Gold-195m: A Steady-State Imaging Agent for Venography That Gives Blood Velocity Measurement

David J. Dowsett, Joseph T. Ennis, Catherine T. Collum, and Rolf B. J. De Jong

Department of Radiology, Mater Hospital, Dublin 7, Ireland; and Byk-Mallinckrodt Inc., Medical Division, Petten, Holland

Gold-195m has found applications in first-pass studies for investigating both right and left ventricular activity as well as lung transit. Owing to its reasonably short half-life of 30 sec we have found it particularly useful for imaging leg veins up to and including the inferior vena cava. Its short half-life prevents recirculation activity from appearing, so continuous perfusion into a superficial foot vein and application of ankle tourniquets yield a steady-state image of the deep veins, with particularly good resolution. Its decay pattern along a vessel is very sensitive to blood velocity, so measurement of activity at various points on a vein in a computer static image can give velocity values that reveal abnormalities due to partial or complete thrombosis. The radiation dosimetry of ^{195m}Au used in this way is lower than contrast and technetium-99m macroaggregated albumin ([^{99m}Tc] MAA) venography, making it particularly useful for investigating deep vein thrombosis (DVT) in pregnancy.

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The major advantage of short-lived radionuclides, when used for vascular functional imaging, is the absence of recirculation activity which can obscure primary information when using longer lived nuclides, such as ^{99m}Tc, for investigating arterial and venous circulation (1). The rapid decay characteristics of krypton-81m (^{81m}Kr) was first used (*2*) for imaging capillary perfusion in organs and selected regions of dogs. Fazio et al. (*3*) described a procedure using ^{81m}Kr for the continuous carotid infusion in patients for measuring regional cerebral blood flow (rCBF), and Sugrue et al. (*4*) demonstrated its use for the continuous gated measurement of right ventricular ejection fraction. Hnatowich et al. (*5*) and Treves et al. (*6*) reported the use of iridium-191m (^{191m}Ir) for lung transit studies in children. Since gold-195m (^{195m}Au) was first reported as a clinically useful radionuclide (*7,8*), it has been used for lung transit as well as first-pass right and left ventricular studies (*9,10*). Its longer half-life of 30 sec suggested that it may be useful for extensive visualization of peripheral vascular pathways, particularly in the venous system (*11*).

We present here the evaluation of ^{195m}Au as a steady-state imaging radionuclide for accurate visualization of deep venous pathways in the legs and abdomen and demonstrate its value for measuring absolute blood velocity.

MATERIALS AND METHODS

^{195m}Au generator

The preparation and construction of the isotope generator has been described elsewhere (*7,8*). The elution of the generator has been modified however, for perfusion studies. Figure 1 shows the gold generator complete with perfusion pump,* which is used for driving a 50 cm^3 plastic syringe at a constant perfusion flow-rate. The shielded generator with its perfusion pump is placed close to the patient. Elution of the gold generator itself can be achieved by using several solutions (*7*), however, only two have been found useful in clinical applications: (a) a very dilute solution of potassium

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For reprints contact David J. Dowsett, M.Sc., Chief Physicist, Mater Hospital, Dublin 7, Ireland.

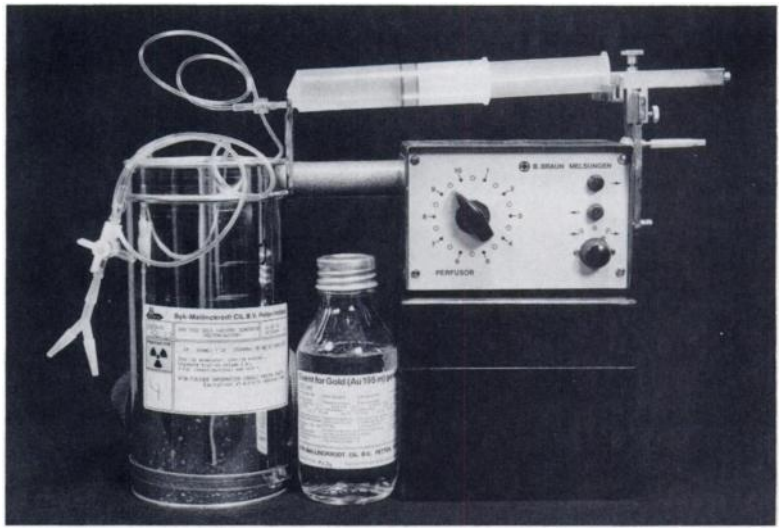

FIGURE 1
Elution of ^{195m}Au Generator for venography. 50 cm^3 plastic syringe, charged with sodium thiosulphate (bottle in foreground), elutes generator (metal cannister) at steady 10 cm^3 per min. Narrow exit tube from generator, fitted with two-way tap, perfuses either single leg or both legs simultaneously. In practice, generator would be surrounded by 2-in. lead blocks as radiation shield

cyanide in physiological saline and (b) a dilute solution of sodium thiosulphate in physiological saline (*8,10*). We use sodium thiosulphate exclusively, which extracts 28–30% of the available ^{195m}Au from the generator column. No adverse effects have been seen by us when using this elutant, even after continuous infusion of 120 cm^3; none have been reported from other workers (*10*). The generator has a useful life of 3 days when used for perfusion vascular imaging; a fourth day can sometimes be achieved in practice.

In vitro evaluation of ^{195m}Au as a vascular agent

The 30.6-sec half-life of ^{195m}Au maintains a sufficient level of activity for the continuous infusion of slow flow-rate venous pathways, making it most suitable for the visualization of the entire leg deep veins and inferior vena cava. Recirculation activity is virtually absent from the steady-state image. Table 1 compares three short-lived isotopes: ^{195m}Au, ^{81m}Kr and ^{191m}Ir, which have potential as venography agents. Recirculation activity is virtually absent in all three, however only ^{195m}Au, with its 30-sec half-life gives sufficient activity to visualize the entire venous pathway, from the legs to the inferior vena cava.

A series of in vitro experiments using ^{195m}Au, was devised for flow evaluation where two different diameter plastic tubes (1.5 mm and 3.0 mm) were stretched over a small-field gamma camera fitted with a medium-energy collimator suitable for imaging the 262 keV gamma photon. These tubes were separately perfused with ^{195m}Au eluted from the generator at different flow rates. The perfusion pump delivered calibrated flow-rates of 0.5, 1.0, 2.0, 5.0, and 10.0 cm^3 per min. Timed static images of 128 × 128 byte were collected with an image count density of ~200k. These were subsequently analyzed using profile measurements to generate time-activity curves.

TABLE 1
Recirculation Activity and Length of Useful Venous Pathway Displayed*

Isotope	Recirculation activity	Useful pathway 50% activity (cm)
^{195m}Au	0.6 μCi/cm^3	142
^{81m}Kr	Exhaled as gas	62
^{191m}Ir	None	9.5

* Comparison of three short-lived nuclides as potential imaging agents for venography, estimated recirculation activity, and length of venous pathway that can be imaged before 50% loss of activity.

Clinical evaluation of ^{195m}Au

Patients for this preliminary clinical trial were selected who had previous contrast venograms so that comparisons could be made for image quality. Informed consent was required and obtained from each patient.

The patient was placed supine, starting with the calf areas, within the gamma camera field of view. A parallel-hole, medium-energy collimator was used (250 keV) and image data collected as timed (2 min) 128 × 128 or 256 × 256 byte mode images. Superficial dorsal foot veins were cannulated using a No. 23 gauge butterfly needle in each foot and tape tourniquets were placed around the ankles in order to encourage deep venous perfusion. The gold generator was eluted from a 50 cm^3 plastic syringe filled with sodium thiosulphate (supplied with the generator). The syringe was driven at 10 cm^3 per min using the perfusion pump. For ^{195m}Au venography, at the start of continuous perfusion, a single 20-sec equilibrium period enabled the ^{195m}Au to traverse the entire leg and establish steady-state conditions before imaging commenced. The gamma camera was re-positioned after each picture, so that the deep veins of the legs were imaged together with the pelvic

TABLE 2
In Vitro Velocity Measurements*

Flow cm³/min	Measured velocity cm/sec D = 1.5	Measured velocity cm/sec D = 3.0	Calculated velocity cm/sec D = 1.5	Calculated velocity cm/sec D = 3.0
0.5	0.47	0.12	0.48	0.12
1.0	0.94	0.24	0.92	0.24
2.0	1.88	0.47	1.87	0.47
5.0	4.72	1.18	4.81	1.10
10.0	9.43	2.36	9.28	2.25

* Results from in vitro velocity measurements using two sizes of tubing: 1.5 mm diam and 3.0 mm diam (D = 1.5 and D = 3.0) and collecting data from standard field gamma camera (240 mm) as 128 × 128 image matrices. Actual velocity from measured flow-rates is compared with calculated velocity from ^{195m}Au velocity/decay values using equation (iv) in text.

area and inferior vena cava. Each 50 cm³ of elutant gave 5 min steady-state imaging.

Distance measurement

The stated collimator resolution for our gamma camera† is 9.1 mm at 0.0 cm. The measured resolution, using a 1-mm-diam line source and collecting the count data as a 128 × 128 pixel matrix, was 9.4 mm full width half maximum (FWHM). This matrix size, therefore, represented the achievable resolution of the system which, at 3 mm/pixel (field of view 387 mm), gives a practical resolution limit of about 3 pixels allowing for resolution degradation with distance from the collimator face. This was used as the distance measurement in the velocity calculations: 3 pixels equivalent to 10 mm, giving about 9% error in distance measurement. The inaccuracy here compares favorably with other more invasive techniques for measuring venous blood flow which achieve an error of 6% (*12*). In the early stages of this project the velocity decay measurements were simply obtained by measuring the ^{195m}Au activity along a chosen tube or vessel length, by selecting two points. This gave an activity profile for a fixed number of pixels, which was used in the velocity calculation. A program is being developed for automatically displaying calculated velocity between chosen points on the computer image.

RESULTS

In vitro measurements

From the results obtained with the in vitro measurements (Table 2) the decay pattern given by the ^{195m}Au for various flow rates obeyed the basic formula:

$$P/v \cdot e^{-\lambda x/v}, \qquad \text{(i)}$$

where P is the isotope perfusion rate, v the blood flow or more accurately the velocity; P/v would describe the dilution effect in a flowing system where a long-lived

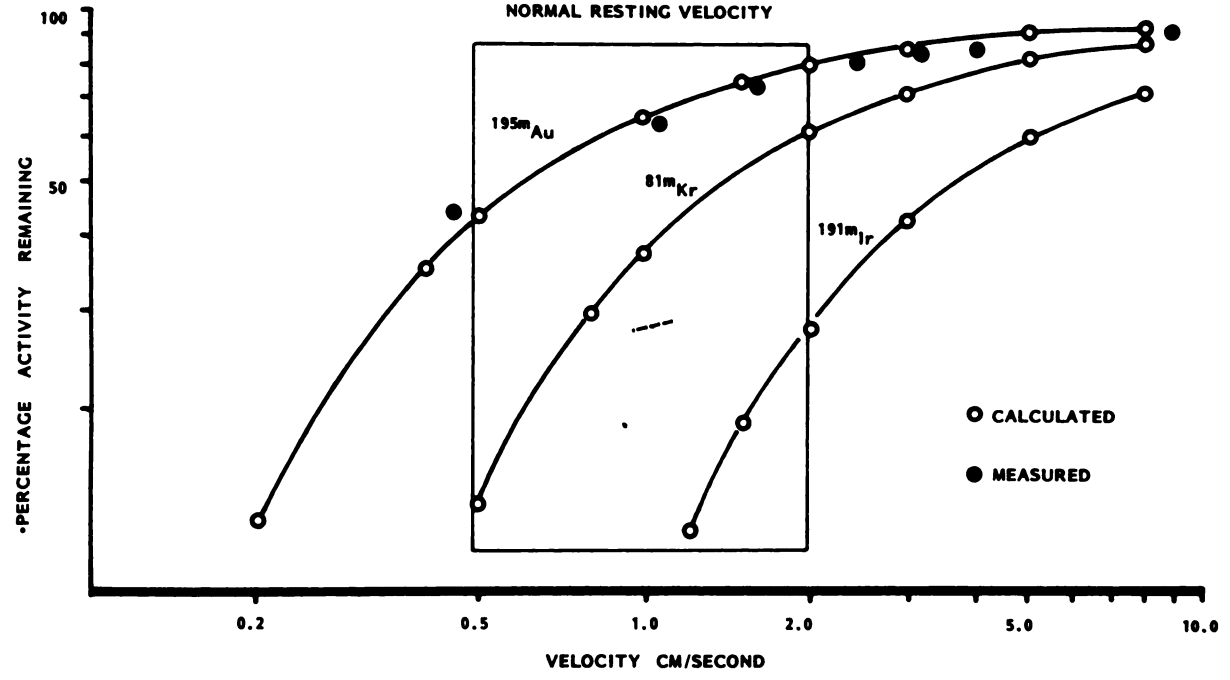

FIGURE 2
Calculated decay for three short-lived nuclides ^{195m}Au (T½ 30 s.); ^{81m}Kr (T½ 13s.); ^{191m}Ir (T½ 5 s.). "Y" axis shows percentage isotope activity remaining at fixed point (18 cm) down-stream from perfusion input. "X" axis plots fluid velocity in cm per sec. Approximate resting velocity seen in normal venous circulation of legs is enclosed by box outline (between 0.5 and 2.0 cm per sec). Results from in vitro flow measurements for various diameter tubes are also plotted (●)

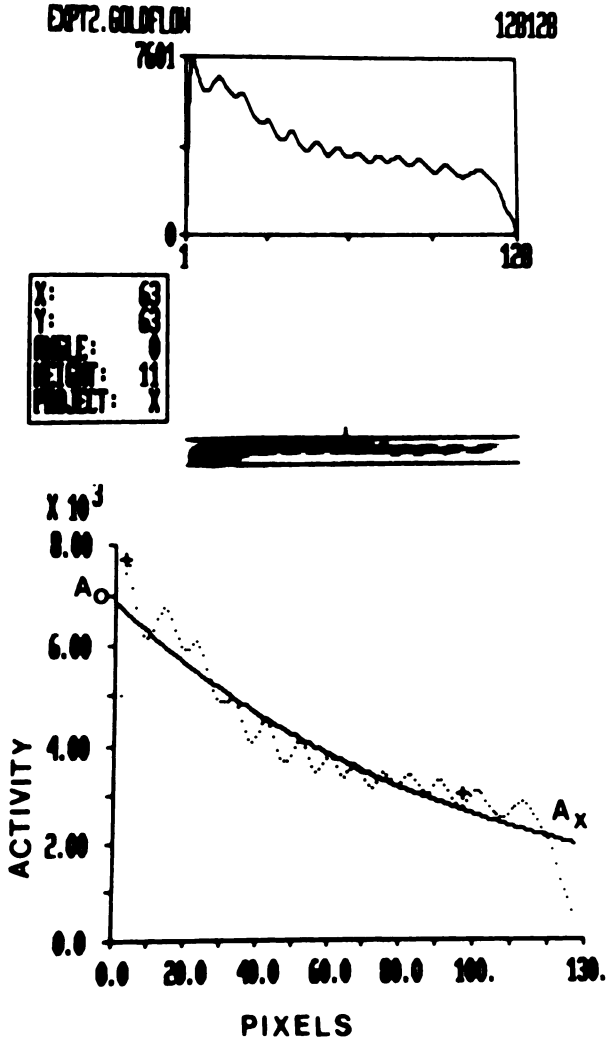

FIGURE 3
Example of an in vitro flow/velocity measurement. Measured flow rate through a 3-mm-diam tube was 2 cm^3 per min yielding velocity of 4.7 mm per sec. Calculated velocity from ^{195m}Au decay along tube length at points A_o (maximum) and A_x (120 pixel point) as marked on lower graph, was 4.6 mm per sec

radionuclide was added. In the case of a short-lived nuclide, however, the exponential decay factor influences the activity concentration according to position along the vessel. Lambda (λ) is the decay constant (0.0231 for ^{195m}Au); x is the distance separating the measured points and so x/v gives a time value. The equation then gives a concentration of isotope at any chosen point x along the vessel. The slower the velocity the more the radionuclide decays so the concentration of the isotope, translated as image density under steady-state conditions, is proportional to fluid or blood velocity for a constant perfusion rate. Table 2 gives a set of results from the in vitro measurements using the five stated flow rates in 1.5-mm- and 3.0-mm-diam tubes, which give ten different velocity readings. The overall accuracy was +1.9%, −4.6%, the worst discrepancies occurring at the fastest flow rates where turbulence was the probable cause. This, however, was not seen as a serious drawback since the slower velocities are pathognomonic. The graph in Fig. 2 plots the decay characteristics for ^{195m}Au, ^{81m}Kr, and ^{191m}Ir for various velocities. The very rapid loss of activity shown by the radionuclides ^{81m}Kr and even more so by ^{191m}Ir, at the lower values of the normal venous velocity shown in Fig. 2, detracts from their usefulness as velocity indicators under steady-state conditions; image detail would be lost. The very low activity levels remaining downstream from the reference point (18 cm in these examples) would be difficult to measure accurately, leading to large velocity calculation errors. For longer vessel lengths and/or under disease conditions this inaccuracy would be significantly increased. The more gradual velocity/decay curve shown by ^{195m}Au gives a superior image and, even over major vessel lengths acceptable accuracy levels can be achieved. For velocity measurements from the steady-state image the formula (i) above, simplifies to:

$$A_x = A_o \cdot e^{-\lambda x/v} \qquad \text{(ii)}$$

where A_o and A_x describe the ^{195m}Au activity levels at origin and distance x along the tube or vessel length. Rearranging this formula in order to measure velocity from these activity levels gives:

$$v = \frac{-\lambda x}{\text{Ln}\,(A_x/A_o)}. \qquad \text{(iii)}$$

A practical formula was developed for including in a computer algorithm which would give a velocity measurement along a chosen length of vessel; length being operator defined with a "joy-stick" or "light-pen" on the computer image in pixels.

$$v = \frac{-\lambda\, xc}{\text{Ln}\,(A_x/A_o) \cdot zm}, \qquad \text{(iv)}$$

where x is the vessel length in image pixels of matrix size m; c the camera field size and z the image magnification or zoom factor.

For the example shown in Fig. 3 an activity profile taken along the entire tube length is plotted above the computer image with the profile defined across the entire 128 pixels. Below this image a "best-fit" exponential follows the decay along the vessel length. Activity points A_o at the origin and A_x at the 120 pixel mark are used in the computer calculation given above (iv). The A_o value from this curve is 7,000 and the A_x value is 2,300; image zoom was not used. The computed velocity of 4.6 mm per sec agreed very closely with the actual velocity of 4.7 mm per sec for this flow rate.

Clinical examples

The two clinical examples that have been selected demonstrate the picture quality and resolution as 256 × 256 steady-state images.

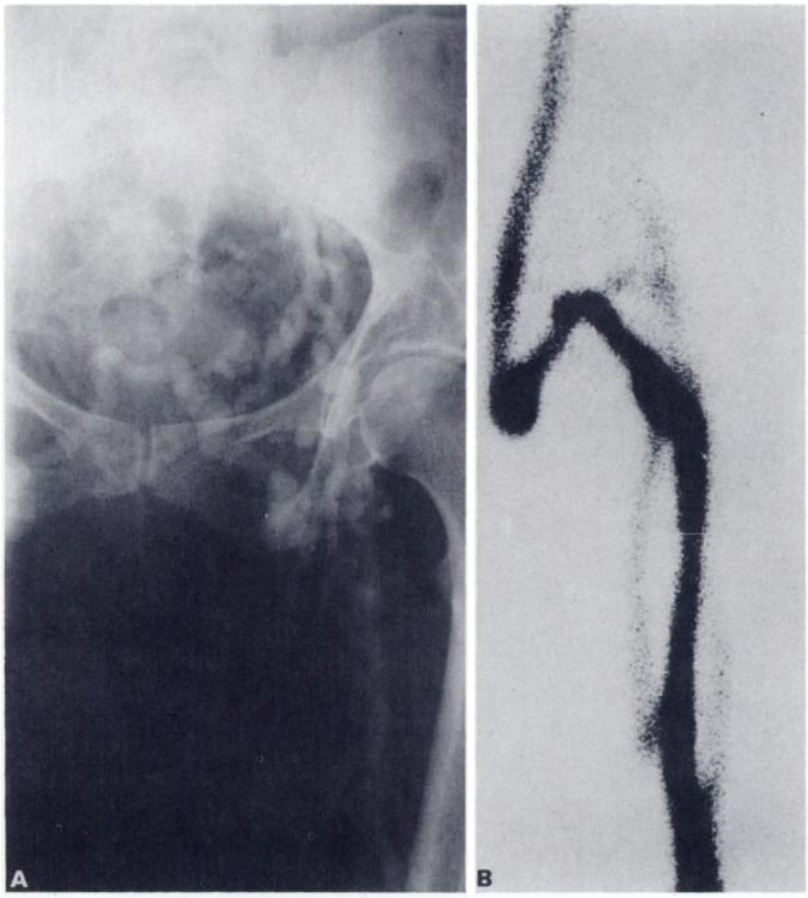

FIGURE 4
A: Contrast venogram of pelvic area from patient with thrombosed left iliac vein and large cross pelvic collaterals. B: ^{195m}Au steady-state venogram from same patient

Case 1

Figure 4A is a contrast venogram of the pelvic area showing a thrombosed left iliac vein and large cross-pelvic collaterals which supply the patient's right iliac veins. Figure 4B shows the ^{195m}Au steady-state venogram of the same patient. The femoral vein is well filled and shows a good flow rate. Tributaries of the saphenous vein can be seen joining this vessel. The cross pelvic collaterals are well demonstrated connecting with the right iliac vein; the activity at this point has diminished and shows radioactive decay along the vessel length.

Case 2

Figure 5 is taken from a patient with extensive deep vein thrombosis (diagnosed from the contrast venogram) causing filling of the superficial venous system. This case serves to illustrate the resolution of the ^{195m}Au image where quite small (~2–3 mm diam) vessels can be seen.

Figure 6 shows a deep vein of the thigh under rest conditions covering 224 pixels of a 256 × 256 image matrix taken from a 387-mm large-field camera; no zoom factor was used. The measured count density at the origin was 176 and the down-stream count density was 17 for equal area regions of interest under steady-state conditions. Using equation (iv) a blood velocity of 0.33 cm per sec was calculated which was somewhat below normal values for this size of vessel. This patient showed a normal contrast venogram.

DISCUSSION

The results from the in vitro flow experiments demonstrate that ^{195m}Au will indicate changes in flow patterns. Its half-life of 30 sec is short enough to give good steady-state pictures of slowly moving venous flow patterns in the leg and abdominal vessels as far as the vena cava. Continuous perfusion of the isotope allows the best view to be selected by adjusting the patient's position during the study in order to delineate venous pathways of diagnostic interest without risk to the patient, unlike contrast venography. The use of constant rate injection techniques has been described (*13*), where if the total amount of injected tracer is known, with no recirculation problems, the flow can be calculated from venous sampling by observing the degree of dilution (as previously shown in equation (i)). The radionuclide ^{195m}Au seems to solve the recirculation problems in such a study, however monitoring absolute activity levels per unit volume at the input and simultaneously at

points along a chosen vessel would present insuperable difficulties. Lung mean transit times could be obtained from external detection using bolus injections (*9,10*) in a similar fashion to [^{99m}Tc]HSA mean transit time studies (*1*).

The results so far obtained with ^{195m}Au, when used for imaging deep veins of the legs and pelvis, complete with inferior vena cava, are promising, as the resolution obtained is superior to other radionuclide techniques. Radionuclide venography using [^{99m}Tc]MAA has been very successful as a noninvasive technique for demonstrating deep vein thrombosis (*1,14*). It shows certain disadvantages, however, in particular, poor detail of the paired veins in the calf and uncertain assymetric arrival of the radionuclide bolus at the iliac veins, which could be an extremely valuable indicator for DVT obstruction. Unfortunately, unsuccessful simultaneous injections, unilateral varicosities or venous compression may mimic delayed arrival and produce confusing information. The [^{99m}Tc]MAA procedure is restricted to a

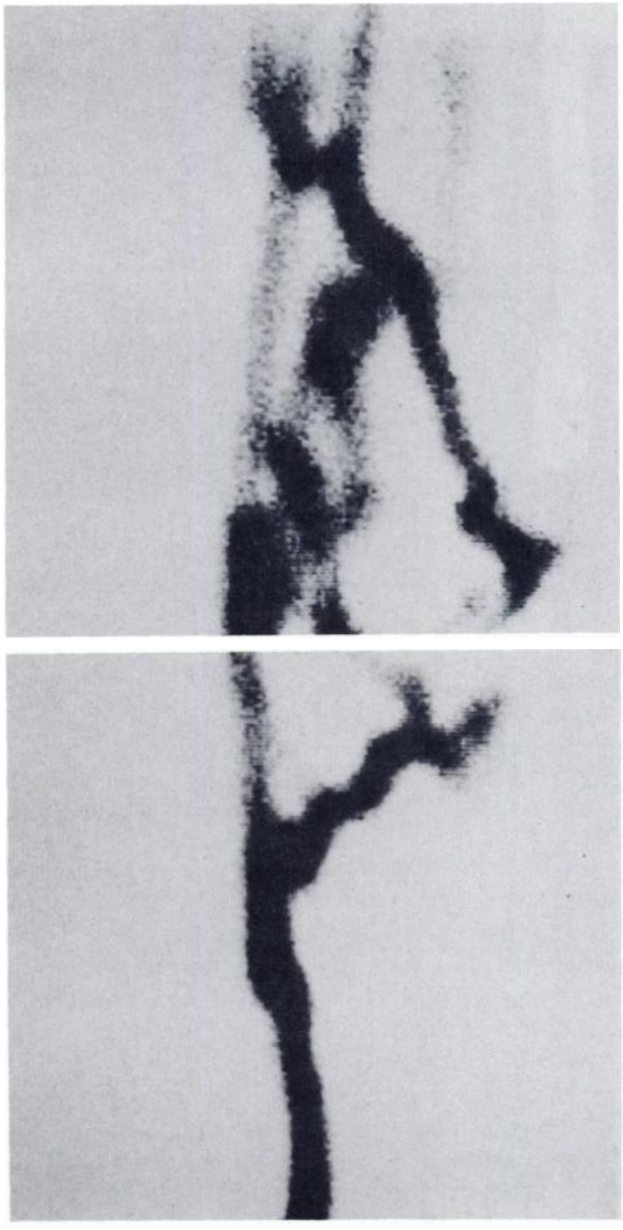

FIGURE 5
Two-image composite picture of saphenous system of left leg from patient with deep-vein thrombosis. Changes of image density from lower image to upper image are due to image gray-scale anomalies and not velocity changes

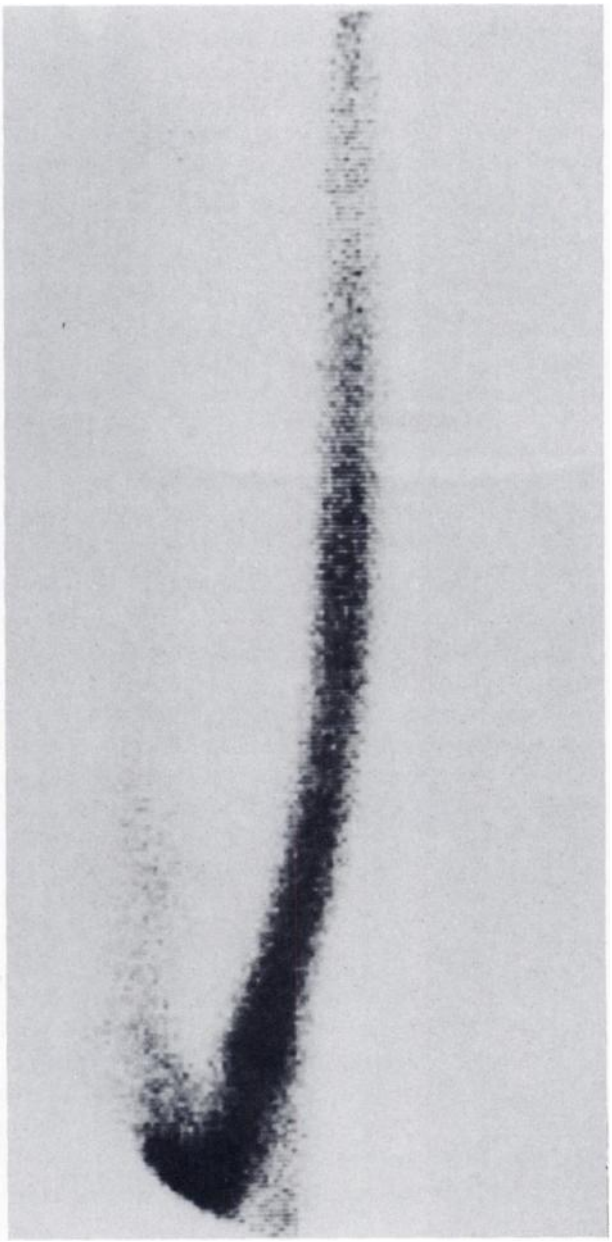

FIGURE 6
Gold-195m steady-state venogram showing deep veins of thigh where profile measurements on most prominent of these gave activity levels for velocity measurement

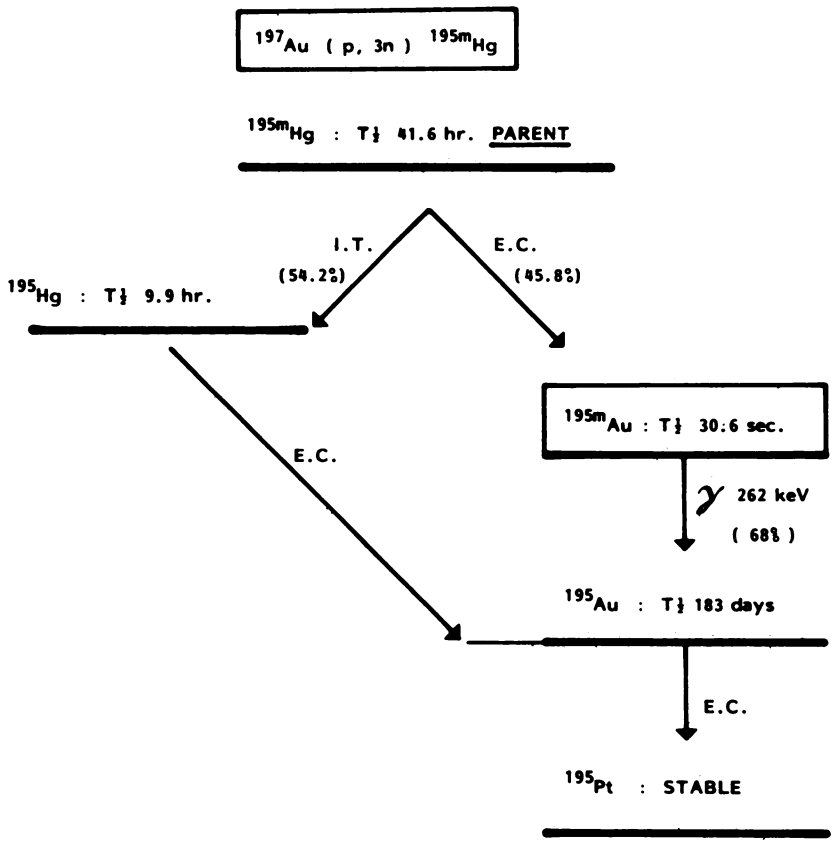

FIGURE 7
(p, 3n) Reaction used for preparation of parent ^{195m}Hg and its decay scheme yielding ^{195m}Au and other decay products which contribute to overall radiation dosimetry shown in Table 3

single image study, the anterior view of both legs, up to the pelvis, being commonly chosen using a whole-body scan from the gamma camera system. Image resolution is lost from such whole-body images and anatomical detail of nonfilling thrombosed vessels, which may not have trapped the MAA particles can be easily missed, unless gross DVT is present. The steady-state images obtained from ^{195m}Au, using either uni- or bilateral perfusion, is not sensitive to injection timing and separate gamma camera images of the legs can be selected during perfusion in order to demonstrate abnormal venous pathways more clearly. Gold venography is most useful in the pelvic region, where it gives a clear indication of the obstructed vessels and collateral pathways. Radiographic contrast venography has limitations in this region owing to contrast dilution, therefore ^{195m}Au venography could act as a useful adjunct in suspected cases of pelvic occlusion.

The high energy of the ^{195m}Au gamma photon (262 keV) is not significantly influenced by tissue absorption and good quality images of deep seated veins have been obtained in our small clinical trial. The morphological information obtained from the steady-state images does not demonstrate the existence of DVT directly but can be inferred in a way similar to radiographic contrast venography using x-rays. The presence of thrombosis, whether complete or partial, compromises venous flow which is indicated by either absence of activity or a rapidly decaying pattern along the vessel length which is partially occluded. Velocity information can be quantified from the decay pattern and follow-up measurements made in order to evaluate therapy.

Further applications

Dynamic venography for assessing venous drainage during exercise where [^{99m}Tc]MAA has certain disadvantages (*15*), is a specific area that would lend itself to steady-state imaging using ^{195m}Au. Dynamic information about the venous circulation could be obtained from these images during exercise or drug intervention studies.

The measure of absolute flow rates through individual vessels, using radionuclide techniques, depends on the accurate measurement of vessel diameter. The method described by Barr et al. (*16*) for investigating stenoses in the superior vena cava is being studied as a suitable computer procedure for measuring vessel diameter so that blood-flow functional images can be generated using steady-state velocity data from ^{195m}Au.

Dosimetry

The decay scheme Fig. 7, shows the contributing decay products of the parent mercury-195m (^{195m}Hg)

TABLE 3
Dosimetry for Continuous Infusion*

Organ	^{195m}Au	$^{195m+195}$Hg	^{195}Au	mRad (mGy) Total
Liver	4.3	39.3	—	43.6 (0.44)
Spleen	1.0	50.0	—	51.0 (0.51)
Kidneys	5.7	442.8	25.7	474.2 (4.74)
Whole body	—	21.4	5.7	27.1 (0.27)

* Estimated radiation dosimetry of 200 μCi per sec infusion of ^{195m}Au over 3-min study period. Total activity 36 mCi.

which are important when considering the radiation burden to the patient. The dosimetry of ^{195m}Au is given in Table 3. Mercury breakthrough from the generator is the major contributor to the overall long-term radiation dose from ^{195m}Au studies, the target organ being the kidneys. However, the use of a chelating agent after each study may serve to wash out the trapped mercury from the kidney tissue; this possibility is being explored. Reduction in mercury break-through from the generator is also being achieved in commercial prototypes, and mercury concentration can be significantly reduced by flushing the generator 15 to 20 times before starting patient investigations and repeating this maneuver, giving five flushes during patient studies. Gold-195m build-up is sufficiently rapid to ensure available isotope activity. As a dosimetric comparison (*9*) it has been estimated that 50 mCi of ^{99m}Tc (equivalent to three first-pass studies) will give a whole-body dose of 500 mR (5 mGy) and 5 rad (50 mGy) to the kidneys. From Table 3, the comparable ^{195m}Au doses for a venogram study would be a kidney dose of 474 mR (4.74 mGy) and a whole-body dose of 27 mR (0.27 mGy). This dose rate compares favorably with contrast venography giving a mean whole-body dose of 350 mR (3.5 mGy) with a maximum figure of 1 rad (10 mGy) for single leg investigations (*17*).

The radiation dose to the injection site is always high when using small volume boluses of large activity (20–50 mCi). This radiation dose is not significantly reduced when using short-lived nuclides. A 25 mCi bolus injection of ^{99m}Tc in 1 cm^3 will deliver an estimated dose of 671 mR (6.7 mGy) to the injection site, assuming a 2 sec residence time within the vessel. Similar estimations for ^{191m}Ir yield 465 mR (4.65 mGy), and for ^{81m}Kr 603 mR (6 mGy). In order to maintain a practical activity level for steady-state imaging, using shorter half-life isotopes than ^{195m}Au for vessel perfusion, much greater activities need to be infused with a consequently very large increase in injection site radiation dose (*4*). Gold-195m, if perfused over a 3-min study, giving a standing activity of 200 mCi per sec, yields an injection site dose of 306 mR (3 mGy).

The cost of the gold generator is approximately double that of our 400 mCi ^{99m}Tc fission generator and, in order to be economical for isotope venography, it would require either a busy clinic seeing 10–20 patients or also be used for first-pass cardiac work.

The preliminary results of this investigation from a small group of patients indicate that ^{195m}Au venography would serve as a complementary diagnostic imaging technique to contrast venography, particularly in cases of pregnancy or contrast agent sensitivity. The single thrombosed vein can be identified by either a more rapid velocity profile, indicating stenosis, or an absence of activity indicating complete thrombosis, which is usually accompanied by a proximal accumulation of venous activity indicating generally obstructed flow. During bilateral perfusion, reference can be made to the other leg when single vein anomalies are encountered. The careful positioning of the patient during ^{195m}Au perfusion allows the best diagnostic views to be selected so that suspect areas can be studied in detail. With a more extended survey of patient material, a library of steady-state images would yield normal blood velocity values that could be used as reference.

CONCLUSION

Gold-195m with a half-life of 30 sec is particularly useful for imaging leg veins up to and including the inferior vena cava. Recirculation activity is not seen and so during perfusion a good resolution steady-state image is formed which gives a functional picture of blood flow. Activity profiles along the vessels can yield absolute blood velocity values. The radiation dose is significantly lower than contrast venography; adverse reactions are absent.

FOOTNOTE

* Braun B, Melsungen AG, West Germany.

† Siemens LFOV: Medium Energy, Siemens Medical Systems, Iselin, NJ.

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