VALIDATION OF SPECTRAL ANALYSIS AS A NONINVASIVE TOOL TO ASSESS AUTONOMIC REGULATION OF CARDIOVASCULAR FUNCTION

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ABSTRACT

A major focus of our program has been to develop a sensitive noninvasive procedure to quantify early weightlessness-induced changes in cardiovascular function or potential dysfunction. Forty studies of healthy young volunteers (10 men and 10 women, each studied twice) were conducted to determine changes in the sympatho-vagal balance of autonomic control of cardiovascular regulation during graded headward and footward blood volume shifts. Changes in sympatho-vagal balance were classified by changes in the mean levels and spectral content of cardiovascular variables and verified by changes in circulating levels of catecholamines and pancreatic polypeptide. Possible shifts in intra/extravascular fluid were assessed from changes in hematocrit and plasma mass density while changes in the stimulus to regulate plasma volume were determined from plasma renin activity (PRA). Autonomic blockade was used to unmask the relative contribution of sympathetic and parasympathetic efferent influences in response to 10 min each of 0, 20 and 40 mmHg lower body negative pressure (LBNP) and 15 and 30 mmHg positive pressure (LBPP). The combination of muscarinic blockade with graded LBNP and LBPP was used to evoke graded increases and decreases in sympathetic activity without parasympathetic contributions. The combination of beta blockade with graded LBNP and LBPP was used to produce graded increases and decreases in parasympathetic activity without beta sympathetic contributions. Finally, a combination of both beta and muscarinic blockades with LBNP and LBPP was used to determine the contribution from other, primarily alpha adrenergic, sources. Mean values, spectral analyses and time frequency analysis of R-R interval (HR), arterial pressure (AP), peripheral blood flow (RF), stroke volume (SV) and peripheral resistance (TPR) were performed for all phases of the study. Skin blood flow (SF) was also measured in other studies and similarly analyzed. Spectra were examined for changes in three frequency regions [low 0.006 - 0.005 Hz (LF), mid 0.05 - 0.15 Hz (MF), and high 0.15 - 0.45 Hz (HF)]. The primary objective of the study was to indicate which changes in the mean values and/or spectra of cardiovascular variables consistently correlated with changes in sympatho-vagal balance in response to headward and footward fluid shifts. A secondary objective was to quantify the vascular and extravascular fluid shifts evoked by LBNP and LBPP. The principal hypothesis being tested was that headward fluid shifts would evoke an increase in parasympathetic activity and footward fluid shifts would evoke an increase in sympathetic activity both of which would be detected by spectral analysis and verified by circulating hormones.

Hematocrit (HCT), plasma mass density and plasma renin activity increased with muscarinic blockade and with LBNP, a response indicative of a plasma shift to extravascular spaces. Beta blockade alone or after muscarinic blockade had no effect on HCT or plasma mass density. With respect to intravascular fluid volume distribution, LBNP and LBPP produced sufficient upper body vascular fluid shifts to evoke appropriate autonomic regulatory responses. Catecholamines increased in response to LBNP and pancreatic polypeptide (PPP) increased in response to LBPP.

In men, at rest and at all levels of LBNP and LBPP, muscarinic blockade resulted in higher mean values of HR, AP, TPR and hand vascular resistance with concomitant decreases in SV, RF, CO and end diastolic volume. The effect of beta blockade was to decrease HR and AP in control and at all levels of LBNP and LBPP. Either beta or muscarinic blockade given alone, resulted in a decrease in AP during LBNP that was either small or not present in the unblocked LBNP cases.

In the resting state, HR spectral power in all frequency ranges was only slightly affected by beta blockade, but was much diminished by muscarinic blockade. The heart rate response to LBNP was

dominated by parasympathetic withdrawal in that the ratios of low to high frequency spectral powers, LF/HF, and mid to high, MF/HF powers were increased by LBNP and were unaffected by beta blockade. In the situations designed to evoke unopposed sympathetic and parasympathetic stimulation and withdrawal to regulate HR, we found that: 1) sympathetic stimulation resulted in an increase (with respect to resting control) in the (LF + MF)/HF spectral power ratio, with no changes in HF power, 2) sympathetic withdrawal resulted in a decrease in (LF + MF)/HF power ratio and a slight increase in HF power, 3) parasympathetic withdrawal resulted in an increase (with respect to resting control) in the (LF + MF)/HF power ratio and a large decrease in HF power, and 4) parasympathetic stimulation resulted in no change in (LF + MF)/HF power ratio or HF power.

In women, mean AP increased with either beta or muscarinic blockades. With muscarinic blockade alone, the increase in AP was due mostly to HR with a slight increase in TPR (SV decreased). With beta blockade alone, the increase in AP was due solely to TPR (HR decreased, SV did not change). The addition of beta to muscarinic blockade brought AP back toward control. Unblocked AP was well controlled during LBNP and LBPP: During LBNP, AP was maintained by increases in HR and TPR that countered the decreases in SV. After muscarinic blockade, the decreases in SV and the increase in TPR were slightly greater. After beta blockade the decrease in SV and increase in TPR were smaller. During LBPP, unblocked AP was maintained by slight decreases in SV and HR that countered increased TPR. After muscarinic blockade, the increase in TPR was greater.

When spectral data from women (1994 Progress Report) were compared with those from men (1993 Progress Report), the following differences were observed:

HORMONAL

1. Men had significantly higher ($p<.0001$) levels of hematocrit than did women indicating lower relative plasma volume in men. The lower relative plasma volume was not due to a reduced signal to retain plasma since men had slightly higher levels of PRA than did the women.

2. In the unblocked state, men had greater levels of PPP than did women. After muscarinic blockade the PPP level of men dropped to equal that of women.

3. Men had greater levels of epinephrine ($p<.01$) than did women, and slightly higher levels of norepinephrine indicating grater sympathetic dominance in men.

MEAN VALUES

1. Men had slightly lower unblocked HR (61 bpm) than women (67 bpm). After combined autonomic blockade HR's were 84 and 85 bpm, respectively, indicating that even though the intrinsic HR was the same, men had greater parasympathetic input in the unblocked state, perhaps to counteract the effects of the greater sympathetic activity. The balance of HR was however tilted toward sympathetic dominance in these men (see above).

2. Women had slightly lower (78 mm Hg) unblocked AP than men (83.5 mm Hg). After combined autonomic blockade, both pressures came to the same value (84 mmHg) via increased TPR in women (HR and SV changes offset each other).

SPECTRAL POWER

1. Men had significantly greater spectral LF power of SV, CO, TPR, RF and SF than did women indicating that these variables (but not HR and AP) could be used to provide noninvasive indices of autonomic balance to detect differences in young men and women.

2. Low, mid and high frequency spectral powers of HR were increased by beta blockade in women. Beta blockade did not effect HR spectral power in men.

3. High frequency spectral power of TPR was increased by muscarinic blockade in men and LF, MF and HF powers were increased by beta blockade in women indicating that women's TPR was normally buffered by beta vasodilation.

4. Men's low frequency spectral power of SV was decreased by muscarinic blockade indicating that muscarinic activity contributed to regulation of SV in men but not women.

In summary our study indicated that the balance of tonic beta adrenergic and muscarinic activity was different for men and women; women had indicators of increased parasympathetic dominance in the regulation of heart rate and men had indicators of sympathetic dominance in the regulation of HR and overall greater sympathetic dominance in the control of CO, SV, TPR, RF and SF.

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1.0 HYPOTHESIS AND OBJECTIVE

A major focus of our overall research program is to develop a sensitive noninvasive procedure to quantify early weightlessness-induced changes in cardiovascular function or potential dysfunction. We recognize that loss of orthostatic tolerance results from a plethora of reactions to the lack of the 1 g gravity vector. In dealing with this problem we have added, to conventional mean value analysis, spectral analysis techniques that will allow identification of spectral characteristics of certain cardiovascular parameters that appear to be sensitive indicators of change during simulated weightlessness. Based on results from previous studies (see **BACKGROUND** section) we began experiments to correlate changes in mean values and/or spectral characteristics with changes in the sympatho-vagal balance of autonomic control of cardiovascular regulation.

Normal human volunteers were noninvasively instrumented to continuously monitor heart rate, arterial pressure, stroke volume, respiration, peripheral blood flows, and peripheral resistance. The experimental protocol consisted of graded lower body negative (LBNP) and positive pressures (LBPP) in combination with beta adrenergic and mucarinic blockades that were used to evoke responses that were unequivocally sympathetic or parasympathetic in origin. The primary objective of the proposed study is to validate which changes in mean values and spectra of cardiovascular variables consistently correlated with changes in sympatho-vagal balance in response to headward and footward fluid shifts. The principal **hypothesis** being tested is that, with respect to short-term responses, headward fluid shifts would evoke an increase in parasympathetic activity and footward fluid shifts will evoke an increase in sympathetic activity. These changes in autonomic activity will be detected by spectral analysis and documented by appropriate autonomic blockade and independent assessment of autonomic activity from plasma levels of pancreatic polypeptide (parasympathetic) and catecholeamines (sympathetic).

2.0 BACKGROUND

Our research, past and current is designed to aid in the resolution of problems in cardiovascular regulation induced by weightlessness during spaceflight. Significant physiological responses to weightlessness include elevated resting heart rate, orthostatic intolerance (possibly leading to syncope) and higher submaximal oxygen consumption for equivalent workloads: situations that could compromise astronaut safety during flight or a postlanding emergency (Bungo 1985, Charles 1986).

2.1 Work by Other Investigators

In the last few years, the frequency content of cardiovascular variables has been added to the conventional mean value data base to quantitate interactions between sympathetic and parasympathetic activity in the regulation of cardiovascular function (e.g. Madwed 1991, Rimoldi 1990). These spectral analysis techniques determined that power in cardiovascular variables occurs in distinct spectral regions and that changes in power in these regions can be diagnostic for a variety of patho-physiological states. The regions defined by these studies are: 1) the respiration-linked rhythm of heart rate which is an indicator of vagal control and constitutes the high frequency (HF) component of a given spectral response, usually in the 0.15 to 0.45 Hz range and 2) a frequency range below 0.1 Hz which, with a sufficiently sensitive analysis technique, can be divided into a mid

frequency (MF) region (0.05 to 0.1 Hz) and a low frequency (LF) region (< 0.05 Hz). The predominant evidence is that the <0.05 Hz range is basically sympathetic (Madwed 1991). The 0. 05 to 0. 1 Hz range has been associated with sympathetic activity (Pagani 1991 and Rimoldi 1990) even though some investigators argued that this range might have a parasympathetic component as well (Saul 1990 and Grossman 1992). The apparent contradiction in interpretation of oscillations below the respiratory frequency could be a consequence of the different techniques used by these investigators.

The availability of information related to these spectral regions has opened new areas of physiologic inquiry. For example: 1) An increase in LF and a decrease in HF power (increasing the LF/BF ratio by as much as 20 times, Pagani 1986) has been determined for heart rate in response to tilt (Vybiral 1989), standing (Pomerantz 1985, Lindqvist 1990), mental arithmetic (Pagani 1991) and some forms of exercise (Pagani 1988), verifying not only an increase in sympathetic but a decrease in parasympathetic efferent activity in response to these stresses. 2) A shift in the LF/HF ratio to less than one has been determined in response to controlled breathing (Pagani 1986) indicating this stress enhances vagal modulation of heart rate. 3) Shifts in the relative powers in these frequency ranges have also recently become diagnostic for a variety of patho physiologic states; hypertension (Guzzetti 1988), ischemic heart disease (Kleiger 1987, Lombardi 1987), heart transplant rejection (Sands 1989), congestive heart failure (Saul 1988) and diabetic neuropathy (Lishner 1987).

2.2 Previous Work by the Present Investigators

Given the sensitivity of spectral analysis to detect changes in sympatho-vagal balance (based on the studies cited above and data presented below) we developed a research program to investigate the potential for using spectral analysis to predict the development of orthostatic intolerance in response to weightlessness.

The data presented below are results of applying spectral analysis techniques (in addition to standard measurements of mean changes) to young men subjects undergoing a short period of simulated weightlessness. The protocol consisted of: 1) a supine resting period followed by a series of step and oscillatory (sinusoidal) LBNP inputs, 2) two hours in the launch position, 3) 20 hours of 6° head down bedrest plus Lasix, 4) a return to supine rest, followed by 5) a repetition of the same step and sinusoidal LBNP inputs. The results from this study are summarized below.

Head down tilt spectra of cardiovascular variables before, during and after the launch position followed by 6^0 head down tilt (HDT, our model of weightlessness).

a. In one analysis we investigated the power spectra (autoregression) of cardiovascular variables of 10 normal men in the supine position before and after simulated weightlessness. The principal finding was that after 22 hrs of simulated weightlessness there were changes in cardiovascular power spectra that were statistically significant and supported our original hypothesis that, after initial adjustments to the headward fluid shift, the long-term response to fluid volume loss would include increased sympathetic neural activity and decreased parasympathetic activity.

b. A separate analysis from that above, was conducted to follow changes in mean values in addition to determining the spectral content of cardiovascular variables during, as well as before and after, the simulated weightlessness. An important finding was that the launch

position caused major changes in arterial pressure (AP) power spectra but did not affect mean AP. Statistical analysis confirms that the power in the low frequency (<0.04 Hz) range in these subjects increased from supine control when the subjects were in the launch position and remained elevated ($p < 0.05$) during 6° HDT and after the return to supine control. In addition responses to the launch position were similar to but more rapid than the overall responses to 6° HDT.

Cardiovascular responses (power spectra) of humans to lower body negative pressure (OLBNP).

This study defined the spectral responses of 10 normal men by examining changes in cardiovascular spectra induced by OLBNP at various input frequencies. From spectral analysis of the responses, we determined that most of the power was at the first harmonic of the LBNP input frequency and that the first harmonic was sufficient to describe the responses of most variables. The net result was that the first harmonic data could be used to separate active, neurally mediated responses from those that resulted from passive fluid shifts.

The effect of simulated weightlessness on the cardiovascular of humans to OLBNP.

The results of analysis of differences in the mean values of cardiovascular variables after short-term weightlessness were explored. The major findings from this study were that peak-to-peak oscillations in heart rate (HR), central venous pressure (CVP) and calf circumference (CC) decreased with increasing frequency. Bedrest increased the amplitudes of oscillations of HR while decreasing the amplitude of CC. The most pronounced difference between sinusoidal LBNP-induced responses before and after bedrest was an increase in the magnitude of HR oscillations at 0.01 Hz which emphasized inappropriate timing of peripheral responses to LBNP-induced blood pooling at this frequency.

Cardiovascular responses (average and power spectra) of humans to step inputs of LBNP before and after simulated weightlessness.

Spectral analysis (autoregression) of the response to LBNP indicated that spectral power in arterial pressure and heart rate at ~0.05 Hz increased as greater levels of LBNP were applied and that the power was increased even more in the simulated weightlessness response to LBNP. Spectral power in radial flow was dramatically increased by simulated weightlessness in control and at all levels of LBNP. Changes in spectral power in the breathing frequency indicated that increasing levels of LBNP decreased the frequency of breathing.

Findings from all of the above studies indicate that:

* At rest, there were significant changes in the spectral content of cardiovascular variables following 22 hrs of simulated weightlessness. These changes indicated a shift of sympatho-vagal balance toward the sympathetic branch of the autonomic nervous system.

* Spectral analysis of the cardiovascular response to OLBNP could be used as a sensitive tool to assess the timing of neurally mediated responses to this type of time-dependent provocation.

- Step increments of LBNP increased low frequency spectral power, indicating a shift of sympatho-vagal balance toward the sympathetic branch of the autonomic nervous system.
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3.0 RATIONALE FOR THE PRESENT EXPERIMENTS

The primary goal of the current study was to determine the spectral components of arterial pressure, heart rate, peripheral flow, stroke volume and peripheral resistance that are of sympathetic (beta) and parasympathetic (muscarinic) origin. Data were taken from subjects in supine rest, and during graded LBNP and LBPP and oscillatory LBNP. By inference the spectral components that remain after combined beta and muscarinic blockades will be ascribed to alpha adrenergic and/or non neural origins.

Graded LBNP and LBPP were used because of their capacity to evoke hypo and hypertensive responses respectively. This approach allowed us to dissect the vascular (limb and whole body peripheral resistance) myocardial (stroke volume) and pacemaker (heart rate) responses into their relative beta adrenergic, and muscarinic components.

The protocol also offered the potential for examining baroreflex regulation of blood pressure. Curves measuring the sensitivity of the baroreflex to evoke heart rate and peripheral resistance changes in response to these graded changes in venous return are being determined for each state of blockade. Correlation of the information gained from the characteristics of these baroreflex curves with the spectral content of these variables has the potential to provide new information about the relative sympathetic and parasympathetic components of the curves.

4.0 METHODS

4.1 Experimental Protocol

DAY 1

Autonomic components of the cardiovascular response to LBNP and LBPP

8:00	Subject admitted to UKMC Clinical Research Center.	
9:05	Subject escorted to experiment room and data recorded: weight, height, calf circumference, age, etc.	
9:15	Subject supine, instrumentation placement began: arterial pressure (Finapres), thoracic impedance (BoMed), ECG (BoMed), calf circumference (Hokansen), Doppler aortic flow (Exerdop), radial artery flow (Parks) and skin perfusion (Perimed).	
9:30	Supine resting control*	The order of these LBNP & LBPP applications was
9:40	-20 mmHg	
9:50	Return to atmosphere	

10:00	-40 mmHg*	}	randomized for each subject. Subsequent tests on the subject were administered in the same order as during this unblocked sequence.
10:10	Return to atmosphere		
10:40	+ 15 mmHg		
10:50	Return to atmosphere		
11:00	+30 mmHg*		
11:10	Return to atmosphere		
11:40	Lunch		

NOTE: The order of β and muscarinic blockades given below was alternated in each subject:

12:00 Bolus injections of isoproterenol 1, 5, 10 or 50 ug IV were given until a 20 bpm increase in heart rate was observed.

12:05 Infused the β antagonist in 0.05 mg/kg increments (IV) to 0.2 mg/kg or until next dose produced no decrease in heart rate. Isoproterenol injected, same dose as above. Propranolol increased if heart rate responded to isoproterenol, time allowed for steady state to be reached.

12:15 Rest, LBNP and LBPP protocols repeated, propranolol added as needed to maintain β blockade.

14:25 β blockade tested to assure full blockade during the preceding test sequence.

14:30 The muscarinic antagonist atropine sulfate infused in 0.005 mg/kg increments (IV) up to 0.04 mg/kg or until subsequent dose produced no further increase in heart rate.

14:35 The β blockade reinstated with appropriate agonist testing. With an established β blockade, a decrease in heart rate was used to indicate the loss of efficacy of muscarinic blockade and appropriate dosages of atropine sulfate were administered. Since the half-life of atropine is 1 hr, atropine sulfate was administered on an hourly basis throughout the subsequent test protocol.

14:40 Rest, LBNP and LBPP protocols repeated, propranolol and/or atropine sulfate were added as discussed above in order to maintain blockades.

16:50 Fluid balance checked, venous catheter removed, subject dismissed.

*Ten ml of venous blood was drawn in the last 2 min of each period and assayed for: HCT, plasma renin activity, pancreatic polypeptide, norepinephrine, epinephrine and plasma mass density. These hormonal analyses were performed to independently assess correlates of plasma volume changes (hematocrit, plasma renin activity and plasma mass density), sympathetic stimulation (epinephrine and norepinephrine) and parasympathetic stimulation (pancreatic polypeptide) (Lake 1976, Schwartz 1983, Hoffler 1977, Fortney 1991).

DAY 2 (one week later)

Same as Day 1 except that which ever blocker was given first on Day 1 was given second on Day 2

4.2 Data Analysis

Data from these experiments are currently being analyzed to examine the effects of LBNP and LBPP at each level of autonomic blockade.

The analysis of data includes: 1) mean level of each variable, 2) slopes of these variables in response to LBNP and LBPP, 3) baroreflex sensitivity and 4) spectral content of each variable as determined by both parametric and nonparametric techniques. In the case of spectral power, the spectra are broken apart into specific frequency ranges and comparisons are being made within these ranges.

4.2.1 Statistical Analysis

A two-factor, repeated measures analysis of variance (ANOVA) was used to assess effects of: 1) stress (none, LBNP or LBPP), 2) level of blockade (unblocked, beta, muscarinic and combined), and 3) interactions between these factors on each cardiovascular variable. Comparisons between men and women were made by adding a gender factor to the ANOVA.

4.2.2 Spectral Estimation

All signals were digitized on-line at the rate of 200 samples/second. A computer program was used to detect peaks of the R wave in the ECG, from which R-R intervals were computed. A new piece-wise constant time series was constructed using these R-R intervals by holding the value of the R-R interval constant within each cardiac cycle. The resulting piece-wise constant series was sampled at the rate of 5 samples/second. All other variables were processed synchronous with cardiac rhythm: the arterial blood pressure signal was integrated with each cardiac cycle to obtain beat to beat mean blood pressure, the beat-to-beat mean, systolic and diastolic pressures were used to construct piece-wise constant time series which were sampled at the rate of 5 samples/second. The remaining variables were integrated within each cardiac cycle, and new time series were calculated from the beat to beat integrated values, similar to R-R interval and blood pressure time series. From the time series sampled at 5 samples/second, outliers, PVC'S, and artifacts were removed by using linear interpolation between the data preceding and succeeding these periods.

Stationary Spectral Estimation

During each experimental run (i.e. control, LBNP, LBPP etc.) stationary data segments were selected by visual inspection, from which spectral estimates were computed using a parametric (autoregressive, AR) and a non-parametric (averaged periodograms, WELCH) technique.

The AR model coefficients were computed by solving the Yule-Walker equations using the Levinson Recursion (Kay 1981). Model orders were selected to be the highest of those predicted by using the Akaike Information Criterion (AIC) (Akaike 1971, Kay 1981), and those predicted by using a test time series consisting of a sinusoid (0.02 Hz) and Gaussian noise with ~10 dB SNR. Data were sectioned into approximately 100 second long segments. Using the same model order for all segments, an AR model was fitted for each segment, and the resulting AR coefficients were averaged to obtain an average AR model for that experimental run. From the complex conjugate poles of the averaged AR models, spectral component powers and frequencies were computed using the method of partial fractions (Johnson 1978).

To compute non-parametric spectral estimates, data were sectioned into approximately 100 second long segments with 50% overlap. A Hanning (Bendat 1986) window was used to reduce

truncation errors. The Discrete Fourier Transforms of all segments were averaged to produce smoothed spectral estimates. Spectra from heart rate, blood pressure, and to a lesser degree all other variables, displayed distribution of power in three frequency regions, centered at about 0.03 Hz (Low Frequency, LF), at about 0.1 Hz (Mid Frequency, MF) and at about 0.25 Hz (High Frequency, HF). Hence, spectral powers were quantified or binned into these three regions. The LF, MF and HF bandwidths were selected as 0.006-0.05 Hz (LF), 0.05-0.15 Hz (MF), and 0.15-0.45 Hz (HF). The spectral powers were computed 1) for AR spectra, adding the power of all spectral components that had their center frequencies within LF, MF or HF bandwidths, and 2) for WELCH spectra (Bendat 1986), by integrating the spectrum within the LF, MF and HF bandwidths.

Non-Stationary Time-Frequency Spectral Estimation

To track the evolution of the spectra during various physiologic interventions (e.g. during administration of muscarinic blockers, application of LBNP or LBPP etc.), we obtained the time-frequency representations by computing the smoothed pseudo Wigner distributions (Hlatwatsch 1992) from the time series sampled at 5 samples/second.

5.0 RESULTS

The information reported below shows results from 40 studies; 20 studies of 10 women (66 $\pm$ 2.5 kg, 162 $\pm$ 2 cm and 25 $\pm$ 1 yr) and 20 studies of 11 men (73.5+ 1.8 kg, 175 $\pm$ 1.4 cm and 24.9 $\pm$ .8 yrs). For one subject, the second study could not be performed, therefore, the second experiment was conducted on an age/physical characteristics-matched subject. Thus the total data set is reported as a group of 10 men and 10 women, each studied twice. Results of hormonal assays, mean values and cardiovascular spectra from subjects in each state of autonomic blockade at rest and during 10 min sessions of lower body negative and positive pressures will be presented. Additional major results have been, or will be, summarized in manuscripts or presented at meetings (see Appendix).

5.1 Hormonal Analyses

In order to validate spectral power in certain frequency ranges as reflecting changes in autonomic activity, several hormonal analyses were performed. The results of assays to indicate changes in plasma volume (HCT and plasma mass density), plasma volume regulation (plasma renin activity), parasympathetic activity (pancreatic polypeptide), and sympathetic activity (catecholamines) are given below.

Plasma volume as indicated by changes in plasma mass density (Hinghofer-Szalkay) were less consistent than those seen for hematocrit but tended to reflect the same changes. We examined hematocrit in six cases: unblocked control [pre beta (PB)], beta blocked (B), beta plus muscarinic blockade (BM), unblocked control [pre-muscarinic (PM)], muscarinic blockade (M) and muscarinic plus beta blockade (MB). Figure 1 shows hematocrit changes in response to LBNP and LBPP for the group of subjects before and after beta, muscarinic and combined blockades. The increase in HCT with LBNP found in this study has previously been reported by Aratow 1993, Hinghofer-Szalkay 1992 and Fortney 1991. Beta blockade had no effect on HCT. The small increases in HCT with LBPP and muscarinic blockade have not been reported previously and will be a subject of further study. The fairly rapid (10 min) hemoconcentration that occurred in response to lower body negative

and positive pressures may reflect the summation of filtration/absorption and/or mixing of macro and micro circulations, secondary to changes in vascular resistance as reported below. The increase in HCT that occurred with muscarinic blockade may imply a tonic activity by muscarinic receptors to regulate plasma volume or an effect that was secondary to the other cardiovascular effects of atropine (i.e. increased heart rate and/or vascular resistance).

Sympathetic activity as indicated by plasma norepinephrine (NE), is illustrated in Figure 2a. In both groups, irrespective of beta and muscarinic blockade, LBNP increased norepinephrine, but the increase in men was greater than that in women $p<.01$. Beta and muscarinic blockades both increased the NE response to LBNP in men. The higher values of NE seen in unblocked women compared to unblocked men appears to have been an artifact of sample storage, since data from another 10 men taken subsequently revealed significantly greater epinephrine and slightly greater NE in men compared to women.

Parasympathetic activity as indicated by the response of pancreatic polypeptide (PPP) to LBPP before and after beta, muscarinic and combined blockades is illustrated in Figure 2b. As with hematocrit, beta blockade had no significant effect on PPP, but muscarinic blockade decreased PPP in men. We had hypothesized the increase in PPP during LBPP (used to evoke an increase in vagal activity), but the gender difference and the decrease in response to atropine are new findings of the present study.

5.2 Mean Values

5.2.1.1 Mean Values, Resting Controls, Men: Group (N= 10) averaged values ± SEM of cardiovascular variables are given for 10 min of supine rest in Figure 3a-i for unblocked, beta blocked, muscarinically blocked and combined blockade states. In Figure 3a, the effect of atropine was to significantly elevate AP when given in the unblocked state, with no effect when given after beta blockade. In both unblocked and beta blocked states, atropine induced an increase in HR (3b) and concomitant decreases in EDV (3c), SV (3d) and RF (3e) with no net effect on CO (3f). The AP response to atropine in the unblocked case (column 4 to column 5) however was greater than in the beta blocked case (column 2 to column 3). This difference lay in the magnitude of the decreases in CO and increases in total vascular resistance (3g) and radial artery resistance (reflecting skin and skeletal muscle changes) (3h) that were greater in the unblocked than in the beta blocked state. The increase in mean TFI (inversely related to thoracic fluid), Figure 3i, indicated that atropine given to unblocked subjects increased thoracic impedance significantly, while the atropine-invoked increase in TFI after beta blockade was much smaller and not statistically significant. The principal responses to beta blockade were significant decreases in HR and AP both before and after muscarinic blockade with no significant changes in any other variables. Differences between (muscarinic + beta) and (beta + muscarinic) blockade states were significant only in HR. Since beta blockade followed muscarinic by -1 hour, we attribute the higher HR in the beta + muscarinic state (column 3 vs column 6) to non muscarinic non adrenergic vagal excess tachycardia (Donald 1967) which had most likely been expended by the time beta blockade was added to muscarinic blockade.

The major conclusions drawn from changes in mean values from resting men in response to beta and/or muscarinic blockades are that the effects of acute beta blockade were small and were confined to decreases in heart rate and heart rate's affect on arterial pressure, In contrast, responses to acute muscarinic blockade were large and appeared to decrease vascular volume, SV, RF and EDV, as well as having excitatory effects on HR, RR and TPR.

5.2.1.2 Mean Values During LBNP and LBPP, Men: Mean (± SEM) values of cardiovascular variables at each stage of autonomic blockade and each level of LBNP and LBPP are given in Figure 4; the control values are the same as in Figure 3. The panels on the left are for the sequence in which muscarinic blockade was followed by beta blockade and panels on the right are for the sequence in which beta blockade was followed by muscarinic blockade. Like resting control, the major effect in each variable was from muscarinic blockade (Δ,⊕). The atropine-induced increases in AP, HR, and TPR and decreases in indices of vascular volume (SV and EDV) were maintained during both lower body negative and positive pressure. Beta blockade, (∇,Ξ) did however lower heart rate (with respect to its preceding state) at all lower body pressure levels.

Lower body negative pressure caused a decrease in stroke volume (Figure 4a) that was counteracted by increases in heart rate (Figured 4a) and peripheral resistance (Figure 4b), resulting in minimal changes in arterial pressure. Either muscarinic or beta blockade when given alone resulted in an LBNP-induced decrease in AP, but combined blockade resulted in a response that was more like the unblocked response.

Mean calf circumference, an index of peripheral fluid shifts, indicated that LBNP increased calf circumference by up to 3%, but there was no change from control during LBPP. In the unblocked state, TFI (Figure 4b) tended to decrease during LBPP, indicating a shift of fluid to the thoracic region. The effect of this fluid shift on cardiovascular regulation is shown by the decrease in HR accompanying this increase in thoracic volume. For all variables other than TFI and HR, the response to LBPP was very similar to LBNP (cardiac output and stroke volume were below control levels and total peripheral resistance was above its control level).

5.2.2.1 Mean Values, Resting Controls, Women: Mean (± SEM) values of cardiovascular variables for the 10 women at each state of autonomic blockade at rest and at each level of LBNP and LBPP are given in Figures 5a and 5b. The panels on the left are for the sequence in which muscarinic blockade was followed by beta blockade and panels on the right are for the sequence in which beta blockade was followed by muscarinic blockade. The center points of each line in Figure 5a and 5b indicate the group (N=10) averaged values ± SEM of a cardiovascular variable for 10 min of supine rest. In Figure 5, top row, the effect of atropine was to significantly elevate AP when given in the unblocked state, and to reduce AP toward control levels when added to beta blockade. Similarly, beta blockade increased AP when given alone and returned AP to control when added to mucarinic blockade. In both unblocked and beta blocked states, atropine induced an increase in HR, a slight increase in TPR and decreases in stroke volume and skin flow. The principal responses to beta blockade were decreases in HR, both before and after muscarinic blockade, and decreases in SV and CO in the unblocked state. The increase in AP mentioned above was due to the increase in TPR in response to beta blockade. There were no significant changes in any other variables. Differences between muscarinic + beta, and beta + muscarinic blockade states were significant for AP, HR and SV. As with the men's data, we attribute the higher HR in the beta + muscarinic state to non muscarinic non adrenergic vagal excess tachycardia (Donald 1967) which had most likely been expended by the time beta blockade was added to muscarinic blockade.

The major conclusions drawn from changes in mean values of resting women in response to beta and/or muscarinic blockades are that acute beta blockade increased TPR and AP and slightly decreased HR and CO. Responses to acute muscarinic blockade were large and consisted of decreases in vascular volume, SV, SF and end diastolic volume (EDV, not shown), and increases in HR and AP.

5.2.2.2 Mean Values During LBNP and LBPP, Women: The atropine-induced increases in mean values of AP, HR, and TPR and decreases in indices of vascular volume (SV and EDV) seen at rest were maintained during both lower body negative and positive pressure (Figures 5a and 5b). In addition beta blockade increased TPR and SF and lowered HR at all lower body pressure levels.

Lower body negative pressure caused decreases in SV and CO that were counteracted by increases in HR and TPR, resulting in minimal changes in AP. Either muscarinic or beta blockade when given alone resulted in a response which was similar to the unblocked response.

For all variables other than HR, the response to LBPP was similar to LBNP (CO and SV were below control levels and TPR was above its control level).

Differences in men and women were that 1) men did not change TPR and AP in response to beta blockade 2) the men's HR and TPR increased more with atropine 3) the men's HR decreased less with beta blockade.

5.3 Spectral Power

5.3.1.1 Spectral Power, Resting Controls, Men: The spectral results from the present study were divided into three regions: low (0.006 to 0.05 Hz), mid (0.05 to 0.15 Hz) and high (0.15 to 0.45 Hz) frequencies. Oscillations in these frequency regions have been classified by others (Akselrod et al) as representative of thermoregulatory, baroreflex, and, respiratory inputs in the regulation of heart rate. Autonomic contributions to both HR and other variable oscillations is the subject of the present study

Unblocked resting HR spectra as a function of time for one subject in control and in response to atropine and propranolol are given in Figure 6a and 6b respectively. The loss of power in response to increasing atropine (0.005 mg/kg dose at arrows) was maintained in all frequency regions throughout the muscarinically blocked study that followed, see Figure 9 below. Spectral changes in HR in response to beta blockade (0.05 mg/kg dose at arrows) are given in Figure 6b. In contrast to the loss of spectral power in all frequency regions that occurred with muscarinic blockade, spectral responses to beta blockade were less obvious. Figure 7a shows heart rate spectra averaged over 9 subjects before (u) muscarinic blockade, after muscarinic blockade (M) and after combined muscarinic and beta blockades (M+B). Arterial pressure, stroke volume and vascular resistance spectra for these same subjects in the same states are given in Figure 7b, 7c and 7d. From these figures, it is clear that muscarinic blockade had dramatic effects; it increased spectral power in AP and TPR and decreased power in HR and SV. However when all subjects were included and the data were normalized to eliminate dominance of the responses by any one subject, some effects seen in Figure 7 were statistically significant and others were not. Spectral power for each subject was normalized by the power in the bin (frequency region) that had the highest value [low, mid or high frequency region for unblocked (pre beta), unblocked (pre muscarinic), beta, muscarinic, beta + muscarinic or muscarinic + beta blocked states, (18 in all)]. This normalization scheme preserved changes in total power that occurred as a function of experimental intervention while giving each subject an equal input into group results.

In order to illustrate significant differences and the effects of beta as well as muscarinic blockades, we will present histogram averages of spectral power. In the results below we are

assuming that changes both in the magnitudes and magnitude ratios of spectral power of variables contribute to the observed responses in the same manner that the mean values of SV and HR contribute to the mean value of CO and mean values of CO and TPR contribute to the mean value of AP. (When the analysis of the phase relationships between variables has been completed, we will be able to quantify the relative contributions of phase and magnitude in a given response.) Figure 8 shows the mean power in each frequency region for all 10 subjects unblocked, after separate beta and muscarinic blockades and after combined blockade states. All spectral powers were plotted on a 0 to 1 scale in order to show overall power distribution in the three frequency regions. Statistically significant changes in response to muscarinic blockade, beta blockade and muscarinic beta interactions are indicated by m, B and mxB in each panel. For the group, muscarinic blockade had no significant effects on AP (Figure 8a) or TFI (Figure 8b) power in any frequency region. For HR (Figure 8a), muscarinic blockade significantly lowered power in all frequency regions and for SV (Figure 8a), power in both the low and mid frequency regions were lower. Beta blockade decreased power in AP (Figure 8a) in the high frequency region due either to non significant decreases in the magnitude or changes in the phase relationship (still to be determined) between TPR (Figure 8a) and CO (Figure 8b). For radial flow (Figure 8b) there was a marginally significant interaction: beta blockade decreased high frequency power in the unblocked state and increased it in the muscarinically blocked state. Beta blockade significantly decreased power in TFI (Figure 8b) in all frequency regions both before and after muscarinic blockade, perhaps reflecting sympathetically mediated modulation of respiratory activity.

5.3.1.2 Spectral Power Responses to LBNP and LBPP, Men: Mean Values ± SEM of spectral responses to 10 min at 2 levels each of lower body negative (LBNP) and positive (LBPP) pressures are shown in Figure 9a-g. Again, spectral powers of each subject were normalized by the power in the bin that contained the most power, however there were now 90 bins for each subject (6 states of blockade x 3 bins x 5 pressure levels). Several results are worth noting:

Muscarinic blockade decreased spectral power in control and during LBNP and LBPP for heart rate (all frequency ranges Figure 9b), stroke volume (low and mid ranges Figure 9c) and cardiac output (mid frequency range Figure 9f) with no consistent effect on AP (Figure 9a), RF (Figure 9g) or TPR (Figure 9d).

Beta blockade decreased spectral power during LBNP and LBPP in cardiac output in the mid frequency range by small decreases in SV, TPR and HR powers.

Lower body negative pressure increased AP spectral power in the mid frequency range and this increase was changed only slightly by beta and muscarinic blockades. The increased AP power in this region occurred in spite of decreased SV and CO power and correlated with increased TPR power; but again, the phase relationships between these variables have not yet been determined. In addition, muscarinic blockade, given alone, increased AP spectral power at -40 mmHg in both low and mid frequency regions. Beta blockade given alone or following muscarinic blockade, reduced (with respect to the preceding state) AP spectral power at -40 mmHg in both low and mid frequency regions. A decrease in HR power in response to LBNP was most obvious in the high frequency region in the unblocked state and was erased by muscarinic blockade.

In addition to the normalized spectral powers presented above, we also looked at the ratios of low/high, mid/high and (low + mid)/high normalized frequency power for each variable. In most cases, no new information was added by this procedure, however in a few cases additional

information about changes in variable power appears; these results are given in Figure 10 for unblocked, muscarinic and beta blocked cases.

Whereas mid frequency spectral power in AP (Figure 9a) had been increased by muscarinic blockade during LBNP, the ratio of mid to high frequency powers (MF/HF) was slightly decreased in control and during LBNP and LBPP (Figure 10a). Decreases in MF/HF in both TPR (10b) and CO (10c) were observed, and the decrease in CO appeared to be due to the decrease in SV MF/HF (10d) which had a more dominant effect on CO than did the increase in HR MF/HF (Figure 10e).

Beta blockade had little effect on MF/HF of all variables. There was a tendency for MF/HF of AP and HR to increase less during -40 mmHg LBNP after beta blockade than in the unblocked state, but this tendency may not be statistically significant.

In the unblocked state, LBNP increased AP MF/HF (10a) and HR MF/HF (10e) while SV MF/HF (Figure 10d) was decreased and TPR MF/HF was unchanged. After muscarinic blockade the increase in AP MF/HF was blunted apparently due to the blunted decrease in SV MF/HF which had a more dominant effect on CO than did the enhanced increase in HR MF/HF.

In the unblocked state, LBPP slightly decreased AP MF/HF (Figure 10a) due to slight decreases in MF/HF of CO (both HR and SV) and TPR. After muscarinic blockade, these LBPP-induced decreases in MF/HF values of SV, CO and TPR were reversed.

In the muscarinically blocked case, the ratio of subrespiratory [(LF + MF)/HF] powers of HR (Figure 10f) increased above control during LBNP and decreased below control during LBPP. This ratio is probably the best means of assessing the level of sympathetic input to the control of heart rate in response to intravascular fluid shifts.

5.3.2 .1 Spectral Power, Resting Controls, Women: The spectral results from these studies are divided into the same three frequency regions as the men's spectral results: low (LF, 0.006 to 0.05 Hz), mid (MF, 0.05 to 0.15 Hz) and high (HF, 0.15 to 0.45 Hz), , however they are illustrated differently.

Figure 11 shows heart rate spectra averaged over 10 women in control, at + 15 and + 30 mmHg LBPP and -20 and -40 mmHg LBNP; TOP: before muscarinic blockade (PM), after muscarinic blockade (M) and after combined muscarinic and beta blockade (MB); BOTTOM: before beta blockade (PB), after beta blockade (B) and after combined beta and muscarinic blockades (BM). Arterial pressure, SV and TPR spectra for these same subjects in the same states are given in Figures 12, 13, 14. From these figures, it is clear that, in women, both beta and muscarinic blockades had dramatic effects; muscarinic blockade decreased spectral power in HR and SV, beta blockade also decreased power in SV and increased power in TPR and HR.

When these data were normalized to eliminate dominance of the responses by any one subject, some effects seen in Figures 11-14 were statistically significant and others were not. In Figures 15-18, spectral power for each subject was normalized by the power in the bin (frequency region) that had the highest values [low, mid or high frequency region for unblocked (pre beta), unblocked (pre muscarinic), beta, muscarinic, beta + muscarinic or muscarinic + beta blocked states, 18 bins in all]. This normalization scheme preserved changes in total power that occurred as a function of experimental intervention while giving each subject an equal input into group results.

As with the men's results, we are assuming that changes both in the magnitudes and magnitude ratios of spectral power of variables contributed to the observed responses in a similar manner as the mean values of SV and HR contributed to the mean value of CO and as mean values of CO and TPR contributed to the mean value of AP. Therefore, when the analysis of the phase relationships between variables has been completed, we will be able to quantify the relative contributions of phase and magnitude in a given response.

5.3.2.2 Spectral Power Responses to LBNP and LBPP, Women: Group averaged spectral power responses (± SEM) to 10 min at 2 levels each of LBNP and LBPP are also shown in Figures 15-18. Again, spectral powers of each subject were normalized by the power in the bin that contained the most power, there were 90 bins for each subject [6 states of blockade x 3 frequencies x 5 pressure levels].

Muscarinic blockade decreased spectral power in control and during LBNP and LBPP for HR (all frequency ranges, Figure 15) and SV (LF and MF, Figure 16). Muscarinic blockade increased spectral power in TPR (LF and HF, Figure 17) during LBNP and LBPP with no consistent effect on AP (Figure 18).

Beta blockade decreased spectral power during LBNP and LBPP for CO in the mid frequency range due to decreased SV power. Beta blockade increased HR power in all frequency ranges in control and during LBNP and LBPP and increased TPR power in all ranges during control and LBPP.

Lower body negative pressure increased AP spectral power in the MF range and this increase was changed only slightly by beta and muscarinic blockades. The increased AP power in this region occurred in spite of decreased SV and CO power and correlated with increased TPR power; but again, the phase relationships between these variables have not yet been determined. In the HF region, HR power in response to LBNP was most obviously decreased in the unblocked state, was slightly enhanced by beta blockade and was erased by muscarinic blockade.

5.3.3 Comparison of Spectral Data Between Women and Men: The results of the 3 factor ANOVA for HR, SV, AP and TPR are given below. The 3 factor ANOVA consisted of one between (gender) and two within (blockades, lower body pressures) factors with repeated measures on both within factors]. Due to the quantity of data, only those factors that were statistically significant are discussed. There were no 3 factor interactions. Results for both spectral power and spectral power normalized by maximum bin power (relative power distribution) were tested and are discussed. In maximum bin normalization, each subject's data is scaled to the bin in which that subject had maximum power, therefore all data are ≤ 1 (this represents the relative shifting of power between LF, MF and HF bins).

Gender: When power at all pressure levels and autonomic blockades were combined, men had greater overall power for all variables (Figure 19); this was true for all frequency bins. However, the relative amounts of power of HR, SV and TPR in MF and HF bins were greater for women than for men. When resting values alone were considered, the gender differences in AP and HR were not significant, but men had significantly greater power of TPR, SV, RF and skin flow than women. These gender differences are discussed in detail in a manuscript submitted to the American Journal of Physiology, Heart and Circulation, February 1997.

Autonomic Blockades (Data Not Shown): Independent of gender and pressure levels, muscarinic blockade decreased total power and the distribution of power in LF and HF bins for HR and in total, LF and MF bins for SV. Muscarinic blockade increased the HF power of SV and total power of AP. In addition muscarinic blockade changed the distribution of power in TPR by shifting power from the MF to LF and HF bins. Beta blockade increased the total, LF and HF power of HR and increased the distribution of HR power in LF and HF bins.

Lower Body Negative and Positive Pressures: When power for both genders and all states of blockade were combined, LBNP decreased power (total, LF, MF and HF) of HR and SV and increased the total, MF and HF powers of TPR and AP (Figure 20). Lower body positive pressure increased total power and the distribution of HR power in MF and HF bins.

Gender by Blockade Interactions (Data Not Shown): Independent of pressure levels, muscarinic blockade decreased SV total and low frequency power more in men than women. In addition, muscarinic blockade increased total and LF power of TPR and AP more in men than women. Beta blockade increased HF HR power (both normalized and compared to MF and LF) in women but not in men. Finally beta blockade decreased HF power of TPR in men and increased it in women. The major difference between men's and women's AP spectral response to autonomic blockade appears to be due to TPR and to some extent HR; in the unblocked (premuscarinic) case, men increased TPR power in response to muscarinic blockade and decreased TPR power in response to beta blockade. Women did the reverse.

Blockade by Lower Body Pressure Interactions: Independent of gender, beta blockade increased, and muscarinic blockade decreased HR HF power in control and at all levels of LBNP and LBPP. In addition beta blockade increased the proportion of HR power and decreased the proportion of TPR power in the HF bin during LBNP.

Gender By Lower Body Pressure Interaction: Independent of blockade level, women had a greater proportion of power in the HR HF bin during LBPP than did men.

6.0 SUMMARY

The present study had as its principal goal the validation of the use of spectral analysis of cardiovascular signals to indicate changes in autonomic inputs to blood pressure regulation. The study was designed to induce fluid shifts into and away from the upper body by applying lower body negative and positive pressures at various stages of autonomic blockade. The combination of these fluid shifts with blockades was done to evoke states of increased vagal and sympathetic stimulation in order to identify regions of the spectra associated with specific autonomic activity. Measurements were made to determine 1) volume shifts into and out of the vasculature (hematocrit and plasma mass density) as well as 2) an index of the relative amounts of volume shifted within vascular compartments (calf circumference, thoracic impedance and end diastolic and stroke volumes). The responses to these intravascular fluid shifts were determined from: a) changes in vasoactive hormones (plasma levels of pancreatic polypeptide, an index of vagal activity, catecholamines an index of sympathetic activity and plasma renin activity, an index of the drive to retain plasma), b) changes in the mean values of reflexly driven responses (heart rate, total peripheral and hand resistances) and c) changes in spectral power of the cardiovascular parameters.

Due to the extensive layering of the factors in this study (2 genders, 6 blockade states, 5 lower body pressure states and, for spectra, 3 frequency bins) we will summarize the major findings in the following categories (unless otherwise stated, findings are for both men and women):

1. Extravascular/vascular fluid volume shifts

   a. Hematocrit, plasma mass density and plasma renin activity increased with LBNP in men and women and, in men, with LBPP, a response indicative of a plasma shift to extravascular spaces and an increase in the drive to retain plasma.

   b. Beta blockade alone or after muscarinic blockade had no effect on HCT or plasma mass density and therefore no apparent effect on extravascular fluid shifts.

   c. Muscarinic blockade alone or after beta blockade increased HCT indicating a shift of fluid to extravascular spaces. LBNP further increased HCT after muscarinic blockade.

2. Intravascular fluid volume shifts

   a. Lower body negative pressure increased calf circumference and thoracic impedance and decreased stroke volume and cardiac output, all indicators of a translocation of fluid from the chest to the periphery during LBNP.

   b. Lower body positive pressure had no effect on calf circumference and its effects on other variables were similar to, but smaller than, the effects of LBNP. The decreases in these other parameters with no change in calf circumference, indicated that LBPP produced a shift of fluid out of the thoracic vasculature, perhaps to upper body extravascular spaces, as listed in la above.

   c. Muscarinic blockade (given alone) increased thoracic impedance, indicating a translocation of fluid away from the chest. This could be the effect of the extravascular fluid shift listed in la above but since:

   d. Beta blockade administered before muscarinic blockade modified the increase in mean TFI seen with muscarinic blockade alone, it could be that beta activity had attenuated the effect of muscarinic blockade to produce either an extravascular or a peripheral fluid shift.

3. Responsiveness to fluid volume shifts

   a. <u>Mean values</u>
      1) Resting controls
         a) The effect of muscarinic blockade was to increase mean heart rate by~30 bpm with concomitant decreases in SV and EDV whether given before or after beta blockade. In addition arterial pressure increased when atropine was given in the unblocked case, due to an increase in total peripheral resistance, but did not increase when atropine was given after beta blockade.
         b) In men, the effect of beta blockade was to decrease both AP and HR in the unblocked (4 mmHg and 5 bpm respectively) and muscarinically blocked (12

mmHg and 17 bpm) states. In women, beta blockade increased TPR and AP and decreased HR and SV.

c) The HR difference between the two states of combined blockade could account for the differences in pressure and flow and was itself most likely due to vagal excess tachycardia (evoked by the initial dose of atropine) that had had about 3 hrs to decay in the muscarinic + beta case and only a few minutes in the beta + muscarinic case.

2) During LBNP and LBPP

a) Like resting control, the principal effect was from muscarinic blockade which resulted in higher mean values of HR, AP, TPR and hand resistance and concomitant decreases in EDV, SV, RF and CO at all levels of LBNP and LBPP.

b) Also, like control, the effect of beta blockade was to decrease HR and AP at all levels of LBNP and LBPP.

c) For most variables, after beta blockade was added to muscarinic blockade, the responses to LBNP and LBPP were more similar to the unblocked responses than they were after muscarinic blockade alone.

d) Either beta or muscarinic blockade given alone, resulted in a decrease in AP during LBNP that was either small or not present in the unblocked LBNP cases.

e) Lower body positive pressure decreased TFI and HR, indicating that the increase in thoracic fluid was sufficient to invoke a reflex decrease HR. The decrease was enhanced after muscarinic blockade.

b. Spectral changes

1) Resting controls

The major effects of autonomic blockade on spectral power in supine resting control consisted of the following:

a) Muscarinic blockade

i) reduced the low frequency spectral power of HR, SV, CO, RF and TFI in men and HR and SV in women.

ii) reduced mid frequency power of HR, SV and CO in men, and HR, SV and CO in women.

iii) reduced high frequency power of HR and CO in both sexes.

b) Beta blockade

i) reduced low frequency spectral power of TFI in men and increased LF power of HR and TPR in women.

ii) reduced mid frequency power of TFI and CO in men and AP and CO in women, increased women's MF power of HR and TPR.

iii) reduced high frequency power of CO of both men and women, increased HF power of HR and TPR in women.

c) Combined muscarinic and beta blockades further reduced mid and low frequency power of CO in men, resulting in a reduction of low frequency power of AP and TPR in both sexes.

d) Spectral changes in HR during combined beta and muscarinic blockades were not different from muscarinic blockade alone in both sexes.

2) During LBNP
   a) Unblocked LBNP spectral power responses indicated:
      i) an increase in AP MF power that was associated with increased TPR and TFI MF powers.
      ii) a decrease in AP LF power that was associated with decreased CO power. The decrease in CO power occurred in all bins and was associated with decreased HR and SV, LF, MF and HF powers.

   b) Muscarinically blocked LBNP spectral power responses indicated that:
      i) increases in AP MF and HF power were enhanced (with respect to the unblocked response) and, in men only, were associated with increased TPR power.
      ii) increased TPR LF power was enough to reverse the LBNP-induced decrease in AP LF power seen in the unblocked state in men and the decreased HR/HF power in women.
      iii) the LBNP induced decreases in HR and SV were blunted or eliminated.

3) During LBPP
   a) Unblocked LBPP spectral power responses indicated:
      i) a decrease in SV and CO LF and MF power in men and slight increases in MF and HF power of HR in women.
      ii) slight increases in TPR LF and MF power and a decrease in HF power in men, with slight increase in TPR LG, MF and HF in women.
      iii) a slight decrease in AP power (LF, MF and HF), both sexes.

   b) Muscarinically blocked LBPP spectral power responses indicated that following blockade, the decreases in SV and CO LF and MF power were enhanced in men, and the increase in TPR in women was also slightly enhanced.

4) Interpretation of spectral changes in men:

The summary of spectral responses presented below will be focused on HR due to: 1) specificity of the blockades to HR control, 2) availability of data in the literature for future comparison and 3) lack of a complete analysis of other variables.

The important spectral features for interpreting changes in HR spectra are illustrated in Figure 21 which is provided to supplement data from Figures 4, 9b and 10. For HR, we found the ratio of (LF + MF)/HF powers, (Figure 21 top) and HF power (Figure 21 bottom) to be the most sensitive spectral indicators of sympathetic/parasympathetic balance in response to intravascular fluid shifts.

Figure 21 has been designed to answer the following four questions: How do HR spectral features change in response to: 1) an increase in sympathetic activity? 2) a decrease in sympathetic activity? 3) an increase in parasympathetic activity?, and 4) a decrease in parasympathetic activity?

The experimental condition which best evoked an unopposed increase in sympathetic regulation of heart rate was -40 mmHg after muscarinic blockade. In this case mean HR increased from muscarinically blocked resting control by 18 b/m. Increased sympathetic activity correlated with

an increase, from control, in the HR (MF + LF)/HF ratio (column 1) as a result of a slight increase in LF power. The experimental condition which best produced an unopposed decrease in sympathetic activity was +30 mmHg LBPP after muscarinic blockade (column 3). In this case mean HR decreased ~7 bpm. The decrease in sympathetic activity correlated with a decrease from control, in the HR (LF + MF)/HF ratio as a result of a small increase in HF power.

The experimental condition which best illustrates an unopposed decrease in parasympathetic regulation was -40 mmHg after beta blockade. In this case mean HR increased by ~5 bpm. Like the case for an increase in sympathetic activity, decreased parasympathetic activity correlated with an increase, from control, in the HR (MF + LF)/HF ratio (column 1), but in this case it was the result of a pronounced decrease in HF power. The experimental condition which best illustrated an unopposed increase in parasympathetic regulation was +30 mmHg after beta blockade. In this case there was no change from control in either mean HR or the HR (LF + MF)/HF ratio.

7.0 CONCLUSIONS

One of the major findings from this study was the difference in the balance of tonic beta adrenergic and muscarinic activity between men and women; men had indicators of increased sympathetic dominance in SV, TPR, RF and SF and women had indicators of parasympathetic dominance in the regulation of HR.

7.1 At Rest

HORMONAL

1. In the unblocked state, men had greater levels of PPP than did women. After muscarinic blockade, the PPP level of men dropped to equal that of women.
2. Men had significantly greater epinephrine and slightly greater norepinephrine than women.
3. Men had greater HCT than women indicating less relative plasma volume in men.
4. Men had slightly greater PRA than women, indicating an equivalent or greater stimulus to retain plasma volume.

MEAN VALUES

1. Men had slightly lower unblocked HR (61 bpm) than women (67 bpm). After combined autonomic blockade, mean HR was 84 and 85 bpm, respectively, indicating that even though the intrinsic HR was the same, men had greater absolute parasympathetic input in the unblocked state even though their autonomic balance was shifted toward sympathetic dominance.
2. Women had slightly lower (78 mmHg) unblocked AP than men (83.5 mmHg). After combined autonomic blockade, both pressures came to the same value (84 mmHg) via increased TPR in women (HR and SV changes offset each other).

SPECTRAL POWER

1. Low, mid and high frequency spectral power of HR and TPR were increased by beta blockade in women. Beta blockade did not affect HR spectral power in men

indicating that women, but not men had tonic beta adrenergic buffering of these variables.

2. High frequency spectral power in TPR was increased by muscarinic blockade in men, but not in women. Muscarinic blockade dramatically decreased SV spectral powers in men,but not in women.

7.2 During LBNP and LBPP

With respect to intravascular fluid volume distribution, as expected, our results indicated that LBNP and LBPP produced sufficient upper body vascular fluid shifts to evoke appropriate autonomic regulatory responses. During resting control and all levels of LBNP and LBPP, the principal effect was from muscarinic blockade which resulted in higher mean values of HR, AP, RR and TPR and concomitant decreases in EDV, SV, RF and CO. Also, like control, the effect of beta blockade was to decrease HR and AP at all levels of LBNP and LBPP. Either beta or muscarinic blockade given alone, resulted in a decrease in AP during LBNP that was either small or not present in the unblocked LBNP cases. The response to LBPP included increases in pancreatic polypeptide and thoracic fluid volume and decreases in mean heart rate.

The heart rate response to LBNP was dominated by parasympathetic withdrawal in that the ratios of LF/HF and MF/HF powers were increased by LBNP and were unaffected by beta blockade. In the situations where we could evoke unopposed sympathetic and parasympathetic stimulation and withdrawal to regulate HR, we found that: 1) sympathetic stimulation resulted in an increase (with respect to resting control) in the (LF + MF)/HF spectral power ratio, with no changes in HF power, 2) sympathetic withdrawal resulted in a decrease in (LF + MF)/HF power ratio and a slight increase in HF power, 3) parasympathetic withdrawal resulted in an increase (with respect to resting control) in the (LF + MF)/HF power ratio and a large decrease in HF power, and 4) parasympathetic stimulation resulted in no change in (LF + MF)/HF power ratio or HF power. Preliminary examination of other variables leads us to conclude that, like HR, the responsiveness of these men and women to LBNP, LBPP and autonomic blockade was dominated by changes in parasympathetic regulation.

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ABSTRACTS AND MANUSCRIPTS

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Thesis:.

Kristin King (M.S. Candidate, Biomedical Engineering, 1997) Time-Frequency and Coarse Graining Spectral Analysis of Heart Rate in Determining Potential for Syncope During Orthostatic Stress.

Charles Kim (M.S. Candidate in Biomedical Engineering, 1997) Sympathetic and Parasympathetic Components of the Human Frequency Response to Oscillatory LBNP.

Abstracts:

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AUTONOMIC BLOCKADE IN HUMANS: EFFECTS ON LOW (.02 Hz) FREQUENCY CARDIOVASCULAR SPECTRAL POWER. J M Evans, A R Patwardhan, B Ott, S Vullurupalli, C S Kim, F M Leonelli, A K Griffin and C F Knapp. Biomedical Engineering and Cardiology, U of Ky, Lexington, KY 40506.

Cardiovascular spectra of arterial pressure (AP), heart rate (HR), stroke volume (SV) and peripheral resistance (TPR) were obtained from 10 supine males (24.9±0.8 yrs, 73.5±1.8 kg, 175±1.4 cm). Each subject was studied twice (3 to 5 weeks apart): unblocked, after either beta (.2 mg/kg inderal) or muscarinic (.02 mg/kg) blockade, and after combined blockade; the order of blockade was reversed on the second day. Half the subjects had beta blockade first, the other half had muscarinic blockade first. Results from 8 subjects indicate that muscarinic blockade increased low frequency spectral power in AP and TPR; low frequency power in HR and SV were significantly decreased. Beta blockade alone did not have a significant effect on HR or SV power. The addition of muscarinic to beta blockade significantly decreased power in TPR, SV and HR. The addition of beta to muscarinic blockade significantly decreased SV power and had no further effect on HR or TPR. We conclude that peripheral muscarinic and, to some extent, beta adrenergic activities are components of normal buffering of low frequency oscillations in vascular resistance.
Supported by NAGW-3786 and NIH GCRC NO1 RR 2602

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FREQUENCY RESPONSE CHARACTERISTICS OF CARDIOVASCULAR CONTROL BEFORE AND AFTER SIMULATED WEIGHTLESSNESS. GRIFFIN, A.K., J.M. Evans, M. Wang, C. Kim, C.F.Knapp. Center for Biomedical Engineering, University of Kentucky, Lexington, KY 40506-0070. We have previously determined the frequency response characteristics of cardiovascular (CV) control for normal males; however, potential changes associated with true and simulated weightlessness (SW) have not been reported. SW-induced changes in the CV frequency response of males were determined following periods of normal activity and after exposure to the following SW protocol: Two hours in launch position, 20 hours 6° head down bed rest, and Furosemide (40mg PO). Following periods of normal activity and SW, ten male volunteers were exposed to oscillatory lower body negative pressure (OLBNP) at seven frequencies (0.004 - 0.1 Hz). Fourier spectra were calculated for arterial pressure (AP), calf circumference (CC), central venous pressure (CVP), heart rate (HR), stroke volume (SV), and total peripheral resistance (TPR). Mean values, first harmonic amplitude, phase angles, cross spectra, and coherence between appropriate variables were determined. Two factor repeated measures analysis of variance was utilized to determine the significant effects of SW and/or OLBNP. Statistically significant differences between means as obtained by Neuman-Keuls Criteria were accepted for $p<0.05$. Cardiovascular frequency response characteristics (first harmonic amplitude vs. OLBNP frequency) showed similar trends after normal activity and after SW. The amplitudes of fluid volume shifted by OLBNP decreased after SW, as evidenced by a decrease in the amplitudes of oscillations of both CC and CVP. However, the amplitude of AP and HR oscillations increased following SW. When the half amplitude of AP was normalized by the half amplitude of CC or CVP, the magnitude of the oscillations more than doubled after SW indicating a change in the regulatory system due to SW. The magnitude of TPR and HR responses, normalized by AP amplitude, were similar after normal activity and following SW suggesting that arterial baroreflex regulation of these responses was less effective. The magnitude and timing of hydraulic and reflex responses in regulation of blood pressure will be the focus of discussion. Supported by NASA NAG9-298 and GCRC M01-RR-2602.

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CHARACTERISTICS OF CARDIOVASCULAR FREQUENCY RESPONSE BEFORE AND AFTER SIMULATED WEIGHTLESSNESS.

Griffin, A.K., J.M. Evans, M. Wang, C. Kim, C.F.Knapp. Center for Biomedical Engineering, University of Kentucky, Lexington, KY 40506.

We previously determined the frequency response characteristics of cardiovascular (CV) control for normal males; however, potential changes associated with true and simulated weightlessness (SW) have not been reported. SW was modeled by the following protocol: Two hours in launch position, followed by 20 hours 6° head down bed rest [with Furosemide (40mg PO)]. Before and after SW, ten male volunteers were exposed to oscillatory lower body negative pressure (OLBNP) at seven frequencies (0.004 - 0.1 Hz). Mean values, first harmonic amplitude, phase angles, cross spectra, and coherence were calculated for arterial pressure (AP), calf circumference (CC), central venous pressure (CVP), and heart rate (HR). The significant effects of SW and/or OLBNP were determined by two factor repeated measures analysis of variance. The volume of fluid shifted by OLBNP decreased post SW, as indicated by a decrease in the amplitudes of oscillations of both CC and CVP. However, the amplitude of AP and HR oscillations increased following SW. When the half amplitude of AP was normalized by the half amplitude of CC or CVP, the magnitude of the oscillations after SW more than doubled from pre SW and peaked in the frequency range between 0.04 and 0.08 Hz, indicating a change in the regulatory system due to SW. An examination of phase relationships between passive and regulatory components (CVP and CC, AP and CC, AP and CVP, HR and AP, HR and CVP) did not indicate that the timing of these responses had changed after SW. Supported by NASA NAG9-298 and GCRC M01-RR-2602.

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HORMONAL RESPONSES OF SYNCOPAL AND NONSYNCOPAL MEN AND WOMEN TO +30 AND -40 mmHg LOWER BODY PRESSURE. J M Evans, B Ott, S Vallurupalli, C S Kim, F M Leonelli, A K Griffin and C F Knapp Biomedical Engineering and Cardiology, UK, Lexington, KY 40506.

Forty studies were conducted on 20 subjects, 10 men (175±1 cm, 74±2 kg, 25±1 yr) and 10 women (162±2 cm, 66±2.5 kg, 25±1 yr). Blood pressure, heart rate, and stroke volume were monitored continuously and blood samples were drawn at the end of 20 min. of supine rest and 10 min. each of lower body positive (LBPP) and negative (LBNP) pressure. Clear presyncopal episodes were detected in 11 LBNP trials (6 men and 5 women), no signs of presyncope were observed in 22 trials with the remaining trials unclear. A three factor ANOVA (syncopal vs. nonsyncopal, men vs. women, and control vs. LBPP or LBNP) was used to test for statistical significance. Significant results included 1) Hematocrit (%), an index of plasma volume: Syncopal subjects had higher resting control values than did nonsyncopal subjects (41.9±.6 to 39.7±.4, $p<.007$). 2) Norepinephrine (NE, pg/ml), an index of sympathetic activity: All groups increased NE in response to -40 mmHg (147.9±8.4 to 215.5±13.7, $p<.0004$) with no response to +30 mmHg. Syncopal men had higher (232±25, $p<.04$) overall NE values compared to nonsyncopal men (173±9), syncopal women (186±19), and nonsyncopal women (173±9). 3) Pancreatic Polypeptide (PPP, pg/ml), an index of parasympathetic activity: Overall, men had significantly higher values than women (57±4 to 43±4, $p<.03$). Responses to +30 mmHg were marginally significant ($p<.1$): syncopal subjects increased PPP (48±5 to 55±5), while nonsyncopal subjects decreased (55±7 to 43±7). These results indicate that in addition to plasma volume, the autonomic response to fluid shifts is different for subjects who are syncopal than for those who are not.
Supported by NASA NAGW-3786 and NIH GCRC NO1 RR 2602.

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COARSE GRAINED SPECTRAL ANALYSIS (CGSA) OF HEART RATE IN DETERMINING POTENTIAL FOR SYNCOPE DURING LBNP. K R King, J M Evans, A R Patwardhan, B Ott, S Vallurupalli, C S Kim, F M Leonelli, A K Griffin, and C F Knapp. Biomedical Engineering and Cardiology, U of Ky, Lexington, KY 40506.

Ten male subjects were studied in resting control and during levels of lower body positive (LBPP) and negative (LBNP) pressure (15,30,-20,-40 mmHg or -20,-40,15,30 mmHg, ten minutes at each pressure level) on 2 different days, one month apart. In 20 trials, 6 were categorized as syncopal, 11 as non-syncopal, and 3 as unclear. Syncopal trials were determined by examination of arterial pressure and heart rate (HR) during -40 mmHg. The following HR spectral indices were determined using CGSA: 1) Harmonic power, high frequency (0.15-0.5 Hz, P_H) and low frequency (0-0.15 Hz, P_L), 2) Fractal power, (P_F), 3) Slope (beta) of log P_F vs. log frequency, 4) Total Power, (P_T), and 5) Indices of parasympathetic (P_H/P_T) and sympathetic (P_L/P_H) activity. Results indicated: 1) During LBNP, P_F was greater ($p<.04$) in syncopal compared to non-syncopal trials. 2) Beta was greater ($p<.06$) in syncopal subjects both in control and during LBNP. These results indicate that CGSA of HR may provide insight into predicting syncope during orthostatic stress. Supported by NASA NAGW-3786 and NIH GCRC NO1 RR 2602.

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LBNP-INDUCED CHANGES OF LEFT VENTRICULAR VOLUME DETERMINED BY ECG-GATED MRI

Griffin, A.K., L. Hilaire, J. Evans, J. Kirsch, K. Wang, F. Leonelli, and C.F. Knapp. Center for Biomedical Engineering, Magnetic Resonance Imaging Spectroscopy Center and Division of Cardiology, University of Kentucky, Lexington, KY 40506-0070.

Hemodynamic changes during two Lower Body Negative Pressure (LBNP) tests were acquired once using Echo Doppler and once with ECG-gated Magnetic Resonance Imaging (MRI, spin echo, 2.34 X 1.56 X 6 mm resolution). Five men (25 ± 4 yrs, 74 ± 3 kg) were exposed to LBNP at -35 mmHg for 20 minutes. Arterial Pressure (AP), Cardiac Output (CO), and Stroke Volume (SV) were measured during Echo. MRI data were analyzed by QuantIm image processing software [Zedec Technologies, Inc.] to determine contours and areas of myocardial tissue and the left ventricle. MRI results indicated a 36 ± 3% decrease in end diastolic volume (EDV) during LBNP. Echo results indicated a 30 ± 6% decrease in SV, a value consistent with the MRI measurement of EDV. Echo results also indicated a 22% decrease in inferior vena cava (IVC) diameter and a 20% decrease in CO during LBNP, further indication of decreased venous return. Agreement between Echo determined SV changes and MRI determined EDV changes indicates the more complete data set of ECG-gated MRI images could enhance assessment of heart size during LBNP-induced fluid volume shifts.

Supported by NASA NAGW-3786 and NIH GCRC NO1 RR 2602.

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INVASIVE AND NONINVASIVE INDICES OF AUTONOMIC BALANCE IN MEN AND WOMEN

K R King, J M Evans, A R Patwardhan, C S Kim, B Ott, F M Leonelli, and CF Knapp Biomedical Engineering and Division of Cardiology, University of Kentucky, Lexington, KY 40506.

Ten each normotensive men (175±1 cm, 74±2 kg, 25±1 yr) and women (162±2 cm, 66±2.5 kg, 25±1 yr) were studied at supine rest, before and after acute autonomic blockade (IV propranolol, .2 mg/kg; atropine, .04 mg/kg). Mean values of hormonal indices were measured: norepinephrine (NE), epinephrine (E), plasma renin activity (PRA), and pancreatic polypeptide (PPP). In addition, mean values of hemodynamic indices for heart rate (HR), arterial pressure (AP), and total peripheral resistance (TPR) were calculated for 20 minute data records, as were mean values of spectral indices: total spectral power (TP), HR low (HRLF) and high (HRHF) frequency power, and HR sympathetic nervous system activity index (HRLF/HRHF, SNS index). HORMONAL INDICES: In the unblocked state, men had significantly higher mean PRA ($p<.02$), E ($p<.0001$), NE ($p<.01$), and PPP ($p<.001$). These data also suggest increased sympathetic and parasympathetic activity in men compared to women. HEMODYNAMIC INDICES: In the unblocked state, men had higher mean AP ($p<.06$) and TPR (NS), while women had higher mean HR ($p<.07$). After autonomic blockade, men and women had the same intrinsic HR, indicating that the unblocked HR difference was due to increased tonic parasympathetic influence in men. SPECTRAL INDICES: In the unblocked state, men had significantly higher mean TP. After autonomic blockade, men and women had similar mean values of TP in all variables. These data suggest an overall increased level of autonomic activity in men as compared to women. Men also had significantly higher HRLF ($p<.07$), and SNS index ($p<.02$), specifically suggesting increased sympathetic activity in men compared to women. The combination of humoral, hemodynamic and spectral indices indicates an enhanced role for both branches of autonomic activity in men compared to women. Supported by NASA NAGW-3786 and NIH GCRC NO1 RR 2602.

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MEN / WOMEN DIFFERENCES IN RESPONSE TO ACUTE BETA ADRENERGIC BLOCKADE

J M Evans, B Ott, A Patwardhan, C Kim, F Leonelli and CF Knapp
Center for Biomedical Engineering and Division of Cardiology, University of Kentucky, Lexington, KY.

Arterial pressure (AP), heart rate (HR) and stroke volume (SV) were measured and peripheral resistance (TPR) was calculated for 10 each normotensive men (175±1 cm, 74±2 kg, 25±1 yr) and women (162±2 cm, 66±2.5 kg, 25±1 yr). Each subject was studied at supine rest, before and after acute beta blockade (IV propranolol, 0.2 mg/kg). Mean values and spectral powers (Welch spectra) of each variable were determined from 20 min data records.

MEAN VALUES: In men, AP decreased slightly after beta blockade, as a result of a decrease in HR accompanied by a slight increase in TPR with no change in SV. In women, AP increased 5% after beta blockade, due to a 26% increase in TPR accompanied by a 12% decrease in HR and a 6% decrease in SV. *Therefore tonic beta adrenergic activity was an important component in maintaining CO (via HR and SV) as well as reducing TPR (via vasodilation) in women but not in men.*

SPECTRAL POWER: In the unblocked state, for all variables, men had greater total spectral power than did women. Beta blockade did not affect spectral power in men. However in women, low (<.15 Hz) frequency spectral powers of HR and TPR were increased and SV power was decreased by beta blockade. *Therefore tonic buffering of vasomotion by beta adrenergic components of regulation appears to be more predominant in the control of blood pressure in women than in men.*

Supported by NASA NAGW-3786 and NIH GCRC NO1 RR 2602.

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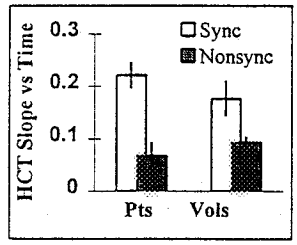
INCREASED RATE OF PLASMA FILTRATION IN SYNCOPAL VS NONSYNCOPAL SUBJECTS DURING 70° TILT. JM Evans, CM McIntosh, LC Taylor, CS Kim, CF Knapp, FM Leonelli. Biomedical Engineering and Cardiology, Univ. of Kentucky, Lexington, KY 40506.

Hematocrit (HCT) values for 15 volunteers (vol) and 18 patients (pts) were determined before and during 30 min of 70° head up tilt (HUT). Blood samples were taken from the antecubital vein at the end of 20 min of supine control and at 8, 18, and 28 min of HUT. Nine of the volunteers and 11 of the patients had syncopal symptoms prior to the end of the 30 min tilt. In all subjects, HCT rose sharply during the first 8 min of tilt, continued to rise as sharply in those subjects who became syncopal but plateaued in nonsyncopal subjects.



Slopes of HCT vs time of tilt (HCT/min) were significantly greater ($p<.0002$) in syncopal subjects compared to nonsyncopal subjects. We conclude that the increased rate of plasma filtration in syncopal subjects may be one factor contributing to syncope in response to head up tilt.
Supported by NASA NAGW 3786 and NIH GCRCM01 RR02602.

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Time-Frequency Analysis of Heart Rate in Determining Potential for Syncope During Head-Up Tilt. King KR, Evans JM, Taylor LC, Julian CD, Patwardhan AR, Knapp, CF and Leonelli FM. Biomedical Engineering and Cardiology, University of Kentucky, Lexington, KY 40508.

Short-time Fourier transform (STFT) of RR-interval was used to investigate the autonomic responses of 20 subjects (10 each men and women) to supine control and to 30 minutes of 80° Head-up tilt (HUT). Subjects were either normal volunteers or patients who had experienced prior episodes of syncope. Subjects were classified as either syncopal or non-syncopal by response to HUT. METHODS. Time series of low (0-.15 Hz) and high (.15-.5 Hz) frequency power in RR interval were generated by performing the STFT with a window length of 100 seconds and binning the power in the high and low frequency ranges at each analysis time. RESULTS: Time-frequency (TF) indices were calculated in supine control and at 80° HUT. TF indices included: mean (over time) high (HF) and low (LF) frequency powers, mean (over time) sympathetic (SNS, LF/LF+HF) and parasympathetic (PNS, HF/LF) indices, and frequency content of the HF (FHF) and LF (FLF) time series (i.e. the intermittentcy in the high and low frequency content in time). RESULTS: PNS and HF decreased during tilt for both groups ($p<.0001$ and $p<.003$, respectively). SNS increased with tilt for all subjects ($p<.03$). FHF increased with tilt for all subjects ($p=.05$). FLF was significantly higher in non-syncopal subjects during control as compared to syncopal subjects. ($p<.02$). These results indicate: 1) Values of HF, LF, PNS, and SNS failed to predict any difference in autonomic response to tilt for syncopal vs. non-syncopal subjects. 2) Parasympathetic activity may become more variable during tilt as evidenced by the increase in FHF. 3) Predisposition to syncope during HUT may be predicted during supine control by examining the intermittentcy (FLF) of low frequency oscillations in RR interval. Supported by NASA EPSCoR WKU 522611 and NIH GCRCM01 RR02602.

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EPINEPHRINE/NOREPINEPHRINE BALANCE IN SYNCOPAL AND NONSYNCOPAL WOMEN. CF Knapp, CM McIntosh, KR King, JB Ott, CS Kim, FM Leonelli, MG Ziegler, JM Evans. Univ of Kentucky, Lexington, KY 40506 and Univ of CA, San Diego, CA 92103

Data were combined from two studies in which 20 women (165 ± 3 cm, 68 ± 3 kg, 25 ± 1 yr, follicular phase) were exposed to 30 lower body negative pressure (LBNP) sesssions. Ten women were tested twice (~1 month apart) using -40 mmHg LBNP and another group of ten women were tested once using 20 min of -35 mmHg LBNP. Continuous measurements of arterial pressure (AP), heart rate (HR), stroke volume (SV), peripheral resistance (TPR) and periodic determinations of hematocrit (HCT), norepinephrine (N) and epinephrine (E) were made. There were nine presyncopal episodes (SYNC), no syncopal symptoms (NONSYNC) occurred in 13 trials, and the other eight trials were not included due to incomplete data sets. Prior to syncope, both groups maintained mean AP at 78 ± 3 mmHg by TPR increases (36% SYNC, 33% NONSYNC) and HR increases (34% SYNC, 24% NONSYNC) to buffer SV decreases (47% SYNC, 44% NONSYNC). Both groups increased NE [162 ± 14 to 208 ± 26 pg/ml (28%) SYNC vs. 156 ± 13 to 247 ± 19 pg/ml (58%) NONSYNC]. However the syncopal group demonstrated a significantly greater increase in E [11 ± 1 to 39 ± 12 pg/ml (255%) SYNC vs 9 ± 1 to 18 ± 2 pg/ml (100%) NONSYNC] in response to LBNP. When syncopal subjects became symptomatic, the decrease in the ratio of NE/E was accompanied by decreases in TPR and AP (22 ± 3%). These data suggest that increasing epinephrine preferentially stimulates beta adrenergic vasodilation and is therefore a factor leading to syncope in young women undergoing LBNP. Supported by NASA NAGW 3786, NASA EPSCoR WKU 522611 and NIH GCRCMO1 RR02602.

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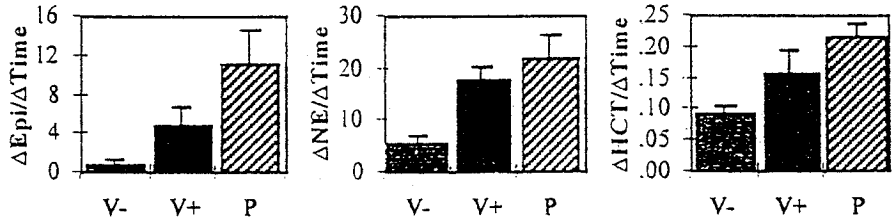
Hematocrit and Catecholamine Response During Head-Up Tilt Induced Syncope

Fabio Leonelli, MD, Ke Wang, MD, Michael Ziegler, PhD, Casey McIntosh, BS, Charles Kim, MS, Abhijit Patwardhan, PhD, Joyce Evans, PhD, Kathleen Rajkovich, RN, Charles Knapp, PhD, University of Kentucky, Lexington, KY, University of California, San Diego, CA

While the factors triggering head up tilt (HUT) induced syncope are still unclear, it is likely that the initiating mechanism is an excessive decrease in venous return to the heart. To investigate some of the factors contributing to this abnormality, we compared Epinephrine (E), Norepinephrine (NE) and Hematocrit (Hct) changes in 6 HUT negative volunteers (V-), 9 HUT positive volunteers (V+) and 11 HUT positive patients (P) with neurocardiogenic syncope during 30 min 80° HUT. Blood samples for E, NE and Hct were drawn at baseline, every 8 min during HUT and at the time of syncope. Each variable's intercept and slope was computed and group comparisons were made with ANOVA.

RESULTS: There was no difference in the intercepts of these variables at rest among the three groups. During HUT the slopes of E, NE and Hct in P and V+ were greater than V- (see Figure). The E/NE ratio was also higher in P (.42±.09) than V+ (.18±.13) and V- (.15±.04), $p<0.02$.



CONCLUSIONS: These results suggest that P and V+ have an increased peripheral fluid filtration, more marked in P, possibly contributing the decrease in venous return. Moreover, the relative increase in E/NE ratio in P could mediate an inappropriate vasodilatory response further decreasing peripheral vascular resistance, thereby contributing to the syncopal event observed in these individuals.

Supported by NASA EPSCoR WKU 522611, Pacesetter Systems Inc., and NIH GCRCM01 RR02602.

ABSTRACT CO-AUTHORS: Names of abstract co-authors (first name, middle initial, last name) and degree (exactly in the ORDER as they appear on original).

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Casey McIntosh, BS

Charles Kim, MS

Abhijit Patwardhan, PhD

Joyce Evans, PhD

Kathleen Rajkovich, R.N.

Charles Knapp, PhD

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CONTENTS

Spectral Indices of Cardiovascular Adaptations t Short-Term Simulated Microgravity Exposure

A.R. PATWARDHAN,[1] J.M. EVANS,[2] M. BERK,[3] K.J. GRANDE,[4] J.B. CHARLES,[5] AND C.F. KNA
[1,2,4&6]*Center for Biomedical Engineering, University of KY, Lexington, KY,*
and [3]*Division of Cardiology, University of KY, Lexington, KY*
[5]*Cardiovascular Laboratory, National Aeronautics and*
Space Administration, Lyndon B. Johnson Space Center, Houston, TX

Abstract—We investigated the effects of exposure to microgravity on the baseline autonomic balance in cardiovascular regulation using spectral analysis of cardiovascular variables measured during supine rest. Heart rate, arterial pressure, radial flow, thoracic fluid impedance and central venous pressure were recorded from nine volunteers before and after simulated microgravity, produced by 20 hours of 6° head down bedrest plus furosemide. Spectral powers increased after simulated microgravity in the low frequency region (centered at about 0.03 Hz) in arterial pressure, heart rate and radial flow, and decreased in the respiratory frequency region (centered at about 0.25 Hz) in heart rate. Reduced heart rate power in the respiratory frequency region indicates reduced parasympathetic influence on the heart. A concurrent increase in the low frequency power in arterial pressure, heart rate, and radial flow indicates increased sympathetic influence. These results suggest that the baseline autonomic balance in cardiovascular regulation is shifted towards increased sympathetic and decreased parasympathetic influence after exposure to short-term simulated microgravity.

Key Words—sympathetic/parasympathetic balance, heart rate and blood pressure spectra, head down bedrest.

EXPOSURE TO MICROGRAVITY during space flight impairs orthostatic tolerance upon ret to the 1 g environment (e.g., Bungo et al., 1985; Charles et al., 1986; Gaffney et al., 19 Nicogossian et al., 1983). Reduced blood volume (≈500 ml) (Blomqvist et al., 19 Convertino et al., 1990), baroreflex impairment (Convertino et al., 1990; Eckberg et 1992; Fritsch et al., 1992; Hughson et al., 1994), and reduced heart rate variabil (Goldberger et al., 1986) have been reported from real and simulated microgravity studi Both blood volume reduction and baroreflex impairment have been suggested to pla role in the development of orthostatic intolerance. Although an increased sympathe response to standing after exposure to simulated microgravity has been reported (T Harkel et al., 1992), it is unclear whether the baseline autonomic balance, i.e., the sym thetic and parasympathetic balance during rest, changes after exposure to simulat microgravity. Altered baseline autonomic balance would suggest changes in sympathet parasympathetic reserves, which may influence orthostatic tolerance. The objective of t present study was to investigate whether exposure to simulated microgravity produc changes in the baseline autonomic balance in cardiovascular regulation. Spectral indices cardiovascular variables measured during supine rest were used as indicators of baseli autonomic balance.

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We measured electrocardiogram (ECG), arterial blood pressure (BP), thoracic fluid index (TFI), central venous pressure (CVP), and radial artery blood flow in supine volunteers for 15 minutes before and after 20 hours of simulated microgravity. The microgravity simulation consisted of 20 hours of 6° head down bedrest plus furosemide. To accelerate fluid loss, we used furosemide to pharmacologically induce diuresis. After exposure to simulated microgravity, heart rate (HR) power decreased in the respiratory frequency region; conversely, there was an increase in the low frequency power in BP, HR, and radial flow. These results suggest that after 20 hours of short-term simulated microgravity, there is a shift in baseline autonomic balance towards increased sympathetic and decreased parasympathetic influence on cardiovascular control.

Methods

Nine healthy male volunteers participated in this study. The mean (± standard error) age, height, and weight were 25.8 ± 1.4 years, 179.6 ± 1.4 cm, and 76.5 ± 2 Kg. Each volunteer was screened prior to the study to verify that no apparent medical problems existed. Volunteers were familiarized with the experimental protocol and signed a consent form approved by the Institutional Review Board at the University of Kentucky.

A catheter (Argyle 14 FR, 70 cm long) was inserted under fluoroscopic guidance, via the median cubital vein into the superior vena cava. This catheter was used to measure CVP (Cobe). Four pairs of impedance leads were placed bilaterally, two on the base of the neck and two midline on the thorax (at the level of the xiphoid), to measure ECG and TFI (BoMed). A photo-plethysmographic cuff (Finapres) was placed on the middle finger of the right hand to measure BP continuously. DeBoer et al. (1987) have shown that arterial pressure spectra computed from pressure measurements made with the Finapres and from pressure measurements made with an intra-arterial catheter are practically identical. Measurements of radial flow were made at the left wrist, using an ultrasonic doppler flow meter (Hokanson). All signals were recorded on strip chart [Astro-Med MT8800R], as well as on analog tape [TEAC XR-510] recorders.

Data were collected during a 20-minute supine presimulated microgravity period. After the presimulated microgravity period, volunteers were exposed to a series of provocative tests consisting of step and oscillatory lower body negative pressure (LBNP). The LBNP tests lasted for about 90 minutes. At the end of LBNP, a short break for lunch was allowed. After lunch, volunteers resumed the supine position for 30 minutes, followed by 2 hours in the launch position. The launch position was followed by 20 hours of head down bedrest, during which furosemide (LASIX, 40 mg) was administered by mouth after 2 hours of bedrest. At the end of 20 hours of bedrest, volunteers were returned to the supine position and analog data were collected for a 20-minute postsimulated microgravity period. This postsimulated microgravity period was followed by the LBNP procedure previously described. Fluid intake by the subjects was ad libitum, however, the amount of fluids consumed and urine output were monitored throughout the experiment. Results from the LBNP tests are reported elsewhere (Levenhagen, 1994). In the present study, results from the 20-minute presimulated microgravity period (prior to LBNP, launch position, and bedrest) and from the 20-minute postsimulated microgravity period immediately after 20 hours of bedrest are reported. Volunteers were in the supine position during both pre- and postsimulated microgravity measurements.

Analysis

All signals were digitized using a DATAQ (CODAS) system, at the rate of 500 samples/second. To reduce transient effects, data from the first 5 minutes of the 20 minute epochs were discarded. Therefore, all subsequent analyses were performed on 15-minute data segments.

The digitized ECG was processed using a R wave peak detection algorithm from which a beat-to-beat heart rate time series was constructed (DeBoer et al., 1984), with each element of the series being the reciprocal of successive R-R intervals. All other variables (BP, TFI, CVP and radial flow) were averaged on a beat-to-beat basis to obtain a mean value for each cardiac cycle, and a time series was constructed using these mean values.

Data were sectioned into six 2.5 minute segments and any linear trends were removed. For each of the six preprocessed data segments an Auto Regressive (AR) model was fitted using the Levinson-Durbin recursion algorithm (Kay and Marple, 1981). An average model estimate was obtained from these six estimates. Estimates of model order were obtained as follows: All data were first processed using the Akaike Information Criterion (AIC). Because AIC can underestimate model orders for short data records (Kay and Marple, 1981), a test time series was constructed by adding Gaussian white noise to a sinusoid with frequency of 0.02 Hz (i.e., the lowest frequency of interest for this study, see Results). The signal to noise ratio was set at -10 dB, and the variance of the test series was linearly scaled to match actual HR data. The test time series was processed with increasing model orders until the peak at 0.02 Hz was resolved. The largest model order from those predicted by the AIC (from all data segments) and from the test time series was then used to process all data. The number of data points in any segment were at least 3 to 4 times the model order used, ensuring satisfactory performance of the AR model estimation (Kay and Marple, 1981). The adequacy of the model order was confirmed by testing the residual series for whiteness (Jenkins and Watts, 1968).

Different model orders (as predicted by criteria such as AIC, or final prediction error) for different data segments have been used by other investigators (Baselli et al., 1987; Pagani et al., 1986; Rimoldi et al., 1990). However, in the present study, because AR models from six segments were averaged, it was essential that the same model order be used in estimating the AR coefficients for each of the six individual data segments. The rationale behind sectioning the data into six segments and using an averaged AR model estimate, instead of obtaining an AR model estimate from one continuous data record, was to increase statistical stability of the model estimate and to reduce the effects of 1/f type nonstationary noise. Heart rate spectra exhibit 1/f type spectral characteristics when computed from long data records (Saul et al., 1988). Because cardiovascular variables are coupled via various control loops, it was presumed that other variables might have 1/f type nonstationarities as well. The effects of 1/f type noise are more pronounced on spectra computed from longer data segments than on those computed from shorter data segments (Yamamoto and Hughson, 1991), hence, averaging spectra from shorter segments better retains the stationary information while reducing the effects of 1/f type noise [Yamamoto and Hughson, 1991, their table 1].

From the averaged model estimates during each state (pre- and postsimulated microgravity), spectral components (power and frequency) were computed using the residues associated with each pair of complex conjugate poles of the averaged model (Johnson and Anderson, 1978). The residues were computed using the method of partial fractions (Kay and Marple, 1981). Because the time series were constructed on a beat-to-beat basis,

the unit of spectral frequency was cycles/ beat. Spectral frequencies were converted from cycles/ beat to cycles/ second (Hz) by multiplying the frequencies by mean heart rate in beats/ second (Pagani et al., 1986).

Spectra obtained in the present study showed concentration of power in three frequency regions (figures 1 and 2). The three frequency regions were, low frequency (LF, centered ≈ 0.03 Hz), mid frequency (MF, ≈ 0.1 Hz), and high frequency (HF, ≈ 0.25 Hz). Hence, spectral components were binned into three different frequency regions, i.e., the powers associated with all the spectral components within each of the three frequency regions were summed (figure 1). As suggested by Pagani et al. (1986), only those spectral components that had power greater than 5% of the total power were used for analysis. The center frequencies of the bins were selected based on the spectral densities obtained in this study (see Results), and were consistent with those reported in the literature (e.g., Akselrod et al., 1985; Madwed et al., 1991; Parati et al., 1990).

To minimize the effects of intersubject variability in total spectral powers, power in each bin, within each subject was normalized (scaled) by the power in that bin which had the maximum value. That is, for each subject, the powers in each of the six bins (pre- and postsimulated microgravity LF, MF, and HF) were divided by the largest power of these six bins. We refer to this normalization method as maximum bin normalization. The maximum bin normalization method was selected because it scales all spectral powers to be between 0 and 1, and at the same time preserves any changes in total power. If the data are normalized by total power, i.e., divided by total power, as suggested by Pagani et al. (1986), and Rimoldi et al. (1990), then information about any changes in total power are not retained in normalized powers. Because all of the six powers within each subject (LF, MF, and HF in pre- and postsimulated microgravity) were divided by the same number (i.e., by the maximum of the six), data were not shifted or biased towards any particular state (i.e., pre- or postsimulated microgravity) by the normalization method. To investigate the effects of normalization method on spectral data, comparisons between pre- and postsimulated microgravity spectra were also conducted after normalization by total power.

Statistics

Analysis of variance (ANOVA) followed by a Newman-Keuls test was used to indicate significant effects of exposure to simulated microgravity. Significance was accepted at $p < 0.05$.

Results

Fluid Balance. Assessment of fluid balance, estimated as the difference between fluid intake and output, indicates a possible change in blood volume, either depletion or redistribution. Average fluid intake and urine output from nine subjects was 2907±380 and 3400±273 ml respectively, with a net fluid loss of 493±181 ml after the simulated microgravity exposure.

Heart Rate. Averaged spectral estimates of HR from 9 subjects during pre- and postsimulated microgravity (dashed and solid lines) are shown in figure 2. Figure 2 shows that HR power was concentrated in three frequency regions, centered at ≈ 0.03 (LF), ≈ 0.1 (MF), and ≈ 0.25 Hz (HF). After inspecting spectral plots from individual subjects and the averaged spectra, cutoff frequencies for binning were selected as 0.006 – 0.075 Hz for LF,

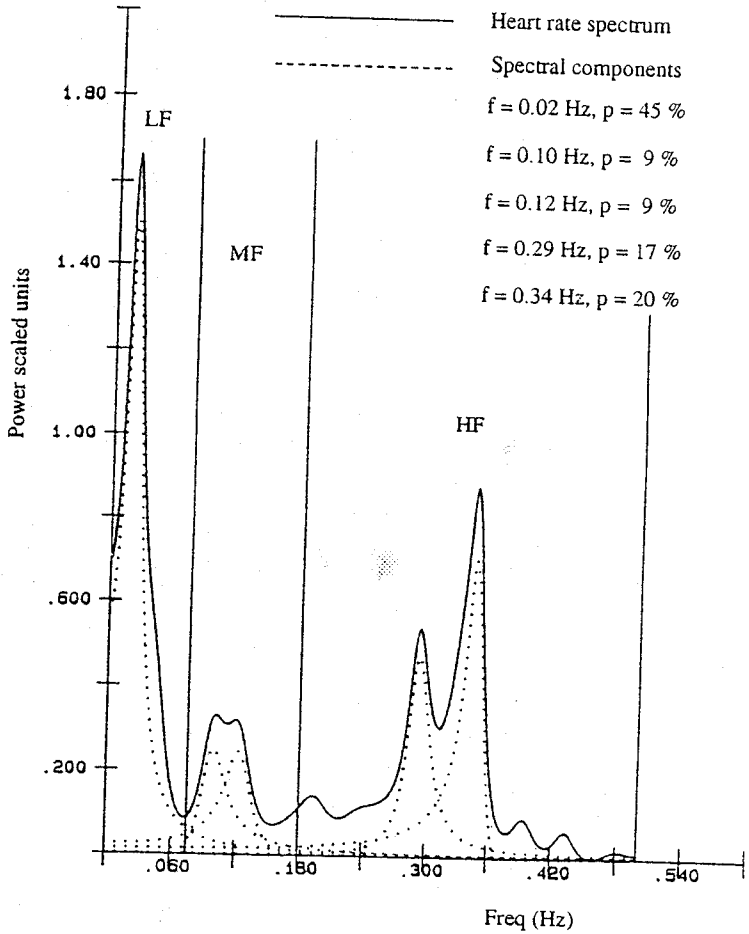

FIG. 1. Illustration of the binning procedure. Heart rate spectrum (solid line) from one subject computed from presimulated microgravity exposure. Distribution of power in three frequency regions (delineated by vertical lines) was observed for spectra from all subjects. Powers of all the spectral components that had center frequencies within each region were added to quantify LF, MF and HF powers. For simplicity, only the largest 5 spectral components (dotted lines) are shown above, in this case, the LF, MF and HF powers would be 45, 18, and 37% of the total power.

0.075 – 0.18 Hz for MF, and 0.18 – 0.5 Hz for HF powers (figure 1). The lower limit for the LF region (0.006 Hz) was selected because each data segment was 150 seconds long. Frequency cutoffs at 0.075, 0.18 and 0.5 Hz were selected to include powers in the appropriate region (i.e., low, mid and high) for all subjects.

Heart rate power in the HF region was reduced ($p < 0.004$) after simulated microgravity in each of the nine subjects (figure 3, top panel). Heart rate power in the HF region, when normalized by total power, also decreased after simulated microgravity ($p < 0.0033$, figure 3, bottom panel). Figure 4 shows that averaged (N=9) HR power in the LF region in-

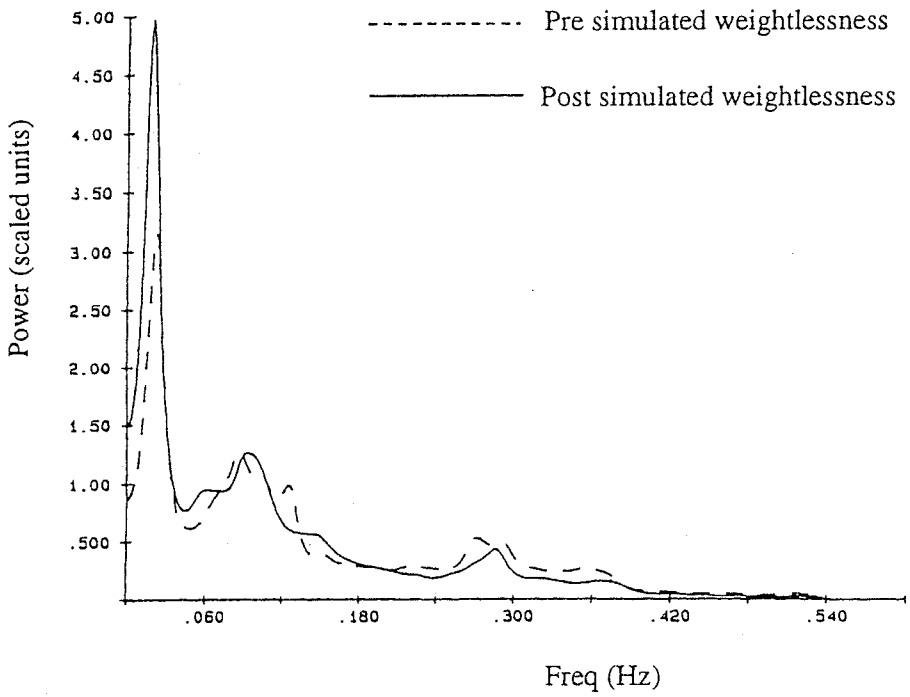

FIG. 2. Averaged HR spectra from nine subjects, before (dashed lines) and after (solid lines) simulated microgravity. These spectra show the power distribution in the low-, mid- and high-frequency regions.

creased after simulated microgravity ($p < 0.05$), while there was no significant change in the MF region.

The LF powers increased and HF powers decreased, hence, LF/HF ratios increased after exposure to microgravity. The LF/HF power ratios are not reported because the ratios carried no additional information than that presented by LF and HF powers. Mean heart rates increased ($p < 0.05$) from 65 to 68 beats/min after simulated microgravity.

Arterial Blood Pressure. Spectral power in BP was predominantly distributed in two frequency regions ≈ 0.03 Hz and at ≈ 0.1 Hz, while the power in the high frequency region was small (figure 5). The differences in spectral powers between pre- and postsimulated microgravity were not significant in either HF, MF or LF regions. However, in the LF region, power was greater after simulated microgravity with $p = 0.065$ (figure 4).

Radial Flow. Spectral characteristics of radial flow were similar to those of BP, i.e., power was mostly concentrated in two frequency regions, at ≈ 0.03 and ≈ 0.1 Hz. Changes in averaged power in the LF, MF and HF regions are shown in Figure 4. After simulated microgravity, power in the LF region of radial flow increased ($p < 0.05$), while there were no statistically significant changes in MF and HF regions.

Thoracic Fluid Index. TFI, a measurement of thoracic impedance, is a function of fluid volume changes in the chest, and thereby reflects respiratory activity. As expected, most of

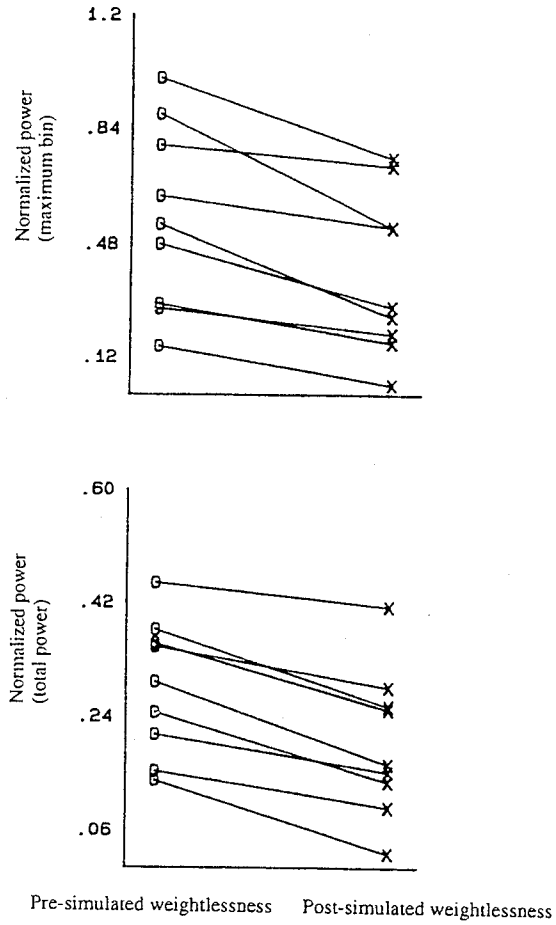

FIG. 3. High-frequency spectral powers in heart rate for nine subjects during pre-(circles) and post-(crosses) microgravity exposure. Power in HF region decreased in each subject after exposure to microgravity. Similar decrease in each subject's HF power was observed when the spectra were normalized by maximum bin (top panel) or the total power (bottom panel).

the power in TFI spectra was concentrated in the respiratory frequency region (≈ 0.25 Hz). No change in the respiratory frequency bandwidth was observed after simulated microgravity, but power in the HF and the MF regions increased significantly ($p < 0.05$, figure 4).

Central Venous Pressure. CVP spectra were rather diffuse, with more power in the HF region relative to LF and MF. There were no statistically significant changes between before and after simulated microgravity, though power in the HF (respiratory frequency) region tended to increase (figure 4). Mean CVP decreased ($p > 0.05$) from 2.9 ± 0.9 mm Hg to 2.0 ± 0.7 mm Hg after simulated microgravity.

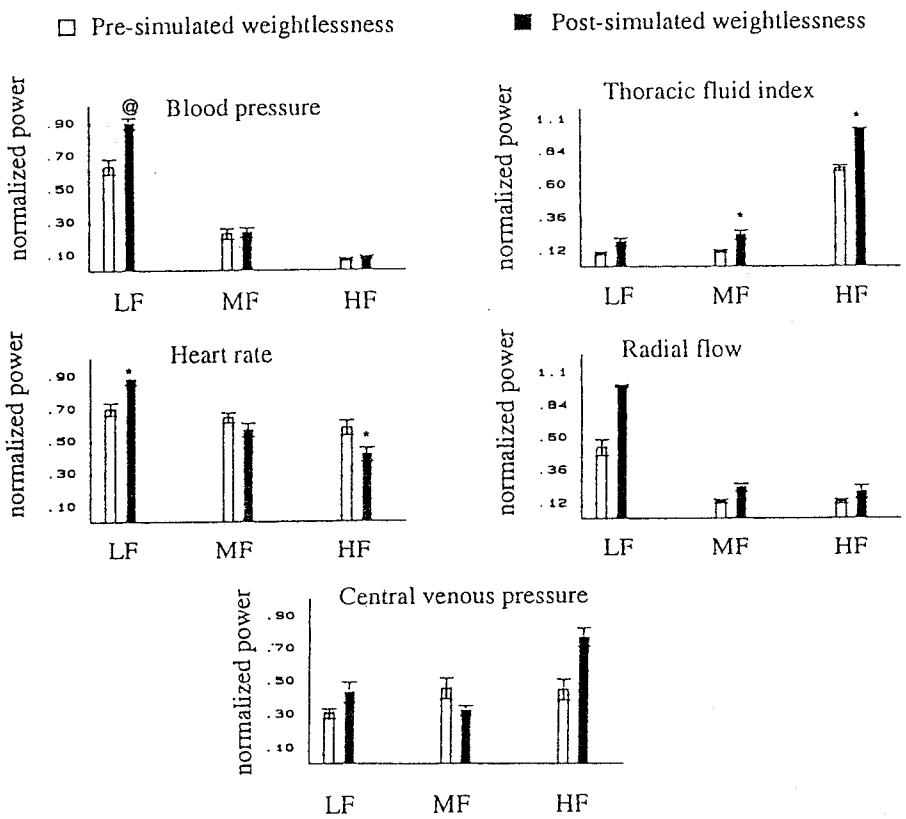

FIG. 4. Averaged spectral powers from nine subjects in arterial pressure, heart rate, thoracic fluid index, radial artery flow, and central venous pressure, before (hollow bars) and after (solid bars) simulated microgravity. High-frequency power decreased in HR and increased in TFI. The low-frequency power increased in HR, radial flow, and BP. * indicates $p < .05$, @ indicates $p = .065$.

Discussion

The objective of this study was to investigate the effects of simulated microgravity on baseline autonomic balance in cardiovascular regulation as indicated by changes in the spectral content of cardiovascular variables measured during supine rest. Nine volunteers were placed in a microgravity simulation that consisted of 20 hours of 6° head down bedrest plus pharmacologically induced diuresis (furosemide). We computed the spectral content of HR, BP, TFI, CVP and radial flow before and after simulated microgravity. Low frequency power in HR, BP, and radial flow increased, and high frequency power in HR decreased after simulated microgravity. As discussed below, the decrease in high frequency power in HR indicates reduced parasympathetic influence, and the increase in

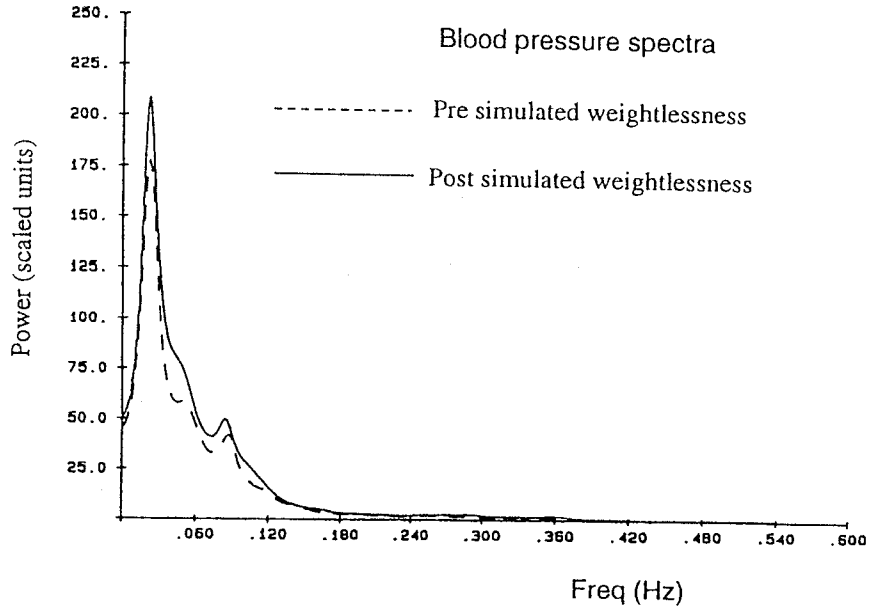

FIG. 5. Averaged BP spectra from nine subjects, pre- and postsimulated microgravity (dashed and solid lines). Most of the power in BP was localized in the low- and mid-frequency regions.

low frequency power in HR, BP, and radial flow indicates increased sympathetic influence on cardiovascular regulation during the resting state. We speculate that the altered autonomic balance was probably a consequence of the blood volume reduction and redistribution that occurs during exposure to simulated microgravity.

We selected 6° head down bedrest because it is a widely used analogue of microgravity (e.g., Baisch et al., 1992; Convertino et al., 1990; Eckberg et al., 1992; Fritsch et al., 1992; Goldberger et al., 1986). We added diuresis to our bedrest protocol to accelerate the fluid loss to about 500 ml, which is usually observed after 2 to 3 days of head down bedrest. Although we did not measure plasma volume, the difference between fluid intake and output (≈ 493 ml) was similar to the reduction in plasma volume (by ≈ 439 ml) reported by Convertino et al. (1990) after 3 days of head down bedrest. In the present study, mean heart rate was slightly (3 beats/min) higher after simulated microgravity, the increase in HR was also similar to that reported by Convertino et al. (≈ 3 beats/min) after 3 days of head down bedrest. Hence, in terms of blood volume reduction and increase in heart rate, our results were similar to those observed after 3 days of head down bedrest.

Spectra for HR, BP and radial flow showed concentration of power in three frequency regions in all subjects during pre- and postsimulated microgravity, although high frequency powers in BP and radial flow were relatively small. The observed concentration of power in three frequency regions in HR spectra is consistent with the results of Parati et al. (1990), and was the rationale behind investigating spectral changes in three frequency regions (LF, MF and HF) rather than just two regions (MF, and HF) as suggested by Malliani et al. (1991).

Spectral changes in respiratory frequency region

Changes in respiratory or HF power in HR reflect changes in efferent parasympathetic activity, as shown in humans with the use of atropine (e.g., Goldberger et al., 1986; Hayano et al., 1991; Pomeranz et al., 1985; Tapp et al., 1990), and in dogs with selective SA nodal surgical denervation (Randall et al., 1991) and direct neural recordings (Katona et al., 1975). It has been suggested in humans that, for small changes in efferent parasympathetic activity (small relative to total or almost total blockade as in the case of denervation or atropine), absolute values of HR variability might be better indicators of vagal activity than normalized (by total power) values (Inoue et al., 1990). Moreover, Hayano et al. (1991), using atropine for complete vagal blockade in humans, found a strong correlation between nonnormalized HR high frequency power and vagal tone but no correlation between normalized (by total power) HF power and vagal tone. The normalization method used in the present study (maximum bin normalization) preserves changes in total power and hence changes in normalized powers are similar (but scaled) to nonnormalized powers. The reduction in high frequency power in HR observed in the present study, however, was significant even when the data were normalized by total power. Thus, the reduced power in the HF region of HR observed in the present study indicates reduced parasympathetic influence after simulated microgravity.

Thoracic fluid impedance is a measurement of the electrical impedance of the thorax, and thus predominantly reflects fluid shifts due to respiration. Because respiration affects heart rate variability in the HF region (Hirsch and Bishop, 1981), we computed TFI spectra to determine changes in respiratory pattern after simulated microgravity. The respiratory bandwidth (as determined from the width of the TFI spectral peak in the HF region) did not change after simulated microgravity. Measurements made in our laboratory during another study (unpublished data) show that, in the supine position, tidal volumes computed by digitally integrating airflow measured using a pneumotachograph (Hans Rudolph) correlated with TFI ($r = 0.74$, $p < .05$). Therefore, the increase in HF power in TFI after simulated microgravity suggests an increase in tidal volume. Because HF power in HR increases with increased tidal volumes (Hirsch and Bishop, 1981), the decrease in HF power that we observed (figures 3 and 4) was probably not a consequence of changes in tidal volumes. It is interesting to note that Pagani et al. (1986) also observed an increase in tidal volumes during sympatho-excitation (i.e., during orthostatic stress). The mechanisms responsible for this increase in tidal volume are unclear. The increase in HF power in CVP (although not statistically significant) was similar to that of TFI, probably also a consequence of changes in tidal volume.

Spectral changes in low- and mid-frequency regions

Saul et al. (1990) observed a significant correlation between muscle sympathetic nerve activity and low frequency power in HR during increasing sympathetic activity but not during baseline or decreasing sympathetic activity. Hence they suggested that low frequency power in HR is indicative of both sympathetic and parasympathetic activity. However, as discussed below, we consider that collective interpretation of results from other studies suggests that in HR spectra, an increase in low frequency power, if concurrent with reduced high frequency power, indicates increased sympathetic activity.

Total spectral power in HR (or R-R interval., HR and R-R intervals both yield similar spectra) decreases and the power in the high frequency region is almost completely abolished after atropine in humans and dogs (Rimoldi et al., 1990; Tapp et al., 1990) and on tilt in humans (Pagani et al., 1986). As a consequence, when normalized powers (by total power) are considered, after muscarinic blockade, the low frequency component becomes larger relative to the high frequency component. In contrast, Pagani et al. (1986) observed an increase in both total and HF power in R-R interval spectra after chronic beta adrenergic blockade. Hence, after normalization, the HF component became larger relative to the low frequency component. Based on these results, Pagani et al. (1986) and Malliani et al. (1991) suggested that the low frequency power is an indicator of changes in sympathetic activity. Inoue et al. (1990) observed an almost complete lack of HR power in the ≈ 0.1 Hz region in neurologically complete quadriplegic patients, while the HF power (non normalized) was similar to that of normal subjects. This also suggests a link between low frequency power and sympathetic activity. Inoue et al. (1990) computed AR spectra using the same technique used by Pagani et al. (1986), which probably explains the location of their low frequency power at ≈ 0.1 Hz rather than at lower frequencies observed in the present study.

Increased low frequency power has also been reported in humans during orthostatic stress, during hypertension, and during daytime relative to nighttime, all suggesting increased sympathetic excitement (Malliani et al., 1991). Madwed et al. (1991) observed, in dogs, increased power in HR spectra at ≈ 0.05 Hz after hemorrhage, which they considered to indicate increased sympathetic activity. Hence, the predominant evidence suggests that increases in low frequency power are indicators of increased sympathetic activity.

Taken collectively, reduced parasympathetic activity tends to reduce nonnormalized power in both LF as well as HF regions (Pagani et al., 1986; Tapp et al., 1990), while increases in sympathetic activity increase low frequency power (Saul et al., 1990). In the present study, HF power in HR decreased after simulated microgravity, which indicated reduced parasympathetic activity. Reduced parasympathetic activity would tend to reduce the total power, and thus reduce the power in the LF region as well. However, we observed an increase in LF power while HF power decreased, and, because maximum bin normalization method preserves (scales) changes in total power, our results indicate increased sympathetic influence after simulated microgravity. The increase in mean heart rate after simulated microgravity observed in the present study, also suggests a shift in the sympathetic/ parasympathetic balance towards the sympathetic branch.

The mechanisms responsible for generation of low- and mid-frequency oscillations in BP are not clear. It has been suggested that the low-frequency oscillations in BP are caused by a resonance-type phenomenon due to delays in the sympathetic loop of the baroreflex (DeBoer et al., 1987). In dogs, Madwed et al. (1991) suggest that low-frequency oscillations in BP may be predicted by the slow temporal response of peripheral (vascular) sympathetic effector mechanisms. In either case, increases in LF power in BP probably also indicate increased sympathetic activity (Malliani et al., 1991). Ten Harkel et al. (1992) compared BP spectra during orthostatic stress before and after 10 days of head down bedrest. They observed that the orthostatic response was enhanced after bedrest, i.e., the increase in power in the 0.1 Hz region on standing was larger after exposure to bedrest, which they considered to be indicative of enhanced sympathetic response to standing after bedrest. Furthermore, Madwed et al. (1991) observed, in dogs, an increase in the low-frequency oscillations in BP at ≈ 0.05 Hz after hemorrhage, reflecting increased sympathetic excitation. Hence, the increased low-frequency power in BP that we observed after simulated microgravity indicates increased sympathetic influence, probably via increased peripheral sympathetic excitation.

If low-frequency oscillations in BP are modulated by changes in peripheral sympathetic excitation, then changes in peripheral resistance should be evident in radial flow in the low-frequency region as well. The radial flow measurement was made at the distal end of the radial artery, thereby reflecting flow to a peripheral vascular bed. The increased low-frequency power in radial flow (figure 4), therefore, was probably also a consequence of increased vasomotion.

It appears that spectral power in HR and BP for frequencies below the respiratory frequency are indicative of sympathetic excitation. However, the exact frequency range of sympathetically modulated oscillations is not clear (whether at ≈ 0.1 Hz or at frequencies below 0.1 Hz, i.e., at ≈ 0.03 to 0.05 Hz). The differences in the frequency ranges could be methodological., i.e., depending on the technique by which spectral powers are quantified, e.g., using either two or three frequency bins. When HR data from the present study were processed using the technique described by Pagani et al. (1986), the resulting spectral power was concentrated in two regions, ≈ 0.1 and ≈ 0.3 Hz (data not shown). Because the spectral components with frequencies below 0.03 Hz were lumped with the DC component and not used in subsequent analysis as suggested by Pagani et al. (1986), the presence of low-frequency power at ≈ 0.1 Hz (rather than at ≈ 0.03 Hz) was not surprising. However, it is also possible, as suggested by Madwed et al. (1991), that the differences in the frequency ranges could be due to different delay times in peripheral and cardiac sympathetic nerves as well as the relative gains of peripheral and cardiac sympathetics.

Limitations

One limitation of the present study was the inability to differentiate any direct effects of furosemide on autonomic function from those effects that were subsequent to the volume reduction due to furosemide. However, because half life of furosemide is relatively short (92±7 minutes) (Goodman and Gilman, 1985), the direct effects were unlikely to influence the data that were collected 18 hours after administration of furosemide. We did not measure plasma volume to determine blood volume reduction. However, the reduction in blood volume reported by other investigators after bedrest (Blomqvist et al., 1983; Convertino et al., 1990), and the similarity of fluid balance and heart rate changes in the present study to that after 3 days of bedrest (Convertino et al., 1990), leads us to speculate that the change in autonomic balance that we observed was probably a consequence of blood volume reduction.

In conclusion, we analyzed the spectral content of cardiovascular variables measured during supine rest before and after 20 hours of simulated microgravity. Our results indicate that there is a shift in the baseline autonomic balance in cardiovascular regulation in favor of the sympathetic branch as a consequence of exposure to simulated microgravity.

Notes

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An Optimized Index of Human Cardiovascular Adaptation to Simulated Weightlessness

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Abstract— **Prolonged exposure to weightlessness is known to produce a variety of cardiovascular changes, some of which may influence the astronaut's performance during a mission. In order to find a reliable indicator of cardiovascular adaptation to weightlessness, we analyzed data from nine male subjects after a 24-hour period of normal activity and after a period of simulated weightlessness produced by two hours in a launch position followed by 20 hours of 6° head-down tilt plus pharmacologically induced diuresis (furosemide). Heart rate, arterial pressure, thoracic fluid index, and radial flow were analyzed. Autoregressive spectral estimation and decomposition were used to obtain the spectral components of each variable from the subjects in the supine position during pre- and post-simulated weightlessness. We found a significant decrease in heart rate power and an increase in thoracic fluid index power in the high frequency region (0.2–0.45 Hz) and significant increases in radial flow and arterial pressure powers in the low frequency region (<0.2 Hz) in response to simulated weightlessness. However, due to the variability among subjects, any single variable appeared limited as a dependable index of cardiovascular adaptation to weightlessness. The backward elimination algorithm was then used to select the best discriminatory features from these spectral components and Fisher's linear discriminant and Bayes' quadratic discriminant were used to combine the selected features to obtain an optimal index of adaptation to simulated weightlessness. Results showed that both techniques provided improved discriminant performance over any single variable and thus have the potential for use as an index to track adaptation and prescribe countermeasures to the effects of weightlessness.**

I. Introduction

EXPOSURE to microgravity or weightlessness is known to produce a variety of cardiovascular (CV) changes or adaptations [1]–[13]. Depending on the length of the exposure, these changes may be relatively subtle or may result in orthostatic hypotension which could influence or significantly compromise the astronaut's performance during a mission.

The majority of studies that examined CV changes in response to actual or simulated weightlessness concentrated on the static levels of cardiovascular variables, such as mean heart rate and blood pressure. The monitoring of mean values alone is not the only way of assessing weightlessness-induced adaptation in cardiovascular regulation. Quantification of the dynamic properties of CV variables through spectral analysis has also been shown to provide an analytical tool to assess relative contributions from neural pathways involved in cardiovascular regulation [14]–[19].

To assess the potential of using the dynamic properties of CV variables as an index to track weightlessness-induced changes in CV regulation, we employed spectral analysis and discrimination techniques to data acquired noninvasively and continuously from human subjects after 24 hours of normal activities and after 22 hours of simulated weightlessness (SW). A schematic diagram for obtaining this index is depicted in Fig. 1. After acquiring data from subjects after 24 hours of normal activity, we exposed these subjects to a simulated weightlessness protocol consisting of two hours in the launch position followed by 20 hours of 6° head-down tilt (HDT) [4], [5], [8]–[12] plus pharmacologically induced diuresis (furosemide) to accelerate volume depletion. Applying discrimination techniques to spectral contents of CV variables in this study allowed us to detect consistent changes in cardiovascular parameters which appear to indicate adaptation to simulated weightlessness.

Our objective is to assess the ability of *spectral* features, acquired from noninvasively and continuously monitored CV variables, to reliably predict cardiovascular adaptation in CV regulation induced by simulated weightlessness. In the present study, we demonstrated that individual CV variables varied considerably across subjects. However, when combined in the form of a Fisher's linear discriminant or Bayes' quadratic discriminant, the variance was considerably decreased and the discrimination performance was improved. In future research, these measures can be tested as reliable indexes of an astronaut's adaptation to spaceflight in microgravity.

II. Simulated Weightlessness

Ten healthy male volunteers [25.8 ± 1.4 yrs, 179.6 ± 1.4 cm, 76.5 ± 2 kg (data are represented as mean ±SEM)] participated in the experiment (a similar study in female subjects in pre SW state is currently being conducted). All but two of the subjects in this study regularly engaged in some form of aerobic exercise ranging from 3–20 miles/week of running, jogging or walking (average 8.1 ± 2.6 miles/week). The volunteers were screened prior to the experiment to verify that no previous medical problem existed. On the day of the experiment, impedance leads were attached for measurement of the electrocardiogram, thoracic fluid index

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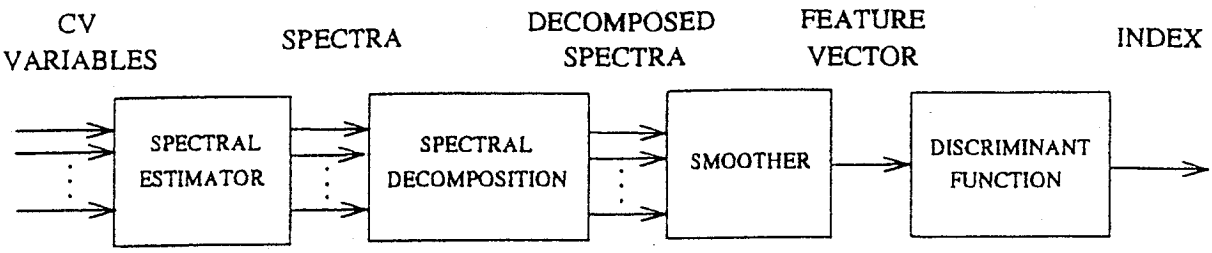

Fig. 1. Schematic diagram for the implementation of an index of adaptation to weightlessness.

(TFI), rate of change of thoracic impedance and beat-by-beat estimates of left ventricular end-diastolic volume (EDV), stroke volume (SV), and cardiac output (CO) (Bomed, Cardiodynamic Monitor, BoMed Inc., Irvine, CA). Continuous measurements of peripheral arterial pressure (AP) [(Finapres, Ohmeda, Englewood, CO), calibrated with an upper arm cuff (Sentry, NBS Medical, Cosa Mesta, CA)], and ascending aortic blood flow velocity using continuous wave doppler (Exerdop, Quinton Instruments, Seattle, WA) and radial flow (RF) (Parks, Model 909 Directional Doppler, Parks Medical, Beaverton, OR) were also made. Heart rate (HR) was calculated from R–R intervals in the ECG. After a 30 min supine control period, the subjects underwent a series of step and sinusoidal lower body negative pressure (LBNP) tests to assess frequency response characteristics of these subjects [20], [21]. After an ambulatory period, the subject was reinstrumented and placed in the launch position for two hours followed by 20 hours of 6° HDT. In order to simulate the fluid loss of space flight, 40 mg of the diuretic furosemide was administered by mouth after two hours of 6° HDT. (Because the half life of furosemide is relatively short, 92 ± 7 minutes [23], the direct effects were unlikely to influence hemodynamic data 18 hours after administration of furosemide.) At the end of the 20 hours of HDT, the subjects were returned to supine for 30 min. Pre- and post-SW data from nine subjects during the 30 min supine rest periods were used to develop the adaptation index; the other subject was used to test the index.

Table I lists mean values of major hemodynamic parameters in these 10 subjects before and after SW. There was a negative fluid balance (fluid in–fluid out) of 497 ± 167 ml ($p < 0.01$) which was reflected in significantly decreased stroke volume and central venous pressure. The regulatory response to the change in fluid balance included an increase in vascular resistance mediated by increases in the vasoactive hormones renin and norepinephrine. The net result, with respect to mean values, was that blood pressure did not reflect the decrease in stroke volume but was actually slightly increased. The blood pressure regulatory capability of these subjects in response to blood pooling induced by graded levels of LBNP was tested before and after SW [20]. We determined that, after SW, the maintenance of blood pressure during LBNP stress required significantly higher levels of mean HR and TPR. This loss of orthostatic reserve is one symptom of the phenomenon labeled orthostatic intolerance or cardiovascular deconditioning which develops with exposure to real or simulated weightlessness [1]–[6]. In the following sections the neural components of the regulatory response to SW will be explored using spectral analysis and discrimination techniques to obtain an optimized index of sympathetic and parasympathetic autonomic balance.

TABLE I
MEAN VALUES OF HEMODYNAMIC PARAMETERS BEFORE AND AFTER SW TAKEN FROM 10 SUBJECTS

Variable	Pre SW	Post SW
HR (bpm)	67.1±4.0	68.5±4.6
AP (mmHg)	89.0±2.2	90.6±2.1
CVP (mmHg)	3.38±0.58	1.55±0.76*
SV (ml)	86.0±12.3	74.8±15.3*
TPR (mmHg/(L/min))	15.4±3.3	18.7±3.3
Plasma renin (ng/ml/hr)	1.81±0.22	3.6±0.58*
Epinephrine (pg/ml)	25.8±4.2	29.7±5.1
Norepinephrine (pg/ml)	79.9±12.3	100.4±13.5*

* Significantly ($p < 0.05$) different from pre SW.
TPR = Total peripheral resistance.

III. SPECTRAL ANALYSIS

The choice of CV variables to include in this index was based on both standard spectral measurements and measurements from variables that could provide insight into the fluid volume shifts associated with SW. The standard spectral indices, HR and AP, have been explored extensively for their ability to provide quantitative information about changes in the balance between sympathetic and parasympathetic components. Previous studies in our laboratory [20], [22] have shown that SW evoked changes in HR and AP spectral power that were statistically significant. The decision to include variables that reflected the fluid volume shifts associated with SW was based on the consistent findings that both true and simulated weightlessness have been shown to translocate vascular volume from peripheral to thoracic regions [1], [2], [4], [11], [13]. Our indices of thoracic fluid index and peripheral flow were therefore used as indicators of the neurally mediated responses to this translocation of fluid.

HR, AP, TFI, and RF were digitized at 500 Hz using DATAQ and analyzed on an IBM RISC/6000. The data for each variable consisted of ~30 min during supine control before and after SW.

Data were low-pass filtered at 0.7 Hz and divided into 2.5-min-long segments that partially overlapped. Autoregressive (AR) spectral estimation techniques (Burg's algorithm [24]) were used to estimate the spectrum (0.003–0.5 Hz) of each

TABLE II
BINNING FREQUENCIES

Variable	Frequency Range (Hz)	
	LF	HF
HR	0.003-0.10	0.20-0.45
TFI	0.003-0.10	0.10-0.45
RF	0.003-0.20	0.20-0.45
AP	0.003-0.05	0.20-0.45

2.5-min data segment. The order of the AR spectrum was determined according to Akaike's final prediction error (FPE) criterion [25] and tests for whiteness [26] of the prediction error. The order ranged from 30–40. To reduce the effect of very low frequency trends on spectral estimation, each data segment was detrended using quadratic polynomial fitting prior to spectral estimation. The spectrum was then decomposed into low-frequency (LF) and high-frequency (HF) bins. HF spectral power has been reported to be indicative of parasympathetic influence on the cardiovascular regulatory system and LF power has been shown to be influenced by both parasympathetic and sympathetic branches of the autonomic nervous system [14]–[19]. The LF and HF bin widths for each variable were chosen to maximize the difference in spectral power in the bin between pre SW (G_1) and post SW (G_0). More specifically, for each variable, the highest frequency contained in the LF bin and the lowest frequency contained in the HF bin were determined so that the difference between the means of spectral power in that bin for G_0 and G_1 was maximum and the variance minimum while the lowest frequency of LF and highest frequency of HF were fixed at 0.003 and 0.4 Hz, respectively. That is, we defined the frequency range of LF and HF such that the distance between two sample class means relative to the dispersion within the classes, or the Mahalanobis distance

$$d^2(f) = \frac{|m_1(f) - m_0(f)|^2}{s_1^2(f) + s_0^2(f)} \tag{1}$$

was maximum, where f is the width of LF or HF in Hz, m_i and s_i^2 are the mean and variance of spectral power in LF or HF for G_i ($i = 0, 1$). The resultant binning frequencies for the variables are listed in Table II.

The power in LF and HF was computed by spectral decomposition. It can be shown that an AR spectrum

$$S(z) = \frac{P_M}{\left|1 + \sum_{i=1}^{M} a_i^{(M)} z^{-i}\right|^2} \tag{2}$$

can be decomposed into

$$S(z) = \sum_{j=1}^{M/2} \left[\frac{\alpha_j}{z - z_j} + \frac{-\left(\frac{1}{z_j^*}\right)^2 \alpha_j^*}{z - \frac{1}{z_j^*}} + \frac{\alpha_j^*}{z - z_j^*} + \frac{-\left(\frac{1}{z_j}\right)^2 \alpha_j}{z - \frac{1}{z_j}} \right] \tag{3}$$

where M (assume even) is the order of the AR model, z_j is the jth pole of $S(z)$, and α_j is the residual of $S(z)$ at z_j. The term in the bracket can be considered as the power attributable to pole z_j and its conjugate. The power in LF or HF can be computed by summation of the power related to the poles in LF or HF. An example of decomposed spectra is depicted in Fig. 2.

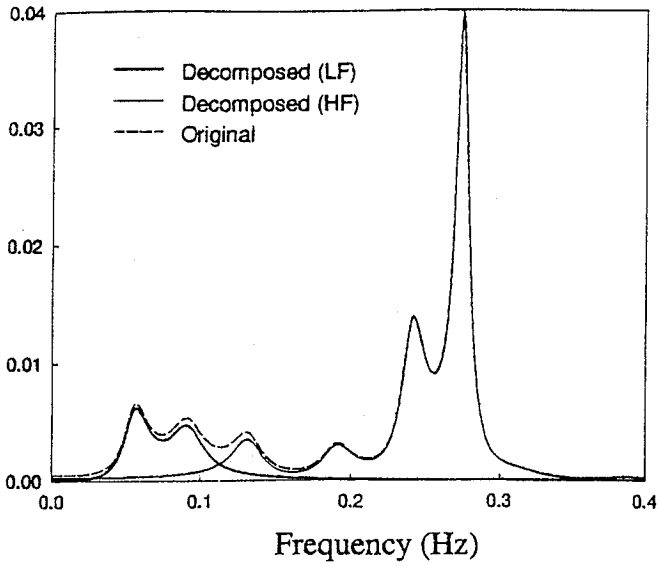

Fig. 2. A TFI spectrum decomposed into LF and HF bins using AR spectral decomposition.

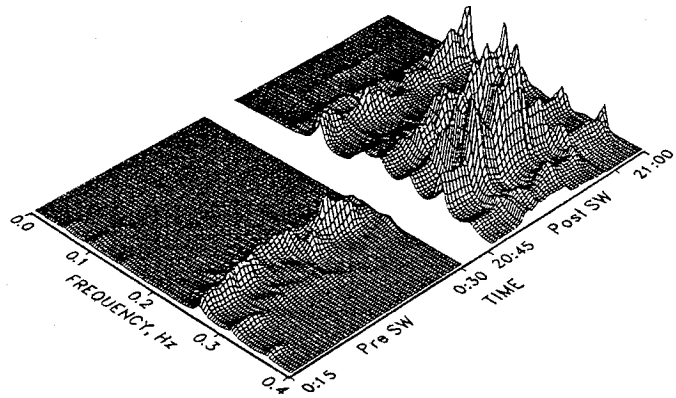

Fig. 3. TFI spectra across time before SW (15 min) and after SW (15 min) in one subject.

Fig. 3 presents TFI spectra across time for the second 15 min of the 30-min supine rest periods before and after SW in one subject, which shows changes in spectra between states as well as stability of spectra across time for each state. Single spectra taken near the end of 30-min supine rest, both before and after SW for each variable in one subject, are shown in Fig. 4. For the group of nine subjects, spectral differences in HR, TFI, RF, and AP were statistically significant after SW

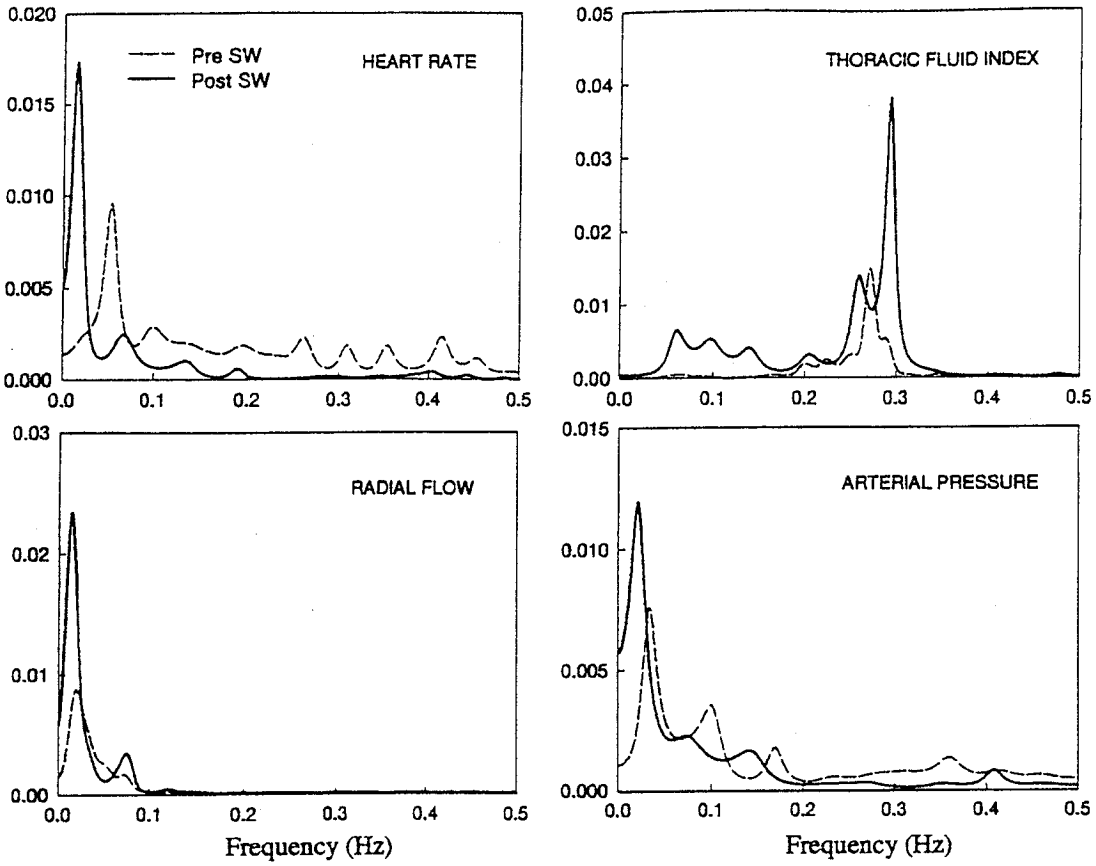

Fig. 4. Single spectra of HR, TFI, RF, and AP for one subject before and after SW.

(Fig. 5). The HF power of HR was significantly reduced after SW, while the HF power of TFI and LF power of RF and AP were significantly increased (Wilcoxon matched-pair signed-rank test [27], $p < 0.05$). The increase in overall total power of TFI in combination with the broadening of TFI spectra indicated that, after SW, breathing frequency was more varied and the depth of breathing was increased. The HR, AP, and RF results indicated a shift in autonomic balance toward reduced parasympathetic (decreased HF, HR power) and increased sympathetic (increased LF, AP, and RF powers) components of CV regulation after SW.

IV. Discriminant Analysis

The spectral components of the CV variables described in Section III were explored in order to obtain a reliable index of adaptation in CV regulation produced by our model of simulated weightlessness. As shown, some spectral components of some CV variables appear promising as features for discrimination of cardiovascular adaptation. However, these individual features exhibited considerable variability across subjects. To obtain an index with improved discriminatory performance, Fisher's linear discriminant function [28] was used to combine the features into an optimal feature, an index of adaptation to weightlessness, defined as a linear function of the feature vector $\underline{x}$

$$l(\underline{x}) = \underline{w}^t \underline{x} \tag{4}$$

where $\underline{w}$, a feature weighting vector, maximizes the Rayleigh quotient

$$\Re(\underline{w}) = \frac{\underline{w}^t S_B \underline{w}}{\underline{w}^t S_W \underline{w}}. \tag{5}$$

S_W is the within-class scatter matrix which is a pooled covariance matrix of the sample covariance matrices of the two classes G_0 and G_1

$$S_W = S_0 + S_1 \tag{6}$$

and S_B is the between-class scatter matrix

$$S_B = (\underline{m}_1 - \underline{m}_0)(\underline{m}_1 - \underline{m}_0)^t \tag{7}$$

where

$$S_i = \sum_{\underline{x} \in G_i} (\underline{x}_i - \underline{m}_i)(\underline{x}_i - \underline{m}_i)^t, \quad i = 0, 1 \tag{8}$$

and $\underline{m}_i$ is the sample mean of G_i. It is easy to show [28] that a vector $\underline{w}$ that maximizes $\Re(\underline{w})$ is

$$\underline{w} = \frac{S_W^{-1}(\underline{m}_1 - \underline{m}_0)}{||S_W^{-1}(\underline{m}_1 - \underline{m}_0)||}. \tag{9}$$

To examine the discriminatory properties of individual CV variables, the discriminant function was first applied to each variable. The feature vector was composed of the LF and HF power of that variable, such that

$$\underline{x} = [x_{\mathrm{LF}} \quad x_{\mathrm{HF}}]^t. \tag{10}$$

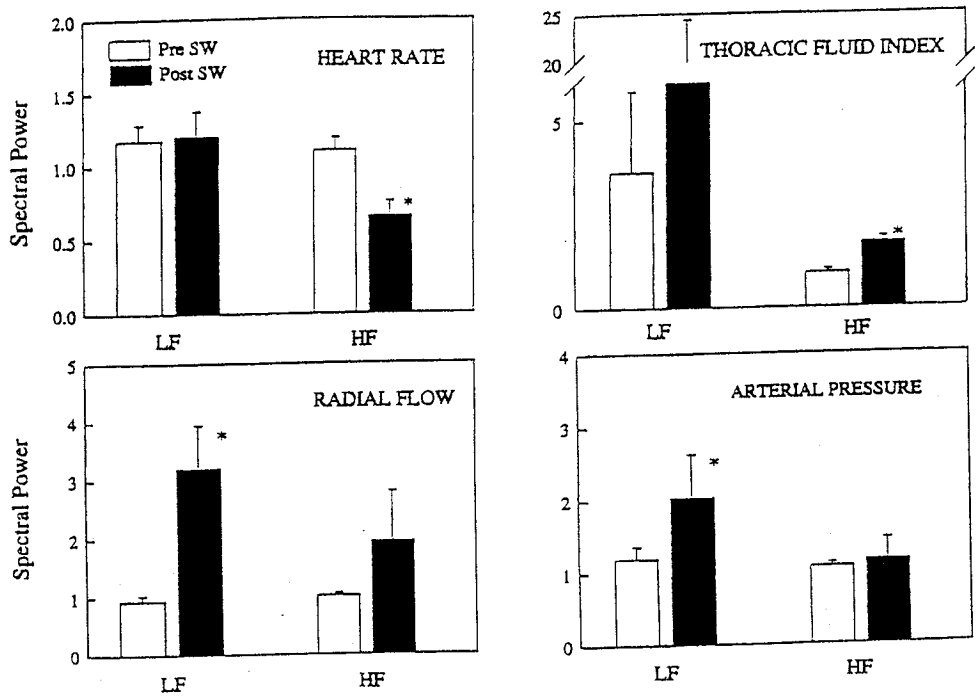

Fig. 5. LF and HF spectral powers of HR, TFI, RF, and AP averaged for nine subjects pre- and post-SW.

Different subjects have large differences in the spectral power of each variable which will introduce large variances. To reduce the variance introduced by each subject, the LF and HF power was normalized to each subjects's baseline (pre SW) spectral power

$$\underline{y} = A^{-1}\underline{x} \tag{11}$$

where A is the normalization matrix

$$A = \mathrm{diag}\,[x^B_{\mathrm{LF}} \quad x^B_{\mathrm{HF}}]. \tag{12}$$

The elements x^B_{LF} and x^B_{HF} are the baseline LF and HF power, respectively, which are obtained from each subject prior to simulated weightlessness. In addition, when several CV variables are combined into a pattern vector, the original variables have physical units which are completely unconnected and may differ considerably in magnitude. Therefore, the round-off errors in the covariance matrices may be serious. This problem was reduced after normalization. Normalization also allows us to eliminate the absolute value from variables so that the weighting coefficient of a variable in $\underline{w}$ indicates the relative importance of discriminant information that the variable contains.

Fig. 6 shows the Fisher's discriminant applied separately to the HR, TFI, RF, and AP spectra (Fig. 4) for each of the nine subjects. If we treat these discriminant values as adaptation measures, we see that for each variable the discriminant of most subjects decreased after SW. However, there was a large deviation across subjects. Some subjects showed large adaptation in some variables and small or even opposite adaptation in the others.

To obtain a better index, we combined the best features from all possible CV variables into one feature vector. Inclusion of all spectral features may lead to unstable estimates of the feature weighting vector (or the discriminant function coefficients) if these features contain redundant information. Also, any feature which does not contribute to the index's predictive ability should be excluded since the more features included, the greater the costs of data collection and computation. The best features to include therefore, had to be determined. A *backward elimination* algorithm [29] was used to select a subset of important features from the complete set. The procedure starts with the complete set and then deletes one feature variable at a time until some stopping criterion is satisfied. The feature to be deleted is the one that decreases D^2 the least, where D^2 is the Mahalanobis distance

$$D^2 = (\underline{m}_1 - \underline{m}_2)^t S_W^{-1}(\underline{m}_1 - \underline{m}_2). \tag{13}$$

The Rao F statistic [30] was used as the stopping criterion to test the significance of a variable's contribution to the discrimination. The elimination procedure is shown in Table III. At stage 1, the LF component of TFI was selected for removal. At stage 2, the HF component of AP was removed. At stage 3, the LF component of HR was removed. At stage 4, the LF component of AP was removed, and at stage 5, the HF component of RF was removed. Elimination was then stopped since all the remaining features were significant at the 0.1 level ($F > 3.39$). The selected feature vector is, thereby

$$\underline{y} = [y_{\mathrm{HR,HF}} \quad y_{\mathrm{TFI,HF}} \quad y_{\mathrm{RF,LF}}]^t. \tag{14}$$

A sample space spanned by HR (HF), TFI (HF), and RF (LF) is shown in Fig. 7, from which we can see that these two classes are separable. The feature weighting vector estimated from the training data set (taken from nine subjects near the beginning of the both pre- and post-SW supine rest periods) is $\underline{w} = [0.58 \ -0.78 \ -0.24]^t$. The corresponding Fisher's linear

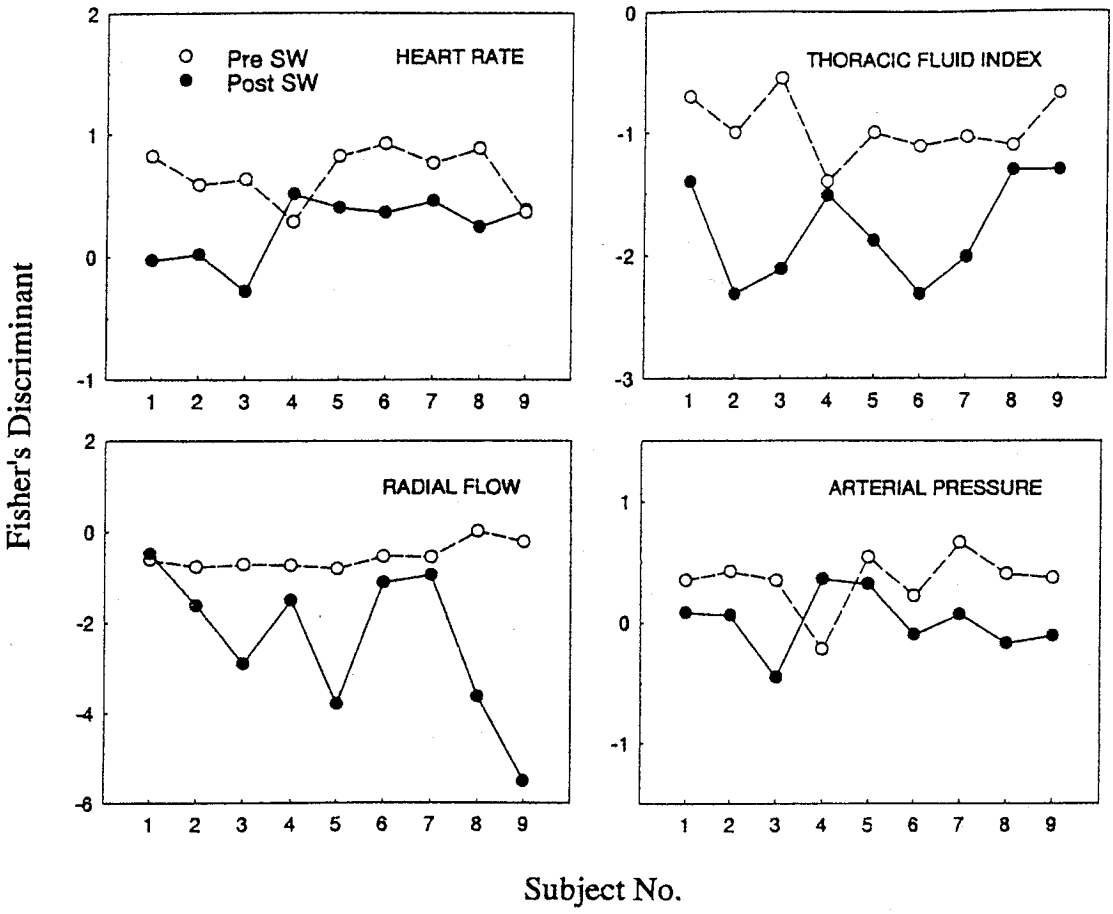

Fig. 6. Fisher's linear discriminants of HR, TFI, RF, and AP for nine subjects before and after SW.

discriminant function is

$$l(\underline{y}) = \underline{w}^t \underline{y} = 0.58y_{\mathrm{HR,HF}} - 0.78y_{\mathrm{TFI,HF}} - 0.24y_{\mathrm{RF,LF}}. \quad (15)$$

If normal distributions are assumed, the minimum error probability decision boundary is -0.77. The adaptation index is then

$$l(\underline{y}) = 0.58y_{\mathrm{HR,HF}} - 0.78y_{\mathrm{TFI,HF}} - 0.24y_{\mathrm{RF,LF}} + 0.77. \quad (16)$$

In Fig. 8 (a) we show the result of applying the above index to the same data as in Fig. 6 (taken near the end of pre- and post-SW supine rest periods). Here we see that Fisher's discriminant for the combined feature vector demonstrates increased separation and reduced deviation over any single variable. Therefore, if we treat the discriminant for the combined feature vector as an index of adaptation to weightlessness, a consistent adaptation across all subjects is observed.

It is worth noting that if the two classes, G_0 and G_1, have unequal variance, Fisher's linear discrimination function may not be optimal. Bayes' quadratic discriminant function [31] may be used (if normal distributions are assumed) such that

$$q(\underline{y}) = \ln \frac{|S_1|}{|S_0|} + (\underline{y} - \underline{m}_1)^t S_1^{-1} (\underline{y} - \underline{m}_1) - (\underline{y} - \underline{m}_0)^t S_0^{-1} (\underline{y} - \underline{m}_0). \quad (17)$$

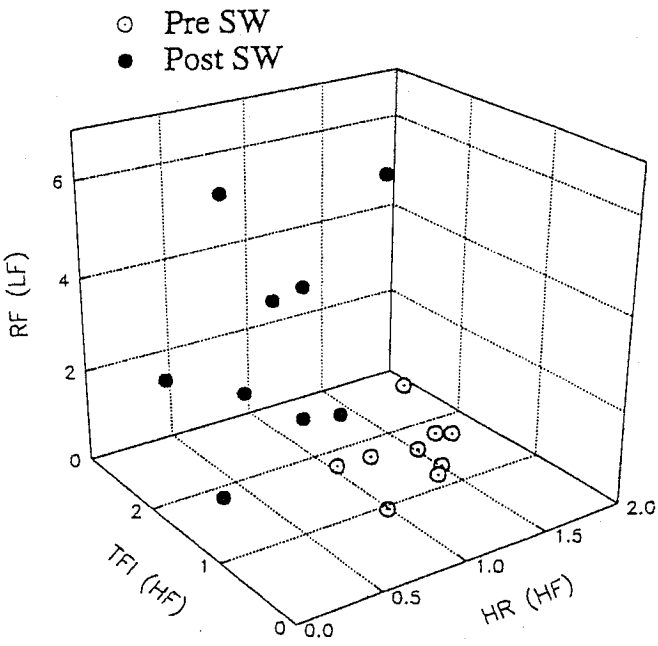

Fig. 7. A sample space spanned by HR (HF), TFI (HF), and RF (LF).

It is evident that if G_0 and G_1 have identical variance, the quadratic discriminant function is reduced to the linear discriminant function. Therefore, the linear discriminant function performs as well as the quadratic function unless there is a

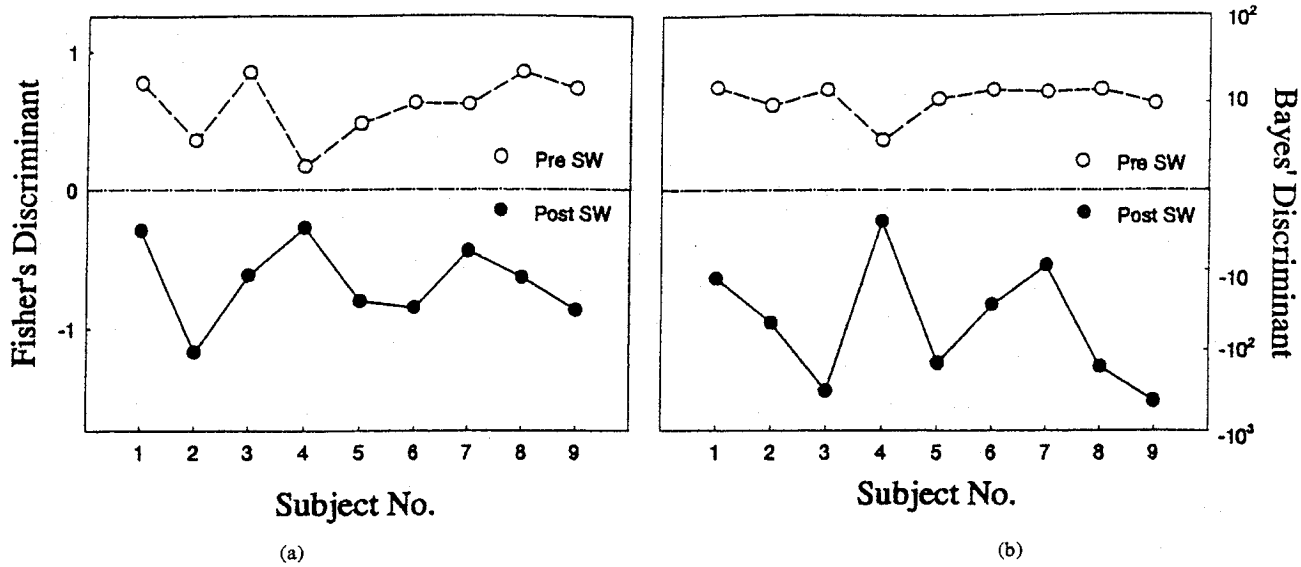

Fig. 8. (a) Fisher's linear discriminant and (b) Bayes' quadratic discriminant for combined features of HR (HF), TFI (HF), and RF (LF) for nine subjects.

TABLE III
FEATURE SELECTION USING BACKWARD ELIMINATION

Stage	1								2						
Variable Deleted	HR (LF)	HR (HF)	**TFI (LF)**	TFI (HF)	RF (LF)	RF (HF)	AP (LF)	AP (HF)	HR (LF)	HR (HF)	TFI (HF)	RF (LF)	RF (HF)	AP (LF)	**AP (HF)**
D^2	11.3	7.2	**12.6**	4.6	6.2	8.9	11.6	12.2	11.2	7.1	4.6	5.6	8.9	11.6	**12.2**
F	0.8	4.5	**0.1**	8.6	5.8	2.6	0.6	0.2	0.9	5.1	9.5	7.4	2.9	0.6	**0.2**

Stage	3						4					5				6		
Variable Deleted	**HR (LF)**	HR (HF)	TFI (LF)	RF (LF)	RF (HF)	AP (LF)	HR (HF)	TFI (HF)	RF (LF)	RF (HF)	**AP (LF)**	HF (HF)	TFI (HF)	RF (LF)	**RF (HF)**	HR (HF)	TFI (HF)	RF (LF)
D^2	**11.2**	7.0	4.0	5.6	8.5	10.9	5.7	4.3	4.2	7.4	**10.0**	5.6	3.8	3.2	**7.4**	4.5	1.2	2.6
F	**0.7**	5.3	10.0	7.7	3.4	1.0	6.6	10.2	10.6	3.6	**1.0**	6.1	10.7	12.6	**3.1**	4.8	17.5	10.7

large difference in the covariance matrix. Bayes' quadratic discriminant for the same data set is shown in Fig. 8(b).

Lilliefors' procedure [27] was used to test the validity of the normality assumption. The hypothesis that the two classes are normally distributed could not be rejected at the 0.05 level and therefore a normal distribution of data in these classes may be assumed.

As seen in Fig. 3, CV variable spectra demonstrate large variance across time due to the "noisy" nature of the cardiovascular system. When the index is used to continuously monitor the adaptation, presmoothing is necessary to eliminate occasional, noise-like transient components and thereby increase the immunity to noise and reduce the risk of making a wrong decision based on transient outlier data. Many data smoothing schemes are available. The simplest one is linear smoothing such as Hanning low-pass filtering. The drawback is that linear filtering is sensitive to outlier data, while some types of nonlinear smoothing, such as median filtering, have the advantage of being less sensitive to outlier data. In the present study, a median filter, used to eliminate outliers, followed by a Hanning filter, demonstrated reasonable performance.

Fig. 9 shows the index (and its spectral components) applied to the test subject pre- and post-SW and at intermediate stages of the SW protocol. Adaptation similar to the set of nine subjects (Fig. 8) was observed in this test subject.

V. DISCUSSION

The weightlessness simulation protocol resulted in a negative fluid balance which resulted in significant decreases in stroke volume and central venous pressure. The AP regulatory response of the system, however, compensated for the decrease in fluid volume by increasing resistance mediated by increasing plasma levels of renin and norepinephrine (an independent marker of increased sympathetic activity). The lack of change in the resting HR, in spite of increased sympathetic activity, is not surprising since peripheral vascular resistance increased, thereby compensating for the SV decrease. The combination of negative fluid balance with decreases in mean CVP and SV and increases in plasma renin and norepinephrine are in general agreement with those from other studies of simulated weightlessness [1], [2], [4], [5], indicating increased sympathetic activity in response to decreased plasma volume. Inflight CV data are rare, but at least one study reported that sympathetic

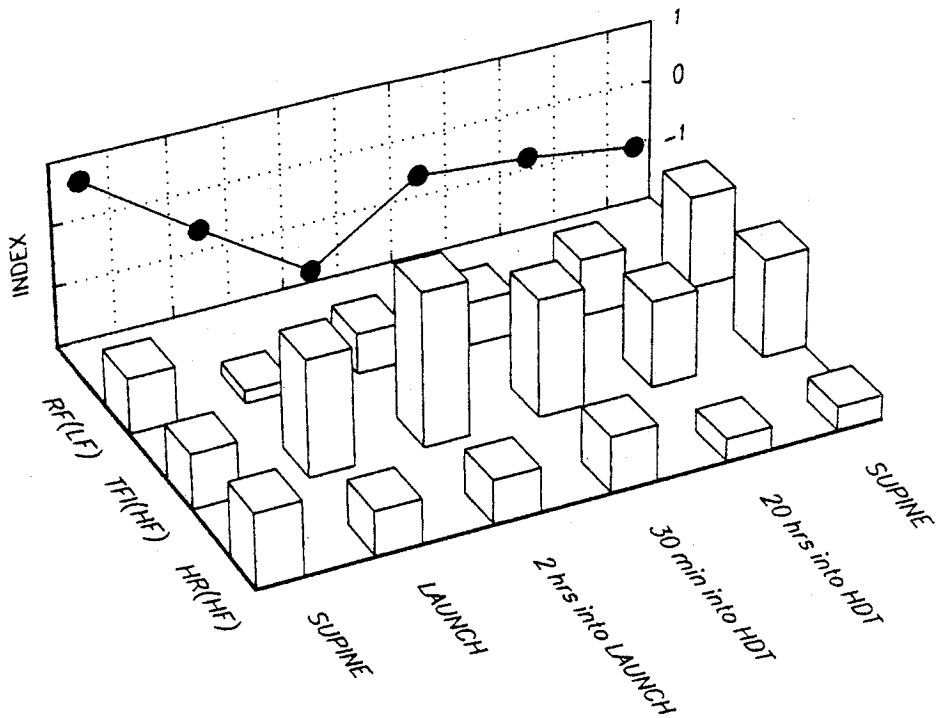

Fig. 9. Adaptation index (Fisher) applied to the test subject pre- and post-SW and all intermediate stages of the SW protocol. The spectral components are also shown.

indices (norepinephrine, HR) were decreased during flight while the post flight response to standing was characterized by reduced parasympathetic and increased sympathetic activity [32].

With respect to the physiological interpretation of the spectral contents of CV variables, studies in dogs and humans indicate that HF oscillations in HR are mediated by the parasympathetic branch of the autonomic nervous system. It has been shown, in dogs, that LF oscillations in HR are mediated by the sympathetic nervous system [14]. In humans, some investigators [17] have found that LF oscillations were influenced by both the parasympathetic and sympathetic branches of the autonomic nervous system, while others [18], [19] concluded that an increase in the LF power was indicative of increased sympathetic influence on the CV regulatory system. With respect to our model of simulated weightlessness, we previously determined that the spectral contents of CV variables indicated a shift in sympathovagal balance toward enhanced sympathetic influence [22].

In the present study, we interpret our spectral results to indicate a similar shift toward enhanced sympathetic control: 1) the significant decrease in the HF component of HR power after simulated weightlessness indicated a shift toward decreased parasympathetic control of HR [Fig. 5(a)] and 2) the increased LF power in RF [Fig. 5(b)], implicated an increase in sympathetic control of vasomotion. The significant increase in HF power of TFI [Fig. 5(c)] could be due either to an increase in tidal volume or to a change in neural control of respiratory parameters, but the present results offer no evidence to relate this parameter to sympathetic/parasympathetic balance.

Our data also indicated that the level of change due to simulated weightlessness varied from variable to variable and subject to subject. That is, some subjects showed larger changes in some CV variables but less change in other variables (Fig. 6), indicating that the spectral components of a single variable may be limited as a dependable index of cardiovascular adaptation to weightlessness.

To build a robust adaptation index, we formed a feature space spanned by the most important features, HR (HF), TFI (HF), and RF (LF), as determined by the backward elimination algorithm. These features were further linearly combined to form an optimal index using Fisher's linear discriminant function which combines features according to the relative importance of discriminant information contained in each feature. Results showed that this integrated and optimized index demonstrated improved discriminatory performance over any single variable. It is worth noting that a multifeature index is not necessarily always better than a single-feature index unless they are appropriately screened and combined in an optimal way.

In conclusion, we verified that the spectral powers in LF and/or HF of some CV variables are promising as a feature space for discrimination of human cardiovascular deconditioning produced by simulated weightlessness. We found that cardiovascular adaptation to simulated weightlessness could be characterized by changes in LF and/or HF spectral power of HR, TFI, and RF. However, due to the large variance across subjects, the reliability of any single variable as an index of cardiovascular adaptation to simulated weightlessness was limited. Discriminatory performance was improved by using multiple CV variables with Fisher's linear discriminant or Bayes' quadratic discriminant function. The ability to discriminate between subjects before and after simulated weightlessness has the potential for use as an index to track

adaptation and prescribe countermeasures to the effects of weightlessness.

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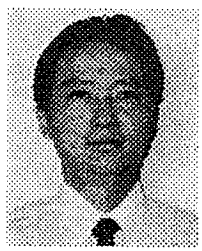

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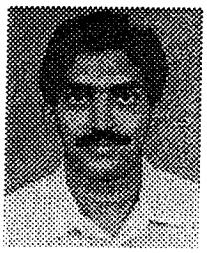

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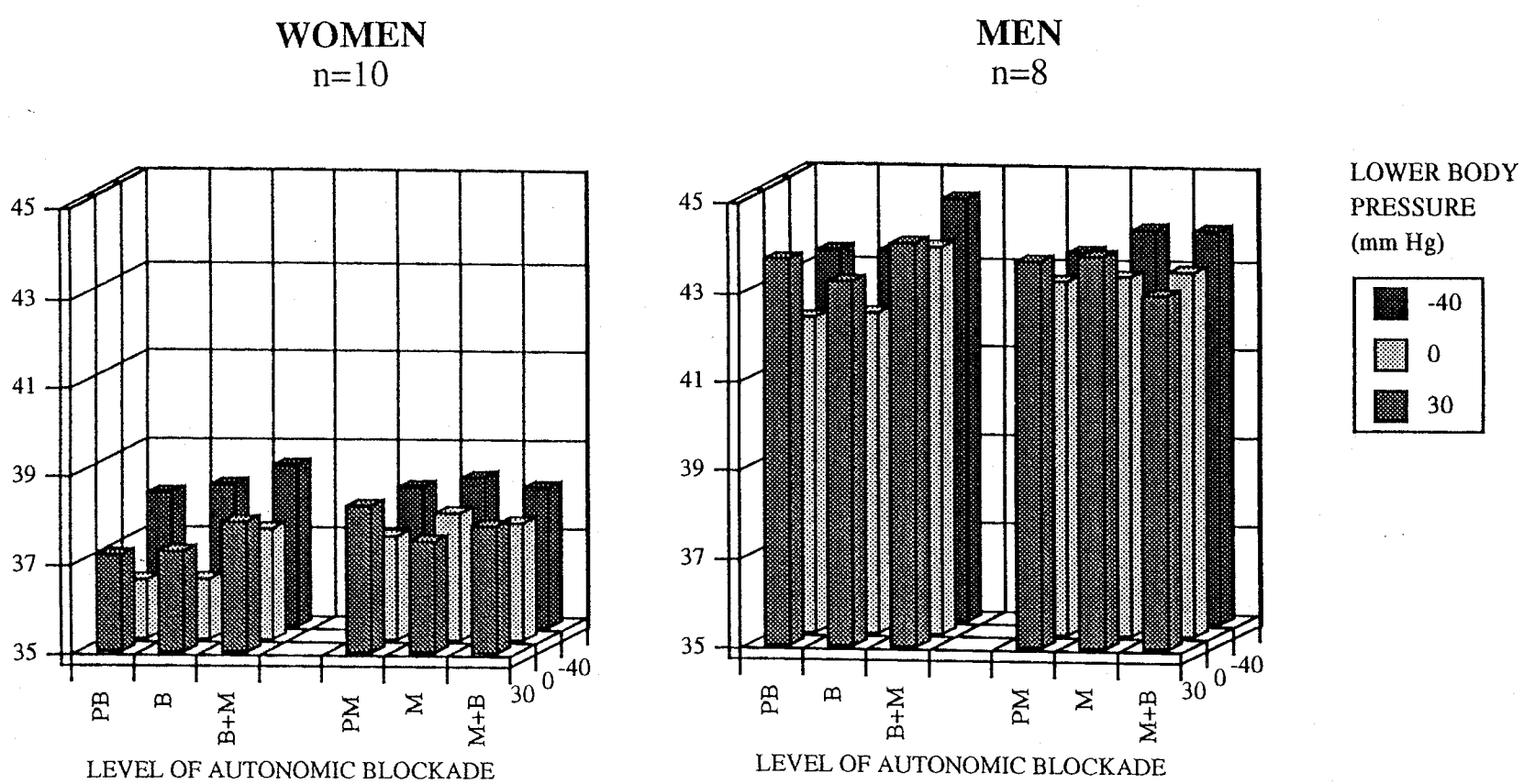


Figure 1: Group-averaged hematocrit values at various stages of autonomic blockade and three levels of lower body pressure.

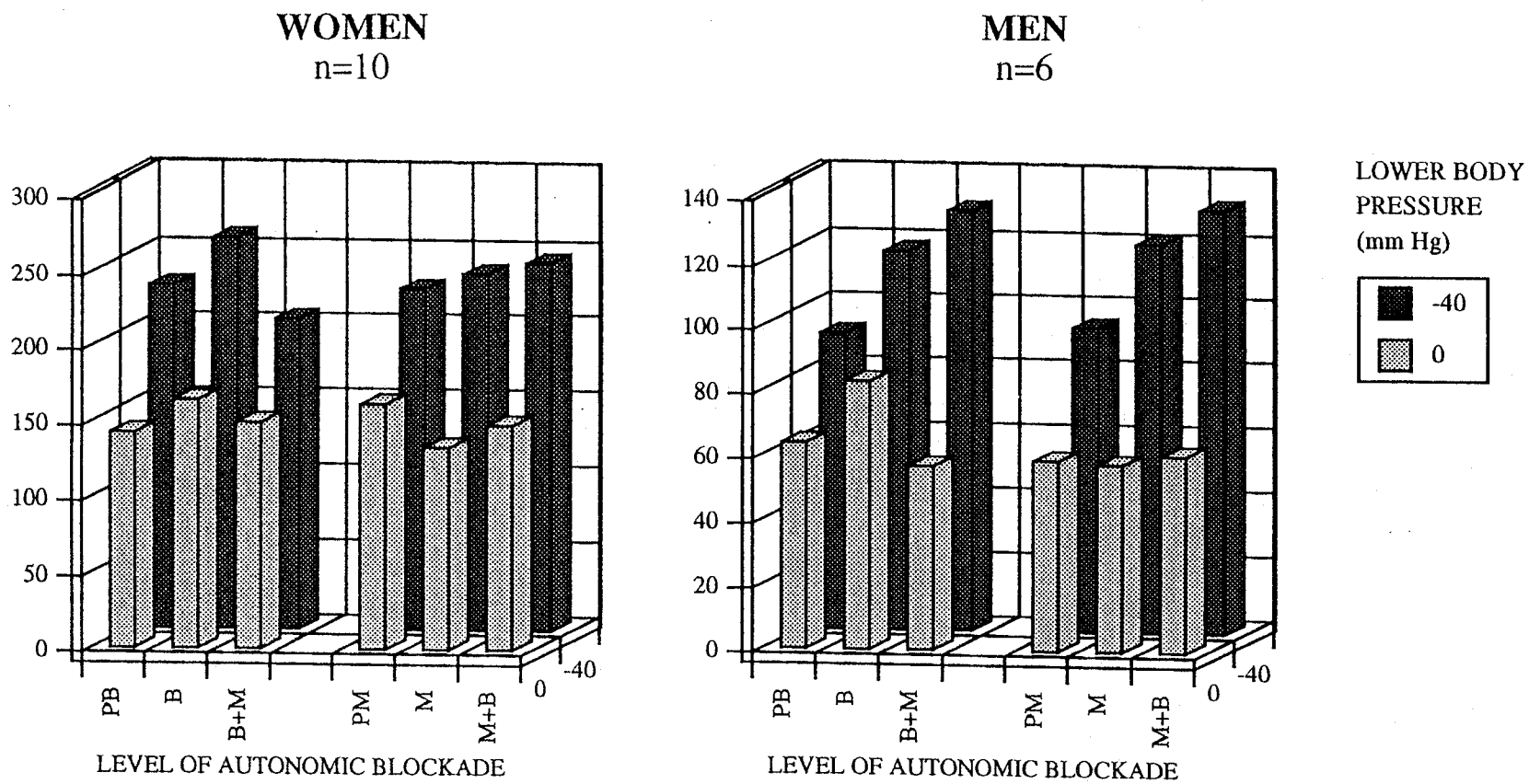


Figure 2a: Group-averaged norepinephrine levels at various stages of autonomic blockade and two levels of lower body pressure.

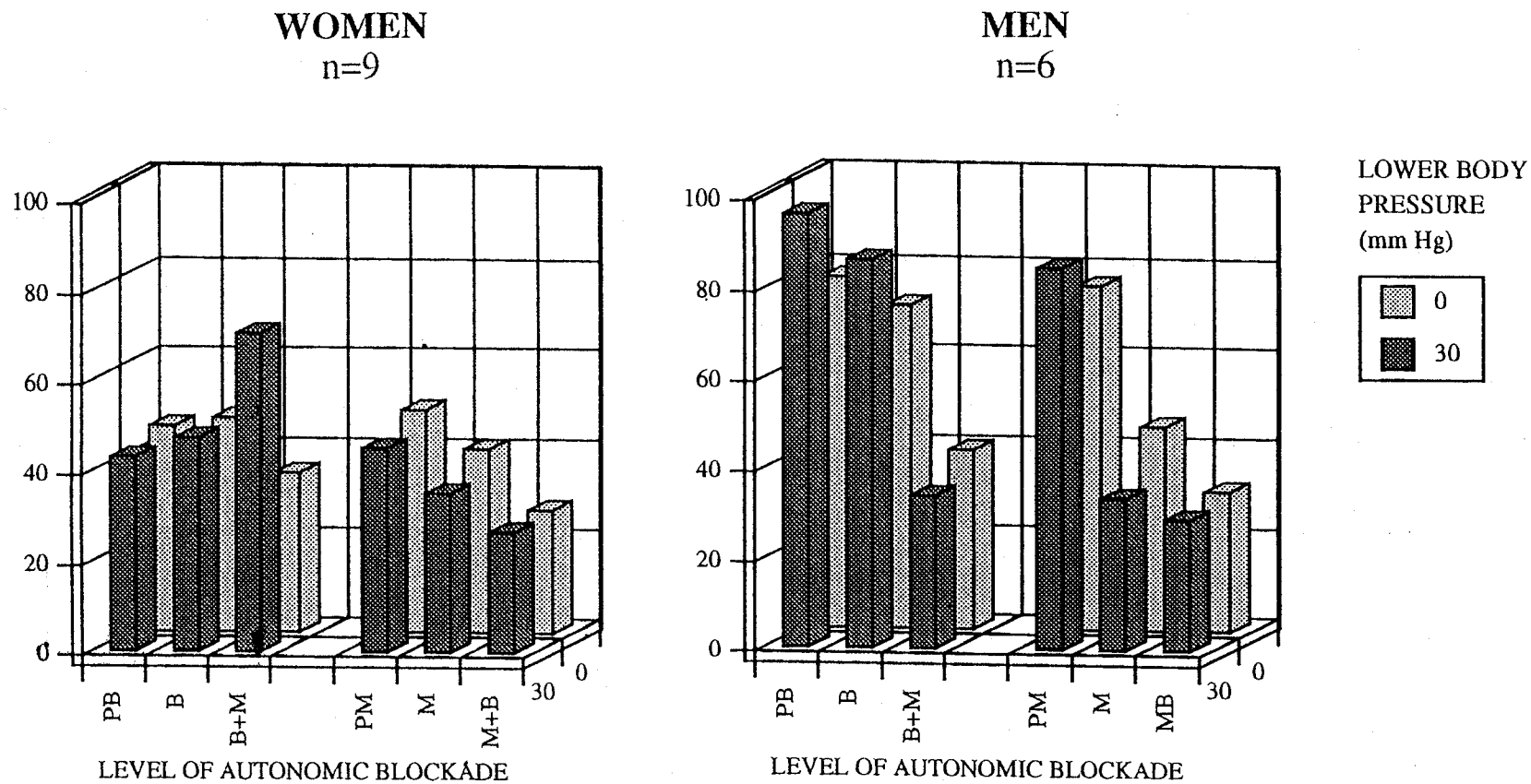
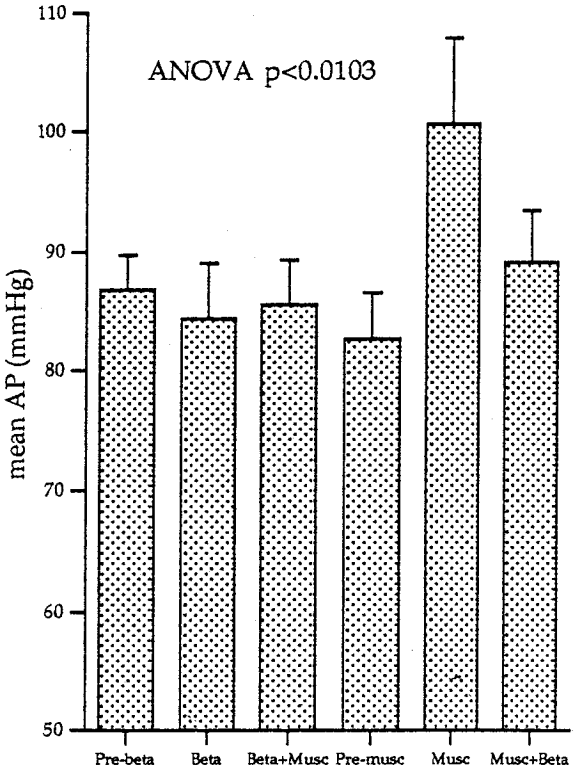


Figure 2b: Group-averaged pancreatic polypeptide levels at various stages of autonomic blockade and two levels of lower body pressure.



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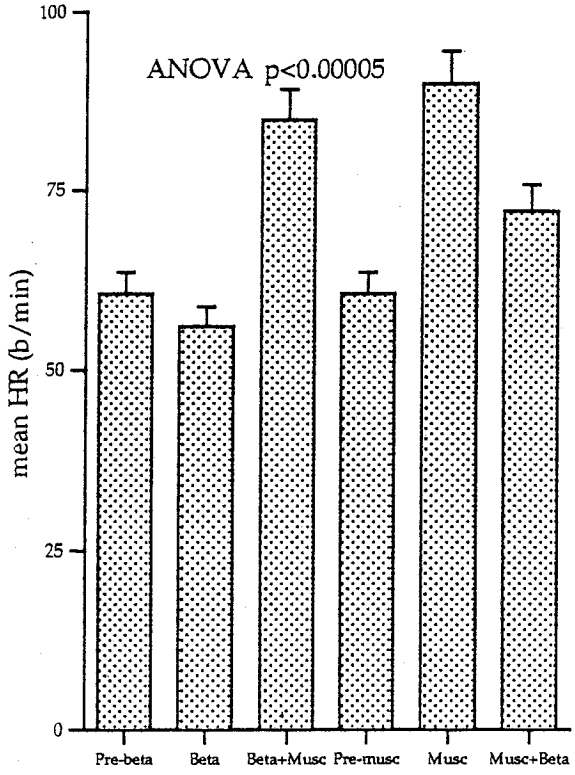

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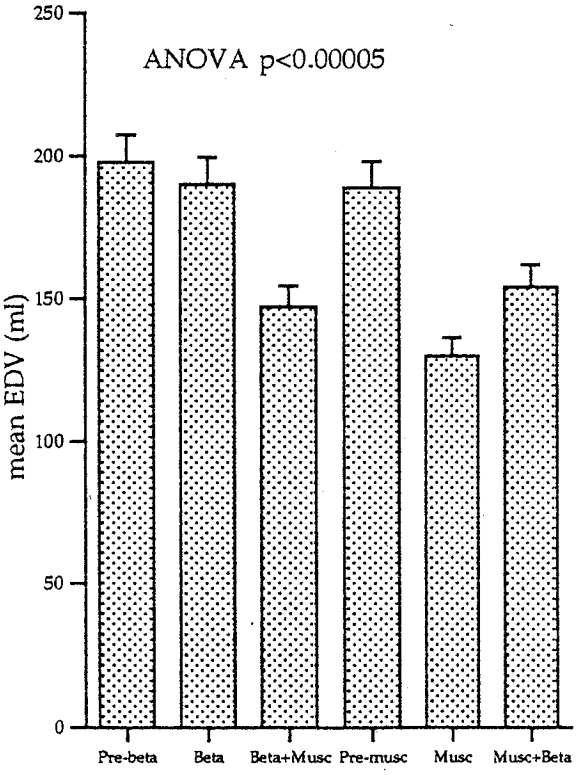

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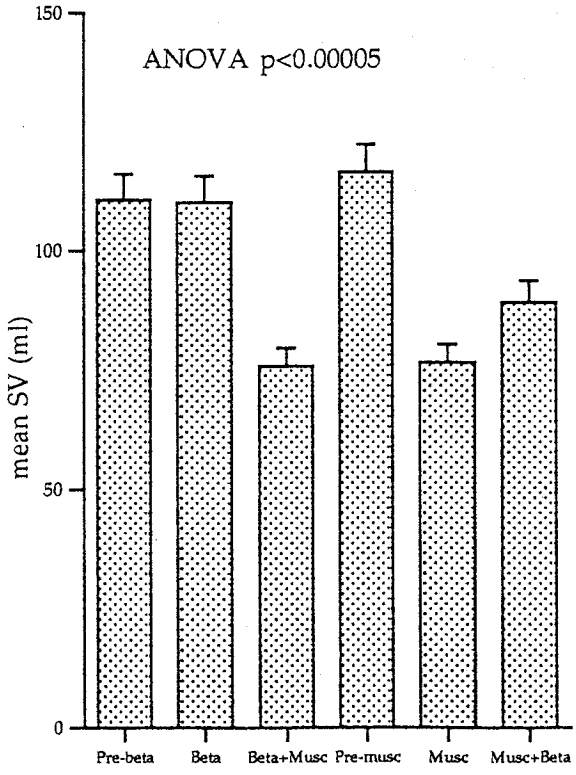

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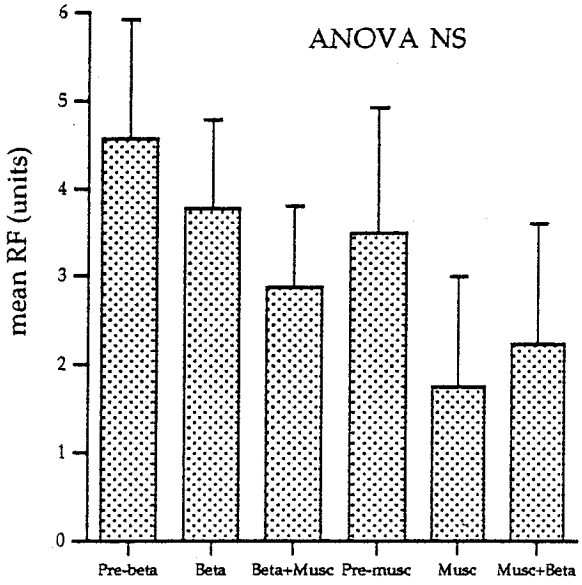
Fig. 3 Mean ± SEM resting values for all states of blockade n = 10 men



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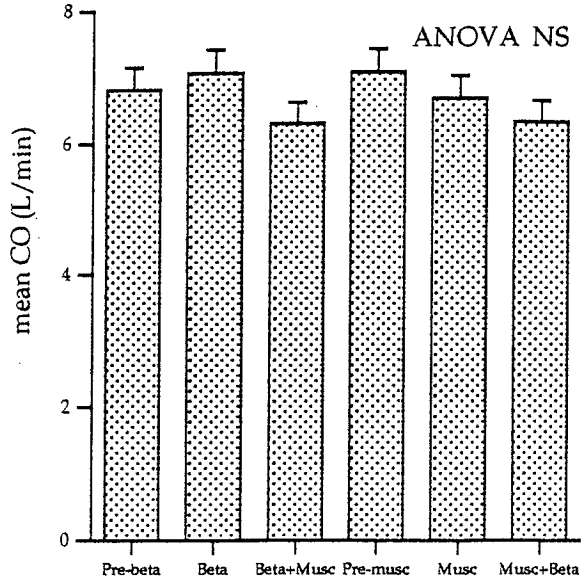

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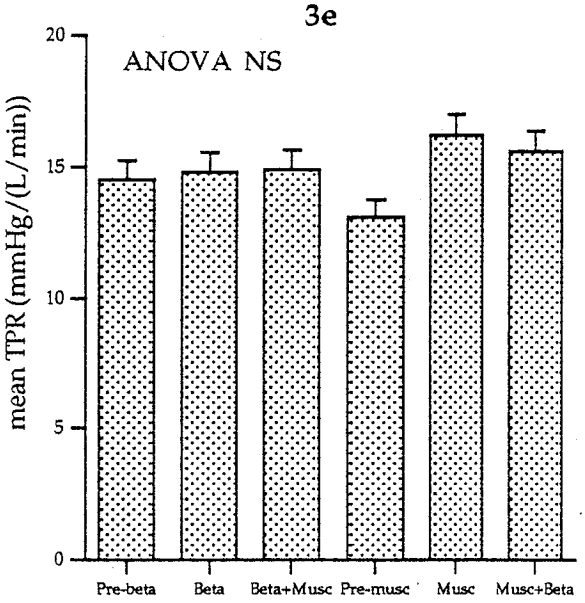

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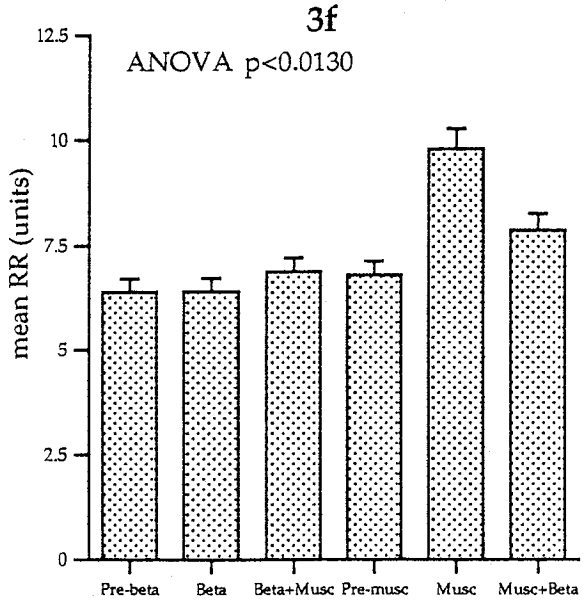

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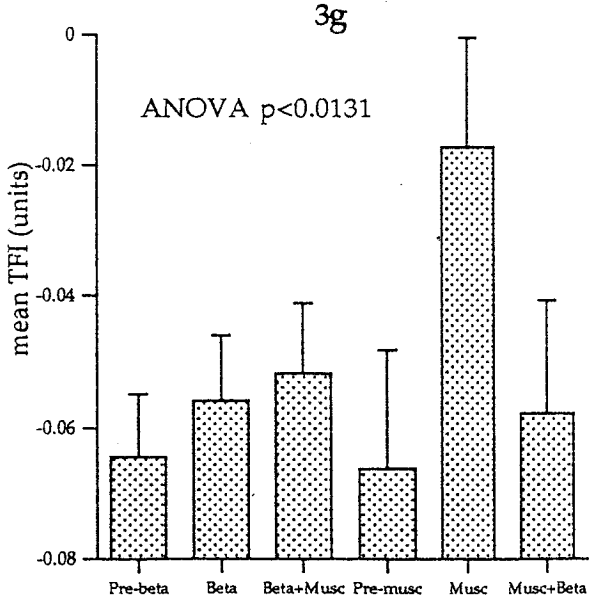

3i

Fig. 3 (continued)
Mean ± SEM resting values for all states of blockade n = 10 men

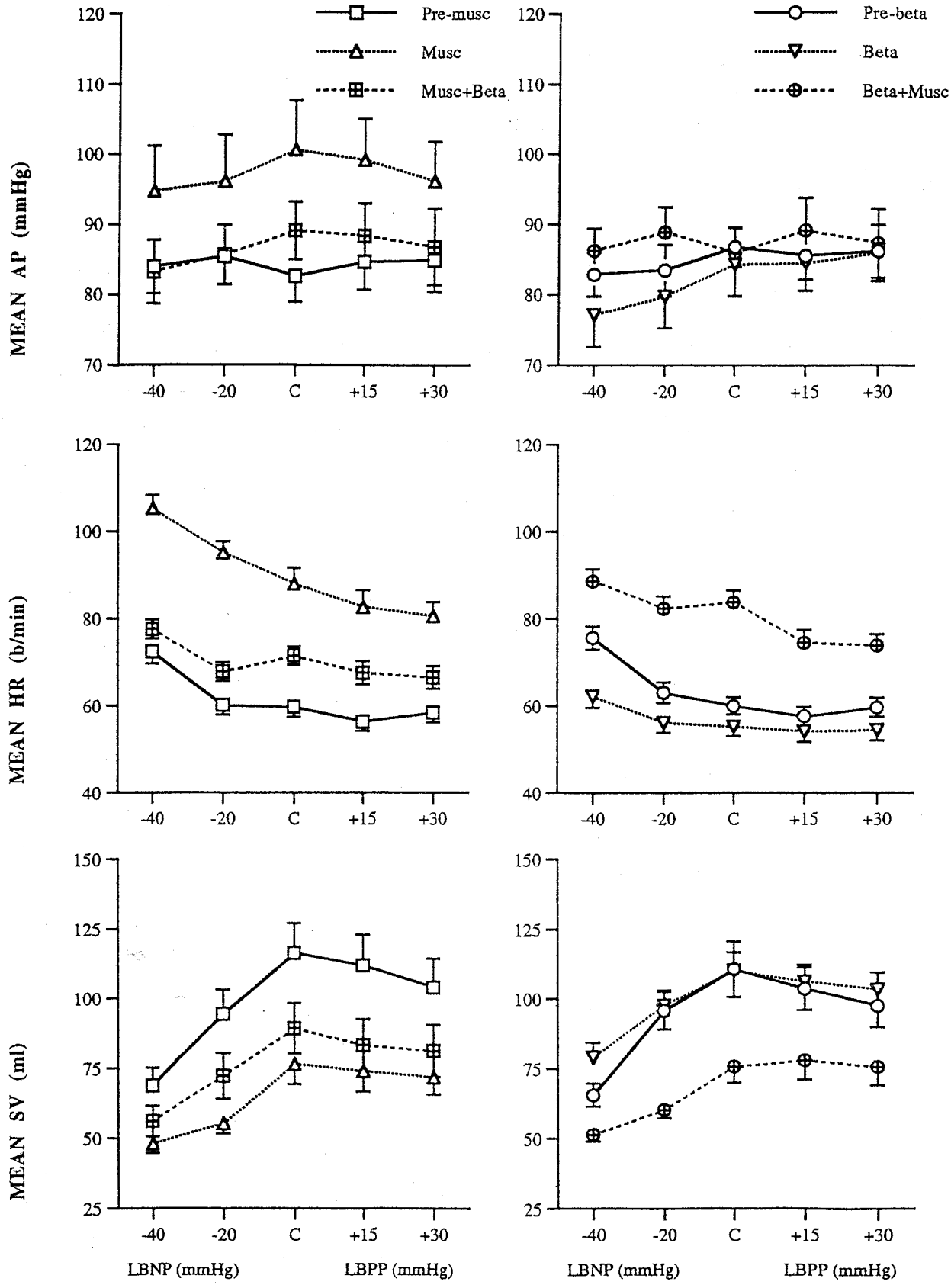

Fig. 4a Mean ± SEM values of Arterial Pressure, Heart Rate and Stroke Volume during control and Lower Body Negative and Positive Pressures n = 10 men.

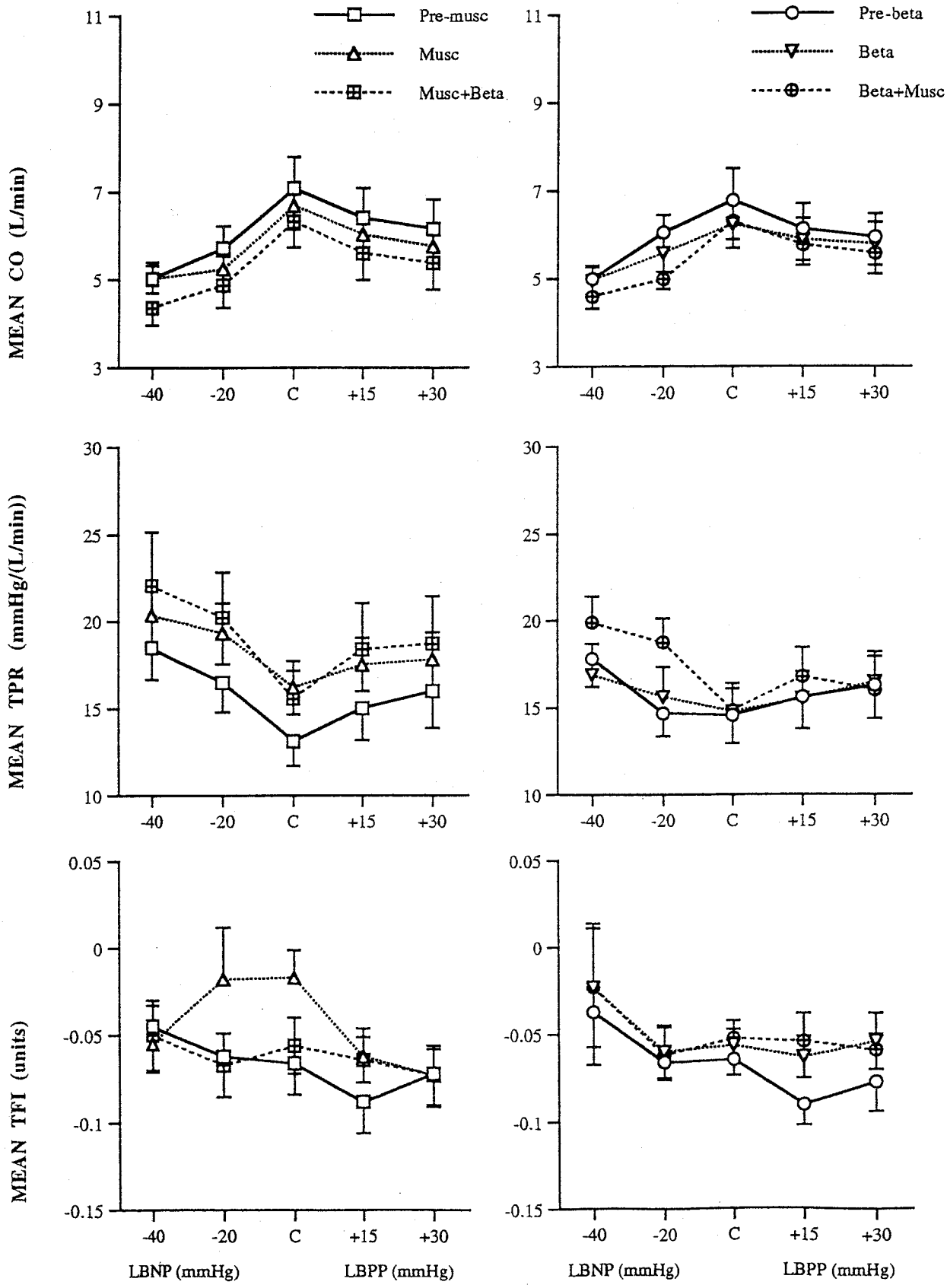

Fig. 4b Mean ± SEM values of Cardiac Output, Total Peripheral Resistance and Thoracic Fluid Index during control and Lower Body Negative and Positive Pressures n = 10 men.

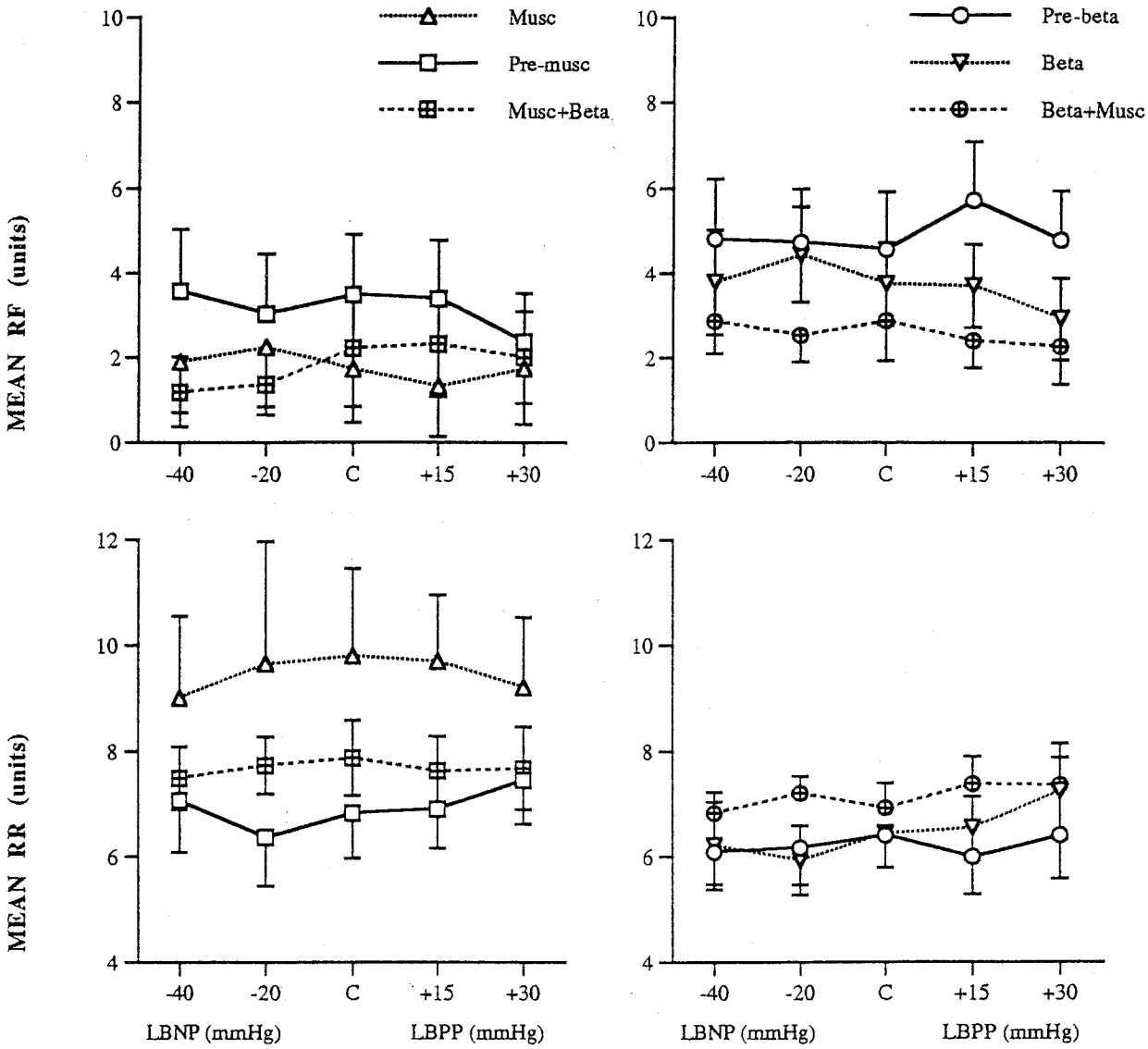

Fig. 4c Mean ± SEM values of Radial Flow and Radial Resistance during control and Lower Body Negative and Positive Pressures n = 10 men.

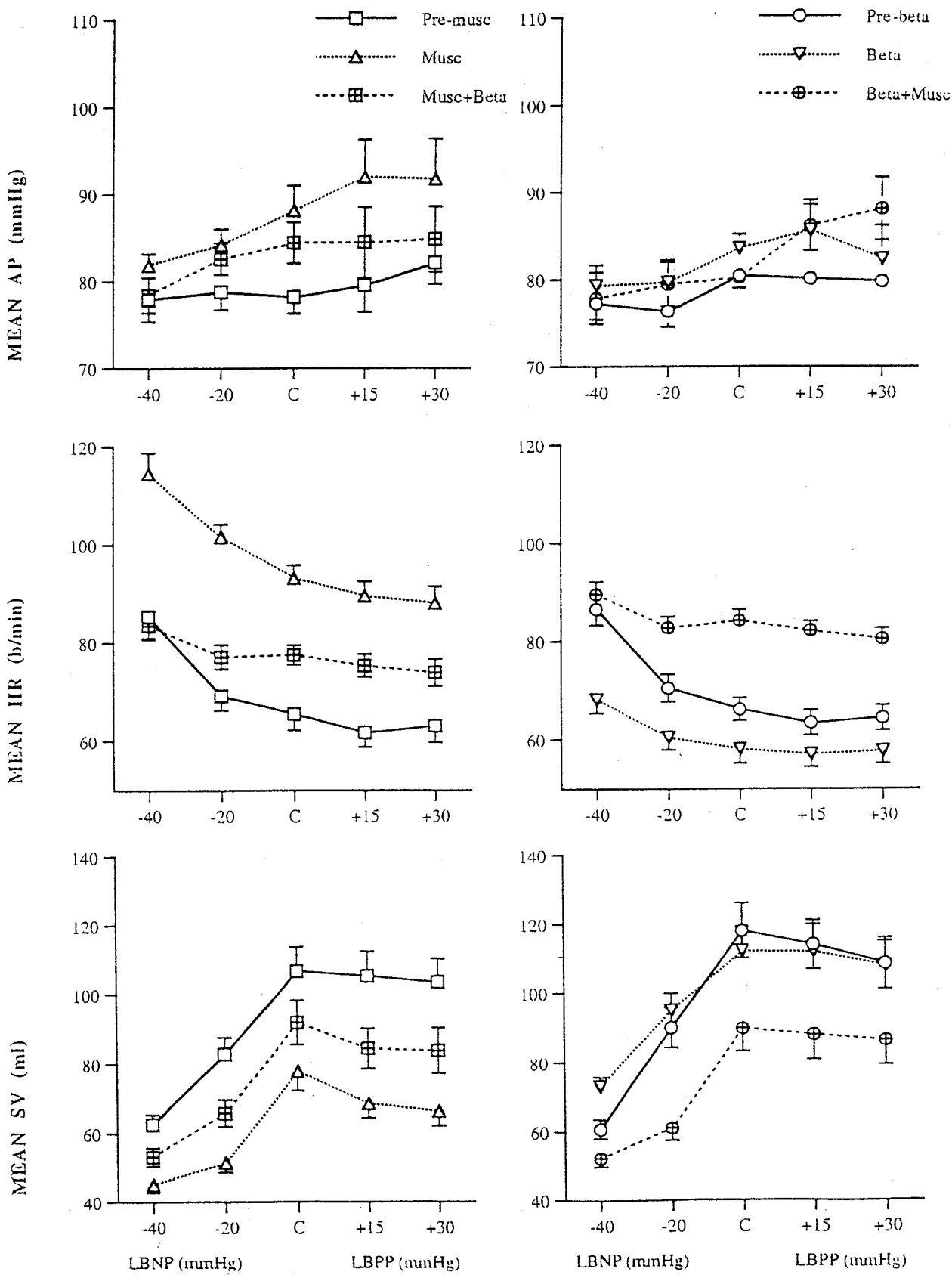

Figure 5a: Mean ± SEM for Arterial Pressure, Heart Rate, and Stroke Volume, n = 10 women

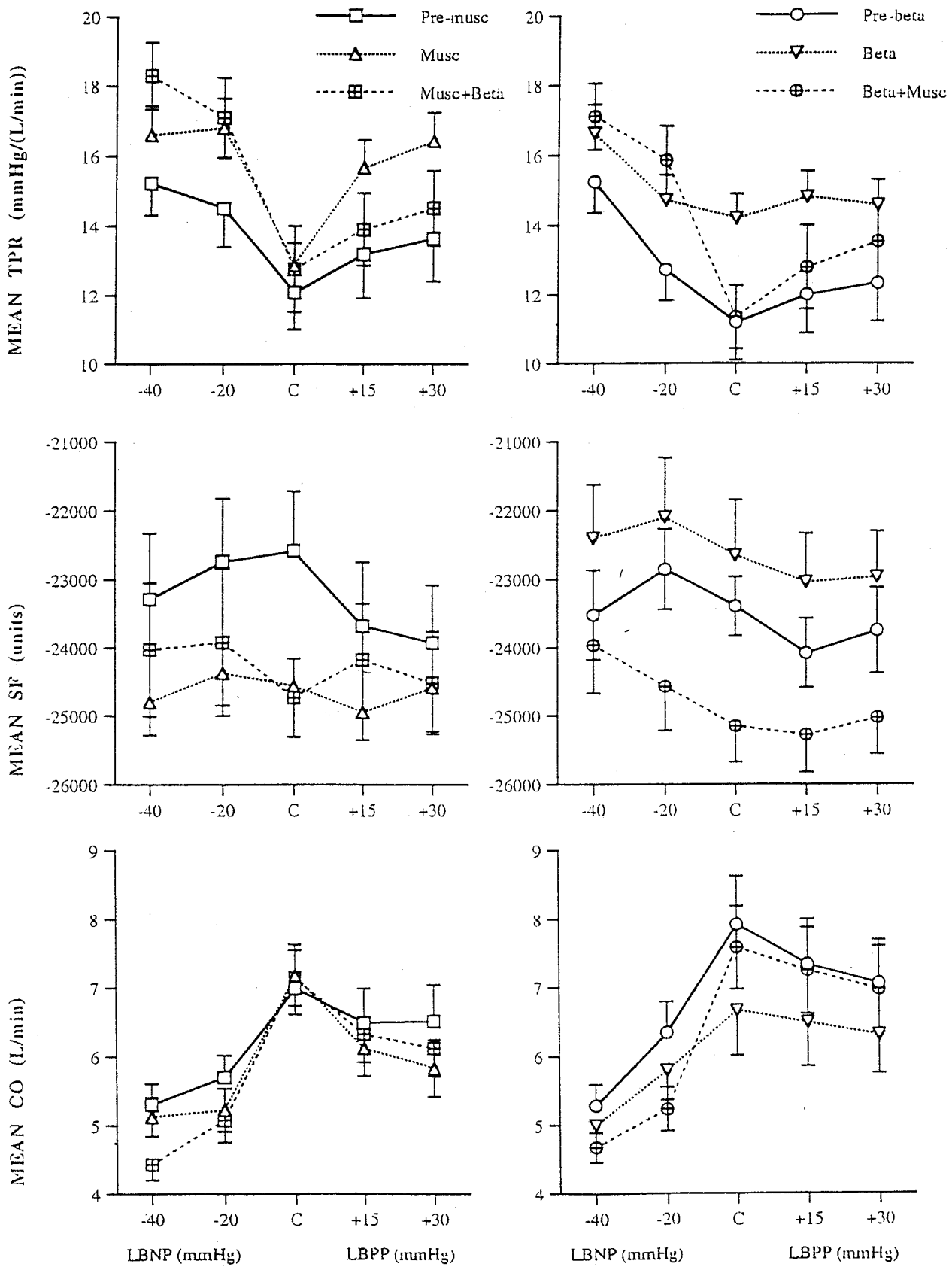

Figure 5b: Mean ± SEM for Total Peripheral Resistance, Skin Blood Flow, and Cardiac Output, n = 10 women

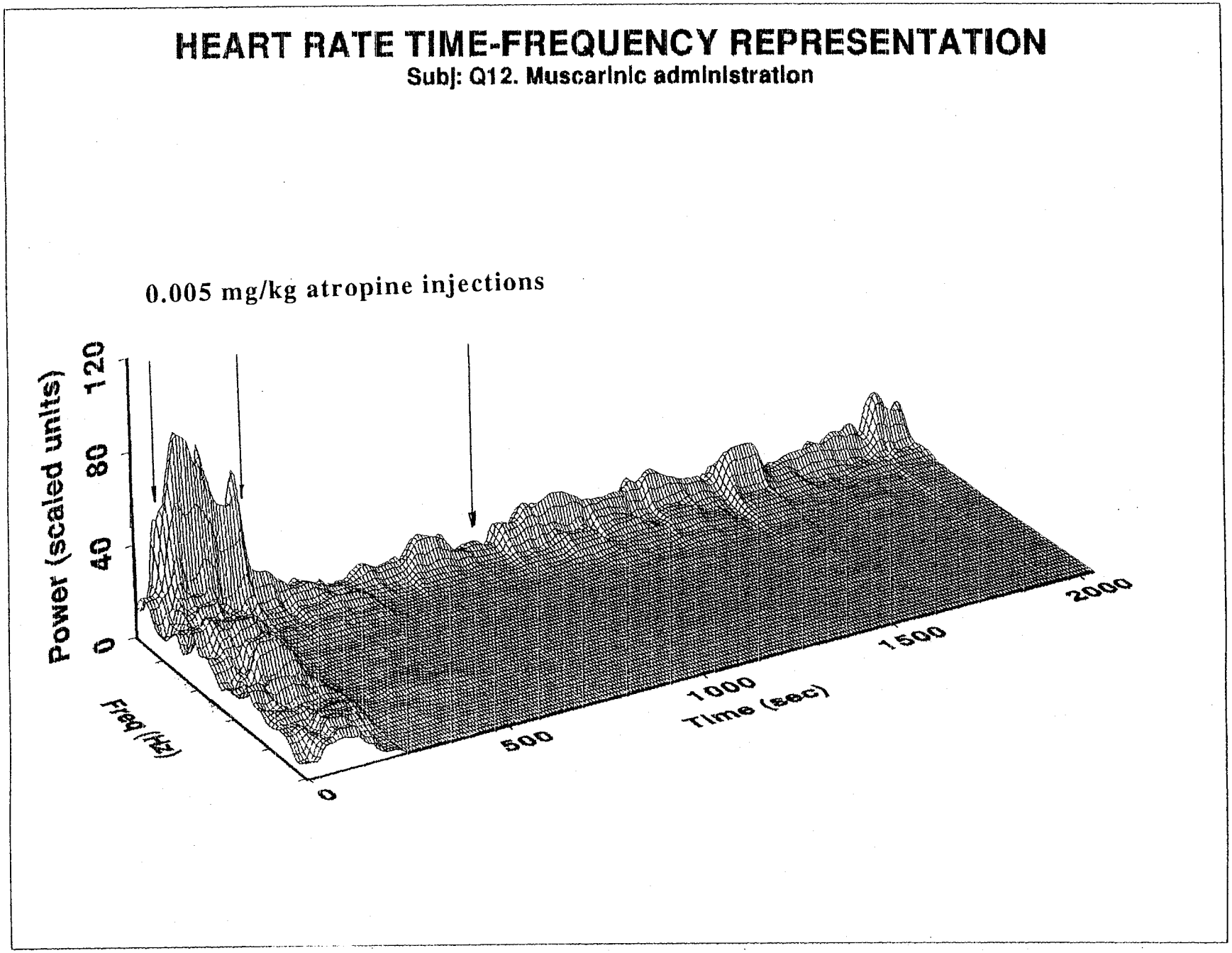

Figure 6a: Heart rate spectral power in one subject during increasing dosage of intravenous atropine.

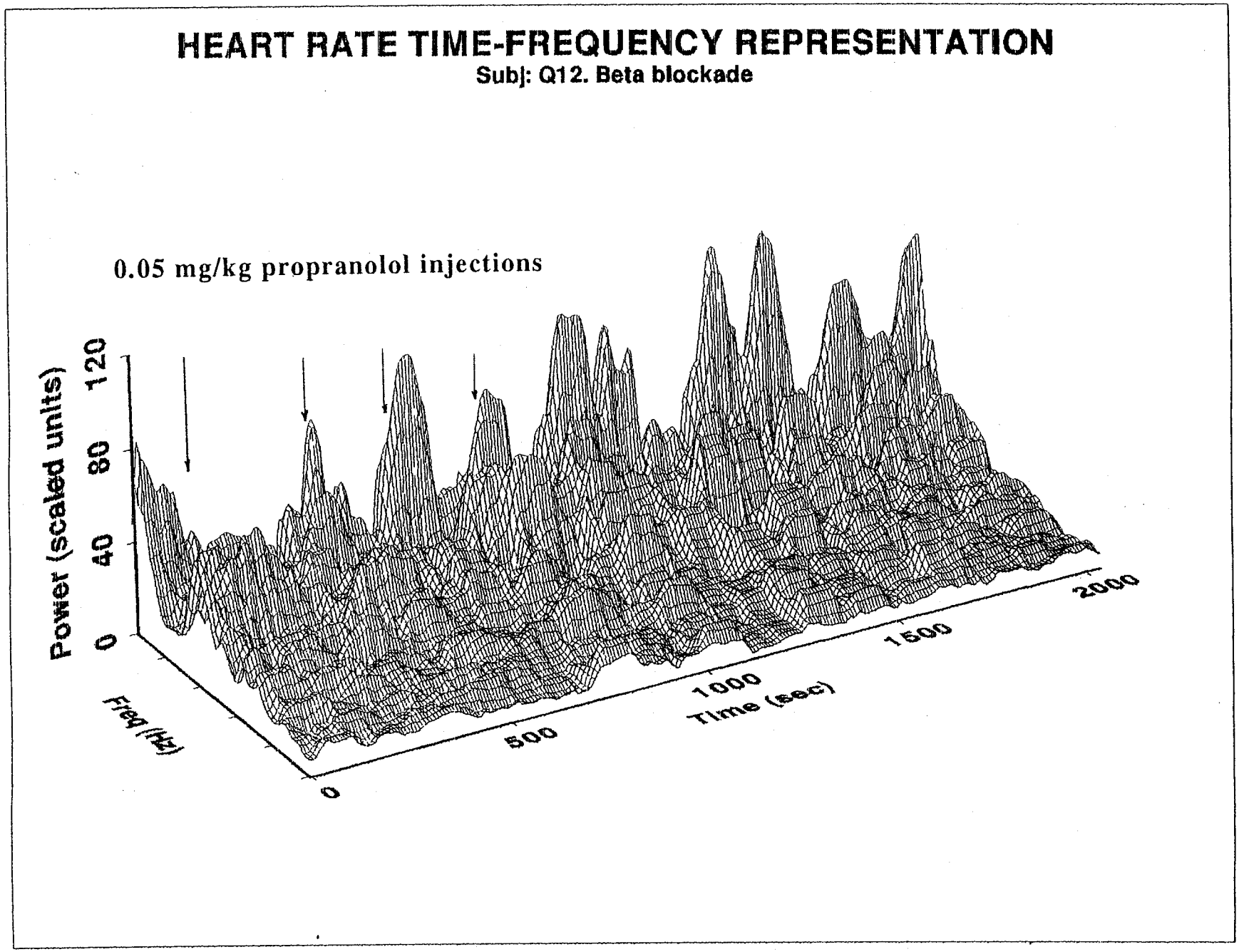

Figure 6b: Heart rate spectral power in one subject during increasing dosage of intravenous propranolol.

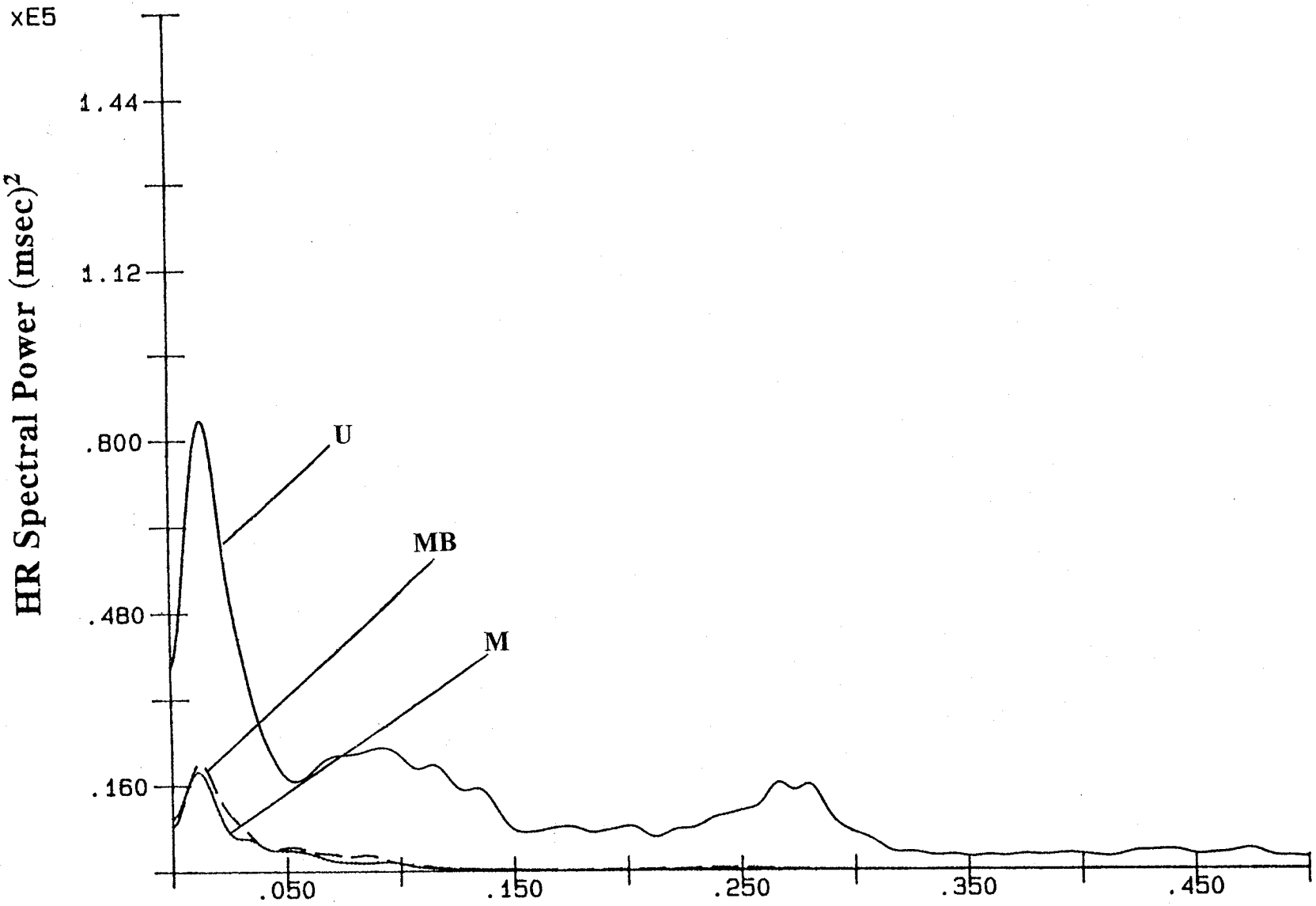

Figure 7a. Averaged heart rate spectra for 9 subjects before (U), after (M) muscarinic blockade and after adding beta to muscarinic (MB) blockade.

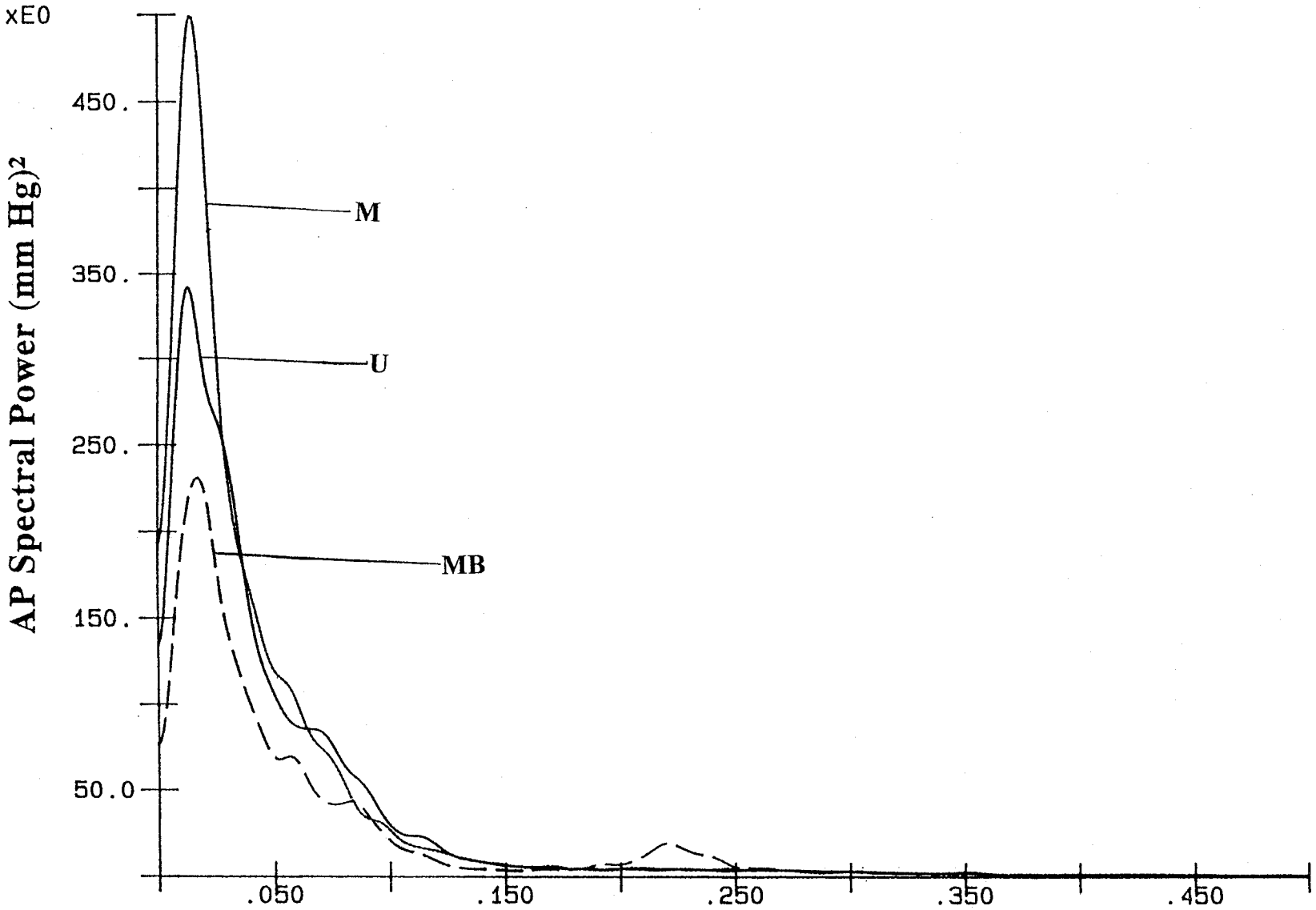

Figure 7b. Averaged arterial pressure spectra for 9 subjects before (U), after (M) muscarinic blockade and after adding beta to muscarinic (MB) blockade.

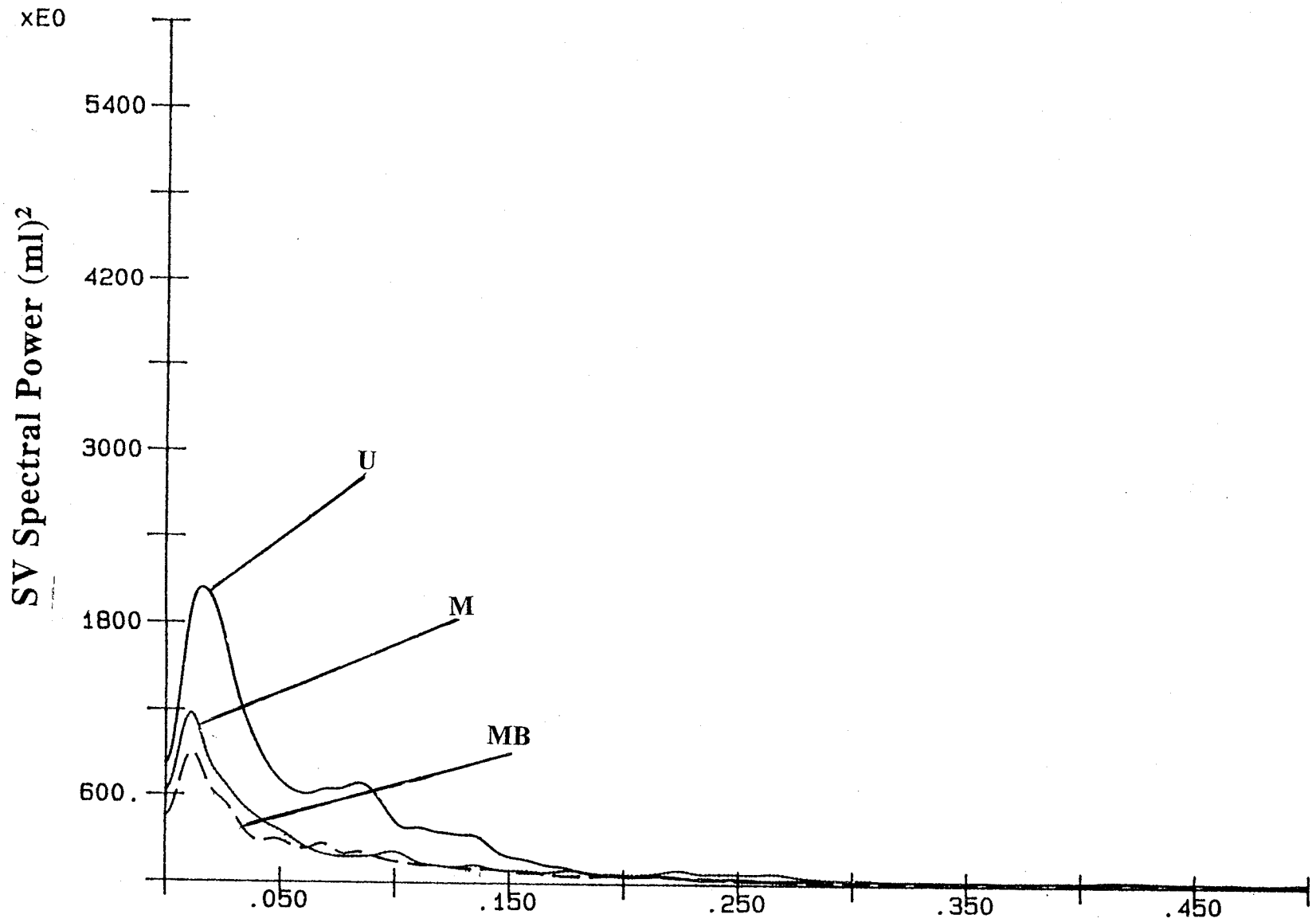

Figure 7c. Averaged stroke volume spectra for 9 subjects before (U), after (M) muscarinic blockade and after adding beta to muscarinic (MB) blockade.

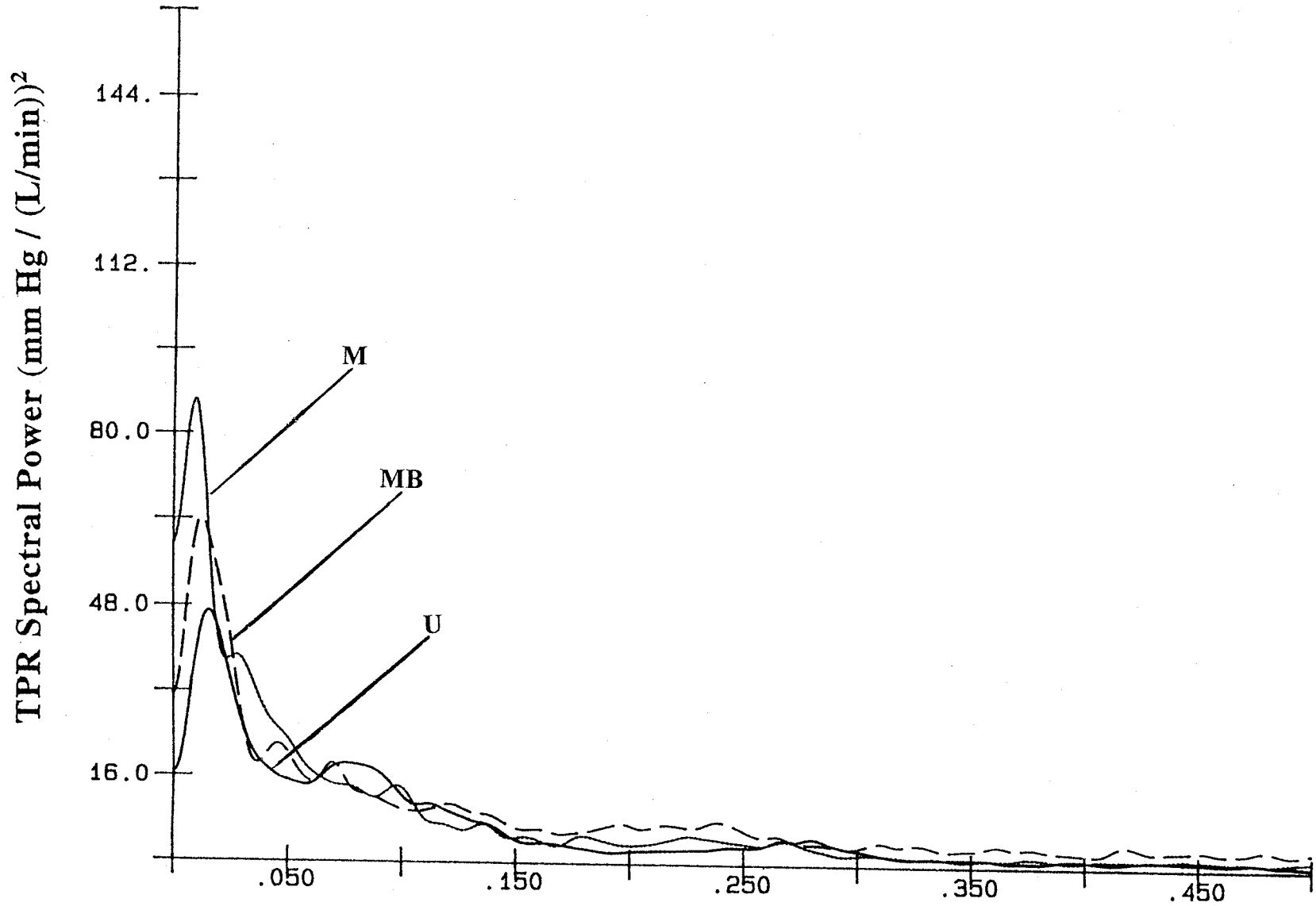

Figure 7d. Averaged total peripheral resistance spectra for 9 subjects before (U), after (M) muscarinic blockade and after adding beta to muscarinic (MB) blockade.

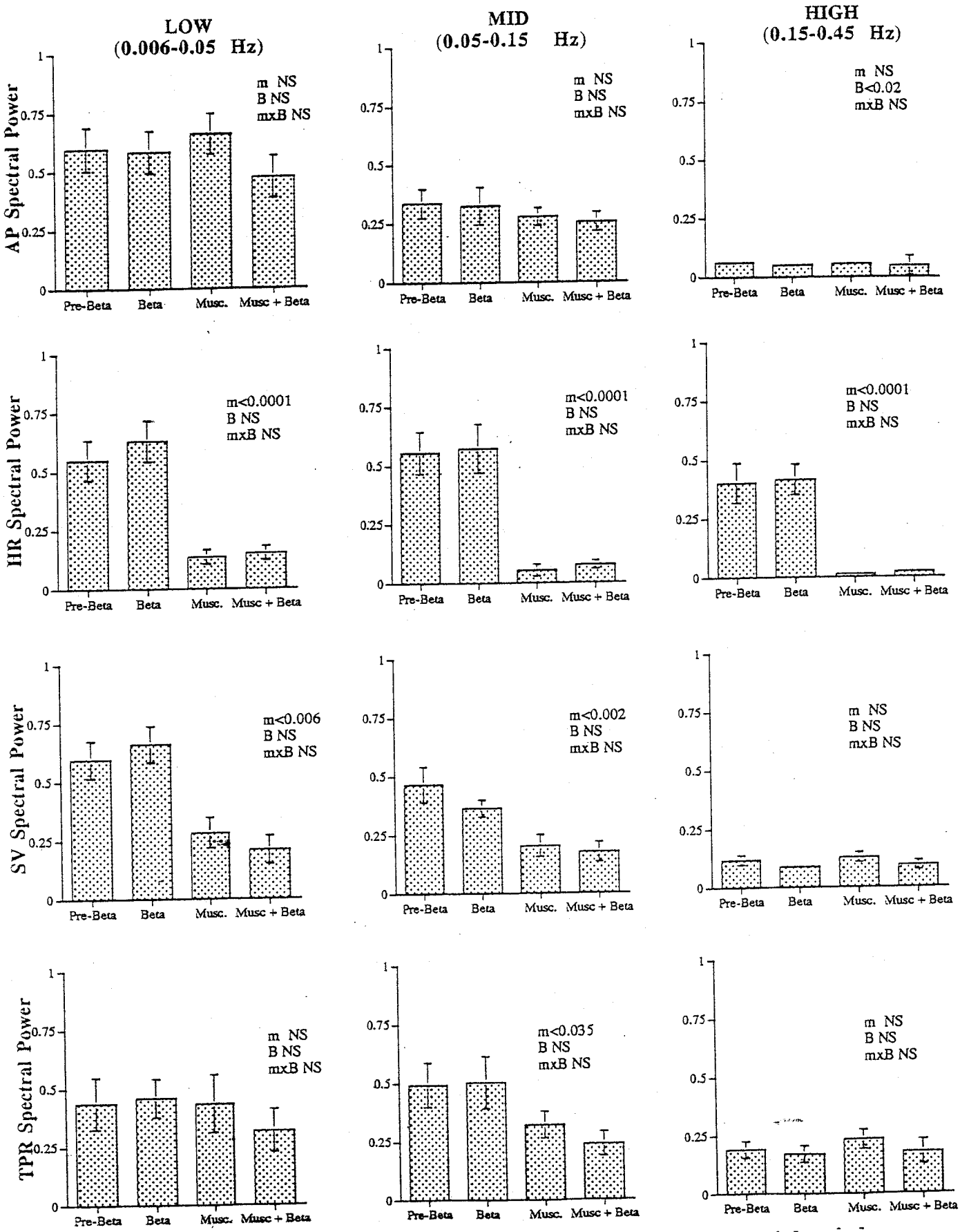

Figure 8a. Group mean (± SEM) resting spectral power for arterial pressure, heart rate, stroke volume and peripheral resistance in low (left column), mid (middle column), and high (right column) frequency regions in unblocked control (PB), after beta blockade (B), after muscarinic blockade (m), and after addition of beta to muscarinic blockade.

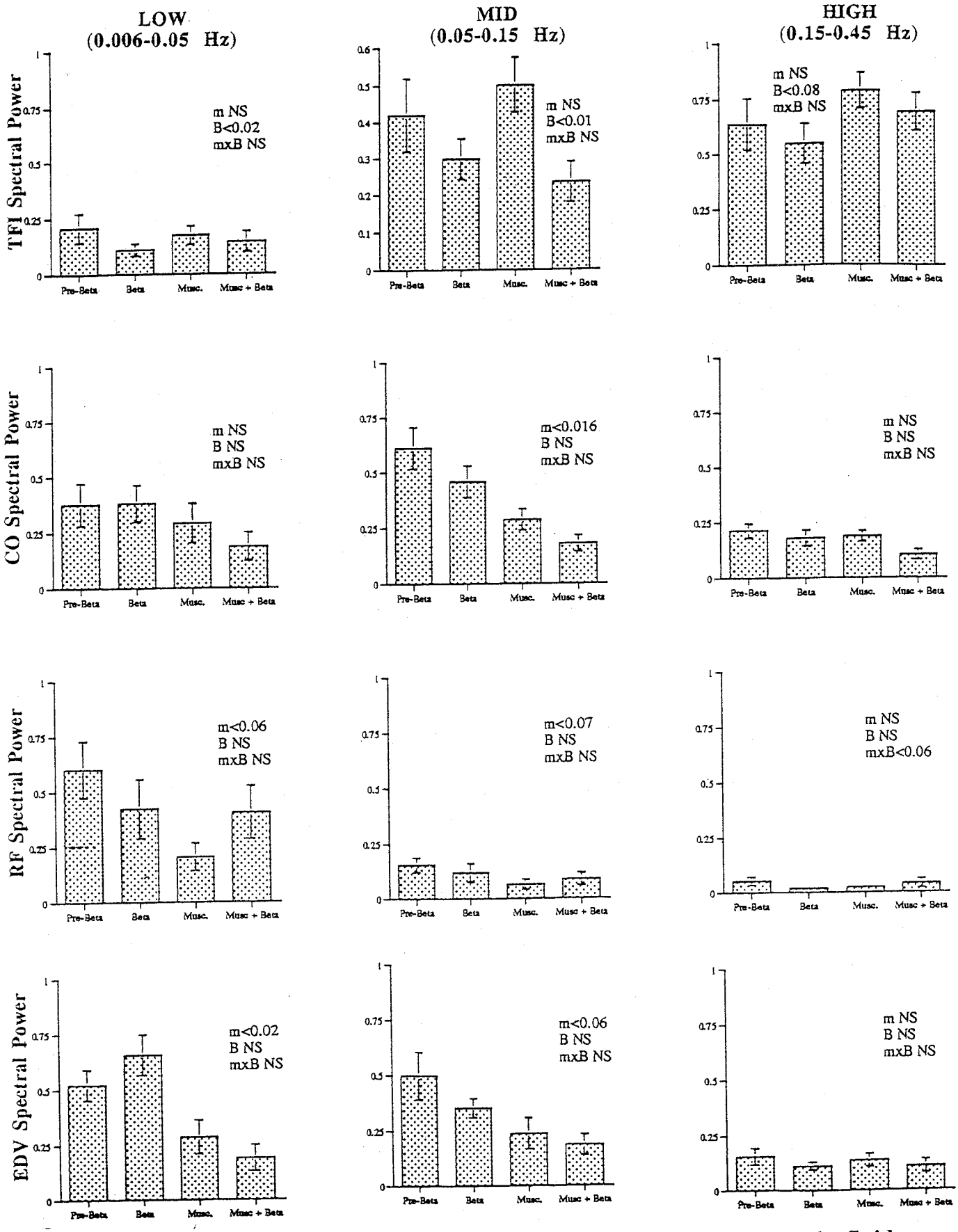

Figure 8b. Group mean (± SEM) resting spectral power for thoracic fluid impedence, cardiac output, radial flow, and end diastolic volume in low (left column), mid (middle column), and high (right column) frequency regions in unblocked control (PB), after beta blockade (B), after muscarinic blockade (m), and after addition of beta to muscarinic blockade.

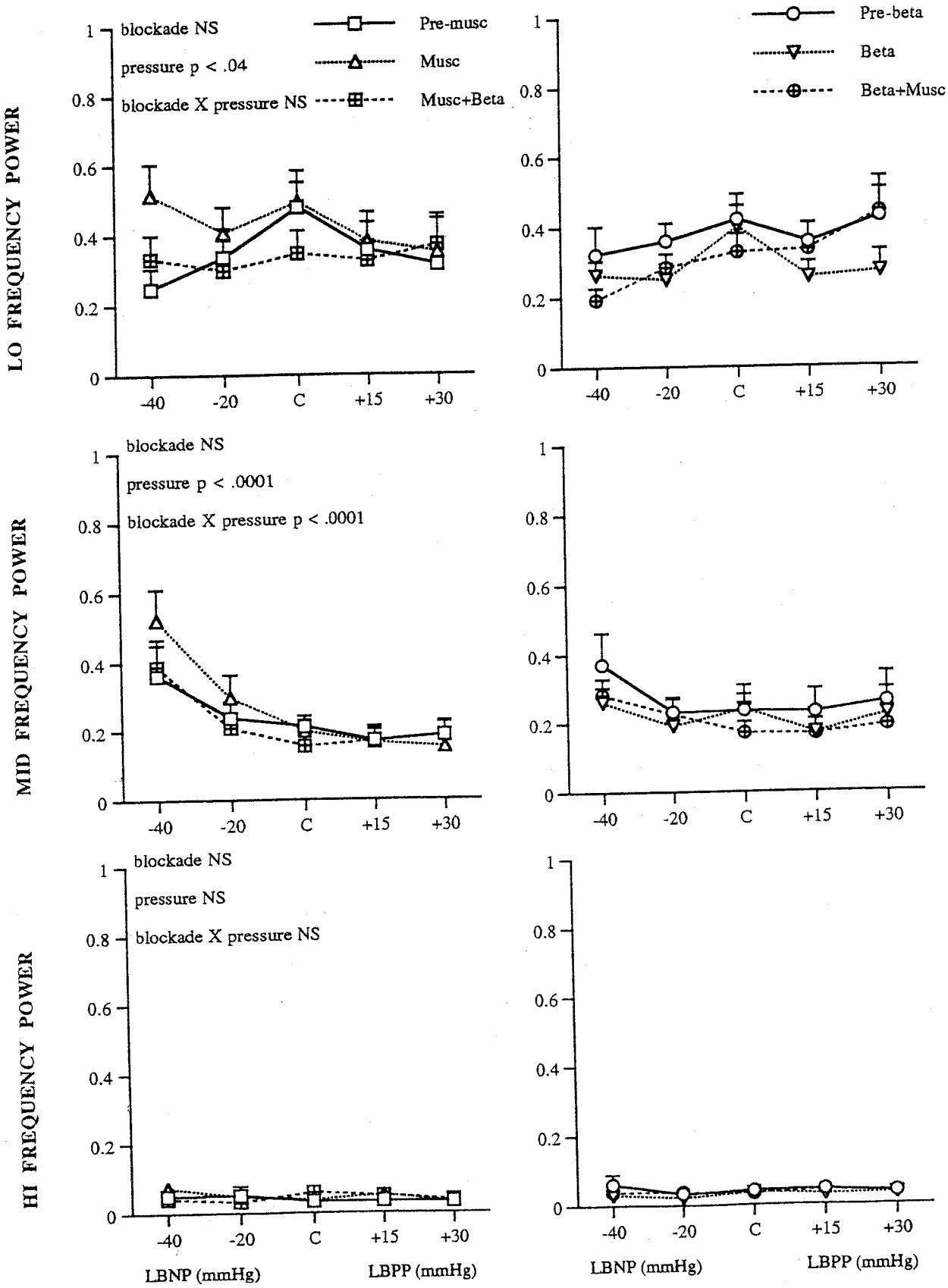

Fig. 9a Arterial Pressure spectral power, normalized by maximum bin power, mean ± SEM, during Control and Lower Body Negative and Positive Pressure n = 10 men.

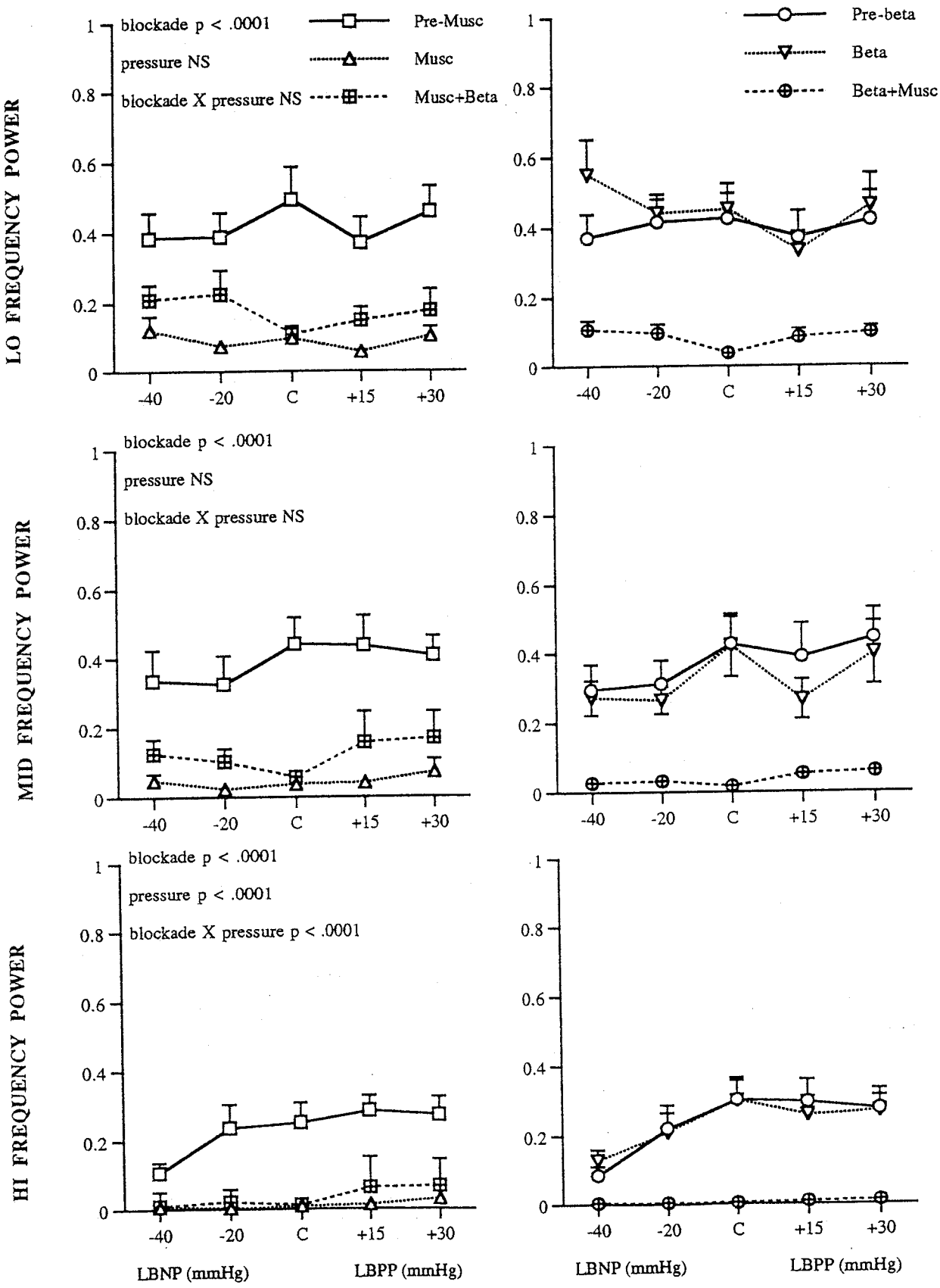

Fig. 9b Heart Rate spectral power, normalized by maximum bin power, mean ± SEM, during Control and Lower Body Negative and Positive Pressure n = 10 men.

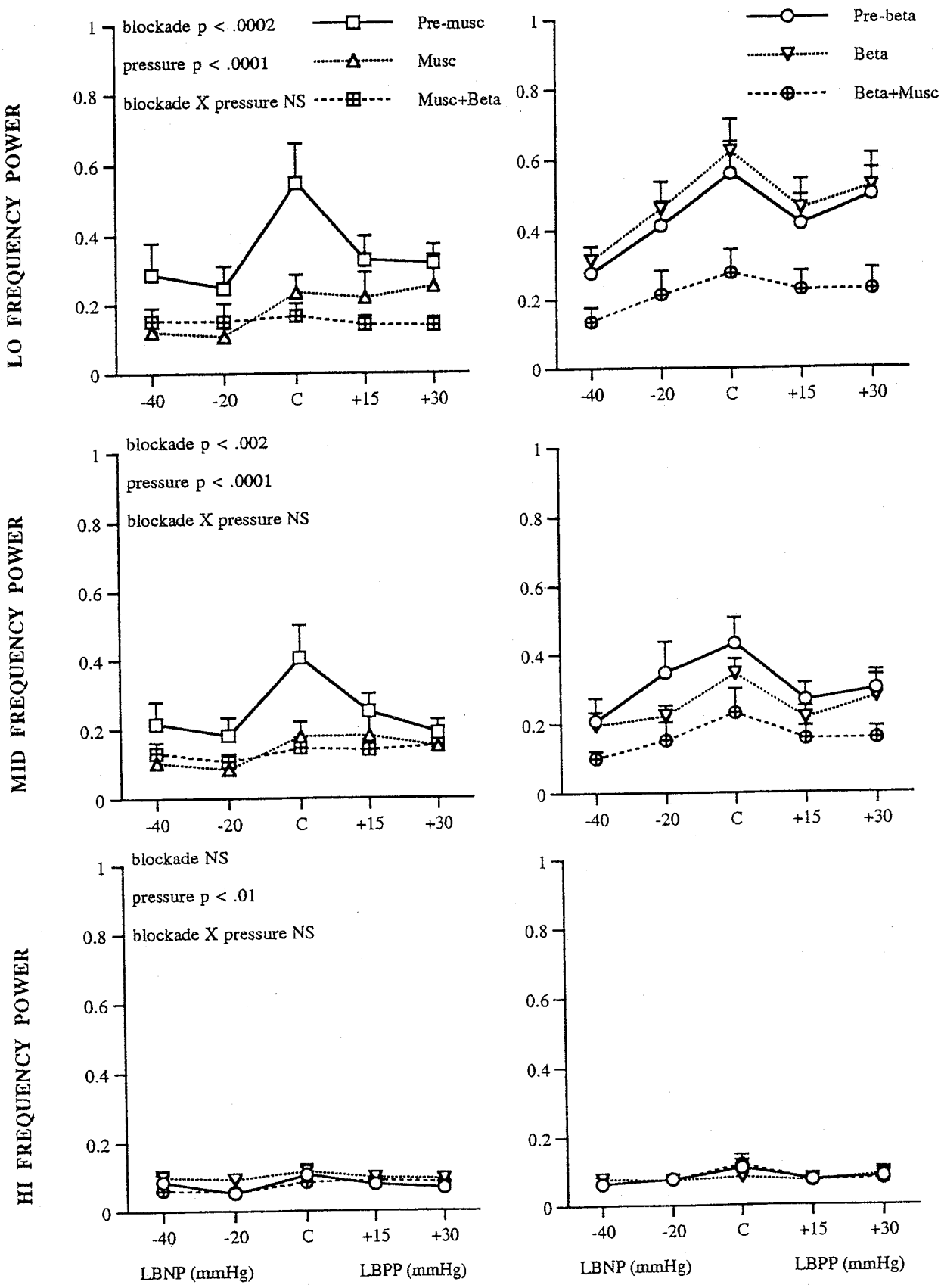

Fig. 9c Stroke Volume spectral power, normalized by maximum bin power, mean ± SEM, during Control and Lower Body Negative and Positive Pressure n = 10 men.

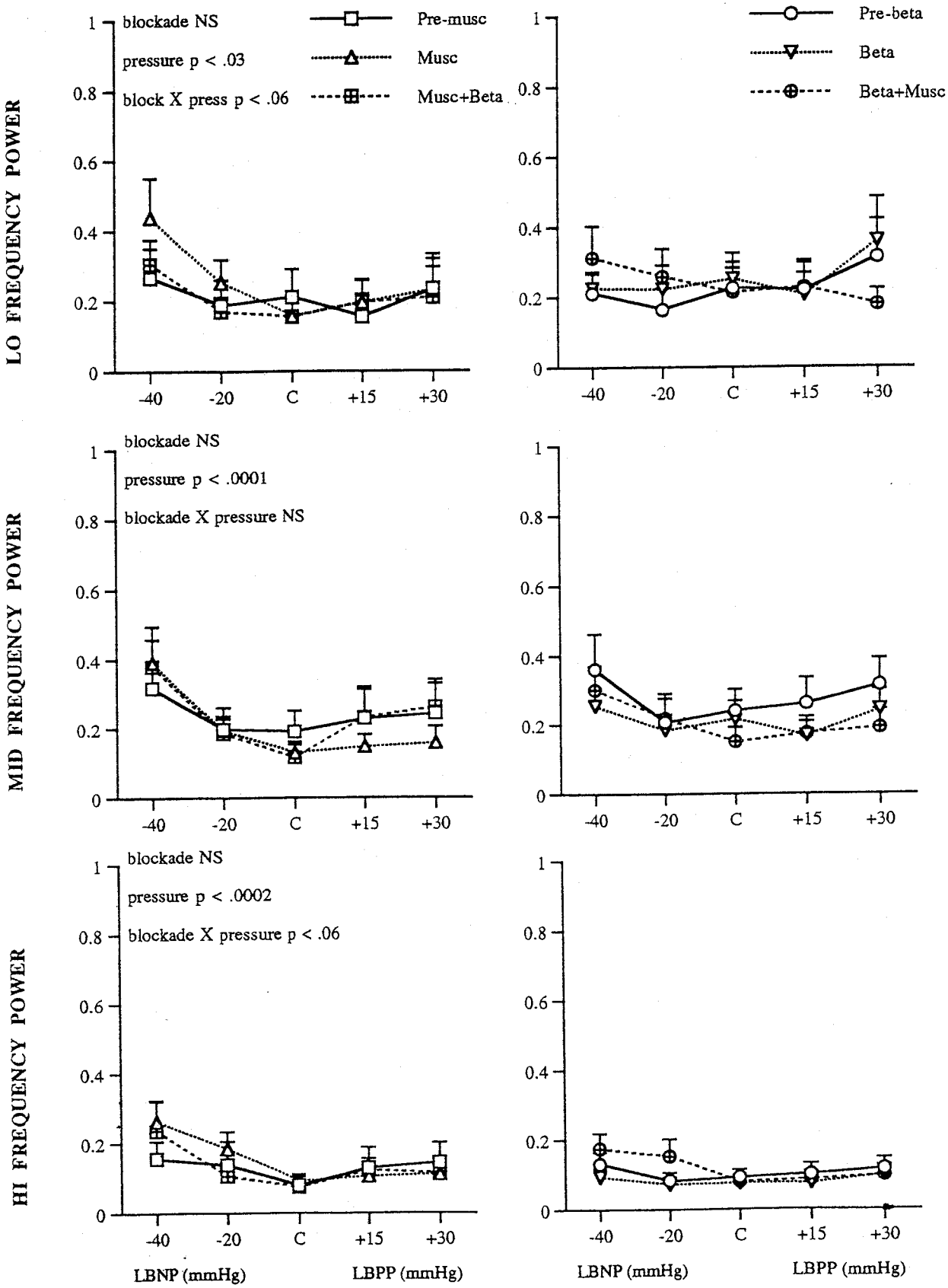

Fig. 9d Total Peripheral Resistance spectral power, normalized by maximum bin power, mean ± SEM, during Control and Lower Body Negative and Positive Pressure n = 10 men.

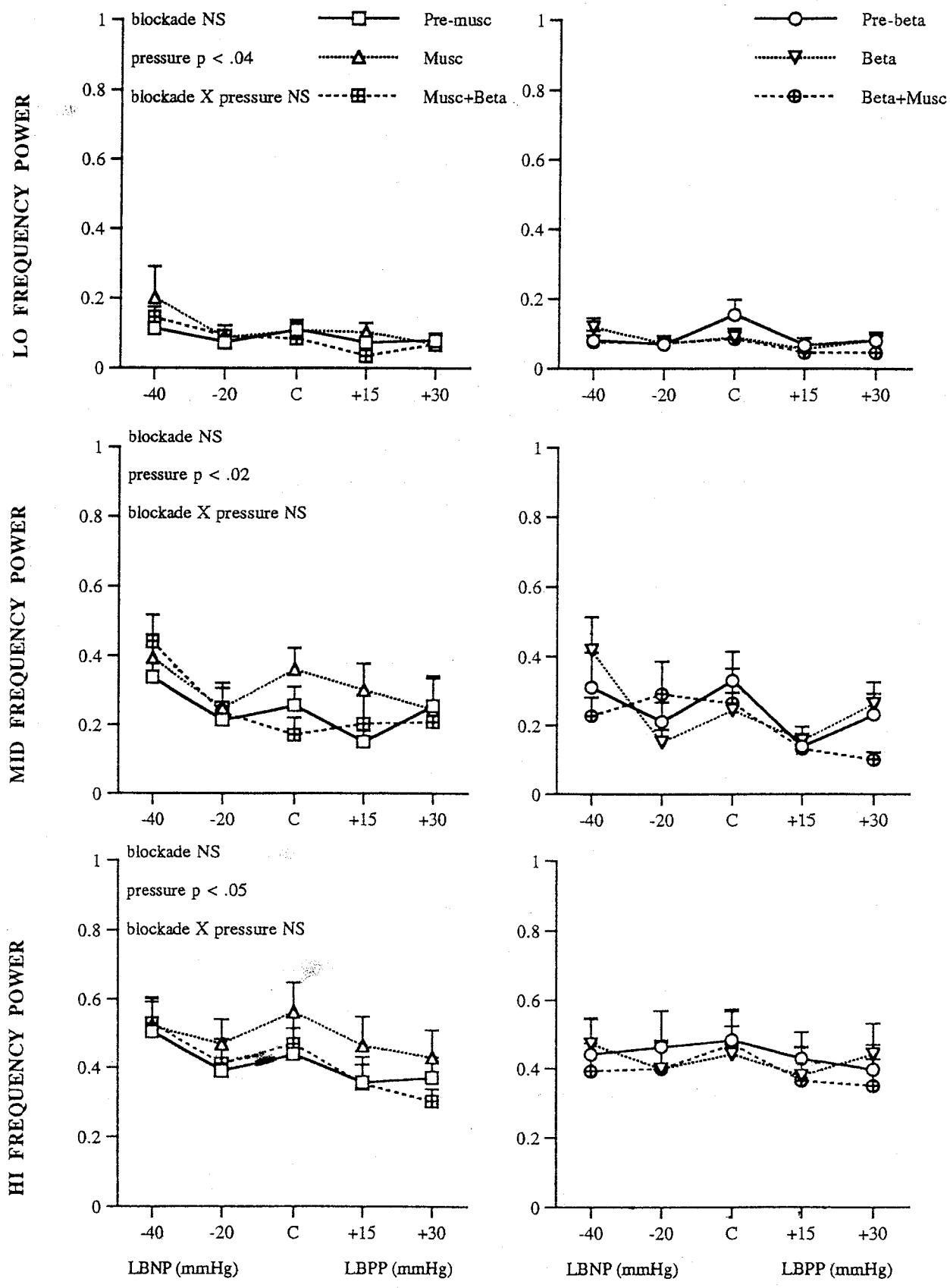

Fig. 9e Thoracic Fluid Index spectral power, normalized by maximum bin power, mean± SEM, during Control and Lower Body Negative and Positive Pressure n = 10 men.

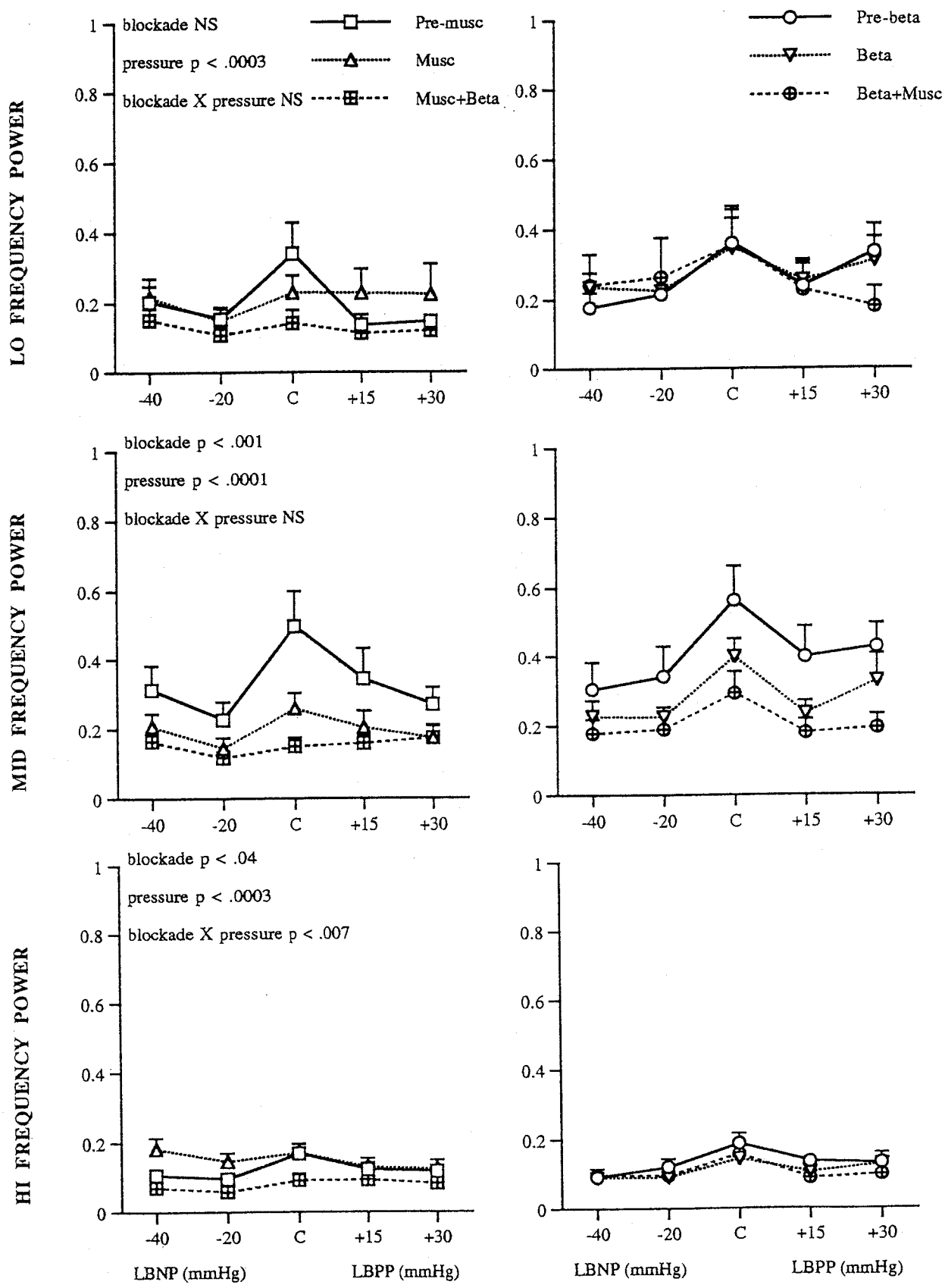

Fig. 9f Cardiac Output spectral power, normalized by maximum bin power, mean± SEM, during Control and Lower Body Negative and Positive Pressure n = 10 men.

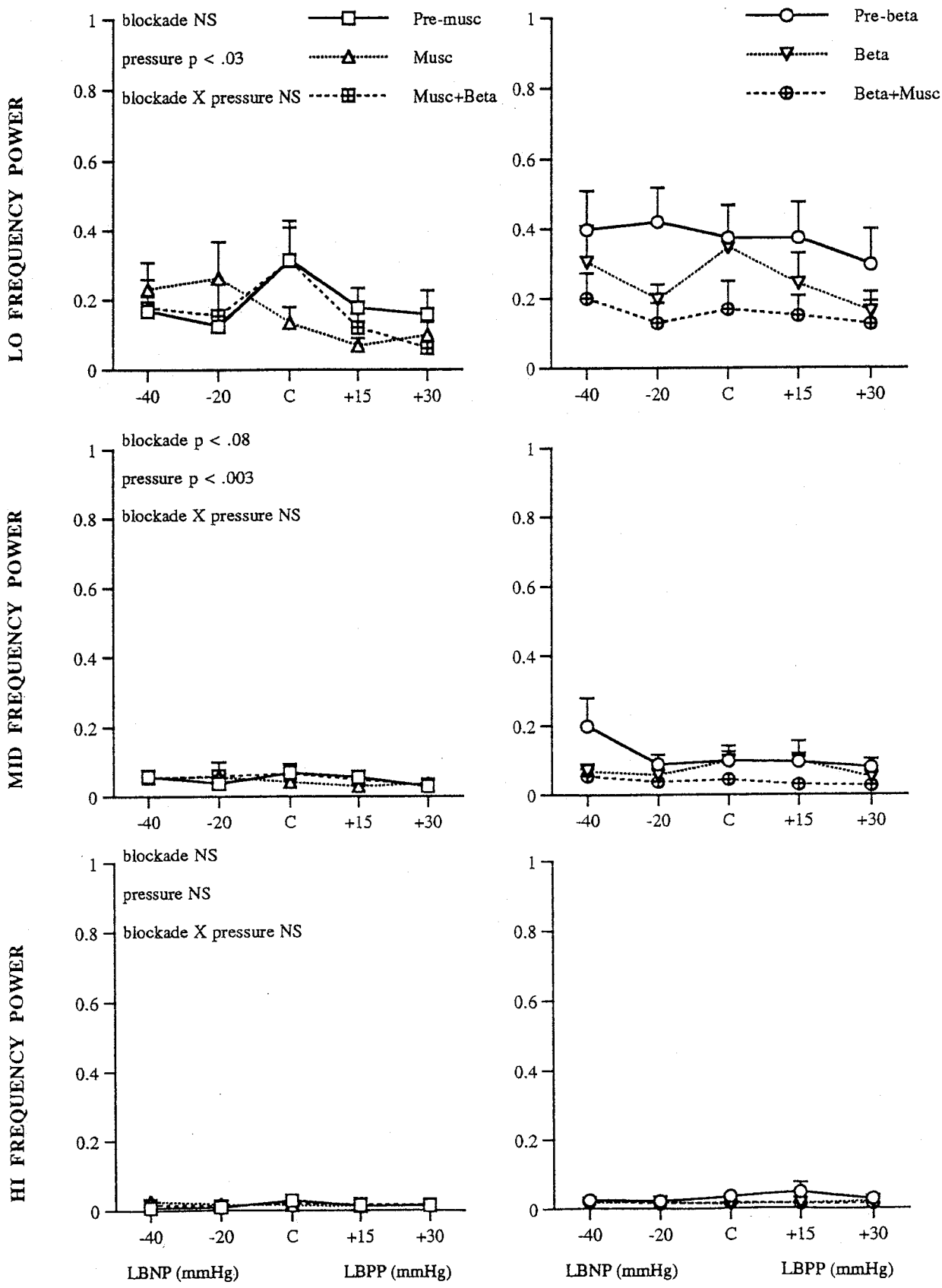

Figure 9g Radial Flow spectral power, normalized by maximum bin power, mean ± SEM, during Control and Lower Body Negative and Positive Pressures n = 10 men.

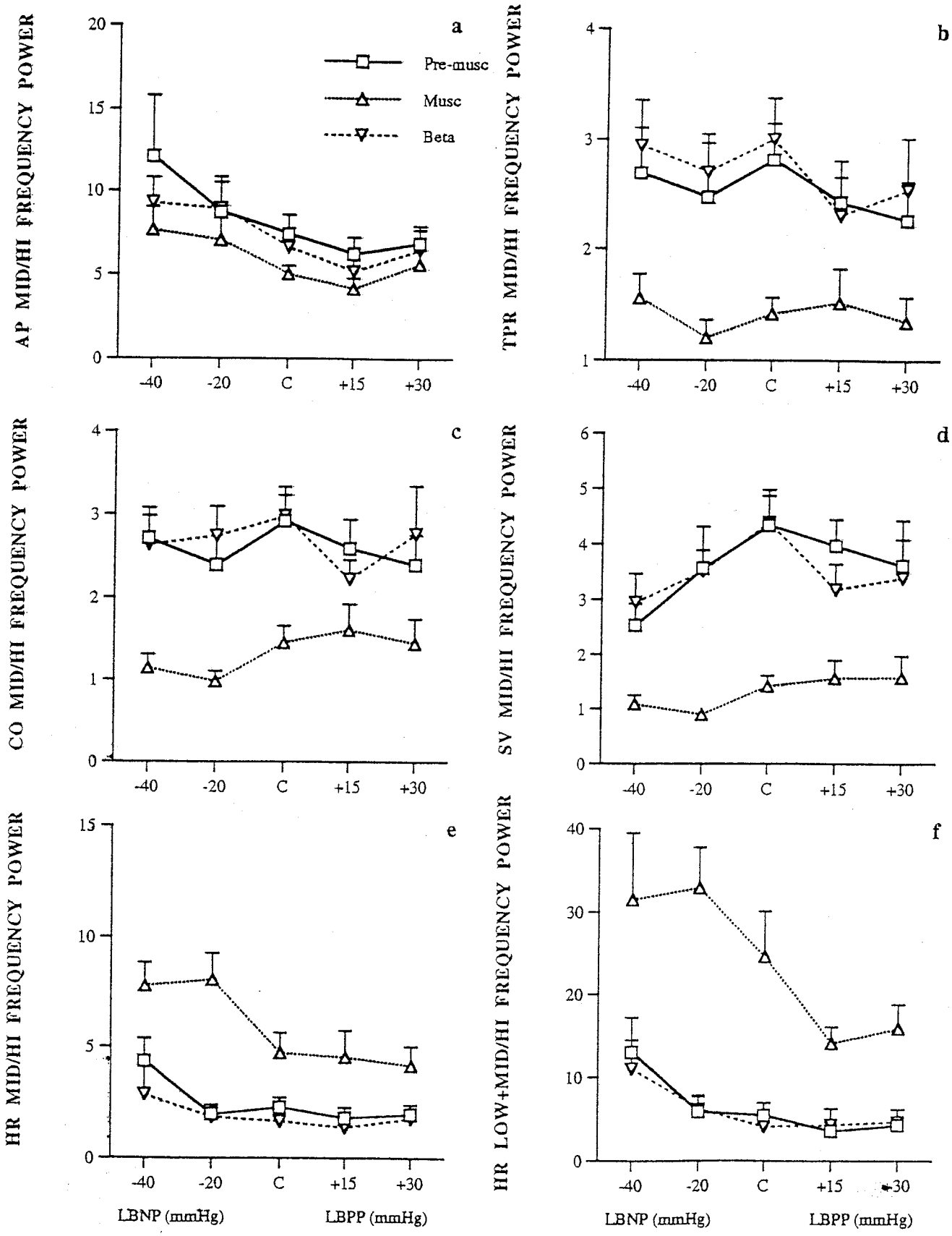

Figure 10 Ratios of MID/HI frequency spectral power, Mean ± SEM during Control and Lower Body Negative and Positive Pressure for (a) AP, (b) TPR, (c) CO, (d) SV, (e) HR, and (f) HR LOW+MID/HI frequency spectral power, Mean± SEM n = 10 men.

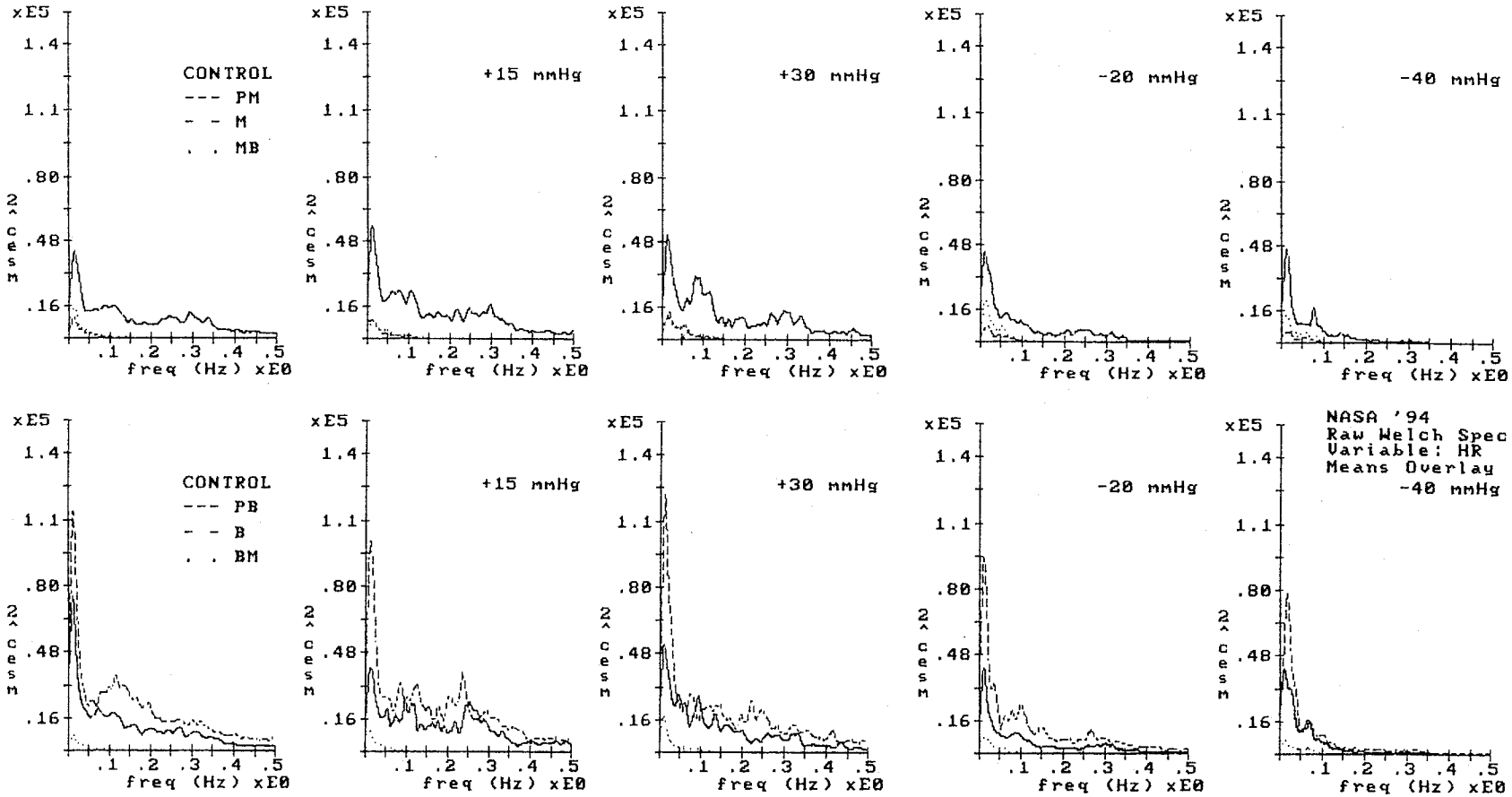

Figure 11: Mean Welch spectra for Heart Rate during each blockade and Lower Body Negative and Positive pressures, n = 10 women.

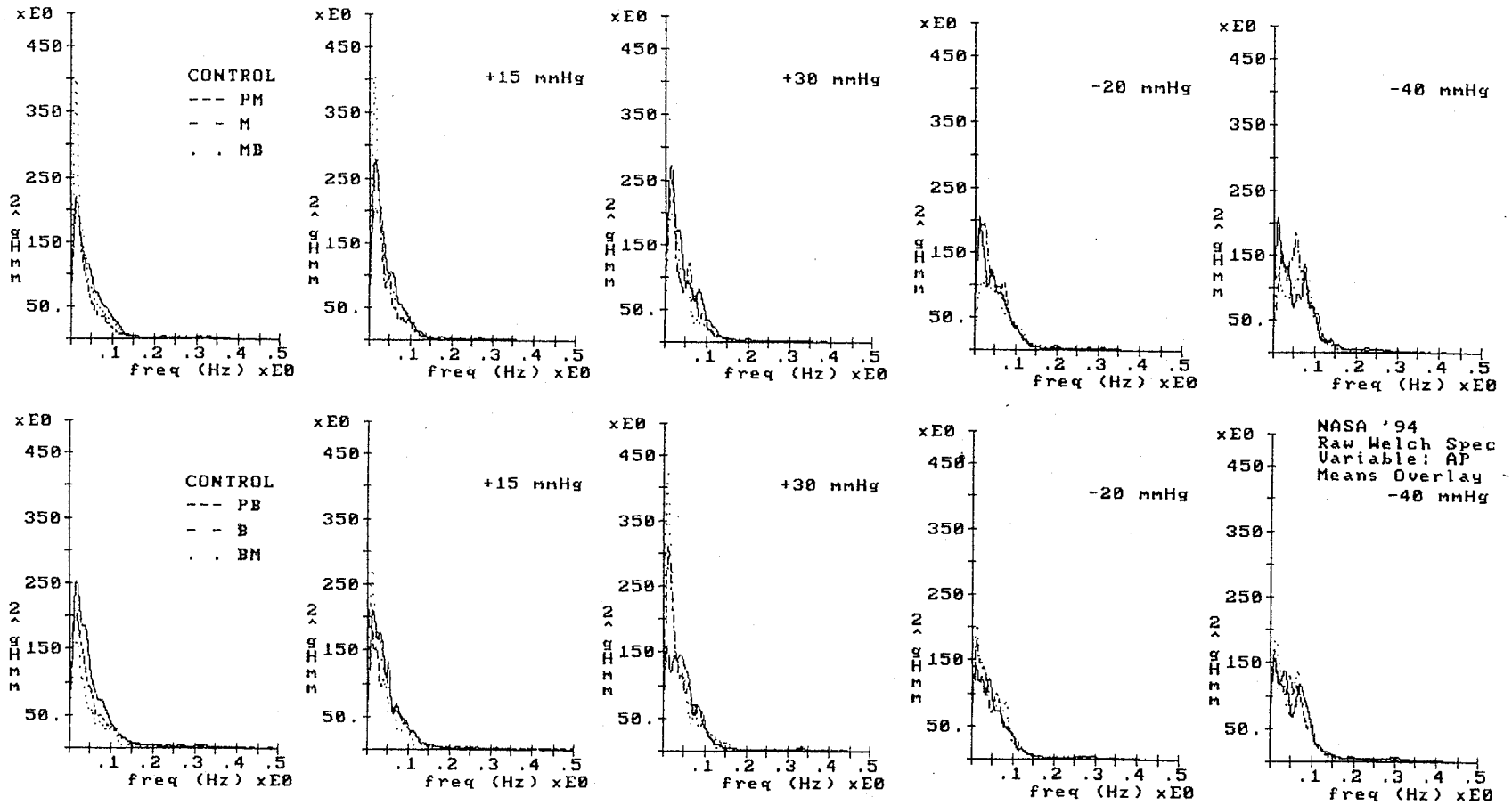

Figure 12: Mean Welch spectra for Arterial Pressure during each blockade and Lower Body Negative and Positive pressures, n = 10 women.

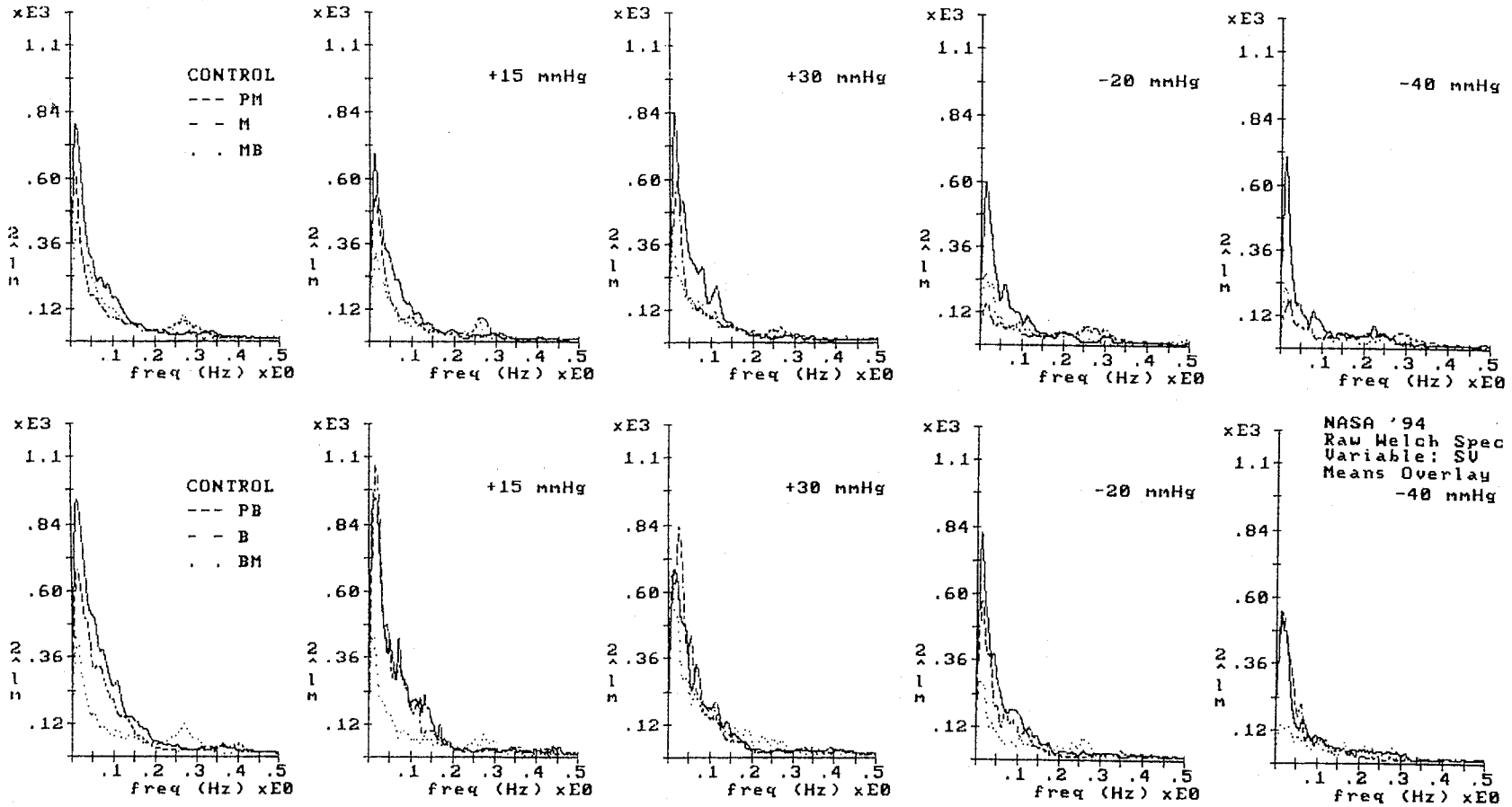

Figure 13: Mean Welch spectra for Stroke Volume during each blockade and Lower Body Negative and Positive pressures, n = 10 women.

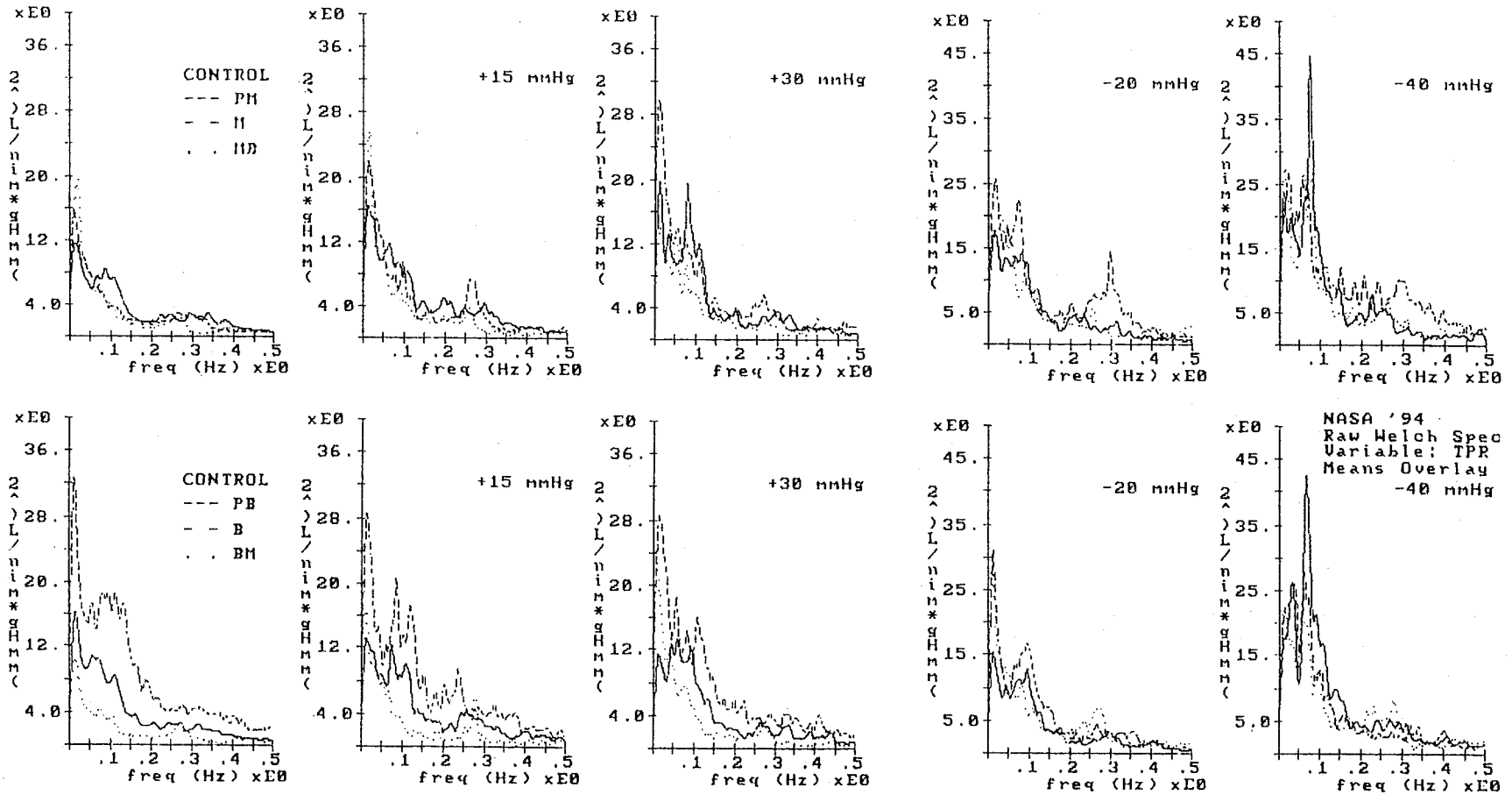

Figure 14: Mean Welch spectra for Total Peripheral Resistance during each blockade and Lower Body Negative and Positive pressures, n = 10 women.

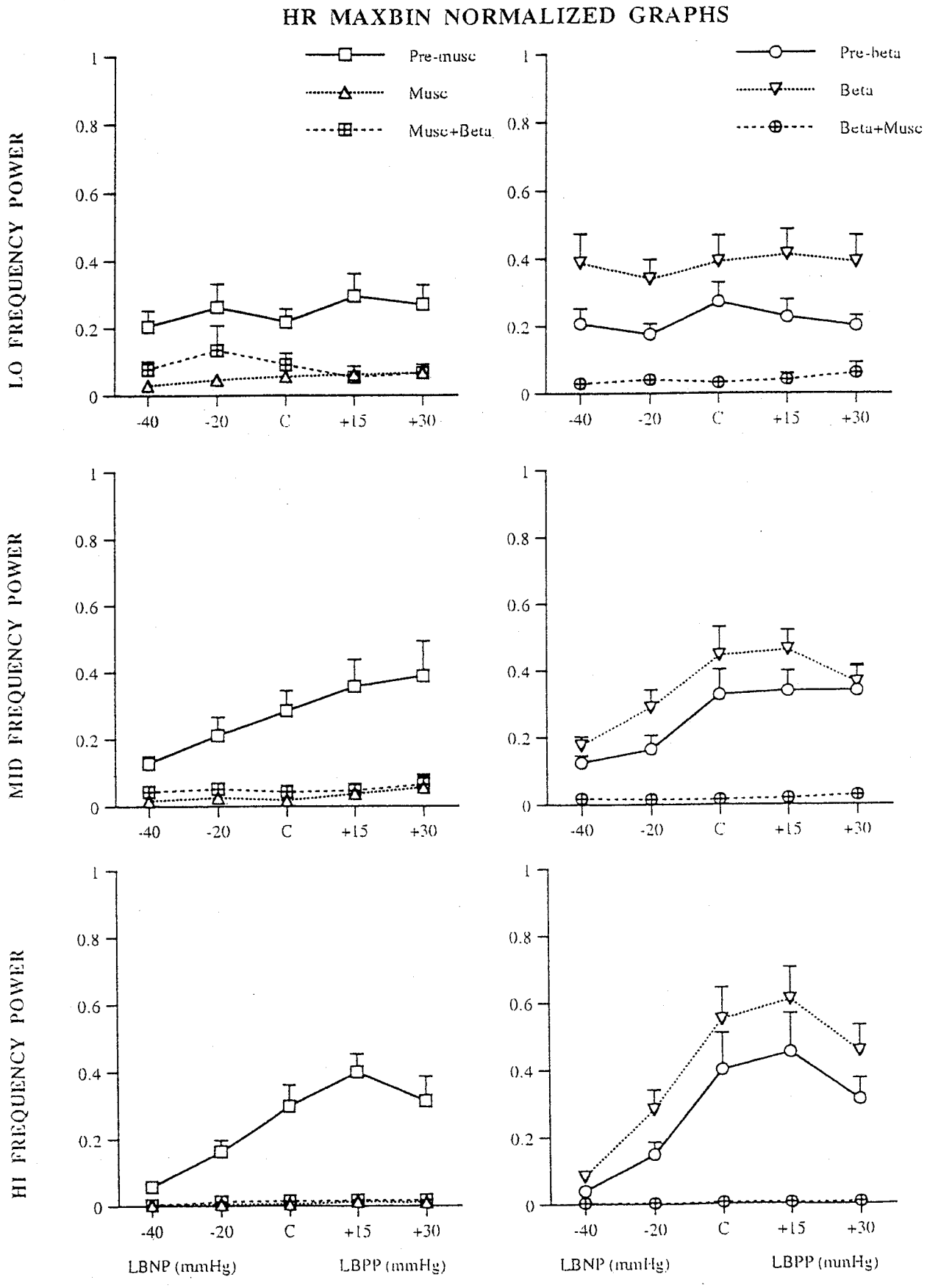

Fig. 15: Maxbin normalized Welch spectra for Heart Rate, n = 10 women

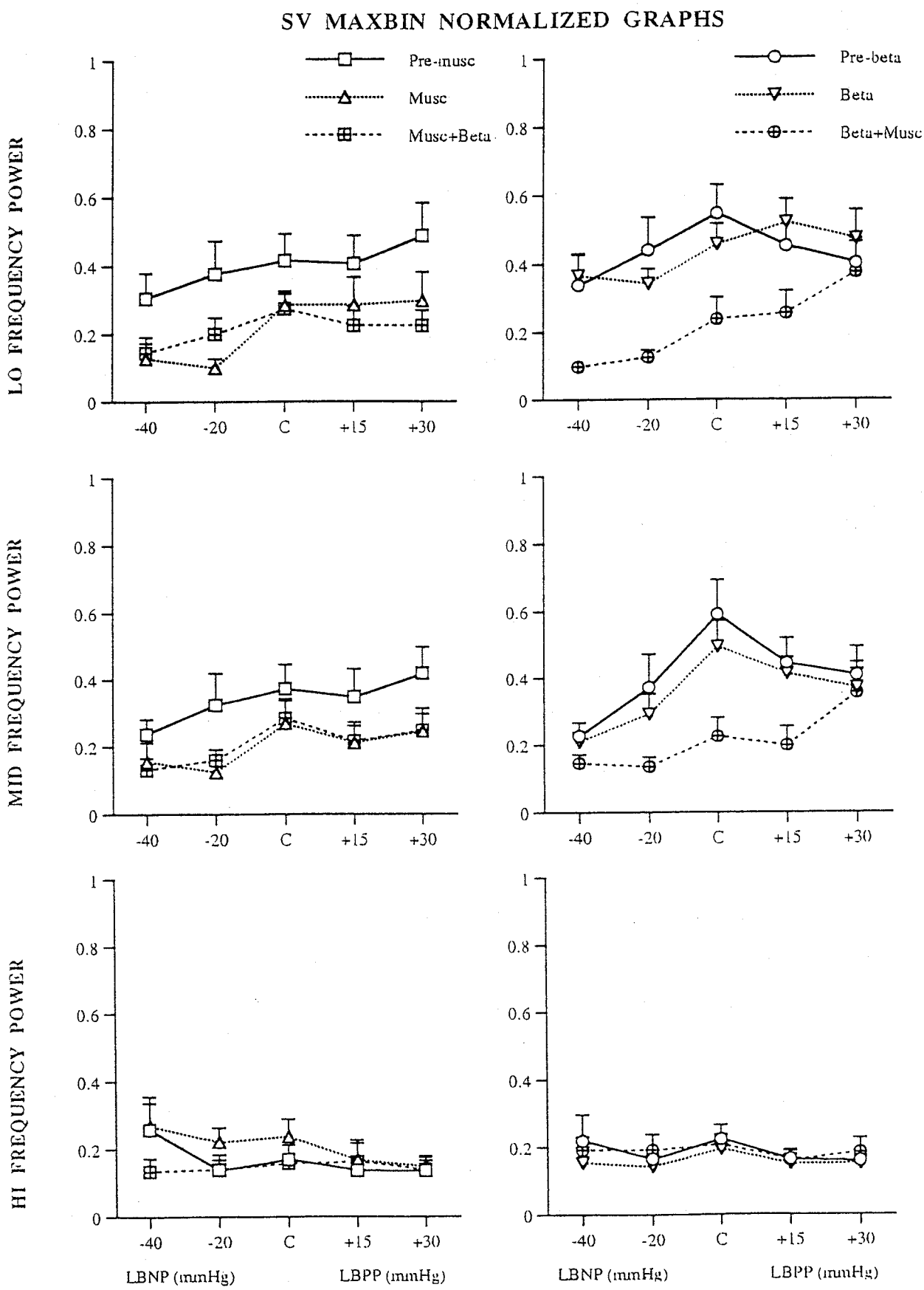

Fig. 16: Maxbin normalized Welch spectra for Stroke Volume, n = 10 women

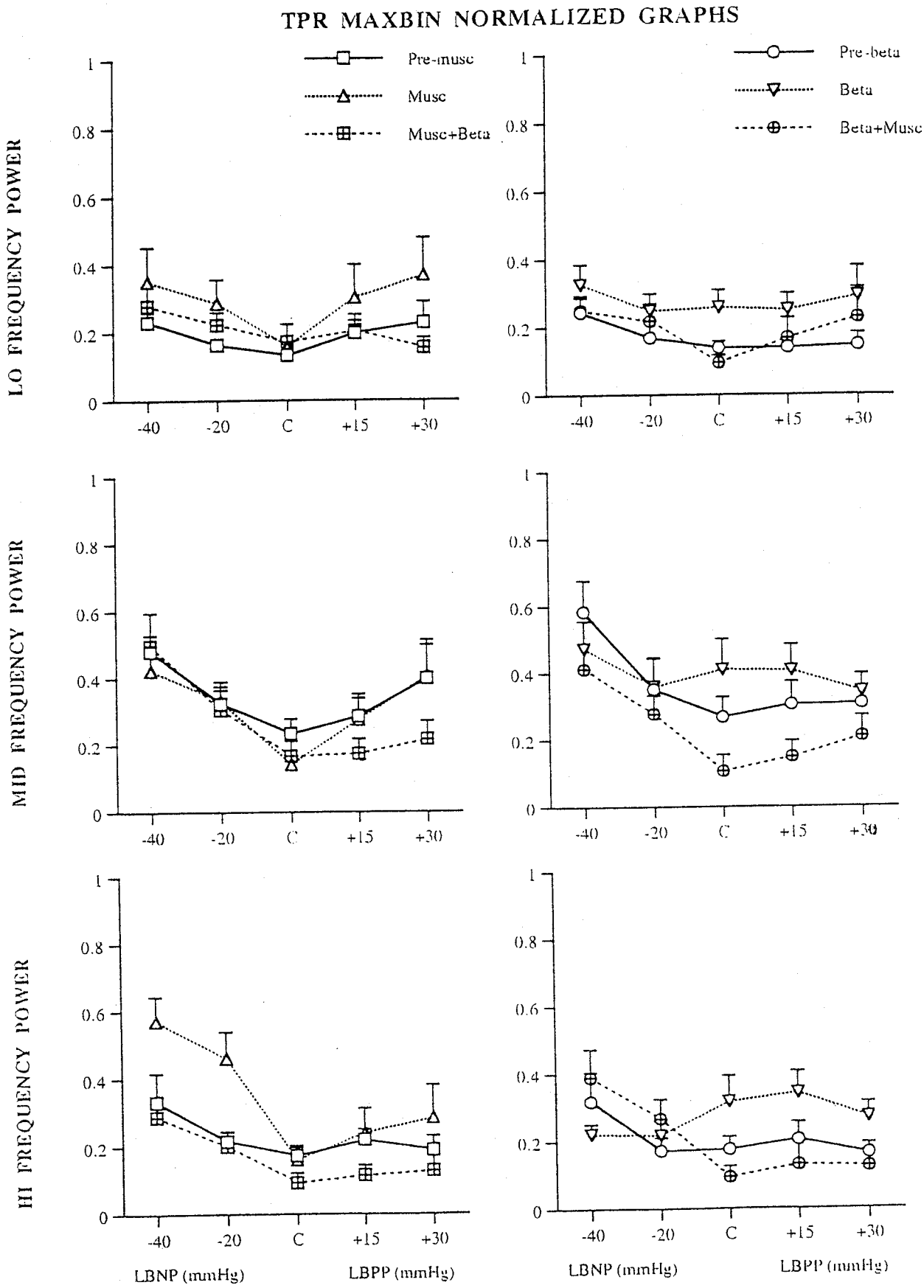

Fig. 17: Maxbin normalized Welch spectra for Total Peripheral Resistance, n = 10 women

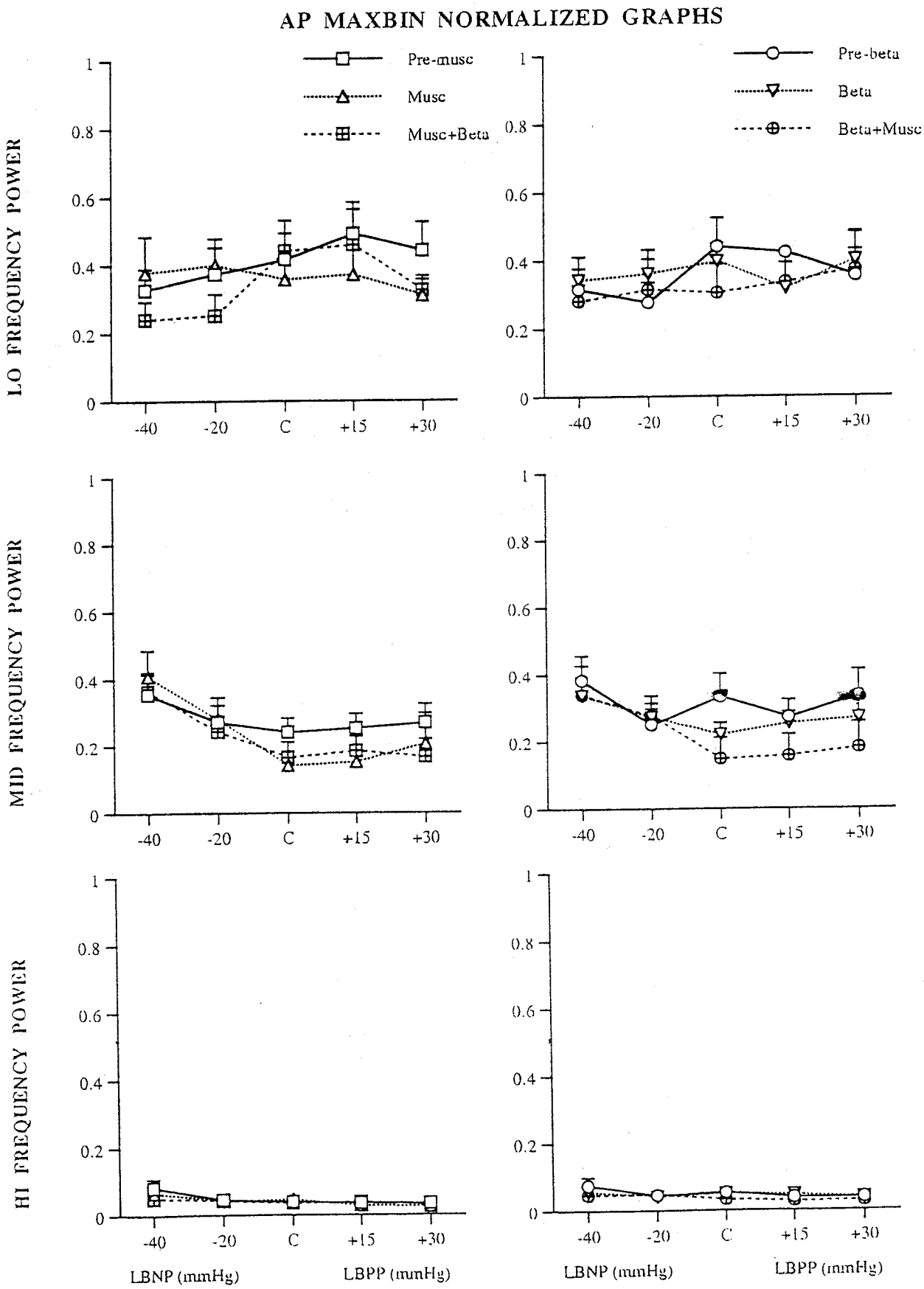

Fig. 18: Maxbin normalized Welch spectra for Arterial Pressure, n = 10 women

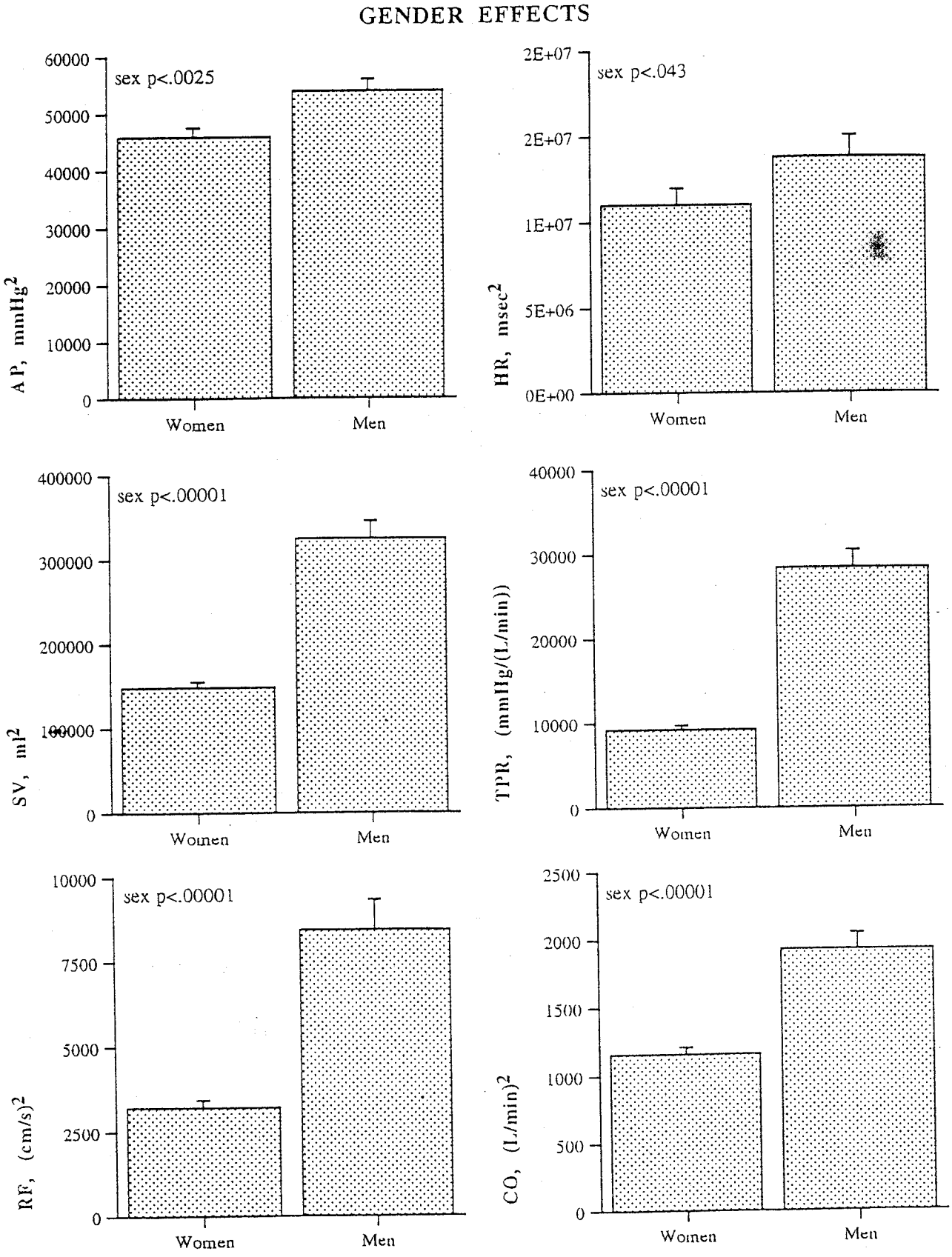

Fig. 19: Mean ± SEM of Total Welch Spectral Power independent of pressure levels and blockade states for male (n = 10) and female (n = 10) subjects for Arterial Pressure, Heart Rate, Stroke Volume, Total Peripheral Resistance, Radial Flow, and Cardiac Output.

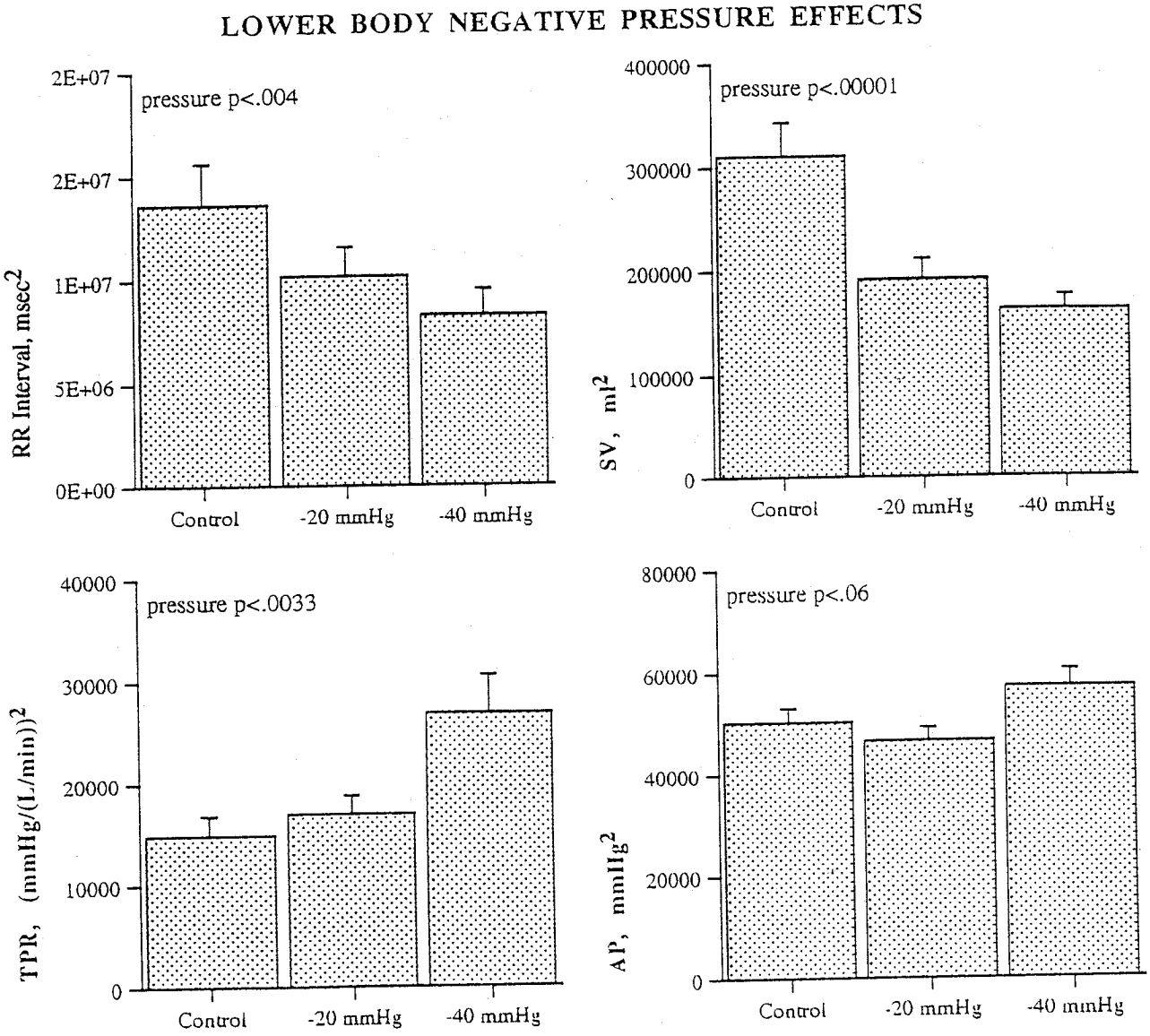

Figure 20 Mean ± SEM for Total Welch Spectral Power independent of sex and blockade states for male (n=10) and female (n=10) subjects for Heart Rate, Stroke Volume, Total Peripheral Resistance, and Arterial Pressure during Control and Lower Body Negative Pressures.

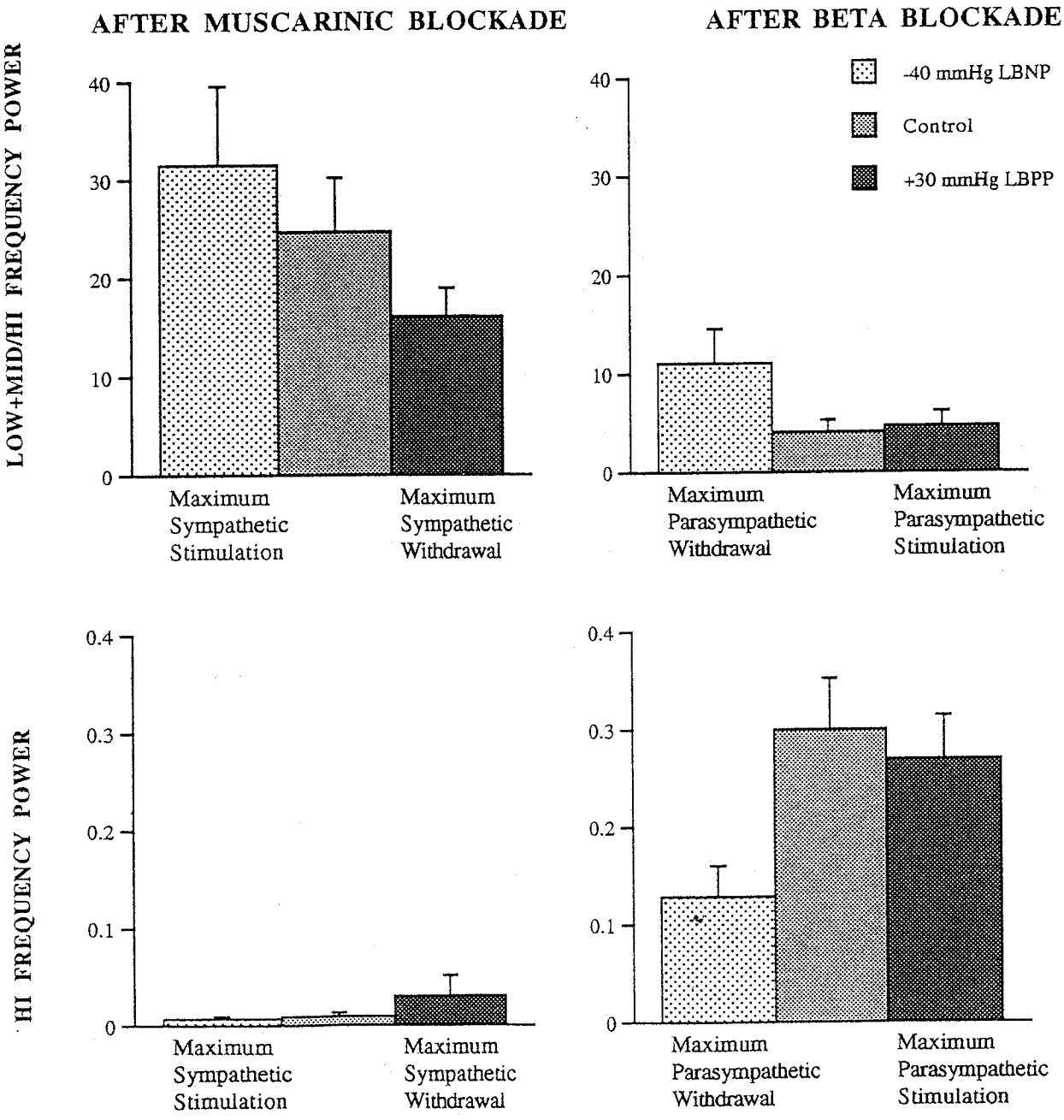

Fig. 21: Group Mean ± SEM ratios of LOW+MID/HI frequency HR spectral power (top) and HI frequency HR spectral power (bottom) for subjects in (left) states of maximum sympathetic stimulation (col. 1) and withdrawal (col. 3) induced by Lower Body Negative and Positive Pressures applied after muscarinic blockade and (right) states of maximum parasympathetic withdrawal (col. 1) and stimulation (col. 3) induced by Lower Body Negative and Positive Pressures after beta blockade.