Combined Technetium Radioisotope Penile Plethysmography and Xenon Washout: A Technique for Evaluating Corpora Cavernosal Inflow and Outflow During Early Tumescence

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Combined technetium radioisotope penile plethysmography and xenon washout is a new technique that measures both corporal arterial inflow and venous sinusoidal outflow during early tumescence in patients with erectile dysfunction. Fourteen patients were studied using ^{99m}Tc-RBCs to measure inflow and ^{133}Xe or ^{127}Xe in saline to measure outflow. Tumescence was induced by injecting papaverine intracorporally. Peak corporal rates corrected for inflow ($r = 0.88$) and uncorrected for outflow ($r = 0.91$) and change in volume over 2 min centered around peak inflow ($r = 0.96$) all correlated with angiography. Outflow measurements did not correlate with intracorporal resistance. Thus, outflow rates alone could not be used to predict venous sinusoidal competence. Normal inflow rate is >20 ml/min; probable normal 12–20; indeterminate inflow 7–12; and abnormal inflow <7 ml/min. Technetium-99m radioisotope penile plethysmography and xenon washout can be performed together and both provide a method for simultaneously evaluating the relationship between corporal inflow and outflow rates in patients with erectile dysfunction.

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New methods for treating erectile dysfunction have made it necessary to define the precise causes of erectile failure. The two major vascular causes for erectile dysfunction are arterial insufficiency and excessive venous sinusoidal leakage. Arterial insufficiency can be assessed by angiography (*1,2*), sonography (*3,4*), systolic occlusion pressures (*3,5*), and radioisotope penile plethysmography (*6*). Venous sinusoidal incompetence can be assessed by cavernosometry (*7*), cavernosonography (*8*), sonography (*3*), and xenon washout studies (*9–11*).

Radioactive xenon has been used to measure tissue blood flow in a wide variety of tissues (*12*). For the evaluation of erectile function, penile xenon washout studies have been used to estimate the rate of blood flowing through the nontumesced penis (*9*) and to calculate the severity of the venous-sinusoidal leak during erections (*10,11*).

Our previous work with radioisotope penile plethysmography (RPP) using technetium-99m-red blood cells (^{99m}Tc-RBCs) (*6*) showed that RPP was simple to perform and useful in determining penile corpora cavernosal artery inflow. However, the plethysmographic approach makes the assumption that venous outflow is negligible during early erection. If there is significant outflow during early erection, the RPP method with ^{99m}Tc-RBCs will underestimate the inflow rates.

To examine the assumption that venous outflow is negligible during early erection and in an attempt to devise a test that could define both arterial integrity and venous sinusoidal competence, we combined xenon washout and RPP.

MATERIALS AND METHODS

Studies were performed at the University of Washington and Seattle Veteran's Administration Hospital, Seattle, Washington between May 1987 and May 1989. Institutional review and informed consent were obtained for all patients. All subjects underwent angiography (*1,2*) and cavernosometry (*7*). The mean age of the patients studied was 57 yr (range: 38–67 yr).

The first group of nine patients were studied sequentially (sequential RPP/Xe). Initially, these patients had their inflow rates studied by RPP as described by Schwartz et al. (*6*) using ^{99m}Tc-RBCs. Xenon-133 studies were performed within approximately one year of the ^{99m}Tc-RBC study. All patients' physiologic states were clinically unchanged. For the ^{133}Xe washout portion of the study, we attempted to reproduce conditions used during RPP, including patient positioning, environment, set-up parameters, and medication dose (papaverine 60 mg). Xenon-133 was used for the sequential studies because of its convenient availability and because it is easily imaged with a high-resolution collimator. There was no interference from the higher energy ^{99m}Tc photons since the two

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studies were done on different days. RPP and xenon washout studies were then combined and analyzed.

Because erectile function may be variable depending on psychologic factors, it is most appropriate to measure inflow and outflow simultaneously. In the second group of five patients, ^{127}Xe washout and RPP were performed simultaneously (simultaneous RPP/Xe). Xenon-127 was used for the simultaneous studies because there is somewhat less scatter associated with the higher energy photons. When ^{127}Xe is used with ^{99m}Tc, it is necessary to correct for the scatter of the higher energy photons into the lower energy window. The scatter fraction was estimated from the increase in apparent ^{99m}Tc count rate when the ^{127}Xe was injected. All of the ^{99m}Tc counts were corrected by subtracting the appropriate fraction of the ^{127}Xe counts. A low-energy, general-purpose collimator was used for the $^{99m}Tc/^{133}Xe$ studies. A medium-energy collimator was used for the $^{99m}Tc/^{127}Xe$ studies. In three subjects, 30 mCi of ^{99m}Tc were used. In two subjects, the dose was reduced to 15 mCi of ^{99m}Tc.

For the RPP portion of the study, the RBCs were labeled with the modified in vivo technique (*13*). Isotope injection and patient positioning are outlined in the method described by Schwartz et al. (*6*).

The camera and computer were set up and peaked to simultaneously acquire dual isotopes through two separate 15% energy windows (^{99m}Tc, 140 keV; ^{127}Xe, 203 keV).

Computer acquisition was initiated and 15-sec frames were acquired. Two 15-sec pretumescent ^{99m}Tc baseline images were obtained. Xenon in saline was then injected through a 25-gauge butterfly needle into the corpora cavernosum.

In the initial group of three patients who received 30 mCi ^{99m}Tc-RBCs, 200 mCi of ^{127}Xe in 0.5 ml saline were injected, and in the two patients who received 15 mCi ^{99m}Tc-RBCs, 400 mCi of ^{127}Xe in 0.5 ml saline were injected. The ^{99m}Tc dose was lowered to minimize radiation dose but was still adequate to accurately measure changes in counts over the penis. The xenon dose was raised to improve the counting statistics with only a small increase in the radiation dose.

For both ^{127}Xe and ^{133}Xe, the xenon was injected into the mid-corpora cavernosum over a 30-sec period. For 3.5 min after injection, images were acquired in order to determine a steady-state prepapaverine baseline for xenon washout. Sixty milligrams (2 ml) papaverine hydrochloride (Eli Lily and Company, Indianapolis, IN) were then injected over 30 sec via a second 25-gauge intracorporal needle. One antecubital needle was maintained throughout the study to assure intravenous access. The studies were performed in a quiet and private room. The subjects were given photographs to view of a provocative sexual nature.

The nuclear medicine images were visually inspected for each isotope in order to qualitatively estimate the erectile response and to determine the distribution of isotope within the penile regions.

Flow rates and volumes were obtained from both the change in counts and the absolute counts, respectively, as determined in the regions of interest (ROIs): the corpora cavernosum, the glans, and the syringe (Fig. 1). The corporal base and body together constitute the corpora cavernosum. The counts were background-corrected and calibrated from the syringe counts. The ROIs were all drawn from the 60-frame composite image. A time-activity curve was calculated

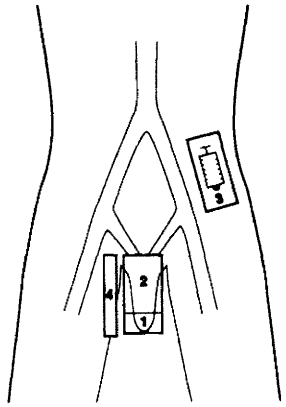

FIGURE 1
Schematic representation of ROI: 1. glans; 2. corpora cavernosum; 3. syringe; and 4. background.

from each ROI. Blood inflow was calculated from the rate of increase of ^{99m}Tc counts calibrated by the count rate over the reference syringe. Blood outflow in ml/min/ml of blood was calculated from the rate constant of the xenon disappearance curve point by point. A partition coefficient of 0.8 was used. Absolute outflow was calculated using the blood volume determined from the ^{99m}Tc data.

This approach assumes rapid mixing of the xenon in the same volume as defined in the ^{99m}Tc ROI. If it distributes in a larger volume, no error is generated since the ROI sees equal volumes of ^{99m}Tc and xenon. If it is confined to a smaller volume, the absolute flow may be overestimated. An additional source of error is that in inhomogeneous tissue the flow is progressively underestimated since activity washes out of highly perfused tissue more rapidly and therefore tissues with low flow are given progressively greater weight. These last two errors may somewhat offset one another. A computer program (Penflow RPP/Xe® © 1990 Alan N. Schwartz and Michael M. Graham. All rights reserved.) was utilized for all calculations.

Inflow rates and corporal volume were compared to angiography. Angiography results were reported as a corrected angiographic score (AngSc) (Table 1) as previously described

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.

† To calculate AngSC, 0.5 points are added to the AngSC if a significant collateral is present.

by Schwartz et al. (6). The scoring system analyzes each internal pudendal artery and its tributaries. A numerical value from zero to four is assigned to each vessel. A value of four represents a normal artery, whereas a value of zero represents a severely diseased or occluded vessel (Table 1). Venous leak was reported as intracorporal outflow resistance (RV) as described by Freidenberg et al. (7).

At the end of the study, the penis was examined for the degree of tumescence. Since all the patients had been screened previously with intracorporal injections of papaverine, the subjects studied were not at risk for developing priaprism and no subject had this problem. Each subject was observed for 1 hr after the study. If a subject developed a rigid prolonged erection, a physician trained to deal with this problem was contacted and adequate detumescence was assured prior to the subject leaving the nuclear medicine department.

The data were analyzed using non-linear regression and Spearman nonparametric correlation coefficient methods:

PCIF	Peak corporal inflow uncorrected for outflow
PCIF*	Peak corporal inflow corrected for outflow
MCIF	Maximum corporal inflow
COF	Corporal outflow
PCOF	Peak corporal outflow
COF*	Corporal outflow occurring at time of peak corporal inflow
RV	Intracorporal resistance
AngSc	Angiography score corrected
COF*/PCIF	Ratio of outflow to inflow at time of peak corporal inflow
TMCIF	Time of maximal corporal inflow
TPCIF	Time of peak corporal inflow
TPCOF	Time of peak corporal outflow
dCV	Change in corporal volume from one minute prior to one minute after peak corporal inflow.

RESULTS

PCIF uncorrected for outflow was calculated from RPP ^{99m}Tc inflow values. PCIF ranged from 5.1 to 67.9 ml/min. There was an excellent correlation between PCIF and angiography (AngSc) results (r = 0.91; Fig. 2).

PCIF (PCIF* = PCIF + COF*) was calculated from the peak RPP ^{99m}Tc inflow value (PCIF) corrected for corporal xenon outflow (COF*) at the time of PCIF. PCIF* ranged from 5.1 to 70.4 ml/min. There was very good correlation between PCIF* and AngSc (r = 0.88; Fig. 2).

MCIF was calculated by identifying the rate at which the sum of corporal inflow (calculated from RPP) and corporal outflow (calculated from xenon washout) were maximal. MCIF ranged from 6.1 to 70.4 ml/min. The correlation between MCIF and AngSc was good (r = 0.84) but not as good as that found for PCIF and PCIF*.

In an attempt to define and integrate the concept of maximal flow and sustained flow rates, we calculated the volume change (dCV) in the corpora from 1 min prior to until 1 min after PCIF. dCV ranged from 3 to 96 ml. The change in volume (dCV) correlated excellently with AngSc (r = 0.96). This measurement correlated more reliably with AngSc than any of the other flow parameters (Fig. 2).

COF* ranged from 0 to 5.7 ml/min. Minus flow values were encountered and were considered to be zero. The negative flow values result from slight changes in geometry and do not include venous backflow. Apparently some subjects have negligible venous outflow at the time of maximal arterial inflow. RV correlated poorly with COF* (r = 0.24).

COF* was compared to inflow (PCIF) by calculating the ratio of outflow to inflow (COF*/PCIF). The correlation between COF*/PCIF and PCIF and AngSc was poor (r = −0.36; r = −0.56, respectively). However, patients with abnormally low inflow rates exhibited a greater percentage of outflow compared to inflow than patients with normal inflow rates (Table 2). PCOF was defined as the maximal rate of corporal outflow as determined by xenon washout. PCOF ranged from 2.4 to 32 ml/min. PCOF correlated poorly with venous sinusoidal resistance, RV (r = 0.39). In general, patients with elevated PCIF and dCV demonstrated more outflow than patients with lower inflow rates. In six patients with normal arterial inflow, the pattern of outflow rates

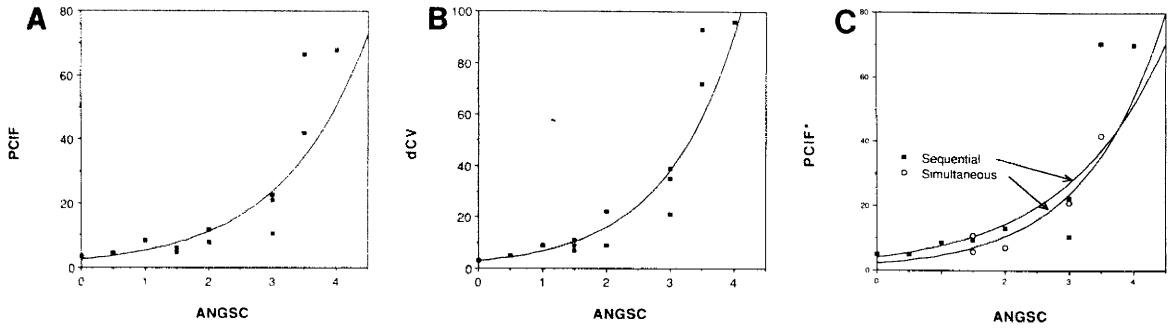

FIGURE 2
(A) Regression of PCIF and corrected angiography score (r = 0.91). (B) Regression of dCV and corrected angiography score (r = 0.96). (C) Regression of PCIF* and corrected angiography score (r = 0.88).

TABLE 2
The Percentage of Outflow/Inflow Compared to Inflow

COF*/PCIF (%)	PCIF* (ml/min)
77–100	4.8
8–11	7.5
0–6	34.0

* Mean PCIF values.

in relationship to inflow rates was useful in determining venous sinusoidal competence (Fig. 3A-B).

The correlation of PCOF to PCIF and dCV were r = 0.75 and r = 0.79, respectively. This may reflect the fact that when patients with large corporal volumes or inflow rates detumesce or leak they generated greater outflow rates.

The time of peak corporal inflow ranged from 2 to 4 min. (most patients peaked between 2.25 and 2.5 min) after the completion of the 30-sec papaverine infusion. There was a significant delay in time between PCIF and PCOF with PCOF occurring 0 to 4.5 min (mean delay was 2.25 min) after PCIF.

Patients who demonstrated abnormal inflow had rates of less than 7 ml/min. Patients who demonstrated excellent blood flow had rates of greater than 20 ml/min. Patients with inflow rates ranging from 7 to 12 ml/min were considered indeterminate. Patients with inflow rates of 12–20 ml/min were considered probably normal (Table 3). In the indeterminate and probably normal groups, the outflow rates were useful in determining arterial integrity. dCV is also categorized in relationship to arterial integrity (Table 3). Graphic displays of the rate of inflow and outflow and volume as a function of time are depicted in Figure 3.

DISCUSSION

There are three phases of erection: initiation, generation, and maintenance. During initiation, a neuropsychogenic or chemical stimulus causes the cavernosal arteries and the corpora sinusoidal smooth muscles to relax. This increases arterial blood flow and expands the sinusoids of the corpora cavernosum. As the sinusoids expand, the venous sinusoidal outflow channels close. Blood is trapped within the corpora cavernosa. Generation occurs as blood continues to flow into but not out of the corpora cavernosa. As a result, blood is stored in the corpora and the corporal bodies expand and become rigid. Maintenance occurs when the arterial inflow and venous sinusoidal outflow are in an equilibrium state, capable of sustaining full expansion and rigidity.

Erectile dysfunction occurs on a vascular basis when either the arterial inflow rate and pressure are too low to generate or maintain erections or when the venous sinusoidal occlusion (resistance) mechanism cannot close completely. A multitude of combinations of arterial inflow rates and pressures and venous sinusoidal occlusion resistances are capable of generating and maintaining erections. Failure of one element of the system may be compensated for by other elements.

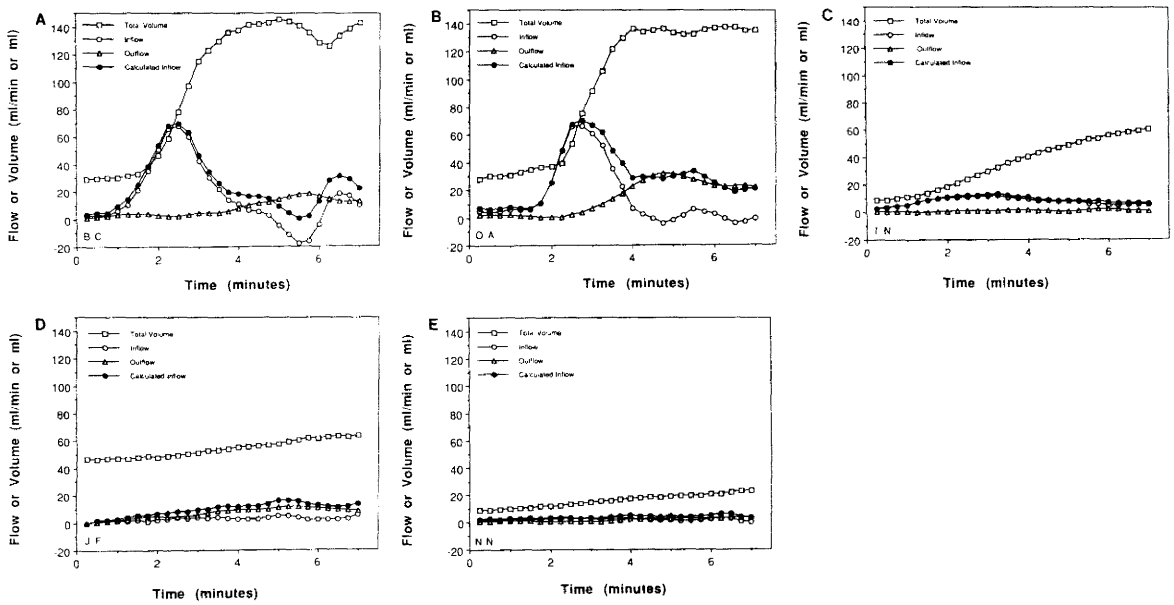

FIGURE 3
Graphs of intracorporal inflow, outflow, and volume. (A) Patient (BC) with normal arteries and veins. (B) Patient (OA) with normal arteries and venous leak. (C) Patient (TN) with intermediate arteries and competent veins. (D) Patient (JF) with a fibrosed corpora cavernosum, abnormal arteries, and veins. (E) Patient (NN) whose arteries are so severely diseased that venous outflow cannot be assessed.

TABLE 3
Categorization of Patients

	AngSc	PCIF (ml/min) 1	PCIF (ml/min) 2	dCV (ml) 3
Normal	≥3	14.7 ± 4.4	≥2.0	87 ± 13.1
Probably normal	≥3	14.7 ± 4.4	≥12 and <20	31.7 ± 9.5
Indeterminate	>1 and <3	9.0 ± 2.9	≥7 and <12	11.6 ± 6.0
Abnormal	≤1	4.8 ± 1.5	<7	5.7 ± 3.1

However, if the requirements of the failing element exceed the capabilities of the compensating elements, dysfunction will occur.

By measuring volumetric changes, radioisotope penile plethysmography noninvasively assesses corpora cavernosal blood inflow during early erections. RPP is not capable of measuring or correcting for corporal outflow and it assumes minimal outflow during peak corporal inflow.

By combining the RPP and xenon washout techniques, corporal inflow and outflow could be assessed. This technique was initially suggested and implemented by both Schwartz et al. (*14*) and Miraldi et al. (*15*). Although the methods described by both authors differ in their design, they both demonstrate the feasibility of combining technetium and xenon isotopes in order to assess corporal inflow and outflow.

Peak corporal inflow rates, uncorrected (PCIF; r = 0.91) and corrected for outflow (PCIF*; r = 0.88), correlated well with angiographic evaluation of the arteries (AngSc). No improvement in correlation was demonstrated when inflow was corrected for outflow during peak arterial inflow. In most patients, PCOF occurred well after PCIF (mean 2.25 min) (Fig. 3A-C). This supports our original hypothesis that for RPP to be accurate "the loss of radioactivity through venosinusoidal outflow during the early phase of tumescence is negligible and the transit of blood through the penis is prolonged such that no significant radioactive blood reaches the venous outflow during this early tumescent phase" (*6*).

However, in one patient with a fibrotic and scarred corpora (most likely the scarring was caused by chronic papaverine injections), outflow increased simultaneously with inflow (Fig. 3D). One explanation is that in patients with abnormal sinusoidal smooth muscles, scarred corporal sinusoids, or inelastic tunica albuginea, the corpora is incapable of the normal expansion during the initiation phase of erections. As a result, the corporal transit time is dramatically reduced and blood that flows into the corpora flows out almost simultaneously.

Outflow is a function of the compliance of the corpora, the resistance to outflow of the venous sinusoidal occlusion mechanism, and the rate at which blood flows into the corpora cavernosa. The outflow parameters COF* and PCOF correlated poorly with both intracorporal resistance (RV) and arterial inflow integrity (AngSc). Prior publications, however, have suggested that xenon washout rates can reliably predict both arterial integrity (*9*) and the severity of the venous-sinusoidal leak (*10,11*). The claim that xenon washout can measure both corporal arterial inflow and corporal venous outflow is confusing. This can, in part, be explained when it is recognized that during erection the rate at which xenon washes out of the penis is a function of both cavernosal artery inflow and venous-sinusoidal closure (e.g., slow washout may reflect slow input).

Xenon washout can measure the outflow of blood from the corpora, but we believe that the xenon washout test alone is insufficient for accurately determining either cavernosal artery integrity or venous-sinusoidal competence. Xenon washout is a multi-variable function dependent on more than one vascular process. This means that in order to understand the significance of outflow (at any given point in time), inflow (biologic inflow or mechanical inflow during cavernosometry) and/or intracorporal pressure must be known. In part, this is because outflow resistance changes throughout tumescence.

The ability to close the outflow channels is dependent upon arterial inflow. Patients with abnormally low cavernosal artery inflow rates and pressures may be incapable of engaging the venous-sinusoidal occlusion mechanism (Fig. 3E). This means that RPP/Xe may be incapable of distinguishing between the abnormal and the intact venous-sinusoidal occlusion mechanism if the arterial inflow rate is too low. The outflow occlusion mechanism is most accurately evaluated when the corpora is maximally distended and the corporal sinusoids are fully relaxed, a condition which may not be achieved in many patients with abnormal arterial inflow or large venous sinusoidal leaks without intracorporal infusion of saline. If, however, it is determined that the arterial inflow is normal, then the combined RPP/Xe, method may be useful in evaluating venous sinusoidal competence. The relationship of the pattern of outflow compared to inflow was useful in predicting competence of the venous sinusoidal mechanism in six patients (Fig. 3). Too few patients have been analyzed to draw a reliable conclusion regarding the usefulness of this technique. In addition, it must be recognized that in some patients psychologic inhibition can result in overestimation of venous leak. This is because despite infusion of vasoactive medications psychologic inhibition may override the venous sinusoidal occlusion mechanism (*16*).

Although the absolute rates of outflow did not predict venous sinusoidal leak or arterial integrity, we did find that the ratio of outflow-to-inflow (COF*/PCIF) in patients with decreased PCIF was greater than that found in patients with normal PCIF values. This is significant because patients with very low inflow rates (< 7 ml/min) may have their arterial inflow underesti-

mated. Although our study has too few patients to draw any statistical conclusion, it is our impression that in patients with significant arterial impairment, RPP underestimates arterial function to a greater degree than it does in patients with more normal function. In general, RPP appears to be sufficient for dividing patients into normal and abnormal categories, but it may have an indeterminate category that is better evaluated by the simultaneous RPP/Xe technique.

In an attempt to define a more accurate measurement of effective inflow, we examined the change in volume from 1 min before to 1 min after peak inflow (dCV). dCV provides a measure not only of maximal inflow, but also of the ability to sustain maximal inflow rates. We found this to be the most accurate predictor of arterial inflow integrity ($r = 0.96$). This is important because the capacity to initiate and generate an erection is dependent upon not only the ability to attain a brief elevation of peak corporal inflow but also the ability to maintain these rates during the early phases of erection.

One of the factors that limits the use and the accuracy of nuclear medicine derived peak inflow rates (PCIF, PCIF*) as a predictor of cavernosal artery integrity is congenital and acquired variations in the configuration of the penile arterial inflow network. A unilateral but otherwise normal penile arterial network may be capable of producing normal erections. However, because the unilateral network has only one inflow channel, the maximal rate of inflow will be considerably lower than if two normal arteries were present. This may result in intermediate flow rates in a patient with adequate arterial inflow. The intracorporal pressure and resistance will not increase as rapidly as in normals. As a result, corporal inflow rates may remain elevated for a more prolonged interval than those in patients with bilaterally normal penile arterial networks. The shape of the inflow curve may prove to be a useful parameter in predicting arterial integrity in patients with arterial anomalies. In addition, the measurement of an internal pudendal artery ROI may provide insight into unilateral versus bilateral arterial integrity. Curve shape, multivariable analysis, and internal pudendal artery ROI all require further investigation to determine if anatomic variations can be accurately predicted.

Table 3 categorizes flow rates for patients with varying degrees of arterial disease. In our previous RPP paper (*6*), we divided peak corporal flow rates into three categories (Column 1). Upon further review, we hypothesize that patients might be better categorized into four groups (Column 2), because patients without significant arterial lesions (minimal disease, AngSc 3 or no arterial disease, AngSc 4) may exhibit a significant range of corporal inflow rates. It is likely that the spectrum of inflow rates in patients with normal penile arterial networks represents varying degrees of psychologic excitation and stimulation.

Although psychologic influences are probably less significant during initiation and early generation than they are during late generation and maintenance, these factors strongly influence corporal inflow rates throughout all aspects of the erectile cycle (*3*). Psychologic factors serve as a source of variability and error in RPP and RPP/Xe studies, as well as all other methods for evaluating erectile function that rely upon chemically-induced erections.

CONCLUSIONS

Technetium-99m radioisotope penile plethysmography and xenon washout (^{133}Xe and ^{127}Xe) can be performed together and provide a method for simultaneously evaluating the relationship between corporal inflow and outflow rates. An excellent correlation was found between RPP and RPP/Xe inflow rates and arterial integrity as determined by angiography.

The disadvantage of these radioisotope procedures is their inability to provide anatomic information and correct for anatomic variations. RPP and RPP/Xe are subject to errors related to psychologic inhibition as are all erectile function tests which rely upon chemically-induced erections.

Although it is possible that some day RPP and RPP/Xe may be used as screening tests, at present we utilize these tests to: (a) follow patients who undergo surgical or interventional procedures and (b) to assess patients who have indeterminate angiographic, ultrasound, or systolic occlusion pressure measurements. Further investigation is suggested in order to determine whether either RPP or RPP/Xe can be utilized for routine screening purposes.

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ADDENDUM

In the article "Radioisotope Penile Plethysmography: A Technique for Evaluating Corpora Cavernosal Blood Flow during Early Tumescence" (*4*), the change in volume within the corpora cavernosa is incorrectly listed as between 16 and 18 ml. The correct change in volume should have been between 16 and 65 ml.

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