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Hexamethonium Modification of Cardiovascular Adjustments During Combined Static-Dynamic Arm Exercise in Monkeys[1]

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GAIDE, M. S., K. J. KLOSE, W. J. GAVIN, N. SCHNEIDERMAN, T. W. ROBERTSON, M. SILBRET AND M. V. FALETTI. *Hexamethonium modification of cardiovascular adjustments during combined static-dynamic arm exercise in monkeys.* PHARMAC. BIOCHEM. BEHAV. 13(6), 851–857, 1980.—In weight lifting and rowing, essentially the same groups of muscles contract in isometric (static) and isotonic (dynamic) fashion. To approximate the combined static-dynamic arm movements involved in rowing or lifting weights, four rhesus monkeys were trained to pull a T-bar and thereby avoid tail shock. Each animal received 8 daily test sessions in which loads (0.4, 0.8, 1.2, 1.6 kg), total pulls (3, 6, 9, 12 at a constant pull frequency, 0.5 Hz) and alternate sessions of pulling after injection of hexamethonium chloride (7 mg/kg) or saline were factorially combined. Our data indicate that heart rate in this model is primarily influenced by the duration of the dynamic exercise component (number of pulls) in this specific exercise task whereas both dynamic and static components affect systolic and diastolic blood pressure. After ganglionic blockade, heart rate and diastolic pressure do not change appreciably during T-bar pulling while the rise in systolic pressure is attenuated and varies primarily as a function of the static exercise component. The clinical implications of these experiments are discussed.

Exercise Blood pressure Heart rate Hexamethonium *Macaca mulatta*

THE cardiovascular response to exercise depends on whether the exercise is static [6, 17, 25], dynamic [2, 22, 25] or some combination of the two [12,16]. During combined static and dynamic exercise (e.g., running on a treadmill while carrying a load or performing handgrip contraction), heart rate, blood pressure and cardiac output are greater than in dynamic [12] or static [16] exercise alone. Walking while carrying a load [12] is a combined dynamic and static exercise in which one group of muscles contracts dynamically while other muscles contract statically. The adjustments in heart and circulation during such combined exercise have been described as reflecting either a linear-additive [23] or possibly a multiplicative [12, 14, 16] relationship. A different form of combined exercise is rowing or lifting a barbell while sitting. In this situation, the same muscle groups can be viewed as contracting both statically and dynamically. The relative contributions of the static and dynamic components to cardiovascular performance have not been explored in such exercise.

Static or isometric work involves muscular tension developed against a load whereas muscle length changes in dynamic or isotonic exercise. "Pure" static conditions do not occur in T-bar pulling. Nevertheless, because contraction against a load is related to static work and pulling more closely reflects dynamic work, one can establish conditions in which the relative contributions of static and dynamic components to cardiovascular performance are assessed. The present study determined the heart rate and blood pressure changes in rhesus monkeys during a specific exercise task, pulling a T-bar. This model approximates the exertion of barbell lifting or rowing in humans. We designed the experiments so as to systematically vary the load and duration of dynamic exercise (number of pulls). Our objective was to statistically dissect the roles of these specific factors in the cardiovascular responses.

Muscular activity and cardiovascular performance also are regulated by neural and humoral factors. As a second objective, we evaluated the relative contributions of the static and dynamic components of the T-bar pulling task in cardiovascular performance after pharmacologic denervation of the autonomic nervous system with the ganglionic blocking agent hexamethonium [4,26].

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METHOD

Four experimentally naive female rhesus monkeys *(Macaca mulatta)* weighing 4 to 5 kg were obtained from Primate Imports, Long Island, NY. Diet consisted of Purina monkey chow supplemented with fruits, vegetables and water and Tang, ad lib. Following one week of chair adaptation, each animal was immobilized with phencyclidine hydrochloride (Sernylan, 3 mg IM) and arterial cannulation performed to provide direct recording of blood pressure. Lidocaine (2%) was used as the local anesthetic at the site of incision. PE tubing (i.d. 0.86 × o.d. 1.52 mm, Clay-Adams) was introduced into the right external iliac artery at a position several millimeters above the bifurcation and threaded into the abdominal aorta for a distance of 2 to 3 cm resting at a point below the renal arteries. The catheter was passed subcutaneously, exited at a point just below the umbilicus and attached to a Statham P23AC blood pressure transducer by a one-way valve (Intraflow CFS-03, Sorenson Research Co.). Patency of the system was maintained with heparinized saline flushes. Blood pressure was recorded with a Grass Model 7P1A preamplifier and Grass Model 7 polygraph. Heart rate was obtained from the pressure recordings.

Each animal sat in a Plaslab primate chair 24 hr per day. A T-bar with pulley was attached to the chair and depending upon the exercise schedule, a lead weight of 0.4, 0.8, 1.2 or 1.6 kg was suspended from the pulley. The exercise was defined by a 10 cm horizontal pull of the T-bar toward the animal followed by the release of the bar to its resting position. The signal light used as the discriminative stimulus was a 6 W (24 V) bulb with a red lens cover mounted on a bud box located at eye level, 45 cm in front of and slightly to the left of the animal.

The tail of the monkey was shaved, brought through a hole cut in the back plate of the seat of the chair and placed within a styrofoam and foam rubber stock. Shock was delivered to the tail via bipolar copper plate electrodes enclosed within the stock. The stock was mounted to the rear of the seat where the tail exited. A Grason-Stadler E6070B shock generator produced an AC shock with a 0.2 sec duration. The level of shock used was the lowest intensity which motivated each monkey to pull the T-bar during exercise training. Shock current ranged between 5 to 10 mA and, once established, was maintained constant for each animal at all exercise combinations. A deactivated refrigerator shell was used as a sound attenuating chamber and a Grason-Stadler noise generator provided masking noise to the animal.

Training

Following one week of post-operative recovery, each monkey received two sessions in which the red signal light was presented alone. Each session consisted of presenting the signal light for 10 trials. The duration of the signal light was 5 sec with a 1 min intertrial interval.

Each animal was trained by the method of successive approximation to avoid shock to the tail by pulling the T-bar during the presentation of the signal light in the ratio of 1 pull/2 sec (0.5 Hz). This fixed ratio for shock termination was gradually incremented during training sessions until the animal consistently pulled the T-bar 12 times within a 24 sec period. Failure to complete the fixed ratio within the required time period resulted in continuation of the light signal and the presentation of 1 shock/sec until the required number of responses was made.

Each monkey was subjected to 1 daily training session, 7 days per week for 4 weeks. Each session consisted of 20 trials with an intertrial interval of 1 min. Drug studies were initiated after completion of the 4 week training period.

Drugs

The quantity of hexamethonium chloride used during test sessions was the dose (IM) which (a) produced consistent heart rate baseline approximating the intrinsic rate of heart [4,15], (b) produced consistent resting systolic and diastolic blood pressures, and (c) produced the least interference with the animal's ability to pull the T-bar. Each monkey met these criteria at 7 mg/kg. In preliminary trials, cardiovascular responses during exercise in the presence of phentolamine hydrochloride (9 mg/kg), atropine methylnitrate (1 mg/kg) and propranolol hydrochloride (9 mg/kg) were identical to those noted in the presence of hexamethonium alone. The dose for hexamethonium is expressed in terms of base. Normal saline (IM) was administered on alternate test days as a control for drug injection.

Test Sessions

Four different load conditions (0.4, 0.8, 1.2, and 1.6 kg) and four different numbers of pulls (3, 6, 9 and 12) at fixed frequency, i.e., 1 pull/2 sec, were combined in the presence of exposure to hexamethonium *or* saline injection (4×4×2 factorial design with repeated measures). There were 4 experimental observations in each cell. The 16 load-pull combinations were randomized and on each of 8 successive days, 4 combinations were used (16 trials/day). Hexamethonium and saline days alternated and were paired. The experimental design was such that on, for example, days 1 and 2, the first randomly selected set of 4 combinations were used; on days 3 and 4, the next 4 combinations were used, etc. The first trial began 15 min after the injection of either saline or hexamethonium. Successive exercise trials were not initiated until heart rate and blood pressure returned to the control values obtained prior to the first exercise trial.

The number of pulls required by the monkeys during test sessions was controlled by onset and offset of the signal light. T-bar pulling commenced immediately after onset of the signal light and continued while the signal light remained on until the last pull in the series was completed. Completion of the last required pull resulted in the offset of the signal light and the end of the exercise trial. In the few instances in which the animal failed to meet the schedule requirement during a test session a maximum of five shocks in the ratio of 1/sec was given. Trials during test sessions in which an animal received any shock were repeated. The very few trials in which shock occurred were discarded from the data analysis. Trials during test sessions also were discarded if the monkeys did not pull the T-bar at a rate of 1 pull/2 sec.

Response Measurement and Statistical Analysis

Pretrial heart rate, systolic and diastolic blood pressure baselines were obtained from the first 5 heart beats occurring within 3 sec periods immediately before each trial. Heart rate and blood pressure responses on each trial were assessed during the 5 beats immediately preceding the last pull of the T-bar and simultaneous termination of the signal light. Both heart rate and blood pressure showed peak responses at this point in exercise. Heart rate was derived from the interresponse time of the last 5 beats and blood pressure was measured as the mean of the systoles and mean of the diastoles occurring within the same time frame. These measurements

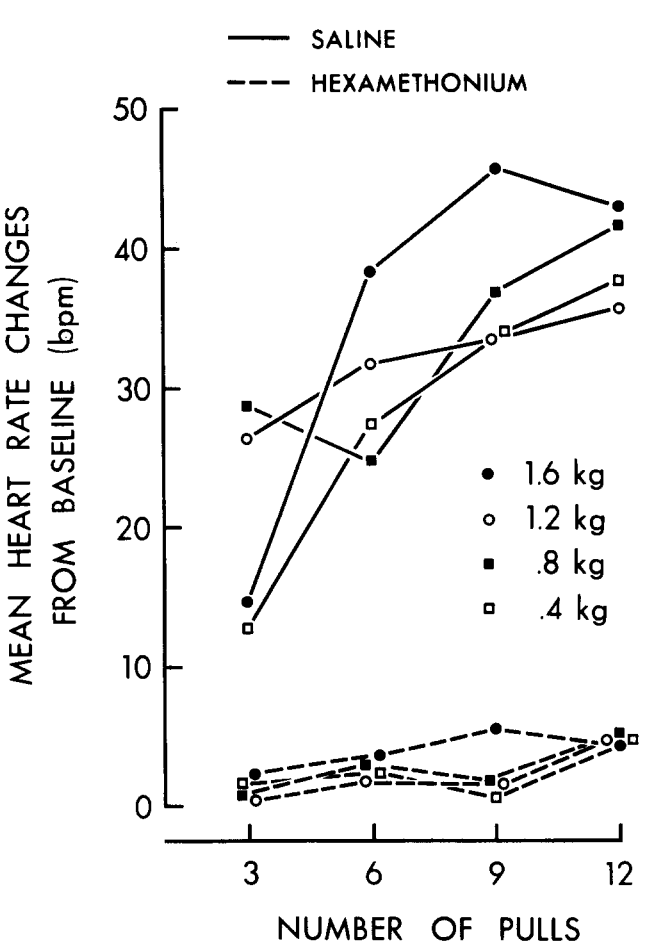

FIG. 1. Mean heart rate changes for 4 numbers of pulls (3, 6, 9, 12) at 4 levels of load (0.4, 0.8, 1.2, 1.6 kg) following injection of hexamethonium vs saline.

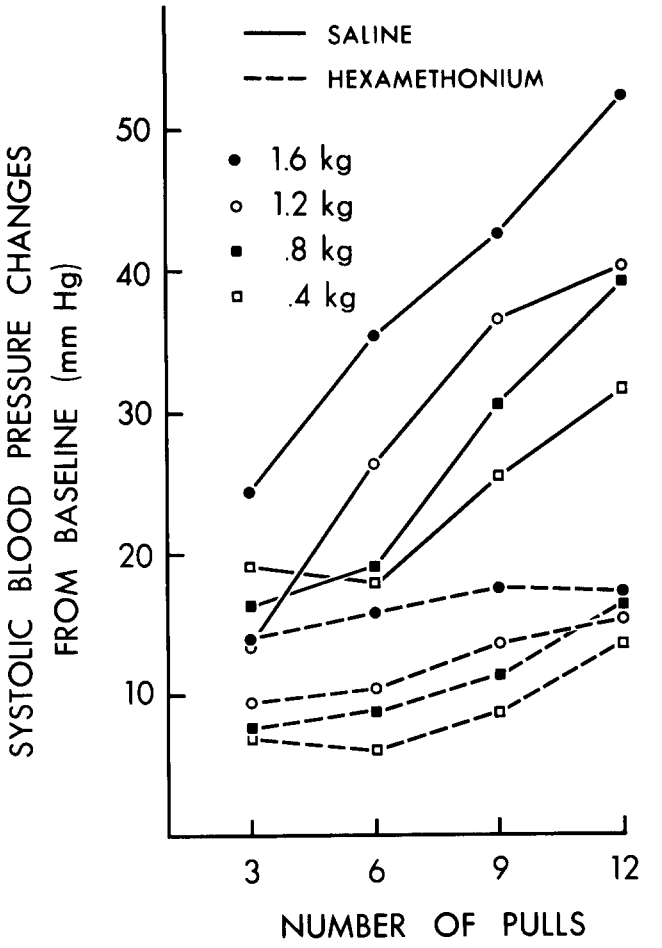

FIG. 2. Systolic blood pressure changes for 4 numbers of pulls (3, 6, 9, 12) at 4 levels of load (0.4, 0.8, 1.2, 1.6 kg) following injection of hexamethonium vs saline.

were then compared with similar measures taken during a baseline period preceding onset of the signal light. Data are expressed as mean ± SD or mean change from control ± SD.

Multifactorial analyses of variance were performed on the treatment and drug conditions as an all-within group design [5]. The relative contributions of load and number of pulls (duration of dynamic exercise component) to the observed changes in heart rate, systolic and diastolic blood pressures obtained under saline and hexamethonium were further assessed by examining the magnitudes and significance of beta weights *(B)* associated with these variables as iterated within a stepwise multiple regression analysis performed for each of the three dependent measures [19]. The analyses of variance examined the possibility of a multiplicative relationship for the effects of load and number of pulls while the regression approach examined a possible linear-additive relationship for these variables.

RESULTS

The resting heart rate for the four monkeys following postoperative recovery was 181 ± 23 (mean ± SD) bpm; systolic and diastolic blood pressures were 112 ± 10 and 52 ± 7 mm Hg, respectively. The pretrial baseline values for heart rate, systolic and diastolic blood pressures measured immediately *prior* to each exercise trial after saline administration were 189 ± 26 bpm, 108 ± 9 and 52 ± 9 mm Hg, respectively. Changes in heart rate after saline, measured immediately prior to the final pull in each combination, are shown in Fig. 1. Heart rate changes were significantly different from baseline for all combinations, $F(1,3)=29.11$, $p<0.025$. Heart rate varied as a function of total pulls, typically showing progressively greater changes from baseline as the number of pulls was increased, $F(3,9)=20.57$, $p<0.001$. Changes in heart rate as a function of load were not significant, $F(3,9)=1.27$, $p>0.05$, although at the highest load there was a tendency for heart rate to increase with increases in number of pulls.

Blood pressure changes during exercise after saline administration, measured immediately prior to the final pull in each combination are shown in Figs. 2 and 3. Both systolic (Fig. 2) and diastolic (Fig. 3) pressure showed similar responses, increasing in a linear fashion as the load and number of pulls were increased. Systolic, $F(1,3)=77.56$, $p<0.005$, and diastolic, $F(1,3)=69.12$, $p<0.005$, pressures changed significantly from baseline during exercise. Both systolic and diastolic pressures increased as a function of load, $F(3,9)=10.99$, $p<0.005$, and, $F(3,9)=9.92$, $p<0.005$,

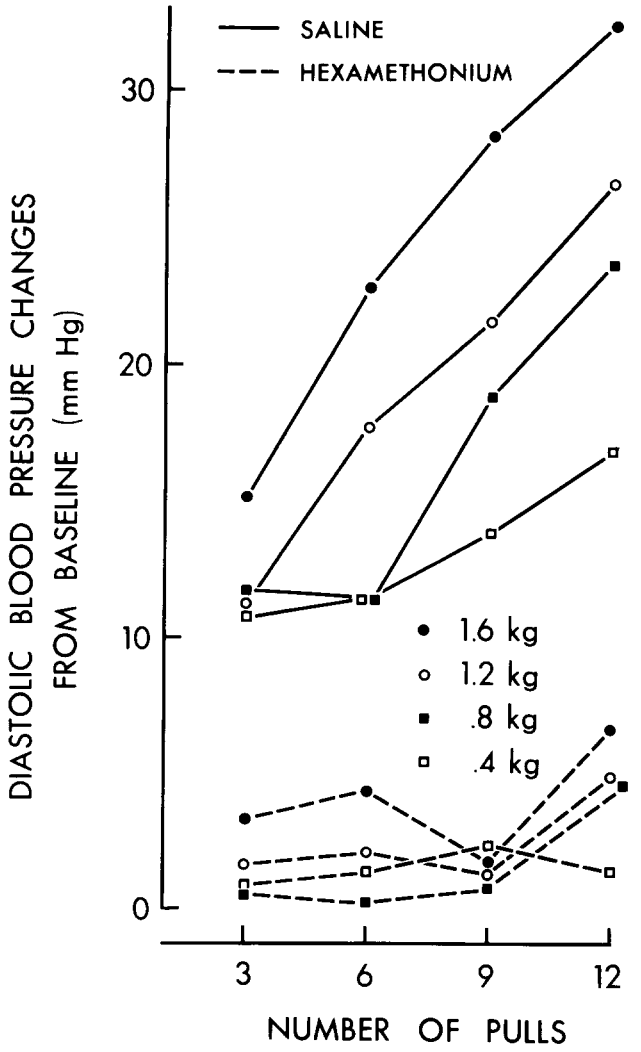

FIG. 3. Diastolic blood pressure changes for 4 numbers of pulls (3, 6, 9, 12) at 4 levels of load (0.4, 0.8, 1.2, 1.6 kg) following injection of hexamethonium vs saline.

respectively, and number of pulls, $F(3,9)=7.84$, $p<0.01$, and $F(3,9)=8.51$, $p<0.01$, respectively.

Hexamethonium reduced heart rate and blood pressure (Fig. 4). Heart rate, systolic and diastolic pressures after administration of hexamethonium, measured prior to each exercise trial, were 147 ± 8 bpm, 51 ± 9 and 20 ± 9 mm Hg, respectively, These values were significantly different from the saline controls, $F(1,3)=23.94$, $p<0.025$; $F(1,3)=39.74$, $p<0.01$; $F(1,3)=56.46$, $p<0.005$, respectively.

Heart rate increased very slightly when the monkeys exercised under hexamethonium (Fig. 1). There was a consistent and significant increase of 2 bpm, from a pretrial baseline of 147 to an exercise heart rate of 149 bpm, $F(1,3)=18.62$, $p<0.025$. Although Fig. 1 suggests that the increase may have been related to load, this was not confirmed by analysis of variance, $F(3,9)=1.85$, $p>0.05$.

Systolic pressure (Fig. 2) showed progressively greater changes from baseline as load and the number of pulls were increased during exercise under hexamethonium, $F(1,3)=268.76$, $p<0.001$. These changes however were smaller than those obtained under saline. Diastolic pressure changes during exercise under hexamethonium (Fig. 3) were variable and small, $F(1,3)=4.53$, $p>0.05$, increasing somewhat as a function of load (Fig. 4).

Systolic pressure varied as a function of the number of pulls, $F(3,9)=4.37$, $p<0.05$, and load, $F(3,9)=6.28$, $p<0.025$. The small changes in diastolic pressure occurred as a function of load, $F(3,9)=5.63$, $p<0.025$.

Multiple Regression Analyses

The results of the regression analyses are shown in Table 1. Number of pulls (B = .38) contributed thrice as much as load (B = .13) to the prediction of heart rate change under saline, a result consistent with the main effect for the number of pulls found in the analysis of variance. The linear combination best predicting heart rate change was significant [Multiple R (MR) = .40; $F(2,253)=24.56$, $p<0.005$].

The magnitude of the Multiple R's associated with the linear combinations best predicting systolic and diastolic pressure changes; the magnitude of the B weights associated with the number of pulls and load in the linear combinations; and the lack of any interaction in the analysis of variance all suggest that load and the number of pulls combined additively to produce the observed increases in blood pressure under saline. The number of pulls contributed more than load to the prediction of both systolic and diastolic pressure change.

The results of the regression analysis on heart rate changes under hexamethonium indicated that load contributed more than number of pulls to the prediction of heart rate change (Table 1). However, the 7% of the total variance accounted for by this linear combination was not substantial.

Regression analysis on systolic pressure changes under hexamethonium indicated that these changes are best described by a linear-additive model. Load contributed twice as much as number of pulls to an effective (MR = .52; $F(2,253)=43.77$, $p<0.005$) prediction equation for systolic pressure changes. These results are consistent with the main effects for load and the number of pulls found in the analysis of variance and indicate that although the effects of load and number of pulls summated, changes in systolic pressure under hexamethonium were influenced much less by the number of pulls. This is in contrast to the results for systolic pressure changes under saline.

Regression analysis on diastolic pressure changes under hexamethonium (Table 1) did not reveal significance for the total linear combination or for the number of pulls. However, load contributed to the prediction of diastolic pressure change under hexamethonium. These results are consistent with the main effect for load found in the analysis of variance and indicate that diastolic pressure changes under hexamethonium were due to the effects of load. This is in contrast to the results for diastolic pressure changes under saline.

In summary, heart rate, systolic and diastolic pressure increased during exercise. Heart rate varied primarily as a function of the number of pulls, whereas, the effect of the number of pulls and load summated in a linear-additive manner to produce increases in systolic and diastolic pressures. During exercise in the presence of hexamethonium, (a) a very small consistent increase in heart rate occurred; (b) changes in systolic pressure were smaller than those during exercise without the drug; (c) the effects of number of pulls and load summated in a linear-additive manner to produce increases in systolic pressure; and (d) diastolic pressure

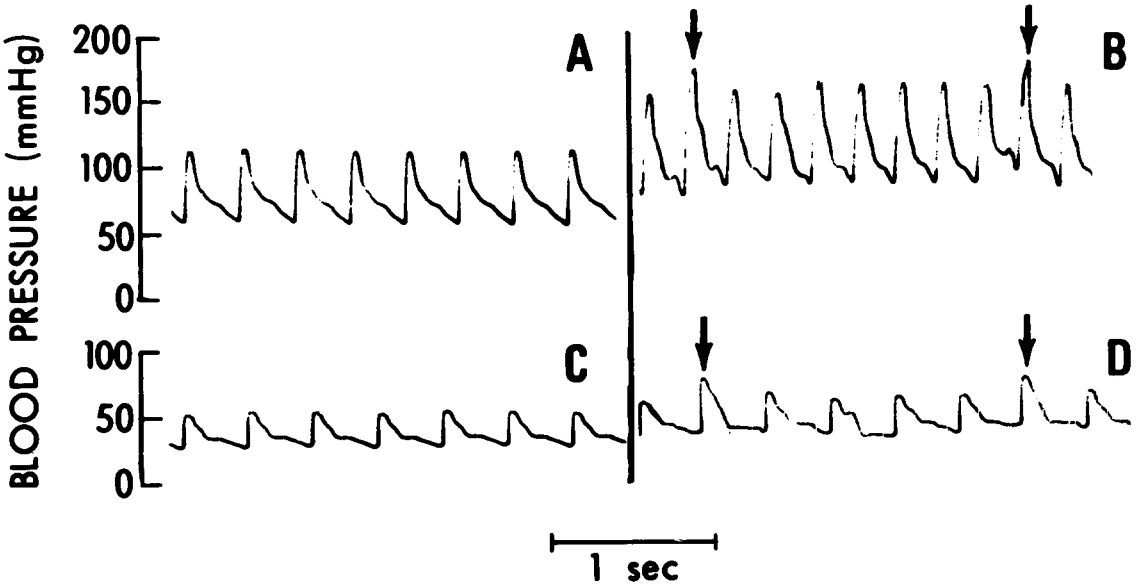

FIG. 4. Representative blood pressure traces recorded during control and exercise periods after saline (Panels A and B, respectively) or hexamethonium (Panels C and D, respectively) administration. Panel A: Control blood pressure recording obtained immediately prior to initiation of a saline exercise trial (Control heart rate = 176 bpm). Panel B: Blood pressure recording showing the last 2 pulls (arrows) of the exercise trial. The monkey was required to pull the T-bar 9 times against a 1.6 kg load (Exercise heart rate = 230 bpm). Panel C: Control pressure trace recorded from the same monkey 15 min after administration of 7 mg/kg hexamethonium and immediately prior to an exercise trial. Note that blood pressure is decreased and heart rate is reduced to 150 bpm; compare to saline control (Panel A). Panel D: Blood pressure recording showing the final 2 pulls (arrows) of the hexamethonium exercise trial. Pull and load requirements were the same as those described in Panel B (Exercise heart rate = 150 bpm). Note the increase in the phasic pressure trace which occurred with each pull on the T-bar (Panels B and D).

TABLE 1

SUMMARY OF REGRESSION ANALYSES

	Saline			Hexamethonium		
Variable	Multiple R (MR)	FR (*B*)	Load (*B*)	Multiple R (MR)	FR (*B*)	Load (*B*)
Heart rate	.40†	.38†	.13*	.27†	.16*	.22†
Systolic blood pressure	.66†	.56†	.35†	.52†	.22†	.46†
Diastolic blood pressure	.58†	.44†	.38†	.15	.01	.15*

*$p<0.05$.
†$p<0.01$.

changes under the drug were small, variable and not significant, although the responses varied somewhat as a function of load.

DISCUSSION

The nature of the cardiovascular changes in muscular exercise depend to a great extent on the type of exercise [2, 6, 12, 16, 17, 22, 25]. Dynamic or isotonic exercise occurs when skeletal muscle contraction induces, primarily, changes in muscle length with little change in tension or force. Static or isometric exercise arises from contractions which induce a change in tension with little alteration in muscle length. During dynamic exercise (e.g., bicycling) there are large increases in cardiac output and heart rate with relatively little change in mean arterial pressure; systolic pressure increases somewhat but diastolic pressure does not [18]. In contrast, during static exercise (e.g., sustained handgrip contraction) there are marked increases in mean arterial pressure as both systolic and diastolic pressures rise, but this is accompanied by relatively small increases in heart rate and cardiac output [18]. These cardiovascular responses reflect the metabolic needs of the contracting muscles. For example, the increased oxygen requirements of dynamically contracting muscle necessitates large increases in cardiac output.

Most human activities are neither purely static or dynamic. Running, swimming, bicycling and rhythmic calisthenics are examples of predominantly dynamic exercise while lifting heavy weights is mainly static exercise [18]. Until quite recently, there have been few studies on the adaptive changes in the cardiovascular system during exercise which combines both static and dynamic work. Lind and

McNicol [16] reported that an additive relationship occurred for combined treadmill and handgrip exercise at low to moderate levels of exertion but that, as the work level was increased, the blood pressure responses were lower than the sum of the effects of the dynamic and static exercises performed alone. On the other hand, Kilbom and Brundin [14] suggested that concomitant dynamic exercise had little effect on the heart and circulation during sustained isometric muscle contraction. Sanchez and Monod [23] used linear regression analyses to dissect the components contributing to cardiovascular responses during various levels of static arm work while cycling on an ergometric bicycle. They noted the cardiovascular, metabolic and ventilatory cost of combined work is not different from the sum of the costs of the static and dynamic contractions measured separately. They concluded that combined static and dynamic contraction were related in an additive manner. Their analyses were based on the performance of different muscle groups since the arms were contracting statically while the legs were performing dynamic work. In contrast Jackson *et al.* [12] reported the cardiovascular effects of isometric and dynamic exercise were greater than those of dynamic exercise alone; exercise in their study consisted of treadmill walking while carrying various loads.

Another human activity which encompasses combined dynamic and static exercise arises from repeated lifting of the weight of a barbell while lying on one's back. In contrast to the forms of exercise described above, manipulation of this type involves only one set of muscle groups. Systematic evaluation of the factors which affect the heart and circulation in this manner of exercise has not been reported and formed the basis of our study in which monkeys were trained to pull against a loaded lever. We recognize the inherent problems in identifying the static and dynamic components of rhythmic exercise in this model [21]. Dynamic work will change as the velocity of muscle shortening changes or the frequency of contraction is altered at constant velocity of muscle shortening. In the present experiments, we maintained pull frequency constant and ignored in our analyses the small changes in the velocity of each individual pull which resulted from alterations in load. (Evaluation of velocity of shortening as a determinant of cardiovascular responses in the form of combined exercise is planned.) Our model does have a practical counterpart since weight lifters generally seek to increase the total number of lifts with a particular weight rather than manipulating the frequency of pulls or the velocity of each pull.

Our experiments indicate that duration of dynamic exercise essentially determines heart rate response in this model while systolic and diastolic blood pressure were influenced by both the static and dynamic-duration components of the exercise task. After blockade of the autonomic ganglia with hexamethonium, only systolic pressure rose during the combined exercise as heart rate and diastolic pressure remained virtually constant. (The slight increase in heart rate may reflect an increase in body temperature.) Our analysis indicated the contribution of the static component of exercise to the rise in systolic pressure apparently increased while that contributed by the duration of dynamic exercise decreased during autonomic blockade. It has been demonstrated that inhibition of the autonomic nervous system alters the circulatory response to dynamic [1, 14, 20, 24] or static [9] muscular exercise. Our study extends this concept by demonstrating that the absence of a functioning autonomic nervous system modifies the cardiac and hemodynamic responses to the combined static-dynamic exercise. The clinical significance of static exercise alone in patients with cardiovascular disease has been emphasized [18] particularly with respect to isometric exercise augmentation of blood pressure in hypertensives [8,10]. Evaluation of combined static-dynamic effort in patients with heart disease has led to several recent studies in this area with conflicting results on the relative contributions of the static and dynamic components to cardiac symptoms or hemodynamic changes [3,12]. Our data describing an altered pattern of cardiac hemodynamic responses to combined static-dynamic exercise during autonomic nerve inhibition raise an additional point. The cardiovascular responses to combined exertion in patients with, for example, diabetic autonomic neuropathy [7,11] should be carefully assessed. Such individuals may not increase heart rate in combined exercise and an increased venous return may prove to be an excessive burden.

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