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Comparative Plasma Catecholamine and Hemodynamic Responses to Handgrip, Cold Pressor and Supine Bicycle Exercise Testing in Normal Subjects

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Serial hemodynamic and plasma catecholamine responses were compared among 10 healthy men (27 ± 3 years) (± 1 standard deviation) during symptom-limited handgrip (33% maximal voluntary contraction for 4.4 ± 1.8 minutes), cold pressor testing (6 minutes) and symptom-limited supine bicycle exercise (22 ± 5 minutes). Plasma catecholamine concentrations were measured by radioenzymatic assays; ejection fraction and changes in cardiac volumes were assessed by equilibrium radionuclide angiography. During maximal supine exercise, plasma norepinephrine and epinephrine concentrations increased three to six times more than during either symptom-limited handgrip or cold pressor testing. Additionally, increases in heart rate, systolic blood pressure, rate-pressure product, stroke volume, ejection fraction and cardiac output were significantly greater during bicycle exercise than during the other two tests. A decrease in ejection fraction of 0.05 units or more was common in young normal subjects during the first 2 minutes of cold pressor testing (6 of 10 subjects) or at symptom-limited handgrip (3 of 10), but never occurred during maximal supine bicycle exercise.

The magnitude of hemodynamic changes with maximal supine bicycle exercise was greater, more consistent and associated with much higher sympathetic nervous system activation, making this a potentially more useful diagnostic stress than either handgrip exercise or cold pressor testing.

Only patients with advanced heart disease exhibit abnormal cardiovascular function when evaluated in the rest state. Patients with less cardiac impairment often have normal hemodynamic function at rest but abnormal hemodynamic responses during stress testing, which may be helpful in defining the presence and severity of disease as well as the effects of therapy. This concept of a functional evaluation of the cardiovascular system during stress has led to the development of numerous diagnostic tests requiring an increase in cardiac work. Although dynamic supine or upright exercise has been the most commonly employed stress, there has been increasing interest in both handgrip and cold pressor testing because their simplicity and lack of patient motion facilitates the recording of radionuclide or echocardiographic measurements. In addition, cold pressor testing is independent of patient motivation and effort. The hemodynamic responses to these stresses are mediated in part by sympathetic nervous system activation (1, 2), which can be assessed by the measurement of plasma concentrations of epinephrine and norepinephrine. However, direct comparisons of the serial hemodynamic and catecholamine responses to these three stresses in normal subjects have not been reported.

The purposes of this study were to: 1) define the serial hemodynamic responses to symptom-limited isometric handgrip exercise, cold pressor testing and symptom-limited supine bicycle exercise in normal subjects; 2) compare the maximal hemodynamic responses to these three stress tests; and 3) define serial plasma norepinephrine and epinephrine responses to these tests to determine whether hemodynamic differences reflect variable degrees of sympathetic activation.

Methods

Subjects. Ten healthy male volunteers with a mean age of 27 years (range 24 to 33) were studied. Normal cardio-

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vascular function was confirmed by a negative history, normal physical examination, normal rest electrocardiogram and normal M-mode and two-dimensional echocardiograms. No subject had taken any medication for at least 1 week before study and none had smoked tobacco or drunk coffee on the day of study. None of the subjects were highly trained athletes. All subjects were informed of the investigational nature of the study and gave their informed consent.

Study protocol. On the morning of study, subjects reported to the laboratory after an overnight fast. Maximal voluntary contraction of the left hand was determined in triplicate using a handgrip dynamometer (Asimon Engineering Company) and the mean was determined. An intravenous catheter was then placed in the right forearm for blood sampling. Ten milliliters of venous blood were removed; the red cells were labeled with 20 to 25 mCi of technetium-99m and reinjected (3,4). After catheter insertion, subjects were kept at supine rest for 30 minutes before baseline catecholamine and hemodynamic measurements were obtained.

All stress testing was performed with the subject supine. Symptom-limited isometric handgrip exercise was done with the left arm at 33% maximal voluntary contraction. A technician coached the subject so that the correct pressure was maintained. Subjects were instructed to avoid performing the Valsalva maneuver during handgrip. All subjects terminated handgrip because of arm fatigue or pain, or both. Cold pressor testing was performed by immersing the left hand in iced water up to the wrist for 6 minutes. Maximal supine bicycle exercise was performed with a bicycle ergometer-imaging table system (Quinton Instruments). Four minute exercise stages began at a work load of 200 kp-m (kilopond-meters/min) and increased by 200 kp-m at each stage to a symptom-limited maximum. All subjects stopped because of fatigue.

Six subjects performed handgrip exercise first, and four performed the cold pressor test first. Bicycle exercise was always performed last, because the recovery time to baseline hemodynamics is longer for bicycle exercise than for the other maneuvers. Between each test, 45 to 60 minutes were allowed for hemodynamic and catecholamine levels to return to baseline. One subject performed bicycle exercise 1 week after the other studies because of equipment failure.

Data collection. Radionuclide left ventricular angiography was performed using electrocardiographic-synchronized blood pool imaging as previously described (3,4). Images were acquired in the left anterior oblique projection which offered the best septal definition using a low energy, high sensitivity, parallel hole collimator and an Ohio-Nuclear, series 100 gamma scintillation camera interfaced to a computer (Medical Data Systems).

For all tests, cardiac blood pool images were acquired for three 2-minute baseline periods at rest and then every 2 minutes during each stress test. Heart rate and sphygmomanometer blood pressure measurements were obtained every 2 minutes during baseline periods and throughout testing. For submaximal bicycle exercise stages, the reported hemodynamic and catecholamine data were obtained during the last 2 minutes of each 4 minute stage. Three subjects completed only the first 2 minutes of their final bicycle exercise stage; the data obtained during these 2 minutes are reported.

For plasma catecholamine determinations, 2.5 ml of venous blood was withdrawn through an indwelling catheter and placed into prechilled glass tubes containing heparin and glutathione (5 mmol/liter final concentration). The samples were immediately placed on ice, and plasma was separated by centrifugation at 4°C and then frozen at −20°C for later analysis by a single isotope radioenzymatic assay (5). The mean basal plasma levels at supine rest in 95 normal subjects using this method were 252 ± 138 pg/ml (± 1 standard deviation [SD]) for norepinephrine and 50 ± 22 pg/ml for epinephrine. Samples were obtained at baseline before each stress, during the cold pressor test at 2, 4 and 6 minutes, during handgrip at 2 and 4 minutes and at termination of handgrip. Because of technical difficulties, catecholamine samples were obtained from only seven subjects at 2 minutes of cold pressor testing, from four subjects at 2 minutes of handgrip and from nine subjects at 4 minutes of handgrip. For the supine bicycle exercise test, catecholamine samples were obtained at rest, during minute 4 of each exercise stage and at maximal exercise.

Data processing. The radionuclide angiocardiograms were analyzed as previously described (3,4). The background-subtracted, composite time-activity curve data for each 2 minute image were used to obtain or derive end-diastolic counts (EDC), end-systolic counts (ESC), stroke counts (SC = EDC − ESC), ejection fraction (EF = SC/ESC) and radionuclide cardiac output (RNCO = SC × HR, where heart rate [HR] is the number of cardiac cycles during a 2 minute collection period). Changes in end-diastolic count volume, end-systolic count volume, stroke count volume and radionuclide cardiac output counts are expressed as a percent change from baseline:

$$\frac{\text{Observed counts} - \text{Baseline counts}}{\text{Baseline counts}} \times 100.$$

Only the relative changes in cardiac volumes and output compared with baseline were determined. Absolute cardiac volumes and cardiac outputs in milliliters of blood were not measured. It has previously been shown in this laboratory (4) that changes in radionuclide-determined cardiac output and stroke volume expressed as a percent change from rest values closely parallel changes in direct Fick cardiac output and stroke volume at all levels of supine exercise in normal subjects.

Statistical analysis. For each intervention, the differences between rest and maximal stress values were compared using Wilcoxon's signed rank test, where each patient

served as his own control. For cold pressor testing, only the 0 to 2 minute data were statistically compared with the rest data, because most changes were greatest during the first 2 minutes. Maximal values among the three stresses were compared by analysis of variance using the baseline values at rest as covariates to correct for minor baseline differences. Because the duration of handgrip and supine bicycle exercise testing varied from patient to patient, the mean hemodynamic and plasma catecholamine responses during the final 2 minutes of symptom-limited exertion for the entire group are presented along with the serial changes in Table 1. Data are expressed as the mean ± 1 standard deviation.

Results

Sustained isometric handgrip exertion. Mean responses to handgrip are presented sequentially in Table 1 and Figure 1. The mean duration of symptom-limited handgrip was 4.4 ± 1.8 minutes (range 3.4 to 6.0). Plasma norepinephrine increased moderately from 335 ± 119 at rest to 609 ± 204 pg/ml at maximal handgrip, and epinephrine increased from 34 ± 22 to 147 ± 98 pg/ml (probability [p] = 0.002 for both). Heart rate increased by 34 ± 16 beats/min, systolic blood pressure by 56 ± 27 mm Hg, mean arterial pressure by 48 ± 21 mm Hg and rate-pressure product by 93 ± 46 mm Hg/min × 10^2 (all p = 0.002). There were no significant changes in radionuclide end-diastolic volume (−1 ± 16%), end-systolic volume (+5 ± 26%) or stroke volume (−5 ± 16%). Cardiac output increased by 49 ± 31% (p = 0.002). The mean ejection fraction was unchanged (0.63 ± 0.08 versus 0.62 ± 0.12).

Cold pressor testing. All subjects completed 6 minutes of the cold pressor test (Fig. 2). Plasma norepinephrine increased slightly from 340 ± 113 at rest to 369 ± 66 at 2 minutes (p = not significant [NS]) and to 558 ± 162 pg/ml at 6 minutes. Plasma epinephrine also increased slightly from 46 ± 26 at rest to 71 ± 54 at 2 minutes (p = 0.02) and to 60 ± 27 pg/ml at 6 minutes. Heart rate increased by 12 ± 8 beats/min, systolic blood pressure by 26 ± 13 mm Hg, mean arterial pressure by 24 ± 8 mm Hg and rate-pressure product by 33 ± 2.1 mm Hg/min × 10^2 (all p ≤ 0.02). End-diastolic volume increased insignificantly at 0 to 2 minutes (5 ± 9%) and increased further at 2 to 4 and 4 to 6 minutes, whereas end-systolic volume increased at 0 to 2 minutes (12 ± 17%, p = 0.01) and remained elevated. Stroke volume decreased significantly at 0 to 2 minutes (5 ± 7%, p = 0.05), remained depressed from 2 to 4 minutes and then returned to baseline. Cardiac output increased only 13 ± 15% (p = 0.02) at 0 to 2 minutes and then declined toward baseline. Mean global ejection fraction decreased at all time periods, from 0.65 ± 0.08 at rest to 0.61 ± 0.09 at 0 to 2 minutes (p = 0.04), 0.60 ± 0.09 at 2 to 4 minutes and 0.61 ± 0.09 at 4 to 6 minutes.

Supine bicycle exercise. The mean duration of bicycle exercise was 22 ± 5 minutes (range 16 to 28). Plasma norepinephrine increased serially from 373 ± 118 at rest to 1,634 ± 1,243 pg/ml at symptom-limited maximal exercise (p = 0.002) (Fig. 3). Plasma epinephrine, which was 54 ± 40 pg/ml at rest, increased only moderately until the 12th minute of exercise after which it increased sequentially to 417 ± 346 pg/ml (p = 0.002). Heart rate increased 97 ± 13 beats/min, systolic blood pressure 92 ± 14 mm Hg, mean arterial pressure 27 ± 12 mm Hg and rate-pressure product 265 ± 41 mm Hg/min × 10^2 (all p = 0.002). End-diastolic volume was constant throughout; end-systolic volume decreased insignificantly by 18 ± 20% (NS). Stroke volume increased by 27 ± 15% (p = 0.002) and cardiac output increased by 212 ± 57% at peak exercise (p = 0.002). Mean ejection fraction increased from 0.69 ± 0.09 at rest to 0.79 ± 0.07 (p = 0.002).

Comparative maximal effects of handgrip, cold pressor and supine bicycle exercise. Catecholamine and hemodynamic responses to symptom-limited handgrip, the first 2 minutes of the cold pressor test and maximal supine bicycle exercise are compared in Figure 4. Only the first 2 minute cold pressor values were utilized for this comparison because most hemodynamic responses were maximal during that time period (Table 1); utilization of the 2 to 4 minute values did not affect the statistical significance of the findings.

Peak plasma norepinephrine and epinephrine concentrations were three to six times greater with bicycle exercise than with handgrip or cold pressor testing (all p ≤ 0.02 versus bicycle exercise). Maximal heart rate, systolic pressure and rate-pressure product were greater with bicycle exercise than with either handgrip or cold pressor testing (all p < 0.001 versus bicycle exercise). In contrast, mean arterial pressure was higher with handgrip than with the other stresses (both p < 0.02 versus handgrip). Whereas end-diastolic volume did not change significantly during any of the three tests, end-systolic volume tended to decrease with bicycle exercise (−18 ± 20%), was unchanged with handgrip (p = NS versus bicycle exercise) and increased with cold pressor testing (p = 0.01 versus bicycle exercise). Thus, stroke volume increased only with maximal bicycle exercise and decreased slightly with either handgrip or cold pressor testing (both p < 0.001 versus bicycle exercise). Mean ejection fraction increased with maximal supine bicycle exercise but decreased slightly with handgrip and cold pressor testing (both p < 0.001 versus bicycle exercise). Cardiac output increased dramatically with maximal bicycle exercise when contrasted with handgrip exercise or cold pressor testing (both p < 0.001 handgrip or cold pressor versus bicycle exercise).

Compared with cold pressor testing, symptom-limited handgrip caused greater changes in plasma catecholamine

Table 1. Mean Catecholamine and Hemodynamic Responses to Isometric Handgrip, Cold Pressor and Supine Bicycle Exercise in Normal Subjects*

	No. of Subjects	NE (pg/ml)	E (pg/ml)	HR (beats/min)	Systolic BP (mm Hg)	Mean BP (mm Hg)	HR·SBP	EDV Counts (% change)	ESV Counts (% change)	SV Counts (% change)	EF	CO (% change)
Handgrip												
Rest	10	335 ± 119	34 ± 22	62 ± 11	116 ± 14	86 ± 12	7245 ± 1579	0	0	0	0.63 ± 0.08	0
0–2 min	10	383 ± 146	73 ± 28	74 ± 10	140 ± 19	108 ± 17	10211 ± 2384	1 ± 6	6 ± 9	−6 ± 11	0.61 ± 0.09	14 ± 17
2–4 min	10	420 ± 171	64 ± 31	83 ± 12	158 ± 27	123 ± 24	13299 ± 3598	−1 ± 13	5 ± 6	−8 ± 14	0.60 ± 0.08	25 ± 13
4–6 min	7	603 ± 237	177 ± 102	99 ± 17	187 ± 21	147 ± 19	18611 ± 5204	2 ± 16	4 ± 29	−1 ± 17	0.63 ± 0.14	62 ± 31
Max† (4.4 ± 1.8 min)	10	609 ± 204	147 ± 98	96 ± 17	172 ± 31	134 ± 26	16517 ± 5522	−1 ± 16	5 ± 26	−5 ± 16	0.62 ± 0.12	49 ± 31
Cold pressor												
Rest	10	340 ± 113	46 ± 26	61 ± 9	114 ± 14	85 ± 12	7015 ± 1297	0	0	9	0.65 ± 0.08	0
0–2 min	10	369 ± 66	71 ± 54	73 ± 11	140 ± 25	109 ± 17	10295 ± 2908	5 ± 9	12 ± 17	−5 ± 7	0.61 ± 0.09	13 ± 15
2–4 min	10	486 ± 145	66 ± 25	65 ± 9	138 ± 20	105 ± 19	9052 ± 2043	8 ± 8	18 ± 13	−6 ± 7	0.60 ± 0.09	0 ± 8
4–6 min	10	558 ± 162	60 ± 27	63 ± 9	136 ± 18	102 ± 16	8617 ± 1449	10 ± 7	16 ± 12	1 ± 9	0.61 ± 0.09	6 ± 12
Supine exercise												
Rest	10	373 ± 118	54 ± 40	65 ± 8	119 ± 15	86 ± 13	7827 ± 1535	0	0	0	0.69 ± 0.09	0
0–4 (200 kp-m)	10	436 ± 117	81 ± 100	93 ± 11	143 ± 16	100 ± 13	13328 ± 2359	−2 ± 12	−8 ± 26	5 ± 11	0.74 ± 0.10	47 ± 20
4–8 (400 kp-m)	10	445 ± 163	54 ± 36	105 ± 11	154 ± 18	103 ± 13	16258 ± 3019	0 ± 15	−15 ± 27	15 ± 13	0.78 ± 0.09	82 ± 28
8–12 (600 kp-m)	10	490 ± 146	77 ± 32	122 ± 15	173 ± 20	106 ± 13	21234 ± 4350	1 ± 11	−20 ± 16	23 ± 15	0.81 ± 0.10	128 ± 35
12–16 (800 kp-m)	10	709 ± 362	162 ± 141	142 ± 16	192 ± 19	109 ± 12	27410 ± 5017	5 ± 13	−15 ± 18	25 ± 14	0.79 ± 0.09	169 ± 45
16–20 (1000 kp-m)	7	910 ± 263	214 ± 68	154 ± 5	204 ± 20	111 ± 10	31545 ± 3241	1 ± 16	−17 ± 23	24 ± 11	0.79 ± 0.07	189 ± 45
20–24 (1200 kp-m)	5	1678 ± 310	462 ± 44	166 ± 6	218 ± 26	112 ± 14	35999 ± 3839	5 ± 12	−17 ± 21	19 ± 16	0.82 ± 0.08	200 ± 62
24–28 (1400 kp-m)	2	2430 ± 1937	530 ± 255	175 ± 1	218 ± 31	101 ± 12	38052 ± 5583	1 ± 5	−21 ± 8	25 ± 3	0.77 ± 0.01	232 ± 35
Max† (22 ± 5 min)	10	1634 ± 1243	417 ± 346	162 ± 10	211 ± 24	113 ± 12	34298 ± 4814	5 ± 15	−18 ± 20	27 ± 15	0.79 ± 0.07	212 ± 57

* = All values are the mean ± 1 standard deviation; † = the maximal values are those obtained during the final 2 minutes of symptom limited handgrip or bicycle exercise.

BP = blood pressure; CO = cardiac output; E = epinephrine; EDV = end-diastolic volume; EF = ejection fraction, ESV = end-systolic volume; HR = heart rate; HR·SBP = rate-pressure product; kp-m = kilopond-meters/min; Max = maximal value, NE = norepinephrine; No. = number; SV = stroke volume.

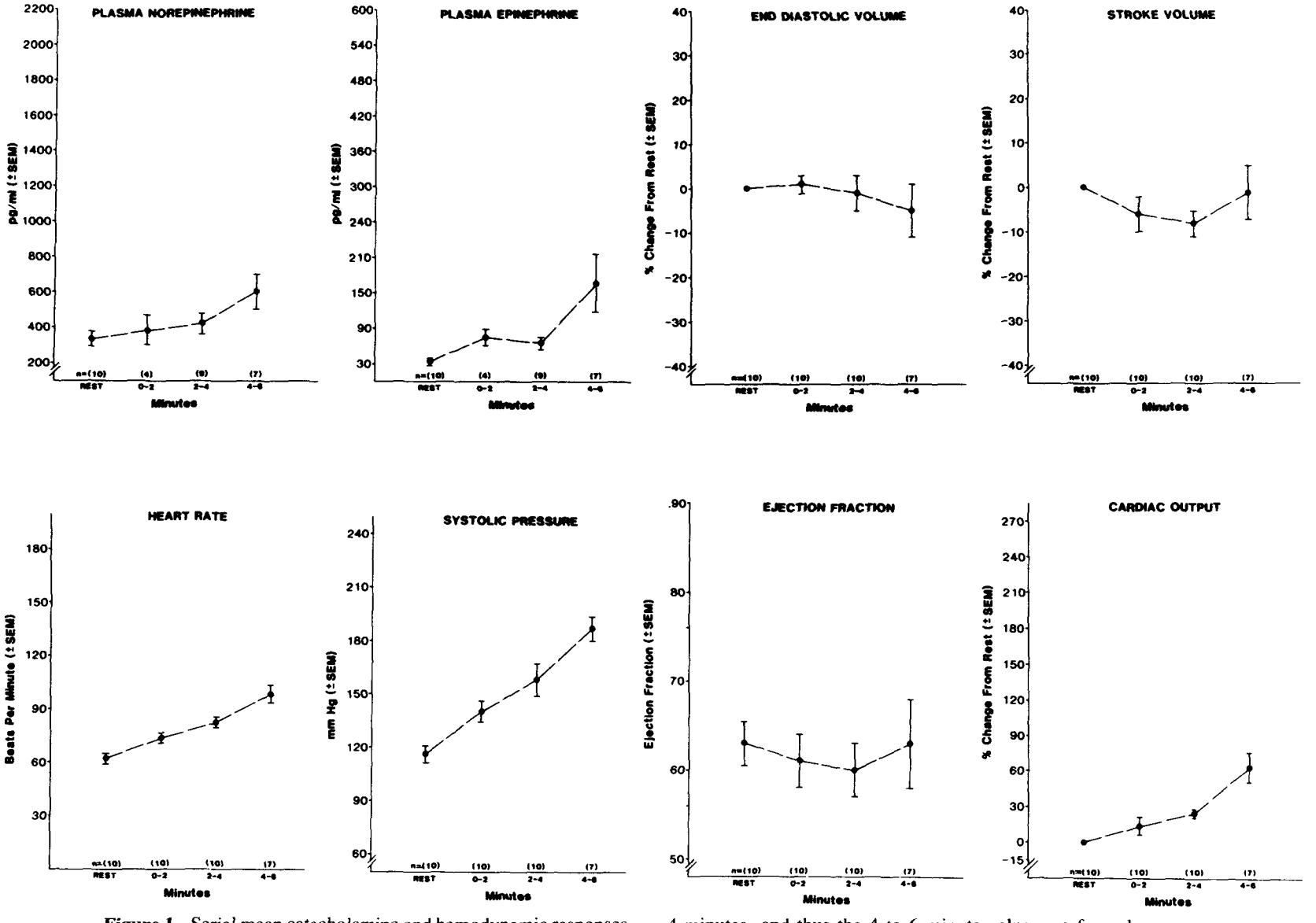

Figure 1. Serial mean catecholamine and hemodynamic responses to symptom-limited isometric handgrip (33% maximal voluntary contraction) in 10 normal subjects. Three subjects exercised only 4 minutes, and thus the 4 to 6 minute values are for only seven subjects. The mean values obtained for all 10 subjects at their individual maximal levels are listed in Table 1.

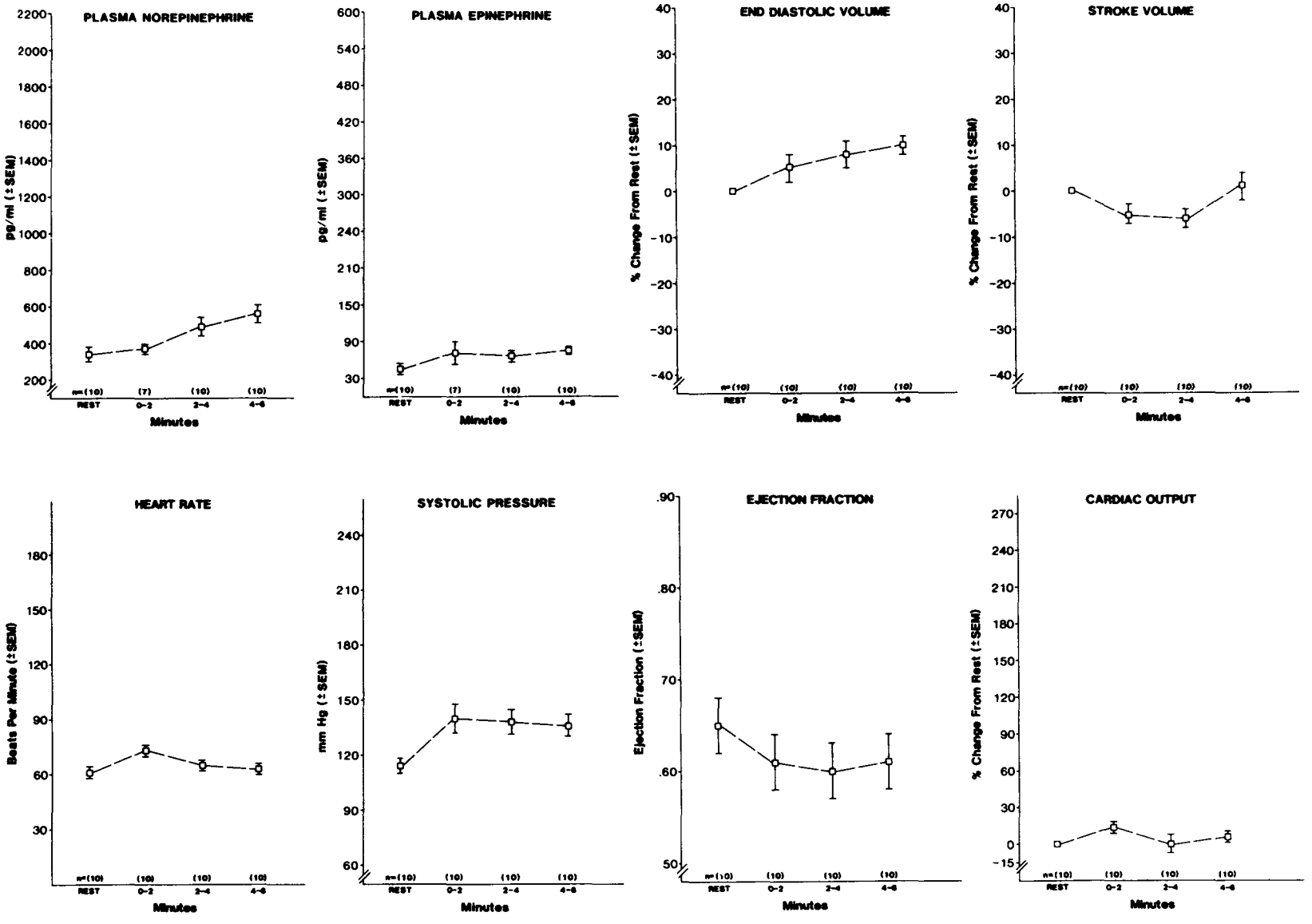

Figure 2. Serial mean catecholamine and hemodynamic responses to 6 minutes of cold pressor testing in 10 normal subjects.

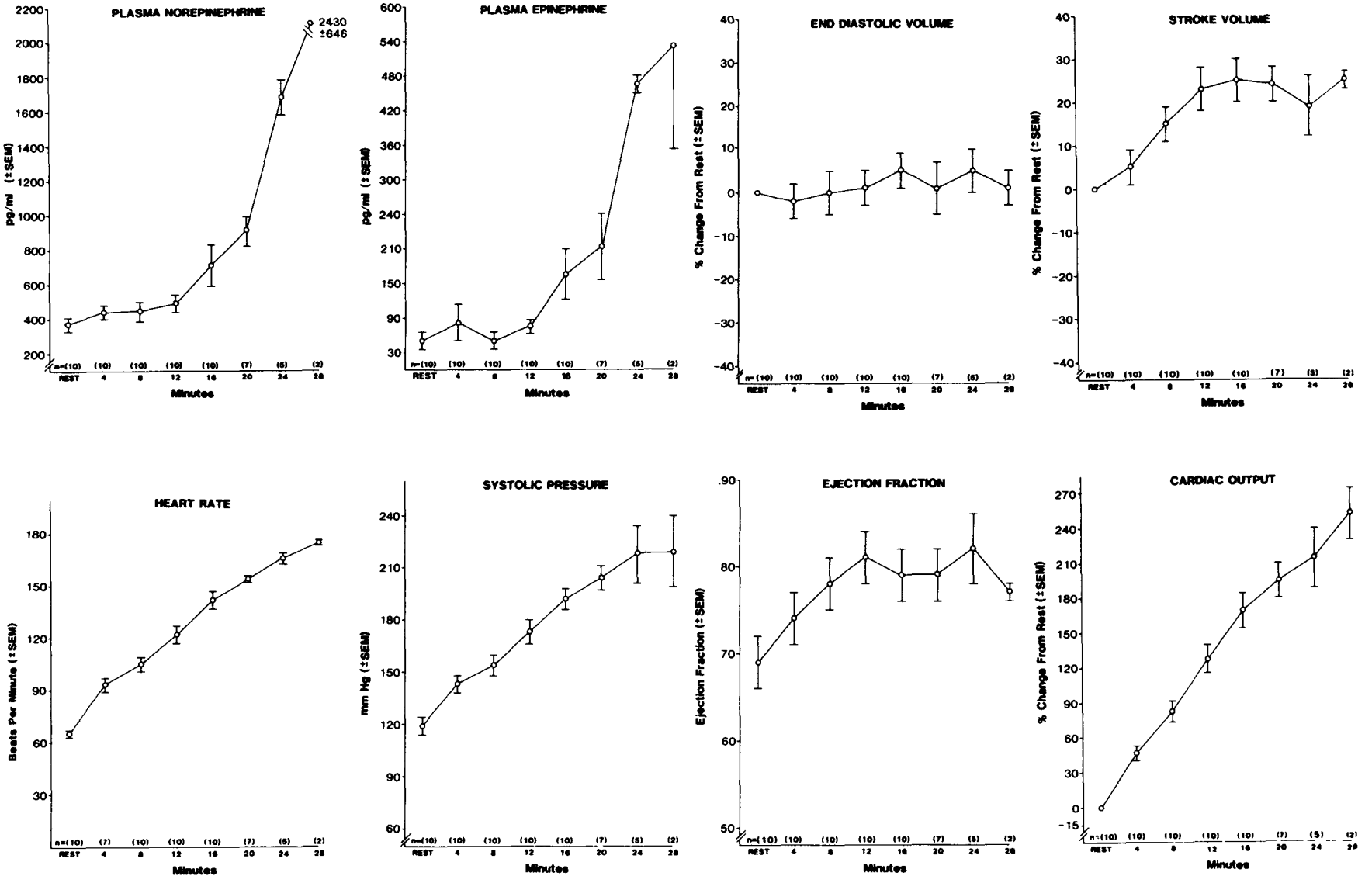

Figure 3. Serial mean catecholamine and hemodynamic responses to symptom-limited maximal supine bicycle exercise, which began at 200 kp-m and increased by 200 kp-m every 4 minutes. Maximal exercise duration varied from 16 to 28 minutes; all subjects exercised at least 16 minutes. The mean values for all 10 subjects at their individual symptom-limited maximal levels are listed in Table 1.

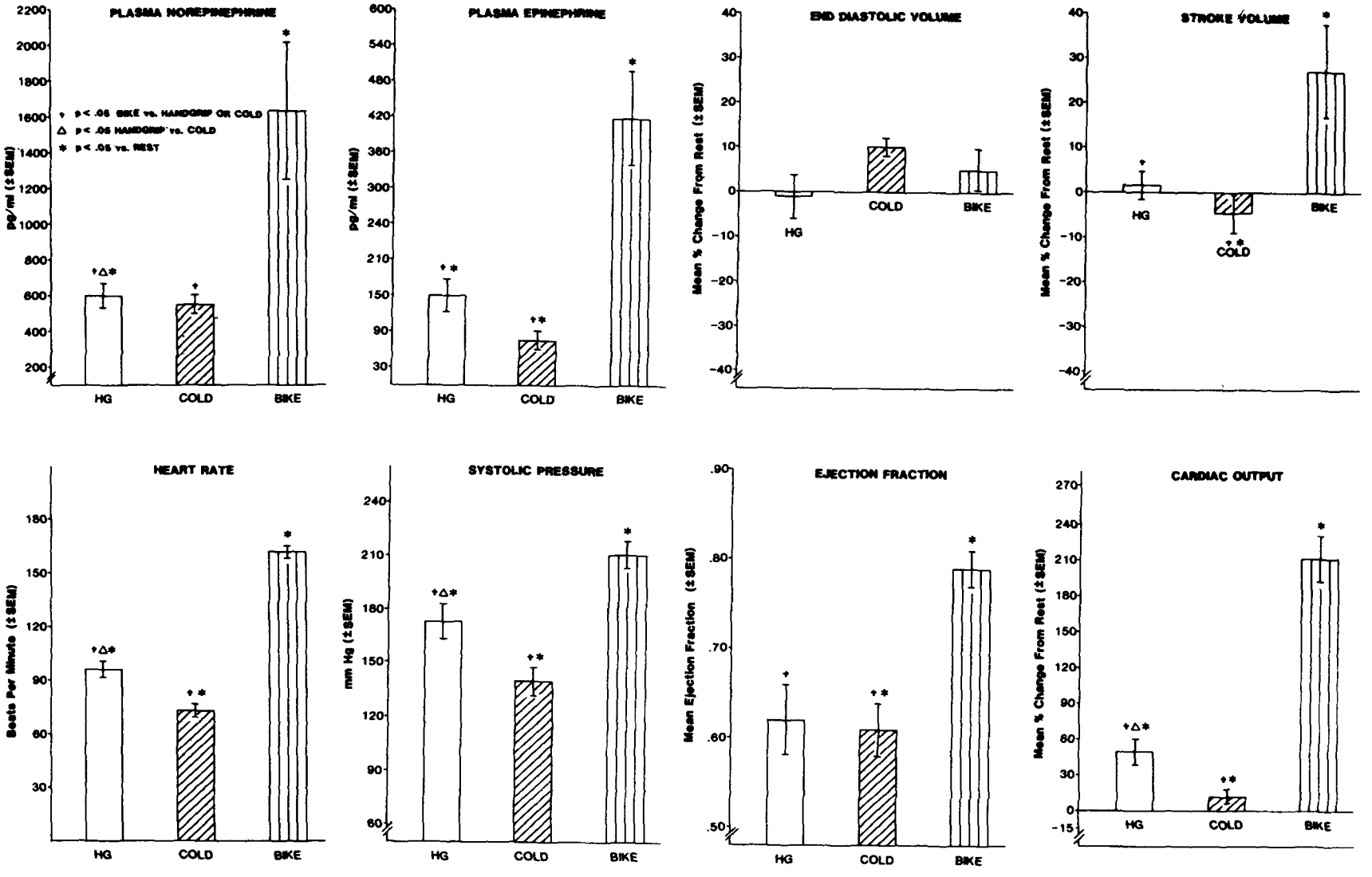

Figure 4. Comparative mean catecholamine and hemodynamic responses to symptom-limited handgrip, the first 2 minutes of the cold pressor test and symptom-limited maximal supine bicycle exercise in 10 normal subjects. For all variables displayed, with the exception of end-diastolic volume changes, bicycle exercise caused the greatest increases. HG = symptom-limited isometric handgrip at 33% maximal voluntary contraction (mean 4.4 ± 1.8 minutes); COLD = cold pressor testing during the first 2 minutes; BIKE = symptom-limited maximal bicycle exercise (mean 22 ± 5 minutes). * = $p < 0.05$ stress versus rest; † = $p < 0.05$ bike versus handgrip or cold; △ = $p < 0.05$ handgrip versus cold.

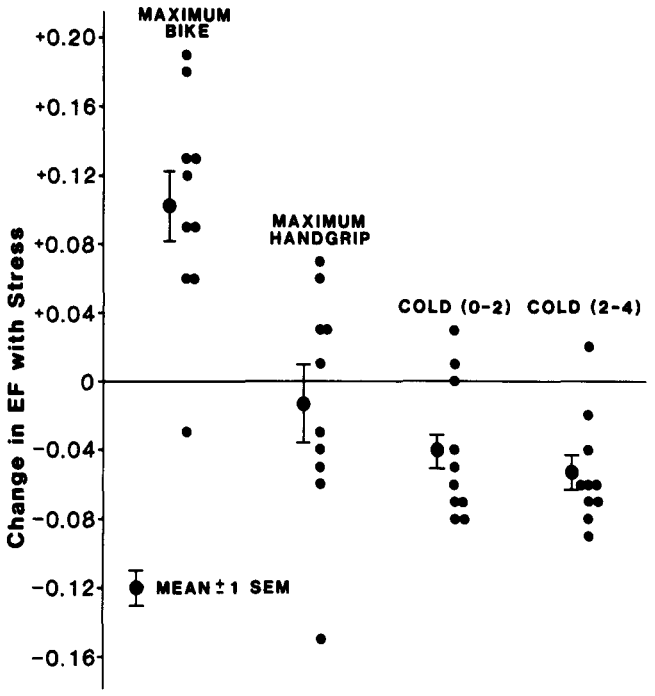

Figure 5. Individual subject changes in ejection fraction (EF) during maximal supine bicycle exercise, symptom-limited isometric handgrip exercise and cold pressor testing at 0 to 2 and 2 to 4 minutes. At maximal bicycle exercise, all but one subject increased his ejection fraction by more than 0.05 unit. In contrast, at symptom-limited handgrip, only two subjects increased their ejection fraction by more than 0.05 unit. During the cold pressor test, none increased the ejection fraction by more than 0.05 unit.

concentrations and most hemodynamic measurements. Handgrip was associated with a greater increase in both plasma norepinephrine and epinephrine than was cold pressor testing (both $p < 0.05$). Handgrip also caused greater increases in heart rate, systolic blood pressure, rate-pressure product, mean arterial pressure and cardiac output than did cold pressor testing (all $p \leq 0.01$ handgrip versus cold pressor). However, changes in end-diastolic volume, end-systolic volume, stroke volume and ejection fraction were not significantly different between handgrip and cold pressor testing.

Individual ejection fraction responses to the three tests differed considerably (Fig. 5). At maximal bicycle exercise, 9 of 10 subjects had increased their ejection fraction by 0.06 unit or more from rest; the 1 patient with a 0.03 unit decrease had a high rest value of 0.79, which increased to 0.86 at 20 minutes, but then fell to 0.76 at peak exercise 4 minutes later. There was a heterogeneous ejection fraction response to symptom-limited handgrip, with five subjects increasing and five decreasing their ejection fraction. Six subjects had a 0.05 or greater decrease in ejection fraction at one or more of the serial sampling times during handgrip testing; in three, the ejection fraction at symptom-limited handgrip had decreased by ≥ 0.05 unit or more from values at rest. The typical response to cold pressor testing was a decrease in ejection fraction. During the first 2 minutes of testing, seven subjects had decreases and during the next 2 minutes, nine subjects had decreases compared with rest values. At one of the three time periods, all subjects had at least a 0.03 unit decline, and seven subjects had a decrease of 0.06 or greater. The maximal decline occurred at 0 to 2 minutes in five subjects, at 2 to 4 minutes in six and at 4 to 6 minutes in two (in three patients, the maximal decline occurred at two of the three imaging times).

Measurements that have a wide variability among normal subjects are unlikely to offer a clear separation between normal subjects and patients with disease. The coefficient of variation of a measurement, which is the standard deviation × 100 divided by the mean, can be used as an index of the variability of a result (6). For all hemodynamic measurements made, with the exception of the end-diastolic volume, the coefficient of variation for maximal bicycle exercise was less than for the other two stresses, indicating that hemodynamic responses were more homogeneous for bicycle exercise than for the other two stresses. For example, the coefficient of variation for the ejection fraction measurement was 9% at maximal bicycle exercise, 19% at symptom-limited handgrip and 15% during cold pressor testing. The differences in coefficients of variation were even greater for measurements of changes in stroke volume (56, 320 and 900%, respectively) and cardiac output (27, 63 and 115%, respectively).

Discussion

This study in normal men compared the serial hemodynamic responses to three commonly performed stress tests: isometric handgrip exercise, the cold pressor test and supine bicycle exercise. Because the sympathetic nervous system partially mediates the hemodynamic responses to stress (1, 2), we serially measured peripheral venous catecholamine concentrations, which are markers of general sympathetic nervous system activation. Our results revealed marked differences in the catecholamine and cardiovascular responses of normal subjects to the three interventions. Heart rate, systolic blood pressure, rate-pressure product, stroke volume, ejection fraction and cardiac output increased significantly more with bicycle exercise than with handgrip exercise or cold pressor testing. The hemodynamic responses to bicycle exercise also had smaller coefficients of variation, indicating that the results were more consistent (that is, more homogeneous). Thus, bicycle exercise produced hemodynamic changes that were both of greater magnitude and lesser variability than were those from the other two stresses. The greater hemodynamic responses were associated with considerably larger increases in plasma norepinephrine and epinephrine, suggesting that variable degrees of sympathetic activation in part account for the hemodynamic differences.

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However, the exact extent to which the observed differences in catecholamine levels caused the hemodynamic differences cannot be determined from the present study.

Plasma catecholamine concentrations during stress tests. Serial catecholamine responses during handgrip exercise have not been previously reported. Both plasma norepinephrine and epinephrine increased serially, but even at symptom-limited handgrip, elevations were small when compared with dynamic exercise. We found a two-fold increase in plasma norepinephrine and a five-fold increase in plasma epinephrine. Investigators using similar symptom-limited protocols in normal subjects found comparable concentrations of arterial or venous plasma norepinephrine at maximal handgrip (7–9), but only a two-fold increase in plasma epinephrine (8). Other studies using less vigorous handgrip stresses have found lesser increases in catecholamines (10,11), similar to the changes we detected during early handgrip. The differences in catecholamine and hemodynamic responses between isometric and dynamic exercise may relate in part to differences in the volume of active muscle mass, which was much smaller during isometric exercise of one forearm than during dynamic bicycle exercise of both legs. Blomqvist et al. (12) noted catecholamine elevations and hemodynamic changes during symptom-limited dynamic exercise of one arm similar to those we detected during symptom-limited isometric exercise of one arm.

The small hemodynamic changes during cold pressor testing were associated with only slight increases in plasma catecholamines. Robertson et al. (11) noted similar increases in plasma norepinephrine (205 to 343 pg/ml) and epinephrine (24 to 51 pg/ml) after 1 minute of cold. Continued exposure in our study led to additional small increases in norepinephrine, but not epinephrine, at 4 and 6 minutes.

The effects of maximal supine exercise on plasma catecholamines have not been previously reported. During maximal supine exercise, catecholamine concentrations, particularly of norepinephrine, were lower than values obtained during maximal upright exercise (13–16). As expected, studies that have utilized submaximal supine exercise protocols have found lesser catecholamine elevations (11,17), similar to the changes we noted at submaximal stages. The increase in catecholamine concentrations is related to the relative work load during both upright (13,14) and supine (17) exercise. Plasma catecholamine concentrations increased only modestly during the early stages, but rose dramatically in the later stages. The striking increase in catecholamines during the final stages was not matched by corresponding increases in most hemodynamic variables. Overall, however, the greater catecholamine response to bicycle exercise paralleled the greater hemodynamic changes compared with the other stress tests.

Hemodynamic changes during the stress tests. Similar changes in hemodynamics during isometric handgrip have been noted using a variety of handgrip protocols (18–25). Although the mean ejection fraction of groups of normal subjects does not change (18,20,26,27), individual normal subjects may have a decline of 0.05 unit or more. Such a decline was noted in 3 of 10 normal subjects at maximal handgrip in the current study and 4 of 10 in another study (18). Thus the normal ejection fraction response to handgrip is heterogeneous, with some subjects having an increase and others a decrease. The mechanism of the decrease in ejection fraction in some patients may be increased afterload (28) or changes in coronary arterial tone (29).

During cold pressor testing, most hemodynamic changes occurred early and then returned toward baseline over the 6 minute study period, as was also noted by Greene et al. (30). We found similar modest elevations in heart rate, blood pressure and cardiac output and a modest decrease in stroke volume as previously described (30–32). Data regarding the ejection fraction response of normal subjects to the cold pressor test are conflicting. Wainwright et al. (31) and Manyari et al. (32) found statistically significant increases in ejection fraction, and Kurtz et al., in a preliminary report (33), found less than a 0.03 unit decrease in normal subjects. However, in the study by Manyari et al. (32), 7 of 20 normal subjects had at least a 0.01 unit decrease. Other preliminary reports (34,35) have noted, as we did, that the ejection fraction typically decreased in normal subjects. The explanation for these discordant findings is unclear, although it may relate to differences in study populations or protocols. Even in studies reporting a mean increase, the increase was modest compared with that during bicycle exercise. The mechanism for the decrease in ejection fraction has not been defined but may be related to changes in coronary vascular tone (28,36) or afterload. In this context, our finding of an elevated mean arterial pressure with only a minimal increase in cardiac output indicates an increase of 15 to 20% in systemic vascular resistance during cold pressor testing.

The serial hemodynamic changes noted during supine exercise in normal subjects are similar to those previously reported (4,37–42). Nearly all normal subjects have an increased ejection fraction during supine exercise (3,4,32,37–39,41). There are differences between the hemodynamic responses of normal subjects to supine and upright dynamic exercise. The most marked difference is in end-diastolic volume, which was not changed in most studies during supine exercise (4,37,41,43,44), but increased by 20 to 40% during upright exercise (18,38,43,44). Thus, normal subjects utilize the Frank-Starling mechanism during upright, but not supine, exercise. Additionally, compared with findings during supine exercise, at peak upright exercise in normal subjects the heart rate was higher (38,43,44); the systolic pressure tended to be lower (41,43,44); the rate-pressure product was similar (38,43,44); the end-systolic volume less (38,43) and the ejection fraction the same (41,44) or higher (38,43).

Clinical implications. Several studies (45–49) comparing handgrip with dynamic exercise have shown that handgrip is of limited value in the diagnosis of coronary artery disease when the end point is angina or ischemic chest pain, or both. In contrast, Bodenheimer et al. (26,27), using a radionuclide ventriculographic regional ejection fraction method during handgrip, found a sensitivity of 86% and a specificity of 87%. However, the usefulness of their findings is limited because most of their subjects with coronary disease had abnormalities detectable at rest. Peters and Jones (18), using a visual analysis of regional wall motion and global ejection fraction, found abnormalities in only 45% of patients with coronary disease during handgrip stress, and Giles et al. (28), in a preliminary report, found that the ejection fraction response did not distinguish patients with coronary artery disease from normal subjects. Similar data have been reported for cold pressor testing. Wainwright et al. (31) noted encouraging results using cold pressor radionuclide angiography for the diagnosis of coronary artery disease, but other authors (32,35) have not substantiated these findings. In contrast, several studies (3,32,50–52) have shown that the ejection fraction response to dynamic supine exercise offers a sensitivity of approximately 90% but a wide range of specificities (54 to 95%) for the detection of coronary artery disease.

In our group of young healthy men, the duration of bicycle exercise greatly exceeded the duration of the other tests. In an older group of patients with heart disease, the duration of bicycle exercise would be shorter, which might lessen the differences we noted among the three tests. Both isometric handgrip exercise and cold pressor testing were limited measures of left ventricular functional reserve compared with dynamic exercise, which produced significantly greater hemodynamic changes for all variables measured with the exception of mean arterial pressure. Because handgrip and cold pressor testing produce lesser hemodynamic changes and have greater intrapatient variability than dynamic exercise, their efficacy as diagnostic stress tests appears limited. The observed differences in hemodynamic responses to the three stress tests may be explained, in part, by the greater sympathetic activation during bicycle exercise.

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