

Prevention of Bedrest-induced Physical Deconditioning by Daily Dobutamine Infusions

Implications for Drug-induced Physical Conditioning

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Abstract

The effects of intermittent infusions of dobutamine were studied in young normal male subjects during a period of bedrest deconditioning to determine whether this synthetic catechol affects physical conditioning processes in humans. 24 volunteers were placed at bedrest and randomized to daily 2-h treatments of saline infusions (control), dobutamine infusions, or maintenance exercise (control). Exercise, hemodynamic, and metabolic studies were performed at base line and at the termination of the 3-wk treatment period. Maximal exercise (duration, oxygen consumption, and workload) fell for the saline group and remained unchanged for the dobutamine and exercise groups. Hemodynamics during exercise were maintained the same as pretreatment base line for the dobutamine and exercise groups, whereas stroke volume and cardiac output dropped and heart rate rose for the saline group. The metabolic profile showed an increased blood lactate response at rest and during submaximal exercise after 3 wk of bedrest for the saline group, and essentially no change for the exercise and the dobutamine groups. Extraction of oxygen across the exercising lower limb rose for the dobutamine group, as did the activity of the skeletal muscle oxidative enzymes, citrate synthetase, and succinate dehydrogenase. In contrast to the exercise control group, the saline and dobutamine groups developed orthostatic hypotension, tachycardia, and accentuation of the renin-aldosterone response over the 3-wk treatment period; for the saline group, this is best explained by the observed fall in blood volume and for the dobutamine group, by the blunting of vascular vasoconstrictive responses. During a period of bedrest deconditioning in humans, infusions of dobutamine maintain many of the physiologic expressions of physical conditioning.

Introduction

Dobutamine, a synthetic catechol, is effective as an agent in providing acute inotropic support for the failing ventricle (1). Our laboratory has shown that 72-h infusions of dobutamine elicit sustained improvement in clinical status and activity tolerance of as many as 68% of patients with chronic congestive heart failure (2, 3). This observation has been confirmed by Liang and associates (4) in a double-blind controlled study. In another heart failure population, weekly 4-h dobutamine infusions for 24 wk improved functional class and exercise capacity without

altering ventricular function (5). The improvement in exercise capacity without concomitant augmentation of cardiac-ventricular function suggests that intermittent infusions of dobutamine may evoke a peripheral physical conditioning response. This hypothesis is supported by a study in dogs showing that intermittent dobutamine infusions over 5 wk elicit many of the characteristics of exercise conditioning including a decrease in resting heart rate and a reduction in heart rate, blood pressure, and cardiac output, and blood lactate, plasma renin, and norepinephrine concentrations during set levels of submaximal exercise (6).

This study was designed to determine whether intermittent dobutamine infusions affect the status and physiologic properties of physical conditioning in normal human subjects by investigating its effects on the pathophysiology of bedrest deconditioning. Saline and maintenance exercise treatment groups served as controls.

Methods

24 normal male subjects, age range 19–31 yr, were studied. All had unremarkable medical histories, normal physical examinations, and normal laboratory findings including chest roentgenography, electrocardiography, echocardiography, systolic time intervals, hemogram, and serum chemistries. All subjects were nonsedentary with exercise habits ranging from moderate activity (team sports three times a week) to marathon training.

The protocol was approved by the institutional human subjects research committee and written informed consent was obtained from each subject before the study.

Protocol. The study protocol lasted 22 d for each subject. The investigation was performed at the Clinical Research Center and in the human research laboratories of the Division of Cardiology of the Ohio State University Medical Center. All testing except evaluation of the autonomic nervous system and the muscle biopsy was done in a post-absorptive state between 7:30 a.m. and 12:00 p.m. The testing schedule was designed to minimize intertest variables. Pretreatment base-line and posttreatment studies and procedures included bicycle ergometry with expiratory gas analysis, bicycle ergometry with multigated radionuclide angiography, evaluation of autonomic nervous system responses, studies on the effects of posture, blood volume determinations, and skeletal muscle biopsies. With the exception of the nursing personnel of the clinical research center and one of the investigators (Dr. Sullivan), the investigators and technical staff (cardiology research nurses and laboratory technicians) responsible for performing the studies were blinded to treatment.

During days 3–22 of the study, all subjects were kept in a state of physical inactivity. They remained in bed, but were allowed to sit in bed (reading, watching television, bed baths). They were wheeled to the bathroom. Intake consisted of a caffeine-free, 5 g of NaCl (per day) diet and ad libitum water. Caloric content was not altered unless a subject's weight changed by $\geq 5\%$ of base-line body weight.

The 24 subjects were randomized (random number system) into three treatment groups: (a) saline control ($n = 8$), (b) dobutamine ($n = 8$), and

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(c) maintenance exercise control ($n = 8$). The treatments, administered on days 3–19 by the nursing personnel of the research center in conjunction with one of the investigators (Dr. Sullivan), lasted 2 h each day (8:00 to 10:00 a.m.). The subjects assumed a sitting position (bedside chair or bicycle) during the 2-h treatment periods. The saline control group received 250 ml of 0.9 N NaCl intravenously over the 2-h period. The treatment administration schedule for dobutamine and for maintenance exercise was based upon the heart rate response of the pretreatment base-line bicycle ergometry study. The exercise heart rate response was taken as the heart rate at maximal exercise minus the heart rate at rest. The dobutamine treatment group received dobutamine in doses, and the exercise treatment group underwent exercise, at levels that increased resting heart rate by an increment of 20% of the exercise heart rate response for 1-h, 40% for 45 minutes, and 60% for 15 min. This schedule was selected because at this level of exercise, a state of physical conditioning is fairly well maintained (7); it was not the intention of the investigators to increase the level of physical conditioning in the exercise treatment group during this study. The exercise control group is therefore more appropriately designated “maintenance exercise control group.” Daily maintenance exercise treatment was administered on a workload-adjustable upright Monark bicycle. Dobutamine was administered intravenously using the admixture of 250 mg of dobutamine HCl in 250 ml of 0.9 N NaCl. Heart rate response to treatments was monitored continuously with an Electronics for Medicine (Pleasantville, NY) M2100 amplification system.

Several issues entered into the design of this protocol. 3 wk of bedrest was selected as the duration and method of deconditioning because this approach has been shown to be effective in eliciting the changes of deconditioning (7–11), and because a duration >3 wk would have greatly affected the recruitment of physically active, conditioned volunteers. The dobutamine doses administered in this study were higher than those used to elicit a conditioning response in congestive heart failure (7.9–15.0 $\mu\text{g}/\text{kg}\cdot\text{min}$); however, the duration of the infusions (72 h) and/or the treatment periods (6 mo) were considerably longer for the heart failure protocols. Higher doses were used in the current study for the purpose of delivering the maximal tolerable pharmacologic intervention over the allotted 3-wk period. The high-dose heart rate (endpoint) method for determining the dobutamine treatment schedule is supported by the study of Liang and colleagues (6) that shows its effectiveness in favorably altering many processes of physical conditioning in a canine model. The daily maintenance exercise treatment was formulated to prevent deconditioning. The goal was to maintain a relatively constant level of physical conditioning, present at base line, throughout the 3-wk bedrest period; this group served as the “no deconditioning” control group. Augmentation of the state of physical conditioning was intentionally avoided. The authors do not equate “prevention of deconditioning with physical activity” with “active physical conditioning” nor imply that the physiologic processes of active physical conditioning are necessarily the exact opposite of those of deconditioning.

Procedures and measurements. Bicycle ergometry with respiratory gas analysis was performed between 7:30 and 10:30 a.m. on days 2 and 21. 1 h before ergometry, a 16-gauge 6 in soft teflon catheter was placed in the right femoral artery and another in the right femoral vein. These catheters, placed under local anesthesia (1% lidocaine), were introduced percutaneously 1–2 cm above the crease separating the right inguinal region from the right anterior thigh. The subjects were allowed to equilibrate and become familiarized with the ergometry and gas analysis systems over a 30–40-min period after catheter insertion. The subjects were then placed in a comfortable sitting position (chair) and interfaced with an Electronics for Medicine M2100 monitoring and amplification system and a Beckman Instruments (Anaheim, CA) metabolic measurement cart (LB-2 carbon dioxide and OM-11 oxygen analysis units). The subjects were allowed to equilibrate an additional 15–20 min, the endpoint of which was indicated by a $\leq 10\%$ variation in oxygen consumption (VO_2) and $<5\%$ variation in the respiratory quotient; these determinations, representing an analysis of 2-min collections, were obtained every 2 min over a duration of 12 min. Base-line resting data were then collected over 30 min with the subject seated in a chair for 15 min and on the

bicycle for 15 min. Bicycle ergometry, employing a Quinton Uniwork model 845 (Quinton Instruments, Seattle, WA) was started at a workload of 200 kilopond-minutes (kpm)¹ and advanced by 100-kpm increments every 2 min. From 8 to 16 min, the workload was held constant at 600 kpm; this interval was chosen as the submaximal exercise testing period for each subject. The maximal exercise endpoint was determined by marked dyspnea and/or fatigue plus a drop in the increment of VO_2 to ≤ 0.10 ml/kg \cdot min during continued exercise with the increasing workload protocol. After exercise, the subjects remained seated on the bicycle for 12 min of data collection (postexercise recovery period). Heart rate and systemic blood pressure (measured by mercury column sphygmomanometer) was determined twice at base line, every 2 min of the exercise and recovery periods, and at max exercise. Respiratory gas analysis, including VO_2 , carbon dioxide production (VCO_2), ventilatory volume, and respiratory quotient, was obtained \geq four times at base-line rest (\geq two readings in chair, \geq two on bicycle), every 2 min during exercise and recovery, and at 30-s intervals from ≥ 60 s before max exercise to max exercise. Anaerobic threshold was defined as the time or VO_2 point at which the VCO_2 and VO_2 curves separated secondary to an augmented increase in VCO_2 (12). This determination was made from a continuous recording of the respiratory parameters using an Hewlett-Packard 85 computer and recorder (Palo Alto, CA).

Indirect Fick methodology, employing the plateau CO_2 rebreathing technique, was used to measure cardiac output; cardiac outputs were obtained at base-line rest, at 12–14 min of the submaximal exercise period, and at max exercise. In our laboratory, this technique has a coefficient of variation of $\leq 9.0\%$ and correlates well ($r = 0.89$, $r^2 = 0.79$, $P < 0.05$) during rest and exercise with the thermodilution and dye-indicator dilution techniques of measuring cardiac output ($n = 8$; VO_2 ranging from 3.2 to 30.1 ml/kg \cdot min); similar validity and reproducibility data have been reported from other laboratories (13, 14). The correction formulas of Jones et al. (15) were applied to all exercise cardiac output determinations. Derived parameters included: mean blood pressure = (systolic – diastolic blood pressure)/3 + diastolic blood pressure; and systemic vascular resistance = mean blood pressure/cardiac output $\times 80$ (dynes-second-centimeter⁻⁵). Blood was drawn from the femoral arterial and venous catheters at base line, 10, 14, and 20 min of exercise, maximal exercise, and 2, 6, and 12 min of the postexercise recovery period. The blood samples were used to measure lactate (modification of the Marbach–Weil method) (16, 17), oxygen saturation (spectrometry with an American Optical Corp. Unistat Oximeter [Southbridge, MA]), and catecholamines (radioenzymatic technique) (18).

Resting and exercise multigated radionuclide angiography was performed on days 2 and 22. The studies were performed in the supine and in the upright (70–80° tilt) positions, separated by a 90-min reequilibration period. Image acquisition and data analysis, obtained at rest, at submaximal (14 min), and at maximal exercise, were done according to techniques previously reported (19). A Quinton Uniwork ergometer (model 845) was used, and the exercise workload protocol was the same as that described above for bicycle ergometry with respiratory gas analysis.

The effects of upright posture were studied on days 2, 3, 21, and 22. On days 2 and 21, after 3 h of postexercise reequilibration, heart rate, blood pressure, echocardiography, and systolic time intervals were obtained in the supine and standing (90° upright) positions. Echocardiography and systolic time intervals were recorded on an Electronics for Medicine Echo IV unit by means of techniques previously described (20). Supine (≥ 8 h) and upright (>60 min) blood samples were obtained at 7:00 a.m. of days 3 and 22 for catecholamine concentrations, plasma renin activity (Rianen angiotensin I [¹²⁵I]), and aldosterone levels (Abbott [¹²⁵I] aldosterone diagnostic kit).

Evaluation of the status of the autonomic nervous system was done on days 2 and 21. With the subject in a 30° head-up position, isoproterenol was infused at 1.0 $\mu\text{g}/\text{min}$ for 12 min followed by a 2.0 $\mu\text{g}/\text{min}$ infusion for an additional 12 min. Heart rate, blood pressure, echocar-

1. *Abbreviations used in this paper:* kpm, kilopond-minute; VO_2 , oxygen consumption.

diography, and systolic time intervals were performed preinfusion and at 10–12 min (1.0 $\mu\text{g}/\text{min}$) and 22–24 min (2.0 $\mu\text{g}/\text{min}$) of the isoproterenol infusion. After a ≥ 90 -min reequilibration period, phenylephrine was infused to achieve an increase in blood pressure to 140 mmHg systolic and/or 90 mmHg diastolic and then, to 150 mmHg systolic and/or 100 mmHg diastolic. Heart rate, blood pressure, and phenylephrine dose were recorded at base line and at the two pressure increments. After another ≥ 90 -min reequilibration period, atropine sulfate, 0.20 $\mu\text{g}/\text{kg}$, was administered intravenously over 2–3 min. Heart rate and blood pressure were obtained before atropine, and 5, 10, and 15 min postadministration.

Blood volume, determined on days 3 and 17, was measured by a ^{131}I -radiiodinated serum albumin technique (21).

Needle biopsy samples of the left vastus lateralis muscle were obtained on days 4 and 18. The biopsy samples were immediately placed in liquid nitrogen and stored in this media until analyzed for the aerobic enzymes, citrate synthetase, succinate dehydrogenase, and cytochrome oxidase (Sullivan et al., manuscript submitted for publication).

Statistical analysis. Intragroup comparisons were made with analysis of variance for repeated measures. Intergroup differences were analyzed with one- and two-way analysis of variance with appropriate aftertesting (Newman-Keuls). The results are expressed as mean ± 1 standard deviation ($\bar{x} \pm \text{SD}$).

Results

None of the subjects violated the bedrest requirements. The maintenance exercise group was uniformly compliant to exercise treatment; coaching to adjust the heart rate response properly was rarely required. The average doses required to achieve the heart rate endpoints for the dobutamine treatment group were 17 ± 4 , 26 ± 9 , and 34 ± 10 $\mu\text{g}/\text{kg} \cdot \text{min}$. The doses required tended to be higher ($P < 0.1$) toward the end of the treatment period. For the highest dose level (last 15 min of the infusion period), the average dose for week 1 was 29 $\mu\text{g}/\text{kg}/\text{min}$ and for week 3, 36 $\mu\text{g}/\text{kg}/\text{min}$. 46 $\mu\text{g}/\text{kg} \cdot \text{min}$ was the highest infusion rate administered to any subject. The 120-min dobutamine infusion was shortened to 105–110 min on six occasions out of the 128 (total) infusions because of nausea and/or vomiting and on one occasion, it was reduced to 100 min because of chest pain.

There were no statistically significant differences between the three treatment groups for any of the pretreatment base-line values for any testing parameter.

Changes in body weight were comparable for the three groups. The saline group gained 1.13 ± 1.79 ($\bar{x} \pm \text{SD}$) kg, the dobutamine group 1.58 ± 1.30 kg, and the exercise group 1.25 ± 1.39 kg.

Bicycle ergometry. Exercise duration, oxygen consumption (VO_2), and workload at maximal exercise fell significantly after 3 wk of bedrest and daily saline treatment (Fig. 1). These parameters of physical conditioning were not altered by 3 wk of bedrest plus daily dobutamine treatment or daily maintenance exercise. For the saline control group, VO_2 fell from 40.1 ± 6.1 to 36.4 ± 3.4 $\text{ml}/\text{kg} \cdot \text{min}$ ($P < 0.05$), for the dobutamine group, from 38.7 ± 8.5 to 38.5 ± 6.5 $\text{ml}/\text{kg} \cdot \text{min}$ ($P > 0.4$), and for the maintenance exercise control group, from 36.4 ± 5.2 to 35.2 ± 6.5 $\text{ml}/\text{kg} \cdot \text{min}$ ($P > 0.4$) (Fig. 1, bottom panel).

Oxygen consumption per workload remained the same for the three treatment groups (Fig. 2 A); except for maximal exercise capacity (duration and max VO_2) for the saline group, the pre- and posttreatment VO_2 curves were virtually identical for each of three groups. CO_2 production remained unchanged after treatment compared to pretreatment values for the dobutamine

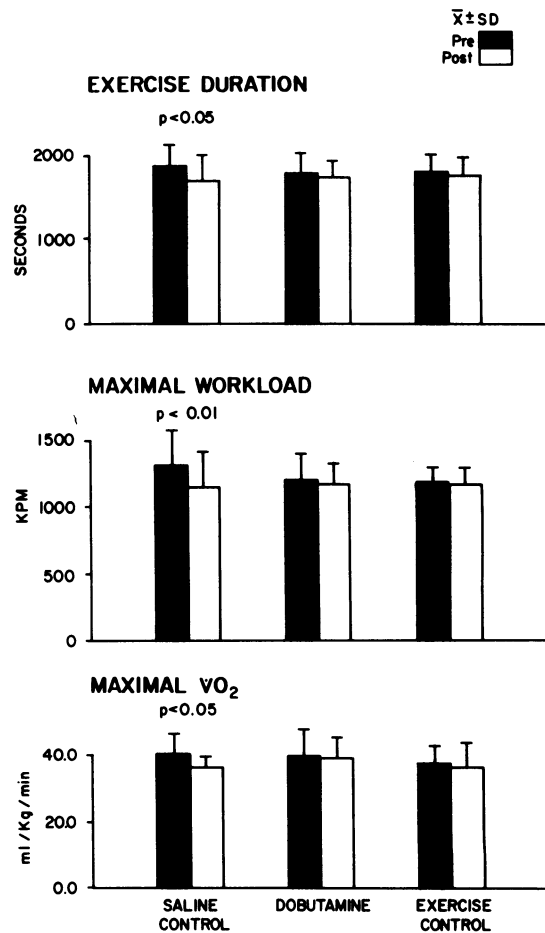


Figure 1. Exercise duration, workload, and oxygen consumption (VO_2) at maximal levels of bicycle exercise for the three treatment groups. Solid bars represent pretreatment data and empty bars represent the data obtained after 3 weeks of bedrest plus saline, dobutamine, or maintenance exercise treatment. KPM, kilopond-minute.

and exercise groups (Fig. 2 B). Whereas the posttreatment VCO_2 values were not significantly different from pretreatment values for the saline control group, the pre- to posttreatment increment (or difference) for this group was significantly greater than the differences between pre- and posttreatment values for the dobutamine and maintenance exercise groups. Similar findings were noted for the respiratory quotient and the ventilatory volume (Fig. 2, C and D). For the saline control group, the pretreatment anaerobic threshold occurred at 20.2 ± 2.3 min ($\text{VO}_2 = 27.9$ $\text{ml}/\text{kg} \cdot \text{min}$) of exercise and posttreatment, fell to 18.0 ± 3.2 min ($\text{VO}_2 = 24.2$ $\text{ml}/\text{kg} \cdot \text{min}$) ($P < 0.1$). The pre- to posttreatment anaerobic thresholds did not change significantly for either the dobutamine group (19.0 ± 3.3 min [$\text{VO}_2 = 26.8$ $\text{ml}/\text{kg} \cdot \text{min}$] to 19.2 ± 4.4 min [$\text{VO}_2 = 26.5$ $\text{ml}/\text{kg} \cdot \text{min}$]) or the maintenance exercise group (18.2 ± 3.7 min [$\text{VO}_2 = 25.1$ $\text{ml}/\text{kg} \cdot \text{min}$] to 18.0 ± 3.9 min [$\text{VO}_2 = 24.5$ $\text{ml}/\text{kg} \cdot \text{min}$]).

The heart rate response at rest and during exercise remained unchanged from the pretreatment base-line response for the subjects treated with 3 wk of bedrest and maintenance exercise (Fig. 3 A). Mild augmentation of the heart rate response was noted in the group receiving daily dobutamine treatment, particularly at rest (bicycle sitting) and during submaximal exercise. Resting and exercise heart rate responses increased significantly after 3 wk of bedrest and saline treatment, compared to pre-

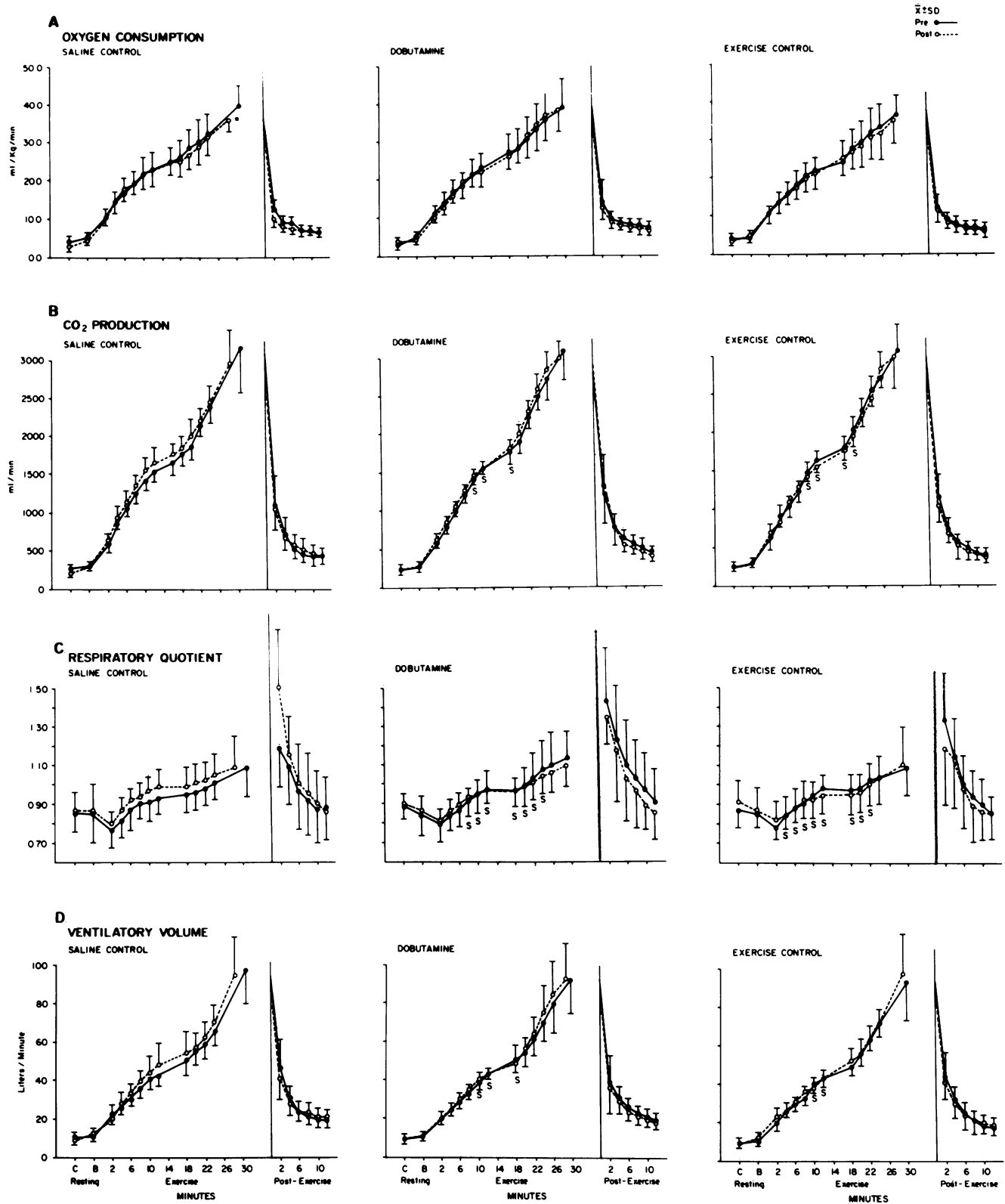


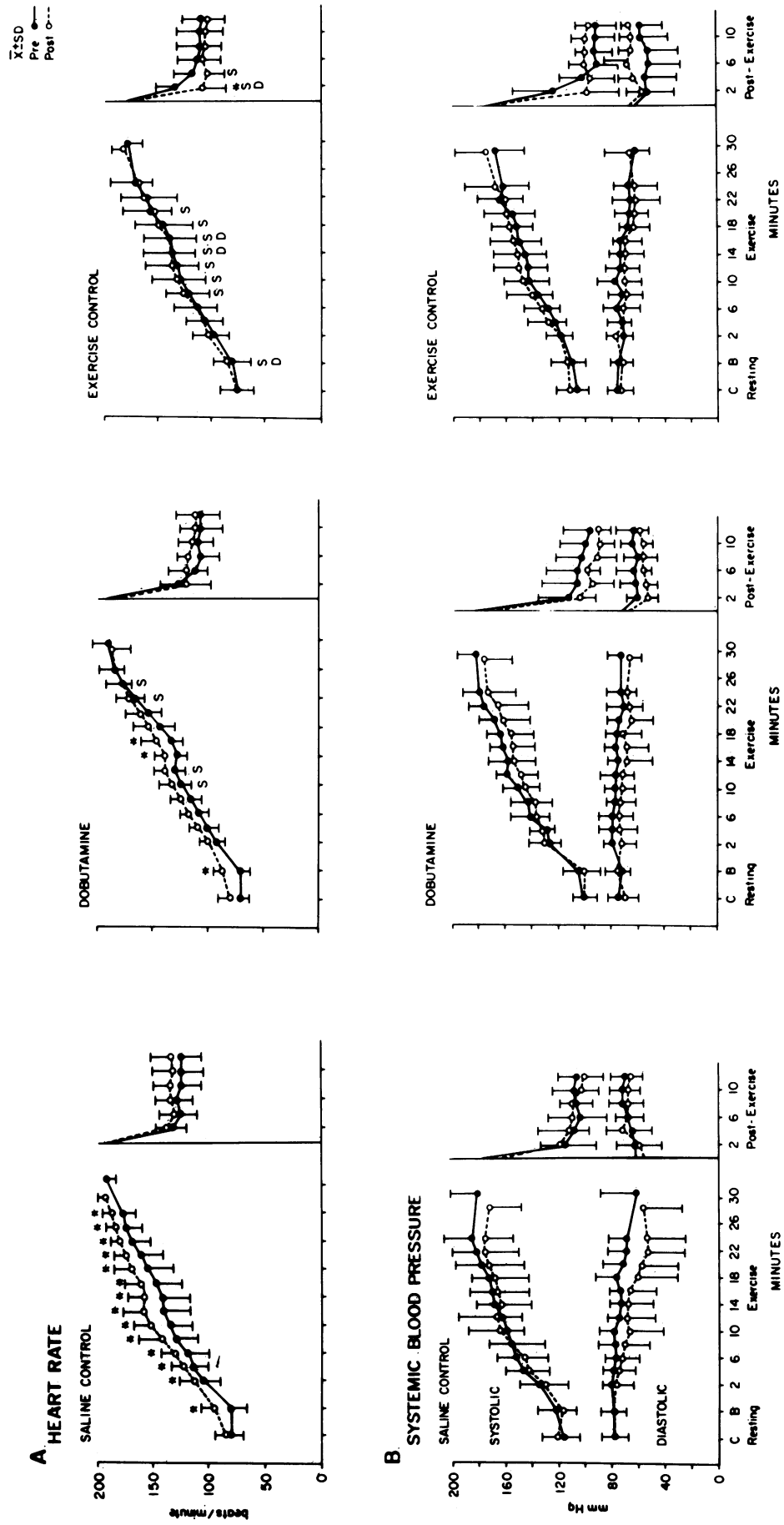
Figure 2. Results of respiratory gas analysis during the preexercise (resting), exercise, and postexercise recovery periods for the three groups. Statistical analysis: * $P < 0.05$ pre- vs. posttreatment difference (Δ); S, $P < 0.05$ for the pre- and posttreatment difference (Δ) com-

pared to the pre- to posttreatment difference (Δ) of the saline-treated control group; D, $P < 0.05$ for the pre- to posttreatment difference (Δ) compared to the pre- to posttreatment difference (Δ) of the dobutamine-treated group. B, bicycle; C, chair.

treatment base-line responses; these increases were significantly greater than the changes noted for the exercise group and some of the changes noted for the dobutamine treatment group. No

intragroup (pre- to posttreatment) and no intergroup differences were noted in systemic blood pressures (Fig. 3 B).

The central hemodynamic responses of these exercise studies



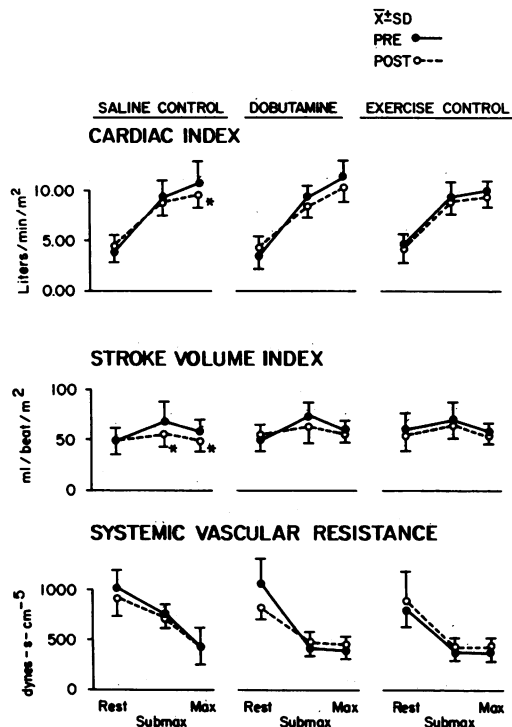


Figure 4. Hemodynamics obtained during rest and submaximal (Submax, 12–14 min) and maximal (max) exercise for the three treatment groups. * $P < 0.05$ pre- vs. posttreatment difference (Δ).

are presented in Fig. 4. Other than a posttreatment decrease in cardiac output at maximal exercise for the saline treatment group, cardiac output at rest, submaximal, or maximal exercise remained unaltered for the three treatment groups. Stroke volume index was significantly reduced at submaximal and maximal exercise after 3 wk of saline treatment compared to pretreatment base line. No significant changes in systemic vascular resistance from pre- to posttreatment were noted in the three groups. None of the central hemodynamic parameters changed from pretreatment base line during rest or exercise for the subjects treated with 3 wk of bedrest and daily maintenance exercise.

Left ventricular ejection fraction did not change significantly from pretreatment values at rest or during submaximal and maximal exercise for the three treatment groups (Table I). This was true for both supine and upright positions.

Metabolic studies during exercise. Saline treatment over 3 wk of bedrest resulted in increases in arterial lactate concentration at rest and during submaximal levels of exercise (Fig. 5 A). After the 3-wk treatment period, an increase in the lactate response occurred only at 20 min of submaximal exercise for the dobutamine treatment group, compared to pretreatment responses. Arterial lactate responses to rest and exercise remained unchanged from pretreatment responses for the subjects treated with 3 wk of bedrest and maintenance exercise.

The arterial and venous oxygen saturations of the lower extremity remained unchanged from pretreatment values during the rest, exercise, and postexercise recovery periods for the saline and maintenance exercise treatment groups (Fig. 5 B); as a result, the posttreatment arterial-venous O_2 differences remained unchanged from those of pretreatment base line. The resting and exercise arterial-venous O_2 difference of the lower extremity increased significantly ($P < 0.05$) after 3 wk of dobutamine treatment; this increase was secondary to a mild, but insignificant, increase in arterial O_2 saturation and a general reduction ($P < 0.1$) in the venous O_2 saturation.

Arterial norepinephrine concentrations (sitting-rest and exercise) did not change from pretreatment responses after 3 wk of bedrest plus saline, dobutamine, or maintenance exercise (Fig. 5 C). Arterial epinephrine concentrations remained unchanged from pretreatment responses for the exercise and the dobutamine treatment groups and increased for the saline group at submaximal exercise (Fig. 5 C).

Response to supine and upright positions. Resting supine heart rate increased above base line after 3 wk of bedrest and saline (Fig. 6 A). The heart rate response to standing rose significantly above pretreatment values for both saline and dobutamine treatment groups. The supine and standing heart rate responses remained unaltered for the maintenance exercise control group. Although systemic blood pressure (systolic and diastolic, supine and standing) generally tended to drop below baseline values after treatment for the three groups, a statistically

Table I. Ejection Fraction by Radionuclide Angiography

	Supine			Upright (70°–80° tilt)		
	Rest	Submax	Max	Rest	Submax	Max
	%	%	%	%	%	%
Saline control						
Pre	66±6	78±8	84±9	63±8	79±8	86±7
Post	69±3	77±7	84±8	58±4	78±9	86±9
Dobutamine						
Pre	66±6	80±6	88±5	65±8	81±7	90±5
Post	66±9	76±8	89±4	69±7	83±6	89±7
Exercise control						
Pre	66±7	75±7	81±6	65±8	79±4	88±5
Post	65±5	75±4	83±5	63±7	76±5	90±6

All values are means±SD. Abbreviations: Max, maximal exercise; Submax, submaximal exercise; Pre, pretreatment, base-line data; Post, post-treatment, data obtained after the 3-wk treatment period.

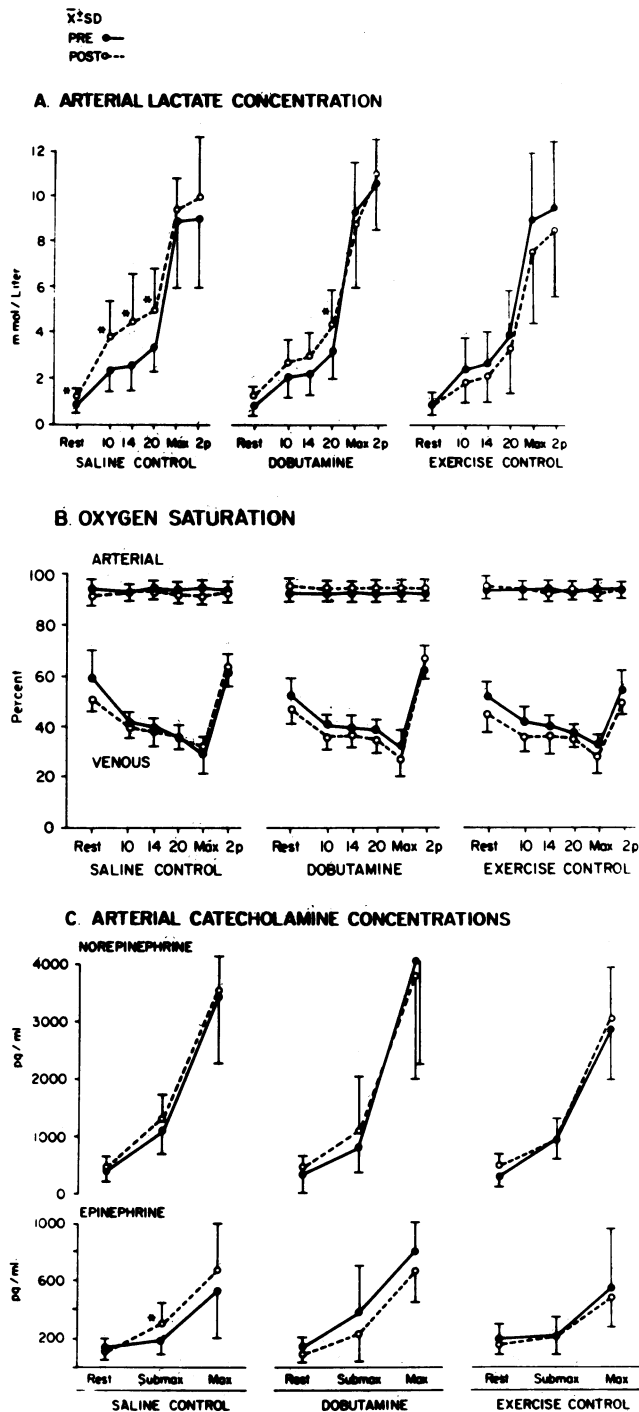


Figure 5. Arterial lactate concentrations (A) and lower limb arterial and venous oxygen saturations (B) obtained at rest, 10, 14, and 20 min of exercise, maximal (max) exercise and 2 min postexercise (2p). Catecholamine concentrations of arterial blood (C) were obtained at rest and during submaximal (Submax, 10 min) and maximal (max) exercise. * $P < 0.05$ pre- vs. posttreatment difference (Δ).

significant change was noted only for systolic blood pressure of the saline control group (Fig. 6 A). Supine and standing end-diastolic volume of the left ventricle did not change significantly from pretreatment values for all three treatment groups (Fig. 6 B). No changes in the noninvasive parameters of left ventricular function occurred in either position after 3 wk of bedrest plus

saline, dobutamine, or maintenance exercise (Fig. 6 B). Although supine and standing plasma catecholamine concentrations did not change from pretreatment values for any of the three treatment groups, plasma renin activity and aldosterone concentrations during standing rose significantly above base-line responses for the saline control and the dobutamine treatment groups (Fig. 6 C).

Blood volume. Blood volume fell for the saline treatment group from a base-line volume of 6.29 ± 1.35 liters to a post-treatment volume of 5.64 ± 0.94 liters ($P < 0.05$). Blood volumes did not change significantly for the dobutamine (base line = 6.01 ± 0.59 liters, posttreatment = 5.94 ± 0.50 liters) or the maintenance exercise (base line = 6.57 ± 0.81 liters, posttreatment = 6.47 ± 0.93 liters) groups. The hemoglobin concentration and hematocrit did not change significantly for the three treatment groups during the 3 wk study.

Assessment of autonomic nervous system. Heart rate responsiveness to isoproterenol and atropine remained unchanged for each of the treatment groups (Fig. 7 A and C). The phenylephrine dose required to elevate systemic blood pressure to preset criteria (see Methods) rose above the pretreatment dose for the dobutamine treatment group and remained unchanged for the exercise and saline treatment groups (Fig. 7 B). The amount of reduction in heart rate in response to the elevations of systemic blood pressure with phenylephrine did not change from the pretreatment response for the maintenance exercise group, decreased for saline control group, and increased for the dobutamine group. Employing the ratio, Δ heart rate/ Δ systemic blood pressure, reduced responsiveness of the baroreceptor reflex occurred after 3 wk of bedrest-saline, heightened activity after bedrest-dobutamine, and no alteration after bedrest-maintenance exercise.

Analysis of aerobic enzyme activity of skeletal muscle. After 3 wk of dobutamine treatment, citrate synthetase activity of skeletal muscle rose from a pretreatment base-line value of 0.50 ± 0.09 ($\mu\text{mol substrate}/\mu\text{mol creatine} \times \text{min}$) to 0.58 ± 0.08 ($P < 0.05$). The activity of this enzyme tended to decrease for the saline treatment group from 0.51 ± 0.15 pretreatment to a posttreatment value of 0.44 ± 0.08 ($P = 0.06$). Succinate dehydrogenase activity tended to increase ($P = 0.07$) for the dobutamine treatment group (pretreatment = 0.15 ± 0.05 to post-treatment = 0.21 ± 0.07 $\mu\text{mol substrate}/\mu\text{mol creatine} \times \text{min}$) and remained unchanged for the saline control group. These aerobic enzymes of skeletal muscle remained unchanged over 3 wk of bedrest and maintenance exercise treatment. Cytochrome oxidase activity was not altered by any of the three treatments.

Discussion

This study has shown that the intermittent administration of the synthetic catechol, dobutamine, significantly affects the status and the physiology of physical conditioning in normal human subjects. The major findings are summarized in Table II. Our approach to the investigation of the effects of dobutamine on the status of physical conditioning was one of examining its effects on the pathophysiology of deconditioning. This approach was used because in the authors' experience, deconditioning processes in humans are more readily reproducibly and reliably attained than those of physical conditioning. A physical conditioning response to intermittent dobutamine may take ≥ 4 wk to develop (5, 6). In addition, pharmacologic interruption of deconditioning has major relevance in a number of human con-

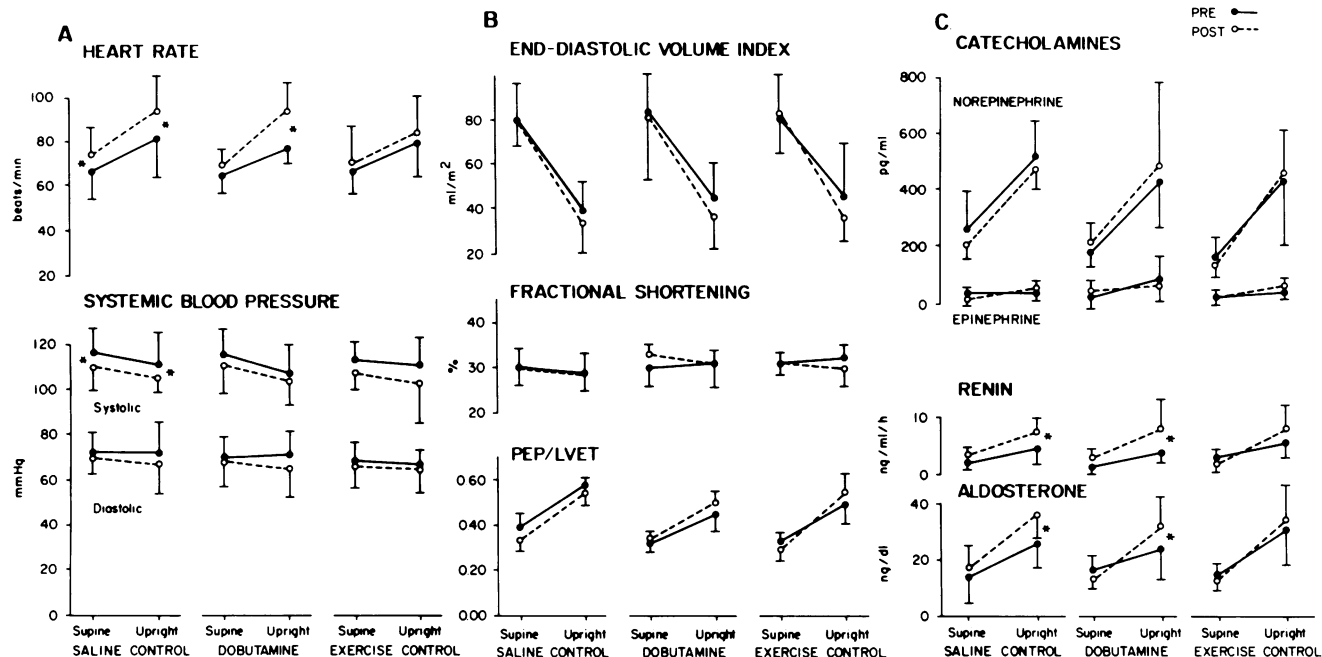


Figure 6. Results of studies performed in supine and upright (standing) body positions. End-diastolic volume index and fractional shortening of the left ventricle were obtained by echocardiography and the

ratio of pre-ejection period to left ventricular ejection time (PEP/LVET) by systolic time intervals. * $P < 0.05$ pre- vs. posttreatment difference (Δ).

ditions associated with physical inactivity (e.g., major illness, fractures, paralysis, space travel).

Bedrest deconditioning elicits a number of pathophysiologic events and adaptations (7–11, 22–24), many of which were pro-

duced in the bedrest-saline control group of this study. Exercise capacity, as assessed by duration, workload, and oxygen consumption at maximal exercise, decreased. Stroke volume at submaximal and maximal exercise decreased with a compensatory increase in heart rate. No significant changes in ventricular function per se (e.g., ejection fraction, fractional shortening, pre-ejection to ejection time ratio) occurred; this suggests that many of the hemodynamic events, including the orthostatic changes in blood pressure and heart rate, noted in the control subjects receiving daily saline treatment (250 ml of 0.9 NaCl) over the 3-wk period of bedrest, were related to the observed reduction in blood volume. This is further supported by augmented responses in plasma renin activity and aldosterone concentrations to standing after the 3-wk treatment period. The heart rate response to blood pressure elevation by phenylephrine was diminished after 3 wk of bedrest for the saline control group suggesting that the baroreceptor response was altered (desensitized) during prolonged bedrest. Bedrest deconditioning affected metabolic processes of skeletal muscle. The reduction in the exercise time to anaerobic threshold and the increase in CO_2 production and the arterial lactate response per exercise workload and VO_2 suggest a shift toward more anaerobic metabolism during exercise for this group. The observed reduction in aerobic enzyme activity of skeletal muscle (e.g., citrate synthetase) may, in part, account for some of this shift. It is unlikely that all the changes in skeletal muscle metabolism (1 VCO_2 , arterial lactate, time to anaerobic threshold) noted for the bedrest saline control group are secondary to the reduction in the activity of one oxidative enzyme of skeletal muscle.

In contrast to the saline control group, the maintenance exercise control group did not demonstrate any evidence of physical deconditioning. In addition, the daily exercise treatment was set at a level which did not result in net improvement in their state of physical conditioning. As such, the maintenance exercise group represents an ideal control to determine if the saline group

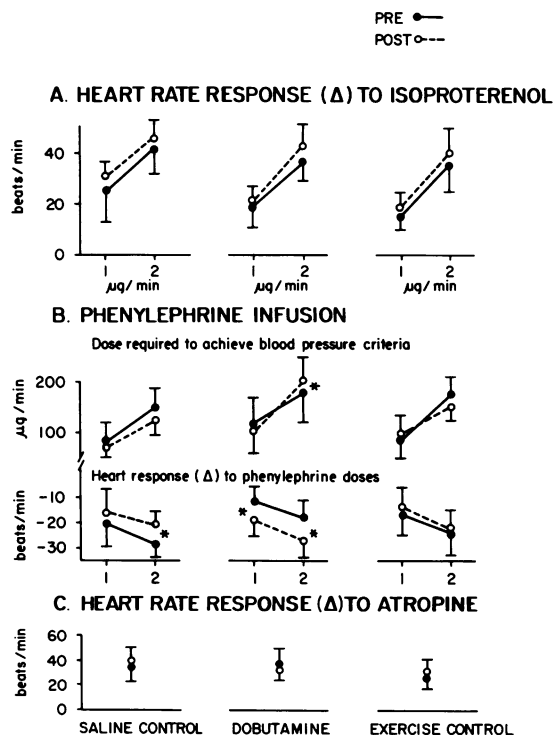


Figure 7. Studies of responsiveness of the autonomic nervous system and related reflexes to β -receptor agonism (A), elevation of systemic blood pressure (B) and parasympathetic blockade (C). See text for testing protocols. * $P < 0.05$ pre- vs. posttreatment difference (Δ).

Table II. Effects of 21 d of Bedrest in the Three Treatment Groups

Parameter	Saline control	Dobutamine	Maintenance exercise control
Exercise			
Duration	reduced	maintained	maintained
Workload	reduced	maintained	maintained
Max VO ₂	reduced	maintained	maintained
Aerobic/anaerobic	reduced	maintained	maintained
Lactate production	increased	slight increase	maintained
Heart rate	increased	slight increase	maintained
Blood pressure	maintained	maintained	maintained
Stroke volume	reduced	maintained	maintained
Aerobic enzyme activity of skeletal muscle	maintained or reduced	maintained or increased	maintained
Responses to standing			
Heart rate	increased	increased	maintained
Blood pressure	reduced (systolic)	maintained	maintained
Left ventricular function	maintained	maintained	maintained
Renin-aldosterone	increased	increased	maintained
Catecholamines	maintained	maintained	maintained
Blood volume	reduced	maintained	maintained

underwent deconditioning and the extent to which their deconditioning occurred, and to determine if daily dobutamine infusions prevented the deconditioning processes and to what extent this occurred.

Daily dobutamine infusions, at doses that elicited the same heart rate response as the daily exercise treatment of the maintenance exercise control group, did prevent the development of many of the deconditioning processes (Table II). Exercise capacity (duration, workload, and VO₂ at maximal exercise) remained unchanged after 3 wk of bedrest plus the daily dobutamine infusions. In contrast to the saline control group, subjects treated with dobutamine did not experience a decrement in exercise hemodynamics; stroke volume and cardiac output during exercise remained unchanged from pretreatment levels. However, the dobutamine treatment group did demonstrate some orthostatic changes after the 3-wk treatment period, specifically tachycardia and augmentation of the renin-aldosterone response to standing. Because blood volume was not reduced in this group, it is likely that vascular tone and responsiveness was blunted by the dobutamine infusions. This is supported by the increased dose of phenylephrine required to increase systemic blood pressure to predetermined levels after the 3-wk treatment period for this group. Dobutamine treatment during 3 wk of bedrest maintained or improved various indicators of peripheral conditioning. Compared to pretreatment base line, only a modest augmentation of the arterial lactate response (at one point of submaximal exercise) occurred in this group. CO₂ production, the respiratory quotient, and ventilatory volume remained unchanged from base line. Dobutamine treatment increased oxygen extraction by the exercising limb, perhaps related in part, to induction of aerobic enzyme activity of skeletal muscle (e.g., citrate synthetase and possibly, succinate dehydrogenase).

Numerous factors and mechanisms are involved in the physiology of physical conditioning and deconditioning in human subjects (7-11, 22-26). It appears that intermittent dobutamine infusions, at doses that increase heart rate to exercise

levels, reproduce or simulate some of the physiologic events of exercise. At the doses used, dobutamine increases heart rate, myocardial contractility, stroke volume, pulse pressure, cardiac output, and limb blood flow with reductions in limb, systemic, and pulmonary vascular resistance (1). All these events occur during exercise and many are mediated by the sympathetic nervous system and catecholamines. Norepinephrine and, to a lesser extent, epinephrine are the catecholamines released during exercise. In addition to its relative safety, dobutamine was selected as the catechol treatment for this study because at rest, the pharmacologic responses to dobutamine infusion are probably similar to those of the epinephrine and norepinephrine released during exercise, when the pharmacologic effects of these endogenous catecholamines are combined with the vasodilation ("autoregulation") occurring in exercising skeletal muscle. From the standpoint of hemodynamics, dobutamine infusions in normal subjects at rest appear to represent a form of pharmacophysiological stress-simulating exercise.

Orthostatic intolerance occurs after prolonged bedrest (8, 10, 24). We attempted to alleviate or minimize this response by allowing all subjects to sit in bed as desired and to sit in a dependent position (bedside chair or bicycle) for 2 h/d. In addition, all subjects were placed on an obligatory 5 g/d sodium chloride diet. Despite these interventions, the saline control group still demonstrated enhanced orthostatic responses in blood pressure, heart rate, and renin-aldosterone after the treatment period. Blood volume dropped 10% in this group. The dobutamine infusions alleviated some of the orthostatic factors and events. Blood volume was not reduced over the 3-wk period for the dobutamine group; the mechanism for this finding was not delineated by this study, but may be related to enhanced renin and/or vasopressin release during catecholamine infusions (27-30). Despite unaltered blood volume for the dobutamine group, an accentuation of the orthostatic increase in heart rate and in the renin-aldosterone response still occurred. As previously noted, the daily dobutamine infusions may have caused some

loss in the ability of the vasculature to vasoconstrict; the blood pressure response to phenylephrine administration supports this concept. After the treatment period for the dobutamine group, more phenylephrine was required to achieve the same increments in systemic blood pressure suggesting a form of "downregulation," possibly at the level of the vascular α -adrenergic receptors (31, 32); dobutamine has vascular α -adrenoceptor agonist properties (1). Superimposing daily maintenance exercise onto bedrest inactivity maintained blood volume and probably preserved autonomic-vascular tone, because accentuation of orthostatic responses were not noted in this group of subjects after the treatment period.

A shift or resetting of baroreceptor responsivity occurred in the bedrest-saline control group and in the bedrest-dobutamine group. 3 wk of bedrest and saline control resulted in a blunted heart rate response to incremental increases in systemic blood pressure. The opposite effect was noted in the dobutamine-bedrest group suggesting that an enhanced level of baroreceptor responsiveness (greater reduction in heart rate for incremental changes in systemic pressure) developed over the 3-wk treatment period for this group. Whether the enhanced responsiveness is secondary to the daily 2-h hemodynamic events (infusion period) or a direct effect of dobutamine on baroreceptor function (33, 34) is uncertain. No changes in parasympathetic tone at rest appeared to develop over the 3-wk treatment period for the three groups; this is based on the lack of change in heart rate response to atropine sulfate. From the results of the isoproterenol challenges, bedrest plus saline, dobutamine, or maintenance exercise over 3 wk did not change the responsivity of heart rate, contractility, or blood pressure to β -adrenergic stimulation. Although there are many steps in the agonist-effect reaction, no physiologic manifestation of either up- or down-regulation of β -adrenergic receptors became apparent in the three groups after 3 wk of treatment.

The increase in oxygen extraction and the unaltered lactate response by the limb during exercise noted for the dobutamine treatment group, compared to those of the saline control group, suggest that the catechol infusions maintained and/or induced a conditioning effect in skeletal muscle. How this effect was mediated is not known. Skeletal myocytes do possess β -adrenergic receptors (35, 36); the stimulation of these receptors generally increases the metabolic and oxidative activity of the cell. If the stimulation is of sufficient duration and/or frequency, the oxidative and metabolic needs could be translated into enzyme induction, which in turn, could provide the cell with the properties to meet the demands of intermittent and/or continuous metabolic stress. This concept is supported by the ability of the dobutamine-treated subjects to perform exercise at the same expenditure of oxygen (and CO_2 production) despite 3 wk of bedrest and by the demonstration of enhanced activity of some of the aerobic enzymes of skeletal muscle in this group. In addition, this laboratory has previously shown that dobutamine infusions also increase cellular (cardiac myocyte) levels of adenine nucleotides and high-energy phosphates (37).

Hypothetically, repeated dobutamine infusions may stimulate skeletal myocytes through metabolic and oxidative stress to increase (or, at least maintain) its capabilities for aerobic metabolism; as such, the catechol infusions may again simulate aerobic exercise. However, the authors do not suggest that dobutamine induction of aerobic enzyme activity (citrate synthetase and perhaps, succinate dehydrogenase) is the only, or even primary, explanation for the increase in limb O_2 extraction during

exercise, for the maintenance of maximal exercise VO_2 and for the unaltered level of aerobic metabolism during exercise in this treatment group. How dobutamine might affect the force-work apparatus (actin-myosin) of skeletal muscle is not known. Interestingly, Tuttle (38) demonstrated an increase in lean muscle mass in dogs chronically receiving a congener of dobutamine, butopamine.

This study supports the concept that the sympathetic nervous system and catecholamines play an important role in the physiology of physical conditioning in humans. This is further supported by a number of studies showing that β -adrenergic blocking drugs may inhibit this process (39-41). The mechanisms involved in the catecholamine-physical conditioning interaction are not fully elucidated by this study, but may include induction of skeletal muscle enzymes and changes in vascular regulation and responsiveness.

The authors are not suggesting, without further study, that intermittent high-dose dobutamine infusions be used at this time to induce physical conditioning or prevent deconditioning. High-dose dobutamine administration is probably not without risk. The authors are also not suggesting that dobutamine is the only catechol or that the catecholamines (sympathomimetics?) are the only drug group capable of eliciting the changes seen in this and previous work (2-6).

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