Radioisotope Penile Plethysmography: A Technique for Evaluating Corpora Cavernosal Blood Flow During Early Tumescence

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Radioisotope penile plethysmography is a nuclear medicine technique which assists in the evaluation of patients with erectile dysfunction. This technique attempts to noninvasively quantitate penile corpora cavernosal blood flow during early penile tumescence using technetium-99m-labeled red blood cells. Penile images and counts were acquired in a steady-state blood-pool phase prior to and after the administration of intracorporal papaverine. Penile counts, images, and time-activity curves were computer analyzed in order to determine peak corporal flow and volume changes. Peak corporal flow rates were compared to arterial integrity (determined by angiography) and venosinusoidal corporal leak (determined by cavernosometry). Peak corporal flow correlated well with arterial integrity (r = 0.91) but did not correlate with venosinusoidal leak parameters (r = 0.01). This report focuses on the methodology and the assumptions which form the foundation of this technique. The strong correlation of peak corporal flow and angiography suggests that radioisotope penile plethysmography could prove useful in the evaluation of arterial inflow disorders in patients with erectile dysfunction.

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Erectile dysfunction can be caused by psychologic or physiologic factors (1-3). Identifying the physiologic factors that contribute to impotence is important in the diagnosis and treatment of this problem. In order to obtain rigid erections, the venosinusoidal occlusion mechanism must be competent (4) and there must be adequate arterial flow into the corpora cavernosum of the penis (5).

The anatomic integrity of the penile arterial network is best assessed invasively by angiography (6,7). Non-invasive methods currently employed for screening penile arterial functional competence include penile brachial index (8) and Doppler ultrasound velocity/diameter measurements (9). Although widely accepted as a screening test, the penile brachial index, a test that compares the blood pressure in the penile arteries to the blood pressure in the arm, is limited because it does not examine the penile arteries during tumescence and because the measurements are obtained without distin-

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guishing the dorsal arteries (the arteries not usually involved in erection), from the cavernosal arteries (the arteries responsible for erection). Although flow can be calculated from Doppler ultrasound velocity measurements, these measurements are compromised by the difficulty of reliably and reproducibly correcting for the Doppler angle.

Radioisotope bolus (10,11), blood-pool (12,13), and washout (14) scans have been utilized to measure penile flow and volume. These have been limited by the lack of a consistent method for inducing tumescence. Recently, intracorporal injections of papaverine have been recognized as a means of pharmacologically inducing tumescence. Papaverine is a nonspecific smooth muscle relaxant that increases arterial inflow and reduces venosinusoidal outflow from the corpora cavernosum (15-18). Although this technique requires the injection of papaverine directly into the penis, this is a benign procedure that can be considered to be no more invasive than a venipuncture and is similar to administering medications intravenously (6,7,16,19).

In an attempt to noninvasively quantitate penile corporal blood flow during early tumescence, we have developed a radioisotope penile plethysmographic technique that utilizes intracorporal papaverine. This technique has its origin in an adaptation of an intrapenile blood volume determination method first described by Shirai in 1976 (12).

This communication focuses on the methodology of acquiring and processing the radioisotope penile plethysmography data. The results of this radioisotope technique are compared to pelvic penile angiography (6,7) and intracorporal resistance (venosinusoidal leak) measurements obtained by cavernosometry (19). The assumptions that form the basis for this technique are outlined and the limitations of the technique discussed. A brief description of relevant penile anatomy and physiology is reviewed.

MATERIALS AND METHODS

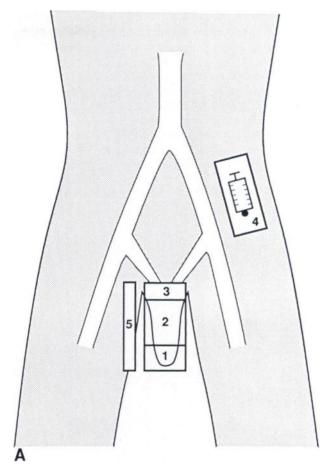
Thirty consecutive patients complaining of impotence being considered for surgical intervention, either prosthetic implantation or penile vein ligation, were studied with radio-isotope penile plethysmography at the Seattle Veterans Administration Medical Center between May 1987 and November 1987. All patients underwent a history and physical examination.

Twenty-nine of 30 patients received angiography. After cavernosometry, a prolonged erection developed in one patient that required repetitive extractions of intracorporal blood in order to achieve detumescence. This patient was a type II responder (17), who had a normal penile brachial index and a history of nocturnal penile erections. Angiography was not performed in this patient whose history and less invasive studies indicated normal arterial inflow.

The underlying medical condition in the 30 patients included insulin or noninsulin dependent diabetics (six patients), atherosclerosis/hypertension (seven patients), neurologic disorder (four patients), prostatectomy (one patient), pelvic vascular surgery (one patient), or no significant medical condition (11 patients). The mean age of the patients studied was 59 yr (range 40 to 76 yr). Each patient consented to the complete impotence workup and was informed of its risks and benefits.

To prepare a patient for radioisotope penile plethysmography, the red blood cells are labeled with the in vivo/in vitro technique (20). This involves the intravenous injection of the reconstituted contents of one vial of stannous pyrophosphate which is allowed to incubate intravascularly a minimum of 20 min. While the pyrophosphate is incubating, the patient is placed supine with a gamma camera and high sensitivity collimator (GE 400 AT, Milwaukee, WI) positioned anteriorly over the patient's pelvis. The field of view includes the aortic bifurcation superiorly and the entire penis inferiorly. A 19-gauge butterfly needle is placed into an antecubital vein of each arm. From the right antecubital vein 5 ml of blood is extracted and collected into a syringe containing 1 ml of ACD (acid citrate dextrose). Both butterfly needles are kept patent with heparin flush solution.

Thirty millicuries of technetium-99m (99mTc) pertechnetate are added to the blood sample and placed on a specimen



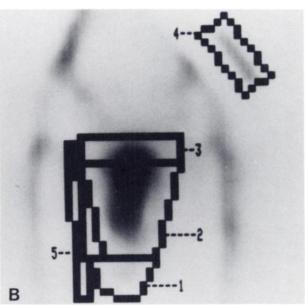


FIGURE 1
A: Schematic representation of regions of interest. The lead strip is placed at the junction of region 1 and region 2.
B: Sixty frame composite image with regions of interest included.

rocker (Labquake, Lab Industries, Berkeley, CA) for at least 10 min. The penis is positioned with the glans pointing towards the feet. A 25-gauge butterfly needle is then placed into the mid-portion of the corpora cavernosum. It is flushed with heparin solution and an injection cap placed on its terminus.

Tape is placed on the undersurface of the distal penis, the penis is stretched slightly, and the opposite end of the tape attached to a 500-ml water bag. A strip of lead (5 cm \times 4 cm \times 0.3 cm) is taped at the glans-corporal junction (Fig. 1).

When incubation is completed, the ^{99m}Tc-labeled red blood cells are injected into the right antecubital vein. The images are monitored to ensure an i.v. injection. Five minutes after injection, 5 ml of red blood cells are withdrawn via the patient's left antecubital catheter and that syringe is discarded.

Using a second syringe, exactly 10 ml of radioactive blood are withdrawn and the syringe placed on a lead shield (14 cm \times 7 cm \times 1 cm) which has been positioned near the left groin just lateral to the left common iliac artery (Fig. 1).

The computer (Siemens Max Delta System, Des Plaines, IL) is programmed to acquire data from the gamma camera dynamically, word mode acquisition, at 15 sec per frame for 60 frames (15 min). After acquiring two 15-sec frames, which represent the prepapaverine base line, an ampule of 60 mg of papaverine hydrochloride (Eli Lilly & Co., Indianapolis, IN) is injected over 30 sec via the 25-gauge intracorporal needle. One antecubital needle is maintained throughout the study to assure an intravenous access site. The study should be performed in a room which is quiet and private. The patient is given photographs to view of a provocative sexual nature.

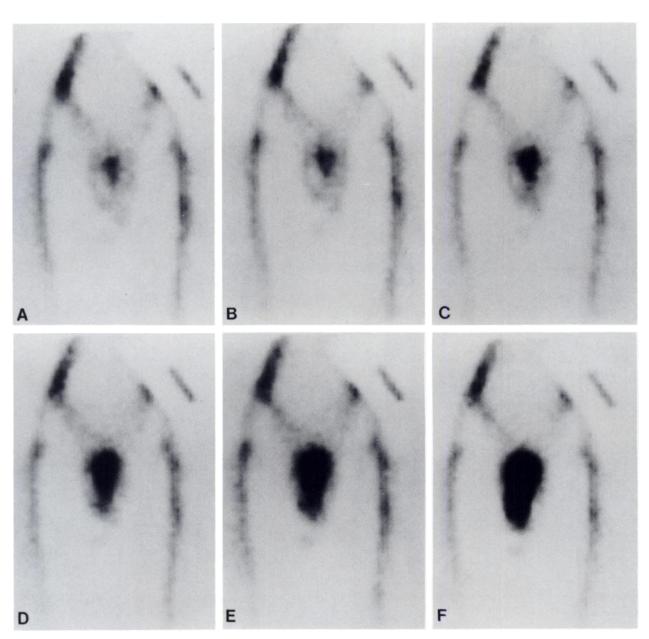


FIGURE 2
Flow images from a normal patient. A: Baseline image prior to intracorporal papaverine injection; B: Image immediately after intracorporal papaverine injection; C: Image at 1 min; D: 2 min; E: 2½ min; F: 5 min.

At the end of the acquisition, the penis is examined for the degree of tumescence. Since all the patients have been screened previously with intracorporal papaverine injections and with cavernosometry, the patients studied should not be at risk for developing priapism. The patient is observed for 1 hr after the study. If a patient should develop a rigid prolonged erection, however, a physician who has been trained to deal with this problem should be contacted and adequate detumescence assured prior to the patient's leaving the nuclear medicine department.

The individual images from each frame are visually inspected in order to qualitatively estimate the erectile response and determine the distribution of isotope within the penile regions (Fig. 2). Flow rates and volumes are obtained from both the change in counts and the absolute counts as determined in three regions of interest (ROIs), which included: the base of the corpora cavernosum, the main corporal body, and the glans (Fig. 1). The counts are background corrected and calibrated from the syringe counts. These ROIs are all drawn from a 60-frame composite image. A time-activity curve is calculated for each region (Fig. 3). A computer program (Penflow™ copyright (c) 1988 Alan N. Schwartz and Michael M. Graham. All rights reserved) is utilized to calculate peak corporal flow from the maximum change in counts that occur between images in the corporal ROI. This assumes venous

outflow is minimal. If there is significant outflow, the inflow values will be underestimated. All calculations were done with raw data and after performing a five-point binomial smooth. Flow (ml/min) is calculated by dividing the rate of change in counts from a region (cts/min/min) by count rate per ml (cts/min/ml) in the syringe ROI.

The corporal base and the main corporal body measurements are added together in order to calculate the corporal volume (CV) and corporal flow (CF) values. The initial corporal volume (ICV), the final corporal volume (FCV), and the change in corporal volume (dCV) are all calculated (dCV = [FCV - ICV]).

The peak corporal flow rates (PCF) are compared to intracorporal resistance (RV) and to angiography. The angiography is reported as an angiography score which represents an attempt to quantitate the angiographic findings. All angiograms were analyzed prior to the nuclear medicine study and therefore were blinded readings. The arteries contributing to the corpora cavernosal blood flow were evaluated, bilaterally. These included the distal aorta, the common iliac, the internal iliac, the internal pudendal and the cavernosal arteries. The scoring system is outlined in Table 1 and is based on the assumption that the most severe arterial lesion defines the flow limiting factor. Each side of arterial inflow is considered separately. Because vessels <3 mm in diameter do not have

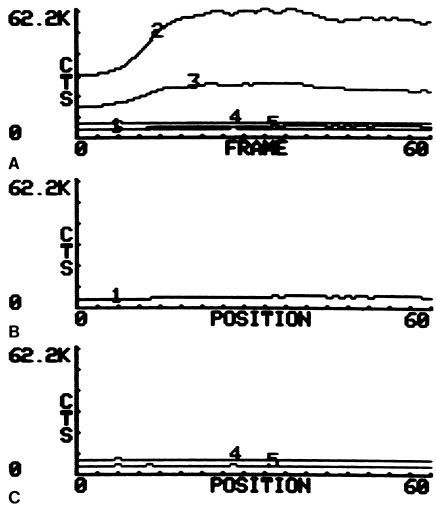


FIGURE 3

Time-activity curves for regions of interest. The numbered regions of interest in Figure 3 correspond to the numbered regions of interest in Figure 1. The x axis which is marked as frame of position represents the time over which the study was performed (15 min; 60 frames). A: The main corporal body (2) and the corporal base (3) increase and plateau at comparable times. B: The glans (1) increases only minimally. C: The syringe (4) and background (5) remain constant throughout the study except for some minimal decay.

TABLE 1
Angiography Scoring System

*Angiography score	Artery >3 mm diameter (% stenosis)	Artery <3 mm diameter (% stenosis)	Estimate of disease and flow restriction
0	Occluded	Occluded	Occluded
1	80-99	70-99	Severe
2	50-79	40-69	Moderate
3	25-49	15-39	Minimal
4	<25	<15	Normal

To calculate the bilateral angiography score (ANGS): (ANGS) = (Right Angiography Score + Left Angiography Score)/2.

the same flow characteristics as vessels >3 mm (21), the small caliber vessels (<3 mm) were considered to undergo flow disturbances with less prominent stenosis than the larger vessels (larger than 3 mm).

In order to correct for collateral flow, a collateral vessel was considered significant if it approximated the proximal diameter of the bypassed vessel, originated from either one or both sides of the iliac artery penile networks, and if the collateral supplied blood flow distal to a severe stenosis (>80%) or an occlusion. A patient with a significant collateral had 0.5 points added to the uncorrected angiography score (ANGS) and this is referred to as corrected angiography score (ANGSC). Multiple spider-like collaterals whose diameters were significantly smaller than the proximal by-passed occluded or stenotic segment did not receive extra points because their contribution to the final intracorporal flow and pressure was considered hemodynamically less significant than the larger collaterals.

The data was analyzed using linear regression and Spearman nonparametric correlation coefficient methods.

RESULTS

Peak corporal penile flow (PCF) ranged from 2.2 ml/min to 66.5 ml/min. There was excellent correlation between peak arterial inflow as judged by corporal flow and angiography scores (ANGS [r = 0.88] and ANGSC [r = 0.91]; Fig. 4A). No correlation was identified between peak corporal flow and intracorporal resistance, a measure of corporal venosinusoidal outflow leak (r = 0.01); Fig. 4B).

The patients were then subdivided by their angiographic findings. The patients with minimal to no arterial changes (ANGSC, \geq 3) had a mean PCF of 14.7 \pm 4.4 ml/min; moderate arterial changes (ANGSC, >1 and <3) had a mean PCF of 9.0 \pm 2.9 ml/min; and severe arterial changes (ANGSC of \leq 1) had a mean PCF of 4.8 \pm 1.5 ml/min.

Patients were also subdivided according to their peak corporal flow rates (PCF), and this was compared to angiography. The mean angiography score (ANGSC) of patients with a PCF of ≥ 11.5 ml/min was 3.11 ± 0.7 indicating minimal arterial disease; a PCF of 7 to 11.5 ml/min was 2.1 ± 0.6 indicating moderate disease, and a PCF of ≤ 7.0 ml/min was 0.77 ± 0.5 indicating severe arterial disease.

Initial volumes ranged from 11 ml to 76 ml (mean 28.97 ± 14.2). Final volumes ranged from 28 ml to 160 ml (mean 73.9 ± 30.2). The change in volume ranged from 16 ml to 18 ml (mean 43.4 ± 21.5).

Two patients were excluded from the regression and from the mean peak corporal flow rate (PCF) calculation. One patient had a peak corporal flow of 66.5 ml/min which was >3 s.d. from the mean (statistical outlier). It would be predicted that this patient should have a normal angiogram which, in fact, this patient did have. The reason for this patient's increased flow is not known. However, this patient had a larger than normal corpora cavernosum and angiographically had larger than normal internal pudendal arteries. His initial corporal volume was 49 ml compared to the population mean of 28 ml.

The second patient was excluded from the regression because he did not undergo angiography. He was considered to have normal arteries by other criteria. He had a PCF of 16.1 ml/min, which lies within 1 s.d. of the mean for a patient with a normal angiogram (mean 14.7 ml/min).

There were no complications and no patient experienced priapism or any untoward cardiovascular effects from intracorporal papaverine injection.

DISCUSSION

The normal penis is composed of two interconnecting corpora cavernosal bodies, each supplied by its own cavernosal artery. The corpora are composed of sinusoidal tissue which, as they become engorged, restrict the outflow of blood by engaging a venosinusoidal occlusion mechanism. This complex series of interrelated neurophysiologic and vascular events results in tumescence. If any component of the erectile mechanism is defective, incomplete tumescence may result (22).

The glans and skin of the penis are supplied by two dorsal arteries which usually do not contribute significantly to corpora cavernosal inflow. The glans tumescences passively. A third sinusoidal body surrounds the urethra and is referred to as the bulbospongiosum. This body also tumescences passively and is supplied by the bulbar artery branches.

The radioisotope penile plethysmography technique is based on three assumptions. The first assumption is hemodynamic and states that the loss of radioactivity through venosinusoidal outflow during the early phase

To calculate the Corrected Angiography Score (ANGSC) 0.5 points are added to the ANGS if a significant collateral is present.

Angiography scoring system is applicable to Right Angiography Score, Left Angiography Score, ANGS and ANGSC.

of tumescence is negligible and the transit time of blood through the penis is prolonged such that no significant radioactive blood reaches the venous outflow during this early tumescent phase. Although we realize that some blood exits from the penis during early tumescence, if arterial inflow greatly exceeds venosinusoidal outflow, the changes in the intracorporal volume will be more dependent on arterial inflow than venosinusoidal outflow. It is this early volume response that is measured by peak corporal flow.

The second assumption is that there is minimal attenuation of radioactivity by structures surrounding the corpora cavernosum. This assumption is closer to true than for any other organ of the body since most of the corpora is covered by only a thin layer of skin and fascia. At the base of the penis there is more overlying tissue and this assumption may be less accurate. However, the base region of interest (ROI) composes a small proportion of the total penile volume (Fig. 1).

The third assumption is that papaverine produces a consistent and equivalent response in penile vasculature during early tumescence. We do know that the final

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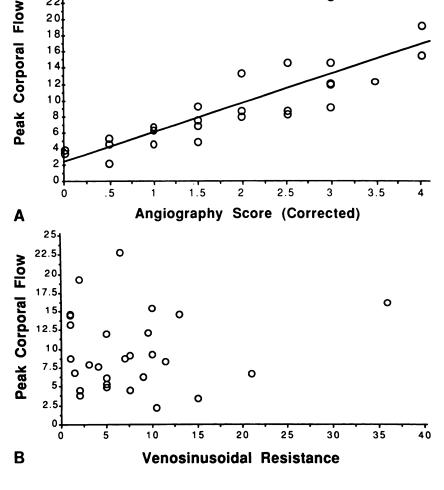
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papaverine response varies between patients and that psychologic factors greatly influence even a normal patient's ability to achieve rigid erections (19). What is not known is whether the variability of the papaverine response is an early or a later corporal event and whether this variability is predominantly arterial or venosinusoidal in nature.

As previously stated, in the normal male, tumescence occurs when arterial inflow increases and venosinusoidal outflow decreases. During early tumescence, arterial inflow is rapid. Although corporal venosinusoidal outflow may be present, outflow is significantly less than inflow. The corporal sinusoids fill and intracorporal pressure increases modestly during this early phase.

During the mid to late tumescent phase, the venosinusoidal outflow becomes minimal at 1 to 5 ml/min (19) while the arterial inflow remains elevated. The intracorporal pressure increases rapidly and the corpora cavernosum expands noticeably. In the normal male, this combination of events leads to rigid erection. However, in the male with significantly decreased arterial



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FIGURE 4 A: Regression of peak corporal flow and corrected angiography score (r = 0.91). B: Regression of peak corporal flow and venosinusoidal resistance (r = 0.01).

inflow and/or excessive venosinusoidal leakage, the corporal expansion will be incomplete.

Volume as well as flow rates to each compartment of the penis have been estimated by dividing the organ into three ROIs. The glans ROI receives its flow from the dorsal penile artery. In most cases, the dorsal artery supplies little contribution to corporal inflow and therefore, usually does not directly influence erectile function. Although the degree of elongation is limited in the impotent male, especially when the penis is stretched, the glans ROI may change its position with penile elongation. For this reason, all regions of interest are drawn from the composite 60-min image. Although the final glans volume should be accurate, the initial glans volume can be underestimated when there is marked elongation.

The main corporal body ROI is predominantly composed of the two corpora cavernosa excluding the base. The corpora cavernosa receive their blood supply from the cavernosal arteries, which are the arteries responsible for erectile function. The bulbospongiosum also lies within this region of interest. However, it is a passive chamber which expands and retains less blood than the corpora cavernosum and therefore contributes less activity to this region. The main corporal body ROI overlies portions of the scrotum and testes. Segments of both the scrotum and testes are included in the background ROI and thus there is an approximate correction for their contribution.

The final ROI is at the base of the penis. This is a complex region composed of the proximal corpora cavernosum and the corporal crura. The base of the bulbospongiosum and the confluence of the deep and superficial venous structures also reside in this region. The penile arteries bifurcate and often collateralize in this region. The slope and time to equilibrium of the base time-activity curve in most cases is very similar to that of the main corporal body suggesting that base activity is predominantly corpora cavernosal in nature (Fig. 3A).

The significant correlation between peak corporal flow rates and angiography suggests that radioisotope penile plethysmography may be a useful way to non-invasively evaluate patients for the integrity of the penile arterial network. Flow rates greater than 11.5 ml/min correlate well with minimal or no significant arterial disease whereas flow rates of <7 ml/min correlate well with severe arterial disease. Intermediate flow rates between 7 ml/min and 11.5 ml/min were associated with arterial variations and moderate arterial disease, placing the patient in an indeterminate category.

Predicting whether a patient has competent arteries may be difficult in patients with moderate arterial disease even when angiography is utilized. Tumescence is dependent on arterial inflow rates and pressures, which in turn are dependent upon the degree of arterial stenosis and whether the lesion is unilateral or bilateral. The radioisotope penile plethysmography technique may prove helpful if used in conjunction with angiography, especially in patient's with moderate arterial disease. By determining whether patients with moderate disease by angiography have flow rates closer to normal or abnormal values, a more accurate assessment of the significance of their vascular lesions may be possible.

The lack of correlation between corporal venosinusoidal resistance (a measure of venous outflow resistance) and peak corporal flow suggests that during early tumescence, corporal flow is independent of the variation in severity of venosinusoidal leakage. This supports the first assumption that during early tumescence the influence of arterial inflow exceeds that of venosinusoidal outflow. The lack of correlation between intracorporal resistance and peak corporal inflow does not imply the absence of corporal outflow during early tumescence, but only that early in tumescence, the relatively long delay from artery to vein results in little activity leaving the penis during this phase.

As intracorporal pressure increases and the corpora cavernosa begin to expand, we postulate that arterial inflow and venosinusoidal outflow approach an equilibrium state. Using the present technique, it is not possible to measure the contribution of outflow. For this reason, peak corporal inflow rates measured by radioisotope plethysmography may underestimate the actual peak biologic arterial inflow rate especially during the mid and late phases of tumescence in impotent males.

It is important to recognize that radioisotope penile plethysmography measures corporal vascular volume changes and that these changes depend greatly on the patient's response to papaverine. The development of medications, capable of overriding the psychologic and neurologic inhibitors of the erectile response would increase the predictive ability for almost all impotence testing including radioisotope penile plethysmography. In addition, the effect of more provocative visual and psychologic stimuli, on radioisotope penile plethysmography remains to be explored. Normal and abnormal inflow values may vary depending on the types of medication, visual stimulation, and psychologic environment utilized to induce tumescence.

Finally, radioisotope penile plethysmography attempts to access only flow into the penis. Generating and maintaining a normal erection is dependent upon vascular factors other than just the rate at which blood flows into the corpora cavernosum. Variables such as the cavernosal artery filling pressures are crucial for normal erectile function. Therefore, radioisotope penile plethysmography inflow rates represent only a part of the complete evaluation of penile artery integrity and presently must be correlated with other diagnostic modalities capable of assessing cavernosal artery pressure, flow, and anatomy.

CONCLUSION

Preliminary evidence suggests that radioisotope penile plethysmography is a useful means of assessing the functional integrity of the penile arterial inflow system in patient's with suspected vascular impotence. A strong correlation (r=0.91) was demonstrated between peak corporal flow rates and the angiographic score of penile arterial integrity. Continued experience with radioisotope penile plethysmography is necessary before the accuracy, sensitivity, and specificity of this test can be determined.

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