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Radionuclide studies of the reproductive system and their significance in clinical practice

Jure Fettich

Department of Nuclear Medicine, Clinical Centre Ljubljana, Slovenia

Radionuclide studies of the reproductive system are used to evaluate perfusion and function of this system and are frequently complementary to morphological studies such as ultrasound and X-ray investigations.

Radionuclide scrotal imaging remains the most effective method in the evaluation of acute hemiscrotum to assess testicular perfusion and differentiate between testicular torsion and epididymitis. Labelled red blod cells are used successfully for varicocele detection in infertile men. Only radionuclide techniques (radionuclide hysterosalpingography) allow for noninvasive assessment of functional tubal patency in infertile women. Assessment of penile blood flow, using labelled red blood cells and/or xenox clearance, can play an important and useful role in evaluating men with impotence due to vascular causes.

Key words: urogenital diseases-radionuclide imaging

Introduction

In contrast to morphological investigations, such as ultrasound, MRI and X-ray, radionuclide studies of the reproductive system are used to evaluate its function and perfusion, and can be frequently considered as complementary rather than competitive to studies mentioned above.

Clinical conditions, where radionuclide investigation have proven useful, are acute hemiscrotum, where perfusion and blood pool imaging of the testes with pertechnetate is used to evaluate its perfusion, male and female sterility, i. e. detection of varicocele in males and determination of functional fallopian tube patency in females, and studies of penile blood flow in the assessment of male impotence (Table 1).

Table 1: Radionuclide studies of the reproductive system.

1.	Evaluation of acute hemiscrotum
	Differentiation between torsion and inflammation
2.	Evaluation of sterility
	Male: detection of varicocele
	Female: functional patency of the fallopian tubes
3.	Evaluation of male impotence
	Diagnosis of arterial insuficiency
	Diagnosis of venous leakage

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Correspondence to: Doc. dr. J.Fettich. Clinical Centre Ljubljana, Department of Nuclear Medicine, Zaloška 7, 61000 Ljubljana, Slovenia

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Acute hemiscrotum

The most common and most widely accepted radionuclide technique of investigation of the reproductive system is perfusion and blood pool imaging of the testes with pertechnetate to evaluate testicular perfusion in the evaluation of acute hemiscrotum, to differentiate between torsion of the testes, which is an absolute surgical emergency, from other less urgent conditions, such as epididymitis, which are usually treated conservatively.

Pathophysiology

The testis, tightly attached to the epididymis, is suspended in the scrotal sac by the spermatic cord composed of the entering arteries and draining veins, the spermatic duct, lymphatics and nerves. Normally, the testes is covered partially by tunica vaginalis and firmly fixed posterolaterally to the epididymis and scrotum, what makes torsion of the cord impossible. Two malformations, complete investment of the testes with tunica vaginalis, which precludes tight fixation of the testis and epididymis to scrotal wall, and elongated mesorchium, i. e. attachment of the testis to epididymis, permit spermatic cord to twist.[1, 2]

Complete torsion will result in infarction of the testis due to impaired arterial blood supply. Spermatogenic capability is lost within a few hours. Incomplete torsion, where arterial blood supply is still sufficient, will also cause ischemia and infarct due to venous obstruction, but more slowly.

Three or more complete turns of the spermatic cord are sufficient for irreversible ischemia to occur within a few hours, whereas up to 24 hours are necessary with a single 360 degree twist. Salvage of the testes has been reported after 30 hours with incomplete twist.[1]

Clinical presentation

Most common causes of acute hemiscrotum include inflammation (epididymitis or rarely orchitis), torsion of the testes and trauma, which can also lead to infection, as well as torsion.

Peak incidence of torsion is in adolescents, around puberty. Patient presents with abrupt, excruciating pain. Fever and urinary tract symptoms are absent and urinalysis is normal. Hemiscrotum is swollen and edematous. Elevation of the scrotum will intensify the pain.

Typical patient with epididymitis is young adult, with more gradual onset of pain, which is also less intense than in torsion. Dysuria and burning with urination are common, as well as moderate to high fever. Elavated number of white cells is present in urine. On physical examination, hemiscrotum is swollen and erythematous. Elevation of the scrotum causes relief of pain.[1]

Unfortunately, clinical presentation of these conditions is often, in up to 50 % of the cases, not sufficiently typical for torsion to be confirmed or excluded with confidence. Without a reliable way to exclude the possibility of testicular torsion in a patient with acute hemiscrotum, immediate surgical exploration has been recommended to maximize testicular salvage, but at the cost of many unnecessary operation. Torsion is easily remedied by detorsion and orchiopexy, but surgical exploration in inflammatory conditions carries a small, but real risk of complications.[3]

Therefore, the difficulty lies not in treatment, but in diagnosis.

Diagnostic methods

Scrotal perfusion scintigraphy, grey scale ultrasonography, continuous-wave and conventional duplex Doppler imaging and colour Doppler have been used for this purpose.

1. Scrotal perfusion scintigraphy.

Usually the study is performed with patient positioned supine, with scrotum elevated, as close to the gamma camera as possible. Penis is taped cephalad, and positioning of the scrotum should be such that raphe are in midline, a necessary condition for comparison of perfusion of both testicles.

600–800 MBq (adult dose) of 99 m Tc pertech-

netate are injected as bolus and dynamic study of the first pass is acquired using magnification. Usually two high quality static images, one with and one without markers, using magnification or pinhole collimator, are acquired immediately after the dynamic phase. In some laboratories a lead shielding interposed between the thighs and scrotum is used for static images.[2]

Additional processing of the data, such as time activity curves over the testicles does not seem to provide any essential additional information.[4]

In cases of normal perfusion of the testes dynamic images show only the iliac and femoral vessels with a low grade blush visible over the scrotum.

Scintigraphic findings in torsion corespond to viability of testes because the extent of ischemia will vary depending on the duration and degree of twist of the spermatic cord. In the early phase increased activity in the testicular artery up to the site of twist ("nubbin sing")[5] is occasionally seen. In the late dynamic and static images there is absent activity in the region of affected testis. Such images are very specific for acute torsion. This phase is seen up to 4--6 hours following complete twist, and can be seen after a longer interval if the twist is incomplete. In this phase surgical salvage is virtually 100 %. Later the testis progresses to infarction and scrotal wall becomes hyperemic, appearing with time as increasingly hot rim around the photon deficient testis. Likelihood of testicular salvage approached zero in one study[5] when scrotal activity exceeded that of the femoral arteries. Images of so called "missed torsion" are not specific, and have been observed also in a number of other conditions.[6, 7, 8]

If spontaneous detorsion occurs the study may be normal or show only reactive hyperemia.[9] In such case immediate emergency surgery is not necessary but there is still deffinite indication for elective operation (orhiopexy) as soon as feasible.

In epididymitis epididymal perfusion is increased, while in epididymo-orchitis both epididymis and testis show an increased tissue phase activity.

Findings in torsion of a testicular appendage are usually normal, or show slight hyperemia as is seen also in mild inflammation or spontaneous detorsion.

In testicular trauma diffuse hyperemia may be seen. In postraumatic torsion photodefficient area of the size of the tesis is seen, and is usually larger than photodeficiency due to testicular hematoma or contusion, if present.[1]

2. Conventional grey scale ultrasonography.

Grey scale sonography provides high resolution images of the testis and epididymis. However, morphological abnormalities on torsion and epididymo-orchitis are identical, and ultrasonography provides no information about blood flow.[10, 11] Therefore it is not adequate for the evaluation of acute scrotal disorder, but is frequently useful in further diagnostic work-up, after normal blood flow to the testes has been documented.

3. Doppler ultrasonography.

Doppler sonography allows also for evaluation of blood flow.

Continuous wave Doppler was found to produce false negative results in up to two thirds of cases, because it is difficult to distinguish arterial flow in peritesticular vessels from intratesticular blood flow with nonimaging equipment.[12]

Duplex Doppler instruments combine pulsed Doppler and gray scale ultrasonography. It was found that this procedure is time consuming, operator dependant and not very reliable in acute hemiscrotum, since testicular arteries are difficult to evaluate because of their small size and low flow even in normal testes.[9, 12]

Colour Doppler ultasound allows simultaneous real-time display of tissue morphology in gray scale and blood flow in colour. Some recent reports have shown the sensitivity in diagnosing testicular torsion to be between 86 and 100 %, and specificity 100 % in small series of patients.[9, 12] It is important, that for the assessment of acute hemiscrotum a high frequency transducer, 7.5 MHz or more is used for high quality results.[13]

Diagnostic value

To be useful, a diagnostic test for acute hemiscrotum must be immediately available, quick to perform and very sensitive. It should be also noninvasive and simple to perform.

The study should be completed as soon as possible after presentation of the patient because viability of the testes can be preserved only if surgery is performed before 4–6 hours after the onset of symptoms. It should not be used in patients with typical symptoms which have to be explored surgically immediately, but to exclude torsion in cases, where conditions other than torsion are suspected.

Scrotal perfusion scintigraphy should be regarded as an evaluation of current testicular perfusion rather than a method to diagnose a specific condition. Properly performed, it has sensitivity and specificity of over 90 % for the presence or absence of intact blood supply to the testes. Normal or moderately increased testicular perfusion does not rule out the possibility if incomplete or spontaneously resolved torsion, in which case surgery is also indicated, but usually not as an imminent emergency. Scintigraphy has no use for the evaluation of neonatal torsion, which is virtually the only condition of scrotal swelling at this age.

Perfusion scintigraphy is more accurate than grey-scale ultrasonography, continuous wave and conventional duplex Doppler imaging, while some reports indicate that colour Doppler might be as accurte as perfusion scintigraphy. Advantages of colour Doppler include its ability to provide also high resolution images of the testis and epididymis, and absence of any radiation to the patient. It is operator dependent and can be difficult to perform properly in a young patient with very painful hemiscrotum. Nevertheless, as with any new technique, a prospective investigation using larger numbers of patients is needed to determine ultimate value and indications for this technique.[12]

At present time, perfusion scintigraphy is still the procedure of choice to evaluate testicular perfusion in acute hemiscrotum, as it has the advantage of many years of clinical validation.[14, 15] It has to be available on an emergency basis.

Male infertility

Varicocele due to varicosities of the pampiniform plexus is an important cause of surgically treatable male infertility.

Left testicular vein is draining into the left renal vein at right angle, with resultant increased pressure, permitting retrograde flow in the left testicular vein. Therefore, varicocele is usually left sided and unilateral. Right sided varicocele may form by extension from the left, further affecting semen quality.[16]

Diagnostic methods

Apart from simple palpation, which may miss small varicoceles, and invasive direct venography, which can be combined with therapeutic occlusion, a number of noninvasive techniques, including contact scrotal thermography, ultrasonography and Doppler imaging, and perfusion and blood pool scintigraphy with labelled red blood cells were developed to detect inpalpable, bilateral, or to confirm clinically suspected varicoceles. Difference more than 0.3 degrees centigrade on contact scrotal thermography, diameter of pampinifirm plexus veins larger than 3 mm on ultrasonography, evidence of retrograde flow on Doppler ultrasonography, and pooling of labelled red blood cells on scintigraphy, is considered as positive for varicocele.[17]

Scrotal perfusion scintigraphy

Red blood cells are labelled in vivo, with patient standing in front of the gamma camera. 99 m Tc pertechnetate is injected as bolus and the first pass is recorded as dynamic study. Static blood pool images are acquired usually with and without Valsalva manouver. Increased radioactivity, due to venous blood pooling is seen in the case of varicocele.

Diagnostic value

Sensitivity of radionuclide investigation has been reported to be 92 %.[18] Similar results are

available also for grey scale and Doppler ultrasonography.[17] Scintigraphy using both dynamic first pass and static blood pool images provides useful data on local hemodynamic in the scrotum. According to some investigators no improvement in the semen quality was seen after surgery in patients who showed no scrotal accumulation of radioactivity in the dynamic images, while semen quality did improve after surgery in those with patchy tracer uptake allready in the dynamic phase of the study,[19] so scintigraphy could have also prognostic importance.

Female infertility

Functional or organic obstruction of fallopian tubes is one of the causes of female infertility, especially in regions where tuberculosis of the adnexes is not uncommon.

Diagnostic methods

To assess fallopian tube patency usually contrast histerosalpingography is performed, where contrast medium is introduced under positive pressure intracervically.

Alternatively, observation of spilling of methylene blue dye from the fimbirated ends of the fallopian tubes into the peritoneum at laparoscopy or surgery, after the dye had been introduced into the cervix under low pressure, can be used.

Also, a radionuclide method to assess fallopian tube patency has been developed.[20]

Radionuclide hysterosalpingography

99 m Tc labelled human serum albumin microspheres (37 Mbq suspended in 1 ml of saline) are applied intravaginally directly onto the cervical mucosa. A nonabsorbable tampon is inserted into the vagina after speculum is removed and the patient is imaged 30 min, 1 hour and, if necessary, delayed images up to 4 hours later can be obtained, using a pinhole collimator with approximately 30 degrees caudal angulation to visualise the region posterior to the uterus, which helps to separate ovaries from the uterus.[21] Labelled microspheres normally migrate spontaneously from the vagina to the ovaries, while in the presence of fallopian tube obstruction, fibrosis or lack of motility, migration does not take place. A fallopian tube is considered patent, if a focus of activity is seen in the area of the adjacent adnex, including outlining of the ovary.

Technical and radiopharmacological improvements of the method described are possible. Using SPECT technique spatial resolution of the investigation can be improved, and the dose of the radiation to the ovaries decreased. Recently a technique of labelling the sperm cells using 99m Tc HMPAO for radionuclide hysterosalpingography has been described in animals.[22]

The radionuclide technique is less invasive than contrast hysterosalpingography or laparoscopy with methylene blue applied intracervically under pressure.

Radiation burden to the ovaries during radionuclide hysterosalpingography is lover than in contrast hysterosalpingography.[21]

Diagnostic value

Both the sensitivity and specificity of radionuclide test for the detection of tubal patency and tubal obstruction was reported to be over 90 % when correlated with anatomic criteria.[23, 24] Due to its high sensitivity and specificity the test is useful not only for the evaluation of female infertility, but also in assessment of surgical reanastomosis or tuboplasty for previously ligated or fibrosed tubes, and, alternatively, to confirm the success of tubal ligation.

It seems that radionuclide histerosalpingography has an important advantage over morphological techniques, because it can detect not only organical, but also functional tubal obstruction, what can be otherwise achieved only by direct observation of tubal motility at surgery. The radionuclide study may facilitate detection of diseased but patent tubes and provide useful information about tubal function.[23, 24] Because of this, it has been even proposed that failure of migration of the tracer to the ovaries may render patients with anatomically patent tubes eligible for in vitro fertilisation.[25]

Male impotence

Normal penile erection requires the co-ordinated function of neurological, arterial and venous systems and, even if these systems are intact the process may be inhibited by psychological factors.

Patophysiology

Erection results following penile smooth muscle relaxation. Dilatation of the cavernosal and helicine arteries increases blood flow into lacunar spaces within lacunar bodies. Relaxation of the trabecular smooth muscle enables dilatation of lacunar spaces. The systemic arterial blood pressure transmitted through dilated arteries expands the relaxed trabecular walls against the nonyielding, rigid tunica albuginea and compresses the subtunical venules causing reduction of venous outflow by so called corporeal veno-occlusive mechanism. This reduces venous outflow and elevates intracavernosal pressure causing erection. The intracavernosal pressure during erection is a result of equilibrium between the perfusion pressure in the cavernosal artery and the resistance to blood outflow through the compressed subtunical venules. In normal erection it approximates systemic arterial blood pressure.[26]

The intracavernous injection of potent smooth muscle vasodilators such as papaverine or phentolamine results in erection in normal subjects, as well as those suffering from neurological and psychological causes.[27]

Causes of male impotence are psychological, neurological or organic. It is estimated, that approximately 50 % of men with impotence have an organic etiology and presumably the majority are vascular in origin.

Normal rigid erection following intracorporeal injection of papaverine can rule out vasculogenic impotence.

Vascular causes of impotence can be either due to reduced arterial supply (arterial insufficiency) of excessive venous outflow (venous leak). Arterial insufficiency is consequent to atherosclerotic occlusive disease of the hypogastric-cavernous arterial bed, while venous leak is due to smooth muscle myopathy or poor compliance of the erectile tissue caused by structural alterations in the fibroelastic components secondary to vascular risk factors such as hypercholesterolemia, diabetes mellitus, ageing, previous priapism, surgery or trauma of the penis.

The differentation bettween the two is important for patient management, eg. restorative surgery or implants for arterial insufficiency and ligation of penile vein for venous leaking.[28]

Diagnostic methods

At this time there is as yet no universally agreed upon diagnostic algorithm for vascular evaluation of impotent patients. Vascular impotence has been evaluated by different radionuclide and nonradionuclide techniques, both usually in association with vasodilatation.

For the evaluation of arterial insufficiency:

1. Selective angiography, which is an invasive technique. Significance of arterial lesions are difficult to assess because no functional information is provided.[29, 30]

2. Penile/brachial systolic pressure index, which is not always accurate, since Doppler signal is often obtained from dorsal penile artery and therefore does not correlate with erectile function.[31, 32]

3. Duplex scanning, which can measure changes in individual arterial diameters and peak flow velocities. This method is still under evaluation and is operator dependent.[31]

4. Radionuclide penile pletismography and radionuclide penile blood flow study using 99m Tc labelled red blood cells in combination with papaverine test were used to determine peak corporeal flow and volume changes. Peak corporeal flow correlates well with arterial disease, but does not correlate with venous leaking.[33]

For evaluation of venous leakage:

1. Dynamic infusion cavernosometry[34] and cavernosography[35] during vasodilataion, which are invasive techniques with infusion of large amounts of saline and contrast media intracorporeally, to determine the flow rate required to mantain erection and to demonstrate opacification of pelvic veins.[32]

2. Several 133-Xe clearance studies have proposed to measure penile blood flow. Subcutaneous injection was not appropriate since circulation of the erectile tissues is largely independent of penile skin circulation.

Cavernosal injection in flaccid penile state was not able to differentiate between normal and impotent men.

Also with cavernosal injection and vasodilatation it was reported that xenon outflow alone could not be used to predict competence of veno-occlusive mechanism.[29, 36-38]

3. Injection of 99mTc labelled red blood cells intracavernosally, instead of xenon, has been proposed to evaluate venous leakage. In this case 18.5 MBq of in vitro labelled red blood cells are injected intracorporeally twice, in flaccid state and after vasodilator injection. Data are acquired for 20 min for each study at the rate of 1 frame/15 seconds. Time activity curves are generated and time to half outflow (T50 %) is calculated.

It is significantly shortened in case of venous leakage as compared with normal venous outflow if the study is performed after appropriate papaverine vasodilatation. High sensitivity (100 %) and specificity (92 %) for differentiating venous leak from normal venous outflow were reported for study after vasodilation in a small group of patients.[39]

To determine, if arterial insufficiency is also present, this technique has to be combined with another radionuclide or duplex sonography study.

3. To assess both arterial and venous problems during the same pharmacological intervention, penile pletismography and xenon washout have been successfully used simultaneously by several groups.[40, 41]

Among several similar protocols the technique used by the Cleveland group is decribed, as an example.[41] Red blood cells are labelled in vivo with 200Mbq of 99mTc. The lower abdomen is covered with lead shields leaving only genitalia exposed. A venous blood sample is obtained to convert count rate into mililiters. A butterfly needle is inserted into cavernosal body at the base of the penis. A gamma camera with an all-purpose collimator, set for dual isotope acquisition, is centered over the penis.

200-400 MBq of 133 Xe in 1 ml saline are injected through the butterfly needle and flushed with 5 ml of saline. Data acquisition is started after 2–3 min, at the rate of 1 frame/ 10 seconds for 15 minutes. Vasodilators (papaverine 45 mg and phentolamine 1 mg) are injected slowly and flushed with 1 ml saline through the indweling butterfly needle. Data acquisition is continued at the same rate for 20 min.

Results are presented as time activity curves after correction for technetium downscatter into xenon window. Arterial and venous flows are calculated according to one compartment model from the flaccid through the tumenescent and erect states. (Erection is reduced prior to discharge of the patient).

Combining the results of arterial and venous blood flow during pharmacologic intervention, this technique was able to differentiate between normals, having normal both peak arterial and peak venous blood flow, arterial insufficiency patients, having decreased peak arterial flow and normal peak venous flow, and patents with venous leak, having essentially normal peak arterial flow and markedly increased peak venous flow in a small group of selected patients.[42]

Diagnostic value

Although not yet properly evaluated, these methods may be useful as a screening test in patients with erectile dysfunction to differentiate patients with arterial insufficiency from those with venous leak. The disadvantage of radionuclide methods is their inability to provide anatomic information in comparison with angiographic and duplex sonography, their advantage however is that they are simple to perform, are operator independent, and should be well reproducible, what is useful, especially to follow up the success of surgical treatment of such patients.

Conclusion

Despite the emergence of new, especially cross sectional imaging approaches, radionuclide

techniques maintain a significant role in genital imaging, since they can demonstrate the physiologic status of organs.

Radionuclide scrotal imaging remains the most effective method for differentiating between testicular torsion and epididymitis.[9] Labelled red blood cells are used successfully for varicocele detection in infertile men. Only radionuclide techniques allow for noninvasive assessment of functional tubal patency in infertile women. They can play an important and useful role in evaluating men with impotence.[15]

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