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PART A

TOLERANCE OF LOWER BODY NEGATIVE PRESSURE (LBNP)

IN ENDURANCE RUNNERS, WEIGHTLIFTERS, SWIMMERS AND NON-ATHLETES

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SUMMARY AND CONCLUSIONS

Thirteen endurance runners (R), 12 weightlifters (WL), 12 swimmers (SW) and 10 non-athletes (NA) were tested for their tolerance of lower body negative pressure (LBNP) in consecutive 5 minute stages at -20, -30, -40, -50 and -60 Torr. Each subject also performed an exercise test on a bicycle ergometer with progressive workloads to exhaustion to determined aerobic capacity ($\dot{V}_{O_2}$max/kg). The R had a much higher $\dot{V}_{O_2}$max/kg than any of the other groups, but a significantly lower LBNP tolerance. While the responses in heart rate and pulse pressure were quite similar in all 4 groups, the rate of increase in leg volume relative to LBNP stress (leg compliance, LC) was considerably greater in R than in the other athletes and NA. The greater LC in R could be attributed not only to a more rapid shift of blood to the lower extremities but also to a greater tendency for edema formation, both contributing to a more rapid loss in effective central blood volume for a given LBNP stress. These results substantiate earlier observations which led to the conclusion that endurance running is not advisable as a training regimen for astronauts. Experiences from the SKYLAB 4 astronauts, two of whom had engaged in a rigorous running schedule pre-lifght, showed that these two had a lower LBNP tolerance and greater leg compliance in-flight than the third astronaut, who exercised less pre- and in-flight. They also found that reduced LBNP tolerance in-flight portends greater difficulties in readapting to earth's gravity after the mission.

INTRODUCTION

Since the beginning of manned space flights great emphasis has been placed on the role of physical fitness of the astronaut's preflight, and its maintenance in-flight by regular physical activity. It is well established that immobilization in bedrest leads among other things to reduced tolerance to exercise and to orthostatic stress. In the Mercury and Gemini missions the astronauts were indeed more or less immobilized in their cockpits and had minimal opportunity to activate their muscles with an expander type exercise device. The loss in exercise and orthostatic tolerance observed on return to earth was attributed to inactivity as much as to the exposure to zero-g.

In the Apollo program much more physical activity was required of the astronauts in the intra- and particularly in extra-vehicular operations associated with the moon landings, docking maneuvers and others. Nevertheless a significant degree of impairment in the responsee to exercise and to orthostatic stress on the tilt table or under lower body negative pressure was still evident on the first few days after return to earth. These results appeared to implicate the exposure to zero-g itself rather than the lack of physical activity for the observed changes in cardiovascular function.

The SKYLAB missions 2, 3 and 4 lasting 23, 59 and 84 days respectively provided more decisive information on the effects of physical conditioning on the cardiovascular system during and after prolonged exposure to the space environment (6). For the first time stress tests with exercise and lower body negative pressure were included as inflight experiments. Apart from the regular exercise test schedule the SKYLAB astronauts were encouraged to engage in various types of exercise involving arm and trunk muscles as well as the legs as often as time permitted and accurate records were kept of

total work performed inflight. The astronauts responded well to this advice because exercise at a given work load was subjectively less stressful in space and afforded some relief from the feeling of "full headedness" and congestion of the face and neck observed at zero-g. Exercise apparently partly reversed the cephalad shift of blood by vasodilation in the leg muscles and calf girth was observed to increase measurably during exercise. Actually the total amount of work performed per day on SKYLAB 4 was double the amount accomplished in SKYLAB 2 attesting to the increasing popularity of this activity. During the pre- and postflight period more sophisticated but noninvasive methods such as the determination of systolic time intervals and echocardiography to estimate stroke volume and end-diastolic volume of the heart during stress tests permitted a more comprehensive evaluation of cardiac function.

One of the most reassuring results of the inflight exercise tests was the fact that aerobic power of the astronauts was not significantly affected by the zero-g environment (6). Indeed the SKYLAB 4 crew increased their maximal work capacity in space as compared to pre-flight values. It was also observed that recovery after vigorous exertion was faster in that the heart rate dropped more rapidly on cessation of exercise.

The exercise test performed on the day of splash-down showed a decrement in cardiovascular response in all astronauts characterized by an increased heart rate for a given metabolic rate (reduced O_2 pulse). Cardiac output during exercise was reduced by a significantly smaller stroke volume in all men in SKYLAB 2 and 3, but only one in SKYLAB 4. Fortunately the loss in cardiovascular competence was of short duration and normal function was restored within a few days. Comparing the results from all 3 SKYLAB flights it would appear that the consistent decrement in the response to exercise

postflight is not related to the duration of exposure to space, since there was a smaller decrement after SKYLAB 4 than in the two previous, shorter ones. On the other hand, the amount of exercise performed daily may have been effective not only in maintaining or improving performance inflight but also in attenuating the loss of performance postflight with a more speedy recovery.

In contrast to the exercise tests, the orthostatic tolerance tests with lower body negative pressure (LBNP) were felt to be much more stressful by the astronauts inflight and the tests had to be terminated prematurely on several occasions due to impending syncope of the subject. According to measurement of calf-girth much more blood was shifted to the legs for the same LBNP in space than on earth and this combined with the significant reduction in circulating blood volume made the difference. The loss of orthostatic tolerance was evident in the first test on each mission and continued to be present throughout the entire mission even in SKYLAB 4 where some had expected that the intensive exercise program might have a beneficial effect. Of practical importance was the observation that inflight response to LBNP gave a good prediction of postflight reactions to orthostasis and LBNP.

The reduced tolerance to LBNP persisted for the first day or two after return to earth in all astronauts. During this time they wore an anti-hypotensive pressurized garment from the waist to the ankles.

The study of systolic time intervals (STI) at rest and under stress early in the post-flight period revealed significant abnormalities, which lasted for several weeks. These might be attributable to any of the following factors: 1. The well documented loss of circulating blood volume, 2. Functional impairment of venous return which persisted after blood volume had

been restored, and; 3. Primary myocardial dysfunction. Additional valuable information was forthcoming from echocardiograms obtained on the SKYLAB 4 astronauts pre- and postflight. These revealed small, but significant reductions in stroke volume in two of the three crew members postflight associated with corresponding decrements in end-diastolic left ventricular volume. These changes gradually subsided over a 30 day period. It was concluded that they were caused by hemodynamic factors and were not due to any deterioration in the myocardium itself. The fact that the pilot (P) and the scientist pilot (SP) who showed significant losses in stroke volume and end diastolic filling, had engaged in much more intensive training runs before the flight, than the command pilot (CP), who was unaffected, raises the question whether the observed changes simply reflected relative "deconditioning" in P and SP for the lack of running during the space mission rather than the effects of the zero-g exposure.

It is also noteworthy that the CP was less susceptible to LBNP than the other two, who had greater increases in heart rate and in leg volume at -50 Torr and also had a greater incidence of pre-syncope inflight. Furthermore, it may not be entirely fortuitous that the SP who showed by far the best maximal performance on the bicycle ergometer inflight, was clearly more susceptible to LBNP than the other two and was unable to complete the test on four occasions. While it might appear plausible theoretically that general conditioning of the cardiovascular system by vigorous exercise might improve tolerance to gravitational stress, none of the numerous studies involving prolonged bed rest with exercise, tilt table and acceleration on the centrifuge have provided convincing evidence in favor of this concept (8). Indeed recent preliminary experiments in our laboratory employing a progressive exposure to LBNP to the point of imminent syncope, have

demonstrated that highly trained long-distance runners have significantly less tolerance to orthostasis than subjects of sedentary habits (4).

In the light of these and other observations it would appear that a reassessment of the role of physical training both before and during future manned space missions is in order.

The purpose of the present study was to determine the tolerance of highly trained endurance runners to progressive LBNP in a larger number of subjects as compared to a peer group of non-athletes and also to other athletes who engaged regularly in other sports activities not predominantly involving the lower extremities, such as competitive swimmers and weightlifters.

METHODS AND PROCEDURES

Subjects:

The group of 13 runners (R) trained regularly averaging 35-50 miles a week and most of them participated frequently in long distance track events and marathon races. As controls we recruited 12 male subjects of comparable age who were in good health but had not recently engaged regularly in any strenuous physical activity (Non-athletes: NA). In addition, two other groups of athletes were enlisted whose sports activities did not involve the lower extremities as exclusively as with the runners. These were 12 competitive weightlifters (WL) and 10 swimmers (SW) who trained regularly. All subjects were thoroughly acquainted with the purpose and procedures involved in the study, including the possible hazards and discomfort. Each of them was familiarized with the LBNP test in a brief trial run prior to the actual test.

Maximal aerobic capacity ($\dot{V}_{O_2}max$):

Within one or two days of the LBNP test each subject performed an exhaustive exercise test on a bicycle ergometer (Monark) to determine his aerobic capacity ($\dot{V}_{O_2}max$). During the first three minutes of the test the subject pedals at 50 rpm to a metronome at a brake load of 300 mkg/min. Every minute thereafter the load is increased by 75 mkg/min until the subject is no longer able to follow the cadence of the metronome. Heart rate and blood pressure are taken by auscultation every minute and the ECG is visualized on an oscilloscope continuously and recorded at regular intervals. The subject breathes through a low resistance, unidirectional valve (Lloyd-Collins) and the expired air is collected via wide-bore tubing into meteorological ballons for measurements of minute ventilation, oxygen uptake

and carbon dioxide production. Bags are collected every 3 minutes early in the test and every minute after the heart rate exceeds 160 bpm to ensure obtaining the maximal value of $\dot{V}_{O_2}$. $\dot{V}_{O_2}$max is divided by body weight (kg) to correct for differences in body size and the oxygen pulse is obtained by dividing $\dot{V}_{O_2}$max by the heart rate during the same minute. The maximal oxygen pulse, being the product of stroke volume x arterio-venous O_2 difference, is a good index of cardiovascular competence.

LBNP test:

The LBNP box was constructed out of 3/4" plywood, 48" long, 26" wide and 16" high. The top and the bottom were reinforced with diagonal two by fours. One end had a semicircular opening partially covered by a sliding baffle adjustable to each subject's circumference at the iliac crests and padded with an inner-tube (motorcycle) and bubble plastic wraps. The entire box was wrapped in a large sheet of clear Mylar (6 mils) which was long enough to encase the subject up the xyphoid and was secured tightly just above the iliac crests with a broad Velcro belt. An adjustable well-padded saddle was mounted on the floor of the box to prevent the subject from bracing his feet against the bottom of the box. Several ports led through the walls of the box and the plastic cover for attaching the pump (heavy duty vacuum cleaner), the ventilation line, a mercury manometer and a thermometer. With this simple and inexpensive device negative pressures in excess of -100 Torr could be attained in a few seconds and held at any desired level with a variable leak in the venting line in the form of a large aluminum 3-way stopcock. Down to -60 Torr, the lowest pressure employed in this study, the pump had enough power to tolerate sufficient leakage throught the bleed valve and around the seal to provide enough ventilation through the box so as to

prevent any significant increase in temperature within the box during the test. The LBNP test was conducted in consecutive stages of 5 minutes duration at -20, -30, -40, -50, and -60 Torr. The test was terminated whenever syncope appeared imminent from objective signs (heart rate, blood pressure, pallor or cold sweat) and/or complaints of dizziness or nausea by the subject. Otherwise the protocol was completed after 5 min at -60 Torr. Ambient pressure was restored in the box instantaneously by fully opening the dump valve and shutting off the pump, whereupon all subjects recovered rapidly without fainting to the point of consciousness. It might have been more appropriate from the statistical point of view to continue the progressive test beyond -60 Torr, with those subjects who tolerated this level, until they also approached syncope. However, already at -60 Torr the suction caused considerable discomfort at the crotch and the seal around the lower abdomen and those painful sensations would probably have affected the test results adversely. Therefore it was decided to terminate the test at 5 min at -60 and all those subjects who completed the protocol were awarded the same score (1000 Torr x min).

In order to specify an individual's LBNP tolerance in this test profile, the duration of the stress as well as the different levels of negative pressure sustained were taken into account by adding up the products of negative pressure and time for each stage to obtain a measure of total cumulative stress in terms of Torr x min, which is a curvilinear function of time (Fig A-1). This parameter was more meaningful as a measure of tolerance with which to correlate physiological responses in heart rate and blood pressure as well as leg volume and edema in the legs. Heart rate and blood pressure were taken every minute for the 5 min baseline period and during the entire test. Changes in circumference of the left calf were recorded

continuously with a mercury-in-silastic strain gauge (Parks Electronic Labs, plethysmograph Model 270) placed around the calf at its widest circumference after the latter had been measured precisely. Calibrati[illegible] and attachment of the gauge and the subsequent ca[illegible]culation of % changes in leg volume (ΔLV) closely followed the procedure described by Holling et al. (2). A deflection of approximately 45 mm for 1% change in leg circumference was obtained on the recorder (Honeywell Visicorder Model 1205) with this arrangement.

Leg volumes and compliance:

The swelling of the legs associated with LBNP reflects not only a larger volume of blood moving into the capacitance vessels of the lower extremities but also leakage of fluid out of the blood vessels into the tissues (edema). When LBNP is released the LV record drops exponentially at first, but after about 45 sec it levels off to a much slower transient, which does not return to the baseline for about 20-30 min. The residual difference in LV from the baseline at 45 sec after release of LBNP (ΔRLV) was assumed to represent the increment in extravascular fluid during the exposure, which is reabsorbed into the circulation much slower than the return of excess blood to the central circulation.

In previous studies (4,5) it had been observed that the rate of change in LV under LBNP differs greatly from one individual to another and is affected not only by the degree of LBNP stress in Torr but also by its duration. Therefore the concept of leg compliance in terms of ΔLV%/Torr x min was introduced. Leg compliance is derived from the slope of the regression line for change in leg volume in percent (ΔLV%) versus cumulative LBNP stress (Torr min) for as many points as available in a given test (see Table A-6). Since this quotient lies in the third decimal place, it is multiplied by 10^5

to give whole numbers. In the previous report on 10 subjects LC showed a highly significant inverse correlation with LBNP tolerance ($r = -.75$, $p < .001$). This same concept was applied in the present study again to differentiate the different groups of subjects as to their propensity to accommodate blood and extravascular fluid in the legs under LBNP. An attempt was also made to distinguish the extravascular from the intravascular components of total LC by dividing ΔRLV% by the cumulative stress (Torr x min) to obtain extravascular compliance (EVC) and subtracting this from total LC to arrive at the intravascular compliance (IVC).

Statistics:

Relationships between LBNP tolerances and the cardiovascular responses during LBNP exposure were evaluated by linear regression (8). Paired, pooled, and separate "t" analyses were also utilized to test for significant differences between mean values where appropriate (9). These same analyses were also applied to evaluate the relationship or significant differences between LBNP induced cardiovascular responses and the cardiovascular responses to exercise stress. All analyses were performed on the individual subgroup data, pooled NR data and pooled data from all subjects. The 95% confidence limit was selected to represent significant differences or relationships among the parameters measured.

RESULTS

Physical characteristics of subjects:

The 47 subjects examined in the study ranged from 19 to 61 years of age. However as seen from Table A-1 the mean age of the runners (R) did not differ much from that of the non-athletes and the weightlifters (WL), but the swimmers (SW) were on the average 17 years older than the three other groups. In the selection of the SW we had the choice between members of the University of New Mexico swimming team whose average age would have been 18 or less and regular participants in a swimming program of the local YMCA who turned out to be mostly middle-aged men. Considering that participants in the space-shuttle would be more likely to include middle-aged persons than teenagers, we chose the older group for our study. The skewed age distribution in our subject population should be kept in mind. However no statistically significant correlation between age and our most important parameter, LBNP tolerance, was present.

As to be expected, the NR's were significantly heavier than the R's ($p < .01$) and the SW were the heaviest of all 4 groups. Needless to say, the heaviest subject (126 kg) of all was a non-athlete (NA). Although the subject population covered a wide range in body weight, there was no significant correlation between weight and LBNP tolerance. There was also no significant difference of mean stature between any of the groups nor between R's and NR's.

LBNP tolerance and aerobic capacity:

Tolerance to LBNP was significantly ($p < .02$) less in R than in NR and since there was no significant difference in tolerance between NA, WL and SW,

the difference between R and each subgroup was about the same (-27%) as with the combined NR, regardless of their physical activities (Table A-2).

On the other hand, aerobic capacity ($\dot{V}_{O_2}$max/kg) was 32% better in R than in NA ($p < .001$), 25% better than in WL ($p < .001$) and 32% better than SW ($p < .001$). Compared with all NR together the R had a 29% greater aerobic capacity ($p < .001$). There was no statistically significant correlation between LBNP tolerance and aerobic capacity when all the groups were pooled. Mean maximal HR during exercise was the same in R as in all NR and it was highest in NA and lowest in SW and the difference between these two was the only significant one between any of the four groups, probably because the SW were on the average 18 years older than the NA. The maximal O_2 pulse (ml O_2 per beat) was 36% larger in R than in NA ($p < .001$) and 23% greater than in all NR ($p < .001$), but only 14% greater than in WL and SW ($p < .01$), whose mean O_2 pulse was nearly identical.

Heart rate and pulse pressure under LBNP (Tables A-3 and A-4):

In an attempt to find possible causes for the marked difference in LBNP tolerance between the R and NR groups, the cardiovascular responses as reflected in heart rate (HR) and pulse pressure (PP) during the LBNP test were scrutinized. The initial heart rate was lowest in the R group and highest in the NA (difference not significant). Without exception all subjects responded to LBNP with an increase in heart rate ($p < .001$). The difference between the baseline control value and at the final minute of LBNP (Δ%HR) was not significantly different between any of the four groups, but the correlation between Δ%HR and LBNP tolerance was statistically significant only for all subjects together, but the correlation coefficient was low ($r = .40$, $p < .01$). It is noteworthy that of the four groups only the R

showed a good correlation between Δ%HR and tolerance (0.71, $p < .01$). In the other three it was not significant.

With only one exception all subjects suffered a loss in pulse pressure between the initial control and the final measurement during LBNP and this difference in pulse pressure (Δ%PP) was statistically significant in all individual categories as well as in the total subject population. However, there was no significant difference in Δ%PP between R and NR nor between the individual groups with the exception of NA and WL, who had the largest (-50%) and the smallest (-36%) difference respectively. Only the R group showed a marginally significant inverse correlation between Δ%PP and LBNP tolerance ($r = -.57$, $p < .05$), but there was a poor but significant correlation between these variables when the data from all subjects were pooled ($r = .39$, $p < .02$). When the data for all subjects was examined for a possible interaction between Δ%PP and Δ%HR, a moderately close inverse correlation was found that was highly significant ($r = .56$, $p < .01$), indicating that there was a tendency for the HR to be the higher, the lower the PP.

Leg volumes and compliance (Table A-5):

The mean increase in leg volume (ΔLV%) was greatest in WL and least in NA but neither the differences between the individual groups nor the mean difference between R and all NR were statistically significant. The average ΔLV% for all subjects was about four percent. The residual leg volume change remaining 45 sec after release of LBNP (ΔRLV%), attributable to extravasation of fluid, was largest in R and least in SW, but the difference between them was not significant, nor between any of the other groups. On the average ΔRLV% was one third of the total ΔLV%. Leg compliance (LC) which quantitates the tendency to accumulate blood and extravascular fluid in the legs under

LBNP independently of duration and degree of the stress, was 73% greater in R than NA ($p < .01$) and 61% higher than in all NR. The second highest LC was observed in WL, but the value for R was still 44% greater than theirs. The NA had the lowest LC of all groups. There was a highly significant inverse correlation ($r = -0.87$, $p < .01$) between LC and LBNP tolerance when all subjects were combined. The regression of tolerance (y) versus LC (x) was:

$$y = 1365 - 1.065x \ (r = .87, \ p < .01); \ SEE = 114$$

Table A-5 also shows the mean values for the intravascular (IVC) and extravascular components of LC. In R the IVC was 80% greater than in NA but only 30% greater than in WL who had the highest IVC of the NR. As compared to all NR, IVC was 49% greater in R.

The R group also had the highest EVC of all subgroups, with 64% more than NA and 140% more than the SW who had the lowest value. R had an 85% greater EVC than all NR together. For all subjects combined the IVC contributed on the average two thirds to the total LC. Both components correlated inversely with LBNP tolerance (IVC: $r = -.78$, $p < .01$ and EVC: $r = -.67$, $p < .01$).

DISCUSSION

Subjects:

The following discussion will address itself primarily to differences observed in the tolerance of and physiological responses to progressive LBNP between trained endurance runners (R) and a group of non-athletes (NA) consisting of men who did not engage regularly in any vigorous physical activity. In addition, two other groups were included in the program, who participated regularly in physical training of a competitive nature, but in exercises which did not involve the lower extremities as exclusively as in the R. These were weightlifters and body builders (WL) and swimmers (SW). Thus comparisons could be made not only between R and NA but also between three different types of physical activities in relation to LBNP tolerance as well as between R and non-runners (NR) comprised of NA, WL and SW together. The distinction between R and NR is probably not as categorical as might be desired, because a number of the WL and SW did a certain amount of running as a supplemental type of exercise in their fitness programs. However the results of the test for aerobic capacity ($\dot{V}_{O_2}$max/kg) which showed a significantly higher mean value for R than for any of the three other categories attests to the much greater involvement of the cardiorespiratory system in the R. However the fact that the maximal O_2 pulse in R was 32% better than in NA while it was only 14% greater than in WL and SW indicates that the latter two groups had a cardiac function well above average and ranked between the NA and the R group in this respect.

Incidentally the difference in mean age of the SW as compared to all other groups (+17 years) was reflected in their lower maximal HR during exercise. Along the same lines, one would expect to find an inverse correlation between age and $\dot{V}_{O_2}$max/kg in our population with ages ranging

from 19 to 61. The poor correlation found in our subjects which was barely significant ($p < .05$) may be because all our subjects except the NA exercised regularly. Little is known so far about possible effects of age on orthostatic tolerance. No correlation was found in this study between age and LBNP tolerance nor any of the responses to it.

LBNP tolerance:

Several years ago we discovered in the course of an investigation on the effects of dehydration by exercising in the heat that endurance runners did not tolerate LBNP nearly as well a non-athletes regardless of their state of hydration (4). These findings made on a relatively small number of subjects (5 R and 5 NA) were verified in the present study where LBNP tolerance in the R group was 27% lower than in all NR, while there was no significant difference between NA, WL and SW indicating that other types of sports activities besides running do not adversely affect an individuals ability to withstand LBNP.

Since the test was terminated when the test profile (Fig A-1) was completed with the maiximum score of 1000 Torr x min, it is obvious that those subjects who showed no signs of impending syncope at this point could have continued further and would have gained a higher score. Thus many of the subjects with good tolerance were underrated in our scoring system. Considering that only 30% of the R reached 1000 Torr x min compared to 74% of the NR, the average score of the latter would have been higher if the test had been continued beyond the chosen end-point and the difference in LBNP tolerance between R and NR would have been more pronounced. Another way to test the significance of the differences in LBNP tolerance between R and NR is to apply a Chi-square test to the number of subjects who completed the

test and those who failed to do so in each group. This test also demonstrated that the difference between R and NR was indeed statistically significant ($p < .025$). The interaction between cardiovascular fitness and the effects of gravitational stress has been examined in several publications of recent years. Klein et al (3) found no significant difference between well-trained athletes and non-athletic subjects to $+G_z$ forces on the centrifuge using central light loss as the criterion. Cooper and Leverett (1) also came to the conclusion that no significant relationship exists between $+G_z$ tolerance and physical fitness after endurance training. Klein et al (3) also tested their athletes and non-athletes for orthostatic tolerance by tilting them to 90° for 20 minutes. There was no significant difference between athletes and non-athletes in the number of subjects who fainted during this procedure and they concluded that orthostatic tolerance is independent of cardiovascular fitness.

Stegemann et al (11) exposed 4 well-trained athletes and 4 non-athletes to simulated weightlessness by 6 hours of immersion in thermo-indifferent water and determined aerobic capacity and tolerance to 10 min vertical tilt before and after immersion. The non-athletes showed a 10% loss in aerobic capacity but tolerated the tilt well after immersion, but the athletes had a 20% lower aerobic capacity and all of them fainted during the tilt. Apparently the athletes were more adversely affected by simulated weightlessness than their untrained counterparts.

The discrepancy between the results of Klein et al (3) who did not find any difference in their tilt-tests between athletes and non-athletes and our study with a lower tolerance of R under LBNP then NR is probably due to the greater cummulative stress in our test profile than on the tilt table. Musgrave et al (7) have estimated that LBNP of -40 Torr produces

redistribution of blood volume to the legs quantitatively similar to that induced by upright posture at one G. Only two of our R did not reach the -40 Torr level and if the test had not gone beyond this level there might not have been a significant difference in LBNP tolerance. As far as the observations by Klein (3) as well as Cooper and Levrett (1) are concerned, that tolerance to $+G_z$ on the centrifuge is independent of physical fitness, it must be considered that the stress of 6.8 G_z imposed in approximately 90 sec is so overwhelming that all physiological adjustments are futile and physical fitness becomes irrelevant.

Although the R in our study, who had the lowest LBNP tolerance, had by far the highest aerobic capacity of all, no significant negative correlation was found between aerobic capacity and LBNP tolerance when all subjects were combined. This is in contradiction to a presentation of the results of our preliminary study on 10 subjects (4) published in a review article by Klein et al (3) where a statistically significant inverse correlation was claimed between LBNP tolerance and aerobic capacity. While the correlation was relatively high ($r = .60$) it was in fact not significant ($p > .05$).

Heart rate and blood pressure:

The well known response in HR in the course of LNBP was observed in all our subjects and the relative increase at the end of the test (ΔHR%) was not significantly different between R, NA nor the other athletes. However the initial HR and also the final HR was on the average lower in R than in the NR. It should be remembered that the R did not tolerate as much LBNP as the others, so that their ΔHR% was greater per unit of stress (Torr x min) than in the other groups. Furthermore the R were the only group where the correlation between ΔHR% and LBNP stress was highly significant ($r = .71$,

$p < .01$). This implies that the HR in R responds more promptly to LBNP stress, possibly because they have a greater loss in effective blood volume than the others for reasons to be discussed below.

The NA showed the largest drop in PP and the WL the smallest and the difference was highly significant ($p < .01$) and yet the LBNP tolerance of these two groups was practically the same presumably because the NA increased their HR more than the WL, thus compensating for their low pulse pressure. As mentioned earlier, the reciprocity between HR and PP was also evident in a highly significant inverse correlation between HR and PP under LBNP in the combined data from all subjects ($r = .56$, $p < .01$).

Leg volumes and compliance:

It is remarkable that the mean values for increase in leg volume (Δ%LV) in the four groups of subjects are very close to each other and the differences between groups were not statistically significant. The mean value for Δ%LV for all 47 subjects was 4.0% and this was very similar to the mean values obtained in two earlier studies (4,5) using exactly the same protocol. In the series reported in 1976 (4) the mean on 10 subjects was 3.95% and in 1978 3.85 for the same number of subjects. One might speculate that LBNP stress becomes critical when Δ%LV reaches about 4%. Using data reported by Musgrave et al (1969), who measured not only Δ%LV but absolute ΔLV with a water plethysmograph on both legs during LBNP, one can estimate that an increase in Δ%LV by 4% corresponds to an actual increase in volume of 650-700 ml for both legs. In this context it is extremely interesting that the SKY-LAB III astronauts, who had an average Δ%LV similar to our subjects namely 3-4% at -50 Torr in preflight tests, had increases in calf volume as great as 11% during weightlessness, when exposed to LBNP. To explain this

discrepancy one must take into account that there is a rapid loss of leg volume in space estimated at 13% (12). Since the major part of this volume loss is recovered within a few hours after return to earth one must assume that most of it is due to a depletion of capacitance vessels in the legs. Thus when LBNP is applied to an astronaut in space his depleted vessels can accommodate a much larger volume of blood which is reflected in a greater Δ%LV.

Just as there was little difference in final Δ%LV between R and NR the values for the residual volume change after 45 sec, believed to represent extravascular fluid (Δ%RLV), were very similar in R and NR (Table 5). Only the SW had a lower Δ%RLV than the others but the difference was barely significant compared to NA only. Whether this tendency of the SW to incur less edema than others under LBNP has anything to do with swimming, where positive hydrostatic pressure is applied to the body is a matter of speculation. Incidentally our previous studies with LBNP have revealed a highly significant inverse correlation between Δ%RLV and loss of plasma volume ($r = .67$, $p < .001$) and this supports the view that Δ%RLV is the result of extravasation of plasma fluid. Whereas we have pointed out, there was no significant difference in the Δ%LV at the end of the test between the various groups of subjects, it is obvious from Table A-2 that the test was terminated at a much lower level of stress in the R than in all the other groups which implies that the rate of change in leg volume relative to the cummulative stress must have been greater in the former than the latter. This rate of change can be expressed numerically in terms of leg compliance (LC) as defined above. The R had a LC 73% greater than the NA and 61% greater than the combined NR. Of the latter the WL had a 20% greater LC than the NA, while that of the SW was only slightly greater than of the NA, who

had the lowest value of all. Because LC differentiates more clearly between R and NR than any other response measured during LBNP a correlation between LC and LBNP tolerance readily suggested itself. The regression for LBNP tolerance versus LC is plotted in Fig A-2 demonstrating an impressive inverse correlation which is statistically highly significant. That low LC is a prerequisite for good LBNP tolerance is also apparent from the fact that of the 29 subjects from all groups who had the top tolerance score (1000 Torr x min) only one had a LC greater than 500 (Subj. No. 10 had a LC = 501).

Since the swelling of the legs is caused both by the engorgement of blood vessels and by edema formation, LC can be separated into two components: intravascular and extravascular compliance (IVC and EVC) shown in Table A-5. The IVC of the R was 49% greater than in the NR while EVC was 85% greater in the former than the latter. This leads to the conclusion that R have not only more compliant blood vessels in the legs but also that the capillaries have a much greater tendency to leak fluid in the presence of increased transmural hydrostatic pressure. Pertinent here are experiments conducted during SKY-LAB 4 (13), where vascular compliance ($\Delta V/\Delta P$) of the calf was measured by the venous occlusion method. The pilot and scientist pilot showed a 3-4 fold increase in vascular compliance during space flight, while there was a much smaller change in the commander. It may or may not be fortuitous that the two former had undergone much more rigorous running training than the latter in the preflight period. The Space Shuttle program may provide opportunities to test this contention on a larger number of astronauts.

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TABLE A-1
Physical Characteristics
Mean Values

	Category	Age (yr)	Ht (cm)	Wt (kg)
	R (n=13)	30 ± 10.68	177 ± 7.26	69.4 ± 6.83
NR	NA (n=12)	29 ± 5.34	178 ± 5.69	78.5 ± 15.57
NR	WL (n=12)	29 ± 5.03	173 ± 5.05	80.7 ± 9.06
NR	SW (n=10)	47 ± 11.01	177 ± 8.42	83.1 ± 7.86
	All NR (n=34)	34 ± 10.91	176 ± 6.64	80.6 ± 11.33
	All Subj. (n=47)	33 ± 9.83	176 ± 6.74	77.5 ± 11.42
	Range All	19 - 61	162 - 190	57 - 126

TABLE A-2
LBNP Tolerance and Aerobic Capacity

	Category	Tolerance (Torr x min)	$\dot{V}_{O_2}$ (L/min)	$\dot{V}_{O_2}$ (ml/min/kg)	max HR (bpm)	Max O_2 Pulse (ml/beat)
	R (n=13)	689 ± 329	3.52 (±0.24)	51.4 (±6.49)	177 (±11.7)	20.0 (±1.72)
NR	NA (n=12)	946 ± 93	2.70 (±0.51)	34.9 (±6.72)	183 (± 6.1)	14.7 (±2.57)
NR	WL (n=12)	939 ± 148	3.08 (±0.30)	38.7 (±6.32)	173 (±12.5)	17.4 (±1.81)
NR	SW (n=10)	944 ± 119	2.89 (±0.57)	35.2 (±8.80)	169 (± 8.5)	17.1 (±3.35)
	All NR (n=34)	943 ± 119	2.89 (±0.48)	36.3 (±7.25)	177 (±10.9)	16.3 (±2.80)

TABLE A-3
Changes in Heart Rate with LBNP

Runners				Non-Athletes				Weightlifters				Swimmers			
No	C	Fin.	Δ%	No	C	Fin.	Δ%	No.	C	Fin.	Δ%	No.	C	Fin.	Δ%
1	64	108	69	14	55	90	64	26	56	89	59	38	71	114	61
2	57	90	58	15	67	108	61	27	48	79	65	39	59	79	34
3	69	92	33	16	66	82	24	28	59	84	42	40	54	81	50
4	54	95	76	17	61	89	46	29	57	77	35	41	69	82	19
5	48	66	38	18	59	86	46	30	65	92	42	42	63	78	24
6	62	70	13	19	68	96	41	31	65	85	31	43	68	100	47
7	43	48	12	20	78	109	40	32	70	90	29	44	65	84	29
8	55	72	31	21	45	80	78	33	55	69	25	45	47	64	36
9	65	120	85	22	64	101	58	34	58	91	57	46	83	120	45
10	84	124	48	23	58	86	48	35	63	88	40	47	64	76	19
11	53	62	19	24	70	97	39	36	73	77	5				
12	48	60	25	25	94	151	61	37	71	117	65				
13	54	75	39												
X	58	83	42		65	98	51		62	87	41		64	88	36
SD	10.8	23.7	23.8		12.2	19.2	14.5		7.5	11.9	18.0		9.8	17.8	14.1

C: Control, Fin: Final min of LBNP

TABLE A-4
Changes in Pulse Pressure with LBNP

Runners				Non-Athletes				Weightlifters				Swimmers			
No	C	Fin.	Δ%	No.	C	Fin.	Δ%	No.	C	Fin.	Δ%	No.	C	Fin.	Δ%
1	40	13	-68	14	39	22	-44	26	46	32	-30	38	47	18	-62
2	54	21	-61	15	36	12	-67	27	46	20	-57	39	36	26	-28
3	54	19	-65	16	49	24	-51	28	44	30	-32	40	42	19	-55
4	52	19	-63	17	38	20	-47	29	43	34	-21	41	43	22	-49
5	31	28	-10	18	52	36	-31	30	47	20	-57	42	54	24	-56
6	38	28	-26	19	36	18	-50	31	52	30	-42	43	36	17	-53
7	34	40	18	20	37	15	-59	32	36	24	-33	44	28	24	-14
8	48	20	-58	21	52	26	-50	33	38	25	-34	45	38	24	-37
9	49	18	-63	22	42	24	-43	34	54	35	-35	46	43	23	-47
10	43	27	-37	23	39	18	-54	35	45	32	-29	47	56	37	-34
11	36	27	-25	24	43	26	-40	36	46	35	-24				
12	48	31	-31	25	32	13	-59	37	53	30	-43				
13	23	15	-35												
$\bar{X}$	40	24	-40		41	21	-50		46	29	-36		42	23	-44
SD	14.3	7.5	25.9		6.6	6.7	9.6		5.5	5.4	11.5		8.5	5.6	14.9

C: Control, Fin: Final minute of LBNP.

TABLE A-5
Changes in Leg Volume and Leg Compliance under LBNP

	Category	ΔLV %	ΔRLV %	LC	IVC	EVC	$\frac{IVC}{LC} \times 100$
	R (n=13)	4.14 ± 1.24	1.40 ± 0.62	637	395	242	62%
NR	NA (n=12)	3.66 ± 0.54	1.37 ± 0.52	368	220	148	60%
NR	WTL (n=12)	4.43 ± 0.75	1.31 ± 0.49	441	303	139	69%
NR	SW (n=10)	3.80 ± 0.71	0.93 ± 0.51	373	272	101	73%
	All NR (n-34)	3.97 ± 0.74	1.22 ± 0.53	395	265	131	67%

ΔLV: Change in leg volume; ΔRLV: Residual leg volume; LC: Leg compliance, IVC and EVC: Intravascular and extravascular components of LC.

TABLE A-6
Leg Volume % Increases Under LBNP

	Torr	-20		-30		-40		-50		-60		Final
	Torr x min	40	100	160	250	330	450	550	700	820	1000	
	Time min	2	5	2	5	2	5	2	5	2	5	--
R	1	0.96	0.94	1.46	1.65	2.47	2.80	3.27	3.65	4.14	4.45	4.45
	2	1.25	1.36	2.32	2.62	3.26	3.46	4.20	4.32	5.01		5.44
	3	0.48	0.48	0.73	0.94	1.75	1.98	2.50	2.84	3.46	3.75	3.75
	4	1.12	1.15	2.25	2.56	3.24	3.62	4.49	5.09	5.85		6.37
	5	1.81	2.11	2.57	3.38	3.60	4.30	4.81				4.94
	6	2.47	2.57	2.89	3.49	3.49						3.93
	7	0.74	0.96	1.86	2.37	2.93						3.45
	8	0.86	0.95	1.56	2.00	2.55						2.98
	9	0.95	1.35	1.92	2.24	2.85	3.08	3.63	4.04	4.62		4.74
	10	1.11	1.15	1.93	2.13	2.78	3.15	3.70	4.07	4.96	5.43	5.50
	11	1.38	1.41	2.05								2.26
	12	1.40	1.66	2.36								2.42
	13	0.68	0.76	1.15	1.31	1.74	1.93	2.35	2.66	3.20	3.60	3.60
	Mean	1.17	1.29	1.77	2.24	2.79	3.04	3.62	3.81	4.46	4.31	4.14
	SD	±0.52	±0.56	±0.79	±0.78	±0.63	±0.80	±0.89	±0.85	±0.93	±0.84	±1.24
NA	14	1.07	1.37	1.66	1.87	2.28	2.63	2.90	3.05	3.39	3.79	3.92
	15	0.58	1.10	1.58	1.23	1.89	2.35	2.68	3.31	3.69		3.82
	16	0.53	0.71	1.22	1.64	2.12	2.53	3.02	3.48			3.71
	17	0.58	0.61	0.96	1.31	1.66	2.01	2.38	2.79	3.28	3.76	3.83
	18	0.52	0.56	1.08	1.41	1.86	2.29	2.72	3.15	3.55	4.02	4.13
	19	0.86	0.84	1.53	1.61	1.90	1.99	2.49	2.73	3.12	3.33	3.38
	20	0.64	0.42	1.20	1.14	1.70	2.04	2.58	2.80	3.49	3.60	3.76
	21	0.25	0.25	0.50	0.63	0.98	1.15	1.70	1.90	2.15	2.63	2.68
	22	0.68	0.59	1.23	1.45	2.26	2.58	2.95	3.22	4.14	4.27	4.27
	23	0.25	0.29	0.46	0.63	1.02	1.22	1.51	1.85	2.45	2.67	2.67
	24	0.71	0.77	0.95	1.16	1.79	1.94	2.48	2.70	3.22		3.41
	25	0.92	0.88	1.27	1.43	2.03	2.33	3.29	3.65	4.11		4.33
	Mean	0.63	0.70	1.14	1.29	1.79	2.09	2.56	2.64	3.33	3.51	3.66
	SD	±0.24	±0.32	±0.38	±0.37	±0.42	±0.48	±0.52	±0.96	±0.61	±0.60	±0.54

TABLE A-6 (continued)

	Torr	-20		-30		-40		-50		-60		Final
	Torr x min	40	100	160	250	330	450	550	700	820	1000	
	Time min	2	5	2	5	2	5	2	5	2	5	--
WL	26	1.37	1.52	2.40	2.54	3.40	3.62	4.15	4.24	5.01	5.22	5.22
	27	0.50	0.67	1.25	1.34	1.83	2.11	2.72	2.83	3.42	3.67	3.67
	28	0.92	1.03	1.50	1.59	2.07	2.21	2.72	2.86	3.72	3.51	3.55
	29	1.06	1.09	1.66	2.02	2.49	2.85	3.49	3.79	4.55	4.74	4.74
	30	0.70	0.93	1.45	1.68	2.12	2.44	3.21	3.53	4.12	4.60	4.60
	31	1.62	1.73	2.47	2.74	3.41	3.64	4.16	4.48	5.26	5.62	5.67
	32	0.52	0.68	1.29	1.48	2.16	2.36	3.29	3.52			4.37
	33	1.37	1.39	2.13	2.39	2.84	3.13	3.76	4.06	4.67	5.15	5.15
	34	0.80	0.86	1.28	1.67	2.44	2.92					3.39
	35	0.39	0.45	1.51	1.53	2.23	2.25	2.74	2.92	3.52	3.89	4.05
	36	0.72	0.84	0.99	1.19	1.86	2.14	2.66	2.95	3.41	3.68	3.71
	37	0.93	1.11	1.62	1.95	2.68	3.12	3.68	3.88	4.60		4.98
	Mean	0.91	1.03	1.63	1.84	2.46	2.73	3.33	3.55	4.23	4.45	4.43
	SD	±0.39	±0.37	±0.47	±0.49	±0.53	±0.56	±0.57	±0.59	±0.68	±0.79	±0.75
SW	38	1.13	1.06	1.69	1.73	2.07	2.16	2.64	2.79	3.39	3.79	3.88
	39	1.05	1.11	1.45	1.49	1.82	2.16	2.59	2.90	3.27	3.54	3.60
	40	1.06	1.07	1.45	1.61	2.06	2.16	2.72	2.93	3.47	3.83	3.83
	41	1.03	1.08	1.36	1.59	2.08	2.49	3.38				3.89
	42	0.47	0.51	1.13	1.50	2.24	2.46	3.27	3.67	4.24	4.55	4.55
	43	0.42	0.43	0.60	0.65	0.91	1.03	1.46	1.54	1.75	2.04	2.04
	44	1.49	1.58	1.79	1.96	2.44	2.71	3.39	4.08			4.60
	45	0.61	0.61	1.12	1.27	1.72	1.86	2.59	2.74	3.52	3.83	3.83
	46	0.68	0.68	1.14	1.20	1.83	1.88	2.29	2.50	2.96	3.57	3.57
	47	0.43	0.43	0.64	0.75	1.31	2.30	2.53	2.83	3.79	4.16	4.16
	Mean	0.84	0.86	1.26	1.38	1.85	2.12	2.69	2.89	3.30	3.66	3.80
	SD	±0.36	±0.38	±0.36	±0.42	±0.45	±0.47	±0.58	±0.71	±0.73	±0.73	±0.71

TABLE A-7

Subj.	Tolerance	Δ%LV	Δ%RLV	TLC	IVC	EVC
R						
1	1000	4.45	1.38	424	286	138
2	952	5.44	1.85	501	307	194
3	1000	3.75	0.79	383	304	79
4	965	6.37	2.17	619	394	225
5	617	4.94	0.65	678	573	105
6	397	3.93	1.83	725	264	461
7	397	3.45	1.53	830	445	385
8	393	2.98	0.87	691	470	221
9	830	4.74	1.77	490	277	213
10	1000	5.50	2.53	501	248	253
11	238	2.26	0.58	828	584	244
12	163	2.42	0.79	1282	797	485
13	1000	3.60	1.47	330	183	147
Mean	689	4.14	1.40	637	395	242
SD	±329	±1.24	±0.62	±253	±174	±128
NA						
14	1000	3.92	1.28	325	197	128
15	865	3.82	1.32	399	246	153
16	700	3.71	1.85	508	244	264
17	1000	3.83	1.61	362	201	161
18	1000	4.13	1.39	401	262	139
19	1000	3.38	0.91	298	207	91
20	1000	3.76	1.92	369	177	192
21	1000	2.68	0.86	264	178	86
22	1000	4.27	1.22	427	305	122
23	1000	2.67	1.14	271	157	114
24	903	3.41	0.48	347	294	53
25	887	4.33	2.40	441	170	271
Mean	946	3.66	1.37	368	220	148
SD	±93	±0.54	±0.52	±73	±49	±67

TABLE A-7 (continued)

Subj.	Tolerance	Δ%LV	Δ%RLV	TLC	IVC	EVC
WL						
26	1000	5.22	1.25	463	338	125
27	1000	3.67	1.36	358	222	136
28	1000	3.55	1.10	314	204	110
29	1000	4.74	1.75	446	271	175
30	1000	4.60	1.70	437	267	170
31	1000	5.67	2.38	486	248	238
32	790	4.37	0.57	511	439	72
33	1000	5.15	1.34	449	315	134
34	510	3.39	0.78	611	458	153
35	1000	4.05	0.97	384	287	97
36	1000	3.71	1.00	358	258	100
37	970	4.98	1.54	479	325	154
Mean	939	4.43	1.31	441	303	139
SD	±148	±0.75	±0.49	±80	±79	±44
SW						
38	1000	3.88	0.81	319	238	81
39	1000	3.60	1.22	313	191	122
40	1000	3.83	1.26	332	206	126
41	683	3.89	0.70	505	403	102
42	1000	4.55	1.46	470	324	146
43	1000	2.04	-0.16	189	205	-16
44	757	4.60	1.33	487	311	176
45	1000	3.83	0.46	367	321	46
46	1000	3.57	0.82	318	236	82
47	1000	4.16	1.41	429	288	141
Mean	944	3.80	0.93	373	272	101
SD	±119	±0.71	±0.51	±99	±68	±56

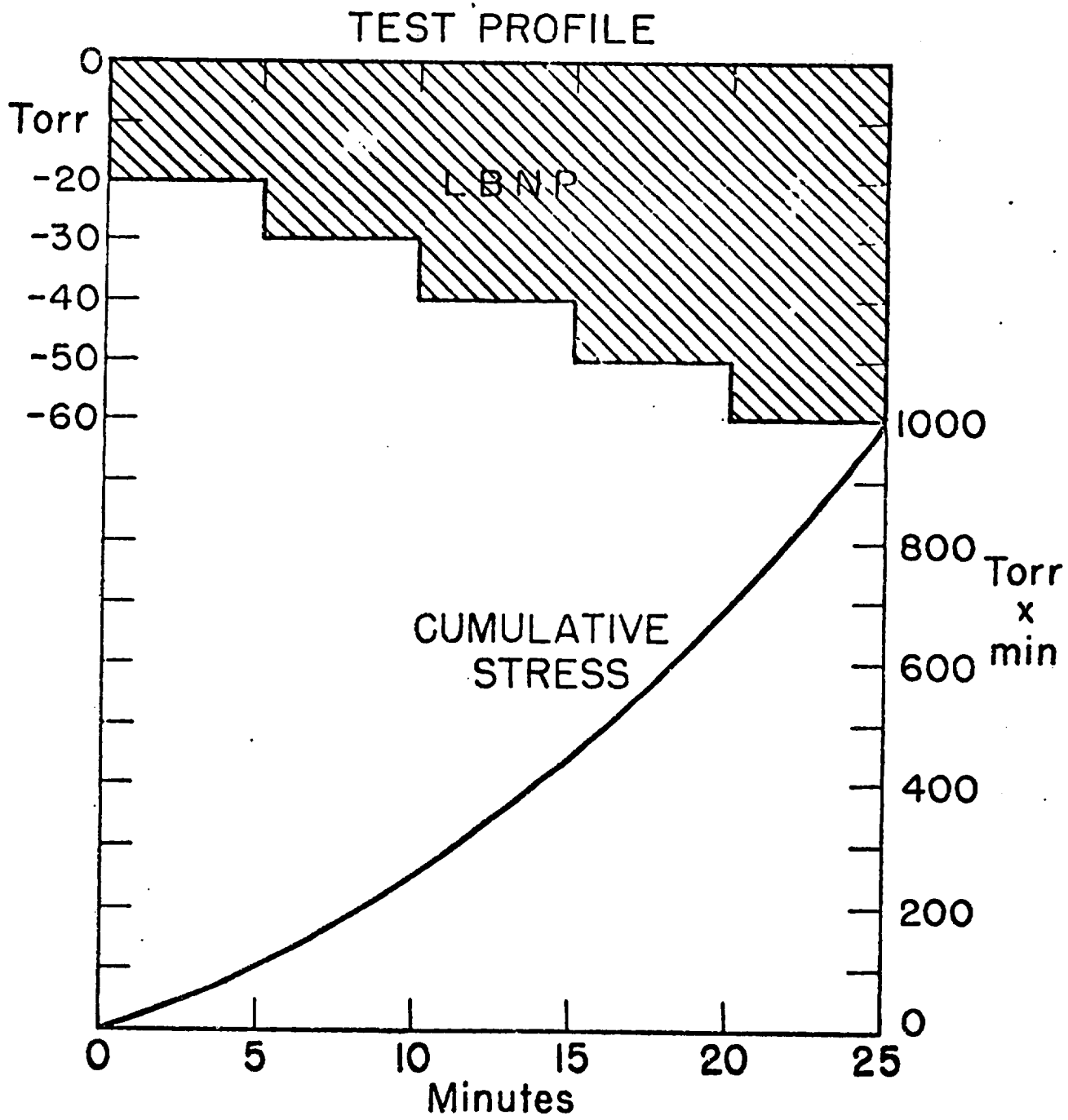

FIGURE A-1. Cumulative stress during progressive lower body negative pressure endurance test.

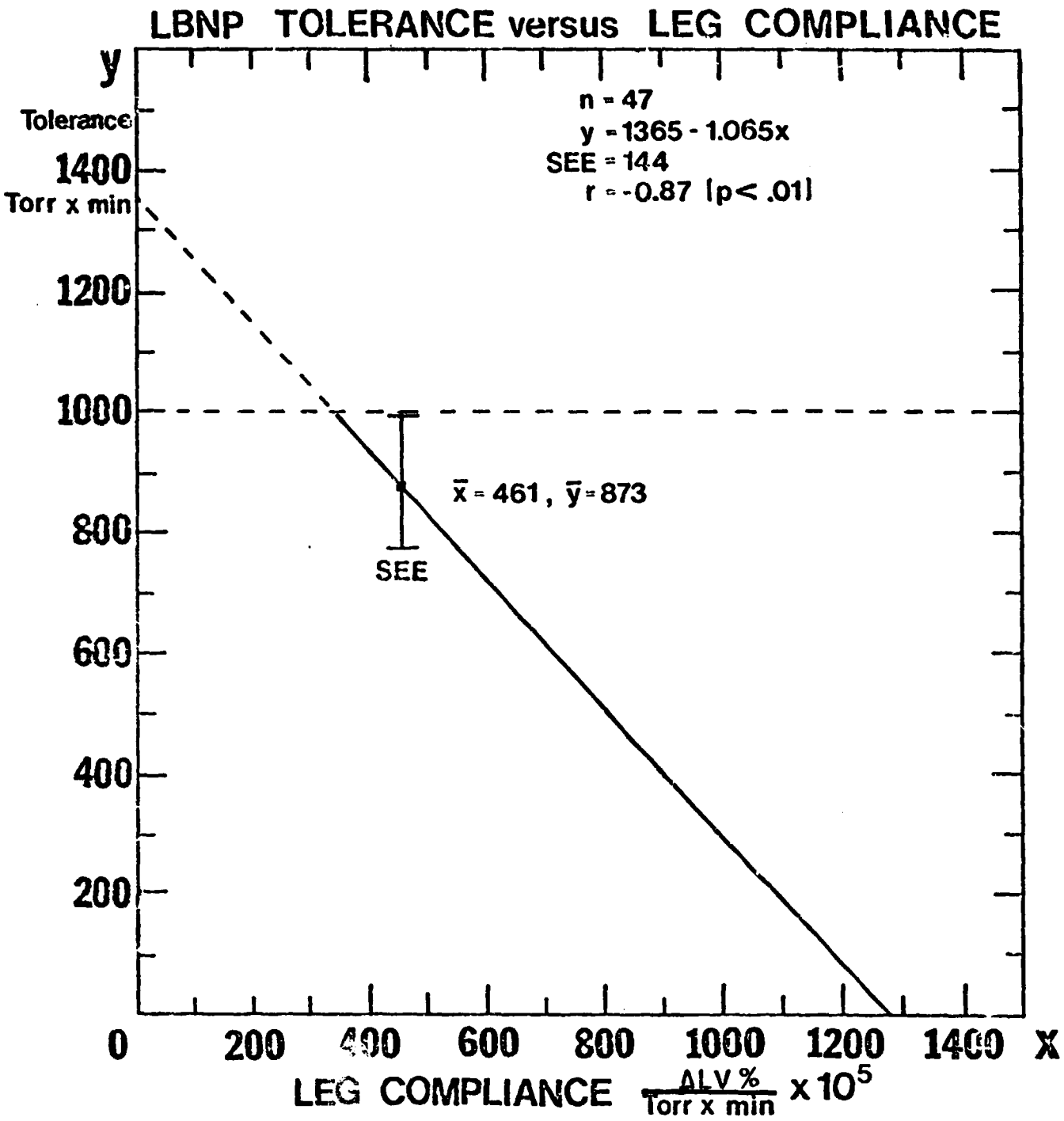

FIGURE A-2. Regression of leg compliance (LC) versus LBNP tolerance.

PART B

NONINVASIVE AORTIC BLOODFLOW BY PULSED DOPPLER ECHOCARDIOGRAPHY (PDE) COMPARED TO CARDIAC OUTPUT BY THE DIRECT FICK PROCEDURE

N81-20709

SUMMARY

Left ventricular stroke volume (SV_{PDE}) was estimated from the systolic velocity integral in the ascending aorta by pulsed Doppler echocardiography (PDE) and the cross-sectional area of the aorta estimated by M-mode echocardiography on 15 patients with coronary disease undergoing right heart catheterization for diagnostic purposes. Cardiac ouptut ($\dot{Q}_{PDE}$) was calculated from SV_{PDE} and heart rate (HR). At the same time $\dot{Q}_{Fick}$ was determined by the direct Fick procedure and SV_{Fick} derived by dividing $\dot{Q}_{Fick}$ by HR. The mean value for $\dot{Q}_{PDE}$ (4.42 L/min) was only 6% lower than for $\dot{Q}_{Fick}$ (4.69 L/min) and the correlation between the two methods was excellent ($r = 0.967$, $p < .01$). The slope of the regression line $\dot{Q}_{PDE}$ versus $\dot{Q}_{Fick}$ was not significantly different from 1.0 (identity). The good agreement between the two methods demonstrates that the PDE technique offers a reliable noninvaisve alternative for estimating cardiac output, requiring no active cooperation by the subject. The pulsed Doppler method is superior to the Fick in that it provides beat-by-beat information on cardiac performance.

INTRODUCTION

Ever since it was recognized early on in the manned space flight program, that certain reversible changes take place in the cardiovascular system during weightlessness, high priority has been given to the assessment of cardiovascular functions during and after space missions. One of the most important of these functions is the amount of blood pumped by the heart per min (cardiac output, $\dot{Q}$) at rest and during exercise or gravitational stress. So far actual measurements of $\dot{Q}$ have been obtained only pre- and post-flight at rest and during submaximal exercise with the single breath method of Kim et al (6) and at rest and during various degrees of LBNP by M-echocardiography (5). And yet much better understanding of the space related alterations in cardiac function and their time course could be gained by systematic measurements of $\dot{Q}$ in space at rest and during various levels of activity. No doubt the space-shuttle program will offer opportunities to apply new technologies for the noninvasive measurement of $\dot{Q}$, not only before and after but also in-flight on larger numbers of subjects than have been available heretofore. The most promising of the recently developed noninvasive techniques is based on the reflection of ultrasound either from interfaces between tissues (M-mode echocardiography) or from blood cells in motion within the heart or blood vessels (Pulsed Doppler Echocardiography, PDE). In the latter the change in frequency between the transmitted and the reflected waves, which is a function of the velocity of red cell motion, is the basic measurement. This study was designed to validate the noninvasive PDE method for estimating aortic bloodflow by comparing the results with those obtained by the direct Fick procedure for $\dot{Q}$, which involves right heart catheterization, arterial cannulation and measurements of oxygen consumption from the mixed expired air.

METHODS

Subjects:

The 15 subjects in this study were all patients with coronary heart disease for whom cardiac catheterization was indicated for diagnostic purposes. Informed consent had been obtained to perform the PDE measurements, which caused no discomfort nor incurred any additional hazards, simultaneously with the Fick procedure. The experiemnts were all conducted in the cardiovascular laboratory of the neighboring V.A. Medical Center under the medical direction of Dr. David Hoekenga, Cardiologist, as co-investigator. All studies were performed in the supine position at rest.

Fick:

After the catheter had been introduced via an antecubital vein under local anesthesia and advanced into the pulmonary artery under fluoroscopic guidance, the patient started to breathe through a unidirectional valve mouthpiece with a noseclip in place to collect expired air for 3 or 4 mintues in a Douglas bag. During the last minute of air collection blood samples were drawn simultaneously from the pulmonary artery and brachial or radial artery previously cannulated under local anesthesia. The blood samples were analyzed for O_2 and CO_2 contents by the method of Van Slyke and Neill in duplicate. Only samples that agreed within 0.2 Vol% were accepted. Mixed expired air was analyzed for O_2 and CO_2 content by the Scholander micromethod in duplicate and the volume of gas measured in a water sealed 120 Liter spirometer. $\dot{Q}$ was calculated in L/min by the Fick equation:

$$\dot{Q}_{Fick} = \frac{\dot{V}_{O_2}}{Ca_{O_2} - \overline{Cv}_{O_2}}$$

where $\dot{V}_{O_2}$ is O_2 consumption in L/min (STPD) and $Ca_{O_2} - Cv_{O_2}$ the arterio-venous difference in O_2 content in liters/liter. The stroke volume (SV_{Fick}) was calculated by dividing $\dot{Q}_{Fick}$ by the heart rate derived from the PDE record. Bloodflow in the ascending aorta was estimated by the PDE method simultaneously with the Fick procedure.

Estimation of SV and $\dot{Q}$ by PDE:

A 3.0 MHz PDE (10 mm diameter) (ATL, Model 500A, Mark IV) was used to obtain instantaneous and continuous blood velocities in the ascending aorta. The advantage of PDE over continuous-wave Doppler methods is the precise depth resolution allowed by the former. In continuous-wave Doppler all bloodflow in the path of the ultrasound beam is measured whereas with PDE a specific flow region (sample volume) can be selected by varying the sample gate or depth control and then fixing it. This removes extraneous information from the received signal and with appropriate signal processing allows an accurate determination of the spatial mean velocity to be made at successive points in time.

The PDE transducer was manually placed and held in the suprasternal notch with the beam angled downward and anteriorly to be co-axial to the flow stream in the aorta and the optimal signal achieved as seen in Fig. 1. This procedure has previously been outlined by Angelsen and Brubakk (1). The angle of the ultrasonic beam to the flow stream was assumed to be 0°. Anatomically, this was substantiated in other patients by x-ray, however a deviation of ±15° during respiratory or body motion artifacts will only result in a 4% underestimation of spatial velocity seen within the sample volume, since the cosine of the angle enters into the Doppler equation (Fig. B-1).

The transducer alternately transmits and receives bursts of ultrasound energy at a frequency of 12.8 KHz as shown in a simplified schematic in Fig. B-1 (1, 2). The receiver output contains reflected echoes with Doppler-shifted components which are amplified. Since reflecting surfaces other than erythrocytes are present, a spectrum of Doppler-shifted frequencies near f_t is received. By demodulation, f_t is changed to zero frequency and only Δf constitutes the audio output which is converted to an analog voltage proportional to the spatially-averaged Δf or velocity and fed to the calibrated audio spectrum decoder (zero crosser). A sample analog systolic ejection waveform during supine rest is shown in Fig. B-1. Appropriate controls allow the Doppler gain and threshold levels to be controlled to achieve a minimum signal to noise ratio of 20/1. Appropriate filters are included to remove echoes characteristic of arterial wall reflections due to inherent elasticity or movement artifacts. These high-pass filters result in a minimum detectable velocity of 5 cm/sec. At the 5 cm depth setting used in these experiments (pulse repetition frequency = 12.8 KHz) the maximum detectable velocity with this instrument is 126 cm/sec. When blood velocities exceed this limit the waveform is distorted (aliasing).

Theoretically, the area under the systolic ejection waveform or systolic velocity integral (SVI) is the fluid displacement during that beat in a properly calibrated system if the sample volume is in the centerline of the flow stream. The displacement is then directly proportional to SV. This has been confirmed by comparing SVI values obtained from continuous-wave Doppler signals with thermodilution SV in animals (4) and man (7) and by comparing SVI values from PDE with SV from electromagnetic flowmeters in animals (12). Fortunately, the developing velocity profiles in the ascending aorta are

relatively blunt and turbulence is minimal (11) so that the precision required in maintaining the sample volume in the centerline is not as stringent as in other vessels. The true representation of fluid displacement by SVI is critically dependent upon careful technique in holding the transducer which must be precisely manipulated during recordings to simultaneously ensure an optimal audio signal and maximal SVI on the on-line visual display.

To obtain absolute values of SV from SVI, the estimate of aortic diameter (AD) is of critical importance for each subject. This was determined by M-mode Echocardiography at rest (5). Reported values for AD demonstrate a great deal of variation between subjects that is not closely related to body size. It has been shown that the values can be between 1.2 and 2.2 cm/m^2 of body surface area (5). Another factor of some importance is the expansion of the aorta during systole. Since AD by M-mode echocardiography is computed at end-diastole, and SVI pertains only to systole, some correction factor is necessary. Recent investigations have shown that AD in man increases about 12% during the peak of each pulse pressure wave (9). Since the AD waveform is similar to the aortic pressure wave the mean expansion throughout systole lies somewhere between 6 and 12%. An average value of 9% was chosen for all our subjects. However, with aging and disease processes this expansion will vary (9). For the computation of SV from displacement all the AD values were increased by 9%, cross-sectional area was calculated and multiplied by displacement. The latter was then multiplied by the corresponding HR to obtain $\dot{Q}$ for that beat.

Signal Processing:

The SVI for each beat was traced manually from the hardcopy recording with a digitizer (Summagraphics) linked to a microcomputer development system (Intel). This system tabulated peak systolic velocity (v_p), mean systolic velocity during systolic ejection (v), the systolic ejection time (ET), HR, SV and $\dot{Q}$ for each beat. The systolic waveforms generally conformed to the shape depicted in Fig. B-1 and in tracing SVI, the secondary components after systole were ignored since they contain signals (often negative flows) resulting from wall reflections and elastic recoil. The upstroke and recovery of the systolic velocity signal were extrapolated to zero flow if onset and end of systole were not clearly delineated (4). The recording paper speed was 5.0 cm/sec and the velocity calibration was maintained at 1.0 cm deflection: 15 cm/sec.

During the resting phase of the steady state and transient experiments SV, $\dot{Q}$, and HR were averaged for 10 beats immediately preceding exercise. Any beat for which SVI was less than 75% of the largest value was excluded. It was assumed that these smaller SVI values were indicative of transducer movement artifacts. Less than 7% of the data were rejected for these reasons.

Paired-t tests were performed to obtain statistical significance of the differences between the two methods and a linear regression for $\dot{Q}_{PDE}$ versus $\dot{Q}_{Fick}$ was calculated to obtain the correlation between the two and its significance.

RESULTS AND COMMENTS

Table B-1 contains the age and physical characteristics of the 15 cardiac patients and the individual values for $\dot{Q}_{Fick}$, $\dot{Q}_{PDE}$ with the corresponding stroke volumes by both methods. The mean value for $\dot{Q}_{PDE}$ was 0.27 L/min less than $\dot{Q}_{Fick}$, a difference of less than 6%, but the difference was statistically significant ($p < .01$). There are several possible reasons for this relatively small discrepancy between the two methods. In the PDE method the minimal detectable velocity is 5 cm/sec and if a small component of the velocity profile was below this value, it would be lost by the systolic velocity integral and resulting SV calculation. Another possible reason for the underestimation of $\dot{Q}$ by PDE could be that the angle of the Doppler beam was not exactly coaxial to the flow stream in the aorta. As pointed out above, a deviation of ±15° might result in a 4% underestimation of spatial velocity seen within the sample volume. Furthermore, an underestimate could also arise in the process of audio spectrum analysis (Fig 1). It is apparent that all possible sources of error would contribute to an underestimation by PDE of the real value, so that it is indeed surprising that the observed discrepancy between the mean values by the two methods is so small.

Fig B-2 gives the regression line for $\dot{Q}_{PDE}$ versus $\dot{Q}_{Fick}$, which is close to the identity line and the difference in slope between the two was not statistically significant. The correlation between $\dot{Q}$ by the two methods was excellent ($r = 0.967$) and highly significant ($p < .01$). However, the fact that only 3 data points were above the identity line and 12 below it, attest to a small, but significant systematic error in the PDE method, if one assumes $\dot{Q}_{Fick}$ to represent the true value, which may not necessarily be the case. The coefficient of variance (SD/mean value x 100) was nearly the same for both methods (22% for $\dot{Q}_{Fick}$ and 23% for $\dot{Q}_{PDE}$), indicating that the

scatter of the data was no greater in the one than in the other. The fact that the coefficient of variance was unusually large in both methods is because the subjects were patients with varying degrees of cardiac insufficiency and had $\dot{Q}$ values ranging from 2.67 to 6.03 L/min. The mean values for $\dot{Q}$ are definitely below the average found in a normal population. The mean cardiac index ($\dot{Q}$/BSA) by the Fick method was 2.37 (L/min/m^2) and 2.23 L/min/m^2 for PDE. According to Wade et al (13) the normal range at rest is 3.2 - 3.8 L/min/m^2 and values below 2.4 are unlikely to occur in healthy subjects.

The results obtained in this comparison of $\dot{Q}_{PDE}$ and $\dot{Q}_{Fick}$ are considerably better than those found in a similar comparison between the single breath (SB) method of Kim et al (8) and the Fick method which were reported from this laboratory in 1973 (10). At that time 28 simultaneous measurements were made on 5 normal subjects at rest and at three levels of submaximal exercise. Although there was good correlation between the two methods ($r = 0.92$) the mean values for $\dot{Q}_{SB}$ were 16% lower than for $\dot{Q}_{Fick}$. The SB method was subsequently used in studies before and after space missions on SKYLAB astronauts (3).

Additional advantages of the PDE method are that the latter requires no active cooperation by the subject, while the SB method involves a controlled slow expiration which is difficult to perform during exercise. The maneuver itself may affect venous return to the heart and thereby $\dot{Q}$. After the SB maneuver several minutes are required to regain a steady state before another measurement can be made. PDE provdes beat-by-beat information and is not affected by normal breathing. The following parts of this report deal with the application of PDE during upright and supine exercise and under constant and progressive lower body negative pressure.

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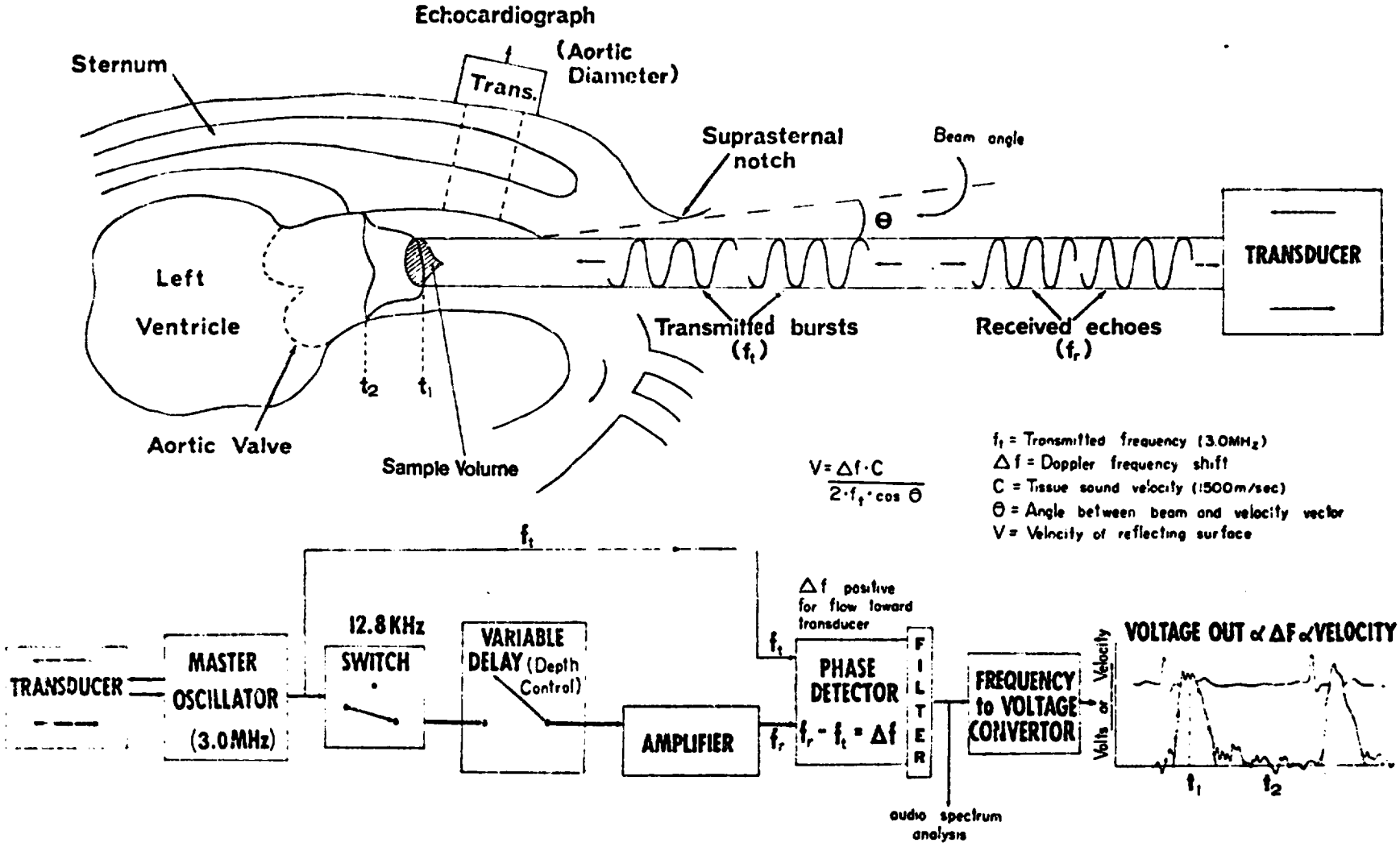
TABLE B-1

	Physical Characteristics				Cardiac Output		Heart Rate	Stroke Volume		
	Age	Ht	Wt	BSA	Fick	PDE	From PDE	Fick	PDE	PDE-Fick
	yr	cm	kg	m^2	L/min	L/min	bpm	ml	ml	ml
1	54	170	73.6	1.85	4.52	3.84	80	57	48	-9
2	54	177	74.5	1.94	4.66	4.10	72	64	57	-7
3	64	193	86.8	2.19	5.88	5.70	92	64	62	-2
4	64	187	67.2	1.91	2.76	2.38	72	38	33	-5
5	58	165	69.0	1.78	4.69	4.37	81	58	54	-4
6	57	167	63.6	1.72	3.69	3.98	71	52	56	+4
7	55	177	65.9	1.82	5.93	5.57	87	68	64	-4
8	62	188	65.9	1.92	4.70	4.18	82	57	51	-6
9	57	191	87.2	2.20	6.03	5.67	90	67	63	-4
10	55	190	99.5	2.30	3.29	3.01	70	47	43	-4
11	59	165	84.1	1.92	5.89	5.92	87	68	68	0
12	61	172	72.3	1.84	3.59	3.80	73	49	52	+3
13	63	178	102.3	2.22	4.91	4.57	83	59	55	-4
14	53	173	80.3	1.94	5.70	5.28	88	64	60	-4
15	59	183	89.1	2.15	4.16	3.90	78	53	58	+5
X	58	178	78.8	1.98	4.69	4.42	80	57.6	54.9	-2.7
SD					±1.05	±1.04	±7.5	±8.7	±8.9	



FIBURE B-1. Simplified diagram of pulsed Doppler echocardiograph to obtain aortic bloodflow.

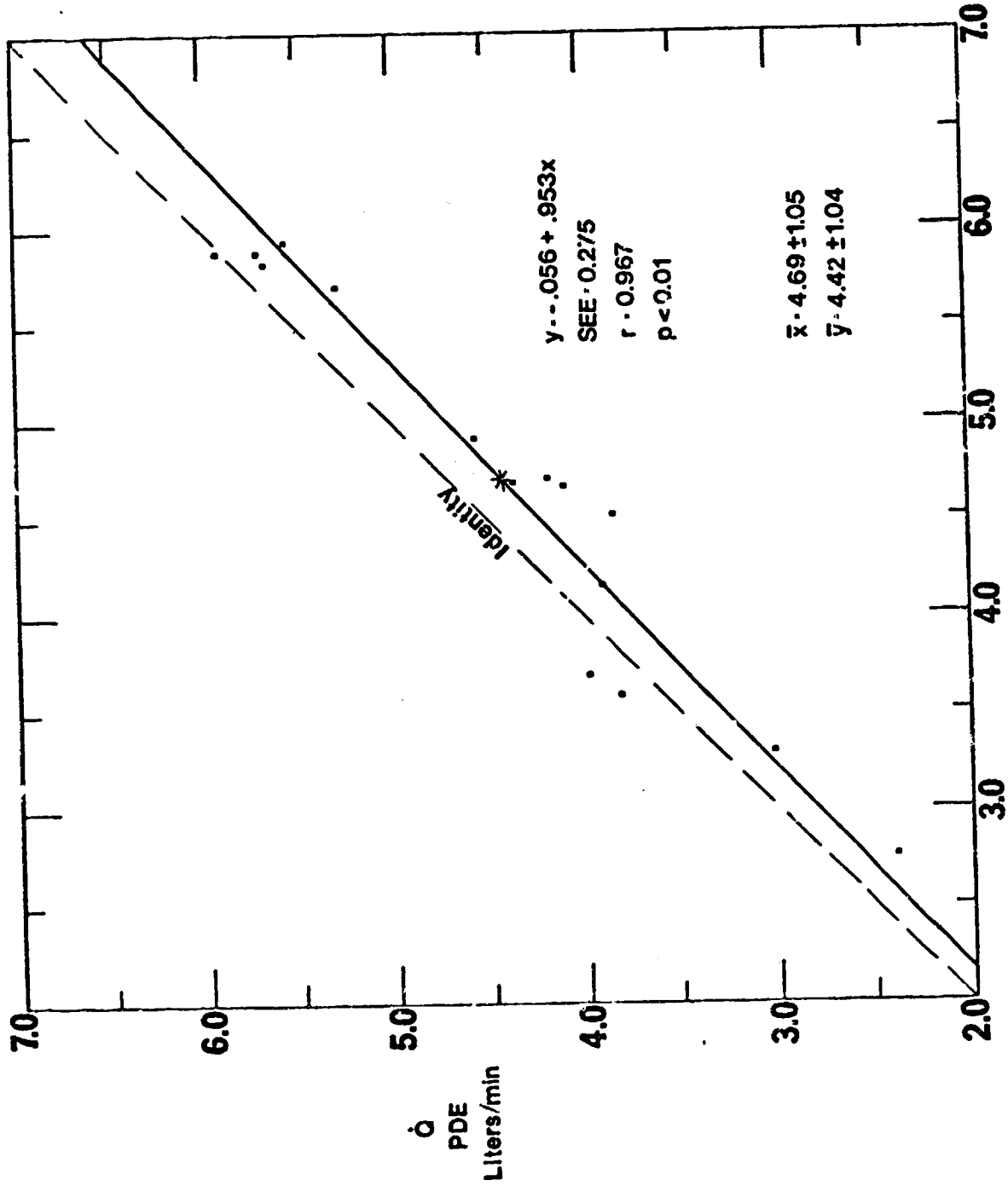


FIGURE B-2. Regression of aortic flow by pulsed Doppler echocardiography ($\dot{Q}_{PDE}$) versus cardiac output by the direct Fick method ($\dot{Q}_{Fick}$).

PART C

BEAT-BY-BEAT STROKE VOLUME ASSESSMENT BY PDE IN UPRIGHT AND SUPINE EXERCISE

N81 20710

SUMMARY

A 3.0 MHz pulse Doppler echocardiograph was used to estimate instantaneous stroke volume (SV) and cardiac output ($\dot{Q}$) in 8 men during steady state supine (S) and upright (U) exercise at 300 kpm/min which were compared with other studies utilizing invasive procedures. The mean transients in heart rate (HR) and SV and $\dot{Q}$ for the first 20 sec of exercise in each posture were then determined. Centerline blood velocities were obtained in the ascending aorta with the transducer positioned manually in the suprasternal notch. Mean supine values for SV and $\dot{Q}$ (parentheses) at rest and exercise were 111 (6.4) and 112 ml (9.7 L/min), respectively, for S. The corresponding results for U were 76 (5.6) and 92 ml (8.4 L/min). These values compare favorably with prior studies. The transient response of $\dot{Q}$ following the onset of U was about twice as fast as in S because of the rapid and almost immediate upsurge in SV. In S, only HR served to augment $\dot{Q}$ as SV initially fell. The faster initial aortic flow in U must represent the rapid mobilization of pooled venous blood from the leg veins which more than accounts for the additional volume (184 ml) of blood passing through the aorta during U compared with S in the first 20 sec.

ABBREVIATIONS

$\dot{Q}$	Cardiac Output
HR	Heart Rate
PDE	Pulse Doppler Echocardiography
SV	Stroke Volume
AD	Aortic Diameter
S	Supine (Semi-Recumbent) Posture with Legs and Upper Torso Elevated
U	Upright (Sitting) Posture
SVI	Systolic Velocity Integral
v_p	Peak Systolic Spatially-Averaged Velocity
$\bar{v}$	Mean Systolic Spatially-Averaged Velocity
ET	Left Ventricular Ejection Time
CC	Cardiac Cycle Duration
CI	Cardiac Index ($L/min/m^2$)
SI	Stroke Index (ml/m^2)
$\dot{V}_I$	Pulmonary Ventilation
SD	Standard Deviation
SE	Standard Error
CV	Coefficient of Variation (SD/mean)

INTRODUCTION

The precise time course of the cardiac output ($\dot{Q}$) response to exercise in man has long been under investigation utilizing various indirect techniques. As early as 1913 Krogh and Lindhard (12) estimated the rapidity of the increase in $\dot{Q}$ during upright work from measurements of heart rate (HR) and O_2 absorption. They inferred a significant increase in $\dot{Q}$ within 12 sec of exercise onset at a variety of workloads and noted its relationship with changes in ventilation. Recently, attempts to estimate $\dot{Q}$ by sampling alveolar gas have been repeated by Weissman et al. (27). They concluded that increases in pulmonary bloodflow were apparent between one and 5 sec of exercise onset and that the initial rise time was largely independent of the work rate. Previous studies from our laboratory (17) and those of Linnarsson (15) and Karlsson et al. (11) have also measured pulmonary gas exchange during exercise onset and attributed postural variations in these measurements to alterations in pulmonary bloodflow. These methods of measuring bloodflow must rely on questionable assumptions about the time course of alveolar gas exchange and how it relates to ventilation and perfusion. A much preferred method would be one which could measure $\dot{Q}$ directly without the dependence on gas equilibria, diffusion rates and circulatory and respiratory time relationships and does not require the subject to alter his ventilation which can affect the circulation in itself.

With the advent of modern noninvasive techniques to measure bloodflow, notably pulse Doppler echocardiography (PDE), it is now possible to estimate bloodflow instantaneously and directly in the ascending aorta in resting man in the supine posture. The theoretical basis of this instrumentation appears sound (3, 14) and some investigations have succeeded in measuring relative changes in velocity and volume flow (1). By determining the diameter of the

ascending aorta by M-mode echocardiography, beat-by-beat stroke volume (SV) can be estimated from the velocity waveform generated by PDE. This laboratory has shown that reasonable values for $\dot{Q}$ and SV are obtainable in this fashion in resting subjects who are exposed to lower body negative pressure and can provide important physiological information (16). The major complicating factors in attempting PDE during exercise, especially in the upright posture, are motion artifacts and increased respiratory excursions because the blood velocity is measured in a precise anatomical location. This difficulty is greatly enhanced in M-mode and two-dimensional echocardiographic estimates of SV where only selected subjects with a suitable anatomical "window" can be studied and then often in some compromising posture which makes exercise difficult or impossible. More recent determinations of $\dot{Q}$ by radionuclide angiocardiography (23) have the advantage of being able to differentiate the influence of end-diastolic volume and ejection fraction on SV on a beat-by-beat basis. However, they contain geometric assumptions and involve the injection of radioactive substance and are not truly noninvasive.

The precise beat-by-beat time course of $\dot{Q}$ and SV in man as a response to exercise has apparently not been described to date. In dog preparations it has been shown by Guyton et al. (9) that $\dot{Q}$ can increase up to 40% within 3 heart beats following muscle contractions stimulated by electric current or mechanical compression of skeletal muscles. In man, any measurements within the first min of exercise are rare or questionable because most techniques require the attainment of a circulatory steady state. Raynaud, et al. (20), utilizing a radioactive krypton method, obtained values after 10 and 28 sec of supine exercise onset at 300 Kpm/min. They noted that 33% of the steady state increase in $\dot{Q}$ had been attained after 10 sec. Jones et al. (10)

obtained values for $\dot{Q}$ from 30 sec to 3 min after supine exercise onset from instantaneous pressure recordings in the ascending aorta by utilizing the Navier-Stokes equation to relate velocity and pressure. They reported that steady state $\dot{Q}$ was reached more slowly at higher workloads.

It has been implied from previous investigations that the pumping action of the muscles on the capacitance vessels is a prime determinant of the initial increase in $\dot{Q}$ with exercise and presumably this influence is relatively greater in the upright posture where there is more venous pooling (17, 21). Any postural differences in $\dot{Q}$ would be reflected primarily in SV since HR is known to increase in both postures. It has been well documented that $\dot{Q}$ is lower at rest and steady state exercise in upright than supine posture, and that the change in $\dot{Q}$ is similar, although HR rises less and SV more in the upright posture (4, 5, 22). The exact time course of $\dot{Q}$ would allow one to estimate and compare the absolute blood volume mobilized by the left ventricle with the onset of exercise in the two postures.

The purpose of this study was two-fold: 1) to determine the feasibility and validity of absolute SV and $\dot{Q}$ determinations by PDE in man at rest and during steady state exercise in supine and upright postures by comparing results to those in the literature utilizing classical, invasive techniques and (2) to measure the absolute beat-by-beat changes of SV and $\dot{Q}$ during the early seconds of exercise and compare these responses in the two postures.

METHODS

Subjects: Eight healthy adult males between the ages of 23 and 37 were subjects in the study. Their physical characteristics are shown in Table 1 with body surface area predicted from a nomogram based on the formula of Dubois (6). Aortic diameter (AD) was obtained during end-diastole (R-wave of the EKG) in the supine position at rest within a few days of the study by M-mode echocardiography (7). The subjects represented a wide range in fitness level, from extremely well-conditioned in distance running (subject ME) to almost completely sedentary (subject AC). The subjects are ranked in Table 1 according to an evaluation of their fitness based on recreational exercise habits.

Experimental Protocol: Steady state and transient exercise in the supine (S) and upright (U) postures were completed in one session in 6 of the subjects. In the other two, a few days elapsed between S and U procedures. The transient data were always obtained prior to the steady state runs, with half of the subjects performing S first and the other half beginning with U. The upright exercises were performed on a Monark bicycle ergometer and supine work on an Ensco (Model BE-5) ergometer mounted on the foot of a bed. At both postures the subjects pedalled at a rate of 40 cycles/min to a metronome. The load for the Monark was set at 1.25 Kp for transient and steady state exercise for all subjects (300 Kpm/min) and an equivalent load was established on the Ensco ergometer from a calibration curve. The equivalent load on the two ergometers was verified on 3 of the subjects prior to the experiments by measuring $\dot{V}O_2$ (0.95 L/min) after 5 min of exercise in each posture. This load constituted about 30% of $\dot{V}O_2max$ for the subjects. The relatively low workload was chosen to avoid excessive body or respiratory

movements which would produce artifacts in the PDE signal. During S, the feet were elevated 20° above the hips, while the upper body was elevated 10° above the hips. The subject rested for at least two min prior to baseline measurements in this position. During U the subjects rested quietly for the same duration before baseline measurements. A standard single-lead EKG was employed in some cases although HR was obtained from the recorded PDE signal.

For the transient procedures, baseline recordings were taken while the subject was given a countdown to exercise onset. He started pedalling at the appropriate rate and continued for at least 20 sec while PDE recordings were continued. This relatively short measurement period was chosen because there is virtually no direct or indirect data for $\dot{Q}$ and SV during this time and much time was required to accurately process and average the data. Following at least 3 min of rest this procedure was repeated until two runs were completed in which few PDE signals were impaired by movement as judged from the on-line scope display and hardcopy recording. Three of every 4 runs was acceptable. For the steady state procedures, 15 sec of continuous resting data were obtained. Following 5 min of exercise, continuous data were recorded for 15 sec during the sixth min of work.

The procedure and instrumentation for the determination of SV and $\dot{Q}$ by PDE was precisely the same as described in Part B of this report (pp 39).

RESULTS

Steady State Experiments

The mean values, range and standard deviation (SD) for the systolic ejection and velocity characteristics and HR, SV and $\dot{Q}$ during rest and exercise for each posture are presented in Table 2. The average coefficient of variation (SD/mean) for each variable is shown, as well as the average changes from rest to exercise (E-R) in these variables.

Systolic ejection and velocity characteristics: It is apparent from Table 2 that ET was significantly lower in U than S, both at rest and exercise. However, the ejection fraction of the cardiac cycle (ET/CC) was essentially unchanged by posture at rest since HR was higher and the cardiac cycle shorter during U. During work the HR was nearly the same for both postures so ET/CC was also significantly lower during U than S. The changes in ET and ET/CC from rest to exercise were not significantly different between S and U.

The v_p values showed no significant difference with posture during rest and exercise and the increase with exercise (E-R) was also quite similar (about 24% in each posture). On the other hand, $\bar{v}$ was significantly higher at rest in S than in U. With v_p being similar in the two postures at rest, this indicates that the systolic ejection waveform was more blunted during S compared to the sharper peaks seen in U. With exercise the waveforms became more similar since both v_p and $\bar{v}$ were nearly identical for U and S. The increase in $\bar{v}$ with exercise was 29% during U, compared with 17% during S, however the difference was not significant.

Aortic bloodflow: At rest, the HR was significantly lower in S than U, but essentially equal during work. The increase in HR with exercise was 31 bpm

(52%) in S and only 19 bpm (25%) for U, a difference which was highly significant and was noted in all subjects. However, SV showed essentially no change with exercise during S, but increased 21% or 16 ml in U. Since the changes in SV tended to be inversely related to those in HR, the rise in $\dot{Q}$ with work was about 3 L/min for exercise in both postures. The mean $\dot{Q}$ was 0.8 and 1.3 L/min lower in U at rest and exercise, respectively, but this difference was not significant.

The averaged coefficients of variation (CV) in Table 2 reflect the true variability between subjects and any intersubject errors of measurement. The 29% and 21% values for SV and $\dot{Q}$, respectively, indicate that the measurement of bloodflow by PDE did not contribute substantial error scatter into the data than that seen for the relatively error-free measurement of HR. The rise in HR from rest to exercise shown in Table 2 demonstrated about the same CV (23%) as the absolute values at rest and exercise. However, the increment in $\dot{Q}$ was considerably more variable (CV: 36%) compared to the 21% in the absolute measurements. This was due to the large variation in the response of SV to exercise (e.g. for S, one subject reduced SV by 10 ml while another increased SV by 11 ml and for U, the response ranged from -1 to 31 ml).

Comparison of cardiovascular variables determined by PDE with invasive studies: Table 3 summarizes the values obtained in 3 investigations which closely parallel those of the present study. In these studies the same subjects were exercised in S and U following resting measurements at each posture. The two studies reported from the laboratory of Bevegård, et al. (4, 5) utilized the direct Fick procedure in healthy, but untrained male subjects with measurements carried out after 5 min of steady state work. All exercise values shown were interpolated or extrapolated to 300 Kpm/min for

this comparison. The study by Stenberg, et al. (22) utilized well-trained male subjects with $\dot{Q}$ being determined by the dye dilution technique. The table indicates that the latter study obtained values for cardiac index (CI) that were about 15% lower than the direct Fick studies, however, the increase with exercise was about the same (2.1 L/min/m^2). The PDE method resulted in resting values during S for CI and stroke index (SI) that were quite similar to the average values of the invasive procedures. The SI was 7% larger by PDE and CI was 11% lower. However, our subjects had a 14% lower HR. With exercise of equal intensities in S our SI and HR values were 5% lower which resulted in a 14% lower CI. The increase in CI with exercise was 50% for PDE and 55% in the other experiments, with our subjects showing a larger change in HR and no change in SI. At rest during U the values for PDE were nearly identical to the others, but during work both SI and CI were about 10% less in the former with mean HR being the same. The HR increase with exercise was slightly greater in the present study, with CI and SI showing relatively smaller increments with work. The latter were the largest discrepancies noted in Table 3 between the invasive and PDE procedures.

Transient responses in HR, SV and $\dot{Q}$

The average HR response by the 8 subjects in the first 20 sec following work onset is shown in Fig. C-1 for the 2 postures. The steady state resting values and those after 5 min of exercise are also shown. It is immediately apparent that during the first 20 sec HR responded faster in S than U, although the same change of 6 bpm was evident in the first 3 sec. After 20 sec, 55% of the 5-min HR change had taken place for S whereas only 37% of the rise during U had occurred. The increment in HR after 1 sec of S was already

statistically significant, whereas for U the same rise was not significant until 3 sec because of the variability in the response between subjects. The transient decline in U from 3 to 5 sec was statistically significant ($p < .05$), but not the fall between 13 and 18 sec.

The instantaneous SV response to exercise onset is shown in Fig C-2. The SV rose rapidly and linearly during the first 6 sec of U, with the increase showing statistical significance after 3 sec. A significant ($p < .01$) decline then followed between 6 and 15 sec with SV thereafter remaining relatively constant. In S the drop during the first 3 sec was statistically significant, with SV then recovering and remaining near the baseline value for the remainder of the measurement period with the exception of a decline between 10 and 14 sec.

The beat-by-beat response of $\dot{Q}$ has been averaged in Fig. C-3. Although the baseline values are different, the curves for U and S are almost superimposed after 3 sec of work and then diverge somewhat after 14 sec. The rise in U was significantly above baseline after 2 sec, whereas $\dot{Q}$ during S did not show a significant response until 5 sec. Both curves show a transient peak at 11 sec, with significant declines taking place in U between 11 and 19 sec, and in S between 11 and 14 sec. After 20 sec of work 61% of the 5-min change in $\dot{Q}$ had taken place during U, whereas only 49% of the rise was completed after 20 sec of S. From curves for each subject the average half-time for $\dot{Q}$ was 4 sec for U (range: 2-7 sec) and 10 sec for S (range: 4-20 sec).

In summarizing the responses to the onset of exercise, during S there was an initial lag in $\dot{Q}$ compared to U which resulted from a transient decline in SV over the first 5 sec. During U the rapid rise in $\dot{Q}$ was the result of an initial upsurge in SV which coincided with a transient reduction in HR. The

average HR change was the same during the first few seconds but SV fell during S and rose during U. Between 10 and 20 sec in U there was a larger drop in $\dot{Q}$ which was contributed to by both a fall in HF and SV whereas for S only SV showed a significant decline.

The differences in the inital changes in these variables with posture is more apparent in Fig. C-4 where they have all been plotted on the same baseline. The difference in SV is largest at 6 sec, then declines slightly and remains relatively constant thereafter. The HR also shows a clear divergence after 5 sec. The response difference for $\dot{Q}$ is apparent after one sec and reaches a maximum at 5 sec but the two curves converge before the end of 20 sec. The area contained under each of the $\dot{Q}$ curves represents the additional volume of blood passing through the ascending aorta during the first 20 sec. This amounted to 341 ml and 525 ml for S and U, respectively, with a difference of 184 ml. These blood shifts determined in a similar fashion for each subject are presented in Table 4. All subjects showed a larger volume shifted during U ($p < .005$) with a great deal of individual variation.

DISCUSSION

In general, the experiments were successfully carried out with minimal subject cooperation. There is no discomfort, apprehension and risk involved in the PDE determination of SV and $\dot{Q}$. This is an inherent advantage over the more traumatic invasive procedures which may well distort baseline values. Hardcopy analog recordings are immediately available and the digital conversion and tabulation of the data and incorporation of appropriate AD values into the calculations can be more fully automated to obtain on-line values for velocity and volume flows.

Steady State Experiments: The comparison of the PDE results with those of the other studies shown in Table 3 was quite favorable. At rest in both postures our values for CI were within the range of those reported from direct Fick and dye-dilution procedures. Our SI values were slightly larger than those reported at rest in S, but our HR values were lower. As far as could be determined in the 3 studies used for comparison, their baseline measurments of SI and $\dot{Q}$ were made with the legs of the subjects resting on the bed, whereas in the present study the legs were elevated with the feet on the pedals. Frick and Somer (8) have shown with the dye-dilution technique that raising of the legs can result in a 19% increase in SV at rest and a reduction in HR of 6 bpm with $\dot{Q}$ remaining relatively unchanged. They attributed this to enhanced venous return and diastolic filling with no change in the circulatory demands. This could be the main reason why our resting SI during S was higher and HR lower than in the other studies and why there was a greater change in HR and no change in SI after 5 min of exercise, although the rise in CI was similar to those previously reported. During U our resting values were smaller than during S, but very similar to the other

studies presented in Table 3. The mean value at rest while supine, based on 23 studies using the direct Fick method and 22 using the dye-dilution procedure, has been reported at between 3.2 and 3.8, with mean values below 2.4 and above 4.6 L/min/m^2 being rare (24). Our mean and standard deviation (3.4 ± 0.7) fell within these limits. The smaller $\dot{Q}$ values in the same subjects sitting compared to supine have been documented by studies other than those shown in Table 3, as have the relatively greater changes in exercise SV during U (24, 25). Therefore, the PDE technique appears to give values of CI at rest in either posture and during supine exercise that are very similar to other techniques. The largest discrepancies in SI and CI in Table 3 were during upright exercise. The values were 10% lower than the 3 reported studies with essentially the same HR, resulting in a smaller percentage increase in our values from rest to exercise. This could reflect a unique response of our subjects or an underestimation error in the PDE method. However, we experienced no additional difficulty in tracking the ascending aorta with exercise in U and the number of spurious waveforms was not greater than during exercise in S. It should be pointed out that the PDE determination of SV, assuming a true AD can only equal the true SV and the tendency will always be to underestimate since the ultrasonic beam angle can and will deviate from zero. Furthermore, electronic processing and filtering of the Doppler audio spectrum will generally underestimate the true average frequency shift (3). It is conceivable that there was a small shift in the location of the ascending aorta from S to U which would result in an underestimate, but this should be consistent during rest and exercise so the percentage increment with exercise should be accurately reflected.

The highest value recorded for v_p was 96 cm/sec in subject ME during upright exercise. With more intense work the maximum detectable velocity of

126 cm/sec would probably be exceeded and aliasing would occur. At what workload this becomes apparent remains in question. With PDE methodology it is also possible to obtain an estimate of cardiac contractility since the upslope of the systolic waveform (Fig.B-1) should be a direct reflection of left ventricular volume reduction. This would be a valuable parameter in the noninvasive evaluation of cardiac patients.

The response of $\dot{Q}$ to exercise in the two postures showed a relatively high variability in our subjects (Table 2). This resulted primarily from the variable response in SV. This relatively larger variability in SV compared to HR is also apparent from previous studies utilizing direct Fick procedures (4, 5). The HR exercise response in U was significantly related in an inverse fashion to that of SV ($r = -.73$, $p < .05$) but not in S ($r = -.32$). We also noted a tendency for the more physically fit subjects (rank order in Table 1) to have a larger increase in SV with exercise during U ($r = +.86$, $p < .01$). This correlation was less evident during S ($r = +.56$). This suggests that some individuals increase exercise $\dot{Q}$ via HR and others by raising SV and this differentiation is more clearly evident during U. The subjects which are accustomed to endurance activities appear to favor the increase in SV. This could relate to them having a more efficient pumping action of the leg muscles to augment venous return, end-diastolic volume and therefore SV (5, 23) or to a better contractile response by the heart in increasing SV when presented with an increasing venous return (Starling mechanism). The correlate of this variability in SV response requires further investigation. Perhaps exercise SV response may be an important aid in the evaluation of diseased cardiac function along with the absolute values at rest and exercise.

Transient Response to Exercise Onset: The general impression of these data, shown in Figs. C-1 through C-4, is that the initial response to work is not necessarily a smooth function of time, as inferred from previous presentations in the literature which assume values based on spot samples which are often taken many seconds after exercise began. If the circulatory adjustment to exercise is the question, then it is advantageous to have beat-by-beat measurements. If one assumes that the output of the ascending aorta reflects the venous return with some time lag, it seems evident from Figs. C-1 and C-2 that the initial rapid rise in SV up to 6 sec during U results in a drop in HR via the baroreceptor reflex similar to that seen in a prior study following the release of lower body negative pressure (16). During the onset of upright exercise the mobilization of previously pooled venous blood to the heart, lungs, and aorta with the initial muscle contractions probably results in the early postural difference in $\dot{Q}$ seen in Fig. C-4 as blood from the venous capacity vessels moves centrally (21). Following this initial translocation of blood reflected by rising SV and $\dot{Q}$, the pressure and flow load is somewhat reduced (Fig. C-2) and HR again rises (Fig. C-1) from the overriding sympathetic stimulus. The latter presumably acts just as strongly during S and the initial increase in HR, although the same as during U, serves to transiently reduce SV since the legs are elevated initially and there is little or no additional venous blood mobilized or increase in end-diastolic volume (23) since there was no prior venous pooling. The added gravitational resistance to bloodflow with the legs elevated may also contribute to the early fall in SV. Presumably, the circulatory and metabolic demands of the working muscles are more appropriately met following these initial transients as HR, SV and $\dot{Q}$ respond more gradually to achieve the steady state values. The latter, smoother

transients are usually the ones measured by conventional methods and in smooth transients the assumption of a steady state does not result in serious errors as long as the measurement times are kept short. In S, diastolic filling and venous return are not limited and $\dot{Q}$ can be elevated relatively smoothly throughout by the rise in HR without any appreciable change in SV. The fact that $\dot{Q}$ is quite similar (Fig. C-3) for the 2 postures after the first few seconds, in spite of a relatively large initial discrepancy in the response of SV and HR points to an initial imbalance in venous return when exercise begins. The reason for the transient decline in $\dot{Q}$ after 11 sec is not clear. In both postures it resulted from a decline in SV although during U it was also partially attributable to a reduction in HR.

The results in Table 4 indicate that an additional blood volume amounting to nearly 200 ml is transported through the ascending aorta during the first 20 sec of U as compared to S. This larger "bolus" seen on the arterial side is probably related to the faster upsurge in venous return (Fig C-4). It seems reasonable to speculate that this greater increment in $\dot{Q}$ in the upright posture is in some way related to the faster rise in ventilation ($\dot{V}_I$) noted after exercise onset in U during the first 40 sec of exercise in a similar protocol from this laboratory (17). Instead of attributing the larger $\dot{V}_I$ in U to a more potent chemoreceptor response arising from the lower P_{O_2} and higher P_{CO_2} in venous blood caused by pooling prior to exercise, the response may also result from the larger influx of blood into the central circulation which was supported by our instantaneous decrease in leg volume after exercise began (17). Ponte and Purves (19) in animal experiments, have clearly shown that hyperpnea in response to infused CO_2 was markedly increased, and that hyperpnea was independently produced with CO_2 held constant, by a sudden rise in venous return with no corresponding change in

arterial blood pressure. Since our faster rise in $\dot{Q}$ while upright seems to correspond to an earlier and greater rise in $\dot{V}_I$ it could well indicate that the mechanism of hyperpnea during the first few sec of upright exercise is predominantly a direct response to flow, especially since cardiodynamic hyperpnea has been shown to be left intact in animals with denervated chemoreceptors (26). It would also seem reasonable to suggest that with the onset of higher workloads with leg exercise during U the venous return and $\dot{Q}$ increase would be greater and would result in the more rapid rise in $\dot{V}_I$ as shown by Astrand and Christensen (2). The slower $\dot{V}_I$ rise observed when exercise is initiated from "zero-load" pedalling instead of stationary rest (13) may be due to the fact that some of the blood pooled in the lower extremities has already been shifted centrally before the "loaded" exercise begins.

Based on our findings we conclude that PDE can serve as a valid technique to estimate steady state as well as subtle beat-by-beat changes in SV and $\dot{Q}$. The technique has been useful in describing notable differences between the circulatory transients following the onset of exercise in upright and supine postures.

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TABLE C-1.

Physical characteristics and aortic diameter (AD) of 8 subjects.

Subject	Age (yr)	Ht (cm)	Wt (kg)	BSA (m^2)	AD (cm)
ME	25	175	64	1.78	3.0
JL	35	179	72	1.90	3.3
DH	37	188	82	2.09	3.4
JD	32	183	68	1.89	3.1
MF	25	171	68	1.80	3.2
BB	23	180	78	1.98	3.3
JA	28	182	74	1.94	3.3
AC	33	182	52	1.68	3.1
Mean	30	180	70	1.88	3.2
SD	5	5	9	0.13	0.1

TABLE C-2.

Left ventricular ejection time (ET) and its fraction of cardiac cycle (CC), peak (v_p) and mean ($\bar{v}$) velocities and cardiac performance at rest (R) and in the 6th min of ergometer exercise (E) at 300 kpm/min in 8 subjects while supine (S) and upright (U).

		ET (sec)	ET/CC	v_p (cm/sec)	$\bar{v}$ (cm/sec)	HR (bpm)	SV (ml)	$\dot{Q}$ (L/min)
S	R	.32 .18-.41 (.07)	.31 .27-.35 (.03)	60 49-73 (8)	35 28-42 (5)	60 45-91 (14)	111 47-145 (32)	6.41 4.28-8.12 (1.46)
	E	.28 .21-.36 (.05)	.41 .35-.49 (.05)	73 46-94 (18)	41 24-50 (9)	91 68-127 (18)	112 46-149 (36)	9.67 5.84-12.51 (2.35)
U	R	.26 .20-.30 (.04)	.32 .25-.38 (.05)	57 40-77 (14)	31 22-38 (6)	76 55-110 (17)	76 42-100 (19)	5.58 4.62-7.70 (1.01)
	E	.24 .20-.30 (.03)	.37 .31-.41 (.04)	72 49-96 (16)	40 25-51 (9)	95 75-128 (17)	92 44-124 (26)	8.38 5.63-10.40 (1.57)
Mean CV(%)		17	12	21	20	21	29	21
ΔS (E-R)		-.04 -.08-.03 (.04)	.10 .02-.15 (.05)	13 -3-40 (14)	6 -4-12 (6)	31 22-39 (6)	1 -10-11 (8)	3.26 1.56-5.07 (1.21)
ΔU (E-R)		-.02 -.06-.01 (.02)	.05 .01-.10 (.03)	15 9-22 (5)	9 2-13 (4)	19 11-28 (5)	16 -1-31 (13)	2.80 1.01-4.18 (0.97)
R-R		*	NS	NS	*	**	**	NS
E-E		*	*	NS	NS	NS	*	NS
ΔS-ΔU		NS	NS	NS	NS	**	**	NS

Values are expressed as mean, range and one SD (parentheses), CV: coefficient of variation (SD/Mean), R-R: difference in rest values between S and U, E-E: difference in exercise values between S and U, ΔS-ΔU: difference in exercise response between S and U, *: $p < .05$, **: $p < .01$.

TABLE C-3.

Comparison of invasive measurements of cardiac index (CI), HR and stroke index (SI) in supine and upright rest and exercise at 300 kpm/min (means in parenthesis) with those obtained by PDE.

		Rest	Exer.	Δ%	Rest	Exer.	Δ%
	Load	0	300	--	0	300	--
Direct	$\dot{V}_{O_2}$	.31	.95	206	.35	.96	174
Fick	CI	4.2	6.3	50	3.2	5.3	66
(4,5)	HR	76	102	34	83	101	22
	SI	55	62	13	38	52	37
	Load	0	300	--	0	300	--
dye-	$\dot{V}_{O_2}$	.33	.94	185	.33	1.01	206
dilu-	CI	3.4	5.5	62	2.7	4.9	81
tion	HR	64	90	41	74	88	19
(27)	SI	55	62	13	37	56	51
	Load	0	300	--	0	300	--
	$\dot{V}_{O_2}$	-(.32)	-(.95)	-(197)	-(.34)	-(.99)	-(191)
PDE	CI	3.4 (3.8)	5.1 (5.9)	50 (55)	3.0 (3.0)	4.5 (5.1)	50 (70)
	HR	60 (70)	91 (96)	52 (37)	76 (79)	95 (95)	25 (20)
	SI	59 (55)	59 (62)	0 (13)	40 (38)	49 (54)	23 (42)

Direct Fick: means of two studies of Bevegård et al. (4, 5), n=6 and 7, values linearly interpolated or extrapolated for 300 kpm/min from workloads varying between 250 and 500 kpm/min. Dye-dilution: study by Stenberg et al. (27), n=6.

TABLE C-4.

Additional volume of blood (ml) flowing through the ascending aorta in 8 subjects during the first 20 sec of supine and upright exercise and the difference (Δ). The difference is significantly different from zero ($p < .005$).

Subject	Supine	Upright	Δ
ME	437	620	183
JL	288	508	220
DH	398	795	397
JD	133	279	146
MF	818	1108	290
BB	223	389	166
JA	314	353	39
AC	120	148	28
Mean	341	525	184
SD	223	310	122
CV (%)	65	59	66

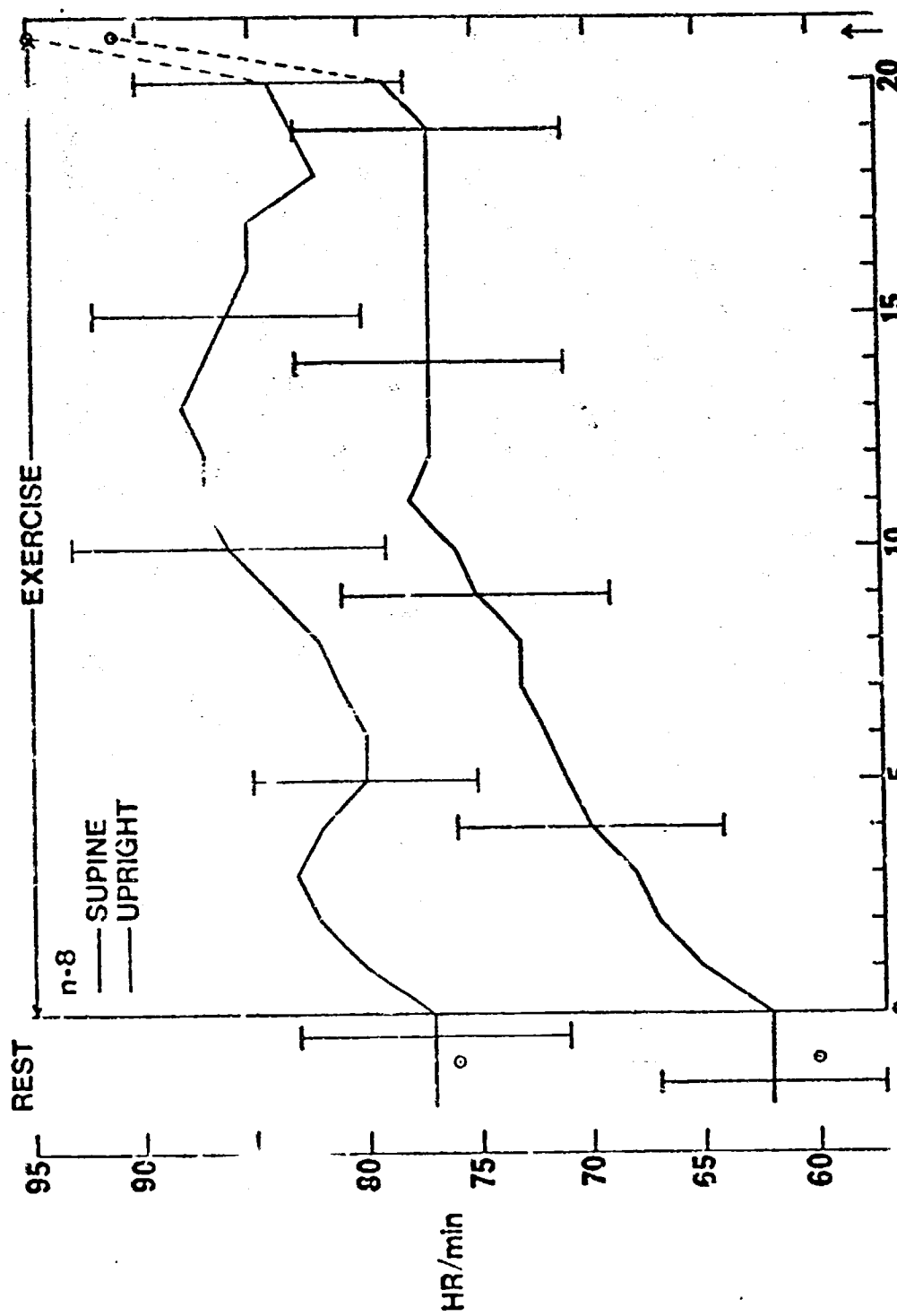

FIGURE C-1. Mean HR response to exercise at 300 kpm/min. Vertical lines are ± one SE of the mean. Dots are means for the steady state procedures.

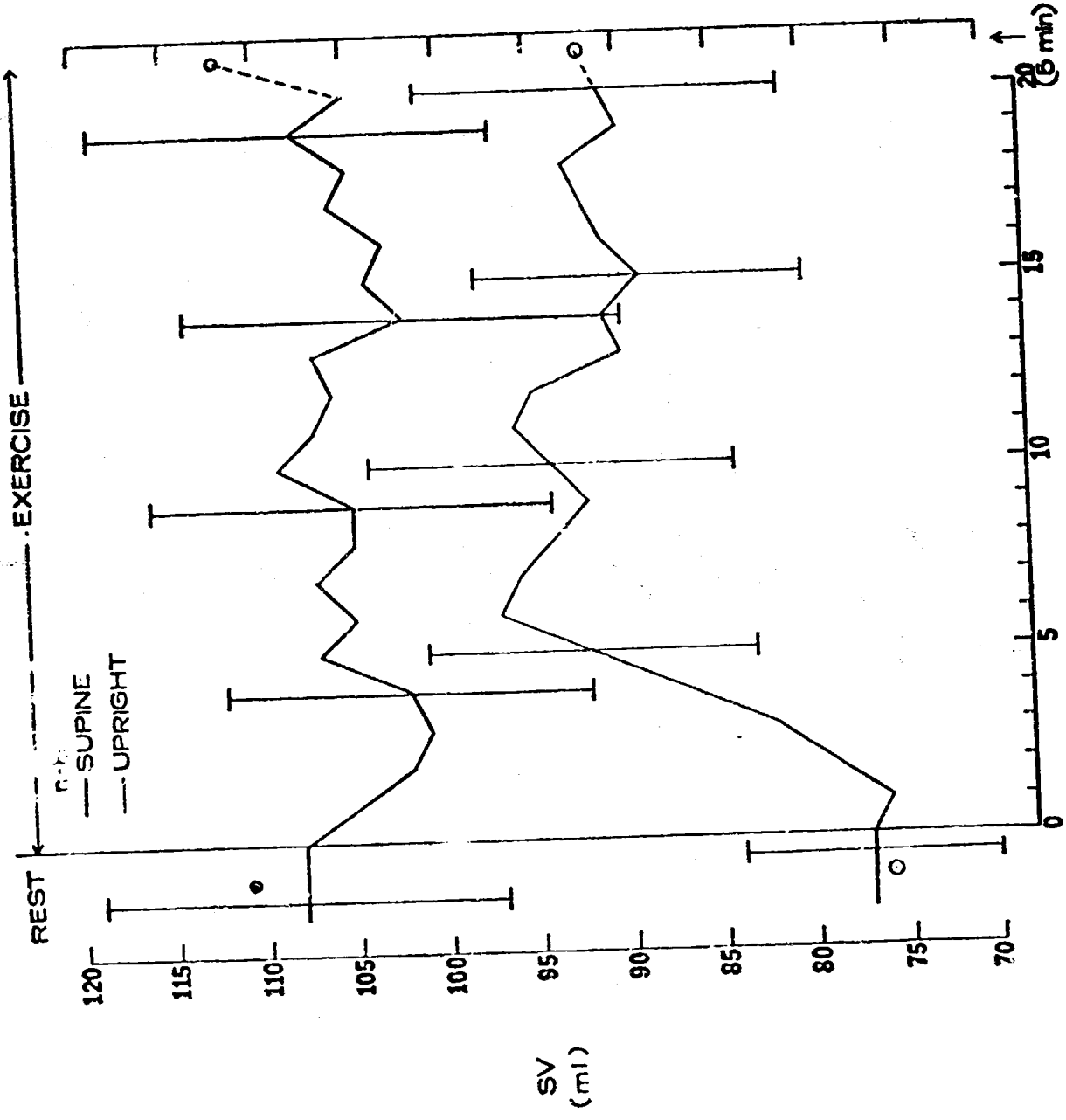

FIGURE C-2. Mean SV response to exercise at 300 kpm/min. See Fig. C-1 for symbols.

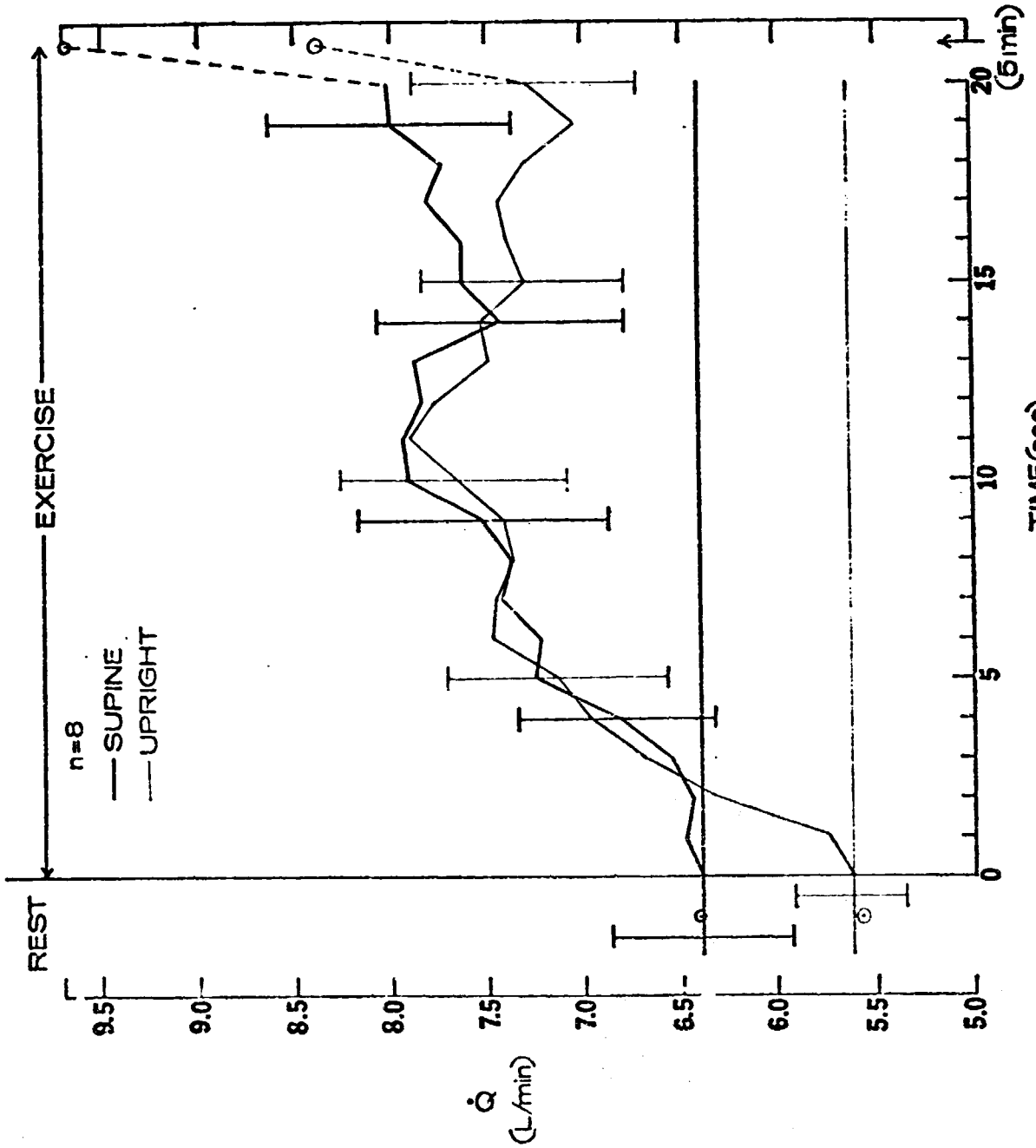

FIGURE C-3. Mean $\dot{Q}$ response to exercise at 300 kpm/min. See Fig. C-1 for symbols.

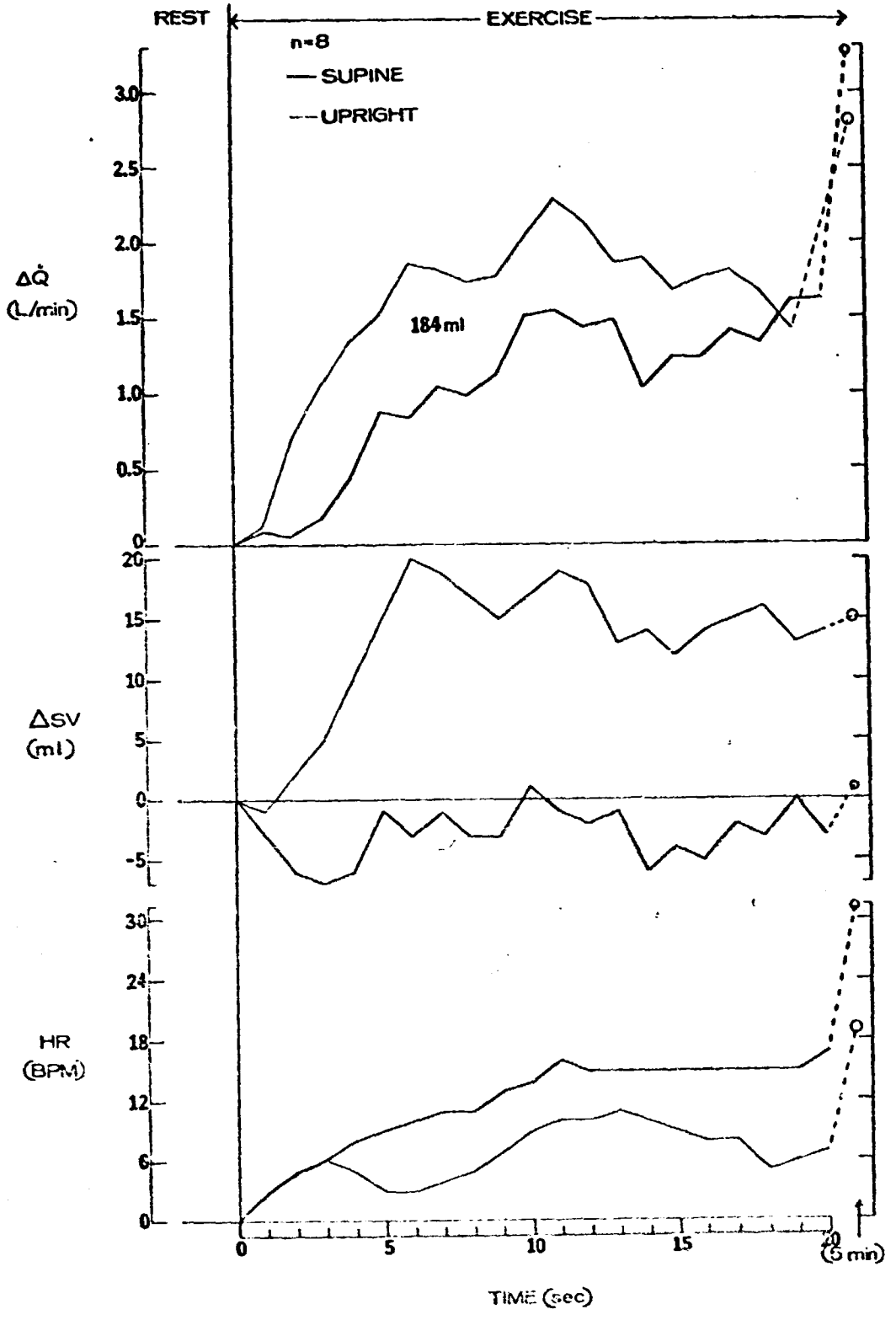

FIGURE C-4. Mean difference in response of HR, SV and $\dot{Q}$ between upright and supine exercise. Values are plotted as changes from resting baseline. The difference in $\dot{Q}$ indicates that an additional 184 ml of blood passed through the ascending aorta in the first 20 sec of upright exercise (by integration).

PART D

INSTANTANEOUS STROKE VOLUME BY PDE DURING AND AFTER CONSTANT LBNP (-50 TORR)

N81-20711

SUMMARY

Six male subjects were exposed to -50 Torr lower body negative pressure (LBNP) for 10 min while stroke volume (SV) was recorded beat-by-beat at regular intervals before, during and after release of LBNP. SV was calculated from the systolic velocity integral in the ascending aorta by pulsed Doppler echocardiography (PDE) and the cross-sectional area of the vessel by M-mode echocardiography. Changes in leg volume (LV) were recorded continuously and blood pressure (BP) was taken every minute. SV dropped by 51% of the control in the first 33 sec of LBNP and continued to decline slowly to -62% toward the end. Heart rate (HR) increased by 15% in the first 10 sec and was 22% above control at the end of exposure. The resulting cardiac output ($\dot{Q}$) closely followed the course of SV (-47% at 33 sec, -53% at 8 min) showing that the modest increase in HR did little to offset the drop in SV. LV increased markedly within the first 10 sec with a more gradual rise reaching +3.5% at the end. Upon sudden release of LBNP, LV dropped significantly during the first 3 sec simultaneously with an increase in SV followed by a substantial decline in HR below the baseline. This strongly suggests that the post-LBNP bradycardia is mediated by baroreceptors responding to the rapid reflux of blood to the heart after LBNP. Systemic peripheral resistance calculated from $\dot{Q}$ and mean BP showed a 150% increase in the course of LBNP.

INTRODUCTION

The measurement of beat-by-beat stroke volume (SV) response to LBNP is important in understanding the cardiovascular transients produced by gravitational stress in man. Unfortunately, the direct or indirect Fick methods require a steady state for valid measurements. Other noninvasive techniques contain assumptions which make even qualitative results questionable. The development of pulsed ultrasonic Doppler velocity meters (PD) in the last 8 years has greatly expanded upon the capabilities of simple echocardiographic (EC) and continuous wave Doppler systems in measuring intracardiac or peripheral vessel flow dyanmics because they measure blood velocities at selected depths and sample volume size (4). The temporal and spatial averaging of vessel velocities by PD conforms well to calibrated flows and theoretical predictions of flow dynamics (2,4) and the technique is well suited to measure rapidly changing flows in the ascending aorta and estimates of SV in man with this system have recently been validated (1).

The purpose of the study was to describe the instantaneous time course of SV and cardiac output ($\dot{Q}$) in response to the onset and release of -50 Torr LBNP applied for 10 min.

METHODS

A unique 3.0 MHz PDE echocardiograph (modified ATL Model 500A) was used to noninvasively obtain centerlamina blood velocities from the ascending aorta with transducer positioned at the suprasternal notch and the beam coaxial to the flow stream. A temporal display of the spatial mean velocity obtained from a calibrated audio spectrum decoder was recorded for each cardiac cycle. The fluid displacement was calculated from the systolic ejection waveform by planimetering the systolic velocity integral (SVI). (For details see Part B, p 39). To obtain SV, the displacement was multiplied by the diastolic cross-sectional area of the aorta which was calculated from the diameter (D) obtained intermittently during the experiments with a high resolution M-mode EC. The validity of SVI as a quantitative representation of SV has been demonstrated in animals (3) and humans (1). Heart rate (HR) was obtained from standard ECG and leg volume (LV) was estimated from a Hg strain gauge on the left calf (5).

Six male subjects (mean age = 30 yr) (Table D-1) were sealed into the box at the iliac crest. Measurements were made continuously for 20 sec prior to and one min after LBNP onset and release, with intermittent recordings during the last 15 sec of min 2, 4, 6, and 8 during LBNP and min 2, 3, 4, and 5 after LBNP. The onset and release of LBNP took place in 1 to 2 sec. The results of the 6 subjects were averaged over time.

RESULTS AND DISCUSSION

The average time course and standard deviations for SV, HR, $\dot{Q}$, and LV are shown in Figs D-1 to D-4. The mean baseline values for SV, HR and $\dot{Q}$ were 61 ml, 68/min and 4.02 L/min, respectively. Fig.D-1clearly demonstrated a linear fall in SV after the onset of LBNP to 49% ($p < .005$) of the baseline value after 33 sec, with HR and LV rising during the first 10 sec (Fig D-3). A second drop in SV occurred between 2 and 4 min and the lowest value (-62%) was seen after 8 min of LBNP, which coincided with the highest HR. Immediately after LBNP, SV rose rapidly to the pre-LBNP baseline in 9 sec (Fig D-2) It was already elevated significantly after 3 sec ($p < .02$) when HR had not yet changed, but LV had fallen (Fig D-4) and presumably venous return had increased. The HR then fell dramatically between 3 and 6 sec after LBNP by 22/min which clearly demonstrates that an increasing SV precedes the fall in HR which must be mediated by the baroreceptors. In Fig D-2, SV fell significantly between 9 and 15 sec while HR rose, and during the next 30 sec SV returned gradually upward to baseline while HR again decreased. This secondary transient probably resulted from the diminishing stimulus to the baroreflex after the initial surge in SV and carotid pressure so that HR was allowed to rise, with SV falling as a result of lesser filling time during diastole. The relationship of filling time and SV is also more generally evident from the almost perfect mirror image of the two curves in Figs D-1 and D-2. The dotted line in Fig D-3 is for $\dot{Q}$ with HR constant at the baseline level and clearly shows tht the HR increase with LBNP onset does little to prevent the fall in $\dot{Q}$. During initial recovery (Fig D-4) the bradycardia delayed the rise in $\dot{Q}$, preventing it from reaching baseline within 5 min. Throughout the experiment LV was inversely related to $\dot{Q}$, demonstrating how blood pooling with LBNP jeopardizes central blood flow and

that the venous reservoir has a greater influence on $\dot{Q}$ than does HR. The failure of LV to return to baseline in 5 min after LBNP reflects extravasation to the tissues in the lower body during LBNP (5). Blood pressure from the right brachial artery by sphygmomanometer and $\dot{Q}$ indicated that total peripheral resistance was increased by 150% above baseline after 8 min and remained 25% elevated throughout 5 min of recovery.

The absolute values for SV in Figs D-1 and D-2 appeared reasonable, suggesting that the electronic decoding and averaging of Doppler-shifted audio spectra to instantaneous velocities is accomplished with minimal systematic error. Since the ascending aorta may expand some 12% during systole (6), any underestimation may be due to using D obtained during diastole. With 10% larger D, the absolute values for SV and $\dot{Q}$ would be 21% greater throughout the experiment. The decline in SV and $\dot{Q}$ after 8 min of LBNP is about 20% greater than that reported using other methods (5). This may be a true response for our subjects or the result of some systematic error. The representation of SV by SVI is primarily determined by careful experimental technique to optimize the audio signal and maximizes SVI on visual display by manipulating the transducer. If the ascending aorta's position within the body was changed by LBNP and the beam angle gradually became greater, but the beam remained centered, the velocity meter would also underestimate true velocity and SV. However, the angle would have to exceed 37° to account for a 10% error which would be clearly noted on the M-mode display. The most likely cause for any overestimation in SV change with LBNP is the inherent cut-off frequency of the high-pass filters to avoid acoustic reflection by movement artifacts of the vessel walls (1) and therefore the minimum detectable velocity which is constant (5 cm/sec) becomes larger in proportion to the true SVI when the latter is small. Assuming a systolic

ejection period of 0.3 sec this effect could account for 9% of the drop in SV between baseline and 8 min. For subsequent work one may compensate for this inherent error source.

Overall, the PD method demonstrated dramatic and rapid transients in SV with LBNP which are reproducible and physiologically reasonable. The conversion of the relative changes to absolute values appears justified.

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TABLE D-1
Physical Characteristics and Performance

Subj.	Age yr	Ht cm	Wt kg	BSA m^2	AD cm	$\dot{V}_{O_2}$max ml/min/kg
1	34	170	75	1.86	2.6	35
2	31	183	68	1.89	3.1	40
3	30	178	72	1.90	3.2	45
4	27	183	75	1.96	2.8	34
5	24	175	64	1.78	3.0	62
6	35	179	72	1.90	3.3	52
$\bar{X}$	30	178	71	1.88	3.0	45
SD	4	5	4	.06	0.3	11

AD: aortic diameter; $\dot{V}_{O_2}$max/kg: aerobic capacity

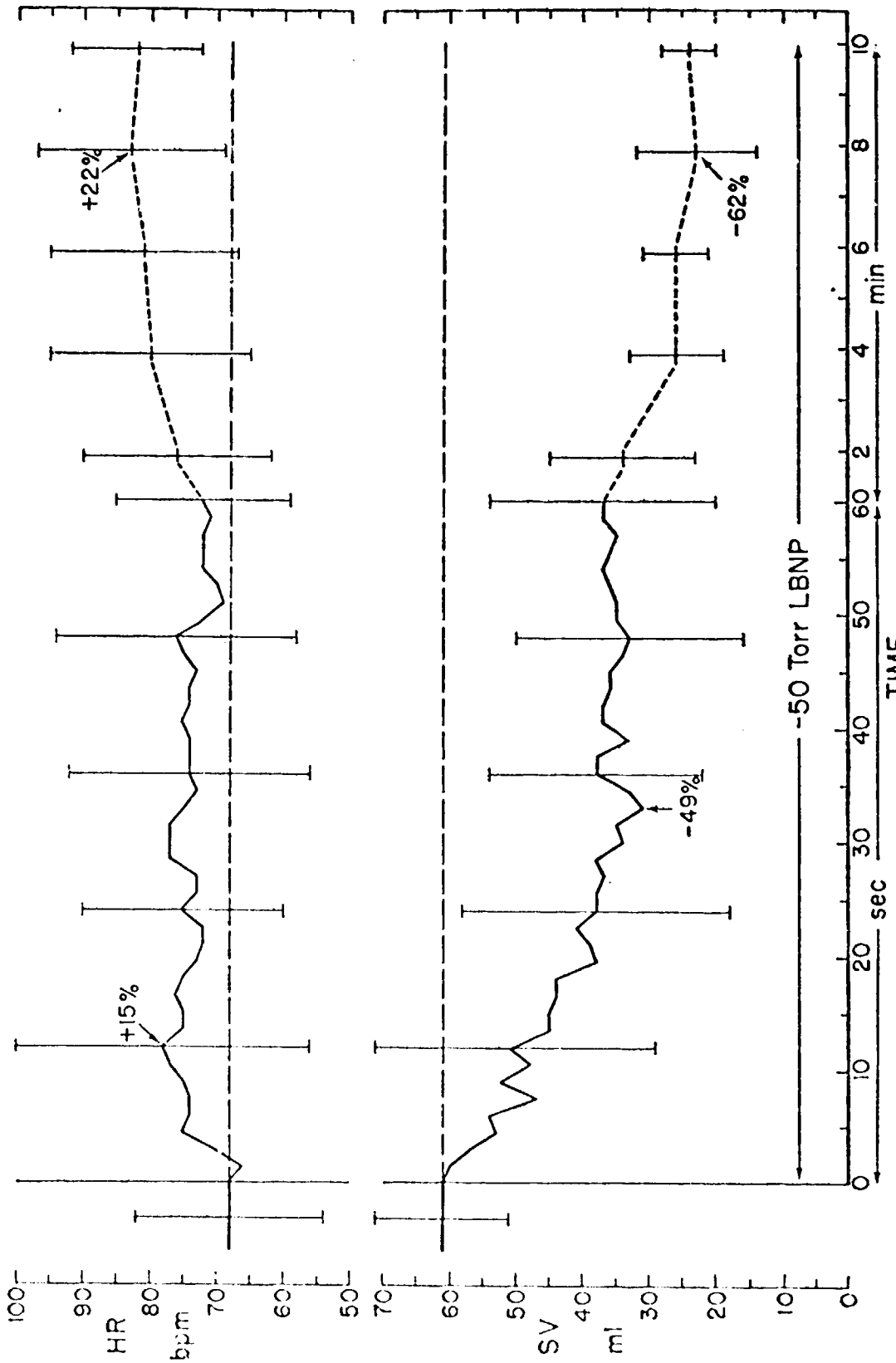

FIGURE D-1. Heart rate (HR) and stroke volume (SV) before and during LBNP.

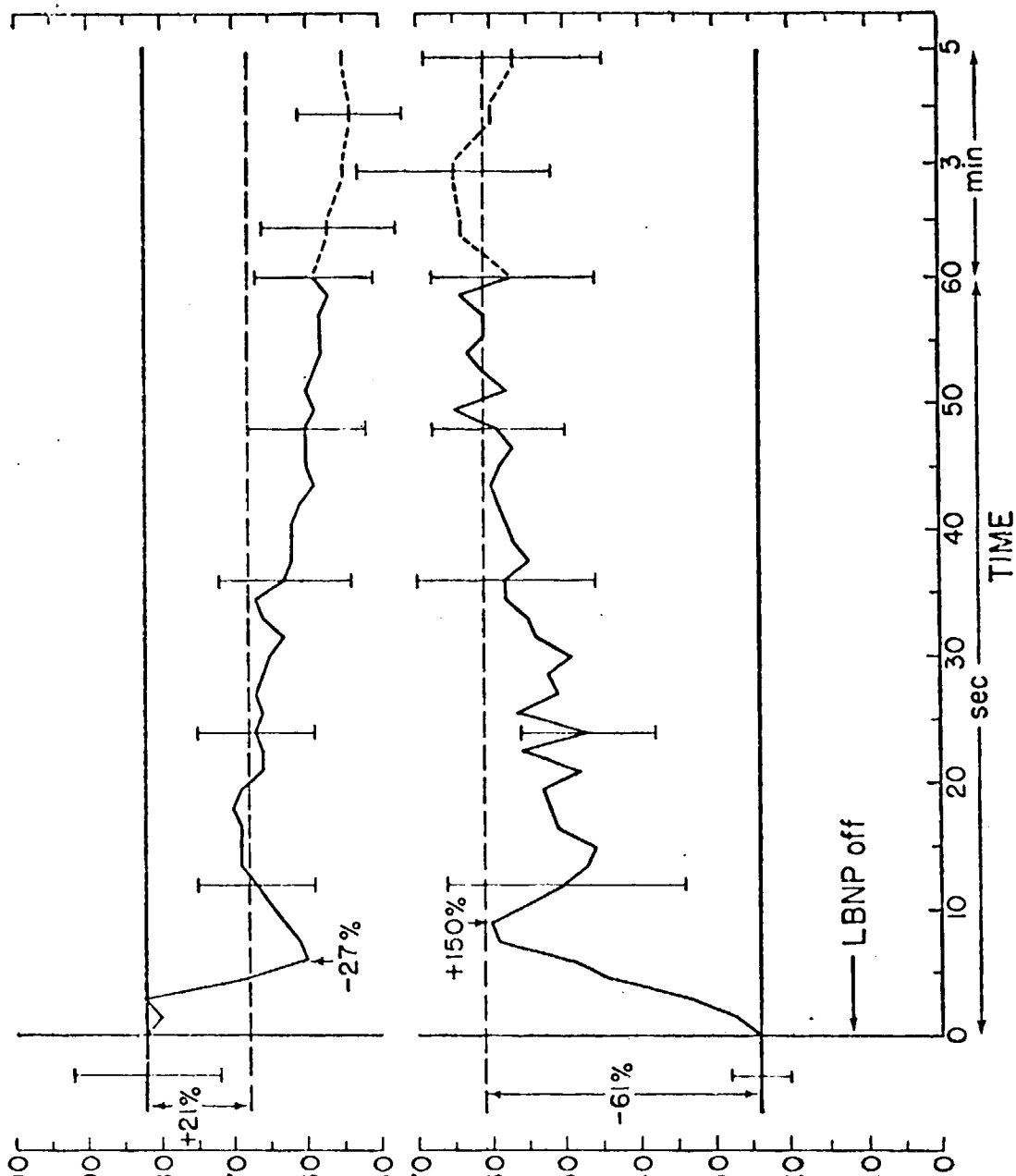

FIGURE D-2. Same as Fig. D-1 at the end of LBNP and after release.

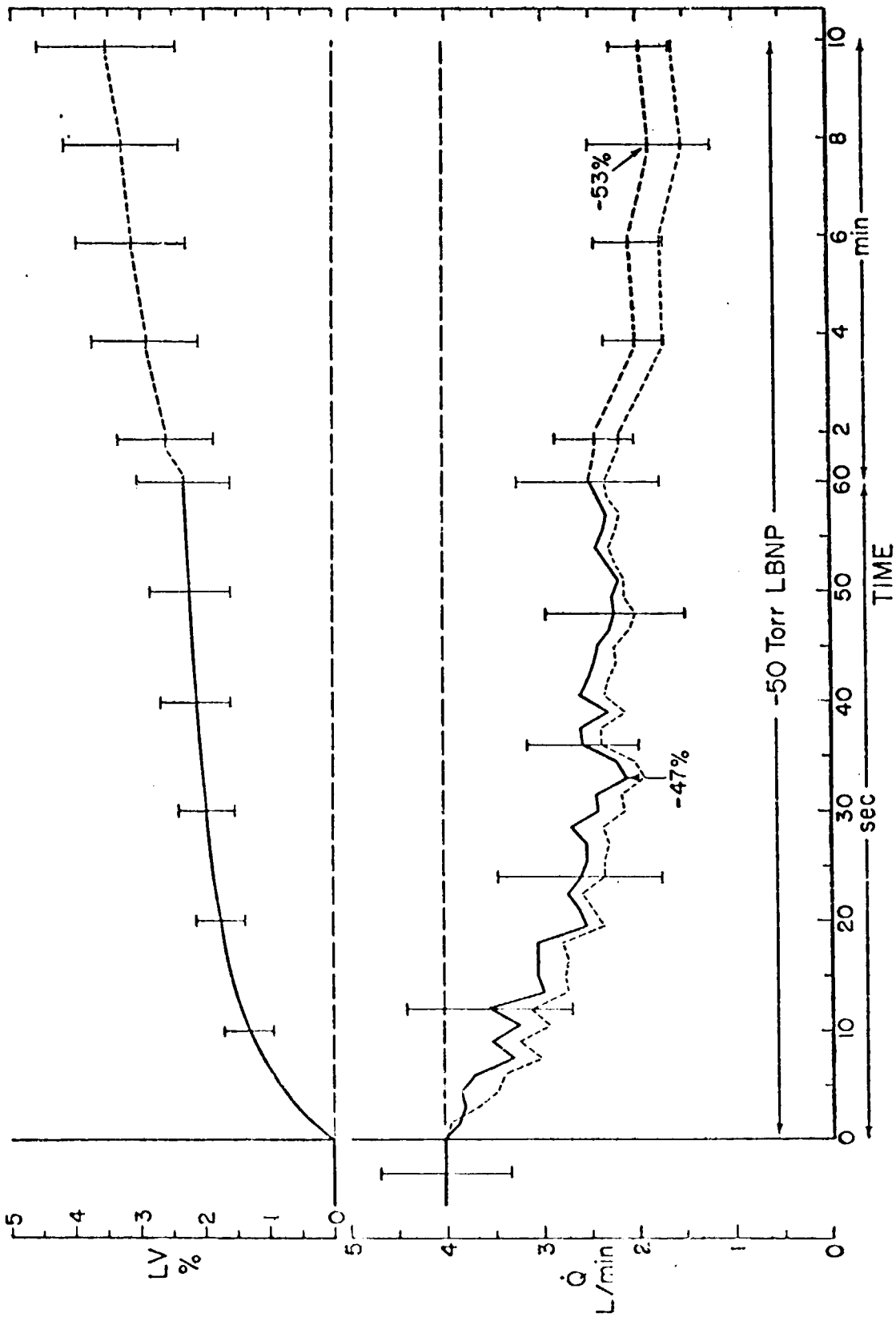

FIGURE D-3. Change in leg volume (LV%) and cardiac output ($\dot{Q}$) during LBNP. Interrupted curve shows $\dot{Q}$ calculated for constant heart rate.

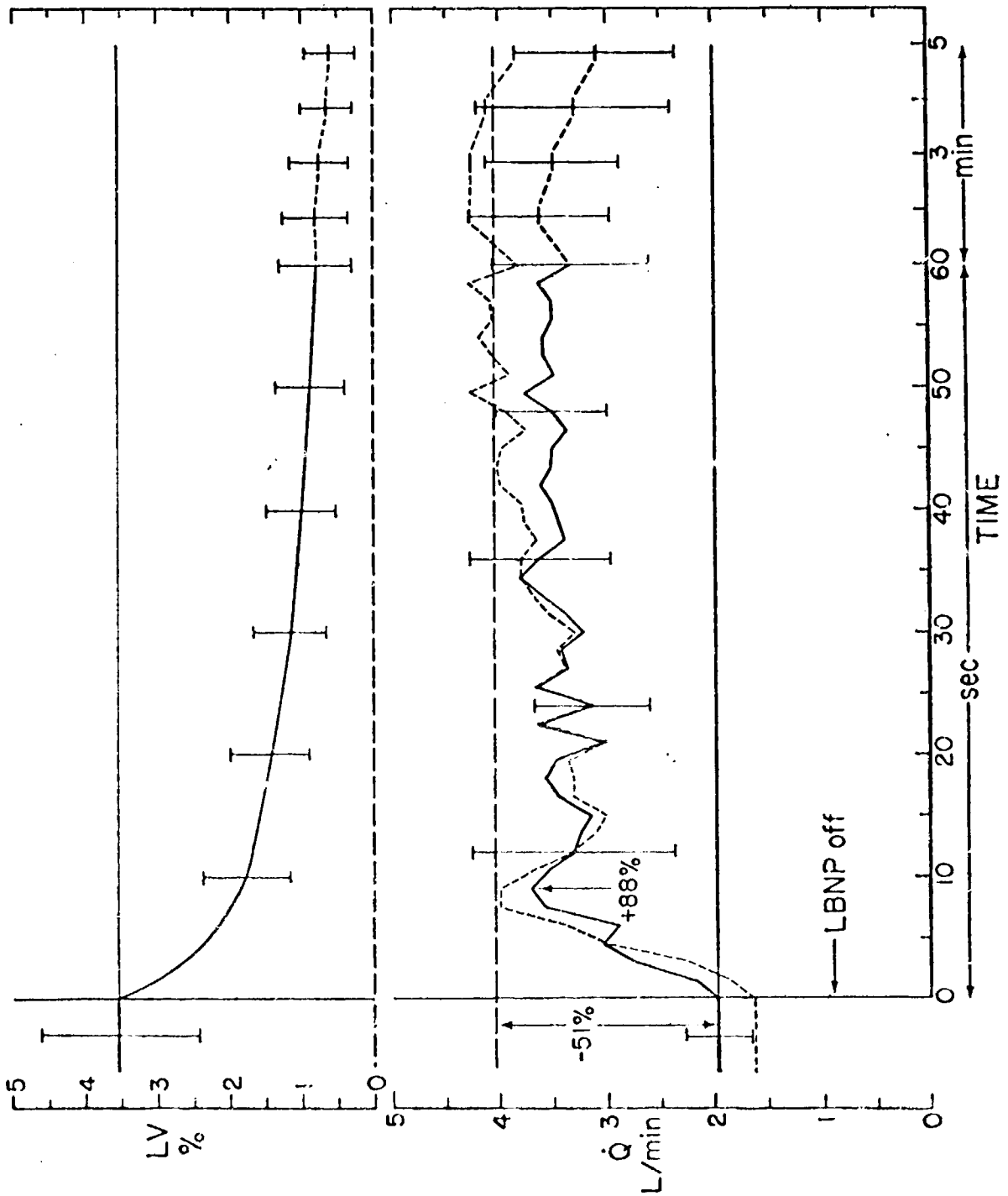

FIGURE D-4. Same as Fig. D-3 at the end of LBNP and after release.

PART E

CHANGES IN CARDIAC OUTPUT AND TIBIAL ARTERY FLOW DURING AND AFTER PROGRESSIVE LBNP

N81-20712

SUMMARY

A 3.0 MHz pulsed Doppler velocity meter (PD) was used to determine blood velocities in the ascending aorta from the suprasternal notch before, during and after progressive 5-min stages of LBNP in 7 subjects. Changes in stroke volume (SV) were calculated from the systolic velocity integrals. A unique 20 MHz PD was used to estimate bloodflow in the posterior tibial artery. With -20 Torr mean SV fell 11% and then continued to decline by 48% before LBNP was terminated. Mean tibial flow fell progressively with LBNP stress, due to an increase in reverse flow component and a reduction in peak forward flow and diameter. SV increased and HR fell dramatically during the first 15 sec of recovery. LBNP was terminated early in 2 subjects because of vasovagal symptoms (V). During V the SV rose 86% which more than compensated for the drop in HR. This implies that V is accompanied by a paradoxical increase in venous return and that the reduction in HR is the primary cardiovascular event. During the first 15 sec of recovery these 2 subjects had a distinctive marked rise in HR reminiscent of the Bainbridge reflex.

INTRODUCTION

The redistribution and alteration of central and peripheral bloodflow in man during gravitational stress has been extensively studied. The problems with measuring these transients during or after the removal of gravitational stress have been that the techniques were often invasive or required respiratory maneuvers which altered pulmonary bloodflow or contained assumptions of respiratory and circulatory steady states which are not applicable to transients. The recent development of non-invasive techniques to estimate cardiac output ($\dot{Q}$) and left ventricular stroke volume (SV) are potentially superior. A suitable method is that of pulsed Doppler echocardiography (PDE) whereby centerline blood velocities in the ascending aorta can be continuously monitored beat-by-beat. Simultaneous bloodflow changes in specific vessels in the lower extremities during LBNP have not been directly measured because they are inaccessable to precise placement of measuring devices. These bloodflows have been inferred from forearm or hand measurements. Appropriate pulse Doppler velocity meters with transcutaneous transducers are now also available to obtain these bloodflows. The purpose of this study was to noninvasively determine the relative changes in SV, $\dot{Q}$, and bloodflow in the posterior tibial artery during progressive LBNP stress and after termination of the stress (T) and to determine whether vasovagal presyncope (V) produced any unique variations in these responses.

METHODS

Seven males served as subjects (Table E-1). The means (±SD) for age, body surface area and $\dot{V}_{O_2}$max were 31(3)yr, 1.88(.09)m^2, and 50(8)ml/min/kg respectively. The LBNP apparatus and procedures have been described previously (Part A). LBNP was applied in 5-min stages, increasing from -20 to -60 Torr in 10-Torr increments. The subjects' response to LBNP was monitored for imminent V with continuous recordings of leg volume (LV) by Hg strain gauge, heart rate (HR) and arm blood pressure (BP) each min. Two subjects developed clear signs of V after 3 min at -60 Torr as BP and HR fell before T (Group S). One subject was terminated after 7 min at -50 Torr due to complaints of nausea with no bradycardia. The remaining 4 subjects completed the protocol, with 2 of them going an additional 5 min at -60 Torr without V. The latter 5 were grouped together (N) since their central circulatory responses were similar during LBNP and after T.

A 3.0 MHz PD (ATL, Model 500A, Mark IV) was used to determine aortic blood velocities at selected times (1, 10). PDE allows a specific flow region (sample volume) to be chosen by varying the sample gate or depth control to prevent the reception of extraneous flow information (Fig B-1, page 48). The transducer was an ATL medium-focus crystal with a focal beam width of approximately 4.0mm (See Part B, page 39 for details). It was manually placed and held in the suprasternal notch with the beam angled toward the heart, co-axial to the flow stream at a beam angle of 0 ± 15°. The Doppler frequency shift is converted by the calibrated audio spectrum decoder (zero-crosser) to a voltage proportional to the spatially-averaged velocity. A typical waveform is shown in Fig 1. The systolic velocity integral (SVI) is proportional to SV (3). The true representation of SV by SI is critically dependent upon maintaining the sample volume in the vessel

center by careful transducer manipulation to ensure an optimal audio signal and maximal SVI on the visual display. Relative SV and $\dot{Q}$ were obtained from SVI and SVI x HR for the same beat (aortic diameters were not measured in this series). Ten to 15 consecutive beats were averaged for each subject after 4 min at each LBNP stage, with continuous recordings from 10 sec before to 30 sec after T.

Tibial artery blood velocities were obtained with a unique 20 MHz pulse Doppler velocity meter (5) which is similar in principle to the VD. A PZT-5A 1.0mm^2 piezoelectric crystal was mounted to a diaphoretic EKG electrode at approximately 30° to the electrode plane, which was attached to the foot prior to entry into the LBNP box. A typical recording is shown in Fig E-1 along with a vessel scan obtained by altering the range-gate to determine the diameter and confirm the sample volume being in the centerline flow stream. Small foot movements could displace the beam from centerline and since the angle could not be determined precisely (but remained constant), only relative changes in velocity characteristics are described which were deemed to be valid based on visual and auditory screenings of the signals. Two flow recordings and one scan were attempted at each LBNP stage. Hardcopy aortic and tibial velocity signals were processed with the aid of a digitizer linked to a microcomputer.

RESULTS AND DISCUSSION

Relative changes in Fig E-2 were computed from mean values of HR, SV and $\dot{Q}$. S responded to the first 3 stages of LBNP with a significantly higher HR than N ($p < .02$) and a larger percentage fall in SV at -20 and -30 Torr, although S had lower baseline values for both. The higher HR served to return $\dot{Q}$ almost to baseline prior to V whereas N continued to decline to -41%. The divergence in $\dot{Q}$ was statistically significant after -30 Torr ($p < .02$). Pulse pressure fell linearly and equally in both groups to 53% of baseline in S prior to V and in N before T with no change in mean BP. This suggests that S had a more responsive baroreceptor or cardiopulmonary reflex to maintain $\dot{Q}$ which may have contributed to V onset. Although the relative fall in SV was about 50% for both groups prior to V or T, group S had a significantly smaller absolute SV prior to V than N (30% lower) since baseline was also lower. A smaller ventricular volume can augment the Bezold-Jarisch reflex whereby vagal fibers in the ventricular wall are stimulated by mechanical distortion to produce a dramatic fall in HR and loss in arterial tone (11). When V occurred (Fig E-2) there was a rapid drop in HR of 20 bpm without loss of consciousness before T, with SV increasing and $\dot{Q}$ actually rising 34% above the pre-LBNP baseline as BP fell precipitously. This points to a marked increase in venous return with LBNP still applied. This blood must have been moblized from the venous capacitance system by venoconstriction which has been shown to occur during V (4). Since LV rose about equally until T in both groups by about 5%, and no decline was noted during V, it would suggest that the additional aortic flow during V came from the splanchnic region which maintains its volume during LBNP (12). SV and $\dot{Q}$ are thought to decline with V, but that occurs only after the splanchnic region is depleted.

After T, markedly divergent response patterns were noted in S and N. The HR in S showed a rise and fall in the first 15 sec, while in N the usual sudden bradycardia occurred, presumably due to baroreceptor stimulation (10). LV showed the usual rapid decline after T in all subjects (8, 10). The HR rise in S is reminiscent of the controversial Bainbridge reflex whereby intravenous volume loading produced an increase in HR (6). Since venous return rose in all subjects after T with the return of pooled blood from the legs it suggests that V produced an "unloading" or blocking effect on the normal bradycardia seen in N (2). The reduction in HR for the first 15 sec of recovery correlated inversely with the HR just prior to T ($r = -.92$, $p < .005$), which has also been noted in animals (6). The response of HR thus serves as a mechanism to maintain or increase SV during volume loading of the heart. If HR is initially low as in S, SV will not be reduced because filling is completed early in diastole and when HR is high, further tachycardia would reduce $\dot{Q}$ because of incomplete filling. This optimization of HR during a rise in venous return seems evident from the nearly identical pattern in the rise of SV after T in both groups above the value prior to T. This feedback loop of HR and SV probably originates in the atria (7). As a result of the equal response of SV and divergent courses in HR, $\dot{Q}$ was markedly increased above baseline in S during the first 30 sec after T, but rose in linear fashion to baseline after 20 sec in N. This must mean that venous return and consequent aortic flow were greater in S than N at this time as well. The rise in $\dot{Q}$ for the first 30 sec accounted for 1.7 and 0.8 L of blood passing through the aorta in S and N respectively, assuming 5 L/min for baseline $\dot{Q}$ in all subjects. Since LV contributed equally in both groups, the extra 0.9 L of blood in S could have originated from the splanchnic region which can hold about 25% of the blood volume. Splanchnic

venoconstriction presumably began with the onset of V (which preceeded T by only 10 to 15 sec), but contributed the majority of the volume after T.

The characteristics of tibial artery flow are summarized in Fig E-3 with means and standard errors, whereby the times were averaged for all subjects since N and S did not differ consistently and no measurements were obtained during V. Flow dropped acutely by 51% at -20 Torr without any change in diameter, but the latter decreased by 23% at -30 Torr reflecting vasoconstriction with minor fluctuations during the remainder of the test, while flow declined progressively to -80% at -60 Torr. Thus vasoconstriction was only partly responsible for the reduction in flow and other factors such as impedance of venous outflow by reversal of the venous pressure gradients must be involved. This is supported by characteristic changes in the velocity patterns. Peak forward flow dropped by 50% during the test, while the reverse component became a larger fraction of the total, further reducing net flow (Fig E-1 and E-3). This is typical of augmented downstream impedance, as is the increase in pulsatility index (P-P/Mean). As a result, with progressive LBNP bloodflow in the legs is at a minimum until LBNP is released. This supports our earlier suggestion of blood sequestration in the lower body during LBNP from indirect measurements of hemoconcentration (9).

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TABLE E-1
Physical Characteristics and Performance

Subj.	Age yr	Ht cm	Wt kg	BSA m^2	$\dot{V}_{O_2}$max ml/kg/min	LBNP Stress Torr x min
1	25	175	64	1.78	62	1300
2	33	175	62	1.75	57	550
3	35	179	72	1.90	52	1300
4	32	183	75	1.96	50	932
5	30	178	74	1.92	44	862
6	30	187	73	1.98	44	1000
7	32	183	68	1.89	40	1000
$\bar{X}$	31	180	70	1.88	50	
SD	3	5	5	.09	8	

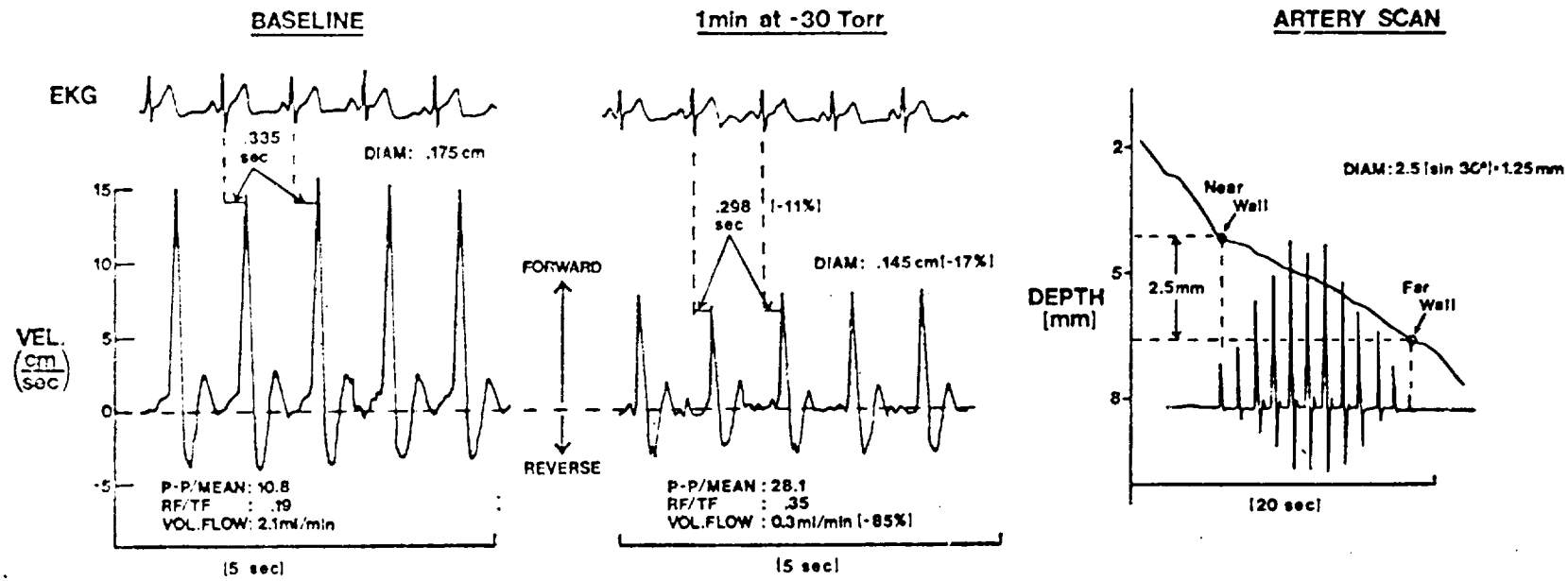

FIGURE E-1. Velocity waveforms in posterior tibial artery and depth scan for determining diameter. P-P/Mean: Peak-to-peak height/mean height, RF/TF: Reverse flow/total reverse and forward flow (by integration), Vol. flow: perfusion.

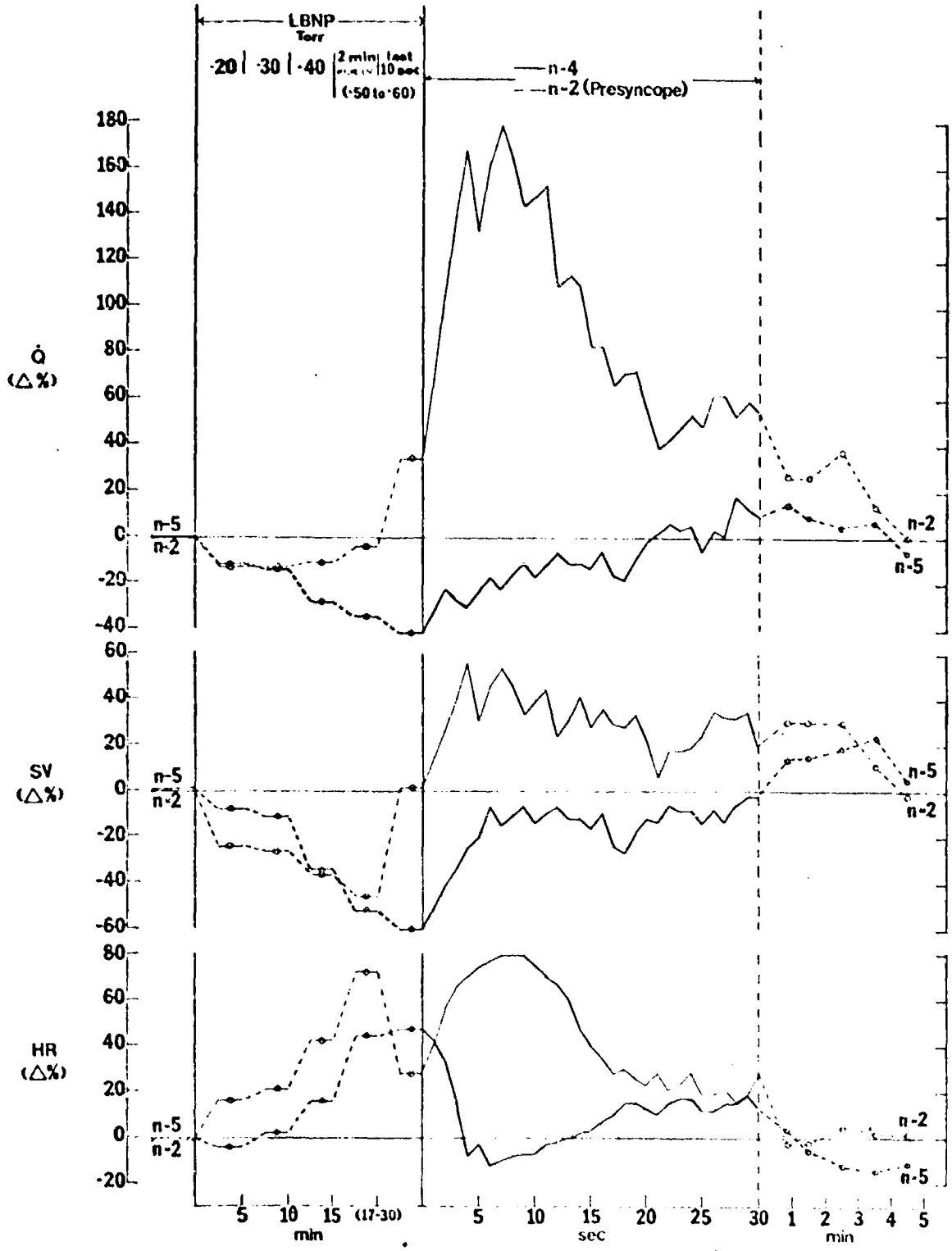

FIGURE E-2. HR, SV and $\dot{Q}$ during and after LBNP (beat-by-beat for 30 sec) as percent of baseline. N=2: subjects who developed clear vasovagal symptoms, N-5 or 4: no symptoms.

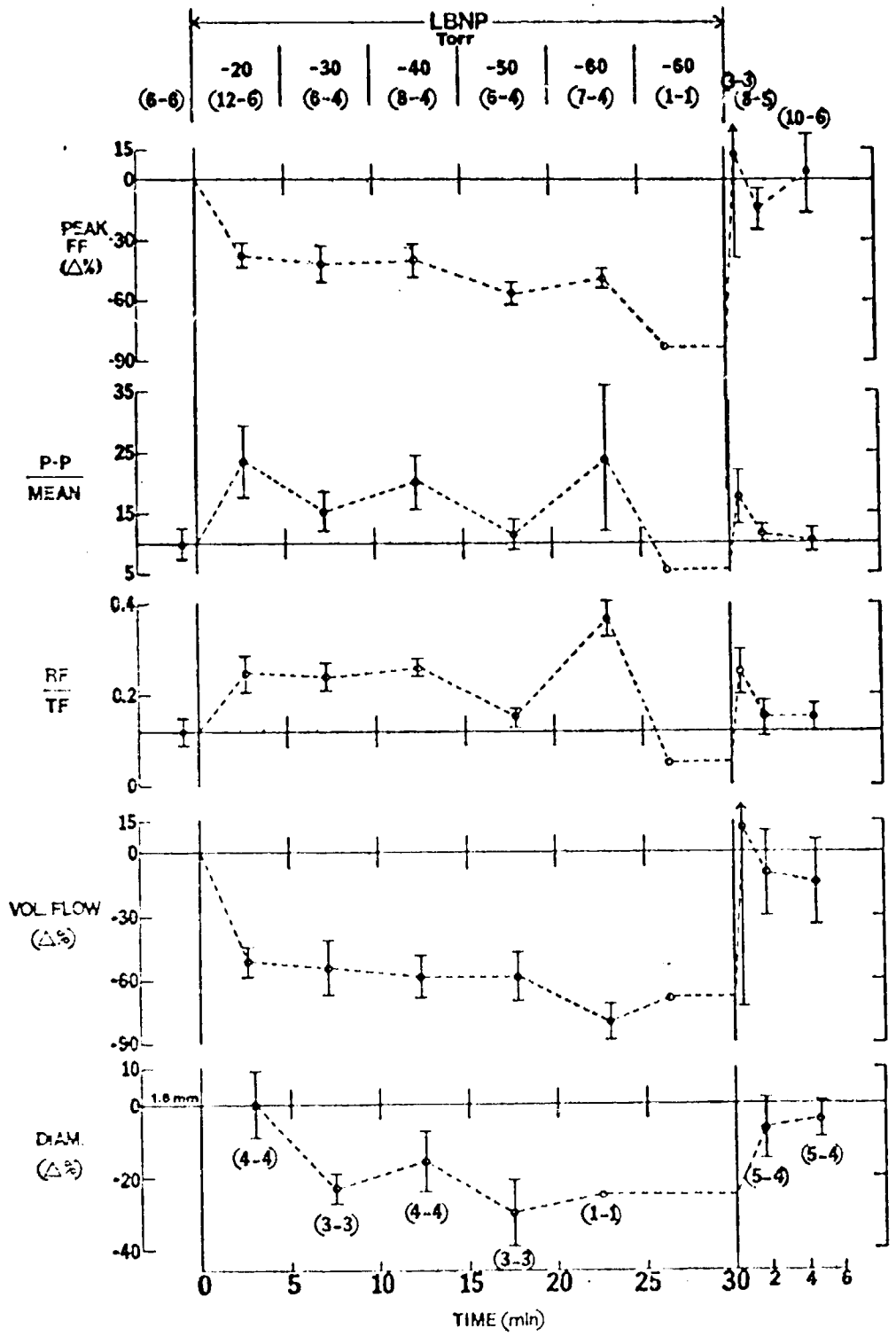

FIGURE E-3. Tibial artery bloodflow characteristics with LBNP. Parentheses: No. of observations-No. of subjects, FF: Forward flow velocity, see Fig. E-2.