PROPRANOLOL AND THE COMPENSATORY CIRCULATORY RESPONSES TO ORTHOSTASIS AT... (U) ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA C S FULCO ET AL.

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Propranolol and the compensatory circulatory responses to orthostasis at high altitude.

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**Abstract:**

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Tachycardia has been shown to be an important response involved in the defense of cardiac output during orthostasis at high altitude. This study was undertaken to determine if tachycardia, mediated by beta-adrenergic sympathetic stimulation, actually represents an essential response. Twelve young, healthy male subjects received either 80 mg propranolol (n=6) or placebo (n=6) treatment, t.i.d. at sea level and for 3 days prior to and during the first 15 days of a 19-day altitude sojourn. Individuals were randomly assigned to each group. Upright tilt tests were performed at sea level on and off treatment, at high altitude during days 2, 7, and 15 on treatment, and on day 19 off treatment. Heart rate, stroke volume, calf blood flow, and blood pressure were obtained during supine rest and after 12 minutes of 60° tilt. There were no differences between groups in any of the circulatory measurements at sea level and altitude while off treatment. While on treatment at sea level and altitude, propranolol caused reductions in heart rate and blood pressure values in each position (p<0.05). Supine and upright cardiac output, however, were found not altered due to compensatory increases in stroke volume (p<0.05). It was concluded that tachycardia, both at rest and during upright tilt at high altitude is important, but not essential to defend cardiac output.

Index terms: Beta-adrenergic, beta-blocker, sympathetic nervous system orthostatic
INTRODUCTION

The sympathetic nervous system is stimulated during high altitude exposure (Maher et al. 1978, Maher et al. 1975). The level of sympathetic activity, as reflected by plasma and urinary catecholamine levels, becomes significantly elevated within 24-36 hours of the initial exposure and remains elevated during high-altitude residence for at least three weeks (Cunningham et al. 1965, Fulco et al. 1985). The increase in sympathetic stimulation results in a tachycardia at rest that helps to defend against an altitude-related reduction in stroke volume for the duration of the sojourn (Fulco et al. 1985, Grover et al. 1976). However, since the reduction in stroke volume is not totally compensated for, resting cardiac output also eventually declines at altitude (Fulco et al. 1985, Hoon et al. 1977). Despite this reduction in cardiac output, blood pressure is maintained or increased above sea-level values (Fulco et al. 1985, Malhotra and Murthy 1977).

The cardiocirculatory responses to a rapid and passive change from the supine to the upright position on a tilt table are similar to the responses which occur during altitude exposure. As with altitude, tilt increases sympathetic activity, plasma catecholamine levels, heart rate, and total peripheral resistance, and reduces stroke volume and cardiac output (Fluck and Salter 1973, Fulco et al. 1985, Loepky 1975). Previously, we had considered that the circulatory demands during orthostasis would not be adequately compensated for during a high-altitude exposure due to the reductions in stroke volume and cardiac output (Fulco et al. 1985). However, contrary to our hypothesis, upright tilt was well tolerated. During the first hour at altitude (4300 m), the major compensatory responses to upright tilt were tachycardia and an increase in total peripheral resistance. As the exposure continued to five days, the ability to maintain orthostatic homeostasis was provided only by tachycardia.

These findings clearly illustrated the importance of tachycardia in defending cardiac output during a central circulatory challenge at altitude. Also, the findings suggested that the increase in heart rate may actually represent an
essential response given that stroke volume was reduced and may not have been able to adequately contribute to the defense of cardiac output. The opportunity to investigate this possibility was made possible during a recent investigation (Moore et al. 1988).

The approach used in the present study was to administer propranolol, a beta-adrenergic blocking agent, to healthy subjects going from sea level to high altitude and to measure heart rate and stroke volume responses to upright tilt. It was hypothesized that by blocking the normal increase in heart rate, upright tilt would be less tolerated at altitude. This study also provided the opportunity to describe for the first time, the effects of propranolol, the sixth most widely-used prescription drug (The National Disease and Therapeutic Index 1984), on the systemic circulation during two weeks of residence at high altitude.

METHODS

The subjects were twelve healthy males with an mean age, height and weight of 21.3 years, 174.9 cm, and 73.7 kg, respectively. None had been exposed to high altitude for at least six months prior to initiation of this study, and none had any contraindications to altitude exposure or to administration of propranolol. All gave their informed consent prior to participation in the study. Prior to any tilt-testing, the subjects were randomly assigned to either a control (n=6) or an experimental group (n=6).

During the study, each subject was tested on a tilt table a total of seven times: three times at sea level (Natick, MA; 50 m, P102=159 Torr) and four times during residence on the summit of Pikes Peak, CO (4300 m, P102=94 Torr). The ambient temperature during testing was 23 ± 2°C. at both locations. After the initial sea level test, the experimental group was given 80 mg propranolol (Inderal; Ayerst Labs) P.O., and the control group an identically-appearing placebo every eight hours for seven days prior to and during the day of the second sea-
level tilt test. The subjects were tested for a third time at sea level after being off treatment for four days. Ten days later, propranolol or placebo treatment was again initiated beginning three days immediately prior to and continuing through the first 15 days of residence at altitude. Tilt tests were performed on days 2, 7 and 15 of the altitude exposure. Four days after termination of treatment at altitude (day 19), the subjects were tilt-tested again. Although the subjects were blind to which treatment they were receiving, investigators were not because of the observed attenuation of heart rate during the tilt table tests.

After seven days of treatment at high altitude, serum propranolol levels were measured in blood samples drawn before and 1.5 hours after ingestion of 80 mg of propranolol to determine minimal and maximal serum propranolol concentrations (Moore et al. 1986). The assays were performed by high-performance liquid chromatography with fluorescence (Aarons et al. 1980).

Testing Protocol Overview

The tilt tests were performed during the same time period each morning to eliminate any potential diurnal effects. The order in which the subjects were tested within the time period was randomised. Smoking, eating and physical activity were prohibited for at least two hours prior to testing. Calf volume was determined by water displacement within a day of each of the sea level and altitude tilt tests. Hemoglobin and hematocrit were determined using a sample obtained from an arm vein during the morning of the tests, for the estimation of any possible change in blood and plasma volume (Dill and Costill 1974).

For each tilt test, impedance electrodes were placed as described below. The subject then laid supine on a slightly padded 60 cm x 200 cm tilt table surface. Securing straps and a steel foot rest allowed subjects to remain passive when changing from one position to another. A blood pressure cuff was placed around the subject's right upper arm, and impedance monitor cables were connected to the electrodes. When the subject was tilted to the upright position, his right arm rested at heart level on a shelf next to the tilt platform.
Blood pressure and heart rate were determined in the supine position every two minutes for at least 12 minutes to insure true baseline values using an electrosphygmonanometer (Vita-stat; model 900s). From minutes 12-14 of supine rest, thoracic and peripheral impedance data were obtained. At minute 15, the subject was tilted (<2 sec) to a head-up 60° angle. Blood pressure and heart rate were determined each minute for the first five minutes in the upright position and every two minutes thereafter. At the end of minutes 5 and 12 of tilt, upright thoracic and peripheral impedance data were obtained.

Impedance

Impedance data were obtained using an impedance cardiograph (Minnesota; model 304b). The methods and the theoretical basis determining physiological variables from impedance data have been presented elsewhere (Baker et al. 1971, Nyboer 1959). During the present investigation, ECG electrodes were used instead of band electrodes. Agreement between these two types of electrodes for impedance measurements has been shown to be excellent (Shvarts et al. 1983). A constant sinusoidal current (4mA, rms) with a frequency of 100 KHz applied to electrodes located on the forehead and lateral malleolus served as excitation current sources. The four pickup electrodes were located as follows: 1. on the base of the neck (3 cm to the right of the first thoracic vertebra); 2. 30 cm directly below on the back, and; 3. two electrodes on the lateral segment of the calf, 10 and 20 cm above the excitation electrode located on the lateral malleolus. Electrode sites were carefully measured for consistency of placement from day to day. Thoracic impedance changes recorded via the back electrodes were used to estimate stroke volume and cardiac output while the other two lower limb electrodes were used to estimate calf blood flow. To eliminate movement artifacts due to respiration during the collection of the impedance signals, subjects were instructed to hold their breath after a normal exhalation.
A minicomputer (MINC; Digital Equipment Corp.) was used to digitize, store and analyse the impedance signals. Calculations of volume and flow were made according to Nyboer (1959) and others (Shvarts et al. 1983, Van De Wall et al. 1973) using the systolic downstroke extrapolation method. Most studies utilizing the impedance technique use constant values for blood resistivity which assumes little or no change in hematocrit (Hoon et al. 1977, Mori et al. 1982, Shvarts et al. 1983). However, because the possibility that hematocrit would be altered due to the altitude exposure, a value for blood resistivity was calculated daily from the hematocrit for use in the impedance equations (Hill and Thompson 1975). Heart rates were calculated from the impedance pulse recordings. Cardiac output and peripheral blood flow were determined by multiplying heart rate by the volume value obtained from the back or calf electrodes, respectively. Systolic and diastolic blood pressure were determined using the electrosphygmomanometer. Mean arterial pressure was calculated by adding 1/3 pulse pressure to the diastolic blood pressure. Total peripheral resistance was calculated as mean arterial pressure divided by cardiac output. The data were analysed using a repeated measures ANOVA and, where appropriate, the Neuman-Keuls post hoc test. Statistical significance was chosen at p<0.05.

RESULTS

There were no significant differences in either of the groups in any of the circulatory parameters measured on the two off-treatment test days at sea level. Therefore, the values collected on the last test day (the closer of the 2 days to the altitude sojourn) were used as the sea-level baseline values. Additionally, since no significant differences were found between the 5th and the 12th minute of tilt in any of the variables measured at sea level or altitude, only the 12th minute was used for comparison. Blood serum levels of propranolol were significantly increased and the increase was sustained between doses (from 65 ± 8
ng·ml⁻¹ immediately before, to \(108 \pm 13\) ng·ml⁻¹ 1.5 hours after, an 80-mg propranolol dose) (Moore et al. 1986). Tables 1 and 2 present the mean values for the cardiocirculatory variables in the supine and upright positions at sea level and on days 2, 7, 15, and 19 of altitude on and off placebo or propranolol treatment.

Both groups had similar values for all of the parameters measured in each position in the sea-level, off-treatment, baseline testing day. Each group also had similar responses to tilt (defined as the change in values from the supine to the upright position). During the sea-level on-treatment day, however, several differences between the groups were apparent. Propranolol caused reductions in supine heart rate and blood pressure, and reductions in upright heart rate and cardiac output. However, the response to tilt was not affected.

Both altitude exposure and propranolol treatment had an affect on supine and upright cardiocirculatory measurements. In the placebo group in both positions, blood pressure, heart rate, and total peripheral resistance increased, while stroke volume and cardiac output decreased with time at altitude relative to sea-level, off-treatment values. Supine, but not upright, calf blood flow in the placebo group increased during the altitude exposure.

In the propranolol group, on treatment at altitude, supine stroke volume and cardiac output decreased, supine total peripheral resistance increased, while the supine values for blood pressure, heart rate and calf blood flow were not altered from the sea level, off-treatment values. The direction of change of most of the circulatory measurements obtained in the upright position were similar to those measured in the supine position. The only notable exception was upright stroke volume which was not significantly reduced below the stroke volume value measured in the same position at sea level, off-treatment.

The most consistent differences between the placebo and propranolol groups on treatment at altitude were lower values for blood pressure and heart rate, and a higher value for stroke volume in the propranolol group. Four days after treatment
was terminated (day 19 of altitude), there were no differences between the groups in any of the cardiocirculatory variables measured. The attenuated heart rate and blood pressure values of the propranolol group measured while on treatment recovered during the off-treatment period to the levels obtained by the placebo group.

In response to tilt at altitude, only the heart rate response on days 7 and 15 of the exposure differed between groups. The heart rate response of the placebo group was increased above their sea-level, off-treatment values throughout the altitude exposure. The heart rate response of the propranolol group (on treatment) was not different from their sea-level values. Off treatment (day 19), the heart rate response to tilt was similar for both groups.

DISCUSSION

It appears that beta-blockade had minimal effects on the relative cardiovascular responses to tilt and the ability to remain in the upright position at sea level and altitude despite significant alterations in the absolute values for heart rate and blood pressure. Our findings at sea level were expected and were consistent with previous work (Loeppky 1975). However, the effects of beta-blockade during upright tilt at altitude were not predictable based on sea-level responses. Prior to this study, it seemed reasonable that the contribution of the beta-adrenergic system would become increasingly important in the maintenance of homeostasis during upright tilt as other factors were attenuated. For example, stroke volume, which decreases during upright tilt at sea level, has been shown to gradually decline and remain below sea-level values for at least 10 days at high altitude due to a reduction in blood volume and/or a reduction in myocardial contractility (Alexander and Grover 1983; Fulco et al. 1985; Tucker et al. 1976). Cardiac output mirrors the reduction in stroke volume after the first few days at altitude (Fulco et al. 1985, Hoon et al. 1977).
In the present study, at altitude, supine and upright heart rates for the propranolol group (on treatment) were not elevated above the sea-level, off-treatment baseline values. However, when compared to the sea-level, on-treatment values, heart rates in both positions were elevated. There are two explanations to account for the increase in heart rate measured in the transition from the supine to the upright position and from sea level to altitude during beta-adrenergic blockade. One is that total beta-blockade was not present during the tilt tests due to insufficient dose of propranolol or the lack of test subject compliance in taking the tablets. These possibilities are not tenable. Serum propranolol levels were measured and found to be increased and sustained between doses (Moore et al. 1986). Furthermore, Maher et al. (1975) showed that with continued exposure to high altitude, the amount of propranolol necessary to produce a comparable level of beta-blockade actually decreased from sea level. The implication for the present study is that if all beta-receptors were not blocked initially, a greater blockade would take place with continued exposure. The fact that heart rate remained constant throughout the exposure is consistent with total beta-blockade. Also, test subject compliance was monitored closely, and all tablets were taken on schedule.

The other, more plausible explanation for the relative tachycardia during beta-adrenergic blockade is a withdrawal of parasympathetic tone. Others have shown that the tachycardia associated with upright tilt at sea level is a combination of an increase in sympathetic tone and a reduction in parasympathetic tone (Loeppky 1975; Malhotra and Murthy 1977; Robinson et al. 1966). There is no increase in heart rate during tilt only when there is total blockade of both legs of the autonomic nervous system (Robinson et al. 1966). The suggestion that parasympathetic withdrawal may contribute to the tachycardia during supine rest from sea level to altitude is new. It cannot be determined from the present study if the increase in heart rate due to the hypothesized parasympathetic withdrawal occurs normally during altitude exposures or is only a compensatory response to help maintain cardiac output and blood pressure. Hartley et al. (1974) showed that
parasympathetic activity contributed to the reduction in maximal exercise heart rate found at altitude, a result consistent with the latter explanation.

Another interesting finding was that the stroke volumes measured in the propranolol group (on treatment) became significantly higher than the corresponding values for the placebo group as the exposure continued. The increase in stroke volume apparently was enough to compensate for the propranolol-induced reduction in heart rate so that cardiac output did not differ between groups in either position on treatment at altitude. This finding was surprising for three reasons.

The first is that plasma volume decreased approximately 22% from sea level. A reduction in plasma volume is consistent with a reduced venous return and stroke volume. Secondly, myocardial contractility may be reduced during chronic exposure to hypoxia (Alexander 1987; Tucker et al. 1976) and during treatment with propranolol (Cohn 1985; Ferguson et al. 1983). It was thought that superposition of these two conditions would further attenuate myocardial contractility and, thus, interfere with adequate cardiocirculatory responses to altitude and to tilt.

The third reason for not expecting stroke volume to increase at altitude, especially in the upright position, is that the increase in total peripheral resistance normally seen in tilt at sea level does not consistently occur in response to tilt at altitude (Fulco et al. 1985). With tilt, there is increased sympathetic activity and a release of catecholamines into the blood stream (Fluck and Salter 1973). Because the levels of catecholamines are already at an elevated level at altitude, the additional sympathetic nerve activity during tilt is thought to be too small to cause a further significant constriction of the resistance vessels (Fulco et al. 1985). Given that total peripheral resistance did not differ between the two groups in this study, it is not likely that the greater stroke volume in the propranolol group during treatment was due to a greater venoconstriction and increased venous return. It is possible that the major reason that stroke volume was increased was that the heart chambers, due to the relative bradycardia, had a longer period of time in which to fill. The increase in end-
Diastolic filling pressure and ventricular dimension would increase stroke volume via the Frank-Starling mechanism (Epstein et al. 1985).

The gradual rise in diastolic and mean blood pressure noted during the altitude exposure in the placebo group is similar to the rise reported in previous studies (Fulco et al. 1985; Malhotra and Murthy 1977; Vogel et al. 1974). The rise was not seen in the propranolol group (on treatment) when compared to themselves at sea level (off treatment) and when compared to the placebo group at altitude. However, when compared to their own blood pressure values obtained while on treatment at sea level, the altitude values for diastolic and mean blood pressures for the propranolol group were elevated. Thus, propranolol is an effective anti-hypertensive agent at altitude, but the effects are not as pronounced as at sea level. This reduced effectiveness may be due, in part, to increased adrenergic activity at altitude. Because propranolol is a nonselective beta-adrenergic blocking agent, peripheral as well as cardiac beta-receptors are blocked during treatment upsetting the balance between the vasoconstrictive action of alpha receptor stimulation and the vasodilative action of beta-receptor stimulation in the periphery in favor of the alpha receptors (McSorley and Warren 1978; Shephard 1985). The relative increase in alpha-mediated sympathetic tone may also explain the reduced blood flow measured in this study as well as in others during treatment with propranolol (Cohn 1985; McSorley and Warren 1978; Nies et al. 1973).

In summary, this study was undertaken to determine if the altitude-induced tachycardia represents an essential response to a cardiocirculatory challenge. The results indicate that tachycardia is not essential in defending cardiac output because of a compensatory increase in stroke volume.
ACKNOWLEDGEMENTS

The authors thank the subjects whose participation made this study possible.

Subjects participated in this study after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC regulation 70-25 in the use of volunteers in research. The views, opinions and findings in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other official documentation.
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Mori S, Sakakibara M, Takabayashi A, Takagi S, Mitarai C (1982). Cardiac output responses in rest and work during acute exposure to simulated altitudes of 3,000, 4,500 and 6,000 m and during overnight sleep at 4500 m. Jap. J. Physiol. 32:337-349.


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Values are means ± S.E.
SL= sea level; Alt= altitude
* Significantly different from the placebo group (p<0.05)
# Significantly different from corresponding SL, off treatment values (p<0.05)
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<tr>
<td>Placebo</td>
<td>120 ± 3</td>
<td>118 ± 2</td>
<td>129 ± 7</td>
<td>123 ± 5</td>
<td>131 ± 5</td>
<td>122 ± 5</td>
</tr>
<tr>
<td>Propranolol</td>
<td>123 ± 3</td>
<td>114 ± 8</td>
<td>120 ± 7</td>
<td>125 ± 9</td>
<td>120 ± 5</td>
<td>129 ± 7</td>
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<td>Diastolic</td>
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<tr>
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<td>77 ± 4</td>
<td>78 ± 4</td>
<td>78 ± 3</td>
<td>85 ± 2</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>Propranolol</td>
<td>78 ± 6</td>
<td>86 ± 3*</td>
<td>73 ± 5</td>
<td>77 ± 5*</td>
<td>74 ± 6</td>
<td>84 ± 4*</td>
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<tr>
<td>Placebo</td>
<td>92 ± 3</td>
<td>90 ± 2</td>
<td>94 ± 4</td>
<td>93 ± 3</td>
<td>100 ± 1</td>
<td>93 ± 2</td>
</tr>
<tr>
<td>Propranolol</td>
<td>91 ± 4</td>
<td>81 ± 4</td>
<td>89 ± 4</td>
<td>92 ± 6*</td>
<td>89 ± 5*</td>
<td>99 ± 5*</td>
</tr>
<tr>
<td><strong>Heart Rate</strong> (beats·min⁻¹)</td>
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<tr>
<td>Placebo</td>
<td>84 ± 8*</td>
<td>71 ± 7*</td>
<td>99 ± 10#</td>
<td>118 ± 6#</td>
<td>122 ± 3#</td>
<td>116 ± 6#</td>
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<tr>
<td>Propranolol</td>
<td>94 ± 6*</td>
<td>82 ± 5*#</td>
<td>82 ± 6*</td>
<td>80 ± 6*#</td>
<td>86 ± 8*#</td>
<td>119 ± 8*#</td>
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<tr>
<td><strong>Stroke Volume</strong> (ml·beat⁻¹)</td>
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<tr>
<td>Placebo</td>
<td>48 ± 5*</td>
<td>47 ± 5*</td>
<td>35 ± 3*#</td>
<td>25 ± 2*#</td>
<td>22 ± 2*#</td>
<td>23 ± 2*#</td>
</tr>
<tr>
<td>Propranolol</td>
<td>46 ± 6*</td>
<td>47 ± 3*</td>
<td>42 ± 4*</td>
<td>34 ± 3*</td>
<td>36 ± 4*</td>
<td>26 ± 3*</td>
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<tr>
<td><strong>Cardiac Output</strong> (L·min⁻¹)</td>
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<tr>
<td>Placebo</td>
<td>3.93 ± 0.35</td>
<td>3.28 ± 0.37</td>
<td>3.39 ± 0.35</td>
<td>2.94 ± 0.30#</td>
<td>2.62 ± 0.19#</td>
<td>2.65 ± 0.23#</td>
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<tr>
<td>Propranolol</td>
<td>4.40 ± 0.58</td>
<td>2.86 ± 0.22#</td>
<td>3.38 ± 0.31#</td>
<td>2.70 ± 0.24#</td>
<td>3.00 ± 0.26#</td>
<td>3.23 ± 0.29#</td>
</tr>
<tr>
<td><strong>Total Peripheral Resistance</strong> (mmHg·L⁻¹·min⁻¹)</td>
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<tr>
<td>Placebo</td>
<td>25.7 ± 2.6*</td>
<td>30.3 ± 4.8*</td>
<td>29.9 ± 4.1*</td>
<td>33.8 ± 3.9#</td>
<td>39.4 ± 2.9#</td>
<td>36.5 ± 2.8#</td>
</tr>
<tr>
<td>Propranolol</td>
<td>23.1 ± 3.8*</td>
<td>29.6 ± 2.9*</td>
<td>27.2 ± 2.4*</td>
<td>35.2 ± 2.1*#</td>
<td>31.3 ± 3.3*</td>
<td>33.6 ± 3.3*</td>
</tr>
<tr>
<td><strong>Calf Blood Flow</strong> (ml·min⁻¹·100ml⁻¹)</td>
<td></td>
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<td></td>
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<tr>
<td>Placebo</td>
<td>4.34 ± 0.45</td>
<td>4.19 ± 0.49*</td>
<td>4.75 ± 0.68*</td>
<td>6.31 ± 0.49*</td>
<td>6.89 ± 1.04*</td>
<td>6.77 ± 0.72*</td>
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<tr>
<td>Propranolol</td>
<td>6.58 ± 1.44</td>
<td>4.00 ± 0.61*</td>
<td>4.58 ± 0.38*</td>
<td>4.65 ± 0.47*</td>
<td>4.82 ± 0.62*</td>
<td>5.66 ± 0.34*</td>
</tr>
</tbody>
</table>

Values are means ± S.E.
SL = sea level; Alt = altitude
* Significantly different from the placebo group (p<0.05)
# Significantly different from corresponding SL, off treatment values (p<0.05)
- Significantly different from supine position (p<0.05)
END
DATE
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6-1988
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