Research Paper

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The effects of midazolam and ephedrine on post-exercise autonomic chronotropic control of the heart in normal subjects

A. Lindqvist MD[1], J. Jalonen MSc[2], L.A. Laitinen MD[1], T. Seppälä MD[3] and C. Strömberg MD[4]

[1]Research Institute of Military Medicine, Central Military Hospital, Helsinki, and Research Unit of Pulmonary Medicine, Department of Medicine, Helsinki University Central Hospital, [2]Cardiorespiratory Research Unit, University of Turku, Turku, [3]National Public Health Institute, Division of Mental Health, Helsinki and [4]National Agency for Medicines, Helsinki, Finland

Correspondence and reprint requests: Ari Lindqvist MD, Clinical Research and Development, Department of Medicine, Helsinki University Central Hospital, FIN-00290 Helsinki, Finland. Tel: (+358) 0 471 2660; Fax: (+358) 0 471 4020

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Benzodiazepines may induce hypotension by inhibiting the pressor response. Ephedrine has adrenergic effects on the circulation. After exercise, changes in cardiovascular control impair orthostatic tolerance. The impaired pressure response can be compensated for by chronotropic control of the heart. We studied the effect of midazolam and ephedrine on post-exercise cardiac autonomic chronotropic control in six 21-year-old female volunteers, who received single doses of 15 mg midazolam, 50 mg ephedrine, or placebo orally according to a placebo-controlled, double-blind, crossover design. After exercise, the subjects assumed the supine position for rest, then a −10° head-down position followed by a 70° head-up position. Power spectral analysis of heart rate variability for 7 min and steady-state brachial arterial blood pressure were measured in each position. After administration of midazolam, three subjects had an abnormal fall in their arterial blood pressure (with one presyncope) as a response to head-up tilt. Changes in heart rate variability exceeded those seen during placebo treatment ($p < 0.01$) and involved oscillations, suggesting activation of both sympathetic and parasympathetic dynamics. After ephedrine administration, arterial blood pressure increased during head-down tilt, but parasympathetic dynamics to the heart were dampened. Head-up tilt induced increased sympathetic stimulation of the heart and a sympathicotonic cardiovascular response ($p < 0.01$). In conclusion, midazolam induced unexpectedly great changes in dynamic cardiac control during cardiovascular stimulation. Ephedrine increased tonic sympathetic activity and stabilized the neural circulatory control of the heart by immobilizing dynamic parasympathetic activation.

Keywords: midazolam; ephedrine heart rate; autonomic nervous system; arterial blood pressure; orthostatic test; head-down tilt; cardiovascular sympathetic and vagal reflexes

Introduction

Midazolam is an imidazobenzodiazepine used as a hypnotic and also as an anaesthetic for premedication before surgical procedures and for intravenous sedation.[1] When used intravenously, midazolam may cause severe hypotension.[2] Marty *et al.*[3] have described a sustained decrease in sympathetic tone in humans caused by midazolam. Midazolam depresses the baroreflex function, which may impair compensation for circulatory disturbances with an enhanced sympathetic tone, especially during hypovolemia.[3] Oral midazolam can also cause hypotension and reflex tachycardia, but its effect on the systemic circulation in normovolemic humans and dogs has been found to be minimal. Reduction of hepatic blood flow in hypovolemia and the reduced clearance and prolonged elimination half-life of midazolam may contribute to its potentiated hypotensive effect and central nervous system depression in blood volume-depleted dogs.[4]

Ephedrine is an adrenergic agent acting directly through stimulation of adrenergic α and β receptors and indirectly through release of catecholamines from sympathetic nerve endings.[5] The sympathomimetic actions of ephedrine are well documented and not different from those of amphetamine.[6] Ephedrine has been reported to have a central hypotensive action.[5] It is suitable for oral use, and in healthy volunteers it has been found to be an effective drug for sympathetic stimulation of autonomic function.

The effects of benzodiazepines on cardiovascular control in the absence of exercise have been studied previously.[7] During exercise, the sympathoadrenal baroreflex is maintained but vagal control of the heart may be lost.[8] A minor degree of post-exercise orthostatic hypotension is common in healthy people.[9] Cardiopulmonary baroreceptor loading by head-down tilt may reduce sympathetic vasomotor control but benzodiazepines may also affect this reflex.[7,10] The autonomic pharmacodynamic profiles of midazolam and ephedrine are different, but the hypotensive effect of both drugs may be potentiated by post-exercise gravitational stress. The aim of the present study was to investigate the effect of midazolam and ephedrine on post-exercise cardiac chronotropic control during gravitationally induced changes of cardiovascular autonomic function in healthy human subjects.

Subjects and methods

Subjects

Six healthy non-smoking 21-year-old female volunteers, who weighed between 49 and 75 kg, gave their informed consent to participate in a study approved

by the Ethics Committee of the Central Military Hospital, Helsinki, Finland. Before entering the study, the subjects were found to be healthy on clinical examination, including a resting electrocardiograph (ECG) and a maximal exercise test on a treadmill. All subjects were regularly engaging in physical activity but none in competitive sports.

Study design

The study had a placebo-controlled, double-blind, crossover design. After briefing and 3-h fasting, the subjects received single doses of 15 mg midazolam or 50 mg ephedrine or placebo, orally. The study drugs were given 20 min before exercise testing on a treadmill. This protocol was repeated three times at 1-week intervals. The heart rate during the trial exercise was adjusted after a warm-up to a level corresponding to 63% of individual maximal oxygen consumption and sustained for three 10-min sessions of treadmill exercise separated by 10-min breaks. Oxygen consumption was always below the anaerobic threshold as determined by a maximal exercise test 1 to 2 weeks before the trial.[11] Fifteen minutes after exercise, sitting subjects assumed the supine position for rest for 7 min, and a −10° head-down position for 7 min, and a 70° head-up position for 7 min, in that sequence on a tilt table. During these periods, signals of the heart rate and respiratory rate were recorded continuously. At the end of each period, steady-state arterial blood pressure was measured.

Signal acquisition and analysis

Signals from a bipolar chest ECG lead were continuously recorded (Olli Monitor 401D, Kone Oy, Finland and Racal Store 4DS, Racal Records Ltd, Southampton, England), the R waves of the ECG were identified using an analogue QRS detector, and the successive R-R intervals measured as previously described.[12] After storage of the whole R-R interval record, the array was checked for artefacts and ectopic beats. Only one to five artefacts or ectopic beats were accepted in the analysed segments, but all R-R interval series were edited using algorithms previously described.[12] The instantaneous heart rate was displayed, and the mean heart rate was computed as the mean of all successive instantaneous heart rates of the record (Figure 1). For measurement of periodic heart rate variability, the R-R interval process was converted to a signal proportional to the heart rate and sampled at equal intervals by means of sin(x)/x digital low pass filtering. In producing the heart rate signal, the cut-off frequency of sin(x)/x filtering was designed by a check of the R-R intervals in the original records to control for aliasing.[12,13] The heart rate signal was band-pass filtered to 0.006–0.700 Hz and sampled at 5 Hz. A fast Fourier transform program was used to compute the power spectral density function of the heart rate signal (Figure 2).[12] The power spectral density functions of

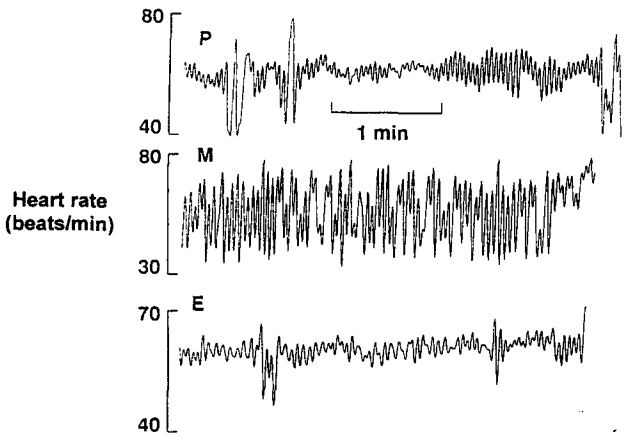

Figure 1. Instantaneous heart rate in a head-down tilted subject during placebo (P), midazolam (M) and ephedrine (E) treatment

the heart rate signal were integrated over the frequency ranges 0.01–0.12 and 0.15–0.42 Hz to estimate low-frequency and high-frequency periodic heart rate variability, respectively.[13] The distribution of heart rate variability between low and high frequencies was also measured as percentages of total variance at 0.01–0.42 Hz.[12] Respiratory signals were recorded using a pneumotachograph (Medikro dynamic spirometer, Medikro Oy, Kuopio, Finland) simultaneously with the heart rate signals to ensure that the respiratory rate did not exceed the range of high-frequency heart rate variability (Figure 2).

Measurement of arterial blood pressure and classification of cardiovascular responses

Left brachial arterial blood pressure was measured using a mercury sphygmomanometer with a 14-cm cuff, according to the method of Kirkendall *et al.*[14] at the end of supine rest, head-down tilt and head-up tilt. The fifth phase of Korotkoff sounds was the criterion for diastolic blood pressure. A decrease in systolic arterial blood pressure > 20 mmHg together with a tachycardia exceeding 100 beats/min after an increase in the heart rate > 25 beats/min in steady state from baseline was used as the criterion of sympathicotonic cardiovascular response to orthostatic stress.[15] The sympathicotonic cardiovascular response does not only occur in organic disease but can be seen in healthy (especially young) subjects in the absence of any organic disease and can be provoked by physiological stress and pharmacological manipulation.[12] Normally, diastolic arterial blood pressure was expected to be increased by head-up tilt.

Statistical analysis

The mean and standard deviations (range) of the variables were expressed. The ANOVA for repeated measures with two within-subjects factors (treatments and positions) was applied (BMDP Statistical Software, Inc.). When the ANOVA showed statistically significant treatment or position effects, pairwise compar-

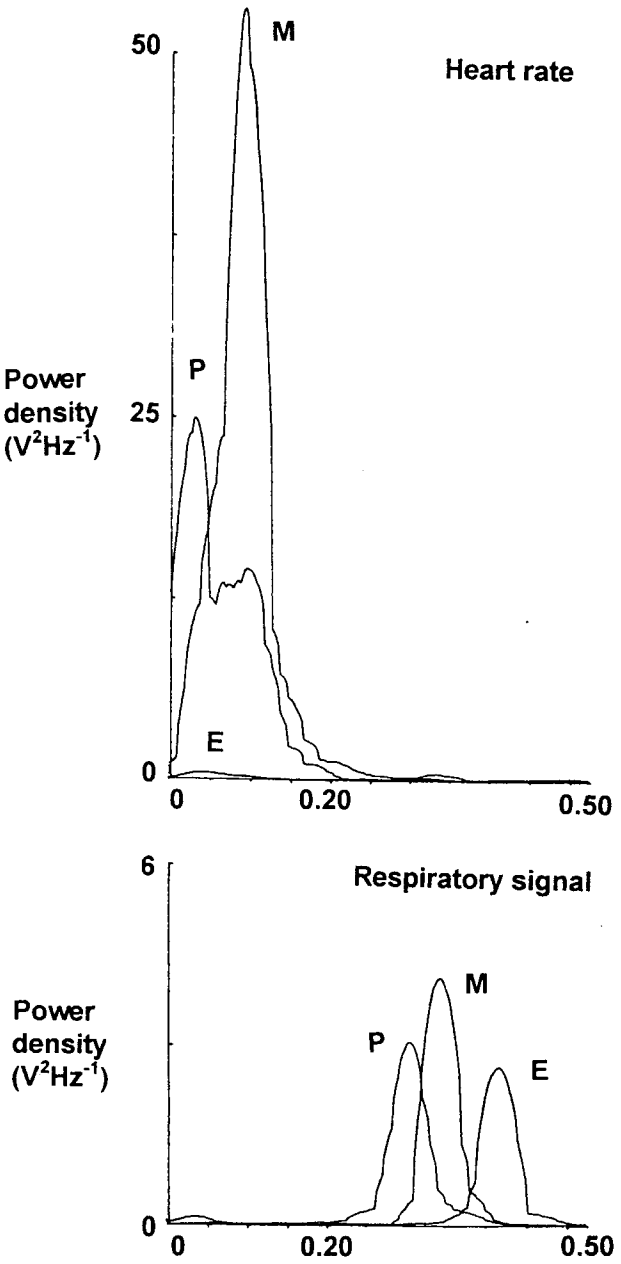

Figure 2. Power spectral-density functions of the heart rate and respiratory signals in a head-down tilted subject during placebo (P), midazolam (M) and ephedrine (E) treatment

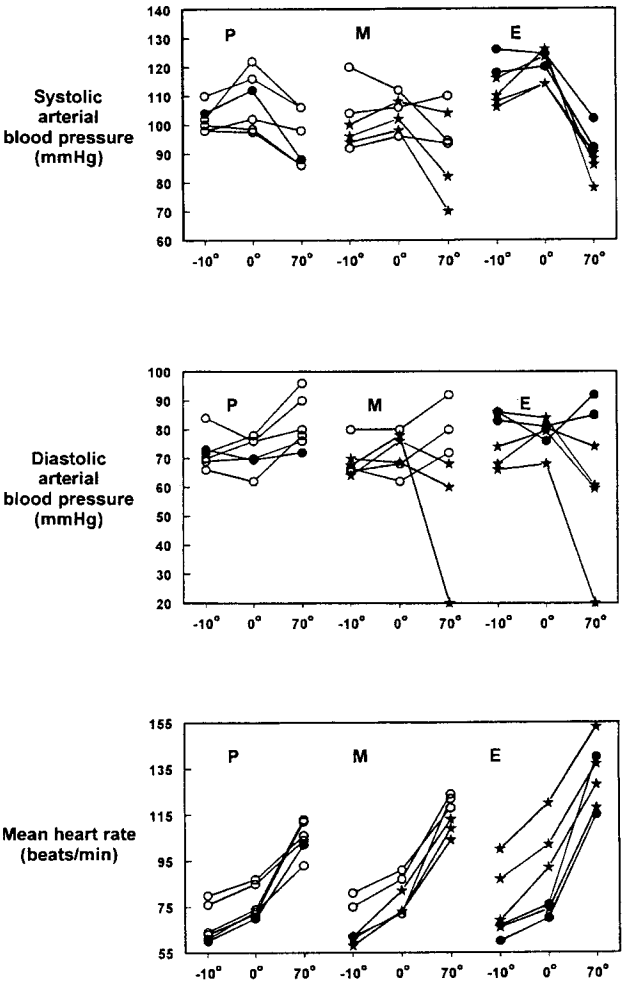

Figure 3. Systolic and diastolic arterial blood pressures and the mean heart rate of six subjects during placebo (P), midazolam (M) and ephedrine (E) treatments during supine rest (0°), head-down tilt (–10°) and head-up tilt (70°). Subjects with cardiovascular sympathicotonic responses (●) and abnormal falls in diastolic arterial blood pressure during head-up tilt (*)

isons were carried out using the Newman–Keuls multiple-range test. If the Newman–Keuls values of p are given, the overall significant values of p from the ANOVA are not presented. If the interaction between treatment and position was significant, *post hoc* analyses were carried out by testing for appropriate interaction contrasts from the ANOVA table. Values of $p \leq 0.05$ were considered statistically significant.

Results

Mean arterial blood pressure and mean heart rate

With placebo treatment, arterial blood pressure was 108 ± 10/72 ± 6 mmHg at supine rest and 102 ± 5/72 ± 6 mmHg during head-down tilt. Systolic arterial blood pressure was significantly lower (95 ± 10 mmHg, $p < 0.01$) in the standing position than at supine rest, but it fell > 20 mmHg in only one subject (Figure 3). The mean heart rate, 77 ± 7 beats/min at supine rest, always decreased during head-down tilt (68±9 beats/min) and always increased during head-up tilt (105 ± 7 beats/min; $p < 0.01$).

After administration of midazolam, arterial blood pressure was 104 ± 6/72 ± 7 mmHg at supine rest, 101 ± 10/69 ± 6 mmHg during head-down tilt and 92 ± 15/62 ± 32 mmHg during head-up tilt ($p > 0.10$, Figure 3). Head-down tilt decreased the mean heart rate by 13±4 beats/min. A sympathicotonic response of systolic arterial blood pressure to head-up tilt was seen in two subjects. Three subjects (two of them with a sympathicotonic response of systolic blood pressure) had a pathological fall in diastolic arterial blood pressure (one presyncope) as a response to head-up tilt. The mean heart rate (80 ± 8 beats/min) always increased during head-up tilt by ≥ 27 beats/min and reached ≥ 104 beats/min in every

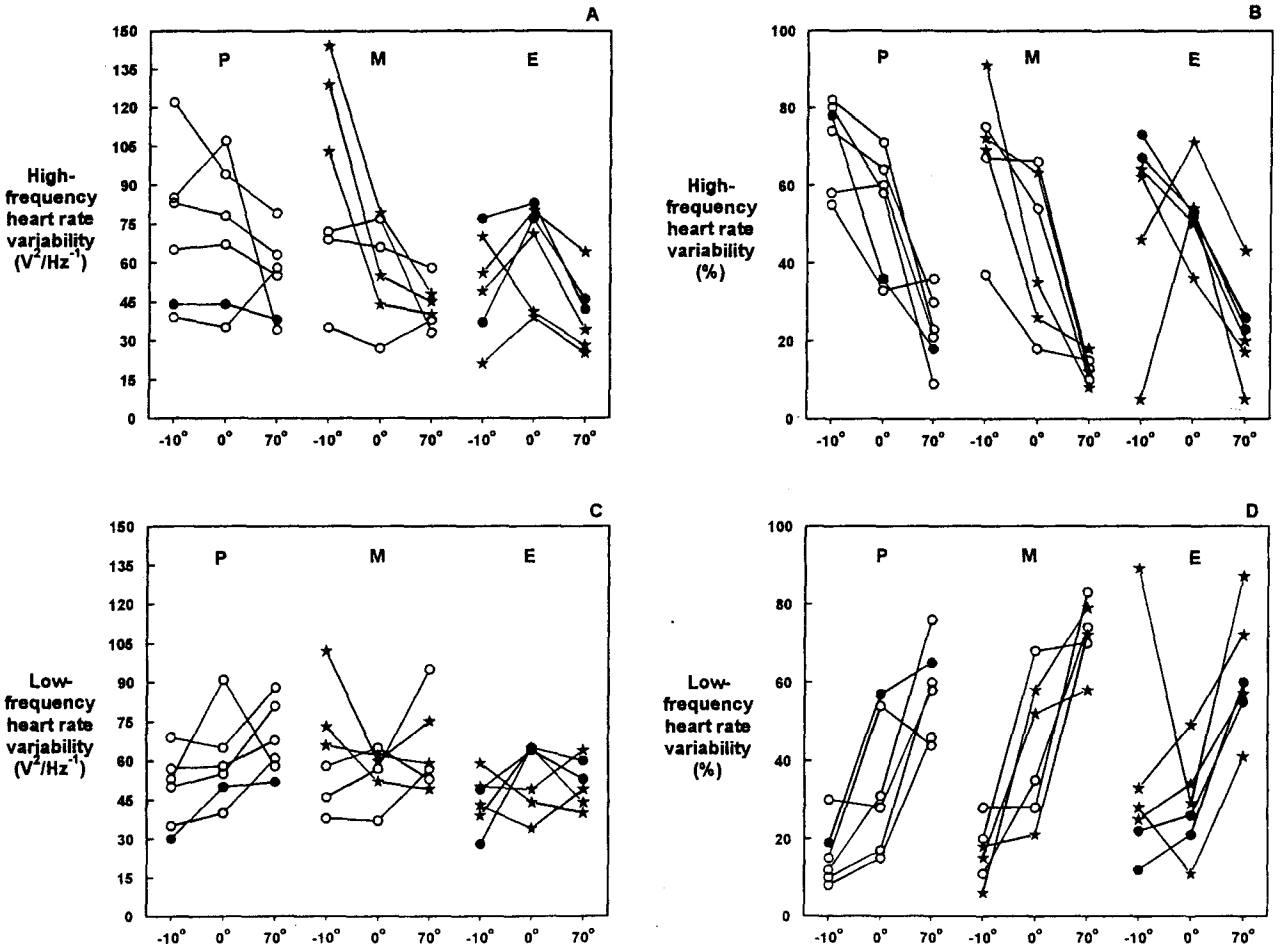

Figure 4. Power density of high-frequency (A) and low-frequency (C) heart rate variability and the percentage distribution of heart rate oscillations to high (B) and low (D) frequencies in six subjects during placebo (P), midazolam (M) and ephedrine (E) treatment during supine rest (0°), head-down tilt (−10°) and head-up tilt (70°). Subjects with cardiovascular sympathicotonic responses (●) and abnormal falls in diastolic arterial blood pressure during head-up tilt (✱)

subject ($p < 0.01$). In no position did the heart rate significantly differ from the corresponding heart rate after placebo treatment, but it was significantly lower during supine rest and head-down tilt (67 ± 9 beats/min) than during head-up tilt, as it was also after placebo treatment ($p < 0.05$, Figure 3).

Compared with placebo treatment values, ephedrine increased systolic arterial blood pressure during supine rest to 120 ± 5 mmHg ($p < 0.01$) and head-down tilt to 114 ± 7 mmHg ($p < 0.05$). The increase in diastolic blood pressure was less (to 78 ± 6 mmHg and 77 ± 9 mmHg, respectively, $p \geq 0.17$) but occurred in five subjects. The heart rate also rose in five subjects during supine rest (12 ± 13 beats/min) and head-down tilt (7 ± 7 beats/min), compared against the corresponding heart rate after placebo treatment (Figure 3).

After administration of ephedrine, all subjects showed a sympathicotonic reaction of systolic arterial blood pressure, which fell ≥ 22 mmHg during change from supine rest to head-up tilt ($p < 0.01$). Diastolic arterial blood pressure fell abnormally in four subjects and increased by 16 mmHg in one subject changing from head-down tilt to head-up tilt ($p \geq 0.17$). The mean heart rate (89 ± 20 beats/min at supine rest) always increased during head-up tilt by ≥33 beats/min and reached ≥115 beats/min in every subject ($p < 0.01$). The standing heart rate during ephedrine treatment was 27 ± 13 beats/min higher than that measured during placebo treatment ($p < 0.05$).

Heart rate variability

During placebo treatment, high-frequency power density tended to decrease during head-up tilt and accounted for 23 ± 10% of heart rate variability during head-up tilt, significantly less than during supine rest (53 ± 16%, $p < 0.01$) or head-down tilt (71 ± 11%, $p < 0.01$, Figure 4). Low-frequency oscillations tended to increase and contributed to heart rate variability significantly more during head-up tilt (58 ± 12%) than supine rest (34 ± 18%, $p < 0.05$) or head-down tilt (16 ± 8%, $p < 0.01$).

During midazolam treatment, a slight decrease in high-frequency heart rate variability (44 ± 20%) tended to increase the contribution of low-frequency oscillations to the heart rate variability (44 ± 18%) of most supine subjects. During head-down tilt, high-frequency power density often increased markedly, and the contribution of high-frequency oscillations to

heart rate variability increased in every subject (68 ± 18%, $p < 0.05$). The contribution of low-frequency heart rate variability decreased during change from supine rest to head-down tilt (17 ± 7%, $p < 0.05$), but low-frequency power density was often greater than during placebo treatment in head-down tilted subjects (Figures 1, 2 and 4). In head-up tilted subjects, high-frequency heart rate variability (13 ± 3%) was less than during supine rest ($p < 0.01$) or head-down tilt ($p < 0.01$) in every subject. Low-frequency heart rate variability increased in every subject during head-up tilt (72 ± 8%, $p < 0.05$).

Ephedrine did not significantly modify heart rate variability at supine rest (Figure 4). During head-down tilt, the high-frequency power density of heart rate variability was an average of 21 V^2/Hz and 40 V^2/Hz lower during ephedrine than during placebo and midazolam treatments, respectively. Simultaneously, the low-frequency power density of heart rate variability decreased (Figures 1, 2 and 4). High-frequency heart rate variability was 53 ± 11% at supine rest and 53 ± 25% during head-down tilt. In head-down tilted subjects, the contribution of high-frequency heart rate variability was 7–50% smaller (but in one subject 4% greater), and the contribution of low-frequency heart rate variability 1–74% greater (all subjects) during ephedrine treatment than during placebo treatment.

During head-up tilt and ephedrine treatment, high-frequency heart rate variability decreased in every subject and at supine rest from 65 ± 19 V^2/Hz to 40 ± 14 V^2/Hz. Head-up tilt decreased the contribution of high-frequency heart rate variability from 53 ± 11% to 22 ± 12% ($p < 0.01$) and increased the contribution of low-frequency heart rate variability from 28 ± 13% to 62 ± 16% ($p < 0.01$).

Discussion

In a previous study, benzodiazepine did not induce hypotension as a response to gravitational stress in the absence of exercise, but it induced tachycardia and vasodilatation in the forearm.[7] The 'central command' and 'exercise pressor reflex' are interfering factors affecting the nervous control of circulation during exercise.[16] In humans and animals, the vagally mediated baroreflex control of the heart rate is found to be diminished by exercise in proportion to the exercise load, whereas the sympathoadrenergic controls of the heart and vessels are not.[8] Peripheral vasodilation by neural and local metabolic mechanisms may be responsible for impaired orthostatic tolerance and changed heart rate variability lasting for up to 1 h after exercise.[8,9,17] In the present study, the effect of midazolam was compared with that of ephedrine (adrenergic agent) on the chronotropic response of the heart to post-exercise gravitational stress. We aimed to differentiate between the vagal and sympathetic effects on the heart by means of frequency-specific analysis of heart rate variability.[12]

During placebo treatment, the chronotropic response of the heart to changes of posture was as expected and in agreement with earlier findings: head-up tilt accelerates and head-down tilt decelerates the heart.[12] Heart rate variability was redistributed to high frequencies during head-down tilt and to low frequencies during head-up tilt so regularly that the changes could only be detected in a small group of six subjects. These cardiac chronotropic responses reflect increased and decreased vagal outflow to the heart with reciprocal changes in sympathetic outflow to the heart.[12]

Oral midazolam 15 mg (about 0.25 mg/kg) had no marked effect on the neural cardiovascular control system in the post-exercise supine steady state in our subjects. As in the study by Patrick *et al.*,[7] arterial blood pressure remained stable, and midazolam did not significantly increase the mean heart rate or low-frequency heart rate variability or decrease high-frequency heart rate variability at supine rest. In healthy humans and coronary patients, midazolam 0.15–0.30 mg/kg given intravenously over 15 s reduces systolic arterial blood pressure by 5% and diastolic arterial blood pressure by 10% and increases the heart rate, which exceeds the corresponding changes induced by an intravenous dose of 0.5 mg/kg diazepam.[1] A reduction in blood pressure activates baroreflexes increasing the heart rate and cardiac contractility with mobilization of splanchnic blood flow into the central circulation.[1] Midazolam decreases cardiac contractility directly in dogs.[1]

Head-down tilt after midazolam administration decreased the mean heart rate and shifted heart rate variability from low-frequency oscillations to high-frequency oscillations, indicating parasympathetic dominance of cardiac neural control. Head-up tilt after midazolam induced tachycardia and shifted heart rate variability from high-frequency oscillations to low-frequency oscillations, indicating sympathetic dominance of cardiac neural control. These changes from baseline at supine rest were seen in every subject. The changes of the heart rate oscillations were frequently greater during midazolam treatment than during placebo treatment. During head-down tilt, increased heart rate oscillations were seen in those subjects who showed sympathicotonic reactions and orthostatic hypotension during gravitational stress, not only on the frequency band of parasympathetic dynamics but also at lower frequencies where parasympathetic and sympathetic dynamics interact.[12] As in the study by Patrick *et al.*,[7] our subjects receiving midazolam required greater than normal reactivity of their neural control mechanisms during post-exercise adaptation to gravitational perturbations. Still, it was not always possible to regulate arterial blood pressure adequately during head-up tilt, and as a result, the sympathicotonic responses increased. This indicated unstable circulatory reactions. Diastolic blood pressure decreased

in three subjects. One subject had a presyncope. Diastolic blood pressure did not fall during placebo treatment; decrease in diastolic blood pressure is not typical of sympathicotonia, either.[12,15]

In our study, the drug doses were smaller and the hypotensive action of midazolam was less pronounced than in the dogs of Adams *et al.*,[4] in which, after a 30% reduction in blood volume, the hypotensive action and sedation of midazolam was potentiated and the compensatory rise in the heart rate was reversed to cardiac deceleration. Normally, baroreflex sensitivity has been found to increase with head-down tilt and decrease with head-up tilt.[18,19] Some evidence indicates that intravenous midazolam 0.3 mg/kg attenuates the catecholamine response to hypotensive stress and transiently depresses baroreflex function.[1,3] Midazolam is also known to cause hypotensive episodes and adverse events during certain combination therapies.[2,20] We have previously shown that exercise impairs the absorption of midazolam.[21]

Ephedrine increased the mean heart rate as well as the systolic and, slightly, diastolic arterial blood pressure. Low-frequency oscillations in the heart rate tended to decrease rather than increase. A strong adrenergic effect might dampen low-frequency heart rate dynamics[12] and explain the sympathicotonic responses of the heart rate and arterial blood pressure of all subjects to head-up tilt during ephedrine treatment. Four of six subjects had an abnormal or inadequate fall in diastolic blood pressure during head-up tilt. One subject had a presyncopal reaction but no vasodepressor or vasovagal pattern[22,23] was recognized. The responses of the diastolic arterial blood pressure to head-up tilt after ephedrine administration were at least as atypical of sympathicotonia as after midazolam treatment. Ephedrine has a modest centrally induced hypotensive action depending on its penetration into the brain and possibly on the stimulation of central α-adrenergic receptors.[5]

Ephedrine inhibited the increase in high-frequency periodic heart rate variability by head-down tilt, which was regularly seen after placebo and midazolam treatments, indicating immobilization of the parasympathetic dynamic control of the heart. During head-down tilt all subjects showed a greater contribution of low-frequency heart rate variability during ephedrine treatment than during placebo or midazolam treatments. This response was marked in some subjects. Tonic sympathetic influence may dampen adrenergic dynamics,[12] and increased central blood volume due to head-down tilt may elicit ephedrine-induced tonic sympathetic activity. Vagolysis and control of tonic sympathetic outflow may take place at the level of the central nervous system, but inhibition of cholinergic neurotransmission is also possible peripherally, as shown earlier in human airways[24] and the canine heart.[25] Exercise does not affect the pharmacokinetics of ephedrine.[21]

In conclusion, we found that a single dose of midazolam induced unexpectedly great changes in autonomic chronotropic control during post-exercise cardiovascular adaptation to gravitational stress. Ephedrine increased tonic sympathetic activity and stabilized the neural circulatory control of the heart by immobilizing dynamic parasympathetic activation but not dynamic sympathetic activation.

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