Reproducibility of Ejection-Fraction Determinations by Equilibrium Radionuclide Angiography in Response to Supine Bicycle Exercise: Concise Communication

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Sixteen patients with stable, chronic coronary artery disease were studied twice within an average of 15 days to evaluate the reproducibility of ejection fraction (EF) determined by equilibrium radionuclide angiography (EQ) at rest, during supine bicycle exercise (ex), and in the recovery period (rec). Following injection of 20–25 mCi of Tc-99m-tagged human serum albumin, data were analyzed for 2-min periods at rest, during several stages of exercise (submax, max), and during recovery (rec_1 = minutes 2 + 3, rec_2 = minutes 9 + 10). Each patient reached similar (heart rate) × (blood pressure) products in the two studies: 21280 ± 5200 compared with 20390 ± 4140 mmHg/min. Mean EFs for the first and second studies were: at rest (53.0 ± 10.8)%, (52.5 ± 10.4)% (r = 0.95); submax ex (51.4 ± 12.0)%, (52.1 ± 12.8)% (r = 0.91); max ex (50.6 ± 12.6)%, (51.6 ± 12.9)% (r = 0.97); rec_1 (62.7 ± 11.6)%, (62.4 ± 12.2)% (r = 0.95); rec_2 (55.5 ± 10.8)%, (57.2 ± 11.7)% (r = 0.91). In stable patients, the reproducibility of EF determined by EQ is excellent during rest, supine bicycle exercise, and recovery from exercise.

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Equilibrium radionuclide angiography (EQ) is an increasingly popular nontraumatic procedure that permits serial determinations of left-ventricular ejection fraction (EF) at rest and during exercise or other interventions. It requires just one peripheral venous injection to be made using an appropriate radiopharmaceutical such as Tc-99m-labeled human serum albumin (*1*). Several investigators have reported the validity of EF as determined by EQ at rest (*2–4*) and during exercise (*4*). In particular, it has been pointed out that changes in left-ventricular EF between rest and exercise constitute a very sensitive means of discriminating between normal individuals and patients with coronary artery disease (CAD)—namely by the absence of an exercise-induced rise in EF in the latter group (*5–7*). Furthermore, EQ has been applied in the investigation of patients with aortic valvular disease and cardiomyopathies and has shown that this technique is a specific indicator of global LV function (*6,8–10*).

If this holds true, gated equilibrium radionuclide angiography may become a most useful tool in the diagnosis and evaluation of patients with various forms of heart disease, particularly patients with suspected CAD. If clinical decisions are to rely on this test of ventricular function, the results of this new method must be shown to be reproducible, not only at rest, but during exercise and in the recovery period as well.

The aim of this study, therefore, was to test the reproducibility of EQ-EF determinations made at rest, during exercise, and in the recovery period.

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METHODS

Patient selection. Sixteen male patients with ages ranging from 32 to 67 yr (mean 51 yr) were included in the study after written informed consent was obtained. All patients were judged clinically to have chronic stable CAD. Twelve patients had a documented old myocardial infarction (6 mo to 5 yr before), while four patients had typical chronic exercise-induced angina pectoris with significant ST depression during pain. No patient showed signs of heart failure at the time of study. Two patients were on propranolol medication and three on digitalis. There were no changes in symptomatology nor in therapy between the two studies.

Equipment and imaging technique. Multiple ECG-gated equilibrium radionuclide angiography was performed after complete mixing throughout the vascular space of 20–25 mCi of Tc-99m-labeled human serum albumin administered in an arm vein (*4*). Imaging was performed by positioning the detector of a single-crystal Anger camera over the chest in a 40–50° left anterior oblique (LAO) projection and a 5–10° caudad tilt in order to isolate optimally the left ventricle from surrounding structures such as the right ventricle and left atrium. Data acquisition was accomplished with a commercially available nuclear medicine computer system that divides the R-R interval into 28 equal time periods (frames) of 20 or 40 msec duration depending upon heart rate. It then assembles several hundred heart cycles at corresponding times to generate composite images throughout the cardiac cycle. In a 2-min acquisition, usually 2500–7000 counts (corrected for background) could be accumulated within the left ventricular region-of-interest at end-diastole in one 40-msec frame.

In order to generate a time-activity curve, a rectangular region-of-interest was arbitrarily placed around the left ventricle at end-diastole. A computer algorithm (MUGE) was then used to determine automatically the edge of the left ventricular chamber using a combination of the second derivative and a count-rate threshold of 5% per element as guidelines. Each subsequent frame was processed at the same level of threshold so that throughout all 28 frames a "variable" region-of-interest was used to determine the changing count rate within the left ventricle. A computer-assigned background region-of-interest outside the left lower quadrant of the LV was used to correct for noncardiac activity. Ejection fraction was then calculated from the time-activity curve according to the formula:

$$EF = \frac{ED_c - ES_c}{ED_c} \times 100,$$

where ED_c = left ventricular counts at end-diastole (usually the first frame of the time-activity curve, corrected for background) and ES_c = left ventricular counts at end-systole (nadir of curve, corrected for background).

Ejection fractions calculated by this technique have been shown to correlate well with those determined from biplane cinenagiography, with correlation coefficients reported by others as ranging between 0.84 and 0.94 (*2,3*) and from our laboratory as 0.91 (*4,6*).

Our laboratory uses set rules that leave the rectangular region-of-interest around the left ventricle as the only variable. The automated computer algorithm (MUGE), as previously described, then provides a virtually negligible inter- and intraobserver variability in any given study. Still, to reduce this factor even more in the analysis of our data, all studies of this series were processed by one observer.

Study protocol. All patients were studied on two separate occasions averaging 14.5 days apart: three patients were restudied after 1 day, four after 7 days, six after 10–17 days, and three after 24–66 days. On each occasion the patient was studied first at rest in a basal state; then during a graded supine bicycle exercise with up to three levels of increasing work, each lasting 3 min and discontinued because of angina or fatigue; and finally during the initial 10 min of the recovery period (Fig. 1). During the initial study, the work load was increased individually so that the patient was symptom-limited at the end of the second or third exercise level. For the repeat study, the same work loads were used as during the initial exercise test. An electronically

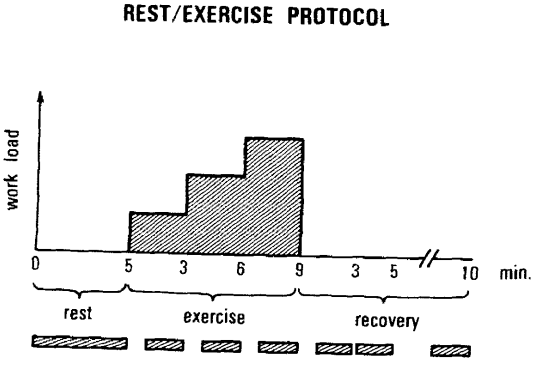

FIG. 1. Protocol that was followed for each patient on each of two days. Times of data acquisition for calculation of ejection fraction are indicated at bottom (EF). Heart rate was recorded continuously, and arm-cuff blood pressure was measured at rest, peak exercise, and 3 min after exercise. Work load was increased individually in similar increments, so that patients had to stop after 6 or 9 min because of angina or fatigue. Work levels chosen during first study were applied again in repeat study.

braked bicycle ergometer* was used and provided a constant work load at a pedal speed of 50–70 rpm, so that the exercise work loads on the two test days could be kept the same. In both studies the patients had their legs elevated about 15° during the exercise period only. Eight patients exercised for a total of 6 min and eight patients for 9 min. The average maximal work load reached was 575 ± 177 kilopounds meter/min. Five patients had to discontinue exercising because of anginal pain, whereas the others stopped because of fatigue. In all patients the exercise-limiting symptoms were the same in both studies.

Recordings of EQ data were made at rest (5 min) and continuously throughout the entire exercise and recovery periods. These data were then divided into serial 2-min periods (Fig. 1): one at the end of each 3-min work load level (i.e., minutes 2 + 3, 5 + 6, and 8 + 9), and three during the recovery period (minutes 2 + 3, 4 + 5, and 9 + 10 after exercise). This was done so that the first minute of each new work level and the first minute postexercise were disregarded in order to avoid periods during which rapid changes in heart rate and other hemodynamic variables might affect the accuracy of the EF calculation by EQ.

In addition, a modified V_5-lead ECG was recorded throughout the entire study, and arm-cuff blood pressures were measured at rest, peak exercise, and 3 min after exercise.

The statistical analyses used in this study were the Student's t-test for paired samples, the standard equation for linear regression [$study_1$ = (slope × $study_2$) + intercept] and significance of differences between correlation coefficients.

RESULTS

The mean heart rate of the 16 patients increased in the first study from 67.0 ± 8.6 (1 s.d.) beats/minute at rest to 119.8 ± 20.9 beats/min at maximal exercise, then fell to 77.9 ± 14.4 beats/minute at 10 min after exercise. In the repeat study, performed on a different day, the corresponding values were 67.6 ± 7.9 at rest, 116.3 ± 19.7 at peak exercise, and 74.9 ± 9.8 beats/min at 10 min after exercise. There were no significant differences between the corresponding pairs. The mean (heart rate) × (blood pressure) product at peak exercise in the first study was (212.8 ± 52.0) × 10^2 mm Hg/min, and in the repeat study (203.9 ± 41.4) × 10^2 mm Hg/min. Again, no significant differences were found between the pairs. Thus, according to these parameters, the patients reached a very similar level of cardiac work in both studies. The results of the EF calculations are listed in Table 1. There were no significant differences between the two studies at any time. The length of time between the two studies of each patient (1 day to 9 wk) did not seem to influence the results in these stable CAD patients. The mean EF did not change significantly from rest to peak exercise in the 11 patients limited by fatigue [(53.8 ± 11.1)% at rest and (54.2 ± 12.5)% at maximal exercise], whereas it decreased significantly in the subgroup of five patients whose exercise was terminated because of angina [(from 51.2 ± 11.2)%, rest, to (42.8 ± 9.3)% at peak exercise, $p < 0.01$]. There was an increase in EF to greater than the resting EF in the early recovery period (minutes 2 + 3) in all patients; this is the overshoot phenomenon previously reported (6).

The comparison of EF results is shown in Table

TABLE 1. EJECTION FRACTIONS OF BOTH STUDIES

Patient No.	Study 1							Study 2							Exercise-limiting symptom
		Exercise			Recovery				Exercise			Recovery			
	Rest	2 + 3	5 + 6	8 + 9	2 + 3	4 + 5	9 + 10	Rest	2 + 3	5 + 6	8 + 9	2 + 3	4 + 5	9 + 10	
1	64	58	54	—	73	74	65	60	57	52	—	68	69	60	angina
2	39	32	29	—	48	44	40	34	29	28	—	44	41	35	angina
3	47	40	41	—	53	57	—	50	46	45	—	57	60	—	angina
4	60	59	65	67	73	61	60	60	66	69	69	77	70	68	fatigue
5	32	32	32	—	41	38	35	33	30	35	—	45	42	42	fatigue
6	62	56	53	48	68	62	64	62	64	62	51	70	60	57	angina
7	63	54	59	52	68	70	67	61	58	59	48	66	73	71	fatigue
8	74	74	74	75	81	76	74	69	73	72	76	86	83	82	fatigue
9	55	52	61	53	75	62	60	56	62	63	54	70	64	63	fatigue
10	43	35	38	—	51	51	46	41	37	36	—	49	55	53	fatigue
11	44	44	42	—	51	47	43	46	41	41	—	44	41	41	angina
12	49	52	52	—	61	52	51	47	57	55	—	61	52	54	fatigue
13	60	62	64	—	72	67	61	56	56	61	—	68	61	60	fatigue
14	55	58	54	55	67	62	55	60	57	54	57	68	59	56	fatigue
15	53	64	62	52	67	65	58	61	56	66	61	69	64	63	fatigue
16	48	50	50	51	54	58	54	48	45	47	52	57	57	57	fatigue
Mean	53.0	51.4	51.9	50.6*	62.7	59.1	55.5	52.5	52.1	52.8	51 6*	62.4	59.4	57.2	
±1 s.d.	10.8	12.0	12.7	12.6	11.6	10.6	10.8	10.4	12.8	13.0	12.9	12.2	11.7	11.7	

* Maximal exercise value of all patients

TABLE 2. COMPARISON OF MEAN EJECTION FRACTIONS FOR BOTH STUDIES

		Exercise			Recovery		
	Rest	2 + 3′	5 + 6′	Max	2 + 3′	4 + 5′	9 + 10′
Mean Study 1	53.0	51.4	51.9	50.6	62.7	59.1	55.5
±1 s.d.	10.8	12.0	12.7	12.6	11.6	10.6	10.8
Mean Study 2	52.5	52.1	52.8	51.6	62.4	59.4	57.2
±1 s.d.	10.4	12.8	13.0	12.9	12.2	11.7	11.7
Correlation coeff.	0.95	0.91	0.97	0.97	0.95	0.92	0.91
Intercept	4.12	2.31	1.43	1.61	− 0.41	− 0.64	3.16
Slope	0.91	0.97	0.91	0.99	1.00	1.02	0.98

Correlation equation: $EF_{study\ 1} = (slope \times EF_{study\ 2}) + intercept$

2 and Fig. 2. The best correlation coefficient was seen at peak exercise, where the patients reached their maximal tolerable work limit. The r value was almost equally good at rest and during the early recovery period at the time of the "overshoot" EF increase. Somewhat poorer correlations were found during the early, submaximal exercise level (minutes 2 + 3) and in the later recovery period (minutes 9 + 10 postexercise), but there were no statistical differences between correlation coefficients obtained during rest, exercise, or recovery periods.

DISCUSSION

The present study was designed to test the reproducibility of ejection-fraction calculations from equilibrium radionuclide angiography at rest, during various levels of supine bicycle exercise, and in the postexercise period. Results suggest that this new method provides excellent reproducibility at rest, at peak exercise, and during the early recovery period. Ejection fraction determinations made during the submaximal and later postexercise periods were somewhat less reproducible than those at peak exercise, but there was no significant difference between their correlation coefficients. The differences in EF between the initial and the second study, as observed during the first level of exercise, might have resulted from a certain anxiety on the part of the patients at the first exercise test; this, in turn, was reflected in a slightly increased heart rate at this point during the initial as compared with the second study (98.3 ± 16.4 against 93.5 ± 15.8 beats/min, $p < 0.05$). This explanation cannot be applied to the late recovery period, in which no significant heart rate differences were noted.

The average difference between the two resting ejection fraction studies was essentially zero, with an upper 95% confidence limit of this difference of two percentage units. For the ejection fraction at peak exercise, the average difference was one, with a 95% confidence limit of three. Thus, any intervention (i.e., beta-blockade or exercise training) must produce a mean change for the same size group in ejection fraction of approximately twice the magnitude of these limits to be significant. Results of the second ejection fraction study could be

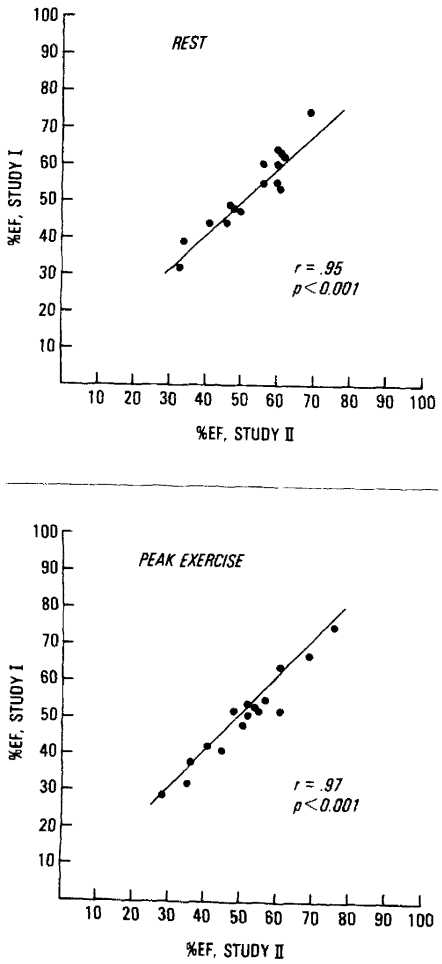

FIG. 2. Correlations between %EF from Study I and Study II, at rest, and at peak exercise.

accepted to be different with 95% confidence if different by more than four at rest and different by more than six at maximal exercise. For a difference to be significant to the 95% confidence level for a given individual, the change must be greater than two times the standard deviation. At rest, the difference should be greater than eight, and at exercise the difference should be greater than six.

Clinically, we find no need to perform more than three stages of exercise. Our experimental protocol has shown us, however, the importance of going to a maximal work load. Some patients will have a normal rise during submaximal workloads but drop at maximal. The recovery "overshoot" shows the importance of using the ejection fraction during maximal exercise for diagnostic purposes rather than a postexercise value.

The normal ejection fraction response to supine exercise is still uncertain. Various criteria have been recommended including an increase of 10 or 15% of the resting value, an exercise value of greater than 55%, or a "significant" rise of 8 percentage units over baseline. All our coronary patients had abnormal responses to both studies by the 10% increase criteria except Patients 4 and 8. Patient 4 was normal both times, whereas Subject 8 was abnormal the first study and normal the second.

Thus, the results suggest that maximal, symptom-limited exercise is important to obtain maximally reproducible ejection fraction results under exercise. As we (*6*) and others (*5,7,11*) have reported previously, EF in this study did not change significantly between rest and peak exercise in CAD patients whose exercise was limited by fatigue, whereas EF fell significantly in individuals who experienced angina before discontinuing exercise. These findings are in contrast to the response in normal subjects, in whom we have observed an average rise of 21% (range 10–51) of the resting EF at peak exercise.

We conclude that ejection fractions determined by equilibrium radionuclide angiography provide reproducible results in clinically stable individuals at rest, during peak supine bicycle exercise, and during the early recovery period. This method is reproducible, thereby permitting clinically useful conclusions to be drawn from measurements of serial changes in ejection fraction.

FOOTNOTE

* Uniwork-845-T, Quinton Instruments, Seattle, WA.

ACKNOWLEDGMENTS

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