Penile Blood Flow by Xenon-133 Washout

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Penile erectile failure is often attributed to abnormalities of vascular supply or drainage, but few direct measurements of penile blood flow have been made. We describe the xenon washout method for measurement of penile blood flow, and present the results obtained in a group of normal and impotent subjects. The procedure was performed with standard nuclear imaging equipment. Flaccid-state penile blood flow in the impotent patients studied was not significantly different from the normal group, suggesting that flaccid-state measurements may not be helpful in evaluation of erectile failure. However, this method can be used to measure penile venous outflow with stimulated or induced erection, and may provide a method for detecting abnormal venous leakage.

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The xenon washout method has been used to measure blood flow in a number of organs and locations, since its original description by Conn in 1955 (*1*). This method provides an absolute value for blood flow in ml/min/100 g of tissue. Lassen et al. described their procedure for measuring human skeletal muscle blood flow using the xenon-133 (^{133}Xe) washout method, and reported their results in 1964 (*2*). Several investigators have used this method for measurement of penile blood flow (*3–6*), but results have not been consistent, there is no established normal range, and a full description of the procedure has not been published. We used penile xenon washout to measure penile blood flow in a group of normal and abnormal subjects. This report describes the method, and presents the results of flaccid-state measurements in these subjects.

METHODS

Patient Selection

Volunteer subjects were obtained from three groups: (a) normal potent subjects, (b) impotent subjects over age 60 yr enrolled in a separate impotence evaluation program, and (c) spinal cord injury patients with neurogenic impotence. Informed consent was obtained from each subject.

Xenon Source

There is, at present, no readily available commercial source for ^{133}Xe dissolved in saline that can be used for parenteral injection in humans. We obtained ampules of ^{133}Xe gas (General Electric Company, Vallecitos Nuclear Center, Pleasanton, CA) and used these to produce xenon-in-saline as described by Carroll et al. (*7*). This technique provided a satisfactory and economical source of ^{133}Xe. An IND from the U.S. Food and Drug Administration was obtained for human use of ^{133}Xe prepared in this way.

Dose Preparation

Xenon-133 dissolved in saline was obtained from the ^{133}Xe source under sterile conditions. Using a saline-rinsed 1-cc syringe, a volume of 0.1 ml to 0.2 ml was obtained, containing 0.5 mCi to 1.2 mCi (18.5 MBq to 44.5 MBq). A 25- or 26-gauge needle was attached, and any bubbles were ejected before the activity was measured.

When ^{133}Xe in saline is contained in a syringe, there is adsorption to the syringe, and a small amount of gas leakage occurs. Plastic and glass syringes have about the same degree of adsorption for xenon in saline (*8*). The dose is best prepared immediately before injection, and the syringe activity must be measured immediately before and immediately after injection to accurately measure the administered dose. With 0.15-ml doses prepared in plastic syringes immediately before injection, and injected without flushing, we found that ~⅔ of the activity contained in the syringe was injected.

Patient Preparation and Injection

Each patient was asked to empty his bladder, and then to lie supine in a comfortable position. The skin of the penis was prepped, and the tracer dose was injected into one corpus cavernosum at about mid-shaft. Injections for this study were made by a urologist (PGK) experienced in intracorporeal injections. Care was taken to see that no bubbles were injected. No anesthesia was used, since the 25- or 26-gauge needle caused minimal discomfort. The injection site was gently compressed, to minimize tracer leakage through the needle tract. A padded lead shield was suspended vertically over the pubis. We attached this to an adjustable table placed over the patient's pelvis. Another lead shield was placed over the

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scrotum. The penis was then attached to the vertical lead shield with tape or other restraint, so that the dorsum of the penis was in contact with the padded lead shield. The ventral side of the penis was exposed to the detector, that was positioned approximately over the patient's knees.

Room Temperature

The effect of ambient temperature on penile xenon washout has not been reported, although skin blood flow is known to be markedly reduced (*9*) when ambient temperature is changed from 25°C (77°F) to 20°C (68°F). We concluded that the room temperature should be comfortably warm. Our studies were obtained at an ambient temperature of 22–24°C (71.6–75.2°F), and all subjects reported that they were comfortable with the environmental temperature at the time of the study.

Data Recording

We used a gamma camera (GE 400 A/T, GE, Milwaukee, WI) with a low-energy parallel-hole collimator as the radiation detector for these studies. The detector was positioned anterior and caudad from the injection site, at a distance of 30 cm. This placed the detector approximately over the subject's knees, and allowed adequate room for subsequent observation, manipulation, or adjustments. The multi-channel analyzer of the gamma camera was used to set the discriminator levels to accept the primary photopeak of ^{133}Xe. For our instrument, this was the energy range of 70 to 100 keV. This resulted in an initial count rate of ~60,000 cpm after an injected dose of 1 mCi. The counting data were acquired on computer disk (DEC PDP 11/34) in frame mode at 10–15-sec intervals. A region of interest was defined to include the injection site, and a time-activity curve was obtained.

Data Analysis

The calculation of blood flow from xenon washout data was described by Lassen et al. (*2*). The formula used is:

$$\text{Flow} = K \times \lambda \times 100 = \text{ml/min/100 g},$$

where K is the disappearance constant of xenon from the injection site and λ is the partition coefficient of muscle/blood for xenon. A computer program (Gamma-11 Curve) was used to provide a least-squares fit of a monoexponential function to the washout data, and the disappearance constant (clearance constant, slope constant) was determined. The disappearance constant K may also be calculated from the disappearance half-time.

Partition Coefficient

Conn (*10*), in 1961, found the muscle/blood partition coefficient of xenon in skeletal muscle to be 0.73, and he concluded that this factor must be used in calculation of muscle blood flow. For their studies of skeletal muscle blood flow in the extremities, Lassen et al. (*2*) combined this factor with a specific gravity of 1.05 and arrived at a correction factor of 0.70 (0.73/1.05) for blood with a hematocrit of ~40. Wagner (*3*) in his studies of penile blood flow, used the 0.70 partition coefficient for flaccid states, but stated that the value is changed when the volume of blood in the corpus cavernosum increases. He used a coefficient of 0.85 for studies done during tumescence. Shirai et al. (*5*) did not follow this convention, however, and instead used a partition coefficient of 1.0. There is no documentation to show which factor is most appropriate. In the abstract by Yeh et al. (*6*) the partition coefficient is not specified. We used a partition coefficient of 0.70 for our calculations.

Dosimetry

The radiation dose to the injection site is highly dependent on the rate of washout of the tracer. For a calculated blood flow of 1 ml/min/100 g, the dose to the injection site was calculated to be ~2.1 rad/mCi. The dose to the testes is quite low, and is approximately the same as for i.v. administration that is calculated to be 0.065 mrad/mCi. A shield over the scrotum was used in our studies, but this is expected to make little difference in exposure to the testes since more than 99% of the absorbed radiation dose is a result of the nonpenetrating beta radiation. The total-body dose has been calculated to be 0.12 mrad/mCi after i.v. injection, and should be the same for intramuscular injection.

RESULTS

Penile xenon washout data were obtained on six normal subjects, five spinal cord injured patients, and 14 elderly impotent subjects. The clinical diagnoses in the elderly impotent subjects were: vascular insufficiency (*4*), diabetic neuropathy (*4*), Peyronie's disease (*1*), hypogonadism (*1*), nondiabetic neuropathy (*1*), psychogenic (*1*), and idiopathic (*2*). The spinal cord injury patients all had complete motor injuries; four were quadriplegic and one was paraplegic. No complication or unexpected reaction was encountered with this procedure. The xenon injection caused very little pain, and no anesthesia was required.

The xenon disappearance curves appeared to be monoexponential, and conformed closely to the fitted curves. In some of our early cases, it appeared that a stable washout rate was not established until 5 to 10 min after injection. We therefore elected to allow an initial stabilization period, and to delay data acquisition until 15 min after xenon injection. With stable flow rates, we recorded the data for a minimum of 10 to 15 min to ensure adequate data for calculations. However, flow rates can be determined for time periods as short as 1 min, if adequate count rates are obtained. The length of time after a single injection for which adequate measurements can be obtained depends on the initial radioactivity dose, the detection system, and the washout rate. We have regularly obtained satisfactory measurements for 1 to 2 hr after a single injection. An example of a xenon disappearance curve, recorded for 30 min, is shown in Figure 1.

The blood flow rates obtained in these subjects, in the flaccid state after intracavernosal injection of xenon, are shown in Table 1. Statistical analysis of this small group of subjects by t-test shows no significant difference between flaccid-state measurements in the three groups studied. Comparing the normal group with the impotent group, the p value is 0.68. The p value for the normal versus the cord-injury group is 0.16.

Results reported by other investigators are also included in Table 1 for comparison. The results of Shirai

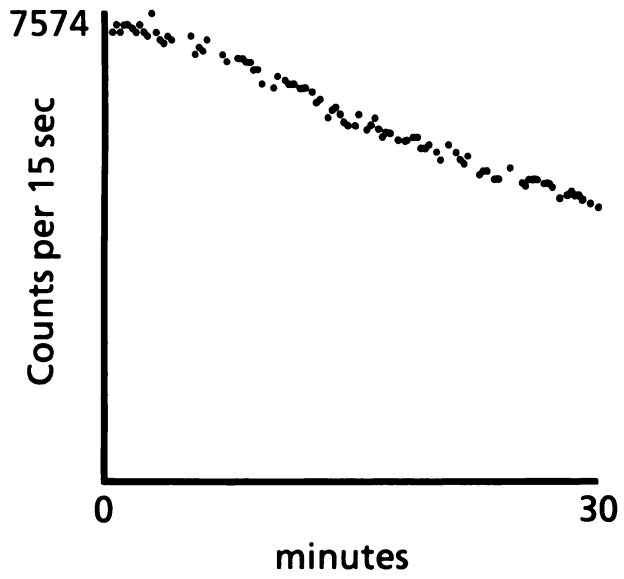

FIGURE 1
Computer display of datapoints obtained from recording of radioactivity after 250 μCi of ^{133}Xe injection into corpus cavernosum. The recording was begun 5 min after injection and was continued for 30 min. Each datapoint represents the total counts recorded for one 15-sec time period. Analysis of each 5-min time period of this washout curve yielded the following blood flow results in ml/min/100 g: 0.4,1.2,1.8,1.3,1.3,1.2. The first 5 min of the curve were excluded. Analysis of the 5- to 30-min segment of the curve yielded a blood flow of 1.3 ml/min/100 g.

et al. have been recalculated using a partition coefficient of 0.7 in order to allow comparison with the results of other investigators.

DISCUSSION

Erectile dysfunction is often attributed to vascular abnormalities, either arterial insufficiency or abnormalities of venous outflow resulting in a "venous leak." The cause of impotence in individual cases may be difficult to determine, and is often uncertain. The usual methods of evaluating arterial supply (penile blood pressure, Doppler pulse-wave analysis, duplex sonography, and angiography) do not provide absolute values and have other disadvantages (*11*). Venous outflow may be evaluated by cavernosography after injection of contrast material into the corpus cavernosum, or cavernosometry utilizing pressures recorded via a needle placed in the corpus cavernosum. None of these methods has been entirely satisfactory for evaluating penile vascular function.

Measurement of penile xenon washout may be useful in evaluation of penile erectile failure. This procedure is simple and easy to perform with standard nuclear imaging equipment, if a source of ^{133}Xe in saline is available. An assumption in the xenon washout method is that blood outflow is equal to blood inflow. This is true in most organs, and is true in the penis when a steady state exists and penile volume is not changing. During tumescence or detumescence, however, penile vascular inflow and outflow are not equal. Measurements of penile xenon washout should be considered to reflect venous outflow, which may or may not equal arterial inflow depending on the circumstances at the time of measurement. Concomitant measurement of penile circumference and rigidity may be required to accurately interpret the xenon washout data.

Three other investigators have reported penile blood flow results obtained in the flaccid state in small groups of subjects, using the xenon washout method. Their results, as presented in Table 1, show what appear to be significant variations between investigators. Although these differences are likely to be technical or methodologic, there is not sufficient information in the published reports to determine the reason for the differences.

Two of these other investigators have reported abnormalities of flaccid-state xenon washout in impotent subjects. Wagner reported that in patients with erectile dysfunction due to arteriosclerosis, a low xenon washout is found compared to normals, while subjects with dysfunction because of leakage from the cavernous bodies have a normal basal flow in the flaccid state (*4*). Detailed data were not given. Wagner also reported the use of the postocclusive blood flow measurement, after cuff compression of the base of the penis for 5 min, to detect a lack of vascular reserve in arteriosclerotic patients. Yeh et al. reported that measurements in the flaccid state can differentiate patients with venous leakage from normals (*6*). Their data are included in Table 1. Their ten patients with venous leakage demonstrated by cavernosography, and with normal arterial supply shown by pudendal arteriogram or Doppler study, had lower than normal penile blood flow in the flaccid state. They suggested that the delayed xenon clearance in patients with venous leakage may result from blood reflux when the penis is flaccid.

The usefulness of measurements in the flaccid state, as reported by these investigators, has not been confirmed by others. We did not find any diagnostic value for flaccid-state measurements. The 14 elderly impotent patients and the five subjects with neurologic injury in our study had penile blood flows in the flaccid state which were not significantly different from the normal group.

The xenon method has also been used to quantitate penile blood flow (washout) during erection induced by visual sexual stimulation (*3,5,12*), and some investigators have recommended this as a diagnostic test (*11*). As presently understood, penile erection involves an initial increase in cavernosal arterial flow, producing tumescence. There may also be an initial increase in venous outflow. As the full rigid erection phase is

TABLE 1
Penile Blood Flow Measurements in Flaccid State

Author and reference	Clinical status	Number subjects	Age (yr)		Blood flow*	
			Mean	Range	Mean ± s.d.	Range
Present study	Normal	6	32.2	28–40	0.7 ± .60	0.1–1.7
Present study	Impotent	14	68.8	66–76	0.8 ± .66	0.1–2.0
Present study	Cord injury	5	38.6	29–55	1.3 ± .54	0.8–2.2
Present study	All cases	25	52.9	28–76	0.9 ± .63	0.1–2.2
Shirai (5)	Normal	7	33.0	29–35	1.3†	0.35–1.9†
Wagner (3)	Normal	4	NA‡	NA	NA	2.5–8
Yeh (6)	Normal	8	NA	NA	4.7 ± 1.7	NA
Yeh (6)	Impotent	10	NA	NA	2.7 ± 1.7	NA

* ml/min/100 g.
† Recalculated for partition coefficient of 0.7.
‡ NA = Not available.

reached, arterial inflow decreases to a low level and the venous outflow is reduced to or below the pre-tumescent level (*13*). The reduction in venous outflow has been attributed to compression of venous channels by expansion of the cavernosal sinusoids within the unyielding tunica albugenia. Other mechanisms for control of venous outflow have been suggested, but have not been demonstrated in normal subjects.

Wagner and co-workers measured penile xenon washout during penile erection. They reported that xenon washout is reduced or unchanged during penile erection in normals, but is considerably increased in subjects with "insufficient venous closure" (*12*). However, Shirai et al. reported conflicting results (*5*). They found increased xenon washout during erection in their group of normal subjects. They did not report the duration of the visual sexual stimulation, but characterized the resulting erection as "complete" in five subjects and "incomplete" in two subjects. Penile erection was accompanied by a markedly increased rate of xenon washout in all of their subjects. Mueller and Lue have suggested that the findings of Shirai et al. are faulty, perhaps because of a short period of sexual stimulation and failure to utilize plethysmographic monitoring of penile volume (*11*). It is now recognized that full tumescence is not necessarily accompanied by a rigid erection. The reduction of venous outflow with erection to less than the baseline flaccid level, as observed by Wagner, may not occur until a full rigid erection is attained. It may be that the subjects studied by Shirai did not maintain a rigid erection throughout the period of measurement. No further xenon washout studies of the rigid erection phase have been reported.

Measurement of penile xenon washout may be useful in studying the physiology of penile erection and in evaluating patients with erectile dysfunction. Our results suggest that measurement in the flaccid state will not be useful for diagnosis. However, this is a promising method for detecting and quantitating venous outflow with stimulated or induced erection, and may provide a means to separate "venous leak" from arterial causes of vascular impotence.

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