 Fr to 12 Fr (in which case they would not be obstructed). Perhaps the authors would like to detail and clarify how they found this technique “quite doable.” In our view retained heavy ureteral stent incrustations greater than 6 mm should not be managed by primary retrograde manipulation at the first instance, since this approach carries a high risk of ureteral trauma/perforation and ureteral stricture in the long run. A staged multimodal procedure preceded by shock wave lithotripsy could be a safer option for these already fragile, infected and stent encrusted ureters. We were interested to know the long-term outcome regarding whether the single session removal resulted in a higher incidence of ureteral strictures.

While the emergence of holmium laser lithotripsy has simplified intracorporeal lithotripsy and encrusted stent dissolution, the authors need to be reminded that even by aiming the beam parallel to the encrusted stent one may still fracture the stents/guidewires since holmium laser acts via a photothermal effect versus the photoacoustic effect of other lasers, and that lithotripsy begins before the collapse of the pear-shaped vapor bubble. Also, due to the “Moses effect,” the holmium optical fiber needs to be positioned immediately snugly and adjacent to the target (stone or encrusted stent in this case) much like the energy required to vaporize the water channel and to maximize target dissolution. Thus, by placing the laser beam parallel to the stent incrustation and also due to the photothermal effect, a higher energy would be needed, resulting in energy wasted and excessive heat generation that may fracture and melt the stents. We fail to appreciate how the authors were able to provide safe laser lithotripsy in a single session by using an “end firing laser fiber” (a parallel beam has a much higher chance of ureteral perforation and trauma). Perhaps they could comment regarding how this was possible.

Despite the high safety margin (optical penetration depth) of holmium:YAG laser energy, guidewires and ureteral catheters are known to melt and fracture and perforate the ureters. A single session laser lithotripsy has the worst safety margin for ureteral perforation. It would be appreciated if the authors could establish certain criteria to be followed for single-step removal of encrusted stents versus staged multimodal sessions as described previously by others. Nevertheless, the authors deserve to be commended for their attempts.

Respectfully,
Iqbal Singh
Department of Surgery
University College of Medical Sciences (University of Delhi) and GTB Hospital
F-14 South Extension Part-2
New Delhi 110049
India


Reply by Authors. Singh raises multiple interesting theoretical points. We, too, used to treat encrusted stents with multiple sessions of extracorporeal shock wave lithotripsy, cystoscopy and percutaneous surgery. However, to our surprise, when we acquired the holmium laser we found how easy it was to treat these patients in 1 step with holmium laser and ureteroscopy. Regarding the question of the caliber of the ureter not being able to accommodate the encrusted stent as well as the guidewire and open-ended catheter, or the ureteroscope, we had no difficulty passing a guidewire and open-ended catheter. Sometimes when the guidewire does not advance because of the calcification, we pass an angled guidewire, which is easily manipulated around the calcification. These ureters are usually dilated because the stents have been in place for some time (in most of our cases for more than 1 year), and, thus, the ureter has passively dilated. Figure 1 in our article showed that one of the patients was referred to us with 2 Double-J stents (Medical Engineering Corp., New York, New York) placed in the ureter. Both of these stents were 7Fr, so the ureter was able to accommodate a 14Fr catheter without difficulty.

When we advanced the ureteroscope parallel to the stent we found the calcifications attached to the stent and growing outward. The laser fiber is placed in direct contact, perpendicular to the stone, parallel to the ureter and parallel to the stent. We found no difficulty breaking the stones. We did not melt any wires and no stents were fractured. In cases with circumferential incrustation we start at one point until the stent is exposed and then directly treat the calcifications, freeing the calcifications from the stent and then directly breaking the free stones with the laser fiber.

We are aware of the limited safety margin of the holmium laser. When managing the cases the most important thing is a clear view. Because we did everything under direct vision and the view was clear, we did not perforate a single ureter, we did not break a wire or stent and to date we have not had a case of ureteral stricture. As most ureteral strictures following ureteroscopy are apparent in the short term, we do not anticipate late development of ureteral strictures.

We currently use this technique for all of our patients with retained stents. The only time we add a percutaneous approach is in patients with a large stone volume in the kidney, or in patients with an obstructed and infected system. Following publication of this article we have successfully treated 2 additional patients. The last case involved a 19-year-old female with cystinuria and bilateral stone encrusted stents, clearly a challenging problem for any technique. The key to success is patience and good visibility. The technique works. Try it and you will believe.

DOI: 10.1097/01.ju.0000127750.56996.8b

RE: AN ARTIFICIAL SOMATIC-CENTRAL NERVOUS SYSTEM-AUTONOMIC REFLEX PATHWAY FOR CONTROLLABLE MICTURATION AFTER SPINAL CORD INJURY: PRELIMINARY RESULTS IN 15 PATIENTS

C. G. Xiao, M.-X. Du, C. Dai, B. Li, V. W. Nitti and W. C. de Groat


To the Editor. Reconstruction of controlled voiding in spinal cord injury still remains a major challenge in medicine. Xiao et al performed an interesting investigation first in animals (rat1 and cat2) and then in clinical patients, by establishing the “skin-central nervous system (CNS)-bladder” artificial reflex pathway to trigger bladder contraction. Based on our understanding and clinical experience in bladder treatment of patients with spinal cord injury, we would like to comment on some points regarding the artificial “somatic-CNS-bladder” reflex pathway for spastic bladder dysfunction.

First is the relationship between naturally triggered voiding and artificially triggered voiding. In patients with suprasacral spinal cord injury one or more nature triggering points usually develops to initiate voiding, for example tapping the lower abdomen, pulling the pubis or scratching the skin below the spinal cord injury level. Does the artificial reflex arc who undergoes that procedure still retain naturally triggered voiding? Furthermore, we do not think the artificial reflex arc can “control” voiding. It may have the same role of trigger point in spastic bladders of spinal cord injury.

In addition, which root should be selected as the recipient? For the donor root in clinic it can be L5, L4, L5 or S1. Considering spine stability, L5 or S1 is preferential. For the recipient root one must consider its normal innervative frequency and efficacy to bladder detrusors. Generally speaking, S2 roots in patients seldom have innervative contribution to bladder detrusor because there is no bladder pressure increase when S2 is stimulated (20 V, 30 Hz). S3 and S4 are the dominant contributors of bladder innervation, with
the right side more efficacious. Furthermore, the proximal lumbar somatic motor ventral roots innervating the hindlimb muscle are much larger than the distal sacral ventral roots innervating the pelvic and perineal muscles. Therefore, it is technically possible to anastomose 1 proximal donor root with 2 or 3 distal recipient roots. So in our opinion the recipient root for neurorrhaphy should be S3 or S4, bilaterally or unilaterally.

Another point centers on how to promote axonal regeneration to pelvic nerves rather than to pudendal nerves. As we know, the ventral root of L6 in rat, S1 in cat, S2 in dog or S3 in man contains somatic motor fibers as well as parasympathetic preganglionic fibers. The former forms pudendal nerve to innervate pelvic striated muscles and sphincters, and the latter forms pelvic nerve to pelvic ganglion and then innervate pelvic organs. Theoretically, the proximal somatic motor fibers are more inclined to regenerate into distal somatic nerves because they can release the same neural trophic and growth factors to attract and induce axonal sprouting and remyelination. However, the aim of this operation is to get more reinnervation to bladder and less reinnervation to sphincter. What can we do to inhibit axonal regeneration to distal somatic nerves and enhance to autonomic nerves?

Another question is which is a more efficacious trigger, skin or tendon afferent? Scratching skin induces a superficial spinal reflex, while purposeful probing by the operator induces a profound reflex. The unmasking produced by tendon reflex seems more robust than that by skin. However, in animal experiments and clinical sacral anterior root stimulation (Brindley electrode) the intensity of electrical stimulus is hundreds to thousands of times higher than the biological current. Is there any difference between the "skin-CNS-bladder" and "tendon-CNS-bladder" reflex pathway? Which one can give a better result?

Another issue regards whether to do deafferentation. It has been proved clinically that sacrificing 4 or even 5 sacral roots has no effect on voluntary voiding or defecation. Selective sacral root rhizotomy in patients with suprapoanal spinal cord injury, whether efferent or afferent, usually gives encouraging initial results but is disappointing in long-term follow-up. Because the plasticity of autonomic nerve and bladder smooth muscle is so strong, only complete denervation could achieve permanent spasm relief. In our opinion the "somatic-CNS-bladder" reflex arc only sets up a new somatic trigger point to initiate voiding. It seldom affects bladder compliance and reservoir function. Thus, establishing a "somatic-CNS-bladder" reflex arc without supplementation of appropriate deafferentation will ultimately lead to a hyperreflexic and spastic bladder. What is the role of deafferentation? Does it diminish the efficacy of the somatically triggered voiding?

Finally, establishing an artificial "somatic-CNS-bladder" reflex arc to trigger voiding in patients with spinal cord injury is a new and promising approach. Congratulations to Xiao et al, who present interesting and informative research work. However, more experimental and clinical studies and long-term follow-up are needed before a definite conclusion is drawn.

Respectfully,
Shi-Min Chang
Department of Orthopedic Surgery
Tongji Hospital Tongji University
389 Xincun Road
Shanghai 200065
People's Republic of China


DOI: 10.1097/01.ju.0000125312.22988.eb

RE: FUNCTIONAL AND NEUROANATOMICAL EFFECTS OF VAGINAL DISTENTION AND PUDENLAL NERVE CRUSH IN THE FEMALE RAT

M. S. Damaser, C. Broxton-King, C. Ferguson, F. J. Kim and J. M. Kerns

To the Editor. The authors present interesting results demonstrating that bilateral pudendal nerve crush and vaginal distention cause a decrease in leak point pressure (LPP). This study puts forward 2 important hypotheses. On the one hand a decrease in LPP indicates a deterioration of external urethral sphincter (EUS) function, which is probably associated with birth trauma as a possible etiology of stress urinary incontinence (SUI). On the other hand it corroborates the theory of EUS innervation via the pudendal nerve.

In this context we would like to address to a few problematic aspects. The authors must have based their study on the supposition of pudendal EUS innervation. However, the question of EUS nerve regulation is still under debate. There are a number of controversial theories on this issue, and the debate continues. We believe that it would have been better to mention this fact in the article.

The authors performed LPP testing via a suprapubic catheter, and, to our mind, the results they achieved are better than those observed by Sievert et al. LPP testing via transurethral catheters not only may cause partial obstruction, but the friction of the catheter against the urethral mucosa may also lead to pathological contractility of the EUS and, as a result, wrong LPP values. In our study we urodynamically investigated EUS function before and after bilateral pudendal nerve cut. We believe that the urodynamic results present a more reliable basis for accurate assessment of EUS function after operations affecting the pudendal nerve.

Regardless of the aforementioned minor reservations, the authors have provided an interesting functional and neuroanatomical study, which confirms that pudendal nerve crush leads to the EUS dysfunction and SUI, thus, confirming the theory of pudendal EUS innervation once more.

Respectfully,
Daniar K. Osmonov and F. J. Martinez Portillo
Department of Urology
University Hospital Schleswig-Holstein, Campus Kiel
Christian-Albrechts-University of Kiel, Kiel, Germany

Reply by Authors. We appreciate the letter by Osmonov and Martinez Portillo and their careful reading of our recently published article. The clinical pathogenesis of SUI is complex and controversial, even in a well designed animal model in which variables can be controlled and relevant outcome measures examined. This complexity was noted in our earlier rat study, in which we stated that "continence depends on the coordinated integrity of several structures (eg mucosal coaptation, smooth muscle of the internal urethral sphincter, pelvic floor muscles, and pubourethral ligaments)." In the more recently published article we attributed intact nerve fascicles to autonomic innervation but, as indicated by Osmonov and Martinez Portillo, some of them may instead represent extrapudendal somatic innervation of the EUS. Experimental evidence to support this view is limited, and further experimentation is needed to clarify this intriguing possibility.

The available literature on the innervation of the EUS suggests the following conclusions: pudendal innervation of the EUS is possible but not dominant. In addition, the innervation of the levator ani and coccygeus muscles is separate from that of the pudendal nerve, although all 3 form a common trunk in the sacral plexus. While the etiology and the nomenclature may at times be confusing, the innervation patterns of the EUS are remarkably similar in humans and rats. These and related anatomical issues have been discussed in detail in the literature, which limited space for discussion often cuts short.

Osmonov and Martinez Portillo seem to agree that our LPP methods are preferred to other published methods, although they suggest that their urodynamic methods are more reliable. Unfortunately, at this time in this writing, the new methods are not yet published, and, therefore, are not available for our evaluation. In summary, we are of the opinion that animal models of SUI are useful despite certain cautions that must be taken in the application of results to clinical procedures. Our conclusion that the LPP is directly affected at least in part by pudendal nerve injury seems to withstand close scrutiny.

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LETTERS TO THE EDITOR

More studies need to be performed to duplicate our results, and clarify related anatomical and other issues.


DOI: 10.1097/01.ju.0000124910.40356.26

RE: A NEW HIGH FREQUENCY ELECTROSTIMULATION DEVICE TO TREAT CHRONIC PROSTATITIS


To the Editor. We have enclosed a photograph of an electrical prostatic heater/stimulator that was used in the 1940s “for the treatment of prostatitis, prostatic absces, seminal vesiculitis and kindred conditions.” It is almost identical to the device used by John et al shown in the figure of their article (a prostatic urethral probe was also available for this antique device). A student of medical history will confirm that there are few really new treatments, only updated variations of therapies applied by our predecessors.

Respectfully,
J. Curtis Nickel and Ian Thompson
Department of Urology
Queen’s University
Kingston General Hospital
Kingston, Ontario, Canada K7L 2V7

Electrical prostatic heater. Device was provided by former colleague of father of IT. It has been placed on permanent loan to historical collection of JCN of items for management of prostatitis.

Reply by Authors. As noted by Nickel and Thompson, prostatic heaters have been used since the early 20th century to treat chronic prostatitis. Transrectal/transurethral microwave hyperthermia or transurethral microwave thermotherapy have been proposed. None of these devices has demonstrated long-term efficacy in controlled studies, and, therefore, an important placebo effect has been considered.1 In contrast to previous techniques, our proposed device is not a simple heater, but a high frequency neuromodulation device. Again, we hypothesize that the stimulation inducesafferent electrostimulation by blocking A δ and C afferent pain nerve fibers with consequent pain relief. A placebo controlled, randomized trial comparing high frequency stimulation with a sham group is ongoing.


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RE: TECTICULAR SPERM EXTRACTION WITH INTRACYTOPLASMIC SPERM INJECTION IS SUCCESSFUL FOR THE TREATMENT OF NONOBSTRUCTIVE AZOOSPERMIA ASSOCIATED WITH CRYPTORCHIDISM

J. D. Raman and P. N. Schlegel


To the Editor. Raman and Schlegel report interesting findings in a large series of testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) results in nonobstructive azoospermia and cryptorchidism. They retrospectively analyzed 321 TESE interventions in 275 male patients with nonobstructive azoospermia. Of these 275 men 38 presented with cryptorchidism in the anamnesis and underwent a total of 47 TESE interventions (30 with bilateral and 8 with unilateral cryptorchidism). Eight interventions were performed by common multiple biopsy and 30 by microdissection technique. Spermatozoa could be extracted successfully in 68% of the bilateral cryptorchidism group, while the same procedure was successful in 100% of the unilateral cryptorchidism group. The authors, at a center of excellence, achieved favorable sperm retrieval and pregnancy rates. They identified testicular volume and age at orchiopexy as independent predictors of sperm retrieval for men with a history of cryptorchidism.

However, some points seem to be worthwhile for further discussion. The data from the 2 cryptorchidism groups were compared to the data from the 237 nonazoospermic cases without cryptorchidism. In the latter group sperm extraction was 58% less successful than in the cryptorchidism groups. It can be assumed that the inhomogeneous size of these different groups makes statistical comparison problematic. To assess these results, it seems mandatory to give the type of statistical testing.

The follicle-stimulating hormone serum was abnormally increased in both groups. Mean testicular volume was given for both groups separately—for the bilateral group as 6.3 cc (standard deviation 3.4 cc) and for the unilateral group as 8.4 cc (4.5 cc). No minimum and maximum values were given. The authors failed to give the testosterone values of the treated patients. It seems questionable to perform testicular tissue isolation for sperm extraction in patients with bilateral cryptorchidism.
azoospermia is clear in our article. In addition, microdissection cryptorchidism on the ability to treat patients with nonobstructive on overall testicular function. The effect of a history of corrected dissection approach minimizes the risks of surgical complications, tiple groups after microdissection. 5

The risk for impaired testosterone production after sperm extraction. Volumes do not have a reasonable chance of sperm retrieval or are at minimum 2 cc). In contrast, men with failed retrieval attempts had a retrieval mean testis volume was 8.4 cc (SD 4.5 cc, maximum 20 cc, predictive factor for sperm retrieval to men with bilateral cryptorchid–noncryptorchid testis), we limited examination of this variable as aism would confound the effects of cryptorchidism (adding volume of a

metric evaluation of these data and is a valid statistical function despite differences in sample size.

Within the cryptorchid cohort testicular volume was evaluated as a predictive factor only in patients with a history of bilateral cryptorchidism. Since consideration of patients with unilateral cryptorchidism would confound the effects of cryptorchidism (adding volume of a noncryptorchid testis), we limited examination of this variable as a predictive factor for sperm retrieval purposes with bilateral cryptorchidism. Mean testis volume was given with standard statistical parameters for description of a population. For men with successful sperm retrieval mean testis volume was 8.4 cc (SD 4.5 cc, maximum 20 cc, minimum 2 cc). In contrast, men with failed retrieval attempts had a mean testis volume of 6.3 cc (SD 3.4 cc, maximum 12 cc, minimum 2 cc).

Complete hormonal evaluation was performed in all patients before attempted sperm retrieval in our study, as described in the first paragraph of the materials and methods section. Van der Horst and Martinez Portillo appear to believe that men with lower testicular volumes do not have a reasonable chance of sperm retrieval or are at risk for impaired testosterone production after sperm extraction. This is not the case in our considerable experience. Men with Klenefelter’s syndrome (and mean testicular volumes less than 3 cc) have a sperm retrieval rate of 68% per retrieval attempt at our center without impairment of testosterone production. Observations from our previous studies as well as the overlap of testicular volumes in successful and unsuccessful TESE procedures for patients with cryptorchidism suggest that no patient should be denied TESE based on low testicular volume. Long-term decreases in serum testosterone are rare in patients after TESE. We have previously reported such results, as have others.1–4

Indeed, we routinely evaluate testicular function with serum testos
terone levels, as well as ultrasound findings as reported by mul
tiple groups after microdissection. Each series has documented the superior safety and efficacy of microdissection TESE compared to standard multi-biopsy procedures for sperm retrieval.6–8 The microdissection approach minimizes the risks of surgical complications, structural changes within the testicle and effects of sperm retrieval on overall testicular function. The effect of a history of corrected cryptorchidism on the ability to treat patients with nonobstructive azoospermia is clear in our article. In addition, microdissection TESE is an effective technique for sperm retrieval. Its safety has been confirmed in multiple controlled clinical trials.4–6


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RE: TADALAFIL HAS NO DETRIMENTAL EFFECT ON HUMAN SPERMATOGENESIS OR REPRODUCTIVE HORMONES


To the Editor. We read with great interest this article assessing the effects on spermatogenesis of placebo vs 10 mg or 20 mg tadala
dal daily. Tadalafil is a potent phosphodiesterase (PDE) type 5 (PDE5) and PDE11 inhibitor. PDE11 was found in the smooth muscles of the internal organs, cardiac and skeletal muscles, pituitary gland, Leydig and germ cells. The physiological function of this enzyme is the breakdown of cAMP. No differences in the inter- and intra-individual variability (al
dering the temporal and spatial physiological conditions. In a recent study involving 10 laboratories, Auger et al assessed the variability in the evaluation of human sperm concentration, motility and vitality. They found mean interindividual variation coefficients of 22.9%, 21.8% and 17.5% for sperm concentration, motility and vitality, respectively. Moreover, concerning the mean intra-individual coefficients of variation, the percentages were 15.8%, 26.2% and 13.1% for sperm concentration, motility and vitality, respectively. In light of these findings, the choice of the 50% decrease in sperm concentration selected by Hellstrom et al was probably too high. Moreover, Auger et al analyzed and found a role of the level of experience and training. In light of these findings, the authors suggest that PDE11 may be a poor model in which to evaluate effects on reproductive parameters in humans but are we sure that the rat model is a good model for investigation of the human physiological function of the PDE11 family? Yuasa et al seem not to agree, suggesting, in fact, that due to the PDE11A species specific expression, the rat is not a good animal model for understanding the physiological roles of human PDE11

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and the consequent effects of its inhibition. Investigations in other animal models will probably elucidate the physiological function of the enzyme.

In conclusion, we can only be grateful to the editors for publishing this study, which represents the first evaluation of tadalafil effects on human semen quality. This is an interesting study and we definitely need to see similar studies to assess the adverse effects of tadalafil, particularly in long-term use and in high-risk groups. Hellstrom et al should be congratulated for highlighting several important questions regarding tadalafil safety. Nevertheless, concerning the effect on PDE11 inhibition we believe that insufficient data are available to date to state that daily administration of tadalafil is completely safe.

Respectfully,
Giorgio Pomara and Girolamo Morelli
Section of Urology
Department of Surgery
S. Chiara Hospital
56100 Pisa University, Italy

Reply by Authors. We are grateful for the opportunity to clarify several points raised by Pomara and Morelli. They question our choice of primary study end point (the proportion of subjects with a 50% or greater decrease in sperm concentration following 26 weeks of treatment), citing an article by Auger et al to argue that the specified cut point of 50% or greater decrease may have been too high. They believe that our choice of this primary end point was clinically and scientifically reasonable because it accounted for the often marked variability of semen quality among men with various physiological conditions.

The routine evaluation of human semen characteristics is complicated by the subjective nature of the assessment and an often high degree of variability among laboratories. The aim of the study by Auger et al was to assess interindividual and intraindividual variability in the evaluation of semen quality—sperm concentration, motility and vitality—among 10 laboratories. They reported significant differences for motility and vitality but not for sperm concentration. However, the mean variability coefficients of 22.9%, 21.8% and 17.5% (for sperm concentration, motility and vitality, respectively) referenced by Pomara and Morelli from the article by Auger et al refer to the variability among laboratory centers, not the variability of semen quality among subjects with time.

In contrast, our choice of primary study end point addressed the variability of semen characteristics among men with time. In consultation with regulatory authorities we chose the cut point of 50% or greater decrease in sperm concentration as the primary study end point because it took into consideration the large variations (fluctuations up to 47%) that can occur among individuals with time. Additional analyses (presented at the 2003 annual meeting of the American Urological Association but not in our article) for the proportion of subjects with sperm concentration decrease using lower cutpoints of 40% or greater, 30% or greater and 20% or greater did not demonstrate any significant differences between the placebo and tadalafil (10 mg and 20 mg) groups. And, as reported in the article, analyses of multiple secondary end points showed that there were no significant differences in semen quality between the placebo and tadalafil groups after 6 months of daily therapy.

To address another question posed by Pomara and Morelli, the technicians in our study attended training sessions before and during the study at the Tulane University Andrology Laboratory (New Orleans, Louisiana) to standardize test interpretation and maintain proficiency. To decrease variability further, a single technician with 14 years of experience in clinical trials and semen analysis interpreted the sperm morphology slides.

Pomara and Morelli state that because of the effect on PDE11 inhibition, there are insufficient data to date that tadalafil administered on a daily basis is completely safe. They also cite a review article that speculates, without supporting data, that the back or muscle pain reported with tadalafil therapy may be associated with PDE11 inhibition. First, back pain and myalgia, which tend to be benign and self-limited, are unlikely to be caused by PDE11 inhibition. This view is supported by the fact that the 2 PDE5 inhibitors sildenafil and vardenafil, neither of which significantly inhibits PDE11 at clinical doses, also cause back pain and myalgia. No obvious pharmacological explanation for the myalgias associated with PDE5 inhibitor therapy has been demonstrated, nor is there any known clinical benefit or risk of PDE11 inhibition. In addition, our study is only one additional piece of evidence regarding the safety of tadalafil.

We appreciate the acknowledgment by Pomara and Morelli that our study represents the first evaluation of the safety of tadalafil on sperm, semen and reproductive hormones. Our data addressing male reproductive safety with daily dosing for 6 months add further reassurance regarding the safety profile of tadalafil.


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