SPECTRAL ANALYSIS OF RESTING CARDIOVASCULAR VARIABLES AND RESPONSES TO OSCILLATORY LBNP BEFORE AND AFTER 6° HEAD DOWN BEDREST

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SUMMARY

A major focus of our research program is to develop noninvasive procedures for determining changes in cardiovascular function associated with the null gravity environment. We define "changes in cardiovascular function" to be 1) the result of the regulatory system operating at values different from 'normal' but with an overall control system basically unchanged by the null gravity exposure or 2) the result of operating with a control system that has significantly different regulatory characteristics after an exposure.

To this end, we have used a model of weightlessness that consisted of exposing humans to 2 hrs. in the launch position, followed by 20 hrs. of 6° head down bedrest. Our principal objective was to use this model to measure cardiovascular responses to the 6° head down bedrest protocol and to develop the most sensitive "systems identification" procedure for indicating change. A second objective, related to future experiments, is to use the procedure in combination with experiments designed to determine the degree to which a regulatory pathway has been altered and to determine the mechanisms responsible for the changes.

From the viewpoint of systems identification, we recently have focused on the use of oscillatory lower body negative pressure (LBNP) and spectral analysis of the resulting cardiovascular responses before and after the bedrest protocol mentioned above. The application of this approach to the bedrest study was prompted by a systematically designed series of experiments that have previously demonstrated its effectiveness in several areas. In the past, we have used oscillatory (sinusoidal) acceleration or LBNP as provocative tests to determine:

1. The overall frequency response characteristics of integrated cardiovascular regulation in response to blood volume shifts induced by sinusoidal whole-body acceleration in dogs (Knapp, et al. 1978, 1982).

2. The relative contributions (amplitude and time of response) of both cardiac and peripheral vascular mechanisms in the regulation of pressure and flow during oscillatory blood volume shifts in dogs (Marquis, et al 1978).

3. The differences in the cardiovascular control mechanisms of endurance trained (treadmill) and untrained dogs in response to oscillatory blood volume shifts (Charles, et al 1983).

4. The chronotropic frequency response characteristics of humans during sinusoidal $\pm 1g_z$ acceleration (Knapp, et al 1983).

5. The relative contributions of cardiac and peripheral mechanisms to blood pressure regulation in dogs during sinusoidal LBNP (Aral, et al 1986).

6. The chronotropic frequency response characteristics of humans during sinusoidal LBNP (Knapp, et al 1987).

7. The differences in stroke volume and heart rate in response to sinusoidal LBNP in the same human subject in salt replete and depleted states (Knapp, et al 1990).

We now seek to evaluate the effectiveness of the oscillatory LBNP (and spectral analysis) protocol to evaluate cardiovascular regulation in humans before and after head down bedrest. We also seek to place the sensitivity of the technique in perspective with other protocols that do not use provocative tests. Our current studies are designed to answer the following specific questions:

1. Can the frequency response characteristics of cardiovascular regulation in normal supine humans be identified by spectral analysis of responses to oscillatory LBNP? How do the results compare to those from the spectral analysis of resting variables?

2. Can bedrest-induced changes in cardiovascular function be identified by spectral analysis of responses to oscillatory LBNP? How do the results compare to those from the spectral analysis of resting variables? If they are more sensitive, does the enhancement justify the extra effort involved with the provocative test?

3. Which spectral analysis technique is the most sensitive to track subtle changes in cardiovascular function during bedrest? Can the details of the spectra provide information about the mechanisms of cardiovascular control and do <u>changes</u> in the spectra associated with bedrest reflect <u>changes</u> in control mechanisms?

In an effort to answer these questions, we have been investigating several approaches to determine the spectral content of resting variables alone and in response to sinusoidal LBNP. At present, we are:

1. measuring the spectral content of resting variables using autoregression and chirp Z transform analysis.

2. measuring the excursions (peak-to-peak differences) in cardiovascular responses as a function of LBNP frequencies.

3. measuring the spectral content of each response to each LBNP input frequency using discrete Fourier transforms, chirp Z transforms (for increased spectral resolution) and autoregression analysis.

4. measuring the spectral content of cardiovascular responses to step changes in LBNP by autoregression.

Preliminary results from some of the above listed approaches are presented below.

SINUSOIDAL LBNP RESPONSES

We are completing a study designed to determine the overall frequency response characteristics of integrated cardiovascular regulation in ten normal supine humans in response to oscillatory LBNP. Another goal of this study was to examine the effects of short term (22 hrs.) head down bedrest (plus Lasix, 40 mg P.O.) on the frequency response characteristics in the same subjects. The response of a typical subject before bedrest to sinusoidal LBNP (0 to ~-60 mm Hg) at .01 Hz (period = 100 sec) is shown in Figure 1. The variables from top to bottom are: LBNP, arterial pressure (AP, Finapres), ascending aortic flow (AF, Exerdop), central venous pressure (CVP, Cobe), stroke volume (SV, beat-by-beat calculation from the AF), heart rate (HR) and total peripheral vascular resistance (TPR, beat-by-beat calculation from (AP - CVP)/(SV X HR)). From this figure several observations can be made: AP was well regulated during the test (the three places without data are a servo control of the system). There were oscillations of AF, SV and CVP that were both large and minimally regulated, i.e. their magnitudes decreased as the level of LBNP increased and vice versa. The oscillations in HR and TPR were also large and were reactive in nature, that is, their magnitudes increased as LBNP level increased and vice versa. Oscillations in cardiac output (not shown) were more similar to those of SV than HR, varying from 5.1 L/min at atmospheric pressure to 3.2 L/min at peak LBNP. In all subjects at the low frequencies (.004 to 0.01 Hz), LBNP induced decreases in SV of ~50% which were associated with large oscillations in HR and TPR, resulting in very small (~2 mm Hg) oscillations of AP.

The Fourier transform results (first harmonic and phase angle with respect to LBNP) for this group of subjects are shown in Figures 2 - 7 for both pre- and post-bedrest states.

PRE-BEDREST: The SV oscillations (Figure 2) lagged the LBNP input by ~20° at the lowest frequency, i.e. minimum values of SV occurred ~20° after the -60 mm Hg LBNP dips. Oscillations were ± 17 ml at .004 Hz and dropped to ± 4 ml at .1 Hz at which time the phase lag had increased by an additional 100°. The CVP oscillations (Figure 3) which lagged the LBNP input by ~10° at the lowest frequency, had associated half amplitude oscillations of ~2.5 mm Hg, dropping to 1 mm Hg at the highest frequency while the phase lag only increased an additional 20°. Peak values of calf circumference (CC, Figure 4) lagged the -60 mm Hg LBNP dip by ~30° (+150°, Figure 4) at the lowest frequency (this peak in CC occurred ~20° after the minimum in CVP). The lag in CC with respect to LBNP increased by an additional 20° at the highest frequency while the half amplitude dropped from 1.1% to 0.3%. Peak values of TPR occurred ~10° after the -60 mm Hg LBNP dip (+170°, Figure 5) at the lowest frequency and increasingly lagged up to

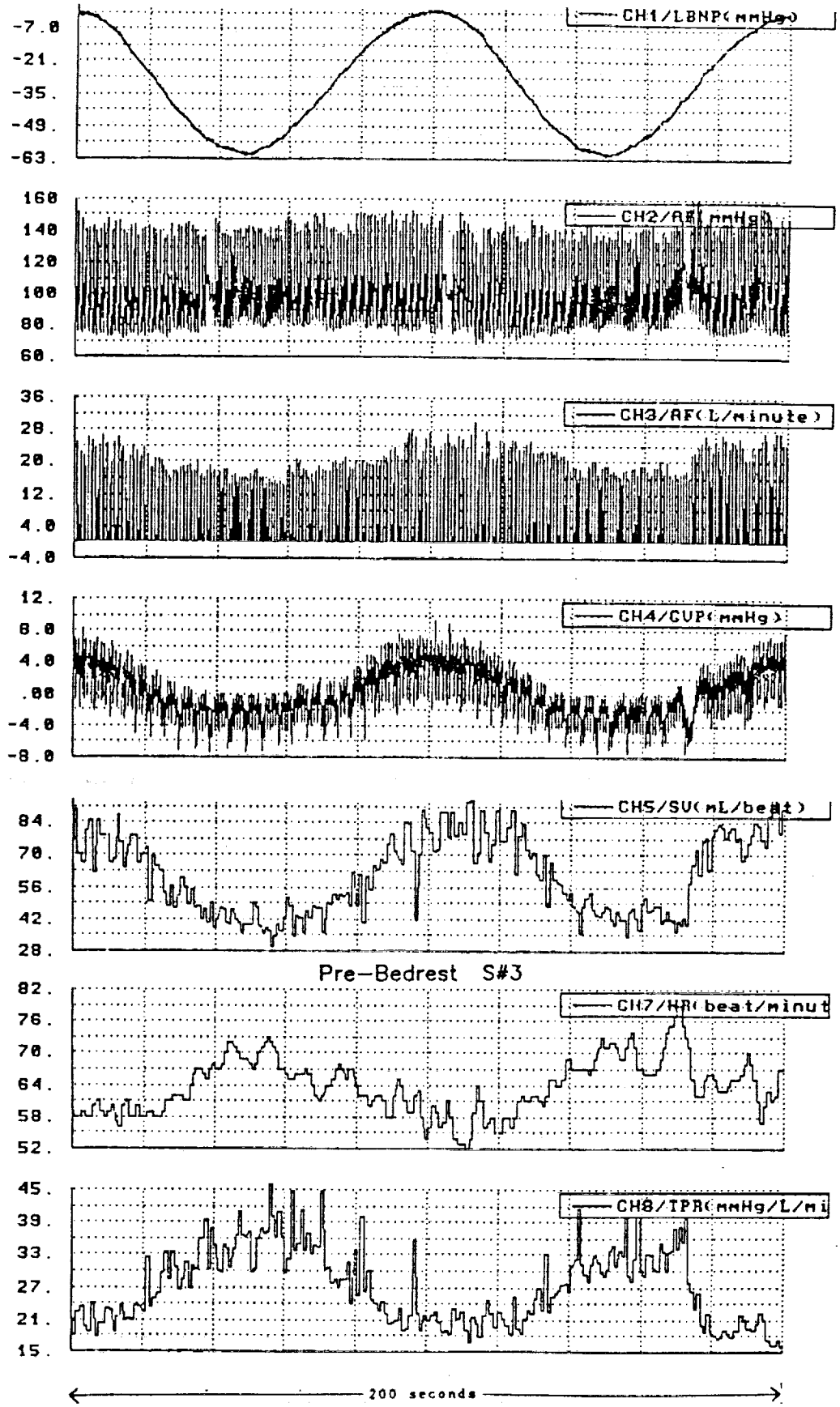

CH1/LBNP(mmHg)
-7.0
-21.
-35.
-49.
-63.
160
140
120
100
80.
60.
CH2/AB(mmHg)
36.
28.
20.
12.
4.0
-4.0
CH3/AF(L/minute)
12.
8.0
4.0
.00
-4.0
-8.0
CH4/CVP(mmHg)
84.
70.
56.
42.
28.
CH5/SV(mL/beat)
Pre-Bedrest S#3
82.
76.
70.
64.
58.
52.
CH7/HR(beat/minut
45.
39.
33.
27.
21.
15.
CH8/TPR(mmHg/L/mi
200 seconds

Figure 1

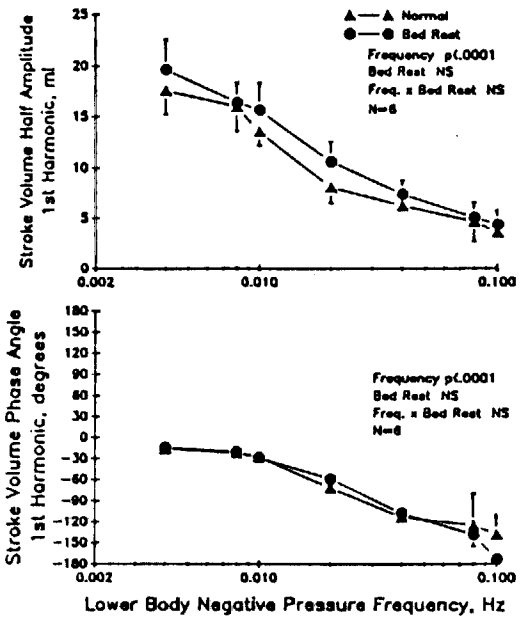


Figure 2

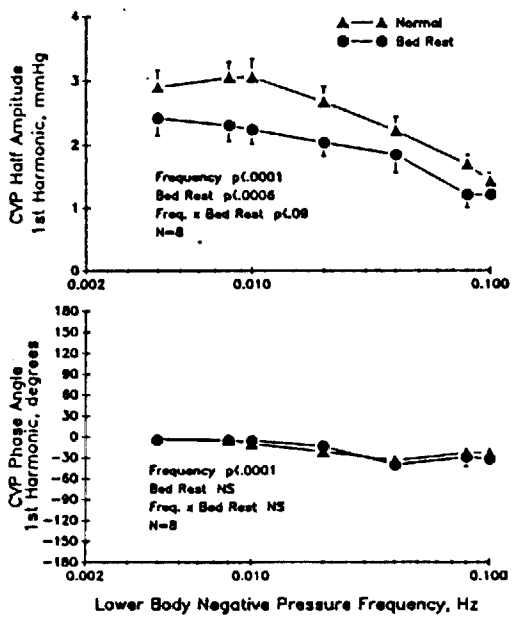


Figure 3

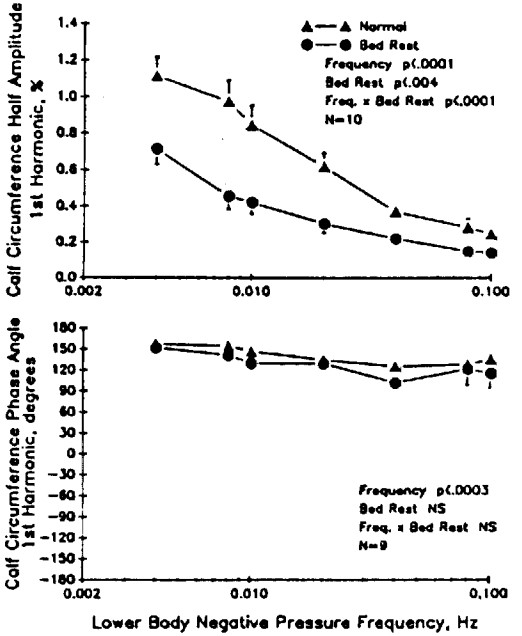


Figure 4

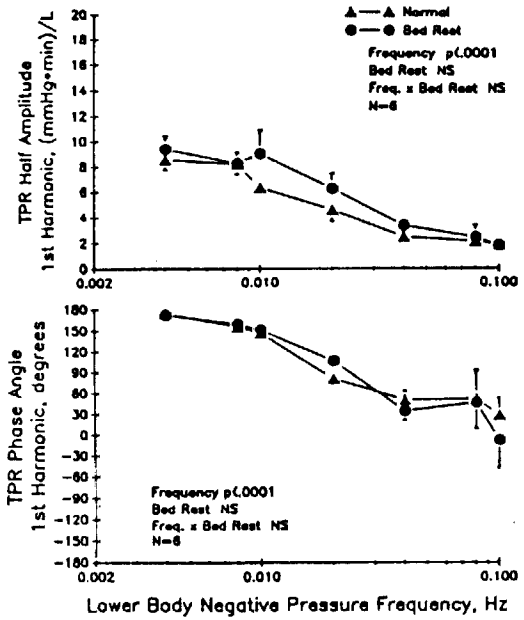


Figure 5

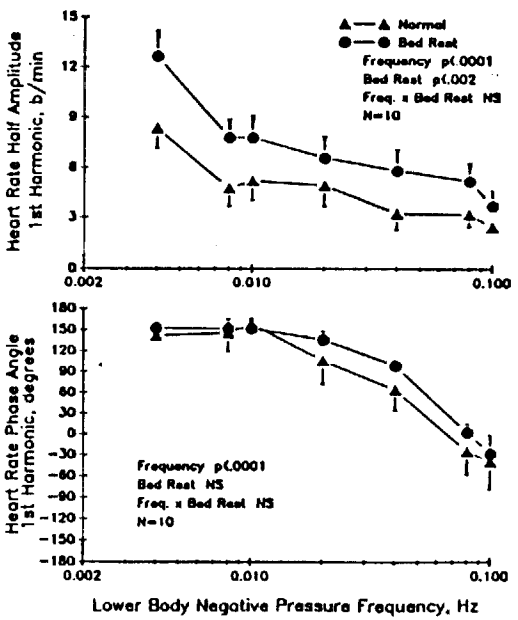


Figure 6

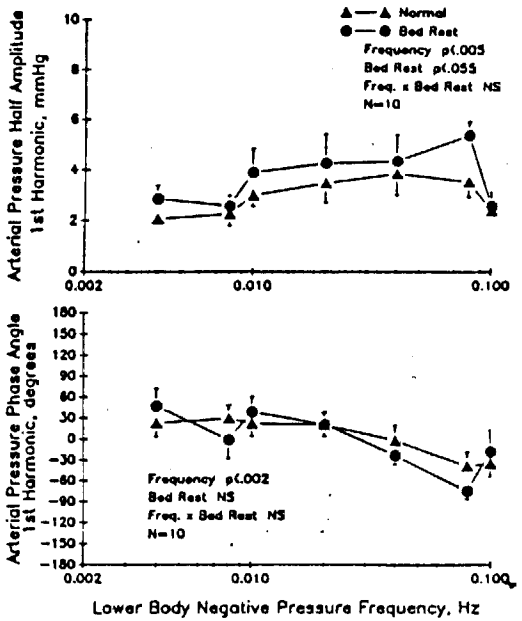


Figure 7

an additional 140° at the highest frequency. The half amplitude of TPR decreased from 8 mm Hg/(L/min) to 2 mm Hg /(L/min) across the range. Peak values of HR (Figure 6) lagged the -60 mm Hg LBNP dip by ˜30° (+150°, Figure 6) at the lowest frequency and increasingly lagged up to an additional 180° at the highest frequency while the half amplitude of HR oscillations decreased from 8 b/min to 3 b/min. The AP half amplitudes (Figure 7) increased with increasing frequency up to 0.04 Hz and then decreased slightly. Peak AP led the -60 mm Hg LBNP dip by ˜30° at the lowest frequency, switching to a phase lag after 0.04 Hz.

POST-BEDREST: The post-bedrest results from this group of subjects indicated several interesting responses: The AP, HR, SV and TPR half amplitudes were larger than those in the pre-bedrest state and the half amplitudes of CVP and CC were smaller. The phase relationships of these variables with respect to the LBNP input were not significantly affected by the short term bedrest.

The principal conclusions from this study were that in normal male subjects: 1) AP was well regulated at LBNP input frequencies below .01 Hz due to the appropriate timing of large amplitudes of oscillations of both HR and TPR which counteracted the large relatively passive oscillations of SV. 2) AP oscillations were largest between .01 and 0.08 Hz due to the inappropriate phasing of relatively small amplitudes of oscillations in SV, HR and TPR. 3) The half amplitudes of oscillations of AP were increased by bedrest even though the amplitude of the vascular volume being shifted was reduced as indicated by the decreased half amplitudes of CVP and CC. 4) The increased half amplitude of AP oscillations in post- vs pre-bedrest were therefore due to the inappropriate timing of larger oscillations of HR, SV and TPR in response to smaller oscillations of vascular volume.

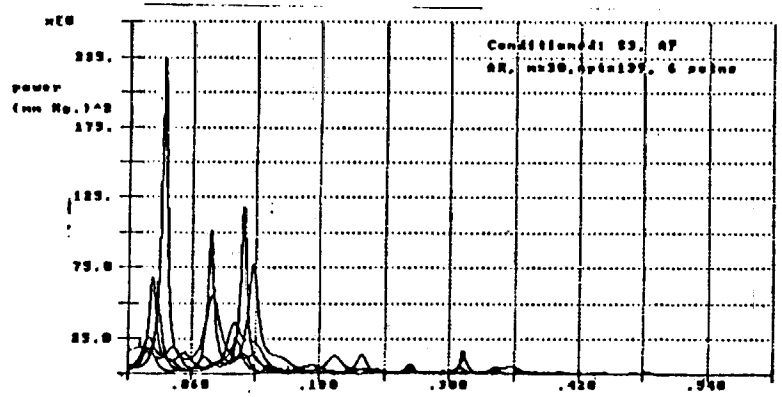
CARDIOVASCULAR SPECTRA FROM RESTING SUBJECTS

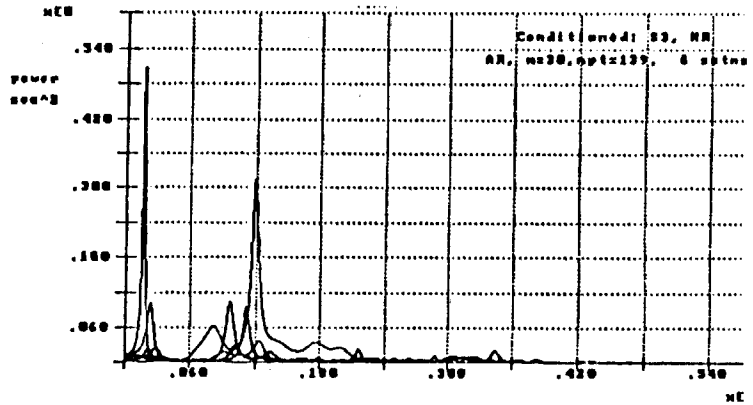
Based on the fact that an increase in heart rate and peripheral resistance has been a consistent finding in bedrest and spaceflight studies, we hypothesized that these deconditioning procedures produce a net increase in peripheral neural sympathetic activity. Previous studies (Akselrod, Rimoldi) by other investigators have demonstrated that changes in neural activity are manifest in changes in arterial pressure (Rimoldi) and heart rate (Akselrod, Rimoldi) spectra. We are currently using autoregressive techniques to calculate the spectral content in data records of resting arterial pressure, heart rate, respiration rate, stroke volume, peripheral resistance, central venous pressure and cardiac output in the same subject before and after our 22 hrs. of 6° head down bedrest. Arterial pressure and heart rate from a supine, freely breathing subject, are shown in Figure 8. The top row shows 6 spectra obtained from consecutive, individually detrended, 2.5 min segments of arterial pressure (left) and heart rate (right). Each data point in the AP time record was obtained by integrating arterial pressure over a beat (one R-R interval). Each data point for HR was obtained by taking the reciprocal of the R-R interval. In the pre-bedrest data (top row), power in AP was localized in two ranges (<.06 Hz and between .06 - .14 Hz) while power in HR spectra was localized in the region <.04 Hz and between .06 - .18 Hz. The

Arterial Pressure, S#3

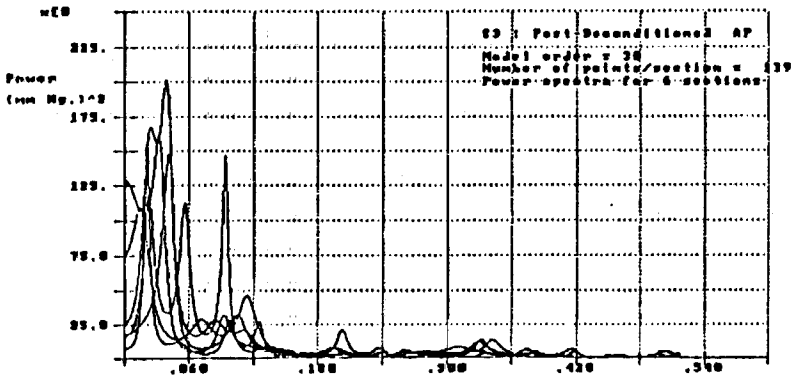
Heart Rate, S#3

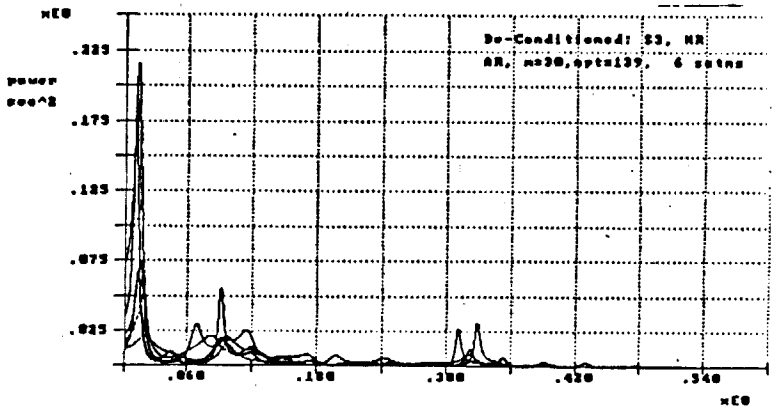
Pre–
Bedrest



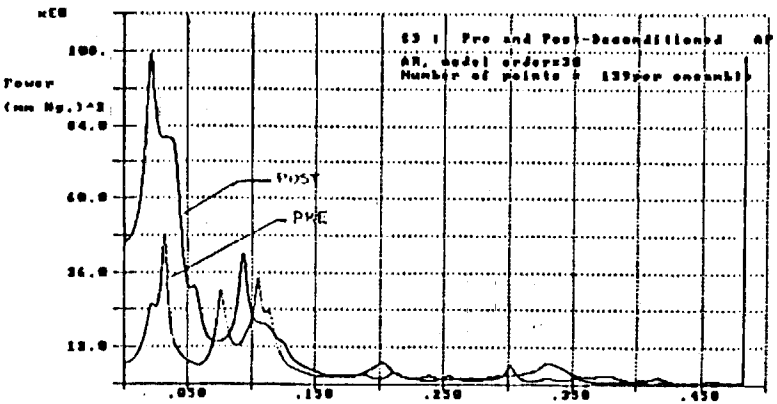


Post–
Bedrest





Pre– &
Post–
Bedrest



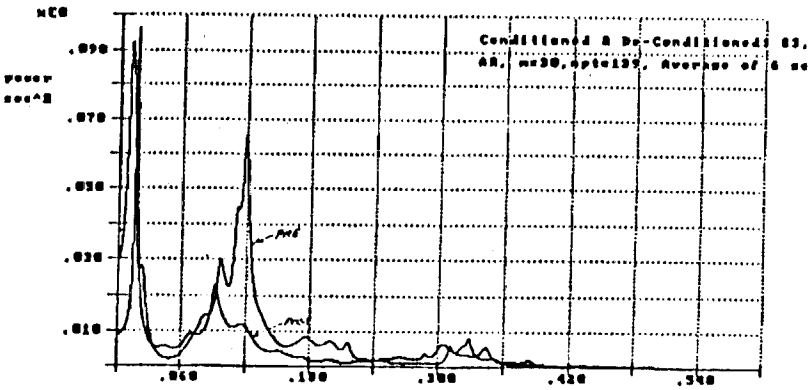
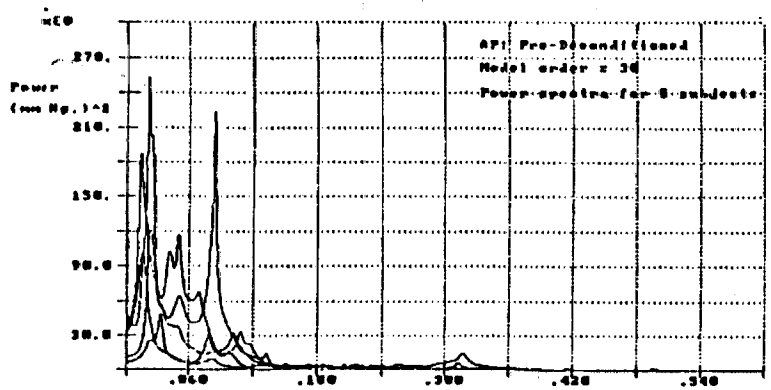


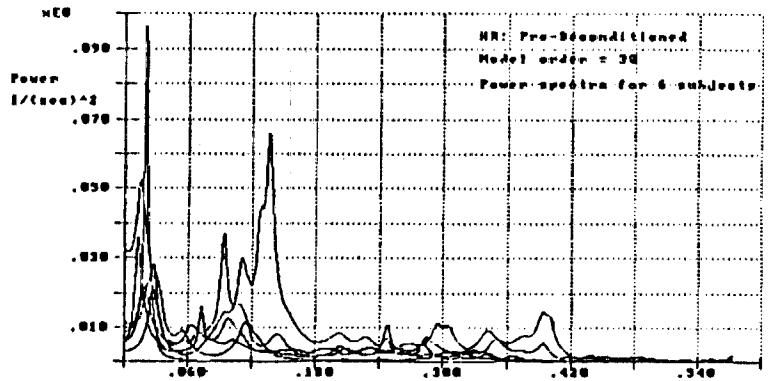
Figure 8

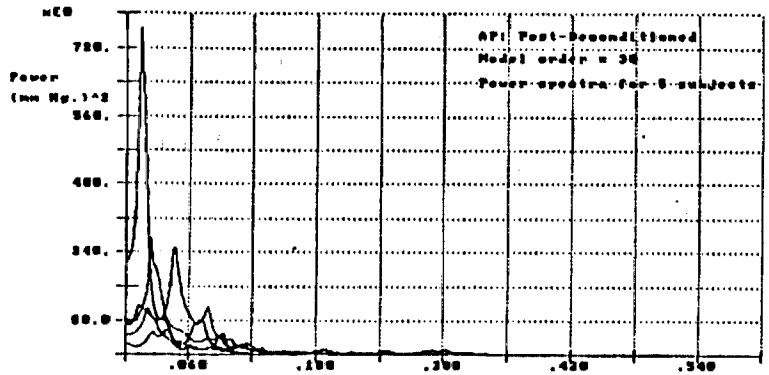
Arterial Pressure, Group (N=5)

Heart Rate, Group (N=6)

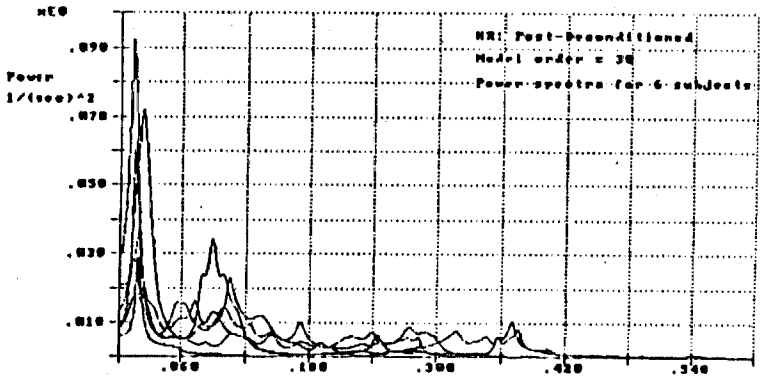


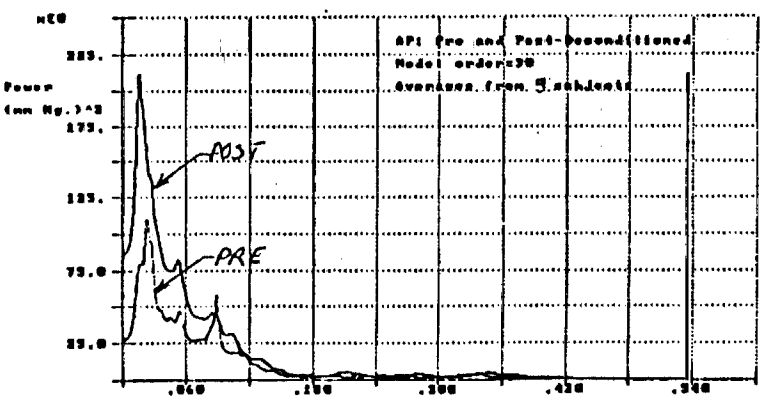
Pre–
Bedrest





Post–
Bedrest





Pre– &
Post–
Bedrest

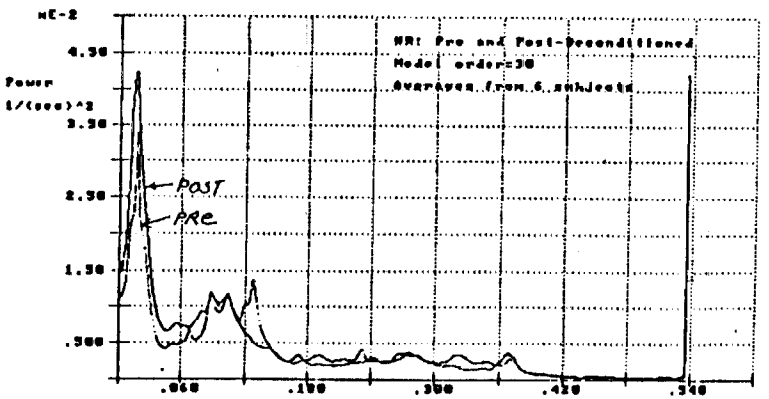


Figure 9

respiratory power (data not shown) for this subject was distributed between 0.08 and 0.4 Hz. The post-bedrest spectra are shown in the second row where increases in AP power are seen at the lowest frequencies. The six spectra for each state were then averaged (to enhance statistical stability) and are shown in the last row for both pre- and post-bedrest. The AP spectral power (area under the curve) was found to increase after bedrest for frequencies below .06 Hz. In this subject, power in the HR spectrum was decreased by bedrest.

Data for the group of subjects are shown in Figure 9. In the top two rows, spectra (one for each subject) are overlaid in plots of AP (left) and HR (right), pre- (first row) and post- (second row) bedrest. Each subjects' spectrum is the average of the 6, 2.5 min segments (in Figure 8). These plots reflect power in the same frequency ranges as those shown for the individual subjects in Figure 8. The pre- and post-bedrest averaged spectra for the group are shown in the bottom row where again, as in the single subject, AP power was increased in both low frequency ranges by bedrest. There did not appear to be a significant effect of bedrest in the HR spectra. Analysis of the remaining subjects and variables and comparison of results with those from the LBNP provocative tests are continuing.

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