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Dynamic Fluctuations in Blood and Spleen Radioactivity: Splenic Contraction and Relation to Clinical Radionuclide Volume Calculations

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Alterations in the blood radioactivity affect ventricular volume calculations using count-based radionuclide ventriculography. To study this phenomenon, the effect of time, posture and supine exercise on blood radioactivity, red blood cell count and splenic radioactivity was evaluated. The red blood cell count, and blood, splanchnic and splenic radioactivity remained stable in five patients studied at rest in the supine position. On standing, blood radioactivity increased 10 ± 3% (standard error of the mean), and abdominal radioactivity decreased 14.5 ± 6.5% (both $p < 0.05$). In 10 patients, splenic radioactivity decreased after supine exercise by 49 ± 7%, while blood radioactivity increased 10.5 ± 1.5% and red blood cell count increased 7.5 ± 1.5% (all $p < 0.001$). Splenic radioactivity increased gradually after exercise and decreased after a second exercise period. In the exercising patients, blood radioactivity increased by 14.5% and correlated with an increase in the red blood cell count ($r = 0.57$, $p = 0.01$, 19 samples from 10 patients). Reduction in splenic radioactivity also correlated with the increase in red blood cell count ($r = -0.51$, $p = 0.025$).

The data demonstrate splenic shrinkage in human beings and an inverse relation between changes in splenic and blood radioactivity. These dynamic fluctuations emphasize the need for simultaneous blood sampling for accurate calculation of left ventricular volume and highlight the importance of regional volume shifts during exercise.

Accurate measurements of left ventricular volume have been made with gated equilibrium radionuclide ventriculography and the radioactivity in peripheral blood samples (1–4) using in vivo red blood cell labeling (5). Marked changes in left ventricular volume may occur with exercise, but recent data (6,7) demonstrate that the blood radioactivity per milliliter also increases. Thus, simultaneous blood samples are needed during peak exercise to quantitate left ventricular volume changes accurately. The mechanisms responsible for the increase in blood radioactivity have not yet been determined. We have noted marked reductions in splenic radioactivity with exercise in patients undergoing supine radionuclide ventriculography. Thus, we imaged the left ventricle and abdomen at rest and after exercise to evaluate the changes induced by exercise in the splanchnic and splenic beds, the erythrocyte count and blood radioactivity.

Methods

Study patients. The study group consisted of 31 patients undergoing radionuclide ventriculography for the assessment of ischemic heart disease. Left ventricular volumes determined by contrast and radionuclide ventriculography were compared in nine patients. In 7 patients, we studied red blood cell labeling efficiency and in an additional 15 patients we compared abdominal and blood radioactivity and the red cell count. Five of the latter 15 patients were studied at rest, and 10 were studied both at rest and after exercise according to the protocols outlined in this section. Thirteen of the 15 patients were men, and all those studied

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in the exercise protocol were men with an average age of 58.9 ± 12.1 years (standard deviation).

Radionuclide studies. Red blood cells were labeled in vivo (5) using 1.5 mg of stannous pyrophosphate (Mallinckrodt) followed by 20 or 25 mCi of technetium-99m pertechnetate for rest or exercise studies, respectively. Images were obtained using a low energy, all purpose collimator attached to a Picker mobile scintillation camera interfaced to a DEC 11/34 computer. Electrocardiographic gated equilibrium cardiac blood pool images were obtained using 30 to 40 ms/frame, 20 frames/cardiac cycle and a 64 × 64 image matrix, with 5 and 3 minute collections for rest and exercise, respectively. Static images of the left side of the abdomen were collected in the left anterior oblique view for 2 minutes using a 64 × 64 matrix. Abdominal background radioactivity was taken to represent an index of splanchnic blood volume and was estimated by drawing a region of interest medial to the spleen, avoiding the liver and other vascular pools. Blood samples for erythrocyte counts and blood radioactivity were drawn from a separate site from that used for isotope injection. Red blood cell counts were determined using a Coulter counter, and the blood radioactivity was estimated from 0.2 ml blood samples counted in duplicate in a well counter (Searle Autogamma). All radioactivity data were corrected to "time zero," defined as the time of technetium injection, and all blood data were expressed per milliliter of sample. In our laboratory, the coefficient of variation for the Coulter counter averages 0.6%, and the combined pipetting technique and gamma scintillation counting had a 0.8% coefficient of variation.

Left ventricular volume estimation. The left ventricular volume on radionuclide ventriculography was compared with the contrast ventriculographic volume in nine patients in stable condition. The contrast ventriculograms were obtained by injection of 40 to 45 ml of a mixture of sodium and meglumine diatrizoate (Renografin-76) injected in the 30° right anterior oblique position and recorded on 35 mm film at 60 frames/s. End-diastolic and end-systolic frames were traced from the first well opacified nonpremature or postpremature contractions. Left ventricular volume was calculated using the area-length method for single plane ventriculography (8). The radionuclide ventriculograms were obtained within 24 hours of the contrast studies by the method outlined. Simultaneous 5.0 ml blood samples were pipetted into a petri dish using a pipette with 0.5% accuracy (Oxford) and counted for 5 minutes on the face of the same camera-collimator system. The radionuclide ventriculographic volumes were calculated using validated user-developed software for border definition (9) and a radionuclide volume equation without attenuation correction (1,2) and compared with the volumes obtained with contrast ventriculography.

Erythrocyte labeling efficiency. This was determined in a separate group of seven patients using the same timing as that in the rest protocol (see later) and using the method described by Callahan et al. (10). In brief, 5 ml of whole blood was injected immediately after withdrawal into a tube containing stannous diethylenetriamine pentaacetic acid in order to chelate free pertechnetate. The hematocrit was determined in duplicate on 0.2 ml aliquots. The remaining blood was centrifuged at 400 *g* for 10 minutes. Duplicate 0.2 ml aliquots of the supernatant plasma were placed in counting tubes and counted with the whole blood fractions on an automatic gamma scintillation counter (Searle Autogamma) with the energy window spanning 120 to 160 keV. The labeling efficiency (L.E.) was calculated with correction for background radioactivity (Bkg) according to the formula:

$$\text{L.E.} = \frac{(\text{Cpm whole blood} - \text{Bkg})}{\text{Cpm whole blood} - \text{Bkg}} - \frac{(\text{Cpm plasma} \times \text{plasmacrit}) - \text{Bkg}}{\text{Cpm whole blood} - \text{Bkg}} \times 100,$$

where Cpm = counts per minute.

Rest protocol. Five patients studied at rest allowed comparison with those studied before and after exercise. Patients rested in the supine position for 10 minutes before the first image collection. Blood samples and abdominal scintigrams for splenic and background radioactivity were obtained sequentially at 10, 20 and 30 minutes after "time zero." The patients then stood upright for 5 minutes before blood, splenic and abdominal radioactivity were remeasured.

Exercise protocol. Ten patients underwent two sequential exercise studies. Each lay supine for 15 minutes after the injection of technetium-99m pertechnetate. Then, a blood sample and an abdominal scintigram were collected. Maximal symptom-limited supine bicycle ergometer exercise was performed for 5 to 6 minutes. A blood sample and a supine abdominal image were repeated immediately after peak exercise (exercise 1). Abdominal scintigrams were obtained sequentially at 2, 6 and 10 minutes after the first exercise period. Each patient was then re-exercised using the same protocol (exercise 2). A blood sample and an abdominal scintigram were obtained immediately after exercise.

Data analysis. Data were entered into a medical data base management system (CLINFO, supplied by the Division of Research Resources, National Institutes of Health, Bethesda, Maryland). Analysis of variance, Student's paired *t* test and linear regression analysis were employed as appropriate. Statistical significance was defined as probability (p) less than 0.05.

Results

Left ventricular volume estimation. The relation between radionuclide and contrast ventriculographic volume estimates performed in our laboratory at supine rest in patients was highly significant ($r = 0.94$, $p < 0.001$, n =

18, combining both the end-diastolic and end-systolic volumes).

Erythrocyte labeling efficiency. The red blood cell labeling efficiency remained stable throughout the study period. At 10 minutes after injection, 94.7 ± 1.8% (standard deviation) ($n = 7$) of the radioactivity was bound within red blood cells. At 30 minutes, 95.8 ± 1.5% of the radioactivity was bound. The increase was not statistically significant. The range of labeling values was 91.6 to 97.5% at 10 minutes and 93.2 to 97.6% at 30 minutes.

Rest data. Changes in blood radioactivity, splenic and abdominal background activity and the erythrocyte count were compared with the initial value for each, normalized as 100%. There were no significant changes in these variables at supine rest (Fig. 1). However, on standing, there was an increase in blood radioactivity of 10 ± 3% (standard error of the mean) ($n = 5$, $p < 0.05$) along with a decrease in abdominal background activity of 14.5 ± 6.5% ($p < 0.05$). The splenic counts tended to decrease on standing, but this change was not statistically significant (Table 1).

Exercise data. Figure 2 shows the changes in splenic and abdominal background radioactivity in a typical patient. Immediately after exercise the splenic and abdominal radioactivity decreased considerably. Splenic activity tended to increase toward control levels during the recovery period, whereas splanchnic activity changed minimally. In 9 of the 10 patients studied after a second exercise period, trends for splenic and splanchnic radioactivity were similar to those of the first exercise period (Table 1). The 10th patient had a decrease in splenic activity after the first exercise period but an increase after the second when compared with the control image.

Exercise results for the 10 patients summarized in Figure 3. Immediately after exercise, splenic radioactivity decreased by 49 ± 7% (standard error of the mean) ($n = 10$, $p < 0.001$) and abdominal background radioactivity decreased by 14 ± 6% ($p < 0.03$). Blood radioactivity increased by 10.5 ± 1.5% ($p < 0.001$), and the erythrocyte count increased by 7.5 ± 1.5% ($p < 0.001$). Splenic radioactivity increased toward control levels during the recovery period, but the mean splanchnic activity did not change significantly. After exercise period 2, splenic radioactivity decreased by 31 ± 11% ($p < 0.003$), although the abdominal background radioactivity did not decrease significantly.

Nineteen postexercise blood samples were available. Blood radioactivity and erythrocyte count increased serially from the control period to completion of the second exercise study by a mean of 14.5 ± 1.5% ($p = 0.001$) and 8.5 ± 1.5% ($p < 0.03$), respectively. Although, there was a significant relation between the changes from control levels in the erythrocyte count and blood radioactivity, the correlation was not tight ($r = 0.57$, $n = 19$, $p = 0.01$) (Fig. 4).

The r value comparing the change in blood radioactivity from control with the first postexercise period was 0.62 ($p = 0.057$, $n = 10$). The r value comparing the change from control with the second postexercise samples was 0.50 ($p = 0.17$, $n = 9$). The changes between the two exercise periods were unrelated ($r = 0.005$, $p = 0.99$, $n = 9$). The decrease in splenic radioactivity was related inversely to the increase in red blood cell count ($r = -0.51$, $p = 0.025$, $n = 19$) (Fig. 5). For 18 of 19 data pairs, the red cell count increased while splenic activity decreased. For the 19th, splenic activity increased and the red cell count increased as well. Excluding that instance, the r value was -0.47 ($p = 0.05$).

Discussion

This study and those of others (1,3,11) show a close relation between the left ventricular volume calculated from radionuclide and contrast ventriculography in human beings.

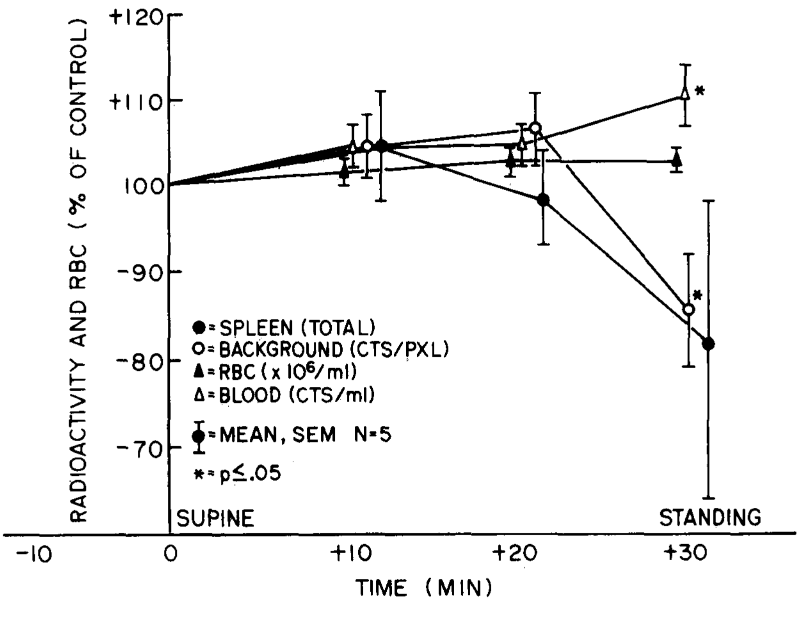


Figure 1. Changes in splenic and splanchnic radioactivity, blood radioactivity and red blood cell (RBC) count in five patients when supine and standing. There was no significant difference in either variable at supine rest over 20 minutes. However, the blood radioactivity per milliliter (CTS/ml) increased and splanchnic (abdominal background) radioactivity per picture element (CTS/PXL) decreased on standing. The decrease in splenic radioactivity did not achieve statistical significance. The red blood cell count was stable. N = number of patients; p = probability; SEM = standard error of the mean.

Table 1. Changes in Splenic and Splanchnic Radioactivity in Patients Studied at Rest and During Exercise

Rest Study

	Supine						Standing	
	0 Min		10 Min		20 Min		30 Min	
Patient	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl
1	104,810	125.0	117,261	117.0	95,931	134.9	59,006	116.3
2	66,964	111.3	55,798	122.7	64,958	116.0	44,073	111.7
3	84,408	148.0	91,510	159.0	98,141	145.0	113,210	100.0
4	90,427	127.0	96,715	127.0	88,644	128.0	96,861	94.0
5	52,113	203.0	58,828	216.6	45,418	238.0	21,908	184.0
Mean	79,744	142.9	84,022	148.5	78,618	152.4	67,012	121.2*
SD	20,561	36.1	26,236	41.4	22,750	49.0	37,583	36.2
SEM	9,195	16.1	11,733	18.5	10,174	21.9	16,808	16.2

Exercise Study

	Pre Ex 1		Post Ex 1		+ 2 Min		+ 6 Min		+ 10 Min		Post Ex 2	
Patient	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl	Spleen	Bkgd/Pxl
1	141,211	117.7	61,419	124.5	99,509	119.7	122,310	120.6	125,869	121.0	78,511	123.1
2	24,754	111.9	7,679	94.2	12,087	94.7	11,945	95.4	13,035	92.8	5,713	103.0
3	55,372	185.4	23,550	166.6	49,200	159.7	67,988	161.0	72,261	148.0	31,154	151.6
4	82,040	137.7	49,560	125.6	62,272	128.7	63,328	129.6	66,079	138.7	59,297	140.0
5	73,518	160.0	40,662	157.9	48,245	155.5	54,619	156.7	75,468	160.4	42,031	155.7
6	82,236	169.1	46,998	111.2	44,594	108.0	46,337	108.9	47,658	108.1	48,079	134.6
7	59,195	112.5	10,311	70.8	75,829	69.5	76,940	70.0	91,793	71.8	17,586	80.8
8	146,516	95.3	83,325	87.9	85,365	85.4	89,968	86.1	93,772	89.8	77,532	94.2
9	135,461	114.9	129,430	67.5	124,438	67.6	130,372	68.1	134,518	70.3	122,879	72.0
10	29,184	132.6	17,702	152.2	32,417	149.7	35,295	150.9	33,660	152.0	42,191	139.0
Mean	82,949	133.7	47,063†	113.8†	633,957*	115.8†	69,910†	114.7†	75,411	115.3†	52,497†	119.4
SD	44,578	29.2	37,519	34.5	33,409	35.8	36,889	34.7	38,220	33.6	33,996	29.9
SEM	14,097	9.2	11,865	10.9	10,565	11.3	11,666	11.0	12,086	10.6	10,751	9.5

*$p \leq 0.05$ compared with supine rest; †$p \leq 0.03$ compared with Pre Ex 1 supine. Splenic radioactivity (total counts corrected for background) and splanchnic radioactivity (background counts per picture element, Bkgd/Pxl) both corrected for time. SD = standard deviation; SEM = standard error of the mean.

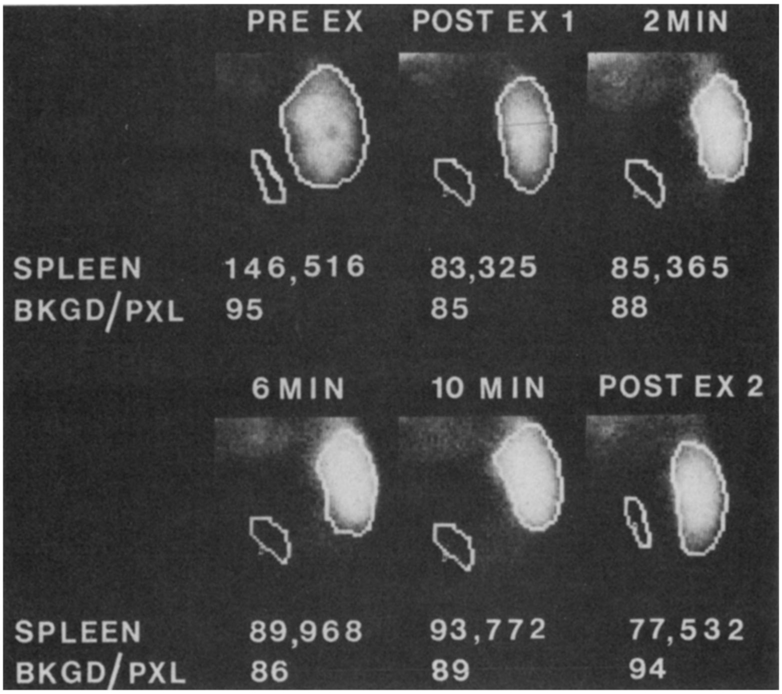


Figure 2. Splenic and splanchnic radioactivity before (PRE) and after (POST) exercise (EX) in a typical patient. Both splenic and splanchnic radioactivity (background counts per picture element, BKGD/PXL) decreased considerably after exercise (EX_1). Splenic radioactivity gradually increased during a 10 minute postexercise period and decreased on repeat exercise testing (EX_2).

This accuracy occurs when simultaneous peripheral venous blood samples are employed to determine the blood radioactivity per unit volume. Red blood cell labeling allows evaluation of not only the cardiac volume, but also the distribution of regional blood volume. Studies of the pulmonary volume (12–14) and the blood volume in the limbs (15) have been performed. The efficiency of red cell labeling that we and others (5,10) have demonstrated allows the general assumption that these estimates of blood volume are accurate in all regions where the hematocrit is the same as the peripheral venous hematocrit.

Changes in splenic radioactivity with supine exercise. This study demonstrates that supine exercise causes marked changes in the abdominal blood distribution, red blood cell count and blood radioactivity. There was a considerable reduction in the splenic radioactivity after exercise. The splenic radioactivity decreased by an average of 49% during exercise, and the changes in splenic radioactivity were greater than the changes in splanchnic radioactivity.

Potential splenic reservoir function during exercise. *Experimental studies.* In dogs, the spleen contracts vigorously both in vivo (16,17) and in vitro (18). Vatner et al. (16) demonstrated splenic contraction in exercising dogs with maintenance of mesenteric and renal flow. After splenectomy there was a significant reduction in mesenteric and renal flow. Guntheroth and Mullins (19) found that splenic volume decreased in response to epinephrine, fright, hemorrhage and exercise. The degree of splenic contraction during exercise decreased both with time and training (19). The mechanism of splenic contraction in the dog is due to contraction of the numerous smooth muscle fibers present in the capsule and trabeculae (20).

Clinical studies. There has been considerable dispute regarding the function of the spleen during exercise in human beings. Ebert and Stead (21) found no evidence for mobilization of blood reserves by exercise, epinephrine or hemorrhage, on the basis of hematocrit, plasma volume and serum protein data. Ayers et al. (18) studied isolated, perfused human spleens and found that electrical stimuli, epinephrine and norepinephrine caused marked increases in splenic vascular resistance but minor changes in splenic volume. However, Bierman et al. (22) angiographically documented splenic artery constriction and reduction in splenic size before and after epinephrine injections with a catheter inserted into the splenic artery. They concluded that this phenomenon was due to arterial and arteriolar constriction

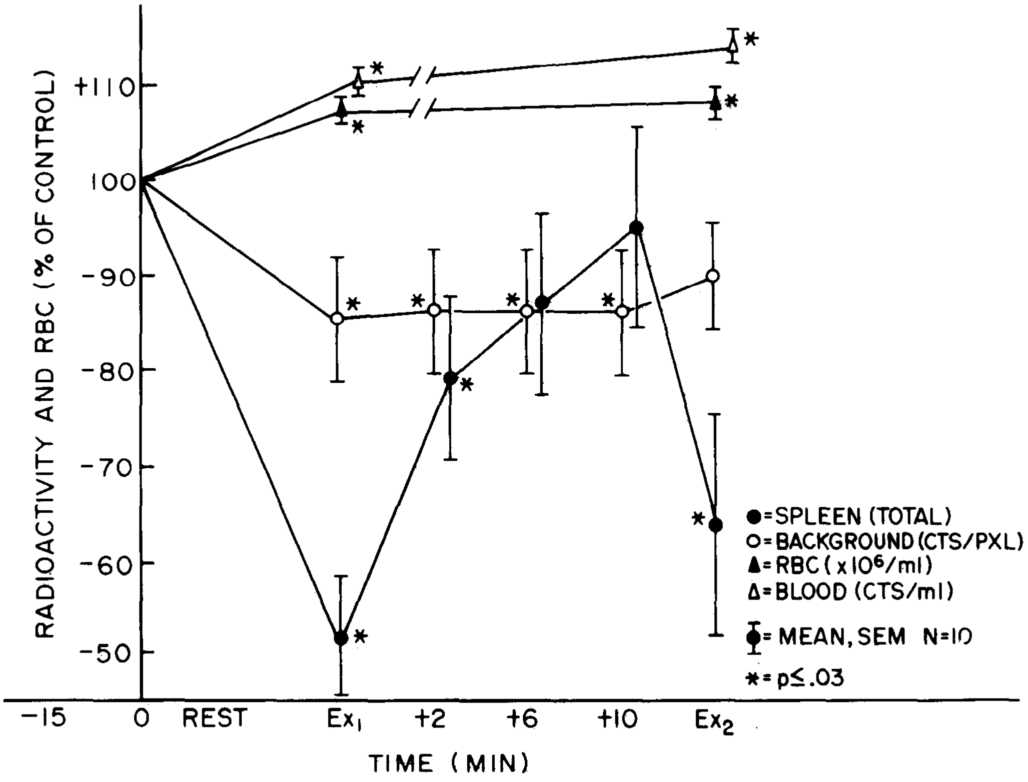


Figure 3. Changes in splenic and splanchnic radioactivity, blood radioactivity and red blood cell (RBC) count in 10 patients after supine exercise. The red cell count and blood radioactivity increased and splenic radioactivity decreased significantly during both exercise periods (EX_1 and EX_2). Abdominal (background) radioactivity decreased significantly during the first exercise study. Abbreviations as in Figure 2.

with subsequent shrinkage of the spleen "by exsanguination" rather than by active contraction. Two previous radionuclide studies (23,24) demonstrated a decrease in radioactivity in response to subcutaneous epinephrine. Catecholamines increase considerably during exercise (25), and thus, sympathoadrenal activation may induce both splenic and splanchnic vasoconstriction.

We believe that our clinical study is the first to demonstrate splenic shrinkage after exercise. Two interpretations of the data are possible. First, the spleen may contract actively. Second, the change may be passive with progressive egress of blood after splanchnic flow is reduced. Regardless of the mechanism, it is apparent that the spleen may have a reservoir function during supine exercise. We found a slightly smaller decrease in splenic radioactivity after the second exercise in our patients and an actual increase in a single patient. This may be related to such training effects as described in the dog model (19).

Changes in splanchnic radioactivity with exercise. The 15% decrease in the abdominal background radioactivity with supine exercise is probably secondary to splanchnic vasoconstriction, which has been documented by other methods in patients undergoing supine exercise studies (26,27). This effect was present but less prominent after the second exercise study. The cause of this blunted response is not clear but may be due to the same neurohumoral or training effects, or both, that we postulate to govern splenic contraction (19).

Changes in radioactivity and red blood cell count at supine rest and with standing. The fluctuations induced by exercise contrast with the stability of these variables at rest. The blood radioactivity, erythrocyte count, abdominal background activity and splenic radioactivity did not change in serial supine studies. This implies mixing of the labeled red cells in the entire vascular space, including the spleen, within approximately 10 minutes after pertechnetate injection. On standing, the blood radioactivity and erythrocyte count increased, and the splanchnic radioactivity declined. However, the decrease in splenic radioactivity did not achieve statistical significance. These data regarding mixing agree with studies in the canine model (28), in which blood radioactivity was constant by 10 minutes in splenectomized dogs and 20 minutes in nonsplenectomized dogs.

Changes in blood radioactivity and red blood cell count with supine exercise. In our patients, the blood radioactivity and erythrocyte count increased significantly after exercise. The blood radioactivity and red cell count increased proportionally after the first exercise period, but the increases were smaller between the first and the second exercise periods. For all 19 postexercise samples, the increase in blood radioactivity correlated loosely with increase in the erythrocyte count ($r = 0.57$, $p = 0.01$). Additional mechanisms may account for this lack of close correlation. One mechanism might be a reduction in plasma volume. Senay et al. (29) demonstrated a decrease in plasma volume during supine bicycle exercise which did not occur in patients undergoing treadmill exercise. Protein leakage from the vascular compartment was postulated. Konstam et al. (6) showed a stronger correlation between these two variables than we found. Neither we nor Konstam et al. measured plasma volume.

Implications. This study demonstrates that the increase in blood radioactivity in patients undergoing radionuclide ventriculography during supine exercise is correlated with a reduction in splenic radioactivity. The magnitude of the change in blood radioactivity makes it important to obtain matched blood samples to calculate left ventricular volume at rest and during exercise. On the basis of our data, failure to take this change in blood radioactivity into account could produce a 14% error in left ventricular volume measurement.

Figure 4. Changes in blood radioactivity and red blood cell count in 19 patients after exercise. Each increased significantly compared with preexercise control (C) levels, but the correlation was not close.

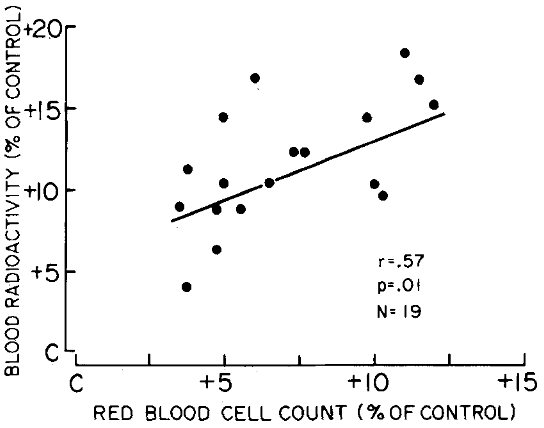
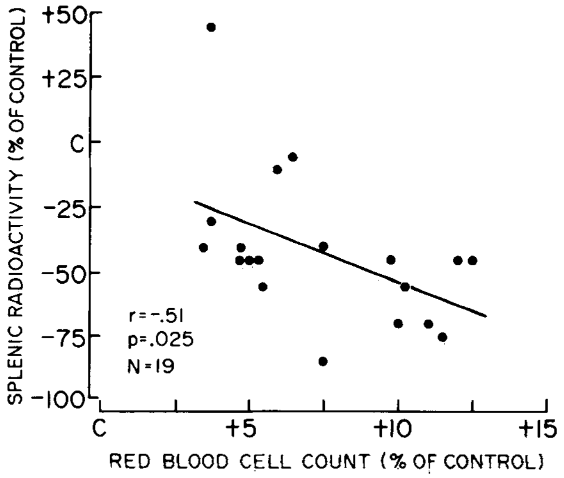


Figure 5. Changes in splenic radioactivity and red blood cell count in 19 patients after exercise. There was a slight inverse relation such that red blood cell count increased as splenic radioactivity decreased.



Studies of the regional distribution of blood volume should be useful to study the integrated response of the circulation to physical maneuvers or vasoactive drugs and in diseased states, such as chronic congestive heart failure. Several studies (12,14,30) demonstrated changes in the lung radioactivity from rest to exercise as an index of pulmonary blood volume. Each showed an increase in an index of pulmonary blood volume on exercise in patients with left ventricular ischemia. However, the absolute change may be less than thought (11), once the changes in the blood radioactivity per milliliter enter the calculation. Rutlen et al. (15) used the red cell labeling method to demonstrate changes in calf and forearm vascular capacity on elevation and external constriction and after nitroglycerin. The accuracy of such changes should be enhanced by comparison with simultaneous blood samples. The splenic and splanchnic volume responses we demonstrated increase the list of vascular regions that are amenable to study by red cell labeling. Our data demonstrate the importance of obtaining simultaneous blood samples during exercise in order to quantify flux in the relative volumes of vascular organs and beds.

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