European Society for Sexual Medicine

Issue 31 – July 2014

ESSMToday

ESSM NEWSLETTER

www.essm.org

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IMPRINT
Publisher: ESSM
Editor-in-Chief: Juan I. Martinez-Salamanca
Layout: CPO HANSER SERVICE

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Welcome Address

I am delighted to welcome you to this 2014 second issue of the ESSM newsletter. We have in our society great things coming soon.

We would like to congratulate again all ESSM members and staff for our successful meeting held in Istanbul last January, which was a good sign of the good health of our Society.
Now, we are preparing with great interest and enthusiasm the next meeting is Copenhagen, we hope it will be a great one.

In this issue, we have included an interesting interview with EAU Chairman of Andrology Section – Prof. Weidner – a world-wide known expert in Sexual Medicine. We cover main topic-highlights that have been presented in Istanbul Meeting prepared by Dra. Egui and myself along with our classic sections by my Associate Editors (Dr. Mondaini & Angulo). Also, we add two very interesting Key from Kols collaborations regarding Penile Cancer & Priapism, done by Giorgio Bozzini and Evangelos Zacharakis. I hope you will enjoy reading.

Finally, I would like to thank you all for your continued support of our society and I look forward to seeing you in Copenhagen next February.

My very best

Juan I. Martínez-Salamanca

Interview with Prof. Weidner

by Juan I. Martinez-Salamanca (JIMS)

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PROF. WOLFGANG WEIDNER is an internationally known figure and world-class leader in the field of Sexual Medicine and especially in Male Infertility & Peyronie´s Disease. He is the current leader of **EAU Section of Andrological Urology (ESAU)** and also a great human being. He is an outstanding contributor to the field of sexual medicine as a researcher, patient advocate, educator, innovator and author. Having you here it is a real pleasure and honor not only for me but also for all ESSM members.

JIMS: Prof. WEIDNER, could you make us a brief journey throughout your professional background?
I was trained in Giessen and became 1990 Professor in the University Department of Urology in Goettingen. My focus in this time was oncological urology, especially partial nephrectomy in kidney cancer, pediatric urology and the whole field of andrological urology. I initiated an andrological subspeciality group, a lab dealing with sperm analysis and tissue freezing and several innovative procedures as TESE and grafting-operations for Peyronie's disease. Until today I am very grateful for this time together with Prof. Rolf Ringert who was an excellent supporter for me. In October 1993 I became the head of the Department of Urology, Pediatric Urology and Andrology of the University of Giessen and I am still there in this position.

JIMS: During you dilated career, which has led to the passage from "Andrology" to "Sexual Medicine", and what do you prefer "Sexual Medicine" or "Men´s Health"?
I am and was convinced that many items of sexual medicine are inborn issues of andrological urology, e.g. erectile dysfunction, hypogonadism, ejaculatory dysfunction…. In my department we try to cover the whole field of this special area and we integrate our sexual specialists of the department of psychosomatics in all cases if necessary. Although, "Men's Health" is a comprehensive term, I prefer to speak about sexual medicine.

JIMS: What do you think the role of the urologist should be in the management of Male Infertility? And what are our major challenges?
The andrological urologist has to cover all aspects of infertility associated with the man in an infertile coupleship. This includes the whole diagnostic armentarium including ultrasonography, knowledge of sperm analysis, endocrinology, reprogenetics, interactions to oncology and malformations. In my opinion, and this is also the consensus of the ESAU, the andrological urologist must also have skills in microsurgery – TESE and refertilisation, varicocelectomy, TURED – and operative knowledge in common penile operations as Peyronie's disease surgery and penile implants. The major challenge for andrologic groups is to become an accepted part of a Comprehensive Reproductive Center (CRC) in a defined cooperation with gynecologist, basic researchers, genetic specialists, endocrinologists, sexologists and even pediatric oncologists.

JIMS: Prof. WEIDNER, PDE 5 Inhibitors (Tadalafil) have been recently approved in U.S. for patients with ED & LUTS, which do you consider being the ultimate role of this drug in all treatment options of this group of patients?
I am convinced, that PDE 5 inhibitors have a positive vascular activity.
One example is ED & LUTs, but even in arteriosclerotic associated infertility there are first experimental hints that these drugs do improve the vascular supply of the spermatogenetic compartment with a positive effect on spermatogenesis.

JIMS: In the field of Peyronie´s disease in which you worked and contributed very hard, what do you think are the main challenges to achieve?
One major challenge is to develop new substances to prevent in an evidence based schedule the progression of the plaque. Concerning surgery we need an international study in "graft"-surgery comparing the small incision technique with plaque excision.

JIMS: Prof. WEIDNER, regarding the latest controversy about Testosterone Replacement Therapy & Cardiovascular Risk, what is your personal opinion about that?
I was very astonished about the new discussion. I follow Dr. Mulhall who analyzed the new data in a very critical way during the EAU in Stockholm. His message is: The book is not closed!

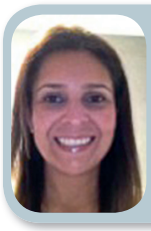
JIMS: And last but not least, which do you consider the most important challenges for our specialty (Sexual Medicine) and for our society (ESSM) in the next 5 years?
For me as head of the ESAU I think it is necessary to bring all items of sexual medicine into the heart of all urologists who are dealing with andrological urology. I think we are on a good way for a comprehensive view of the whole area.

It was a great pleasure to interview you; I am convinced that your points of view, fruits of a lifetime devoted to your work, will be highly appreciated by our readers.

Thanks once again.

Highlights from the "ESSM Meeting Istanbul"

by Alejandra Egui / JIMS



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Dear ESSM members / friends:
The past 29 January to 1 February, in the city of Istanbul, Turkey, we celebrated the 16th ESSM Congress, with the participation of 73 countries, becoming in the most important event of the Andrological community in Europe. In this event, we reviewed the updates in the field of Andrology by a large panel of international experts. Similarly, the innovations that were introduced this year were presented. The top 5 of the represented countries have been Turkey, Italy, Spain, the United Kingdom and Germany. Briefly, we will summarize the top important topics:

Podium Session

Prostate

Chairs: Mustafa Faruk Usta (Turkey), Andreas Bannowsky (Germany)

In this session commented the relative to treatment with PDE5 inhibitors, in patients with LUTS (Lower Urinary Tract Symptoms) and Erectile dysfunction. The association between both conditions has a multifactorial origin (decreased NO /cGMP, Rhoquinase / Endotelin-1 decreased activity, increased noradrenergic system, pelvic atherosclerosis) and age-related. Tadalafil 5 mg daily seems to be a reasonable treatment option.

Another interesting issue commented several times throughout the congress was the role of PDE5 inhibitors in penile rehabilitation appeared, according to the results of **REACTT** study: A multicenter, randomized, double-blind, placebo-controlled trial conducted in 50 centers in Europe and Canada , that included 423 men younger than 68 years, undergoing NSRP for prostate cancer (Gleason < 7) and good preoperative erectile function, to determine the rehabilitative potential and the protective effect of PDE5 inhibitors on penile function after NSRP.

They compare the efficacy of tadalafil 5 mg once daily (N = 139), tadalafil 20 mg on demand (N = 1423) and placebo (N = 141) for 9 months, followed by a drug-free washout (DFW) of 6 weeks, and by an open label of 3 months with 5 mg tadalafil once daily for all patients.
The primary endpoint was to determine the effect on erectile function, measured by the proportion of patients achieving an International Index of Erectile Function (IIEF)> 22, after washout period of 6 weeks. Secondary endpoints were the erectile function domain of the IIEF, the Question 3 of the Sex Encounter Profile (SEP3) and the penile length.

The 20.9%, 16.9%, and 19.1% of patients in the tadalafil once daily, tadalafil on demand, and placebo groups, respectively, achieved IIEF EF scores ≥ 22 after DFW. At the end of double-blind treatment (EDT), the mean IIEF-EF score improvement significantly exceeded the minimally clinically important difference in both tadalafil groups; and in the case of SEP 3 just for tadalafil daily (p = 0.019). All groups experienced a worsening of erectile function was during the DFW period, which improved again during the open label of the study. After 9 months of treatment, decreased penile length was lower in patients treated with tadalafil daily (p = 0.032).
In conclusion, tadalafil daily proved to be the most effective drug in the recovery of erectile function in patients undergoing NSRP. Daily administration of tadalafil early after surgery contributes to the restoration of erectile function, possibly exerting a protective role against the structural changes of the penis. In those patients who did not received early treatment with PDE5 inhibitors, erectile function did not improve after discontinuing treatment with PDE5 inhibitors.

Featured Round Tables

Pharmacology of Premature Ejaculation (PE): A critical reappraisal

Chairs: Ege Can Serefoglu (Turkey), Patrick Jern (Finland)

Speakers: Pierre Clement (France), François Giulinao (France), Mario Maggi (Italy), Ignacio Moncada (Spain) and Enmanuele A Jannini (Italy).

The fundamental concepts and the current role of Dapoxetine (Priligy) was reviewed

An overview of the physiology of ejaculation and pathophysiology of PE was made, as well as the different treatments that have been used historically in the treatment of this disorder, with special emphasis on dapoxetine, as the only approved treatment with this indication. Again, the controversy of what should be the optimal dose to start treatment, even though the manufacturer recommends starting with 30 mg dose and increase if the clinical response is not ideal arises. There were several comments from those present in the room, where it seems that an increasing proportion of andrologists, opts for starting treatment with full doses. The details of the new scientific evidence available on the use of dapoxetine, discussed below in the section on trade symposiums.

La Peyronie's disease (PD): Still only failures (or so?)
Chairs: Carlo Bettochi (Italy), Ian Eardly (United Kingdom)
Speakers: Fabio Castiglione (Italy), Wayne Hellstrom (USA), Önder Kayigil (Turkey), Mustafa Faruk Usta (Turkey), David Ralph (United Kingdom).

In this field there have been significant developments during the past year: The approval of collagenase Clostridium hystolyticum (CCh) intralesional in the treatment of PD and the publication of Spanish study on the treatment of the acute phase of Peyronie's disease through the use of penile extender devices and its correlation with ultrasound.

Xiaflex® is an injectable collagenase preparation consisting in a predetermined mixture of 2 distinct collagenases that cleave collagen strands at different sites. AUX I (a class I C histolyticum collagenase) cleaves the terminal ends of collagen, and AUX II (a class II C histolyticum collagenase) cleaves internal sections of collagen. Recently the FDA approved Xiaflex® for non surgical treatment of men with PD that have a curvature of 30 degrees or more and tangible scar tissue plaque in their penis.

The results of a multicenter IIb study and two phase III, prospective, randomized, double-blind, placebo-controlled studies, conducted by Gelbard et al, were presented. The clinical efficacy and safety of the intralesional therapy with CCh was evaluated; that allowed drug approval. Throughout these studies, were evaluated over 1000 patients who were administered up to 4 cycles of 0.58 mg of CCh, with 2 injections per cycle, followed by penile modeling. The results showed, an average increase and improvement of penile curvature as 34 % ($p < 0.0001$) and on the scale of "discomfort" ($p < 0.0037$) using the PDQ (first validated questionnaire that determines the psychosexual impact on PD patients). Adverse effects are common: Pain, swelling and bruising at the site of injection, and resolved spontaneously in most patients, although 3 cases of rupture of the corpora cavernosa which required surgical treatment.

Similarly, they commented the results of a prospective, randomized controlled trial conducted in Spain by Martinez-Salamanca et al, whose objective was to determine the effectiveness and safety of penile traction therapy (PTT), in the conservative treatment of acute phase of PD. A total of 55 patients underwent PTT for 6 months and compared with 41 patients with acute phase of PD who did not receive active treatment ("No Intervention group"(NIG)). After 6 months of treatment, with a mean follow up of 9 months, the mean curvature decreased from 33º at baseline to 15º at 6 months and 13º at 9 months with a mean decrease 20º ($p<0.05$). It also showed an increase in penile length and girth. ($p = 0.03$).

Likewise, predictors associated with treatment success were identified: Penile curvature < 45° at baseline, visual analog scale (VAS) pain > 5, time to diagnosis < 3 months, absence of visible plaque on ultrasound and age < 45 years.

Pre-Clinical Research: Novel Insights and Treatment Targets in the Pathophysiology of Erectile Dysfunction
Chairs: Stefan Ückert (Germany), Javier Angulo (Spain)
Speakers: Selim Cellek (UK), Carla Costa (Portugal), Maarten Albersen (Belgium) and Trinity J. Bivalaqua (USA).

Mainly emphasizes the large amount of research being carried out at present on erectile dysfunction, focused on the pathophysiology of the disease and its relationship to other conditions such as diabetes mellitus, hypercholesterolemia and the metabolic syndrome, and the impact of cardiovascular risk factors and age on this disease.

Treatment with stem cells derived from adipose tissue, appears to be the new target of research in the treatment of Peyronie's disease, performed by several work groups (Sakaya University of Turkey; University Vita-Salute San Raffaele of Milan, Italy; University of Leuven, Belgium and the John Hopkins Medical, Baltimore, USA); showing encouraging results, although a long way ahead will be necessary to translate these results into clinical practice. Another interesting field is the penile rehabilitation by administration of PDE5 inhibitors in prostatectomy rat models.

A field with renewed interest, is the treatment with testosterone and its theoretical benefits, as a combined treatment in patients with metabolic syndrome, accelerating weight loss and improving glycemic control.

Video-Courses

In this section, several videos were presented, most of them focused in penile surgery for the treatment of PD and prosthetic surgery. The highlighted videos include:

Total phallic reconstruction and rehabilitation after penile amputation
presented by Dr Javier Romero from Spain; where the multidisciplinary approach is essential and the urologist should be the leader of the surgical team.

Simultaneous implantation of penile prosthesis and artificial urinary sphincter through a single incision
presented by Dr Juan Ignacio Martinez-Salamanca from Spain as the ideal approach in those patients in whom both conditions coexist, usually after radical pelvic surgery.

Incision and venous patch in Peyronie's patients with hourglass deformity
by Dr Ates Kadioglu from Turkey, and the **transposition of the corpora cavernosa for the treatment of PD**
presented by Dr Natalio Cruz from Spain as nearly ideal grafts, with a low complication rate and acceptable functional results.

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Different surgical approaches employed in prosthetic reservoir placement
by Dr Marco Spilotros and Dr David Ralph, from the United Kingdom as an updated topic; because patients who demand penile implant surgery are more complex everyday.

Sponsored Symposia

Avanafil: A new treatment to meet your ED patients need
Speakers: Vincenzo Mirone (Italy), François Giuliano (France), John P Mulhall (USA).

Important advances in the field of treatment of erectile dysfunction were presented, with the launch and presentation at European level of Avanafil, a new inhibitor of phosphodiesterase type 5 (PDE5 inhibitor), which will be marketed by Menarini Group.

Avanafil is a PDE5 inhibitor with a fast and highly selective action, approved by the Food and Drug Administration (FDA) for the treatment of erectile dysfunction in April 2012, and recently approved in the European Union. It will be marketed under the name of Spedra, and will be available in doses of 50, 100 and 200 mg.

Avanafil strongly inhibits PDE5 in a competitive manner. The drug is more potent (100 fold) and show higher selectivity (120 fold) for PDE5 and for PDE6 than sildenafil (16 fold) and Vardenafil (21 fold); and its selectivity for PDE5 versus PDE1 is greater than 10 000 fold (sildenafil 380 fold and Vardenafil 1000 fold). In contrast to Tadalafil, considerable inhibition by Avanafil of PDE 11 was not registered.

Avanafil compared with other PDE5 inhibitors available, has a unique selectivity profile, which results in a rapid onset of action and an increase in potency that allows patients to maintain satisfactory sexual intercourse within 15 minutes after administration of the drug, improving the spontaneity of sexual activity. Adverse effects are mostly mild to moderate in nature. Moreover Avanafil had significantly lower rates of hemodynamic side effects and shorter duration of interaction in combination with NO-releasing drugs, become in a suitable medication for patients with ED who taking nitrates.

Premature ejaculation: Treating a highly impacting multidimensional condition (Sponsored by Menarini Group).
Speakers: Emmanuele A Jannini (Italy), Stanley Althof (USA), Andrea Burri (United Kingdom), Cris Mc Mahon (Australia)

Recent advances, in the field treatment of premature ejaculation (PE), were presented. The results of the PAUSE study were discussed; a prospective, observational, multicenter study conducted in 7 European countries, with a duration of 12 weeks; whose objective was to evaluate the safety profile and adverse effects (AEs) in 6712 patients treated with 30-60 mg Dapoxetine (group A) vs. 3316 treated with other standard treatment options (group B), involving long half-life SSRIs (n = 1515), topical therapy (n = 952), condoms (n = 432), behavioral therapy (n = 1182) and other treatments (n = 362).

The study concluded that in both groups, treatment was well tolerated, with 12% of AEs reported in group A and 8.9 % in group B, which increase in patients older than 65 years (21.4%). The most common adverse effects were nausea, headache and dizziness and in a higher proportion in group A, although they did not reach 5%. No cases of syncope in group A and one case of syncope in group B were reported. In treatment group A, 58 patients (0.9 %) were taking some medications contraindicated during the course of the study (usually antidepressants) and 540 patients (8.8%) were taking treatment with some type of caution about its use (PDE5 inhibitors, alpha blockers). The total number of patients experiencing at least one adverse event was higher in the group of patients treated with Dapoxetine, especially in patients who increased the dose from 30 to 60 mg over the course of the study, compared with patients who maintained the 30mg dose. Twelve (0.2 %) severe AEs in group A and 10 (0.3 %) in group B were reported; however, none of these events were considered related to treatment.

The dropout rate was 1.5% in group A and 0.2 % in group B, most relating to AEs; however, 0.3 % of patients discontinued treatment despite not having reported any AE. Although the proportion of AEs was slightly higher in the group of Dapoxetine, is important to note that more than two thirds of patients in group B were treated with behavioral therapy or topical treatments, which have no systemic adverse effects.

The results of this observational study demonstrated that Dapoxetine has a good safety profile and low prevalence of AEs. The high level of adherence by healthcare providers to the contraindications, special warnings, and precautions for Dapoxetine minimizes the risk for its use in routine clinical practice. Dapoxetine in doses of 30 mg and 60 mg has shown to be superior to placebo in all efficacy variables. Efficacy results were similar in both individual analysis and the combined analysis of the studies, which concluded that Dapoxetine is "consistently" superior than placebo, regardless of the demographic characteristics of the patients.

Posters

In the conference facilities, a great amount of posters were exhibited, including some which aroused great interest:

New highlights for postorgasmic syndrome
presented by Dr Juan Ignacio Martinez-Salamanca et al, from Spain; based on a survey in a virtual forum. New approaches suggest that this syndrome may be defined as neurobiochemistry sequel related to orgasm, to generate new treatment hypotheses.

Relationship between a history of nocturnal enuresis (NE) in childhood and lower intravaginal ejaculatory latency time (IELT) by Dr Ahmet Gokce, from Sakarya University, Turkey; finding a relationship between NE and lower IELT in 49 patients, respect to 49 healthy controls, concluding that NE could be a possible risk factor in the development of PE.

Diagnosis of venous leakage in patients with ED using CT Cavernography (CT-C) presented by Dr M Chocholaty et al from Universitiy Hospital Motol in Prague. The study present the results in 20 patients with a suspicion on venous ED underwent CT cavernography after intracavernal injection of contrast medium 10 to 15 min after the pharmacologically induced erection, demonstrating a sensitivity of 89.5%. In 68.4%, of patients the CT-C, detected a combined deep and superficial drainage. In conclusion CTr-C allows an exact evaluation and individualized approach for each patient.

Use of oral mucosa graft in the treatment of Peyronie's disease presented by B Gvasalia from Russia: Where the experience of 33 cavernoplastys performed using this type of graft was discussed, with satisfactory results.

The 'Faculty of 1000' has offered three best poster prizes for pre-clinical, male clinical and female clinical research. A jury of Selim Cellek, Asif Muneer and Johannes Bitzer has been composed to select the F1000 posters during the congress.

The awardees of this year were:

Preclinical Research

Endopeptidase inhibition attenuates the contraction induced by big endothelin-1 of isolated human penile erectile tissue by Pejman Shahin, from Hannover Medical School, Germany. This study demonstrated in vitro that inhibition of endopeptidase activity can antagonize the contraction of human penile erectile tissue induced by Big endothelin-1, these findings might be of significance regarding to future pharmacological treatment options for ED.

Clinical Research

Evaluating of the efficacy of the surgical procedures and the complications at patients with penile curvature due to Peyronie's disease by Emrah Okulu et al from Ataturk Training and Research, Hospital Urology Clinics, Ankara, Turkey. In this work compared the satisfaction of 94 patients treated surgically due to PD, divided in 3 groups according to the surgical procedure: Plication (n=41), plication and venous grafting (n=22), and plication, venous grafting and lateral imbrication for cavernous saculation (n=31). The IIEF score and Quality of Life (QoL) form were used to evaluate the patient satisfaction at preoperative period and postoperative follow up, up to 18 months. The results conclude that combined surgical procedures have better cosmetic outcomes and patient satisfaction than single procedures.

Sexual satisfaction in the elderly women by Sandra Vilarinho from Portugal. The aim this cross-sectional study was to examine predictors of women´s sexual satisfaction with ageing, particularly explore the role of sexual functioning, relationship variables, and sexual beliefs, assessed by questionnaires: Menopause status; life satisfaction (SWLS); relationship (GRIMS); sexual beliefs (QCSD); affect (PANAS-X); sexual self esteem (SSEs); sexual functioning (FSFI); and sexual satisfaction (GRISS). Results revealed that relationship satisfaction ($p<0.01$), sexual beliefs ($p<0.001$), negative affect ($p<0.001$) and sexual functioning ($p<0.5$) as main predictors of sexual satisfaction in elderly women. They concluded the important role played by sexual beliefs in older women's sexual satisfaction, together with affect and relationship dimensions, instead sexual satisfaction, appear to play a secondary role in elder women.

Grants and Scholarships

In this section we have to mention specially those posters and communications resulted winners including best presentation:

1. Prize for the best presentation on FSD (preclinical)
Linda Vignozzi from the University of Florence, Italy, for the work entitled: Androgens positively regulate no-mediated relaxant pathway in rat clitoris. This work evaluate sex esteroid regulation of the NO-dependent relaxant and Rho/ROCK contractily pathways in clitoris, demonstrating that in vivo treatment with testosterone improves the NO-mediated signalling, whilst E2 stimulates the contractile Rho/ROCK signalling in clitoris.

2. Prize for the best presentation on FSD (clinical)
Michael Krychman from New England Research Institute, Watertown, USA; with the work entitled: **Improvement in sexual function as measured by the female sexual function index in premenopausal women during a 12-week placebo-controlled dose-ranging study of self-administered subcutaneous bremelanotide** (BMT, a melanocortin agonist, analogue of the alpha melanocyte stimulating hormone), for female sexual dysfunctions, to evaluate to efficacy of BMT to improve sexual function in 327 premenopausal women with female sexual dysfunctions (hypoactive sexual desire disorder and/or female sexual arousal disorder), demonstrating statistically significant improvement of desire, arousal, lubrication, and satisfaction domain of the FSFI.

3. Prize for the best presentation on MSD (preclinical)
Dr Ahmet Gokce from Sakarya University, Turkey in collaboration with the Tulane Universitiy (New Orleans, USA), presented his work: **Using stem cells derived from adipose tissue in the prevention and treatment of erectile dysfunction in a rat model of Peyronie's**

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disease, demonstrating a statistically significant improvement in erectile function, in treated animals. Therapy from adipose tissue stem cells was the subject of several studies, with encouraging results.

4. Prize for the best presentation on MSD (clinical)

Dr Lars Lund from the Odense University Hospital, Denmark, presented a prospective, randomized, placebo-controlled study in 112 patients with ED treated by extracorporeal lithotripsy shock wave for 5 weeks, showing an increase in the quality of erectile function in 59% of treated patients compared to placebo, with good tolerance.

5. Prize for the best surgical presentation

The award for the best surgical presentation was for Dr Faruk Mustafa Usta, from Akdeniz University, Turkey; with the video entitled: **Feasibility of placing an inflatable penile prosthesis of 3 components (IPP) in patients undergoing radical pelvic surgery** (RPS), which retrospectively evaluated 302 patients, underwent IPP implantation. The 23% of patients had a history of RPS (radical cystectomy, radical prostatectomy). The study concludes that IPP implantation can be safely perform by either penoescrotal or infrapubic approach in men who previously underwent RPS.

Prestige Awards

The Executive Committee of ESSM decided to establish two awards to be presented during the annual meetings of the society:

Career Award

This award presented to a senior scientist who has made an outstanding contribution in the field. This year was given to our colleague and member Dr. Antonio Martín Morales from Spain.

ESSM Award of Excellence

This award is presented annually to a physician or scientist under the age of 40 years (either in basic sciences or clinical practice) who has made recent exceptional achievement in the field. This year´s awardee is: Linda Vignozzi, from Italy.

Finally, remember that the venue of the next meeting of the ESSM in 2015 will be Copenhagen, Denmark. We would like to invite you to this event.

Key from Kols: Penile Cancer

by Giorgio Bozzini

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Is there a wider space for Doppler US in the Penile Cancer diagnostic pathway?

Penile Cancer is mostly a Squamous Cell Carcinoma (that accounts for more than 95% of cases of malignant diseases of the penis) and has an incidence of less than 1 per 100.000 males in Europe.

Currently, as EAU Guidelines stated, the diagnostic pathway to be followed before the surgical procedure, requires a careful diagnosis and adequate staging. A greater role is played by Magnetic Resonance Imaging (MRI) in combination with artificial erection obtained with prostaglandin E 1. This is done to achieve better preoperative informations to exclude (or confirm) corpora cavernosa infiltration and to better plan an organ sparing surgical approach.

Nodal involvement although can be assessed with clinical examination and US help is described (as CT and PET), but not for micro-metastasis.
Each of this statements has a level C of recommendation so they are made despite the absence of directly applicable clinical studies of good quality.

Doppler US of the penis can play a wider role in this diagnostic field?
Almost ten years ago Bertolotto and Lont with their papers started to empathized this concept. Doppler US could be a feasible diagnostic tool to evidence a corpora cavernosa malignant involvement as it is already for lymphnodes.

The YAUWP (Young Academic Urologist Working Party of the EAU) Men's Health expertise group is drawing up a study to assess what could be the correct role of Penile Doppler US and even if this role can be similar to the one played by MRI.

What can be the points that strengthen this thesis?
Doppler US is easier and faster to be done if we compare it to MRI. Not all hospitals have the same possibilities to get an early MRI for our patients. Also, not all the radiologists are properly trained to perform a good test that will drive the next surgical procedure. Despite this prostaglandin E 1 injection is similarly performed in the two tests.

MRI is surely more expensive than Doppler US. The cost of the two devices are so different and the time exploited is much more for MRI. MRI also needs at least one technician to be performed and one radiologist to be read. Doppler US has not the same need.

A well trained urologist on Penile Cancer and on Doppler US of the penis can be the correct answer. He will be the one who get the information from the US to drive his surgical strategy.
Not all the patients that has a penile cancer can at least perform an MRI investigation. An objective contraindication is represented by claustrophobia. Another can be found in a patient who previously has done hip prosthesis surgery or a patient that had a pacemaker implant (actually new generation devices will allow MRI).

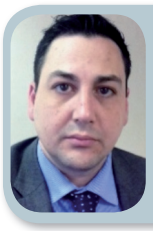
This is to underline that some problems can come out if, following guidelines, we need to perform an MRI.

It will be interesting, as we are currently doing, to better understand the role of Frozen Section Examination (FSE) during the surgical procedure planned on the evidences got from the imaging. Is its role important? It will be important with a new US role in Penile Cancer?
A urologist who had previously done by himself the Doppler US study will be more or less confident on a procedure, on the other hand, driven by an MRI? Will his FSE, performed to exclude corpora malignant involvement, be done with more or less consciousness?

Currently there are no sure answers to that questions but it is interesting that they are rising.
A new role for Doppler US in discovering malignant infiltration could come out, but not only. The new 3D imaging for US device can play a role to plan the correct surgical strategy. Intraoperative use of US is already a fact, and can be used to amend the surgical strategy if needed. With a previous Doppler US and a planned sparing-surgery it will be easier to assess a postoperative or preoperative presence of an Erectile Dysfunction. This possibilities confirm how wide can be the applications of the Penile US and how valuable could be his help.
To achieve this goal another key point should be reached. This key point is the centralization of the procedures and of the diseases as it is done already done in some countries. As we know the penile cancer incidence is not high, and even with a good knowledge of the subject a urologist needs cases to still offer to his patients the gold standard treatment for this disease. Numbers also guarantee good clinical and research outcomes thus lowering the costs.
I hope that this approach may fuel interest among urologist to integrate clinical best practice and scientific research in the field of penile cancer.

Key from Kols: Priapism

by Evangelos Zacharakis



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Strategies for the management of ischaemic priapism

The pathophysiology of ischaemic priapism is still not completely understood although the initiating mechanisms are likely to be multifactorial involving central neuronal pathways, alterations in the corpus cavernosum microenvironment, modulation of the smooth muscle contractile machinery and aberrant neurotransmitter regulation in the corpus cavernosum leading to dysregulation of the smooth muscle.

Introduction

Priapism is defined as a prolonged penile erection that lasts longer than 4 hours in the absence of sexual stimulation and remains despite orgasm. It is commonly classified into non ischaemic (high flow), ischaemic (low flow) and stuttering (recurrent) subtypes (1-5). Ischemic priapism is the most common type of priapism accounting for more than 95% of all episodes. Obstruction of the penile venous outflow leads to stasis of blood witin the corpus cavernosum formatting a a compartment syndrome which results in the development of hypoxia, acidosis and glucopenia (6).

Ischemic priapism is a medical emergency as the progressive ischemia within the cavernosal tissue is associated with time-dependent changes in the corporal metabolic environment, which leads to smooth muscle necrosis. The absolute time point at which irreversible damage to the corpus cavernosum smooth muscle occurs is unknown and may vary according to the aetiology of ischemic priapism and the degree of pre-existing smooth muscle dysfunction. There is evidence, however, that even after 6 h of ischemia, irreversible changes have already started to occur (7–10). Broderick and Harkaway analysed the change in the cavernous blood gas alterations in the pO2, pH and pCO2 during the erection and found out that fter 240 minutes the cavernous tissue is no longer perfused by highly oxygenated blood (11). Histologically the components of the corpus cavernosum undergo progressive changes as the duration of priapism increases. In cases where priapism is of a short duration (less than 12 hours) the tissue consisted of minor endothelial defects with occasional lymphocytic infiltration with no alteration in the smooth muscle cells. It is only after 12 to 14 hours of low-flow priapism that trabecular smooth muscle cells show the beginning of focal cytoplasmic transformation which manifests as an increase in size of the perinuclear cytoplasm, endoplasmic reticulum, ribosomes and Golgi apparatus. At between 24 to 48 hours duration widespread endothelial destruction and exposure of the basement membrane occurs with subsequent thrombocyte adherence. In addition to this the smooth muscle cells undergo a transformation as described above as well as necrosis. Persistent blood stasis for longer than two days is associated with infiltration of the trabecular tissue with inflammatory cells and smooth muscle cells undergoing necrosis or phenotypic change into fibroblast like cells (12).

Even if left untreated, unless secondary to direct malignant infiltration of the corpora, the degree of tumescene tends to subside spontaneously with time and the necrotic cavernosal tissue undergoes fibrosis, resulting in erectile dysfunction refractory to medical treatment and in a shortened indurated penis (7).

Diagnosis of ischaemic priapism

The diagnosis of ischaemic priapism is based on the clincial history and examination, radiological imaging and blood gas analysis, whilst urine toxicology, haematological screening and abdominal imaging are required to investigate the underlying cause.
Color Doppler Ultrasonography of the penis is used to assess the flow in the cavernosal arteries and corpus cavernosum to differentiate ischaemic from non-ischaemic priapism. Penile Doppler will demonstrate reduced or absent flow within the cavernosal arteries and impaired perfusion of the distal corpus cavernosum. However, after corporal blood aspiration the interpretation of penile Doppler can be difficult due to aberrant high flow in segments of the corpus cavernosum (13, 14). Therefore a more reliable investigation to distinguish between ischaemic and non-ischaemic priapism corporal blood gas analysis, which will typically show ischaemic, venous blood with pO2 <30mmHg and pCO2 >60 mmHg and pH <7.25 in cases of low flow priapism. A recent series of 23 patients, in which the radiological findings have been correlated with biopsies from the corpus cavernosum, Gadolinium enhanced high-definition Magnetic Resonance Imaging (MRI) of the penis has a sensitivity of 100% when used to detect the presence of necrosis of the cavernosal smooth muscle (15). Therefore, this imaging modality may represent an extremely useful imaging modality to asses the corporal tissue viability (Fig 1).

Management of ischaemic priapism

The goal of management of ischemic priapism involves successful detumescence and presevation of cavernosal smooth muscle function in order to prevent penile shortening and refractory erectile dysfunction in the long term.

The initial conservative management of IP, if the duration of the erection is between 4 to 24 hours, involves ejaculation, vigorous physical exercise and cold baths with the aim to stimulate the noradrenergic system to release cathecolamines, which would stimulate smooth muscle contaction via sympathomimetics and induce detumescence.

1) Aspiration and instillation of sympathomimetics

If conservative management fails, the next step involves aspiration of ischaemic blood from the corpora cavernosa using 19G 'butterfly' needle through the glans penis and into the corpora or

insertion into the shaft at the 2 or 10 o clock position avoiding the neurovascular bundles which can be performed under local or general anaesthetic followed by repeated instillations of α-adrenergic agonists such as phenylephrine (usually 200μg repeated to a maximum of 1500μg) in an attempt to increase the smooth muscle tone and promote detumescence. Alternative α-adrenergic agonists include metaraminol and adrenaline. High dose phenylephrine has also been successfully utilised in small case series (16) although in refractory cases it is unlikely to be successful due to irreversible smooth muscle dysfunction (17). Aspiration of ischaemic blood alone may resolve the ischemic priapism in up to one third of cases and therefore should always be attempted, before injecting the phenylephrine as the smooth muscle contraction is impaired in an ischaemic microenvironment (18). Treatment with phenylephrine should be performed with continuous monitoring of the blood pressure, especially in patients with hypertension or cardiovascular disease, as phenylephrine has a ionotropic and chronotropic effects and may potentially precipitate a vascular event.
Although corporal blood aspiration and instillation of α-adrenergic agonists should be performed in all patients, irrespective of the time of presentation, priapism episodes lasting more than 24–36 hours are unlikely to respond to this intervention per se due to the presence of irreversible damage to the cavernosal smooth muscle. However, aspiration of the corpora cavernosa and instillation of phenylephrine can lead to detumescence in up to 100% of cases, if performed within 12 hours from the onset of priapism (19).

2) Shunt surgery

Patients who do not respond to aspiration and instillation of α-adrenergic agonists undergo penile shunt surgery as second line intervention. The basis of the shunt surgery consists of a fistula formation between the corpus cavernosum and the glans penis, corpus spongiosum or the saphenous vein. The aim of any of these surgical techniques is to decompress the corpora cavernosum of the veno occlusion and re-establishes the arterial inflow with a resultant complete flaccidity after the shunting procedure (20).
The Winter and Ebbehoj shunts are the most widely used minimally invasive distal percutaneous shunts. The Winter shunt, characterized by the placement of a large-bore needle into the distal glans and corpus cavernosum is the less invasive technique but is associated with higher failure rate. The Ebbehoj technique consists of a simple stab incision with a No 10 scalpel into the corpora cavernosa through the distal aspect of the glans penis. In case of failure of percutaneous shunt surgery, an Al-Ghorab shunt, which is an open corporoglanular shunt involving the excision of a segment of tunica albuginea at the tip of the corpora (21).

Some authors have described a new shunt technique, which involves the creation of a wide connection between the distal corpora and glans penis. This technique, also known as the T-shunt, involves the insertion of a No 10 blade through the glans penis into the ipsilateral corpus cavernosum and then rotated of 90 degrees laterally, away from the urethra, and pulled out, to create a large fistula (Fig 2) (22).

The procedure can be repeated on the contralateral side if detumescence is not achieved (TT shunt procedure). In case of TT shunt failure, a tunnelling manoeuvre should be attempted with the aim to allow the blood to be drained from the proximal aspect of the corpora cavernosa. This procedure, also known as the corporal snake manouvre, inserts of a 20–22 French urethral sound through the previous T- or Al-Ghorab shunt (Fig 3) (23, 24).

Initial reports considered the combination of a distal shunt with the tunnelling manoeuvre a safe technique, which allowed the resolution of the priapism episode in almost all cases and excellent recovery of erectile function (22).

However, a recent series of 45 patients has shown that the success of T shunt and tunnelling manoeuvre is dependent on the duration of priapism. In particular, if carried out within 24 hours from the onset of priapism, this manoeuvre allows the resolution of the priapism episode in almost all cases, but long term refractory erectile dysfunction is still present in 50% of patients (Table 1). The outcome is even more dissatisfactory if the duration of priapism is greater than 48 hours as the manoeuvre always fails to resolve the priapism episode and all of the patients develop refractory erectile dysfunction (25).

3) Penile prosthesis implantation

Penile prosthesis implantation, which is the gold standard treatment in patients who have developed severe erectile dysfunction as a result of prolonged priapism, has in the last decade offered an alternative option to shunt surgery for the management of refractory ischaemic priapism. Acute implantation of a penile prosthesis in patients with refractory ischaemic priapism is now proposed by a number of institutions (26–28).
In particular, patients with ischaemic priapism >48–72 hrs, unresponsive to the initial management with blood aspiration and intracorporal instillation of α-adrenergic agonists, are likely to develop irreversible damage of the cavernosal smooth muscle, which will lead to fibrosis, penile shortening and refractory erectile dysfunction. Therefore, immediate penile prosthesis implantation in these patients can resolve the painful erection, guarantee the adequate long term rigidity for sexual penetration and prevent the otherwise inevitable penile shortening (29). In fact, immediate penile prosthesis implantation in patients with prolonged iscaemic priapism and cavernosal smooth muscle necrosis reduces the painful priapic episode, guarantees the adequate long term rigidity necessary for sexual intercourse and prevents the otherwise inevitable penile shortening secondary to the development of corporal fibrosis.

Potential overtreatment of patients with no evidence of necrosis in the cavernosal smooth muscle is one of the risks associatied with this approach and therefore the correct timing of surgery

Key from Kols: Priapism

is paramount. Preoperative penile MRI and cavernosal smooth muscle biopsies during the shunt procedure or frozen sections during the implant surgery are essential to confirm the presence of necrosis and to assist the surgeon in the decision to proceed with the immediate implantation of a penile prosthesis (Fig 4) (15, 25).
The main risk associated with acute penile prosthesis implantation is prosthesis infection which can be as high as 6%, more than 3 times higher than reported for virgin cases (29, 30). This is because the previous introduction of aspiration needles and shunt surgery within the corpora cavernosa, in the attempt to induce detumescence, may increase the risk of infection, particularly if there is diffuse bruising and oedema of the dartos and tunica albuginea.

Therefore, it is suggested that the penile prosthesis implantation should be delayed for a few days in order to give enough time for the oedema and bruising to subside and for the broad spectrum antibiotics to clear any possible bacterial contamination in the corporeal tissue (31). Although the exact time beyond which the necrotic corporal smooth muscle is substituted by fibrotic connective is not known, Sedigh et al. have described easy dilatation of the corpora after 1 week of priapism. In this series dilatation was also simple after a 2 week interval.

Although both malleable an inflatable penile prostheses have been successfully implanted in patients with acute ischaemic priapism (32–34), semirigid devices are the first choice implant in this group of patients. This is because it preserves the penile length, without the need to cycle the device and it is easier to explant if there is an infection. After 3 to 6 months it can be electively exchanged to an inflatable device in compliant patients.

During early penile prosthesis implantation, the corporal dilatation is generally easy, however distal perforation can occur in up to 6% of patients who have undergone previous shunt surgery, especially when a malleable device is placed (33, 34). According to Salem et al, distal erosion can be minimized by applying a non absorbable sling suture to fix the rear tip of the malleable device to the tunica albuginea of the penis (33). Delayed penile prosthesis implantation in patients with severe corporal fibrosis due to ischaemic priapism represents a real challenge for the surgeon and is associated with higher complication rates and lower patients' satisfaction.

Due to the formation of dense fibrosis in the distal corpora, adequate exposure of the penile shaft and of the crura is often required. This can be achieved by combining a penoscrotal and total or semi circumferential subcoronal incision with partial or complete degloving of the penile shaft (Fig 5). Other authors have described a wide corporal excision of the scar tissue, which involves extensive incisions of the tunica albuginea. As the dissection can be technically challenging, the operative time is prolonged, complication rates can be as high as 65%, with up to 30% of patients experiencing infection of the device, and an overall prosthesis survival of only 50% at 1 year (35).

Wilson et al. described the concept of drilling into the fibrous cavernous tissue avoiding an extensive albugineal incision and time consuming excision of the fibrotic tissue with the use of Carrion-Rossello or Uramix cavernotomes (30). This technique allows a channel to be created in the dense fibrotic tissue minimizing the risk of inadvertent urethral injury. Using this technique, Wilson et al. were able to successfully implant an inflatable device without the use of grafting in 32 consecutive patients with severe corporal fibrosis. The infection rate in this series was 6.3% with an overall 1 year survival of the implant of 87% (30). Despite of all these caveats, the revision rate for complications is as high as 12% at 15.7 months, but prosthesis implantation in acute priapism remains a simple and reproducible procedure that allows the quick resolution of the priapism with preservation of penile length and guarantees the rigidity necessary for intercourse (29).

Conclusions

Cavernosal tissue damage in ischaemic priapism is time related. Conservative measures and aspiration with or without intracorporeal instillation of α- adrenergic agonists are usually successful in the early stages, before the metabolic changes in the corporal milieu have led to necrosis of the smooth muscle.

Shunt surgery in patients remains debatable, as the lack of response to aspiration and instillation of α-adrenergic agonists indicates that irreversible changes in the cavernosal smooth muscle are likely to have already occurred. Therefore shunt surgery may relieve the painful erection but will not prevent the formation of fibrosis and the consequent erectile dysfunction, which is not the actual aim of the treatment.

Immediate penile prosthesis implantation in patients with refractory ischaemic priapism settles the priapic episode, maintains the long term rigidity necessary to engage in penetrative sexual intercourse and prevents the otherwise inevitable penile shortening (Fig 6).

Athough complication rates after penile prosthesis implantation in acute priapism are higher than in virgin cases, they are still lower than after implantation in patients with severe corporal fibrosis due to chronic priapism. Furthermore, complication rates following acute implantation could be potentially further reduced if unncecessary shunt surgery is avoided or delaying surgery for a few days to allow the bruising and oedema to settle and the broad spectrum antibiotics to clear bacterial contamination.

Regardless of the complication rates, penile prosthesis implantation in refractory ischaemic priapism should be preferred as it allows the preservation of penile length, which is one of the main factors influencing postoperative patient's satisfaction following surgery.

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Key from Kols: Priapism

Tables

Table 1: Comparison of studies using a combination of a distal shunt and intracavernosal tunneling

Senior Author	Year	No of patients	Median duration of priapism (hrs)	Success rate shunt + tunneling	Post op ED
Burnett [24]	2009	10	60	80%	40%
Lue [23]	2009	13	64	92%	38%
Ralph [25]	2013	45	96	64%	93%

Figure 1
Penile MRI detects the presence of necrosis within the corpora cavernosa

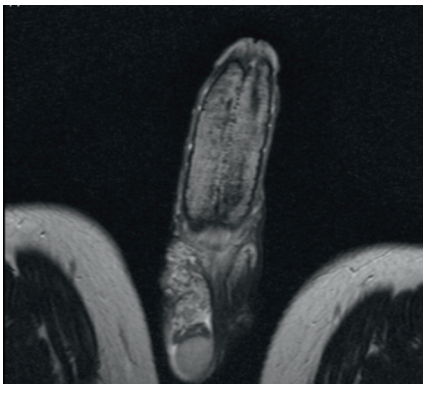


Figure 2
The T shunt performed bilaterally. The scalpel blade is inserted through the glans and into the corpora cavernosum, rotated 90 degrees and withdrawn [25]

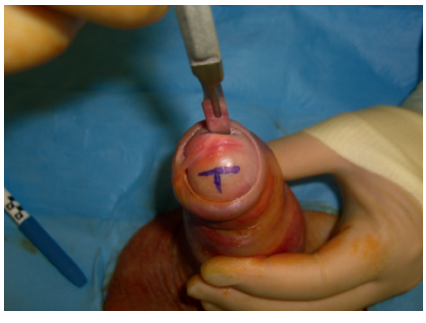


Figure 3
Tunnelling using an 8 Hegar dilator to the penoscrotal junction [25]

Figure 4
Cavernosal muscle biopsy taken with a trocar gun prior to tunnelling [25]

Figure 5
Difficult corporal dilation requiring a second corporal incision [29]

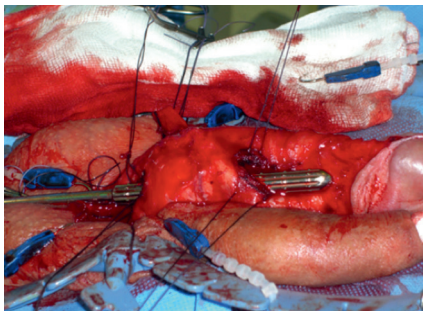
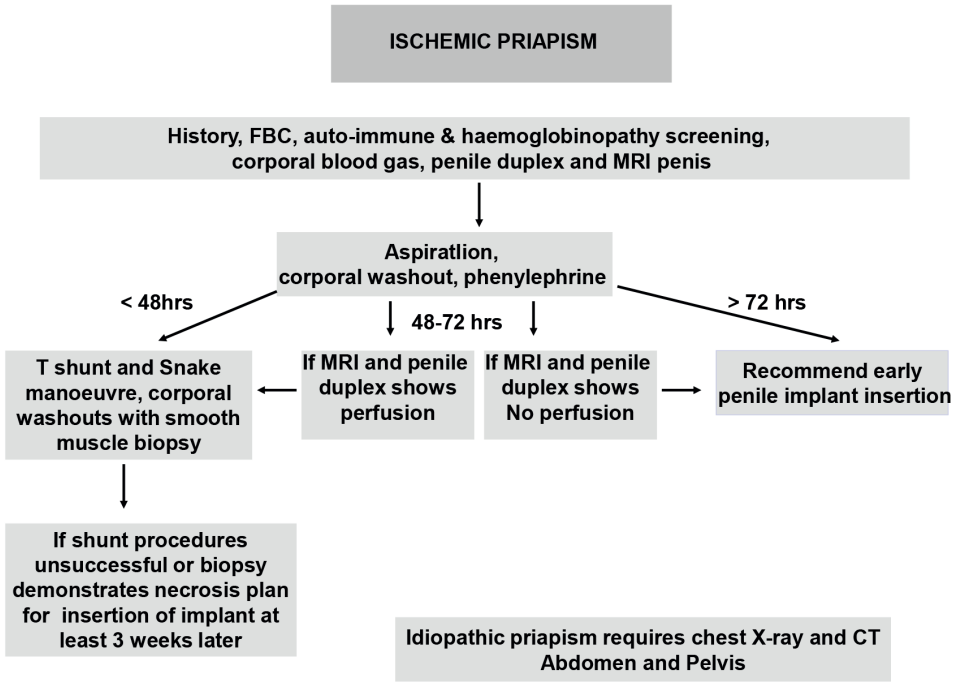


Figure 6

Proposed Algorithm for the management of ischaemic priapism [29]



Have you read? Best of the Best: Basic Research

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Physiology of erection – Myosin-5 for active localization of nNOS

Myosin Va plays a role in nitrergic smooth muscle relaxation in gastric fundus and corpora cavernosa of penis. *Chaudhury A, Cristofaro V, Carew JA, Goyal RK, Sullivan MP.* PLoS One 2014, 9: e86778.

Myosin 5a is a molecular motor that moves cargo along actin filaments in the cell. This means that facilitates the trafficking of proteins between the different compartments of the cell. Myosin 5a is known to transport melanosomes in melanocytes and also play a role in neuronal transport. Many proteins are active or not depending on its cellular localization. This may involve localizations at the nucleus, mitocondria, etc. and, in an important number of cases, cytosolic vs. membrane bound localizations.

Nitergic relaxation of penile smooth muscle is a key event in penile erection. In fact, a defective nitrergic relaxation of corpus cavernosum from men with erectile dysfunction (ED) has been demonstrated. nNOS is the enzyme responsible for NO generation in this response. Defective nitrergic neurotransmission may result from reduction in the amount of nNOS or from impairment in its catalytic activity. Subcellular localization of nNOS regulates its catalytic activity. It has been demonstrated in enteric nerve terminals that membrane localization of nNOS is necessary for optimal NO synthesis. Interestingly, the protein responsible for binding of nNOS to the membrane [light chain 8kDa (LC8) or protein inhibitor of nNOS (PIN)] is also **abundantly expressed in rodent cavernosal tissue where co-localizes with nNOS**.

Based on the requirement of a transport of nNOS to the membrane for achieving its optimal activity, Chaudhury and collaborators have evaluated the role of the motor protein, myosin 5a, in nitrergic relaxation in enteric and cavernosal innervations. For this purpose they used the DBA mouse model that bears a frameshift mutation in MYO5A gene. These animals display a light colour phenotype due to the defective melanosome transport that results for the lack of an active myosin 5a. In wild type mice, myosin 5a is expressed in nitrergic nerves in both gastric fundus and corpus cavernosum as revealed by confocal microscopy. Co-immunoprecipitation assays confirm the molecular interaction between myosin 5a and nNOS. With respect to the functional outcome, DBA mice lacking myosin 5a display reduced nitrergic relaxation induced by electrical filed stimulation (EFS) of cavernosal strips that is not related to post-junctional impairment of NO-mediated signaling. Defective nitrergic relaxations are also observed in gastric fundus from DBA mice. In fact, the impairment of nitergic relaxations due to myosin 5a deficiency is greater in this last tissue. This difference in the magnitude of myosin 5a dependency could be related to the structural difference between the isoform of nNOS expressed in enteric nerves (nNOSμ) and that expressed in cavernosal tissue (PnNOS), which is identical to that expressed in skeletal and cardiac muscles (nNOSμ).

These results point to **myosin 5a as an important player in the functional efficacy of nitrergic neurotransmission in cavernosal tissue**. Thus, any defect in myosin 5a expression or activity could hamper nitrergic relaxation of corpus cavernosum and, therefore, compromise erectile function. However, further research is needed **to ascertain if any defect in myosin 5a expression or activity is involved in any form of ED**, especially those associated with nitrergic impairment, such as diabetes and post-prostatectomy ED. Furthermore, the role of myosin 5 on nNOS activity and nitrergic relaxation should be evaluated in human corpus cavernosum **to validate this target in humans**.

Diabetic ED – Chloride channel inhibition

Possibility of inhibition of calcium-activated chloride channel rescuing erectile failures in diabetes. *Lau LC, Adaikan PG.* Int J Impot Res 2014, doi: 10.1038/ijir.2014.1 – Feb 13 [Epub ahead of print].

Ion channels regulate membrane potential of penile smooth muscle cells, therefore controlling cavernosal tone. Calcium-activated chloride channels (ClCa) are membrane ion channels that have been demonstrated to participate in the regulation of cavernosal smooth muscle contraction. Upon stimulation by intracellular calcium, activation of these chloride channels causes depolarization secondary to an outward chloride current, allowing calcium entry through voltage-gated calcium channels that results in further depolarization and contraction. These excitatory outward currents driven by chloride channel activation are present in cavernosal smooth muscle cells from rats, rabbits, and humans. In fact, ClCa blockade produces relaxation and increases erectile responses in rats. Lau and Adaikan have analysed the effects of ClCa inhibition on cavernosal function in diabetes. They evaluate the efficacy of two ClCa blockers, niflumic acid (NFA) and anthracene-9-carboxylic acid (A9C) to cause direct relaxation, to inhibit neurogenic contractions and to improve nitrergic relaxation in corpus cavernosum from alloxan-induced diabetic rabbits. NFA and A9C caused concentration-dependent relaxations in rabbit corpus cavernosum strips which were not modified by the presence of diabetes. NFA (100 μM) and A9C (1 mM) inhibited neurogenic contractions induced by electrical field stimulation in rabbit corpus cavernosum strips with similar efficacy in diabetic and non-diabetic animals. In contrast, the ability of NFA to enhance nitrergic relaxations was unaltered by diabetes while diabetic cavernosal tissue

was more sensitive to the improving effects of A9C on nitrergic relaxations. Thus, **these two compounds, although both considered as ClCa blockers, could differ in their pharmacodynamic profile**.

The results obtained by Lau and Adaikan suggest that **ClCa inhibition could be of potential therapeutic benefit in the management of diabetic ED**. Probably the obtaining of **more potent** (NFA and A9C work at quite high concentrations) **and specific blockers of ClCa would improve the potential of these therapeutic strategy**. In addition, once again, although **NFA has been shown to inhibit chloride currents in isolated human cavernosal myocytes**, the effects of ClCa inhibition on contractile and relaxant responses of human corpus cavernosum should be evaluated to confirm the potential utility of this pharmacological approach.

Female orgasm – A review of its pharmacology

The pharmacology of the human female orgasm – Its biological and physiological backgrounds. *Levin RJ.*
Pharmacol Biochem Behav 2014, doi: 10.1016/j.pbb.2014.02.010 - Feb 20 [Epub ahead of print].

Although not being a preclinical research original article, I bring to this section an extensive review of the pharmacology of the female orgasm prompted by the scarcity of research and knowledge on the physiology and pharmacology of female orgasm.

Levin has reviewed the knowledge of the physiology and pharmacology of the human female orgasm. The review mostly points to the existence of knowledge gaps and the lack of supportive evidence for many concepts related to female orgasm. Orgasm is here defined as a variable, transient peak sensation of intense pleasure creating an altered state of consciousness usually accompanied by rhythmic contractions of the pelvic striated circumvaginal musculature, often with concomitant uterine and anal contractions and myotonia that resolves the sexually induced vasocongestion, usually with an induction of well-being and contentment. Muscular contractions seem to play an important role in the female orgasm. In most women, pulsatile musculature contractions of the pelvic floor are concomitant with each wave of pleasure during orgasm. It is not clear how these contractions are triggered but it has been suggested that vasocongestive distension causes its repetitive contractions by firing stretch receptors in the pelvic musculature. In addition, pontine tegmentum area in the brain related to pelvic musculature is activated by orgasm. The ventrolateral (right) part named "pelvic floor stimulating center" was only activated during orgasm with direct connections to the pelvic floor musculature. However there is no known pharmacological to enhance the function on these muscles although the presence of androgen receptors makes interesting the characterization of the role of androgens in this process. Although less studied, uterine contraction seems to occur at orgasm and this event has named the uterine orgasm that is terminal and turns off the female arousal/desire. Contractions of the rectum occur during orgasm in both men and women but are considered the best objective indicator of female orgasm. The pressure changes in the rectum probably reflect the involuntary pelvic floor musculature contractions.

In the brain, from a simplistic point of view dopaminergic and adrenergic transmission is prosexual and orgasm-promoting while serotonergic is inhibitory of arousal and orgasm. However, controversial evidences question this view and many other neurotransmission systems namely cholinergic, GABAergic, glutaminergic, oxytocinergic, prolactinergic and opioidergic would integrate a very complex process. Thus, the cerebral mechanisms of orgasm are far for being fully understood. On the other hand, the identification of cerebral areas involved in orgasm through obtaining brain images yields non-consistent outcomes, probably resulting from the lack of standard criteria for determining significant activation or inhibition with respect to the basal activity levels. In this sense, it has been suggested that the area activated with the orgasm is the cerebellar cluster encompassing the left anterior vermix and deep cerebellar nuclei while temporal and prefrontal areas of the brain viz in the amygdala and in the ventromedial prefrontal cortex become inactivated. Other studies suggest a widespread, non-uniform sequence of activations of different brain regions leading up to orgasm with greater activation in the right hemisphere than the left.

Female orgasmic dysfunction is a common problem affecting 11– 41% of women worldwide. Pharmacological knowledge of orgasm has accrued from attempts to treat orgasmic dysfunction and from the alterations caused by psychotropic drug treatments. In this sense, outstands the orgasm impairments caused by serotonin-reuptake inhibitors.

Androgens influence the perceived intensity of orgasm in women while **estrogens** do not seem to have a specific effect on orgasm. It has recently suggested that the oxytocin released at orgasm is involved in feelings of well-being including calmness. Several illicit drugs such as amyl nitrite (poppers), heroin and MDMA (ecstasy) have been reported **to intensify orgasm** while some therapeutic drugs such as clomipramine, oxytocin, venlafaxine, paroxetine, mirtazapine, and dopamine agonists have been reported to **induce orgasm as an unusual side effect**.

A better understanding of the neurophysiology of female orgasm is necessary to produce advances in its pharmacology. The **scarcity of the research** on the pharmacology of female orgasm has impeded the **availability of any approved drug for the treatment of orgasmic disorders**.

Have you read? Best of the Best: Clinical

A brief summary of the best papers and abstracts published in the main journals related to Sexual Medicine **by Nicola Mondaini**

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Erectile Dysfunction

Avanafil for male erectile dysfunction: A systematic review and meta-analysis

Cui YS et alt. Asian J Androl. 2014 Feb 25

Avanafil, a potent new selective phosphodiesterase type 5 (PDE5) inhibitor, has been developed for the treatment of erectile dysfunction (ED). We carried out a systematic review and meta-analysis to assess the efficacy and safety of this drug for the treatment of ED. A literature review was performed to identify all published randomized, double-blind, placebo-controlled trials of avanafil for the treatment of ED. The search included the following databases: MEDLINE, EMBASE and the Cochrane Controlled Trials Register. The reference lists of the retrieved studies were also investigated. Four publications, involving a total of 1381 patients, were used in the analysis, including four randomized controlled trials (RCTs) that compared avanafil with a placebo. Among the co-primary efficacy end points indicating that avanafil 100 mg was more effective than a placebo were successful vaginal penetration (SEP2) (the odds ratio (OR) =5.06, 95% confidence interval (CI) =3.29-7.78, P< 0.00001) and successful intercourse (SEP3) (OR = 3.99, 95% CI = 2.80-5.67, P< 0.00001). Men randomized to receive avanafil were less likely than those receiving the placebo to drop out due to an adverse event (AE) (OR = 1.48, 95% CI = 0.54-4.08, P= 0.44). Specific AEs with avanafil included headache and flushing, which were significantly less likely to occur with placebo. This meta-analysis indicates that avanafil 100 or 200 mg is an effective and well-tolerated treatment for ED. Compared with avanafil 100 mg, patients who take avanafil 200 mg are more likely to experience headaches.

Prospective comparison of the impact of robotic-assisted laparoscopic radical prostatectomy versus open radical prostatectomy on health-related quality of life and decision regret

Davison BJ: Can Urol Assoc J. 2014 Jan-Feb; 8(1-2):E68-72

There is no conclusive evidence that the robotic-assisted laparoscopic radical prostatectomy (RARP) is superior to conventional open radical prostatectomy (ORP) when it comes to recovery of urinary and sexual function, and that the former surgical option results in less decision regret. Patients scheduled for both surgical procedures were surveyed prior to surgery, and then again at 6 and 12 months following treatment using the sexual and urinary modules of the Expanded Prostate Cancer Index Composite (EPIC) measure. Decision regret was measured at 12 months. Propensity score regression adjustment was used to account for differences between treatment groups by summarizing all covariate information into a single probability and to simulate randomization.

At 12 months, urinary summary scores approached baseline levels, while urinary bother scores had returned to baseline. Sexual summary and bother mean scores decreased by about half of what they were at baseline for both treatment groups at 6 and 12 months. No significant differences in the groups' sexual summary and bother domains were identified at either 6 or 12 months. Both groups' scores for decision regret were low. Moderate correlations (r(2) range -0.333 to -0.368) were between current levels of urinary and sexual function and decision regret at 12 months. The results of our study found no significant difference in health-related quality of life outcomes based on surgical procedure at 12 months. Moreover, patients in both groups reported low levels of decision regret at 12 months. Further multi-site prospective studies are required to address this study's limitations.

Penile Surgery

Sexual quality of life after total phalloplasty in men with penile deficiency: An exploratory study

Callens N et alt . World J Urol. 2014 Mar 29

Total phalloplasty is rarely performed today in males with severe penile deficiency, despite its successful use in the transgender population. Can phalloplasty replicate the complexity of penile anatomy and function on the long term? Sexual quality of life (QoL) was assessed in 10 men (aged 20–43 years) at least 1 year after phalloplasty in a single institution (80% radial forearm flap and 20% anterolateral thigh flap). In all but one, an erectile prosthesis was implanted on average 1 year after phallic reconstruction. Sexual QoL outcomes were compared to those of men with hypospadias repair (n = 73) and control men (n = 50). After phalloplasty (mean 36.9 months, 14–92 months), all men were sexually active (80% intercourse and 100% masturbation with orgasm and ejaculation). However, 75% indicated to be inhibited in seeking sexual contacts, compared to 40% of hypospadias patients ($p < 0.05$) and 11% of controls ($p < 0.01$). Although 90% were satisfied with the final surgical result, dissatisfaction with some aspects of genital appearance was present in 50%. Erogenous neophallus sensitivity was said to be less than previously hoped for. Six men developed urinary complications (urethral stricture and/or fistula), and one man underwent revision of the erectile implant because of dysfunction. Nevertheless, all indicated they would choose again for phalloplasty if necessary. Total phalloplasty opens new horizons for the treatment of men with penile deficiency, but limitations of the technique should be emphasized prior to surgery. An exploration of patient expectations and continued follow-up including psychological support is important for optimizing psychosexual comfort.

Have you read ? Best of the Best: Clinical

Penile straightening maneuvers employed during penile prosthesis surgery: Technical options and outcome

Segal RL: Int J Impot Res. 2014 Mar 20

Straightening maneuvers (SM), including manual penile modeling, tunical relaxing incisions and corporal reconstruction using grafting techniques, are occasionally required during inflatable penile prosthesis (IPP) implantation to ensure functional penile straightness. The aim of this study was to compare the outcomes of men undergoing SM employed during IPP implantation compared with those wherein these maneuvers were not required. A retrospective review of 391 patients undergoing IPP implantation at the Johns Hopkins Hospital from January 2000 to December 2011 was performed. Patients in whom some SM was employed (SM, n=93, 23.9% of the overall cohort) were compared with those for whom SM was not required (IPP group, n=298). Seven patients were excluded from final analysis (6 patients with IPPs inserted in neophalli (SM group), and 1 patient with incomplete data (IPP group). Patients in whom a SM was used were younger (55.4 vs 62.3 years), more likely to have Peyronie's disease, and less likely to have prostate cancer, radical prostatectomy or to have previously used erectile aids (all P<0.05). Mean operating room time in the SM group was longer (173.8 vs 152.9 min, P=0.003). Within the SM group, modeling was performed in 40 (43%), tunical relaxing incisions in 37 (39.8%) and tunical reconstruction in 16 (17.2%) (most commonly using allograft dermis or pericardium, or synthetic gore-tex grafts). There were no significant differences in terms of device infection (P=0.15), mechanical failure (P=0.23) or erosion (P=0.96). Although limited in size, this cohort study suggests that IPP implantation in men with penile deformity requiring complex reconstruction to achieve straightening may be done proficiently and without increased adverse outcome risk.

FSD

Apple consumption is related to better sexual quality of life in young women

Cai T et alt: Arch Gynecol Obstet. 2014 Feb 12

Even if some evidence exists of a positive correlation between regular intake of phytoestrogens, polyphenols, antioxidants and women's sexual health, there is not a study addressing the potential correlation between daily apple consumption and women's sexual function. We aim to assess whether there is a tie between daily apple intake and sexual function in a sample of healthy young sexually active Italian women, not complaining of any sexual disorders. Seven hundred and thirty-one women (mean age 31.9, range 18 – 43) were enrolled in this cross-sectional study (from September 2011 to April 2012). All participants completed anonymously the Female Sexual Function Index (FSFI) and were asked to report on their amount of daily apple consumption and their eating habits. On the basis of apple consumption all women were split into two groups: Group A – regular daily apple consumption, Group B – no regular apple consumption (<1 apple/day). The main outcome measure was the FSFI questionnaire result.Three hundred and forty-three women reported a regular daily apple intake and were classified in Group A, while 388 were included in Group B. Group A had a significantly higher total ($p = 0.001$; Cohen's $d = 3.39$) and lubrication domain ($p = 0.001$; Cohen's $d = 3.02$) FSFI scores than participants in Group B. Multivariate analysis demonstrated that daily apple intake must be considered as an independent parameter ($p = 0.002$) in predicting a better score at questionnaire examination.This study suggests a potential relationship between regular daily apple consumption and better sexuality in our young women population.

Gynecomastia

Gynecomastia in subjects with sexual dysfunction

Maseroli E et alt; Endocrinol Invest. 2014 Feb 11

To analyze possible relationships between gynecomastia and clinical and biochemical parameters in a large cohort of subjects with sexual dysfunction (SD). A consecutive series of 4,023 men attending our Outpatient Clinic for SD was retrospectively studied. After excluding Klinefelter's syndrome patients, the prevalence of gynecomastia was 3.1 %. Subjects with gynecomastia had significantly lower testosterone (T) levels; the association retained statistical significance after adjusting for age and life-style. However, only 33.3% of subjects with gynecomastia were hypogonadal. Gynecomastia was associated with delayed puberty, history of testicular or hepatic diseases, as well as cannabis abuse. Patients with gynecomastia more frequently reported sexual complaints, such as severe erectile dysfunction [odds ratio (OR) = 2.19 (1.26-3.86), $p = 0.006$], lower sexual desire and intercourse frequency [OR = 1.23 (1.06-1.58) and OR = 1.84 (1.22-2.78), respectively; both $p < 0.05$], orgasm difficulties [OR = 0.49 (0.28-0.83), $p = 0.008$], delayed ejaculation and lower ejaculate volume [OR = 1.89 (1.10-3.26) and OR = 1.51 (1.23-1.86), respectively; both $p < 0.05$]. Gynecomastia was also positively associated with severe obesity, lower testis volume and LH, and negatively with prostate-specific antigen levels. The further adjustment for T did not affect these results, except for obesity. After introducing body mass index as a further covariate, all the associations retained statistical significance, except for delayed ejaculation and ANDROTEST score. When considering gynecomastia severity, we found a step-wise, T-independent, decrease and increase of testis volume and LH, respectively. Gynecomastia was also associated with the use of several drugs in almost 40 % of our patients. Gynecomastia is a rare condition in subjects with SD, and could indicate a testosterone deficiency that deserves further investigation.

Case Report by ISSM Case List

by Natalio Cruz

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May 2014

Dr. Sergio Moreno Figueroa, head of department of Urology, Clínica Universidad de los Andes and Clínica Santa María posted on ISSM-FORUM in April 27th:

Dear Colleagues,
I need your help. I have a 19-year-old patient. Patient reported that their erections were always bad, but in the last two years have been deteriorating. The patient has had a poor response to PDE5i. Penile Doppler with alprostadil reveals flow just about above 35cm/sec. with continuous venous flow. Hormonal study is normal (including total and free testosterone).

I tried treatment with ICI and vacuum device, but the erections achieved are not firm. Considering the age of the patient, it is a little difficult for me to consider penile prosthesis surgery. Do you believe that there is another treatment option? Do you think that nocturnal tumescence test would be useful? Thank you very much for your help.
Sincerely, Sergio Moreno F.

It is a very interesting issue. The post has received 161 views so far. Primary erectile dysfunction is still worrying, furthermore when the patient is not responding to any medical treatment. When the prosthesis implant is the only solution for a young patient, the urologist usually experiences an unpleasant feeling.

Some colleagues in the forum have tried to summarize just the main causes of primary erectile dysfunction in daily practice:

Dear,
We do see cases like that young ED patient.
In daily practice there are three main causes.

1. Congenital abnormal venous channels ie Venous leakage with primary ED…he will need a Dynamic cavernosometry\cavernosography and this will plan for the future management.
2. GAD (General; anxiety disorder), with heightened sympathetic flow and inhibition of full smooth ms relaxation and poor response to every treatment option. Those will benefit from SSRIs, Anxiolytics in combination with PDE5 inhibitors ,chronic small dosing.
3. Erectolytics: Heavy smoking, Alcohol, recreational drugs, steroid abuse etc., Treatment is dealing with the cause.

Hope you get the proper diagnosis and management

Several comments from ISSM-FORUM have pointed out the interest in diagnosing some potential curative etiology in these cases. They suggested venous leak as main diagnosis.

Some of them suggested repeating Doppler-duplex, or doing cavernosography. Some others added very interesting publications for technical details related to cavernosograms and different approaches and diagnostic tools.

Different authors have expressed in the forum their opinions regarding venous leak as a potential cause of primary erectile dysfunction.

Dr. Ahmed M. Al-Salih, from Iraq-Baghdad posted:

Dear Dr.,
I saw such patients every other time….
I suggest repeating duplex u/s with ICI. If still the most prominent cause is venous leakage, so:
Either proceeds to cavernosography & accordingly you will decide the next step (venous leakage surgery or may be at last penile prosthesis).
Or you can try again a continuous use of tadalafil 5mg daily + vacuum device & follow him.
I have seen males with arterial erectile dysfunction who responded well to continuous tadalafil 5 mg regime. Besides you are dealing with a young boy, so reassure him & advise him to stop any personal & social habit that could affect his sexual activity & erection (smoking, alcohol, recreational drugs) & to practice fitness exercises.
Best Regards Ahmed M. Al-Salih

Dr. Robert Valenzuela, MD, Prosthetic Urologist, Assistant Attending at the New York Presbyterian Hospital posted:

Hello Dr. Figueroa,
I recently saw a 22 yo male with a similar condition. Pt had been using anabolic steroids since the age of 17. His penile duplex revealed normal Qmax. but had "leaky veins".
I agree it is difficult to recommend penile prosthesis placement to such a young individual. Perhaps you can consider cavernosogram to identify the venous leak. This can be managed with surgical venous ligation or embolization.
J Urol. 1992 Mar;147(3): 618-22. Preoperative and postoperative dynamic cavernosography and cavernosometry: Objective assessment of venous ligation for impotence.
Yu GW1, Schwab FJ, Melograna FS, DePalma RG, Miller HC, Rickholt AL.
http://www.ncbi.nlm.nih.gov/pubmed/1538442

Even if it proves to be futile, a penile prosthesis still remains as the last option.

As for the 22 yo. he was seen by multiple urologists and ultimately found one that was willing to place a penile prosthesis.
Sincerely, Robert Valenzuela, MD

However, the success of management of this condition with surgical venous ligation or embolization is still controversial, and extremely different points of views are expressed in the forum.

Dr. Jelto Drenth, MD, from the Netherlands, posted:

Dear colleague,
In patients as young as this one, I would always add an intensive psycho-diagnostic phase. It is, in my experience, quite rare that at that age the ED is exclusively somatogenic. In Holland, the diagnosis of "venous leaks" is almost obsolete now, and those who once were supporters of venous ligation have all come to the conclusion that success has almost never been longstanding.
If he is in a steady relation, let his partner join in. She (or he) has often observations and/or ideas that are helpful to come to an understanding of the situation.
Regards, Jelto Drenth, MD

The opposite position was clearly defended by **Prof. Dr. Shedeed Ashour**, Andrologist at Cairo University. He posted:

Dear J.J. Drenth,
I agree with you on the venous leakage opinion for all acquired and co morbid patients. But for young primary or abnormal congenital venous channels it's still valid.
Prof Dr. Shedeed Ashour

Editorial Comment

Everyone who deals with patients suffering from erectile dysfunctions will be at sometime facing these kinds of cases. It is a very challenging situation, as, besides some other potential etiologies such as endocrinology conditions, psychogenic causes or traumatic history, the diagnosis of venous leak is very common in these patients using Doppler.

Two main points, closely linked, can be identified from my personal point of view as the real problem:

The first point is related to the diagnosis, which is mostly based on Doppler findings. We have to bear in mind that Doppler is just an indirect way to explore the flow, and it is always influenced by the adrenergic tone and external circumstances, while also being very observer-dependent.

Even when we try to confirm these findings with cavernosometry, the results are always very generic and non-specific. We can get a "diagnosis" of venous leak using Doppler + cavernosometry either from real venous leak (congenital, anatomical) or from patients with early Peyronie's disease, or just from a very anxious young man (psychogenic).

The second point is related to treatment. As the diagnosis is very imprecise, it seems to be very risky in terms of good results to do the same procedure (i.e. venous ligation) for all patients with this diagnosis based on such unspecific findings. The venous leak ligation or embolization should only be based on morphological assessment of the leak.

In this regard Dr. Virag has tried to clarify the difference between several classes of venous leaks. In his publication "Virag R and Paul JF. New classification of anomalous venous drainage using caverno-CT in men with erectile dysfunction. J Sex Med 2011; 8:1439–1444", they conclude that multidetector computed tomography after ICI contrast media was able to differentiate between various venous pathways in men with venous origin ED, leading to a new anatomical classification.

The adequate diagnosis of a venous leak, both hemodynamic and morphological, seems to be the best way of approaching this condition. After properly identifying the anatomy of the problem we´ll be able to solve it more precisely and with the likelihood of good results in the long term. Hopefully, in the near future a more accurate diagnostic tool will be available in daily practice for such challenging cases, and we'll have the possibility of offering these patients a better, less aggressive solution as an alternative to the penile implant.

Natalio Cruz MD.

MEETINGS AND EVENTS CALENDAR 2014

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July 2014

SSR 2014
Society for the Study of Reproduction
July 19 – 23, 2014
Location: Grand Rapids, Michigan, USA
Website: www.ssr.org

August 2014

ANDROFEST. The 12th International Symposium on Spermatology & The 9th Biennial Conference of the AAAA (Association for Applied Animal Andrology)
August 8 – 14, 2014
Location: Newcastle, Australia
Contact: androfest@newcastle.edu.au

The 9th Biennial Conference of the AAAA (Association for Applied Animal Andrology)
August 8 – 10, 2014
Location: Newcastle, Australia
Contact: androfest@newcastle.edu.au

The 12th International Symposium on Spermatology
August 10 – 14, 2014
Location: Newcastle, Australia
Contact: androfest@newcastle.edu.au

September

Canadian Fertility and Andrology Society Annual Meeting
September 11 – 14, 2014
Location: Hilton Quebec & Quebec City Convention Centre, Quebec City, Quebec, Canada
Website: www.cfas.ca/

October

12th Scientific Meeting of the SLAMS and the
16th World Meeting of the ISSM
October 8 – 12, 2014
Location: São Paulo, Brasil
Website: www.issmslams2014.org/

8th European Congress of Andrology
October 15 – 17, 2014
Location: Barcelona, Spain
Website: www.eca2014.com/

70th Annual Meeting of the ASRM
October 18 – 22, 2014
Location: Honolulu, HI, USA
Contact: asrm[at]asrm.org
Website: www.asrm.org/ASRM2014/

November

XI Congress of the National Society Italy of Andrology and Sexual Medicine
XI Congresso Nazionale Società Italiana di Andrologia e Medicina della Sessualità
November 13 – 15, 2014
Location: Cagliari, Italy
Email: info[at]fasiweb.com
Website: www.fasiweb.com

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