A Nonimaging Scintillation Probe to Measure Penile Hemodynamics

Lionel S. Zuckier, Gopal R. Korupolu, Mark Gladshteyn, Ronald Sattenberg, Richard Goldstein, Richard Ricciardi, Paul Goodwin, Arnold Melman and M. Donald Blaufox

Departments of Nuclear Medicine and Urology, Albert Einstein College of Medicine, Bronx, New York

We have developed a penile nonimaging scintillation (PNIS) probe consisting of a plastic well-type scintillation crystal interfaced to a portable computer and acquisition board. This report describes the design of the PNIS probe, performance characteristics, mode of usage and illustrative results which demonstrate its capabilities. **Methods:** With the PNIS probe, penile blood-pool studies were performed in nine patients utilizing 3.7 MBq (100 μCi) autologous ^{99m}Tc-labeled red blood cells (RBCs). Venous blood standards were assayed to enable conversion of the count rate to volummetric measurements. Washin of peripherally administered ^{99m}Tc-RBCs was mathematically analyzed to estimate penile blood volume and cavernosal flow rate in the flaccid state. The rate of change of penile blood volume after intracavernosal vasodilators was used to generate measures of stimulated flow. **Results:** A major advantage of this device over the gamma-camera is a 3300-fold increase in count rate sensitivity, which allows for markedly improved temporal resolution while significantly reducing the radiopharmaceutical dosage. Additionally, the PNIS probe is portable, economical and is not dependent on operator-defined regions of interest. Count rate sensitivity is relatively constant within the bore, with the exception of the proximal region adjacent to the opening, where geometric efficiency is reduced. **Conclusion:** The PNIS probe is an effective device for measuring penile activity in radionuclide studies, allowing for acquisition of time-activity curves of the penis during flaccid washin of peripherally labeled red blood cells and after pharmacologic stimulation to induce erection.

Key Words: erectile dysfunction; scintillation probe; technetium-99m-red-blood cells; penile hemodynamics

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The development of potent intracavernosal pharmacologic methods to induce erection (*1,2*), in conjunction with innovative therapeutic options for treating erectile dysfunction (*3–5*) has led to renewed and heightened interest in methods of quantitating erectile function (*6*). Radionuclide methods of measuring penile blood flow (*7–10*) were initiated in the early 1970s when Shirai and coworkers utilized labeled blood-pool techniques to evaluate changes in penile blood volume as measured by nonimaging scintillation probes (*11–14*). Shirai et al. (*15*) and Wagner et al. (*16*) also used probe systems to measure intracavernosal xenon washout in the flaccid and stimulated penis, thereby estimating cavernosal blood flow at rest and poststimulation. A limitation of the simple probe systems was that they could not be directed to exclusively sample activity from the penis and not the adjacent structures. Shielding of neighboring and underlying regions was often attempted, but in itself was technically difficult.

Subsequent blood-pool (*17–24*) and xenon washout (*25–29*) investigators universally replaced simple nonimaging probes with the gamma camera to measure penile radioactivity. Spatial data inherent in gamma camera images have only been of value in defining penile regions of interest (ROIs) and have not yielded diagnostic information in their own right (*30*). In fact, quantitative gamma camera studies have shown that the main corporal body and base of the penis after pharmacologic stimulation demonstrate indistinguishable blood-pool, time-activity curves (TACs) (*18,19*) while the glans penis, an extension of the corpus spongiosum, exhibits minimal blood-pool activity when either flaccid or erect (*19*). A major drawback of gamma camera methods is the substantial reduction in counts effected by the associated collimation, which markedly attenuates photon flux, thereby necessitating larger does of radionuclides and longer framing rates to achieve statistical validity. Fifteen second (*19,22*) or greater (*17,18,20,23,24*) framing rates have typically been used in gamma camera studies of the penile blood pool.

We set out to design a penile nonimaging scintillation (PNIS) probe that would provide a cost-effective alternative to the gamma camera for hemodynamic measurements of the penis in the investigation of erectile dysfunction (*30*). This portable device would be easily transportable to the Sexual Dysfunction Clinic within the Department of Urology for integration into preexisting diagnostic protocols. In contrast to the early probe systems, the PNIS probe surrounds the organ, largely excluding counts from external structures. In comparison with gamma camera methods, it does not require collimation; therefore, count rate sensitivity is superior and permits the use of fractional quantities of radionuclides while maintaining elevated count rates and

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For correspondence or reprints contact: Lionel S. Zuckier, MD, Department of Nuclear Medicine, 1300 Morris Park Ave., Bronx, NY 10461.

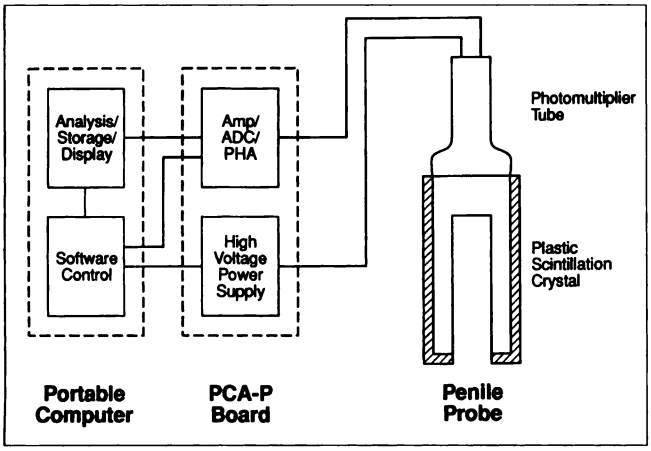

FIGURE 1. Schematic view of the PNIS probe and electronics.

statistically reliable data. A venous blood sample can be easily counted within the well of the crystal to convert penile count rate TACs to volummetric curves (*14,19*).

Although the goal of this report is to describe the PNIS probe and its use, we also briefly discuss a quantitative method of analyzing flaccid penile blood flow.

MATERIALS AND METHODS

Instrumentation

The PNIS probe system consists of a custom-designed well-type scintillation crystal and photomultiplier (PM) tube attached to a commercially available portable computer-based spectroscopy board and high-voltage source (Tennelec/Nucleus PCA-P, Oxford Instruments Inc., Oak Ridge, TN) (Figs. 1,2). The crystal is composed of a BC-400 plastic scintillator (*31,32*) (Bicron Corp., Newbury, OH), which is relatively inexpensive, rugged and easy to fabricate. External dimensions of the hollowed-out cylinder are 8.3 cm (3.25″) in diameter and 21 cm (8.25″) in length, with the central bore measuring 5.1 cm (2″) in diameter and 18 cm (7″) in depth and designed according to limited published data regarding erect penile size (*33,34*). The crystal and PM tube are enclosed in a protective steel casing which encircles the periphery of the assembly and is folded down to overlap the front rim of the detector. Another 2.5 mm of lead shields the lateral walls and anterior lip of the crystal.

FIGURE 2. Photograph of the complete PNIS probe system. The outer dimensions of the crystal measure 8.3 cm in diameter by 21 cm in length. The software setup menu is visible on the computer's CRT screen.

Signal and high-voltage cables connect the PNIS probe to the spectroscopy high-voltage and data acquisition board housed in a portable computer (T3200, Toshiba America Information Systems, Inc., Irvine, CA). Through software-selectable switches, the PM tube is operated at 1200 volts DC with gain optimized for detection of the ^{99m}Tc signal pulses. Vendor-supplied software was customized to allow acquisition of time-activity curves with user-definable framing rates of 1 sec or greater. During dynamic studies, the data matrix generated by the crystal was written to the hard-disk from where it was subsequently imported for analysis and display into a standard spreadsheet program (Quattro Pro, Borland International, Inc., Scotts Valley, CA). Prior to use in patients, the basic performance characteristics of the PNIS probe were determined, including count rate linearity, sensitivity, geometric efficiency and adequacy of external shielding.

Clinical Studies

The research protocol for clinical studies was approved by both the Montefiore Medical Center Institutional Review Board and Human Use Radioisotope Committee. Informed consent was obtained from all participants.

Acquisitions were performed at 1- to 2-sec/frame temporal resolution. The patients were comfortably seated in a private room with their legs slightly abducted. A disposable plastic liner was inserted into the bore of the crystal into which the penis was placed. The distal portion of the PNIS probe was supported on a slightly elevated stool while the patient firmly held the proximal end of the crystal against his body. Approximately 10 ml blood were aseptically drawn prior to the study and labeled with 3.7 MBq (0.1 mCi) ^{99m}Tc by an in vitro technique. Labeled blood was thereafter reinjected into an antecubital vein followed by a flaccid washin acquisition lasting approximately 20 min. The probe was then removed and 30 mg papaverine, in a 1-ml volume, were injected into one of the corpora cavernosa to induce erection. The crystal was quickly repositioned and another 20–30 min of data collection was performed to characterize the erectile response. At the conclusion of the study, approximately 5 ml of peripheral venous blood were withdrawn from the opposite arm into an evacuated preweighed phlebotomy tube. The blood was counted within the bore of the probe and subsequently reweighed on an analytic balance to determine the sample volume. With this aliquot as a reference standard, penile count-rate data were converted to absolute blood volumes after subtraction of background and correction for isotopic decay.

Data Analysis

We applied a new mathematical approach for analysis of the washin curves of the flaccid penis based on assumptions that washin of activity into the blood pool of the flaccid penis is considerably slower than the rapid dilution of labeled RBCs within the body and that the concentration of activity within peripheral blood remains constant throughout the study. Experimental data were fit to the differential equation appropriate for this model of washin, $B(t) = V \times (1 - e^{-t \times F/V}) + Bk$ (see Appendix for derivation), using an algorithm for least squares minimization in which B(t) represents the amount of labeled blood within the corpora cavernosa. The initial half-minute of data were excluded from curve fitting to avoid potential errors due to variation in background during the initial distribution of activity throughout

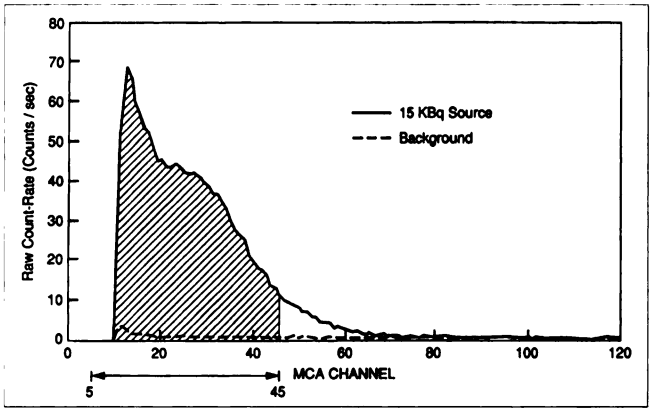

FIGURE 3. Spectra for background and 15-KBq ^{99m}Tc source. As with other plastic scintillators, BC-400 has poor energy resolution, resulting in a broad photopeak. The energy window used for ^{99m}Tc is indicated.

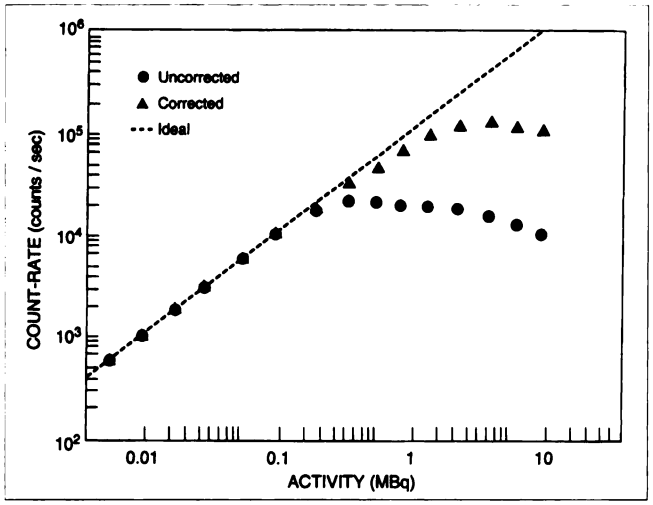

FIGURE 4. Background-corrected count rate as a function of activity. Both deadtime corrected and uncorrected count rates are illustrated. An ideal curve, extrapolated from the lower count rate points, is plotted for reference purposes.

the body. Fitting of the flaccid washin curves to the above equation generated values for total cavernosal blood volume (V), flaccid blood flow (F) and extraneous background activity (Bk), the latter expressed as an equivalent volume of labeled blood.

For analysis of the post-papaverine TAC, the time of peak flow was identified based on a derivative of the smoothed blood-volume curve. Average flow over the subsequent 1-min period was determined by dividing the change in volume during this interval over the elapsed time. This measurement is similar to the method of Schwartz et al. who initially theorized (*19*) and subsequently demonstrated (*35*) that venous outflow during the period of early and rapid filling is negligible and therefore correction of inflow rates to account for egress of blood from the penis during this early period is not needed.

RESULTS

Energy Spectrum

At a PM tube voltage of 1200 volts and optimal amplifier gain, ^{99m}Tc and background spectra were obtained (Fig. 3). An energy window within the ^{99m}Tc photopeak was selected for use in all subsequent measurements.

Count Rate Linearity and Sensitivity

The range of count rate linearity was determined by decaying a 9.2-MBq (250 μCi) source of ^{99m}Tc within the crystal bore over 3 days, during which time, multiple sequential acquisitions were performed both with and without intrinsic deadtime correction (Fig. 4). Using correction, the count rate response remained essentially linear up to an activity of approximately 0.74 MBq (20 μCi), which corresponds to a count rate of approximately 70,000 cps. Subsequent studies were performed using deadtime correction within the linear count range.

Count rate sensitivity of the probe was compared to that of the gamma camera. Technetium-99m (1.5 MBq, 41 μCi) was placed in a fluid-filled 50-ml conical test-tube and images of this source were acquired on a portable gamma camera with a low-energy, all-purpose collimator interfaced to a nuclear medicine computer. Counts in the computer-derived ROI were compared to the count rate obtained using the PNIS probe and a 100-fold diluted source. Sensitivity of the gamma camera was 25 cps/MBq, while that of the probe was 8.4×10^4 cps/MBq or approximately 3300-fold greater than that of the gamma camera.

Geometric Efficiency

Count rate response was also determined as a function of position both within and external to the crystal. An 18-KBq (0.48 μCi) source was mechanically translated along three axial rays (center, midradius and periphery) within the cavity of the PNIS probe at a rate of approximately 1.7 cm/min using a mechanical high-capacity infusion pump apparatus to generate linear motion. Simultaneously, multiple sequential 15-sec acquisitions were obtained to map regional count rate sensitivity (Fig. 5). Sensitivity was slightly higher at the periphery of the cavity compared to the center and midradius and diminished towards the front opening as geometric efficiency decreased.

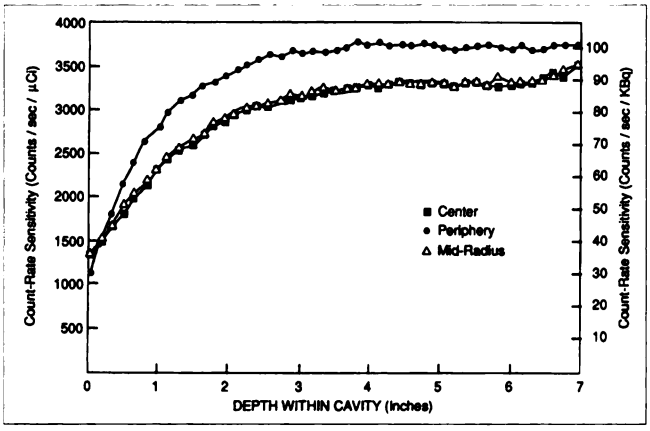

FIGURE 5. Count rate response to an 18-KBq source, as a function of position within the crystal's cavity, along three-designated axial rays. Both SI (right axis) and per microcurie (left axis) scales are provided.

TABLE 1
Relative Count Rate Sensitivities

Axial position	Central axis	19 cm lateral to center	38 cm lateral to center
Midbore	100%	0.02%	0.01%
2.5 cm anterior to crystal	26.6%	0.02%	0.003%
15 cm anterior to crystal	1.6%	0.25%	0.04%
30 cm anterior to crystal	0.48%	0.23%	0.06%

Count rate sensitivity outside of the crystal was compared to sensitivity within the bore by positioning a point source of 0.33 MBq (8.8 μCi) ^{99m}Tc at multiple external locations (Table 1). With the exception of positions directly opposite the bore (central axis), sensitivity was less than 0.25% of the midbore.

Clinical Studies

Feasibility of the PNIS probe was demonstrated in a pilot group of nine patients, and the procedure was well tolerated without any adverse occurrences. One patient (a 38-yr-old man unable to maintain an erection) with both washin and postpapaverine TACs demonstrates the utility of the PNIS probe and highlights its features. After administration of papaverine i.c., previously performed Doppler ultrasonography demonstrated pathologically decreased flow in the left cavernosal artery and borderline flow on the right side; the resultant erection was graded as 3 on a scale of 1 to 5 (1 flaccid; 5 normal erection). Thickening of the arterial walls was noted bilaterally, suggestive of arteriogenic erectile dysfunction.

Initial inspection of the flaccid TAC demonstrates washin over the course of approximately 20 min to a volume of approximately 15 ml (Fig. 6). Based on the fit of the experimental data to the theoretical model, the flaccid penile blood volume was estimated to be 12.9 ml, the flaccid blood flow was 2.9 ml/min and a constant background component was determined to be 2.8 ml.

After injection of 1 mg papaverine i.c., penile blood volume increased to approximately 24 ml over the course of an additional 25 min. The slow increase in blood volume is consistent with described patterns of arterial insufficiency (*20*). Flow peaked immediately following papaverine administration. Average flow during the first minute following papaverine administration was calculated by measuring the change in volume over this interval, yielding a rate of 3.5 ml/min. In comparison to values generated using the gamma camera (*19,35*), these findings are suggestive of arterial disease and demonstrate impaired filling of the corpora cavernosa after pharmacologic stimulation, with only a slight increase in the flow rate compared to baseline.

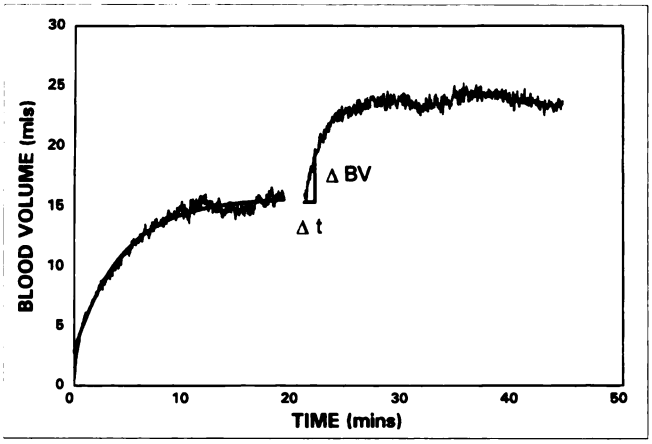

FIGURE 6. Flaccid washin and postpapaverine data from a 38-yr-old man.

DISCUSSION

Utility

As greater understanding of the pathophysiology of erectile dysfunction evolves (*36–38*) and innovative treatments are developed (*4,5*), increasing interest has been focused on improving diagnostic methods of quantitating erectile function (*39–41*). A recent National Institutes of Health consensus panel concluded that "the development of methods to quantify the degree of erectile dysfunction objectively would be extremely useful in the assessment both of the problem and of treatment outcomes" (*6*). The present study demonstrates the feasibility and advantages of using a nonimaging probe to measure penile hemodynamics. Some of the advantages include low equipment cost, portability, increased count rate sensitivity, improved temporal resolution and the lack of operator-defined ROIs.

The PNIS probe was successfully used in nine patients who were administered 3.7 MBq (100 μCi) ^{99m}Tc-RBCs, which is less than 1% of the clinical dose used in conventional blood-pool studies. In addition, the improved temporal resolution of the PNIS probe relative to the gamma camera may permit observation of previously unresolvable phenomena. In an initial trial which preceded the current series of patients, two subjects were studied with a prototype configuration of the probe consisting of the present crystal interfaced to a dedicated multichannel analyzer. In one subject, cyclic oscillations of approximately 1 min frequency superimposed upon a gradually rising baseline were observed following i.c. injection of 1 mg papaverine (Fig. 7). This finding clearly emphasizes the PNIS probe's ability to resolve periodic events occurring at frequencies that would not be easily identifiable with gamma camera methods. The present phenomenon may represent a continuum with coarser fluctuations in penile TACs, occurring from 10 to 20 min, that have been observed in gamma camera studies and are postulated to represent a normal rhythmic flow pattern consistent with episodic penile vascular and trabecular smooth muscle relaxation (*23,24*).

Design

For construction of the PNIS probe, we used a plastic scintillation crystal rather than one made of sodium iodide, which is a higher resolution scintillation material commonly used in nuclear medicine. This decision was based on du-

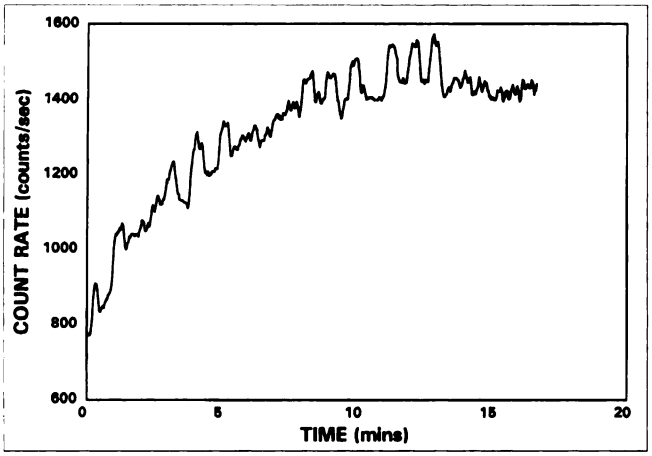

FIGURE 7. Five-point smoothed count rate curve from a patient studied using a prototype configuration of the PNIS probe composed of summed 2-sec data points.

rability, cost and ease of fabrication of the plastic scintillator, even though poor energy resolution of this material would preclude performance of simultaneous dual-isotope studies (*35,42–44*). It would be possible to independently perform ^{133}Xe (*26–29*) or ^{99m}Tc-RBC washout (*45*) studies with this instrument. A NaI crystal for dual-isotope studies with similar geometry could be built but at increased cost and the risk of potential mechanical and thermal damage. For counting electronics, we paired the plastic scintillation crystal with an acquisition board housed in a portable computer, which represents a low cost and highly versatile acquisition platform for nuclear medicine applications (*46*). We chose to perform the studies in a sitting position rather than supine, as this is in accord with the observation that a semi-erect posture is superior for producing reliable pharmacologically induced erection (*43*).

Limitations

Two potentially significant limitations of the probe relate to inclusion of extraneous extrapenile counts and incomplete measurement of corporal cavernosal counts. The former concern is reasonable because of the large blood pool within the patient's body which is external to the probe. To minimize this problem, the outer surfaces of the crystal were shielded with 2.5 mm of lead. An estimate of the level of extracavernosal background, as derived from fitting the washin curves to their theoretical model, was relatively minimal. Furthermore, with the theoretical exception of excretion into the urinary tract, the distribution of activity external to the probe remains relatively constant during the course of the study, once the initial bolus of activity has passed through the body, and would therefore not spuriously lead to perceived changes in penile blood volume counts. To limit the effect of urinary activity, a combination of shielding, optimal in vitro RBC labeling and caudal tilting of the crystal effectively minimized contribution from the urinary bladder which, based on our experience in positioning the device, did not noticeably affect the measured penile activity.

The problem of incomplete measurement of corpora cavernosal counts is due to two factors: a drop in count rate sensitivity within the crystal cavity as one approaches the opening of the bore (Fig. 5) and extension of the cavernosal bodies outside the probe cavity to their point of attachment on the pubic arches (*33*). Sensitivity of the crystal to a ^{99m}Tc source located 2.5 cm opposite its opening is 26% (Table 1), which corresponds to the approximate location of activity within the crura of the corpora cavernosa. The net effect of undersampling the more proximal portions of the corpora cavernosa during washin measurements, such as those we performed, would be to underestimate flaccid penile blood volume and blood flow. Measurement of the change in blood volume after papaverine is affected less by undersampling of the proximal penis because, during attainment of erection, much of the increase in blood volume of the penis occurs through longitudinal growth within the distal portion of the bore where a more linear count-rate sensitivity prevails. More judicious positioning of the venous standard to mimic the average position of the penis might be helpful in improving the quantitative accuracy of the flaccid studies. Alternatively, correction factors could be developed for each patient based on the known response of the instrument and the length of the penis before and after vasodilator administration.

Although the problem of underestimation of proximal counts is intrinsic to the design of the PNIS probe and cannot be completely circumvented, gamma camera methods of measuring cavernosal activity also do not completely sample the most proximal cavernosal activity because of attenuation (*19*) and obscuration by the bladder and soft-tissue structures. The effect of auto-attenuation is greater in a camera system than with the probe because of 180° versus 360° sampling. There is also the potential of overestimating penile counts when using a gamma camera due to inclusion of count-contributing soft tissues, including the testes and especially the bladder (*19*), stemming from overlap of neighboring structures and ambiguity in defining penile and background ROIs.

Siraj has raised the issue of hemodilution of the penile blood pool after intracorporal injection of a vasodilator (*47*). In our study, we injected only 1 ml papaverine in contrast to the 7 ml of medication and flush used in his investigation. Assuming the worst-case scenario in our patients, that the complete volume of vasodilator remains within the corpora cavernosa, thereby displacing radiolabeled blood, the postpapaverine blood volume would only be underestimated by 1 ml.

The calculated values for flaccid blood flow and blood volume in the patient we described are in general agreement with normal values in the literature, as determined by other radionuclide techniques. The patient's flaccid penile blood volume and resting blood flow were estimated at 12.9 ml and 2.9 ml/min, respectively. Based on analysis of Shirai's blood volume data (*14*), Wagner calculated an average flaccid blood volume of approximately 8 ml in normal subjects (*34*). In their gamma camera study, Schwartz et al.

(*19*) described initial flaccid volumes averaging 30 ml, with a range of 11–76 ml. Our value of 12.9 ml, which is based on positioning of the standard and may slightly underestimate the actual value, is in good agreement with these figures.

The rate of flaccid flow in the corpora cavernosa of the flaccid penis has also been previously determined by xenon washout studies, in which flow is expressed per 100 cc of tissue volume. Assuming a flaccid penile volume of 53 cc (*34*) and a partition coefficient of 0.7, the most common estimates of flaccid flow are in the 1.3 to 4.8 ml/min range (*16,28,34,48,49*), although some estimates have been under 1 ml/min (*15,27*). The flaccid blood flow of 2.9 ml/min, as estimated in our patient, is in good agreement with normal values as determined by the majority of investigators.

CONCLUSION

The PNIS probe has potential for both clinical and research applications, but the validation needed for these uses varies. The feasibility of the probe as a diagnostic tool rests on its ability to discriminate between differing etiologies of erectile dysfunction, including arterial, venous, neurologic and stress-related causes (*7,8*). A systematic under or overestimation of volume would not be prohibitive as long as it does not interfere with differentiation of various disease categories. Additional studies in well-defined patient groups are therefore planned to evaluate the hemodynamic curves generated by this instrument and to validate various indices of function, as described in previous gamma camera studies (*7,8*).

In human and animal investigations, the high temporal resolution and absolute quantitative nature of the PNIS probe also may prove useful in contributing to a quantitative understanding of the physiology of erection and the pathophysiology of dysfunction. High frequency phenomena, not readily resolved by gamma camera methods, can be observed with the superior framing rate of this device. From a count rate linearity and radiation safety standpoint, there is still considerable room to increase the dose of labeled RBCs to further improve the statistical reliability of the data. Quantitative analysis of the wash-in data, as demonstrated in this study, can be a powerful technique of extracting physiologic information from the TACs. Flaccid blood flow patterns have attracted attention (*9,23*), although they have not been investigated by mathematical fitting. One must caution that the use of the PNIS probe as a quantitative tool to measure absolute blood volume and flow rate is a rigorous demand that will require further validation in view of the count rate sensitivity considerations previously discussed.

APPENDIX

Analysis of Flaccid Washin

After acquisition of the TACs, an aliquot of venous blood is obtained from the arm and counted within the probe to establish a relationship between count rate and labeled blood volume. This factor is then used to convert the penile TAC to a labeled blood volume curve [B(t)] that reflects the volume of labeled blood being counted within the bore of the probe. At the steady-state of flaccid equilibrium, the rate of blood flow into and out of the corpora cavernosa is equal and constant (F), and the total blood volume of the corpora cavernosa also is constant (V). At any time, the fraction of the cavernosal blood pool which is labeled B(t)/V and represents the labeled blood present within the corpora cavernosa divided by its total volume. The change in volume of intracavernosal labeled blood at any time (dB(t)/dt) is equal to labeled blood entering the corpora (F) less the labeled blood leaving, the latter term being equal to flow out of the corpus cavernosa (F) multiplied by the fraction of labeled blood in this space (B(t)/V). Expressing this in mathematical terms,

$$dB(t)/dt = F - F \times B(t)/V.$$

This can be rearranged in the form of

$$dB(t)/(1 - B(t)/V) = F \times dt$$

and integrated to yield

$$-V \times \ln(1 - B(t)/V) = F \times t + K.$$

Solving for B(t) we find

$$B(t) = V \times (1 + K' \times e^{-t \times F/V}).$$

At $t = 0$, we know that the volume of labeled blood within the penis is zero, therefore $K' = -1$. Rewriting the equation yields

$$B(t) = V \times (1 - e^{-t \times F/V}).$$

The experimental washin curve consists of the above component in addition to a constant term representing noncavernosal background activity (Bk), expressed as an equivalent volume of labeled blood. The patient data can be fit to these terms to yield estimates of flaccid blood flow (F), equilibrium cavernosal blood volume (V) and Bk.

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