# A Dual-Radioisotope Technique for the Evaluation of Penile Blood Flow During Tumescence

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A technique is described for concomitant study of both arterial and venous penile blood flow during tumescence. Dual-isotope acquisition is started after labeling red cells in vivo with $^{99m}$Tc. Xenon-133 in saline is then injected into the corpus cavernosum followed with vasoactive drugs to induce an erection. The resulting xenon and technetium time-activity curves are inputs for a one-compartment model. In 14 subjects, the average peak arterial flow rate (PAF) for normal males was calculated as 13.0 ± 1.28 ml/min (avg ± s.d.) compared to 16.1 ± 5.14 and 5.02 ± 1.78 ml/min for patients with venous leak (VL) or arterial insufficiency (AI), respectively. Peak venous flows (PVF) were 4.25 ± 1.17, 12.1 ± 3.75, and 3.78 ± 1.00 ml/min for normal, VL and AL respectively. AI patients have significantly lower PAF than normal (p = 0.002) or VL patients (p = 0.018), and VL patients had significantly higher PVF than normal (p = 0.012) or AI (p = 0.018). The technique may be helpful in the study of impotence.

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I t is estimated that approximately 50% of men with impotence have an organic etiology and presumably the majority are vascular in origin (*1,2*). The vascular problem can be either reduced arterial supply (arterial insufficiency) or excessive venous outflow (venous leak) and the differentiation between the two is important for patient management. A number of techniques have been employed to examine penile blood flow, including invasive methods such as angiography (*3*) as well as less invasive techniques such as cavernosography (*4,5*) and cavernosometry (*6*), sonography (*7,8*) or radioisotope techniques (*9–18*). The ideal examination would be a noninvasive one that yields a dynamic description of both the arterial supply and venous outflow of the penis simultaneously and continuously during tumescence. Combined with the now commonly used technique of direct injection of vasoactive

agents into the corpus cavernosum to induce penile erection (*19–22*), the result would be a complete description of the vascular flow during the flaccid, tumescent and erect states. In this report, we describe a scintigraphic method for performing such a dynamic vascular description of penile blood flow.

## MODEL

The penis can be represented by a one-compartment model with a given arterial inflow $f_a(t)$ and a venous outflow $f_v(t)$. What is desired is the description of $f_a$ and $f_v$ during stimulation to examine the changes in the arterial and venous supply from the flaccid through the erect states. The model we have chosen to obtain these flows employs a dual-isotope imaging technique in which the xenon washout method is used simultaneously with a labeled red cell study to obtain the flow relationships. The models are shown in Figures 1 and 2.

With the model of Figure 1, an equation is written for the rate of change of total xenon, Q, in the penis after direct injection of a bolus into the corpora cavernosum as a function of time as follows:

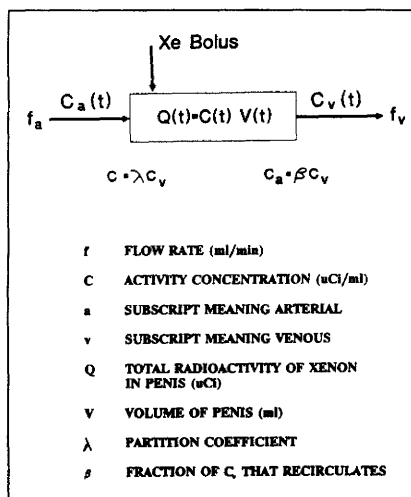$$\frac{dQ}{dt} = -f_v C_v(t) + f_a C_a(t). \qquad \text{Eq. 1}$$


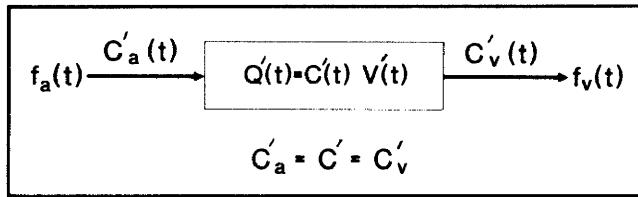
FIGURE 1. Penis xenon washout model.

**FIGURE 2.** Penis labeled red cell model. The prime refers to the $^{99m}$Tc label of radioactivity; otherwise, all symbols carry the same definition as in Figure 1.

Equation 1 merely states that the rate of change of xenon in the penis is equal to what flows in minus what flows out. However, since $\beta$ is the fraction of recirculating venous blood, then

$$\frac{dQ}{dt} = -f_v C_v(t) + f_a \beta C_v(t - \tau), \qquad \text{Eq. 2}$$

where $\tau$ is the venous blood recirculation time. Because most of the venous xenon will be expired when it reaches the lungs, the amount recirculating is small and the effect on Q should be small. Additionally, because of the dispersion of xenon as it traverses the circulation, $C_a(t)$ will be relatively slowly varying. Accordingly, there is little error in assuming $C_v(t)$ to be approximately equal to $C_v(t - \tau)$. With this assumption, Equation 2 can be rewritten as:

$$f_v = \beta f_a - \frac{\lambda V}{Q} \frac{dQ}{dt}. \qquad \text{Eq. 3}$$

The main assumption in rewriting Equation 2 as Equation 3 is that the concentration of xenon in the venous blood is directly proportional to the concentration of xenon in the tissue of the penis with proportionality constant, $\lambda$, the partition coefficient for xenon between blood and tissue. Because of the bolus injection of xenon directly into the penis, there is a short delay before the xenon can diffuse throughout the penis and be washed out in the venous blood. Thus, this assumption is violated for a short time after the introduction of xenon but undoubtedly is met quickly since xenon is rapidly diffusible in tissue.

Based on the compartment model shown in Figure 2, an equation is written for the activity of labeled red cells in the penis.

$$\frac{dQ'}{dt} = f_a C'_a - f_v C'_v \qquad \text{Eq. 4}$$

or

$$f_a = f_v + \frac{dV}{dt} \qquad \text{Eq. 5}$$

since in this case the concentration of $^{99m}$Tc activity in the blood remains constant; i.e., $C_a = C = C_v$. Equation 5 simply states that the arterial inflow must equal the venous

outflow plus the penis volume change. Substituting $f_v$ of Equation 3 into Equation 5 and rearranging yields:

$$f_a = \frac{-\lambda V}{(1 - \beta)Q} \frac{dQ}{dt} + \frac{1}{(1 - \beta)} \frac{dV}{dt}. \qquad \text{Eq. 6}$$

Venous flow can also be written in a similar manner as:

$$f_v = \frac{-\lambda V}{(1 - \beta)Q} \frac{dQ}{dt} + \frac{\beta}{(1 - \beta)} \frac{dV}{dt}. \qquad \text{Eq. 7}$$

Equations 6 and 7 are the working equations for the arterial and venous flow rates. The volume V and total activity Q are measured directly by the gamma camera, while $\lambda$ and $\beta$ must be obtained independently from other laboratory measurements.

To obtain a conversion from camera count rate to volume, a sample of the patient's blood of measured volume is counted in the field of view of the detector. If s is the count rate and v is the sample volume, then (s/v) is the count rate per unit volume. The count rate from a region of interest placed around the technetium image of the penis yields the red cell activity in the penis $A_p$ (t). The penis volume V(t) is then:

$$V(t) = \frac{A_p(t)}{(s/v)}. \qquad \text{Eq. 8}$$

Following the time course of the volume allows calculation of dV/dt as the slope of the volume curve.

The time course of the total xenon radioactivity in the penis Q is obtained following the xenon washout in the same region of interest over the penis image used to obtain the volume curve which then yields Q and dQ/dt. Because of the interrelation of the equations from the two models, both the technetium volume curve and the xenon washout must be done simultaneously. Accordingly, a dual-isotope technique is required.

If the blood flow for only one stage of the process in equilibrium were required, such as the flaccid state, then only the xenon washout portion of the study would be needed. In this case V(t) and f(t) are both constants and Equation 3 is rewritten with $\beta = 0$ as:

$$-\frac{dQ}{Q} = \frac{f_v}{\lambda V} dt \qquad \text{Eq. 9}$$

which integrates to

$$Q = Q_o \exp(- f_v/\lambda V) \qquad \text{Eq. 10}$$

a well known result (23). This is generally not a very useful result for evaluation of impotency and what is needed is the change in both arterial and venous flows during the erection process. The introduction of the technique of injecting vasoactive agents directly into the corpus cavernosum for the induction of penile erection allows the use of the Equations 6 and 7 to obtain the entire course of arterial and venous flows from the flaccid through the tumescent and erect states.

## MATERIALS AND METHODS

Twenty-three men ranging in age from 25 to 68 yr and having a mean age of 54 yr were studied. The study was approved by the University Hospitals of Cleveland Investigational Review Board and all patients provided written informed consent. Nine of the subjects refused confirmatory studies by angiography or cavernosography and are, therefore, not included in our results. Of the remaining fourteen, six of the men were volunteers that were considered normal because they were all sexually active. Selective arteriography of the internal iliac arteries enhanced by intracorporal injection of vasoactive drugs (3) was used for evaluation of the internal pudendal artery and its branches in patients considered to have vascular disease. Three men showed severe arterial disease (greater than 80% stenosis of the pudendal or central artery) leading to the diagnosis of arterial insufficiency (AI). Five men were diagnosed as having venous leak (VL) that was confirmed with cavernosometry and cavernosography (4-6). In all cases of venous leak, infusion flows greater than 100 ml/min were required to induce an erection and the erection could not be maintained at an infusion rate of less than 60 ml/min. (Intercorporal pressures in these patients were between 40 and 60 mm of mercury at these flow rates.)

The red cells of the patient were labeled in vivo with 5 mCi of $^{99m}$Tc using standard techniques (24). The patient was then positioned on a tilt-table and shields were positioned to cover all areas of the lower abdomen, pelvis, and upper extremities that were in the field of view leaving only the genitalia exposed. The penis was loosely restrained to point in a cephalad direction to avoid overlay of the testicles. A small blood sample of approximately 1 ml was obtained in a pre-weighed syringe to obtain the calibration necessary to convert the count rate of technetium into blood volume as per Equation 8.

A butterfly needle was then placed into the cavernosal body at the base of the penis. The patient was then covered to provide privacy and elevated to approximately a 70° position. The camera was placed so that the penis was essentially in the center of the field. The elevation of the patient to a high vertical angle aids in the production of an erection and is not crucial to the study, but was found to be helpful. A Searle LFOV gamma camera was used with an all-purpose collimator and set for dual-isotope acquisition. Data were digitally collected on an MDS $A^2$ System. Five to 10 mCi of $^{133}$Xe in 1 ml of saline solution were then injected through the butterfly followed by a 5-ml flush. List-mode acquisition was started 2-3 min later and continued for 15 min. Data were later post-processed into 5- or 10-sec frames. It was found that 5-10-sec time frames are adequate for analysis and list-mode acquisition is no longer an essential part of our procedure. The delay in starting imaging is used to allow the dispersion of any initial effects from the injection of the xenon or saline flush in the washout. At the completion of the initial imaging portion, the vasoactive agent was injected through the butterfly with a 1-ml saline flush. In our studies, 45 mg of papaverine and 1 mg of phenotlamine were used as vasodilators. Data collection was continued for approximately 15-20 min, at which time the study was terminated. Patients were given a contact number if the erection did not subside within 4 hr. Two patients returned for reduction of their erection, which was accomplished with adrenergic agents and evacuation. At the present time, we reduce all erections prior to discharge of the patient to avoid such problems.

Analysis was carried out by obtaining the time-activity curves for both technetium and xenon from a region of interest over the entire penis. A subtraction correction of 14% of technetium counts was applied to the xenon data for scatter down of technetium gammas into the xenon window. This value was obtained by separate measurements for our camera by measuring the fraction of technetium counts in the xenon window from a 50-ml syringe filled with a $^{99m}$Tc solution to simulate the penis. Curves were then filtered and fitted with a polynomial function. Using the data from the blood sample, the technetium curve was converted to a volume curve from which V(t) and dV/dt were obtained. From the xenon curve, 1/Q and dQ/dt were obtained. Venous and arterial curves were then prepared as per Equations 6 and 8 with $\beta = 0$ and $\lambda = 1$.

The partition coefficient $\lambda$ is an unknown in the penis and to the best of our knowledge has not been measured. For simplicity in these calculations, a $\lambda$ value of 1 was assumed in all calculations. Because of the penile structure and tissue composition and because of the known rapid diffusibility of xenon, it would seem that a value close to 1 would be reasonable. This subject needs further clarification and is under investigation at this time.

The recirculation constant $\beta$ was assumed to be zero in this study. In a single independent patient study, the arterial xenon concentration was measured and found to be negligibly small. Additional measurements are planned to confirm this assumption.

Peak arterial flow and peak venous flow for normals, patients with AI and patients with VL were compared using a Kruskal-Wallis test (25). Pair-wise group comparisons were performed using the Mann-Whitney U-test (26).

## RESULTS

Typical results are shown in Figures 3 and 4. Figure 3 shows the xenon washout curve and the technetium volume curve for a normal patient. Figure 4 presents the arterial and venous curves for a normal patient, a patient with AI, and a patient with VL. A number of features of these curves are noted:

1. In the xenon curve of Figure 3, there is a change in slope immediately following the vasodilator injection. The abrupt change in slope of the washout curve signals a decrease in venous flow as can be seen in Figure 4. In the case shown, the washout not only changes slope, but actually obtains a slightly positive slope. This has been seen in many patients that we have examined. There are several possible explanations for the positive upslope, which include improper accounting for downscatter of technetium gammas, recirculation of xenon or shielding problems associated with partial shielding of the base of the penis. All of these possibilities are presently under investigation.

2. The technetium curve shows an abrupt increase in activity following vasodilator injection. The increase signals an increase in arterial flow as demonstrated in Figure 4.

3. The result of the normal patient flow curves shown in Figure 4 closely resemble the data observed by Lue (27) during his description of the five phases of
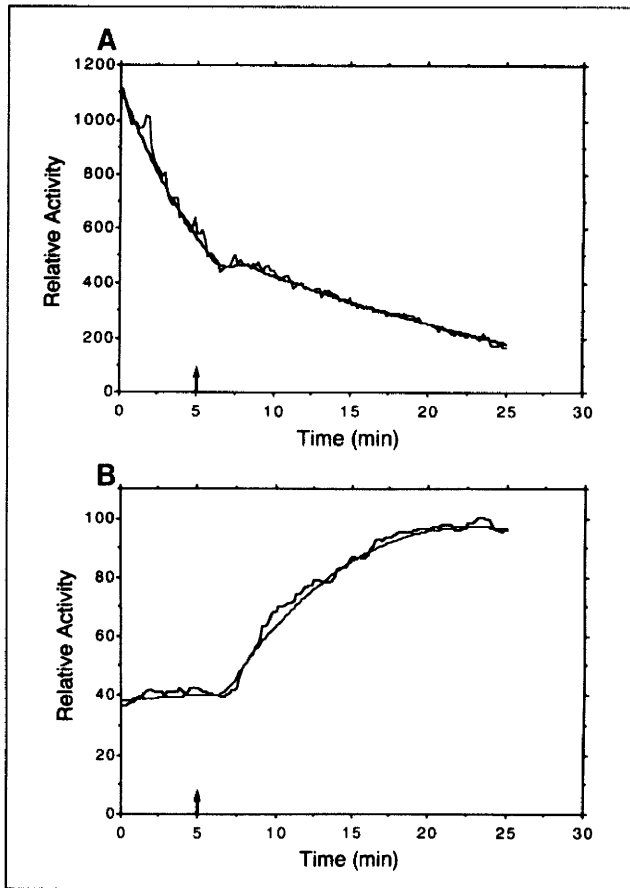
**FIGURE 3.** Input time-activity curves for a normal volunteer. (A) Xenon washout curve. (B) Technetium-red cell activity curve. Arrow indicates time of injection of vasoactive drug. Smooth curve is polynomial fit to data.

erection. As the full erection is reached, the arterial and venous flows tend toward equality with values close to those during the flaccid state.

4. The venous flow rate shows an abrupt drop immediately after injection of vasodilator with recovery to the baseline or slightly higher value in both the normal and the AI cases. The drop in venous flow is also seen in the VL case shown; however, it does not tend to return to a value close to baseline.

5. The VL pattern is different from the others. Following the initial rise, the arterial flow again increases or remains high with venous flow increasing almost in a parallel fashion. The final flow rates attain levels much higher than the baseline flow rates for both venous and arterial flows. The picture is one of arterial flow not being able to overcome venous flow in such patients.

In Figure 5, the peak arterial and peak venous flow rates are presented for the three subgroups described. Although the number of patients examined is small, there appears to be a clear distinction in peak arterial flow rate, with the AI cases much lower than the others. Similarly, the peak
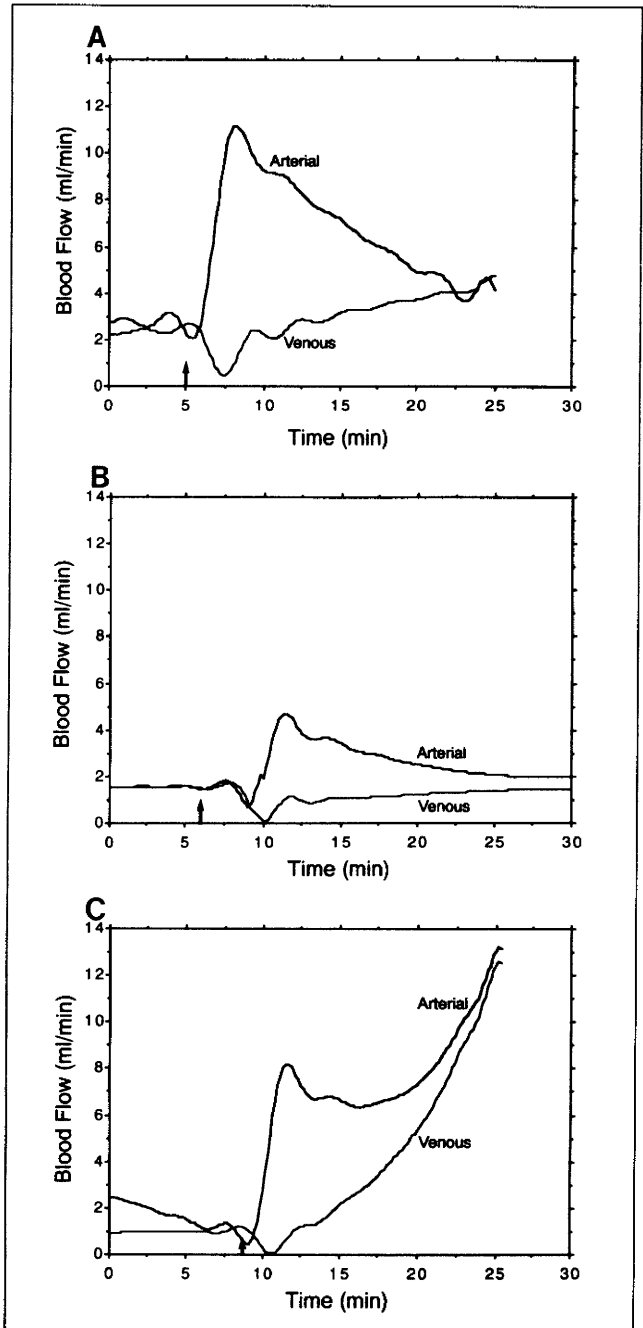


**FIGURE 4.** Arterial and venous blood flow during tumescence. (A) Normal patient. (B) Arterial insufficiency patient. (C) Venous leak patient. Arrow indicates time of injection of vasoactive drug.

venous flow rates are noted to be high for the VL patients compared to the other two groups. The three subject groups were compared for significant differences in peak arterial and peak venous flows with a Kruskal-Wallis test (25). The three groups differed for peak arterial flow (H = 9.45, df = 2, and p < 0.05) and for peak venous flow (H = 7.02, df = 2, p < 0.05). Pair-wise group comparisons were also performed using the Mann-Whitney U-test. Patients with AI had lower peak arterial flow than normals
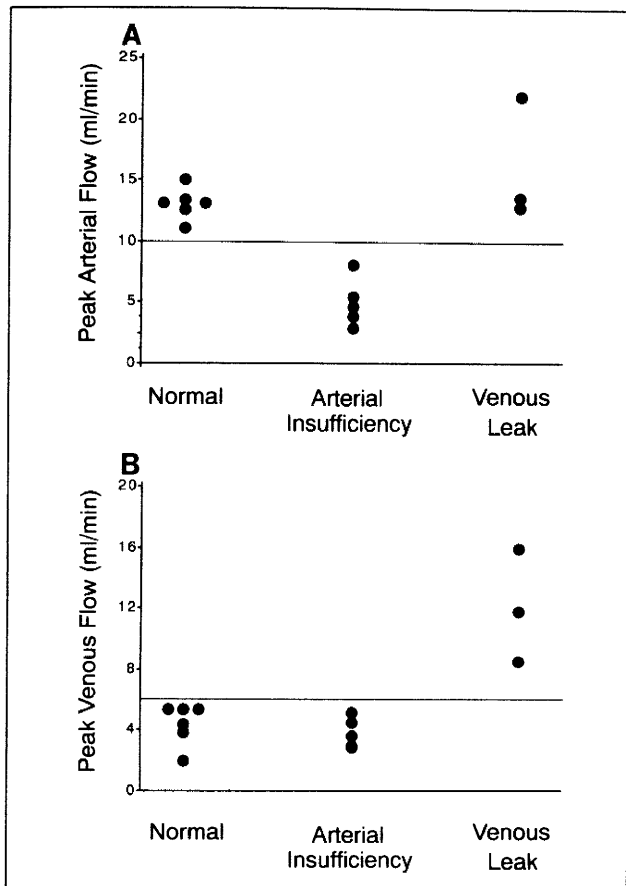
**FIGURE 5.** Peak penile blood flow for three subject groups studied. (A) Peak arterial flow. (B) Peak venous flow.

(p = 0.002) or patients with VL (p = 0.018). VL patients did not differ from normals in peak arterial flow (p = 0.29, ns). Patients with VL had higher peak venous flow than normals (p = 0.012) or patients with AI (p = 0.018). Normal and AI patients did not differ in peak venous flow (p = 0.4, ns). A summary of the group average peak flows is presented in Table 1.

## DISCUSSION

Evaluation of arterial supply and venous outflow of the penis has been difficult. Measurement of penile blood pressure using the Doppler stethoscope with calculation of the penile brachial index (PBI) and penile plethysmogra-

**TABLE 1**

| Subject group | Peak blood flow (ml/min)* | |
| --- | --- | --- |
| | Arterial | Venous |
| Normal | 13.0 ± 1.28 | 4.25 ± 1.17 |
| VL | 16.1 ± 5.14 | 12.1 ± 3.75 |
| AI | 5.02 ± 1.78 | 3.78 ± 1.00 |
| * Values are group averages ± s.d. | | |

phy are screening tests usually performed only in the flaccid state and do not accurately assess arterial blood flow to the penis. Duplex ultrasonic scanning is capable of recording the diameter of the cavernosal artery, but the recording is not always a dynamic one since arterial measurements and flow are usually recorded at specific points during the development of an erection. Recently, Schwartz (8) has shown that sonography can be used to obtain a dynamic reading of arterial inflow. Selective arteriography of the internal iliac arteries is an excellent method of evaluating the internal pudendal artery and its branches, but it is invasive and sometimes painful. Evaluation of venous leakage is possible with intracorporal injection of vasoactive drugs combined with cavernosometry and cavernosography. In an attempt to avoid invasive techniques, a number of studies have been performed using radioisotopes to evaluate penile blood flow. Shirai used $^{131}$I-human serum albumin in 1970 and in 1975 modified his technique by using $^{99m}$Tc (9,10). He observed the blood flow change occurring during visual sexual stimulation. The studies actually were observing net blood flow accumulation in the penis or volume change. Fanous et al. attempted to evaluate penile blood flow by monitoring changes in isotope activity of the penis after the intravenous injection of the vasodilator isoxsuprine HCl (Vasodilan) using [$^{99m}$Tc]pertechnetate in 1982 (11). In 1986 Shirai et al., also reported the use of intravenous isoxsuprine to cause vasodilation but used $^{99m}$Tc-labeled red blood cells to monitor blood volume change (12). Still others have used xenon washout techniques to attempt to record penile blood flow, which is obviously the venous outflow (13–15). In 1989, Schwartz and Graham used labeled red blood cells and vasodilators to relate arterial blood flow to volume change (16). Miraldi (17) introduced the dual-isotope technique in 1989 and demonstrated the various patterns of blood flow for the normal patient versus patients with vascular problems. In a more recent paper, Schwartz and Graham also modified their technique to include xenon washout in a slightly different dual-isotope method (18). Most of the radioisotope techniques do not accurately assess arterial and venous flow of the penis throughout the dynamic phases of an erection because of the interplay of venous and arterial flows as illustrated by the above equations. By use of the dual-isotope methods, the interplay of arterial and venous flows can be examined to provide a true measurement of the vascular dynamics.

Although the pathologic cases presented showed rather distinct curves and values compared to each other and the normal, it must be emphasized that these patients had severe disease. In general, one expects an entire spectrum of curves and values with essentially normal values in patients with mild disease to obviously abnormal curves and values for severe disease. Also, combinations of abnormality may be confusing since it is known that many problems of impotency are not pure patterns as described in the subgroups we present. The combination of VL and

AI were seen in two cases we examined, but the patients did not undergo sufficient testing to verify the results. Thus, further study with many more patients covering a wide spectrum of disease is needed before true group values are determined for diagnostic purposes.

## CONCLUSION

The dual-radioisotope technique has several significant advantages in the evaluation of impotent men. The procedure is easy to perform and takes less than 1 hr. It is much less invasive, painful, or embarrassing than some other techniques, such as selective pelvic arteriography. When a pharmacologic erection is produced, the genital area is shielded by the scintillation camera as well as by drapes and the erection is not readily observed by assisting personnel. More importantly, the study reveals information about both arterial inflow and venous outflow in a continuous manner that other methods of evaluation have been incapable of demonstrating in a routine way. Finally, since most hospitals have nuclear medicine facilities, the technology to implement the study on a wide basis is readily available. The procedure warrants further investigation and is by no means standardized at this point in time. Our early success, however, leads us to believe that this method will be an important diagnostic study in the evaluation of male impotence and may also be an important tool for the study of male erection physiology.

## ACKNOWLEDGMENTS

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## EDITORIAL
# Vascular Testing for Impotence

Miraldi et al. present a scintigraphic method for evaluation of the hemodynamic integrity of arterial inflow and veno-occlusive function during pharmacologically-induced erections. In their paper, they describe a dual-isotope technique to "provide a true measurement of the vascular dynamics."

In this report on 14 subjects, 6 were chosen as "sexually active" controls, 3 had arterial insufficiency on the basis of selective pudendal arteriography, and 5 were diagnosed as having corporal veno-occlusive dysfunction based on abnormal pharmacocavernosometry and pharmacocovernosog-