Quantitative Measurement of Skin Perfusion with Xenon-133

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Quantitative assessment of skin perfusion has value in both medical and surgical therapeutic decision-making. We have adapted a technique using intradermal xenon-133 dissolved in saline for use with a gamma camera interfaced to a minicomputer. It allows rapid evaluation of several sites simultaneously. The monoexponential washout rate of the injected tracer during the first 6 min is entered into the Schmidt-Kety equation to provide blood-flow rates in ml/min per 100 g. Reproducibility of the method in normal subjects is satisfactory. An important experimental variable is ambient temperature, since perfusion rates in normal limbs at low temperatures can approach those levels found in ischemic limbs. The intradermal technique has practical advantages over other methods for study of limb or skin perfusion.

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Evaluation of limb and skin perfusion using radionuclides has been useful in amputation-site selection for ischemic limb disease (*1*), in choosing appropriate treatment for chronic skin ulcers (*2*), and in assessing the maturation of pedicle flaps in reconstructive surgery (*3*). Following the amputation of a gangrenous limb, for example, the success of healing and acceptance of a prosthesis depends on the capillary perfusion of the skin at the level of amputation. The presence of healthy-appearing skin at a proposed amputation level is no guarantee that there will be adequate blood flow for wound healing because the blood supply required to heal an incision is greater than that required to maintain viability of intact skin. For the determination of the optimal amputation level, objective criteria based on skin temperature, level of distal pulse, or angiographic patterns have not been reliable, and surgeons often rely on clinical judgment and experience (*4*).

Xenon-133 has gained wide acceptance as an indicator of the perfusion of various organs, including kidneys, brains, and heart (*5*). Several investigators have used the clearance from the skin of Xe-133, intradermally or epicutaneously applied, to quantitate skin blood flow (*6,7*). The reported methods used probes, ratemeters, and strip chart recorders to measure the washout of Xe-133 from the skin, usually limited to a single site. Although determination of optimal amputation level by measurement of skin perfusion with intradermal Xe-133 has been reported, previous studies in humans neither documented the reproducibility of this technique nor carefully controlled variables such as sex, site and volume of injection, or ambient temperature, all of which may affect the measurements (*8*).

The first objective of this study was to adapt the method of measurement of skin-capillary perfusion, using intradermal Xe-133, to a gamma camera with minicomputer, making possible the simultaneous examination of several sites and rapid data processing. Next, we wished to determine the reproducibility of skin-perfusion measurements using intradermal Xe-133, and to evaluate the effects of ambient temperature and injection volume on the perfusion measurement. Because normal values for skin blood flow at different levels in the lower extremities are not readily available, we obtained representative values for selected sites in normal subjects.

MATERIALS AND METHODS

Five normal male volunteers ages 31–43, were studied

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at ambient temperatures between 25 and 30°C. The subjects rested supine for 15 min to stabilize body temperature. Using saline-rinsed tuberculin syringes and 26-gauge needles, 0.05 ml of Xe-133 in saline was administered intradermally at one of three locations on the anterior surface of the lower limb: 10 cm above the knee (AK), or 10 cm below the tibial tuberosity (BK), or at the dorsal junction of the foot and ankle. These sites were selected because they are on the incision lines for lower-extremity amputations, and the values obtained would eventually be compared with data obtained in patients with ischemic limb disease. The needle was kept in place for 10 sec after injection, and removal was followed by slight pressure for 5 sec to minimize any backflow through the perforation. Depth of injection was the same as for a TB skin test and the typical bleb of ID deposition resulted. The legs were lightly covered with a sheet before and after the injection to prevent heat loss by convection.

After both legs were injected, the xenon activity was monitored for 10 min, at four frames per minute, by a gamma camera with a low-energy parallel-hole collimator interfaced to a minicomputer scintigraphic system. The injection sites were displayed on the CRT, and areas of interest limited to these sites were chosen to generate time-activity curves. Using a least-squares fit for a monoexponential function, the slope constant of xenon washout was calculated for the first 6 min after injection. This slope value provides an essential component for the Schmidt-Kety equation:

$$F = \frac{100 \cdot \lambda \cdot K}{P},$$

where F = perfusion in ml/min per 100 g; K = slope constant of Xe-133 washout from the intradermal site (ml/min^{-1}); λ = blood-skin partition coefficient (= 0.7 ml/g); P = specific gravity of skin (= 1.05).

Duplicate perfusion determinations, 30 min apart, were used to assess the reproducibility of this technique in three subjects. The second injection was made 2 cm medial or lateral to the first but at the same level. Reproducibility of the procedure in the same subjects on different days was also evaluated. The injections were made in the same sites with the same volume and at the same ambient temperature.

The relationship between ambient temperature and skin perfusion at the BK and ankle levels was studied in two normal subjects, on four different days and at room temperatures varying from 20 to 35°C. Another variable, volume of injection, was studied in ten normal limbs (three subjects) by injecting one leg with 0.1 ml of Xe-133 in saline and 0.05 ml into the other. After 10 min of data collection, the procedure was repeated but the dosages were reversed. To examine the possibility that Xe-133 might escape through the injection track, fresh devitalized human skin contained in a 37°C water bath was injected with Xe-133 in saline intradermally, and measurement of the washout rate was determined with the same technique as in the volunteers.

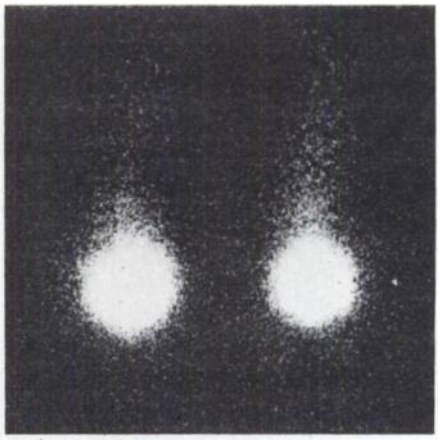

FIG. 1. Bilateral injections 10 cm below tibial tuberosity in normal subject. Note streaming of Xe-133 proximally. Time-activity curves are generated from areas of interest limited to injection sites.

RESULTS

Figure 1 shows camera images of bilateral intradermal Xe-133 injections below the knee in a normal subject. Figure 2 shows the first 10 min of the time-activity curve of Xe-133 washout from the skin of a normal volunteer. The slope of the initial 6 min was monoexponential in this study and in virtually all the other studies in normal subjects that allowed calculation of perfusion with the Schmidt-Kety equation ($r \geq 0.98$ in 93%, and $r \geq 0.90$ in 99% of 98 determinations). In a few experiments

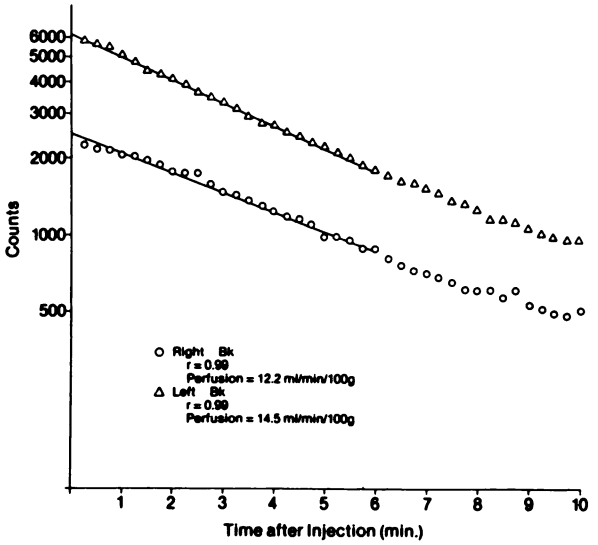

FIG. 2. Semilog plot of time-activity curve for intradermal Xe-133 washout from normal below-the-knee sites. Rate of washout is monoexponential for at least 6 min after injection.

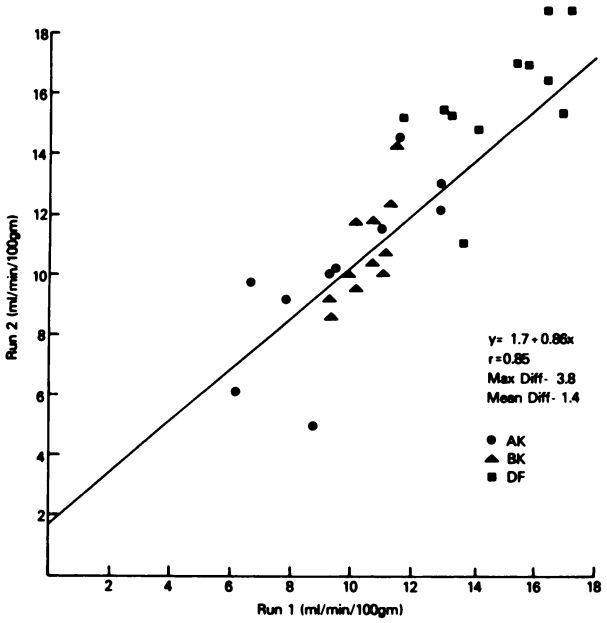

FIG. 3. Comparison of duplicate skin-perfusion measurements at three sites in three normal subjects on same day. Regression line is close to line of identity.

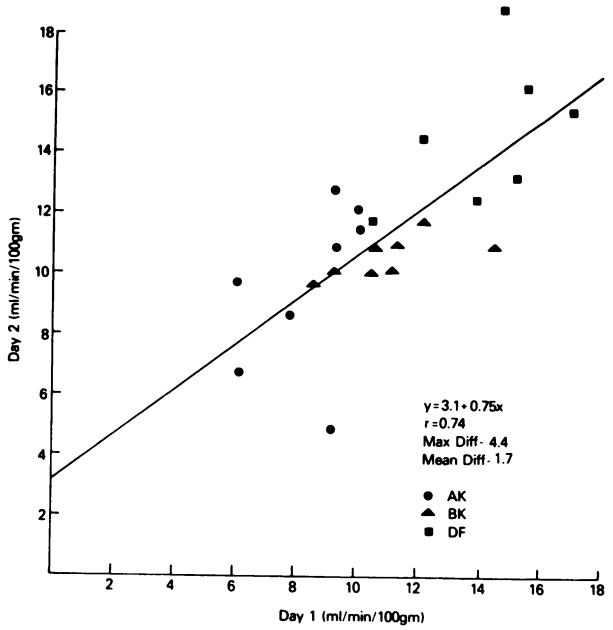

FIG. 4. Comparison of skin-perfusion measurements at three sites in two normal subjects on different days.

carried beyond 10 min, a second curve component was observed, probably due to diffusion of xenon from the injection site into the subcutaneous tissue and adherence to subcutaneous fat.

We assessed the reproducibility of the intradermal technique by performing duplicate perfusion determinations, either 30 min apart or 1 to 5 days apart, in normal volunteers at an ambient temperature of 28–29°C. As shown in Fig. 3, the regression line for duplicate skin perfusion measurements, performed at the same sites on the same day, approaches the line of identity, with a correlation coefficient of 0.85. The mean absolute difference between pairs was 1.4 ml/min per 100 g. Figure 4 shows the comparison between the perfusion rates on Day 1 and Day 2. The correlation coefficient was slightly less (0.75) and the mean absolute difference (1.7) was larger than the difference between same-day tests. Student's t-tests for paired data indicate that the differences between the two test runs on the same or different days were not significant ($p > 0.1$). The ranges of skin perfusion rates in ml/min per 100 g in the five normal subjects were 6.1–14.5 at the AK level, 8.6–14.5 at the BK site, and 10.4–18.8 at the ankle, with means of 8.9, 10.8, and 14.3.

The relationship between ambient temperature and skin perfusion in a normal volunteer is shown in Fig. 5. The below-knee and ankle sites in two subjects were tested at the four temperatures on four different days. At 20°C perfusion below the knee was low, and almost doubled at 25° and above. Perfusion in the ankle region at 20°C was even lower than below the knee, and rose in proportion to the increase in ambient temperature. At 20°C, skin blood flow in the two feet of one of the subjects was 1.3 and 3.1 ml/min per 100 g, values that are in the range found in ischemic limbs at warmer temperatures. In another subject a similar but less marked response to a change in ambient temperature was observed. Perfusion at the BK site fell slightly at 20°C, whereas at the ankle it fell to less than half the rate at 30°C (12.6 to 6.2 ml/min per 100 g).

Use of injection volumes of 0.1 or 0.05 ml in ten limbs resulted in average perfusion values (±s.e.m.) of 11.6 ± 0.7 and 10.9 ± 0.9 ml/min per 100 g, which are not

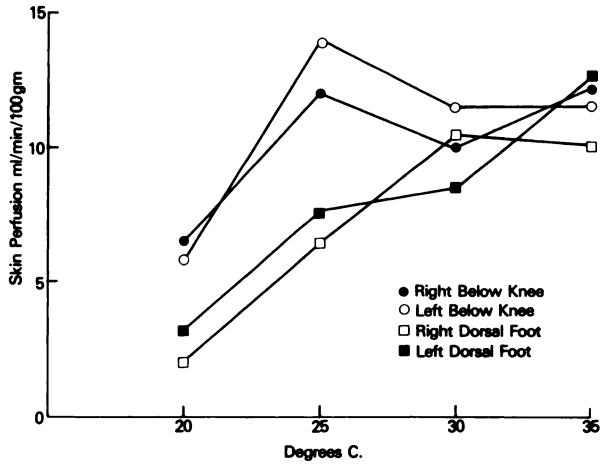

FIG. 5. Effect of temperature on skin perfusion at below-the-knee and ankle sites in a normal subject. Skin blood flow is temperature dependent, and at lower temperatures approached rates observed in ischemic limbs. Reproducibility studies were done at 28–30°C to avoid extreme values.

significantly different by the t-test for paired data. Nevertheless, in all other determinations we used a carefully measured volume of 0.05 ml.

A plot of the activity over the intradermal injection site in fresh, devitalized, full-thickness skin was essentially flat, with less than 2% variation in counts over 10 min. This indicates that Xe-133 does not escape through the epidermal barrier or along the injection track.

DISCUSSION

Systems using a gamma camera and computer have replaced probe-and-ratemeter systems for many diagnostic procedures. The former appear particularly helpful in measuring perfusion of the skin. After the data are acquired, only 10 min of operator time are necessary to set areas of interest, generate curves, and obtain a printed report of the perfusion at the injection sites. Of more importance is the ability of the camera system to examine several sites simultaneously. In this report only two sites were studied at one time, but we have performed four simultaneous measurements in one patient's gangrenous fingers. Complete examination of this patient would have been difficult to perform with a standard probe because of interfering activity from previously injected sites.

Radiotracers used in evaluating limb perfusion have included macroaggregated albumin particles tagged with Tc-99m, Tl-201, and Xe-133 (*2,9,10*). The major drawbacks of the tagged-particle method are the need for intra-arterial injections, and the comparative rather than quantitative nature of the data obtained. Although Tl-201 may be given intravenously, it has the same disadvantage as the tagged particles in that relative changes in limb perfusion are obtained, rather than absolute perfusion measurements. A major limitation to Tl-201 and tagged particles is that they do not allow isolated study of the overlying skin, which is the "target organ" most at risk following surgery for ischemia.

Although we used intradermal injection to deliver Xe-133, epicutaneous application has also been used. In the latter method, 2 to 5 mCi of xenon is deposited in a 1-ml reservoir formed by draping an adhesive polythylene sheet over the selected skin site followed by a 5- to 10-min wait for adequate labeling of the skin (*11*). Because the epicutaneous technique also labels subcutaneous tissue, which has greater affinity for xenon than the dermis, curve-peeling is needed to eliminate the slow component of subcutaneous washout. This lower-slope component cannot be approximated until 30 min after injection, which prolongs the test and impairs its clinical utility (*7*). In contrast, the washout rate for intradermal xenon is essentially monoexponential for the first 10 min, and although some labeling of the subcutaneous tissue may occur later, its contribution to the early washout curve is negligible.

Theoretical objections to the intradermal technique include possible backflow of the xenon through the injection track, and reactive hyperemia immediately following injection, both causing a false elevation of perfusion values (*12*). Our experiments with intact devitalized skin indicate that backflow or diffusion to the environment is not a significant concern. Reactive hyperemia would be expected to cause deviation from the monoexponential slope, which would be apparent in the first 10 min of the washout curve; such a deviation, however, was not observed. Moreover, if reactive hyperemia secondary to injection contributed significantly to the rate of washout, a higher flow rate would be expected with a larger injection volume, but we found no significant difference when the volume of injection was doubled. Perfusion values obtained with intradermal xenon have been validated by comparison with values obtained by venous occlusion plethysmography by Chimosky (*13*).

Our results show good reproducibility of the intradermal method on the same and different days when injection volume and ambient temperature were held constant. The values obtained with the camera- and-computer system in normal subjects agree with data reported in normal subjects using probe-and-ratemeter systems (*14*). The slightly higher perfusion at the ankle site, compared with the more proximal BK and AK sites, may be due to a more pronounced vasoactive response of the vessels in the distal portion of the leg. One other investigator has reported increased perfusion in the feet with intradermal xenon, but he did not note the experimental conditions of the test (*6*).

The effect of ambient temperature on skin perfusion was striking. A marked vasoconstrictive effect was seen at the normal ankle at 20°C, with skin-perfusion values similar to those seen in severe ischemia (*11*). A plateau was reached at approximately 25 to 35°C for the BK and ankle levels. Because of the low perfusion values obtained at low ambient temperatures, and because at high temperatures xenon can escape with sweat and give a falsely high perfusion value (*15*), we performed the reproducibility studies and clinical studies in patients at 25–30° in order to avoid spurious results.

The utility of skin-perfusion measurements with Xe-133 for clinical and research application has already been demonstrated in studies of ischemic limbs where an objective estimate of optimal amputation level was desired (*1*). The present computer-assisted study documents the reproducibility of the intradermal technique using Xe-133 as long as the ambient temperature is maintained relatively constant. The increasing availability of camera-computer systems in nuclear medicine departments suggests that this clinically useful procedure will have increasing application for the evaluation of patients with peripheral vascular disease.

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