Effects of Isometric Handgrip and Dynamic Exercise on Left-Ventricular Function

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Radionuclide angiocardiography was used to assess cardiac function during isometric handgrip and bicycle exercise in ten normal volunteers and in 20 patients with documented coronary artery disease. Handgrip stress evoked a small increase in cardiac output that resulted from a concomitant increase in heart rate and no change in left-ventricular function. The most reliable criterion for diagnosis of coronary artery disease by handgrip was development of a new wall-motion abnormality. However, abnormal wall motion was observed in only 45% of patients with coronary artery disease and in one of the ten normal subjects. In normal subjects, left ventricular function during bicycle exercise was characterized by an increase in left-ventricular ejection fraction with little change in cardiac volumes. The failure to increase left-ventricular ejection fraction by at least 0.05 identified 19 of 20 patients with coronary artery disease with no false positives. Therefore, bicycle exercise evokes a more dramatic cardiovascular response than handgrip stress and is the preferable stress modality for inducing abnormalities of left-ventricular function for detection of coronary artery disease.

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Radionuclide angiocardiography permits noninvasive measurement of myocardial function of subjects during different physiologic conditions (*1*). Recent studies suggest that dynamic exercise results in a decrease in left-ventricular ejection fraction in patients with coronary artery disease in contrast to the normal increase in ejection fraction during exercise (*2,3*). These changes elicited by dynamic exercise appear to be very sensitive indicators of coronary artery disease (*4*). Isometric handgrip has also been advocated as a mechanism to evoke stress for diagnosis of coronary artery disease (*5,6*). Handgrip stress is easier to perform and safer than dynamic exercise and, therefore, would be a preferable stress technique if the two evoked similar responses. This study was designed to examine the effect of both stress techniques on left-ventricular function in normal individuals and patients with documented coronary artery disease.

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METHODS

Patient selection. Studies were performed in ten normal volunteers (mean age 26 ± 2 yr) and 20 patients with coronary artery disease (mean age 54 ± 7 yr). The normal group consisted of eight men and two women with no cardiac disease suggested by history, physical examination, or electrocardiogram. The coronary disease group included 16 men and four women admitted to the medical center for cardiac catheterization because of angina pectoris. None of these patients had evidence of earlier myocardial infarction by history or electrocardiogram. All patients on propranolol therapy had the drug discontinued at least 48 hr before the test. Significant coronary disease was diagnosed by coronary arteriogram as a 75% stenosis in one or more coronary arteries, and four additional patients who did not have significant coronary disease by this criterion were not included in the study.

In normal subjects, the rest-handgrip and rest-exercise comparisons were made 2 days apart on separate study periods. To avoid bias introduced by a higher level of excitement on the first test experience, the type of stress used during the first study period was alternated. In the normal group, blood pressure and heart rate returned to baseline values within 1 min after completion of the handgrip test in each subject. Studies in the patient group were done consecutively during the same study period a day before cardiac catheterization. A radionuclide angiocardiogram at rest was followed by a study during handgrip. After a 15-min recovery period, a dynamic exercise study was obtained to complete the evaluation.

Data acquisition. With informed consent from each subject, a 20-gauge Teflon catheter was inserted into the external jugular vein. An eight-lead electrocardiogram (I, II, III, aVR, aVL, aVF, V_5, V_6) was continuously observed on an oscilloscope display, and representative tracings were recorded each minute throughout the study. Systemic arterial pressure was monitored by sphygmomanometry. All radionuclide angiocardiograms were performed using a computerized multicrystal gamma camera* equipped with a 1-in. parallel hole collimator. A 10-mCi pertechnetate (Tc-99m) injection was made for each measurement with subjects sitting in the erect position. Counts were recorded for 1 min with an anterior projection and 25 msec frames.

After completion of a rest study, subjects compressed the dynamometer to maximum and then maintained one third of the maximal compression for 3.5 min. The blood pressure was measured after 1 and 2 min and at the time of the injection which was made at the third minute. Handgrip stress was maintained during a further 30-sec period to ensure complete transit of the radiotracer through the heart.

Dynamic exercise tests were performed using an isokinetic bicycle ergometer. Heart rate, blood pressure, and ECG were monitored during the erect exercise and subsequent recovery period until both returned to baseline values. Exercise was begun at a 200 kpm/min workload, and the workload was increased by 100 kpm/min every minute until a study endpoint was achieved. Endpoints used to time the injection for the exercise study included achievement of target heart rate for age, onset of angina, occurrence or increase in arrhythmia, or 2 mm ST segment depression on ECG.

Data processing. The radionuclide angiocardiograms were analyzed as previously described (*7–9*). Observed counts were corrected for variation in detector efficiency and electronic dead-time loss of the instrument. Data obtained during the handgrip and exercise studies were also corrected for background activity, which was determined by a 15-sec measurement obtained just before the study. Data recorded over the left-ventricular region of interest produced a high-frequency time-activity curve that had sufficient time resolution to reflect count changes that occur within individual cardiac cycles. An average cardiac cycle was obtained by summing counts from several contractions recorded at the time when the radioactivity was maximal within the chamber. Background counts were subtracted by defining the spatial distribution of radioactivity just before the tracer filled the left ventricle, and multiplying this image by an intensity factor derived to describe the average change in counts outside the left ventricle during the levophase.

Left-ventricular ejection fraction was determined from the background-corrected representative cycle as ED counts − ES counts/ED counts where ED = end-diastole and ES = end-systole. The 21% isocount contour of the end-diastolic image was used to calculate the end-diastolic volume (EDV) in milliliters. The area of the end-diastolic image was obtained by planimetry, and the length of the major axis was measured using a sonic digitizing device coupled to a computer. The EDV, calculated by the area-length method of Sandler and Dodge (*10*), was multiplied by the ejection fraction to provide the stroke volume, which was multiplied by heart rate to give cardiac output. A regional ejection-fraction image was generated by subtracting end-systolic counts from end-diastolic counts and dividing by end-diastolic counts for each crystal within the left-ventricular region. The resulting counts were displayed as a 16-color isocount picture normalized to unity so that each color change represented a 6.25% range of ejection fraction.

Regional wall motion was assessed by concurrent inspection of static images of the computer-generated perimeters of systole and diastole, regional ejection-fraction images, and cine format display of the radionuclide ventriculogram. These two latter approaches may reflect count change in depth and do not require count changes in the plane of the field of view. Wall motion was categorized as normal, hypokinetic, akinetic, or dyskinetic in the anterolateral, apical and inferoseptal segments.

Statistical analysis. Group mean values are reported ± one standard deviation. Changes in individual measurements were analyzed by Student's paired t-test. Group responses were compared by two-way analysis of variance. A $p < 0.05$ was considered significant.

RESULTS

Left-ventricular function in normal subjects. The handgrip stress in ten normal subjects evoked an average heart-rate increase of 17 beats/min and an average mean blood-pressure increase of 21 mm Hg (Fig. 1). The mean cardiac output increased 1.5 l/min, and this change resulted fully from the increase in heart rate, since the ejection fraction, end-diastolic volume, end-systolic

	R	H	P
HEART RATE (beats/min)	70 ± 12	87 ± 22	<0.05
BLOOD PRESSURE (mean, mmHg)	85 ± 15	106 ± 15	$<10^{-3}$
CARDIAC OUTPUT (L/min)	5.9 ± 1.9	7.4 ± 2.0	<0.05

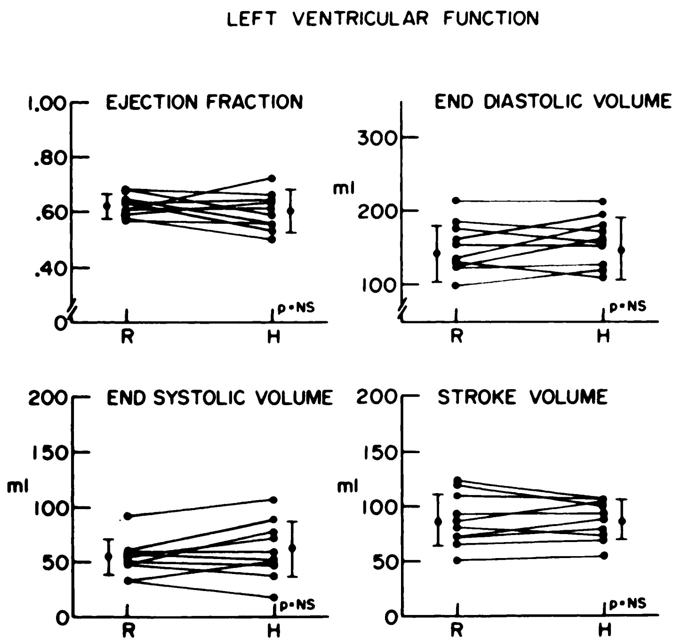

FIG. 1. Cardiac response to isometric handgrip in ten normal subjects. R = rest, H = handgrip.

volume, and stroke volume were not altered. Although there was no significant group change in ejection fraction, four subjects decreased ejection fraction by more than 0.05, and one of these normal subjects developed a definite wall-motion abnormality during handgrip stress.

In response to the dynamic bicycle exercise, the normal subjects showed an average increase of 97 beats/min in heart rate and no significant change in mean blood pressure (Fig. 2). The average cardiac output increased by 13.8 l/min. The increased output resulted from an increase in heart rate, but the left-ventricular ejection fraction also increased in each individual. The average end-diastolic volume increased from 130 ± 31 ml to 154 ± 38 ml, and the stroke volume from 79 ± 20 ml to 116 ± 29 ml so that the end-systolic volume of 51 ± 16 ml at rest decreased to 39 ± 17 ml during exercise. None of these normal subjects had an abnormality of left-ventricular wall motion at rest, although bicycle exercise enhanced wall motion throughout the group.

Left ventricular function in patients with coronary artery disease. Handgrip stress in the 20 coronary patients evoked an average heart-rate increase of 22 beats/min and an average mean blood-pressure increase of 27 mm Hg (Fig. 3). Cardiac output increased from 6.2 ± 1.9 l/min at rest to 7.3 ± 2.2 l/min during stress. The average ejection fraction in these 20 patients decreased by 0.07 without consistent change in stroke volume or end-diastolic volume. Consequently, the end-systolic volume rose from 56 ± 32 ml at rest to 69 ± 37 ml during handgrip stress. It follows that the small increase in cardiac output resulted solely from an increase in heart rate. Four patients with coronary disease had hypokinesia of the left ventricle during rest. During handgrip stress, nine patients developed a new focal abnormality of wall motion or increased one already present at rest.

Bicycle exercise in group patient of 20 increased the heart rate from 79 ± 20 at rest to 133 ± 23 during exercise (Fig. 4). The mean blood pressure increased by 12 mm Hg for the group. Cardiac output was 6.2 ± 1.9 l/min at rest and 11.5 ± 4.2 l/min during exercise. The average ejection fraction during exercise was 0.07 lower than that during rest. All but four of the 20 patients decreased ejection fraction during exercise, and the remaining increase was small in the four subjects without a decrease in ejection fraction during exercise. The end-diastolic volume increased from 136 ± 49 ml at rest to 171 ± 60 ml during exercise. The stroke volume remained unchanged, and the end-systolic volume increased from 56 ± 13 ml at rest to 82 ± 48 ml during exercise. Exercise elicited a new wall-motion abnormality, or increased one present at rest, in 12 of the 20 patients with coronary disease.

Comparison between the normal subjects and the patients with coronary artery disease. The response of the left ventricular ejection fraction (LVEF) to isometric handgrip provided some discrimination between normal

	R	E	P
HEART RATE (beats/min)	67±8	164±7	$<10^{-10}$
BLOOD PRESSURE (mean, mmHg)	95±7	100±21	NS
CARDIAC OUTPUT (L/min)	5.2±1.2	19.0±4.7	$<10^{-6}$

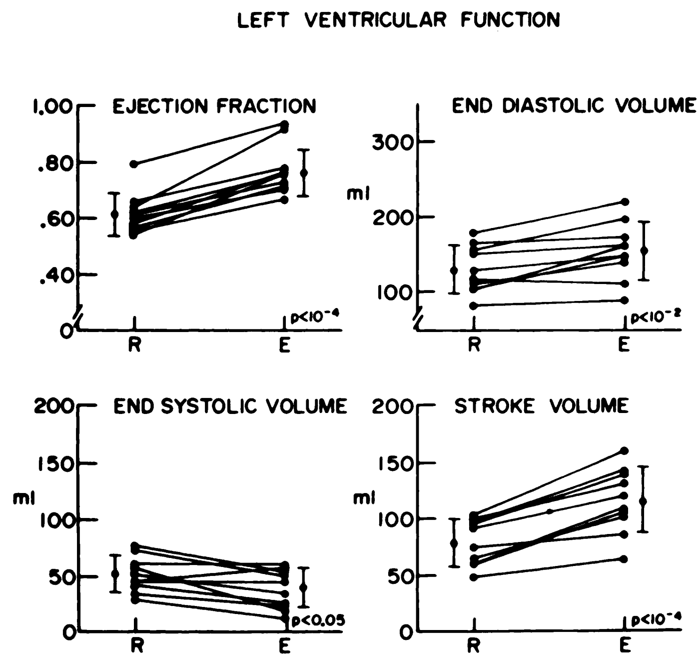

FIG. 2. Cardiac response to bicycle exercise in ten normal subjects. R = rest, E = exercise.

subjects and coronary patients (Fig. 5), but overlap in the response prohibited use of this measurement to separate normal from abnormal individuals. In contrast, the change in EF during dynamic exercise clearly separated patients with coronary artery disease from normal subjects. All ten normal subjects increased left ventricular ejection fraction by at least 0.07 during dynamic exercise. Four patients with coronary artery disease increased the ejection fraction less than 0.07, and the remainder of the group with disease did not change or actually decreased ejection fraction. The change in end-systolic volume during isometric handgrip provided no discrimination between normal patients (Fig. 6). By contrast, individual discrimination was possible using the response of the end-systolic volume to dynamic exercise. Nine of the ten normal subjects decreased end-systolic volume, whereas 17 of the 20 coronary patients increased end-systolic volume during dynamic exercise. The appearance or enhancement of a wall-motion abnormality was indicative of coronary artery disease in that only one normal subject showed a wall-motion abnormality during isometric stress, and no such abnormality occurred in normal subjects during dynamic exercise. However, wall motion assessment was not a sensitive discriminator; 11 patients had normal wall motion during handgrip stress and eight patients during dynamic exercise.

DISCUSSION

Myocardial ischemia implies an imbalance between myocardial blood supply and metabolic demand. In patients with stable coronary artery disease, myocardial ischemia rarely occurs at rest when metabolic demands are low. Under stress conditions, delivery of blood through stenosed vessels may be inadequate to meet the increased metabolic demand. We are comparing the results of two kinds of stress.

Isokinetic bicycle exercise and isometric handgrip are known to cause different hemodynamic responses. During bicycle exercise, systolic arterial pressure rises but diastolic does not, and there is relatively little change in mean arterial pressure. Heart rate and cardiac output rise markedly, and the amount of change, related to the degree of exertion, imposes a volume load on the left ventricle. In contrast, handgrip evokes only small changes in heart rate and cardiac output. Systolic and diastolic arterial pressures rise, and the increase in mean arterial pressure imposes a pressure load on the left ventricle (*11–14*).

The clinical importance of electrocardiography during dynamic exercise is well recognized (*15*). Recent studies using radionuclide angiocardiography at rest and during bicycle exercise have induced marked regional and global alterations in left-ventricular function in patients with coronary artery disease (*3*). In contrast to a normal increase in ejection fraction during exercise, patients with myocardial ischemia decrease the ejection fraction. The decrease is caused primarily by an increase in end-diastolic volume with a constant or slightly increased stroke

	R	H	P
HEART RATE (beats/min)	79 ± 20	101 ± 20	$<10^{-7}$
BLOOD PRESSURE (mean, mm Hg)	95 ± 12	122 ± 18	$<10^{-7}$
CARDIAC OUTPUT (L/min)	6.2 ± 1.9	7.3 ± 2.2	<0.05

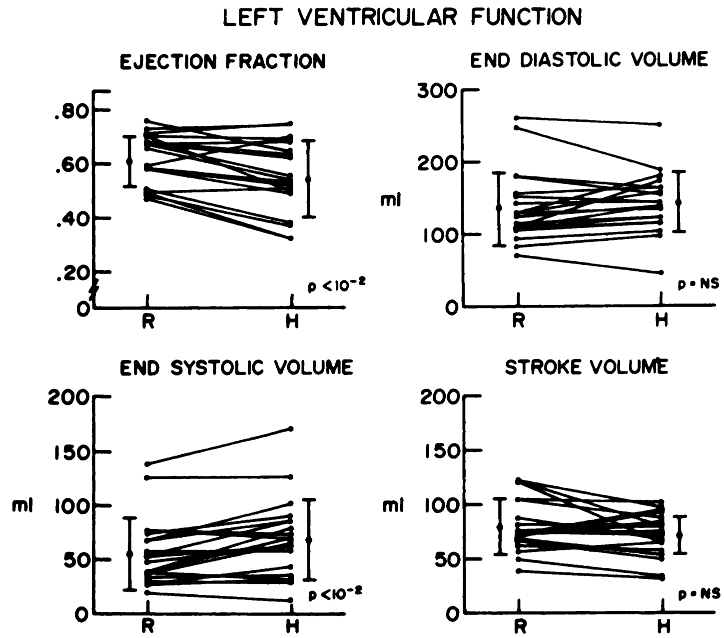

FIG. 3. Cardiac response to isometric handgrip in 20 patients with coronary artery disease.

volume, which suggests that the ischemic myocardium uses the Starling mechanism to increase efficiency in response to increased workload.

Early clinical studies using handgrip tests evaluated the safety of static exercise in patients involved in daily weight carrying activity (*16*). When combined with contrast ventriculography, handgrip stress has been shown to provide additional information on left-ventricular performance in patients with coronary artery disease (*17,18*). More recently, handgrip has been reported as a sensitive and specific method for the diagnosis of coronary artery disease using radionuclide techniques (*19*). Compared with bicycle exercise, handgrip stress seems to be an attractive technique because of simplicity and safety. The purpose of this investigation was to compare the response of normal subjects and patients with coronary artery disease to the two stress modalities.

The ideal control population for this study would have been asymptomatic subjects with normal coronary arteriograms. Since obtaining this ideal population is not feasible, the choice of controls rested between either asymptomatic subjects or patients with chest pain and normal coronary arteries. Patients with normal major coronary arteries by arteriography cannot be considered entirely normal since they have sufficient symptoms to undergo the risks of catheterization. The problem in using asymptomatic subjects without catheterization to provide control data is that asymptomatic coronary artery disease cannot be excluded particularly in older individuals. The asymptomatic volunteers with a mean age of 26 used for this study, however, would be expected to have a low frequency of asymptomatic coronary artery disease. Handgrip stress provided poor discrimination of young, healthy volunteers from those patients with definite coronary artery disease. The test would have been even less likely to discriminate older, normal volunteers or patients with chest pain and normal coronary arteries from those with coronary artery disease.

Such a study of effects on cardiac function requires an accurate measurement with well-defined limits of reproducibility. The radionuclide measurements used in this study have previously been validated in our laboratory. In 33 patients with coronary artery disease, supine radionuclide angiocardiograms were performed immediately before cardiac catheterization. The radionuclide measurements of ejection fraction and end-diastolic volume were compared with those made by contrast ventriculography, and the correlation coefficient was 0.89 for the two sets of measurements (*9*). In 18 healthy young adults, stroke volume and cardiac output were simultaneously measured by radionuclide and dye-dilution methods at rest and during various levels of exercise. A close correlation was observed between the duplicate measurements of stroke volume ($r = 0.89$) and cardiac output ($r = 0.94$) (*9*). A comparison between radionuclide angiocardiography and minor-axis dimensions at end-diastole as measured by implanted sonar crystals in 20 dogs revealed a correlation coefficient of 0.92 (*20*). The variability of measurements on 2 separate

	R	E	P
HEART RATE (beats/min)	79 ± 20	133 ± 23	$<10^{-14}$
BLOOD PRESSURE (mean, mm Hg)	95 ± 12	107 ± 15	$<10^{-4}$
CARDIAC OUTPUT (L/min)	6.2 ± 1.9	11.5 ± 4.2	$<10^{-5}$

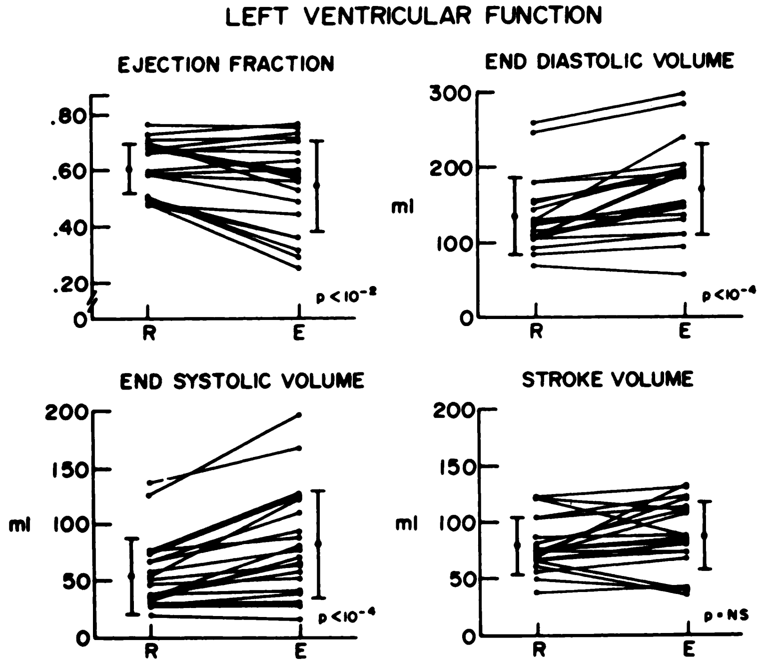

FIG. 4. Cardiac response to bicycle exercise in 20 patients with coronary artery disease.

days was assessed in ten normal subjects studied at rest and exercise (*21*). The mean variability (±1 s.d.) in ejection fraction was 4 ± 4% at rest and 3 ± 2% during exercise. In the same study, the mean variability in end-diastolic volume was less than 10 ml, both at rest and during exercise.

In the present study, wall motion was analyzed by a qualitative interpretation of dynamic images, by computer-derived perimeters at end-diastole and end-systole, and by an image depicting the fractional count loss during dystole. A wall-motion abnormality to be considered valid was required to be present by at least two of the three imaging approaches. However, 80% of the wall-motion abnormalities in these patients were apparent by all three imaging approaches for analyzing wall motion. Occasionally, abnormalities in the region of the descending aorta were apparent in the image of fractional decrease during systole, and this cause of an apparent abnormality was readily identified on the dynamic image of left-ventricular wall motion. The fact that exercise-induced wall-motion abnormalities were apparent in only 12 of the 20 coronary patients suggests

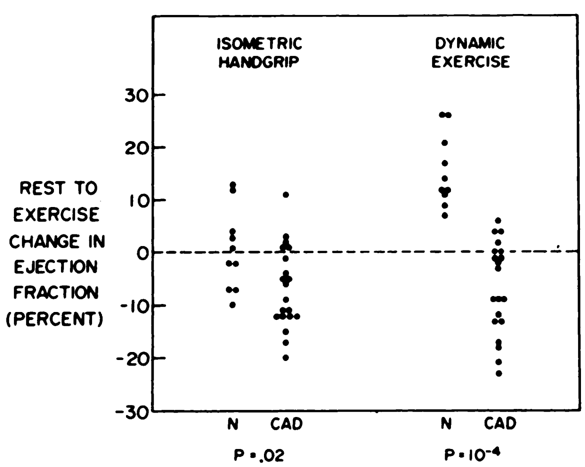

FIG. 5. Comparisons of changes in ejection fraction elicited by isometric handgrip and dynamic exercise.

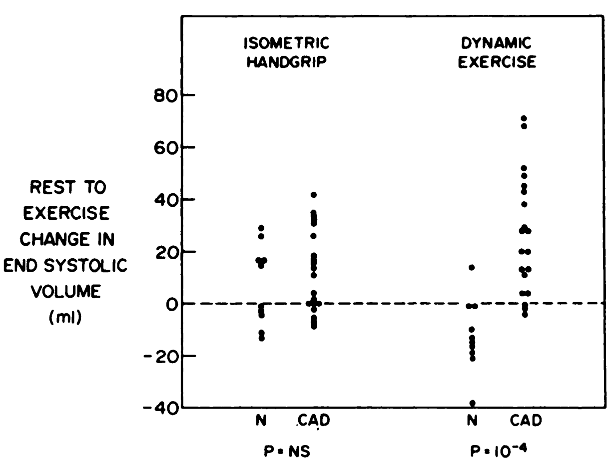

FIG. 6. Comparisons of changes in end-systolic volume elicited by isometric handgrip and dynamic exercise.

that the criteria used to define an abnormality may have been excessively rigorous. However, this observed frequency of exercise-induced wall-motion abnormality in patients with coronary disease was similar to that reported by Berger et al. (*22*). In addition, only one projection was used, and more wall-motion abnormalities might have been appreciated if other views could have been obtained. Despite these two factors of study design, which tended to decrease the number of wall-motion abnormalities recognized, one normal subject had a definite wall-motion abnormality induced by handgrip stress.

The response of a group of patients with coronary artery disease to bicycle exercise has been clearly documented to differ from that of normal subjects, and is characterized by the tendency of patients with coronary disease to fail to increase or to actually decrease ejection fraction during exercise (*23,24*). The magnitude of left-ventricular response to dynamic exercise in individual coronary patients appears to be a complex phenomenon. Therefore, specific criteria that differentiate normal from abnormal response to dynamic exercise have not been clearly established. The simple criterion of requiring the ejection fraction to increase by at least 0.05 has been shown to provide a good separation of patients with disease from normal subjects (*3*). This criterion would provide good separation in the present study, in which all ten normal subjects increased ejection fraction by at least this amount, whereas only one of the 20 coronary patients did. In our group of patients, therefore, this criterion would provide a sensitive and specific discriminator of coronary artery disease. Studies using this approach in larger groups of patients with chest pain have found this criterion to provide a sensitivity of 85% and a specificity of 76% for the diagnosis of coronary artery disease (*25*). Further refinement of criteria for a normal hemodynamic response to exercise—with attention to differences in resting hemodynamics and level of exercise—may enhance the diagnostic accuracy of this approach. In our study, however, no measurement of left-ventricular function was useful in assessing the response of an individual patient to handgrip stress. Moreover, the small amount of hemodynamic change observed in response to handgrip suggested that no approach could prove fruitful for identification of patients with disease by alterations of cardiac function.

The major criterion for an abnormal handgrip stress test in previous studies has been the enhancement or development of a wall-motion abnormality (*26*). However, in the 20 patients with coronary disease evaluated by handgrip in this study, only 45% developed a definite wall-motion abnormality, so that this did not prove to be a sensitive criterion. It was a relatively specific finding, however, which was present in only one of the normal subjects. A wall-motion abnormality during bicycle exercise was also not a sensitive discriminator, being present in only 60% of patients with coronary artery disease. No normal subject developed a wall-motion abnormality during bicycle exercise so that the finding was completely specific in this small group of patients. The present study is not well suited for determining the sensitivity and specificity of radionuclide measurements of cardiac function during handgrip and bicycle exercise, because of the small sample of patients studied and because of the dissimilarity between the normal subjects and the patient group in age and reason for study. However, the data provided are adequate to conclude that isometric handgrip is inferior to dynamic bicycle exercise in evoking alterations of left-ventricular function that can be used to diagnose coronary artery disease.

FOOTNOTE

* Baird Corp. System Seventy-Seven.

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