Radionuclide Assessment of Peripheral Intravascular Capacity: A Technique to Measure Intravascular Volume Changes in the Capacitance Circulation in Man

DAVID L. RUTLEN, M.D., FRANS J. TH. WACKERS, M.D., AND BARRY L. ZARET, M.D.

SUMMARY Changes in the capacitance vasculature influence venous return and cardiac performance, so an understanding of the effects of pathophysiologic states on the human capacitance vasculature is necessary to understand integrated cardiovascular function in man. Techniques available to assess the capacitance vasculature in man, however, have limitations. We performed radionuclide imaging of the calf or forearm in 51 patients whose erythrocytes had been labeled in vivo with technetium-99m, basing our approach on the principle that counts from the radiolabeled intravascular space are proportional to blood volume. Two-minute or 15-second count acquisitions were obtained from the calf in 42 patients. Counts obtained at rest demonstrated little variation. With veno-occlusion at 15 and 30 mm Hg, counts increased 8 ± 1% (± SEM) (p < 0.001) and 28 ± 2% (p < 0.001), respectively. After 0.4 mg of sublingual nitroglycerin, counts increased 9 ± 1% (p < 0.001). With leg elevation, counts decreased 34 ± 4% (p < 0.001). Response patterns were similar with 2-minute and 15-second acquisitions. In nine patients who underwent forearm imaging (2-minute acquisitions), counts increased 14 ± 2% (p < 0.001) and 26 ± 4% (p < 0.001) at 15- and 30-mm Hg veno-occlusion and 15 ± 3% (p < 0.001) after nitroglycerin. Volume displacements, recorded simultaneously with a fluid-filled plethysmograph about the contralateral forearm, correlated linearly in all nine patients. Thus, gamma camera imaging of the radiolabeled peripheral intravascular space provides a quantitative and reliable assessment of peripheral vascular capacity in man. The technique could be used in conjunction with gated cardiac imaging in order to assess the interactions of peripheral vascular capacity and ventricular performance.

CARDIAC PERFORMANCE is influenced by ventricular preload. Ventricular preload is dependent, in part, on venous return, so cardiac performance is related importantly to the peripheral capacitance vasculature. Thus, an understanding of the behavior of the capacitance vasculature is important to an understanding of integrated cardiovascular function in man. Such knowledge is particularly relevant in view of the large number of pharmacologic agents that are thought to exert at least a portion of their influence on cardiac performance by affecting the peripheral capacitance vasculature.

However, understanding of the systemic capacitance vasculature is restricted by limitations in the techniques used to assess the capacitance circulation in man. Pressure determinations in a cutaneous vein at constant volume have required surgical isolation of the vessel.1 Diameter determinations of a cutaneous vein2 or circumference determinations of a forearm3 are noninvasive, but the techniques do not directly quantitate intravascular volume changes. Fluid displacement plethysmography directly measures total intravascular volume changes in the forearm,4-6 but it submits the capacitance vessels to venocompressive influences and is not ideally suited for continuous assessments of intravascular volume for periods of several hours. Such suitability is necessary to assess changes in the capacitance vasculature that might occur with particular pathophysiologic phenomena, such as spontaneously occurring coronary insufficiency, or with administration of pharmacologic agents, such as vasodilators.

The principles used to assess left ventricular function by ECG-gated equilibrium cardiac blood pool imaging7 should be applicable to assessment of the capacitance circulation in man. By labeling the patient's own erythrocytes with technetium-99m, 95% of the injected radionuclide is confined to the intravascular space.8 Within a few minutes of injection, radioactivity is distributed uniformly throughout the intravascular space. Consequently, radioactivity emanating from any region is proportional to the blood volume of the region, and thus, changes in count rate reflect changes in intravascular volume. This concept has been widely used to assess left ventricular ejection fraction, regional wall motion and relative chamber size.9 Okada et al.10 used quantitative blood pool imaging to demonstrate relative changes in pulmonary vascular blood volume during exercise-induced myocardial ischemia. We used these same principles to measure sequential blood volume changes in the systemic capacitance circulation. Specifically, in the present study we assessed quan-

From the Cardiology Section, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut. Supported by the Duberg Cardiovascular Research Fund and NHLBI grant R01-HL20690-03. Dr. Rutlen is the Duberg Scholar in Cardiovascular Disease. Presented in part at the American Heart Association Clinical Research National Meeting, May 10-12, 1980, Washington, D.C. Address for correspondence: David L. Rutlen, M.D., Cardiology Section, Yale University School of Medicine, 333 Cedar Street, 87 LMP, P.O. Box 3333, New Haven, Connecticut 06510. Received June 17, 1980; revision accepted October 21, 1980. Circulation 64, No. 1, 1981.
titative radionuclide imaging of the calf or forearm as a means of measuring both increases and decreases in intravascular volume during selective physiologic or pharmacologic interventions. Volume changes assessed in this fashion were correlated with volume changes assessed with a standard fluid-displacement plethysmograph.

Methods

Fifty-one subjects were selected for study from patients undergoing equilibrium gated cardiac blood pool imaging. Thirty patients had coronary artery disease, 13 had cardiomyopathy, seven had valvular heart disease, and one patient had congenital heart disease. The major considerations in patient selection were logistic and patient willingness to participate. The only patients excluded specifically from consideration as subjects were those receiving long-acting nitrates.

Each patient’s own erythrocytes were labeled in vivo with technetium-99m according to standard techniques. In brief, 15 mg of nonlabeled stannous pyrophosphate dissolved in 1.5 ml of normal saline solution were injected intravenously. Fifteen to 30 minutes later, 25 mCi of technetium-99m pertechnetate were injected. Cardiac imaging was begun 5 minutes after technetium injection. A single-crystal mobile gamma camera and mobile computer system (Ohio Nuclear VIP 550) were used. The camera was equipped with a general-purpose parallel-hole collimator. A 20% energy window was set symmetrically at 140 keV. All patients were studied in the supine position. After gated cardiac blood pool imaging was completed, the camera head was positioned as closely as possible above either a lower leg or forearm and parallel to the examining table. The camera was centered at midcalf or midforearm so that images were obtained from just below the knee or elbow to just above the ankle or wrist. No scatter of radioactivity from the trunk or contralateral leg was apparent in the periphery of any image. Subjects were urged to keep their limbs as immobile as possible during data acquisitions. Radioactive counts per unit time in the entire field of view were collected continuously by a self-prompting serial static acquisition computer program. Serial 2-minute acquisitions were collected in 29 patients. To ascertain whether briefer acquisition periods could be used, serial 15-second acquisitions were obtained in the remaining 22 patients. All data were stored on floppy discs. Count rates obtained in each subject were printed at the end of each study. All count rates obtained after the first count rate were corrected for physical decay of technetium-99m.

Calf Studies

The calf was imaged for 30–36 minutes in all subjects. To assess the reproducibility of the method, serial count acquisitions were obtained from 14 of these patients under entirely resting conditions: In four patients, acquisitions were obtained every 2 minutes and in 10 patients, every 15 seconds.

In 16 patients, 2-minute acquisitions were obtained before and during venodilation produced in two different manners. A control acquisition was obtained and the femoral blood pressure cuff was then inflated to 15 mm Hg for 4 minutes. An acquisition was obtained during the final 2 minutes of cuff inflation. The cuff was deflated for 2 minutes, and imaging then was repeated immediately before and during cuff inflation to 30 mm Hg as before. After the cuff was deflated the second time for 2 minutes, three baseline count acquisitions were obtained. Sublingual nitroglycerin (0.4 mg) then was administered and seven more count acquisitions were obtained. In four other patients, acquisitions were obtained every 15 seconds; cuffs were inflated and nitroglycerin was administered as before, except the cuffs were inflated for only 1½-minute periods.

To determine if decreases in intravascular volume could also be measured with this technique, 15-second-count acquisitions were obtained with leg elevation in eight subjects. Counts were obtained before, during, and after leg elevation to 20° with the ankle raised approximately 20 cm above the examining table. The gamma camera was carefully positioned to be parallel to the calf, to be at the same distance from the calf, and to be above the same region of the calf with the leg elevated as with the leg at rest.

Forearm Studies

To determine if changes in intravascular volume obtained by imaging the radiolabeled blood pool correlated with changes recorded with a standard plethysmographic technique, volume changes were recorded simultaneously with the radionuclide method in one forearm and by fluid-displacement plethysmography in the contralateral forearm in nine other patients. The specially designed fluid-displacement plethysmograph was made of clear plastic and was 17.5 cm long, 16.5 cm wide, and 17.0 cm high. The forearm was placed in an inner sleeve made of pliable dental rubber dam material and attached to the plethysmograph at both ends. The plethysmograph was filled with water at room temperature. Changes in forearm volume were obtained from changes in the height of water in a 19-mm-diameter plastic column attached to the top of the plethysmograph. Before insertion of the forearm in the plethysmograph, one of several different-sized heavy rubber rings was placed at the proximal end of the plethysmograph. The size was selected so that the rubber sleeve would not bulge out of the plethysmograph when filled with water but so that the proximal forearm was compressed as little as possible by the ring. The rubber sleeve was held in place at the distal end of the plethysmograph by a heavy rubber plate with an aperture which produced a secure fit around the wrist. A blood pressure cuff was placed around the upper arm just proximal to the plethysmograph. Brachial blood pressure cuffs about both arms were inflated simultaneously to 15–30 mm Hg and nitroglycerin was administered as described previously. Fluid displacements and count ac-
acquisitions were obtained every 2 minutes. Fourteen pairs of data were thus obtained for each of the nine patients, and linear regression was performed on these pairs in each patient.

Statistical Analyses

Paired t tests or analysis of variance was used in all cases. Statistical significance was at the p < 0.05 level.

Results

Calf Studies

In the 16 patients in whom 2-minute acquisitions were obtained from the calf, intravascular volume increased 8 ± 1% (± SEM) (p < 0.001) above control values with a cuff pressure of 15 mm Hg and 28 ± 2% (p < 0.001) with a cuff pressure of 30 mm Hg (fig. 1). These changes were also significantly different from each other (p < 0.001). After nitroglycerin, intravascular capacity increased to a maximum of 9 ± 1% (p < 0.001) above baseline. In the eight patients who underwent leg elevation, intravascular volume decreased 34 ± 4% (p < 0.001) (fig. 1). The absolute count values associated with cuff occlusion and nitroglycerin administration are illustrated in figure 2. Counts returned to baseline after release of the occlusion cuff on both occasions. Counts peaked 9 minutes after nitroglycerin administration and then returned toward baseline.

The reproducibility of count acquisitions in the 14 patients studied under resting conditions is shown in table 1. Small standard deviations for the means of the values were obtained during both 2-minute and 15-second count acquisitions. In the 10 patients who underwent 15-second acquisitions, every eight consecutive 15-second acquisitions were added in order to obtain consecutive 2-minute acquisitions. Two-minute acquisitions obtained at the same periods of time during resting conditions were then averaged for all 14 patients. The means are illustrated in figure 3. Note the stable baseline throughout the 30-minute period during which count acquisitions were obtained under resting conditions. The standard errors of the means (figs. 2 and 3) are relatively large because 25 mCi of technetium-99m were administered to all patients regardless of body weight or limb size. Furthermore, studies were not begun at the same time after technetium, allowing varying amounts of radioactive decay before the limb studies were begun and the first count acquisitions obtained.

In the four subjects in whom 15-second count acquisitions were obtained during interventions, counts increased 16 ± 9% (NS) with 15 mm Hg cuff occlusion, 26 ± 6% (p < 0.025) with 30 mm Hg occlusion, and 10 ± 3% with nitroglycerin administration (p < 0.05). Figure 4 illustrates the data from one of these patients.

Forearm Studies

In the nine patients in whom 2-minute count acquisitions were obtained from the forearm, counts increased 14 ± 2% (p < 0.001) above control with a cuff

<table>
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<tr>
<th>Pt</th>
<th>Mean counts (± SD)</th>
<th>SD/mean</th>
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<tbody>
<tr>
<td>1</td>
<td>17,872 ± 197</td>
<td>0.011</td>
</tr>
<tr>
<td>2</td>
<td>49,255 ± 614</td>
<td>0.013</td>
</tr>
<tr>
<td>3</td>
<td>17,573 ± 280</td>
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<td>4</td>
<td>12,602 ± 205</td>
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<td>5</td>
<td>20,600 ± 385</td>
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<tr>
<td>6</td>
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<td>7</td>
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<tr>
<td>8</td>
<td>8,966 ± 306</td>
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<tr>
<td>9</td>
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<td>10</td>
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<th>Pt</th>
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<th>SD/mean</th>
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<td>12</td>
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<td>13</td>
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<tr>
<td>14</td>
<td>175,000 ± 5,170</td>
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*The relatively large standard deviation of the mean for patient 10 was due to a slight but constant increase in counts throughout the 30-minute period.
pressure of 15 mm Hg and 26 ± 4% (p < 0.001) with a cuff pressure of 30 mm Hg (fig. 5). These changes were significantly different from each other (p < 0.01). After nitroglycerin, intravascular capacity increased to a maximum of 15 ± 3% (p < 0.001) above baseline (fig. 5). The absolute count values are shown in figure 6. Counts returned to or toward baseline after the peak effect of each intervention. The associated changes in intravascular volume measured simultaneously in the contralateral forearm with a fluid-displacement plethysmograph are shown in figure 6. In each patient, changes in radionuclide counts and volume displacements correlated in a linear fashion: \( r = 0.71, 0.73, 0.80, 0.81, 0.82, 0.91, 0.92, 0.94 \) and 0.98.

**Discussion**

The present study demonstrates the efficacy of quantitative scintillation camera imaging of the radionuclide-labeled peripheral blood pool for assessing intravascular blood volume changes in the capacitance vasculature in man. Measurements can be made quantitatively and rapidly and can detect both increases and decreases in intravascular volume in major portions of the systemic capacitance vasculature. Measurements made in this fashion correlate well with those made with a standard fluid-displacement plethysmograph.

The method we describe is sensitive enough to record intravascular volume changes during both physiologic and pharmacologic interventions. Increases in peripheral intravascular volume are recorded when peripheral venous pressures are increased to 15 and 30 mm Hg. Furthermore, significant differences in capacitance volume increments are detected at 15-mm Hg venous pressure compared with 30 mm Hg. Change in volume is also recorded after nitroglycerin is administered at a dose used clinically. Both a prompt increase in peripheral vascular volume after nitroglycerin and a subsequent decrease toward
baseline are recorded. Finally, a decrease in peripheral intravascular volume in the calf is recorded during leg elevation. The capacitance volume change produced by leg elevation is similar to the change expected with a patient moving from a standing to a recumbent position or with calf skeletal muscle contractions associated with walking.

Radionuclide assessments of peripheral vascular volume are reproducible and correlate well with a conventional assessment of capacitance volume. Nearly identical sequential count acquisitions are obtained under resting conditions (fig. 3). Variations in the sequential count acquisitions in individual subjects are very small (table 1). Similar patterns of response are recorded with both the gamma camera and the fluid-displacement plethysmograph (fig. 6). The two techniques correlate in a linear fashion in individual patients.

Imaging of the radionuclide-labeled peripheral blood pool possesses many advantages over other techniques. Pressure determinations in a surgically isolated and occluded forearm vein1 or diameter determinations in a cutaneous vein2 allow assessments of venous tone in large veins. The major portion of the capacitance blood volume, however, lies in small postcapillary veins and venules.12 Thus, pressure and diameter determinations of large veins do not record changes in the major capacitance vessels. Furthermore, surgical isolation of a forearm vein is likely to injure perivascular nerves important to venoregulation. Strain-gauge plethysmography is noninvasive and measures circumference changes in a limb,3 reflecting volume changes in postcapillary venules and veins. Such measurements may not always accurately reflect volume changes, however, because limb circumference is altered not only by volume changes, but also by geometric changes in the limb. Fluid-displacement plethysmography measures total intravascular volume changes in a limb,1*1* but it produces compressive forces on small cutaneous vessels. It is possible that when central venous pressure is low, important changes in limb intravascular volume are not recorded because some of the limb capacitance vessels are compressed by the pressure generated in the fluid-filled plethysmograph. Also, resting intravascular volume cannot be measured by fluid-displacement plethysmography, so volume changes cannot be determined as a percentage of resting intravascular volume. Finally, a patient is likely to be uncomfortable with his arm in a fluid-filled plethysmograph for several hours, as would be necessary to measure capacitance volume changes during several therapeutic interventions. Imaging of the radiolabeled blood pool in the peripheral capacitance vasculature avoids all of these problems. Total intravascular volume changes in the forearm or calf can be assessed noninvasively and without external venocompressive forces. Volume contributions from all vessels, small postcapillary veins and venules and large veins and arteries, are measured in the region of interest. The measurements can be obtained over long

Figure 4. Absolute count values obtained with serial 15-second count acquisitions in a patient's calf.

Figure 5. Percentage change in forearm counts during interventions. Abbreviations and symbols are as in figure 1.
periods with no discomfort to the patient. Also, volume changes can be measured as percent changes compared to resting intravascular volume. Although we could have used a nonimaging gamma detector, a scintillation camera was used because it is readily available to most investigators.

Greyson et al. measured calf volume changes using a radionuclide technique similar to ours. Their study, however, was directed at the diagnosis of venous diseases. They did not correlate radionuclide changes with changes measured with a standard plethysmographic technique, produce graded increments in vascular volume, perform assessments after the administration of vasoactive agents, or demonstrate that count acquisitions could be obtained reliably for less than a minute.

Our method is ideal for examining the capacitance vasculature under various physiologic and clinical conditions. Volume assessments can be made as often as every 15 seconds, allowing assessment of the possible reflex autonomic influences of such brief events as spontaneously occurring coronary insufficiency on peripheral intravascular volume or the rate at which peripheral volume is changed after the administration of rapidly acting vasoactive drugs. Such capacity assessments might be used in conjunction with assessments of ventricular performance. Hoffer et al. demonstrated that left ventricular ejection fraction can be monitored reliably with a miniaturized 175-g module using a cadmium telluride semiconductor detector. The module is strapped directly to the chest and detects volume-related changes in left ventricular radioactivity such that ejection fraction can be determined in the conventional ECG-gated mode. With such a module positioned over the left ventricle and either a gamma camera or a second module positioned over the calf, the interaction of left ventricular function and peripheral intravascular blood volume could be examined readily.

As with other studies of absolute ventricular volume, our method might be further refined in order to measure absolute peripheral intravascular volume. By measuring the radioactivity of a venous blood sample and considering limb geometry and attenuation of counts by limb tissue, it should be possible to measure the absolute volume of the radiolabeled intravascular space within the field of the gamma camera. Such assessments might be correlated with absolute changes in ventricular volume during various interventions.

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