Pol J Aviat Med Bioeng Psychol 2021; 27(4): 5-18
DOI: 10.13174/pjambp.17.12.2024.01

ORIGINAL ARTICLE

HOW DO MODAFINIL AND GALANTAMINE AFFECT HEART RATE DURING +GZ STRESS

Anna Przewodzka[1], Joanna Łaszczyńska[2], Anna Czerwińska[2], Krzysztof Kowalczuk[3], Marcin Biernacki[4], Rafał Lewkowicz[3]

1 Creative Neuroscience Lab – CNS Lab, Military Institute of Aviation Medicine, Warsaw, Poland
2 Military Institute of Aviation Medicine, Warsaw, Poland
3 Department of Simulator Studies and Aeromedical Training, Military Institute of Aviation Medicine, Poland
4 Department of Aviation Psychology, Military Institute of Aviation Medicine, Poland

Source of support: This work was supported by the National Centre for Research and Development (Poland) under Grant [No. OR00004208], titled: "Improving the psychophysical fitness of a soldier during combat tasks by means of pharmacological stimulation".

Author's address: A. Przewodzka, Military Institute of Aviation Medicine; Krasinskiego 54/56 Street, 01-755 Warsaw, Poland, email: aprzewodzka@wiml.waw.pl

Introduction: Fatigue remains a significant challenge in the field of aviation safety. This is particularly the case in military aviation, where aircrews are expected to perform complex and cognitively demanding tasks, often with unpredictable working hours, insufficient sleep and disrupted circadian rhythms. The aim of the present study was to determine the effect of a single dose of modafinil on the physiological response (based on heart rate) to variable acceleration up to +3Gz during a limited period of sleep deprivation, compared with that of placebo and a single dose of galantamine.

Methods: To determine the effect of stimulant use, 12 male volunteers with a mean age of 24 ± 2.5 years were tested under three night-time conditions, after an average of 27 hours of sleep deprivation. Participants received placebo, galantamine 10 mg, and modafinil 100 mg, and were tested in a human centrifuge during a daytime control session. Heart rate, blood pressure, core body temperature, and body hydration were measured in participants during the experiment.

Results: As we expected, both galantamine and modafinil counteracted the effects of fatigue on the physiological response to variable acceleration up to +3Gz compared to placebo, with the beneficial effect of galantamine being greater than that of modafinil. A single administration of galantamine (10 mg) to participants after 27 hours of wakefulness resulted in a statistically significant reduction in heart rate relative to both placebo and modafinil.

Figures: 5 • **Table:** 1 • **References:** 64 • **Full-text PDF:** http://www.pjambp.com • **Copyright** © 2024 Military Institute of Aviation Medicine, ul. Krasińskiego 54/56, 01-755 Warsaw, license WIML • **Indexation:** Index Copernicus, Polish Ministry of Science and Higher Education

Conclusions: None of the drugs tested (modafinil or galantamine) at a single dose had a negative effect on the physiological response to variable acceleration reaching +3Gz. Therefore, if there are no contraindications to their use, they may be useful in combating the symptoms of fatigue in flight attendants exposed to overload during prolonged flights.

Keywords: acceleration, G-forces, stimulant, sleep deprivation, Go pills

INTRODUCTION

Military flight missions are particularly demanding, mainly because of their frequency, long duration and the fact that they are mostly performed at night. These factors contribute to the prevalence of aircrew fatigue, which remains a major concern for flight safety [24,60]. Exhaustion-related fatigue is a combination of physical and mental fatigue, including fatigue caused by the desynchronization of activity and sleep cycles. Disregarding the effects of prolonged fatigue results in numerous psychophysical deficits that may jeopardize crew safety [13,64]. Impairments of the central nervous system, including disturbances in short-term memory functioning, prolonged reaction time, loss of alertness, mood changes, and episodes of micro-sleep, are just some of the consequences [4,5]. As a result, specific skills such as radio communication, dexterity, or motor control during flight operations deteriorate [8]. Therefore, improper fatigue management worsens pilot performance and often leads to aviation incidents with tragic consequences, both in military and civilian aviation [60]. According to a recent study [25], exhaustion, poor sleep quality, and inconsistent shift patterns at work are widespread among U.S. Army aviators. 94% of pilots and navigators observed worsening effects of tiredness, while 65% of flight attendants in the US Air Force reported inadvertent in-flight snooze, according to a 2005 survey [35].

Caffeine, which is widely available, is often used to counteract fatigue and is permitted by military aviation [9,34]. This substance, by causing vasodilation, increases blood flow in the body, which stimulates the central nervous system (improving concentration and enhancing cognitive processes) [33]. It also has a stimulating effect on the circulatory system by increasing heart rate and raising blood pressure. Its effectiveness may depend on the level of daily consumption [44]. However, aircrew members have observed that caffeine pills do not effectively reduce tiredness [37]. This may be because caffeine's relatively short half-life (T1/2) of 4-6 hours renders it less useful for extended nighttime operations that call for attentiveness. Furthermore, in case many of these individuals consume substantial amounts of caffeine on a regular basis, the pilot's organism can become accustomed to its presence in the body. Concerns have also been expressed over caffeine's diuretic effect and how it may affect the pilot's level of hydration [37]. The effects of caffeine are also influenced by genetic variability within the population. Polymorphism in the CYP1A2 and ADORA2A nucleotide regions may weaken the effects of caffeine in the body, as confirmed by recent studies [21,22,39].

Another method of combating fatigue, although not accepted by most aviation organizations, is the use of pharmacological stimulants, also known as psychostimulants, which enhance alertness and reduce fatigue [16,38,45].

Pharmaceutical countermeasures for fatigue in aviation

One of the first stimulants used in military aviation was amphetamine. Today, it is used in the form of dextroamphetamine, the more dopaminergic enantiomer of amphetamine. Dextroamphetamine doses of 10 to 20 mg (not exceeding 60 mg per day) are recommended for severely fatigued military pilots who have experienced dangerous levels of sleep deprivation [9]. For certain types of flight missions (i.e. 12 or more hours), doses of 5 to 10 mg have also been authorized for use by all three U.S. services [9]. The efficacy of dextroamphetamine in military settings has been demonstrated in numerous combat scenarios [10,17,47]. Although no serious side effects or other problems have been reported to date in relation to the medical use of dextroamphetamine in a military setting [9], this agent was deemed unsuitable because of its a high potential for abuse and addiction [62].

While civil aviation does not allow the use of pharmacological alertness enhancers, military aviation allows the use of modafinil, along with stimulants such as caffeine and dextroamphetamine [9]. Unlike dextroamphetamine, modafinil has a much lower potential for abuse [3]; it is thought to exert its stimulant effects by altering levels of several neurotransmitters, including serotonin, nor-

epinephrine, dopamine and gamma-aminobutyric acid [1,28]. Although modafinil is less effective [36], for 40-hour periods of sleep deprivation, its effects can be considered equivalent to dextroamphetamine [7,40,57].

Modafinil has been approved as a fatigue countermeasure by the air forces of the United States, India, France, and Singapore [9,38]. However, the Republic of Singapore Air Force prohibits the use of modafinil among aviators with poorly controlled hypertension and/or heart disease [38]. Some countries, including the Royal Netherlands Air Force, are considering allowing the use of modafinil [34,60], despite its adverse effects observed in aviation studies still being not fully understood [27,29,32,57,58].

Studies to date have shown that modafinil improves psychomotor performance [6,19], cognitive functions [32,57], reaction speed, executive control [27], and mood [8]. However, some studies [1,11,26,29] have indicated that under normal sleep conditions, modafinil may only slightly enhance cognitive functions. Although modafinil has been extensively tested in simulated conditions and through ground-based tests, its effects in the actual operational environment of pilots have not been sufficiently verified [6–9].

The most commonly reported side effect of modafinil is headache [60]. Other side effects include dizziness, visual disturbances, disorientation, concentration problems, dry mouth, reduced appetite, tremors, anxiety, tachycardia, as well as insomnia or drowsiness [38]. Less common side effects include hypertension, agitation, arrhythmias, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-induced rash with eosinophilia and systemic symptoms [11,60].

Modafinil dosing (from a single to multiple doses) is mainly dependent on the duration of sleep deprivation [60]. Caldwell et al. [6] noted that the severity of modafinil side-effect symptoms may be dose-related. However, unlike other stimulants such as dextroamphetamine, modafinil is not addictive [3]. In the context of military aviation, the scenario of a 24-hour period of wakefulness (which is likely to occur during operational missions) and the intake of a single dose of modafinil is of particular interest.

In-flight accelerations and psychostimulants

Due to performing the high +Gz flight maneuvers, military fighter pilots endure severe physiological demands after extended durations of wakefulness. It was found that chronic fatigue and longer periods of sustained wakefulness may contribute to G-induced loss of consciousness (G-LOC) mishaps [42]. Therefore in modern aviation the absence of duty-relevant side effects associated with the use of pharmacological stimulation also has important implications for acceleration tolerance. This applies not only to pilots of high-performance aircraft, but also to pilots of helicopters, such as AH-64, UH-60 or Mi-24, which, during manoeuvering flight, can generate overloads of up to +3Gz and even more [48].

Depending on the magnitude and duration, G-forces contribute to the displacement of bodily fluids, causing hypoxia of the central nervous system [15], as well as visual [30,63] and cognitive impairments [2,18,54]. These changes negatively impact psychomotor responses [14,53,55]. The primary physiological compensatory mechanisms that counteract the displacement of significant blood volumes from the head toward the lower parts of the body and, consequently, prevent G-LOC (G-force induced loss of consciousness) - rely on an increased heart rate and a rise in the cardiac output of blood pumped by the heart. Studies [42] have observed that administering modafinil during prolonged fatigue positively affects the difficulty of performing anti-G straining maneuvers (AGSM). Training in the Rapid Onset Rate (ROR) program, in which acceleration was linearly increased, was subjectively perceived as less exhausting after the use of modafinil and methylphenidate [42]. However, the authors did not specify whether modafinil had a negative impact on acceleration tolerance. Another study [20] found that administering modafinil had no significant effect on G-force tolerance in rhesus monkeys compared to the control group. The authors emphasized, however, that this result requires confirmation in humans.

Improving acceleration tolerance in pilots is a critical aspect of ensuring the safety of flight crews in dynamically changing flight environments. In the search for new methods to mitigate prolonged fatigue, it is essential to continuously analyze effective pharmacological stimulants that enhance alertness and provide multiple benefits in the comprehensive assessment of pilots' psychophysiological states under G-forces. For this reason, our research also aimed to evaluate the effects of galantamine, a substance that has not yet been assessed in terms of its ability to counteract fatigue or its impact on acceleration tolerance. Galantamine is an acetylcholinesterase inhibitor that enhances cholinergic transmission, which is particularly significant in treating cognitive

impairments. This substance is used to increase cognitive functions, improve memory and the information reproduction process. An improvement in skeletal muscle tone, a reduction in blood pressure and heart rate, and an increase in sweat and digestive juices secretion have also been observed after taking this substance [12,23,51].

Although the adverse effects of the aforementioned pharmacological agents appear to be not fully understood in aviation [27,29,32,57,58], some countries are considering permitting the use of modafinil [60]. Nevertheless, despite the promising results observed in fatigue reduction with modafinil, its effectiveness has not yet been extensively studied in military aviation [60,62].

Assumptions regarding the effects of modafinil and galantamine on HR

Modafinil may cause a moderate increase in heart rate [49], as a result of increased sympathetic activity (stimulation of adrenergic and dopaminergic receptors in the brain) [50,52]. In high-G environments, monitoring HR is crucial to prevent excessive increases (>180 bpm), which could lead to a decrease in stroke volume.

In the case of galantamine, an inhibitor that enhances parasympathetic activity, a reduction in HR may occur [23]. Through modulation of the parasympathetic system, galantamine may improve cardiac efficiency by maintaining a lower resting HR and presumably preventing excessive increases in response to acceleration forces [12,51]. Such a mechanism, associated with reducing HR, is particularly desirable during exposure to high G-forces (> +7Gz), where a significant increase in HR can negatively impact on stroke volume.

We hypothesize that at appropriate doses and without impairing low-G tolerance, both substances should not negatively affect heart rate in individuals exposed to G-forces up to +3Gz.

Aim of the study

The present study aimed to determine the effect of a single dose of modafinil and galantamine on the response of the cardiovascular system subjected to variable overloads of up to +3Gz during a limited period of sleep deprivation (27 h) compared with those of placebo. The assessment of the effect of pharmaceutical stimulants on the cardiovascular response was based on the analysis of changes in heart rate.

We expected that both galantamine and modafinil to counteract the effects of fatigue on the physiological response (HR) to variable acceleration reaching +3Gz compared with placebo.

This study was conducted as part of a larger study that investigated the use of pharmacological stimulation to enhance soldier performance during combat [31,41]. However, the study mentioned above mainly focused on initial attempt to assess the effect of two pharmacological stimulants on hypoxia tolerance during the performance of the primary flight task.

METHODS

Participants

Twelve healthy male participants aged 20-25 years (M=24; SD=2.5) with current medical clearance by the District Military Aviation and Medical Board (min. internal medicine, otolaryngology and neurology examination including EEG) attended to the study. The participants, students of the Academy of Physical Education in Warsaw, were qualified for the study by a special aviation and medical committee on the basis of the results of recent medical examinations (internal medicine, ophthalmology, laryngology, neurology, ECG, EEG, tonal audiometry, cardiopulmonary exercise test (VO2max), blood pressure (BP), core body temperature (Tc), blood and urine analysis, anthropometric measurements) and the opinion of an occupational physician. Participants were also screened to rule out any pre-existing sleep disorders.

Exclusion criteria were mainly based on potential side effects or interactions with one or both drugs (modafinil and galantamine). An additional medical qualification was conducted by a physician immediately before exposure to acceleration in the centrifuge. Participants in the experiment were required to meet the following conditions:

- possess a valid certificate confirming their ability to participate in the study,
- refrain from consuming alcohol or excessive amounts of other stimulants, such as coffee or cigarettes, on the day preceding the experiment,
- on the day of the experiment, abstain from smoking tobacco or using any other nicotine-containing substances,
- drink at least 0.25 liters of fluid at least 30 minutes before the start of the experiment (centrifuge exposure),
- consume a meal at least 2 hours prior to the start of the experiment,
- report any health issues or discomfort, both before and during the experiment, directly to the physician supervising the acceleration exposure in the centrifuge.

The study was conducted at the Military Institute of Aviation Medicine (WIML) in Warsaw, Poland, and adhered to the principles of the Declaration of Helsinki. The research received a positive opinion from the WIML Ethics Committee, in accordance with the requirements for conducting research involving human subjects. Participants were informed about the known side effects of each study drug and the risks of accelerated testing. Each participant signed an informed consent form.

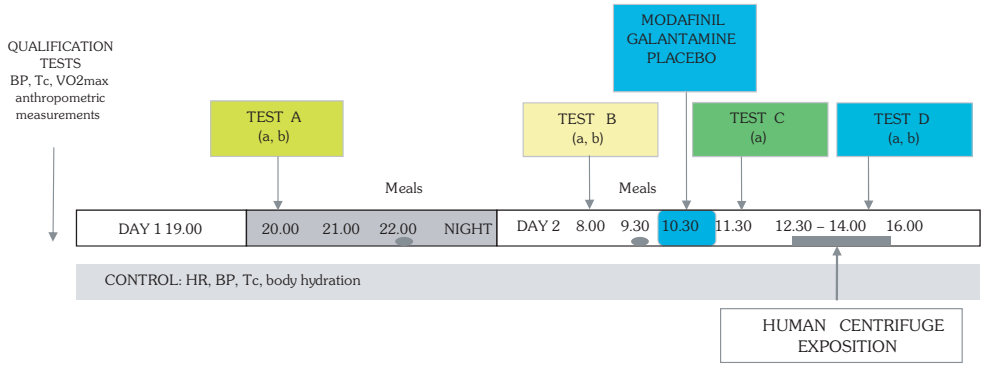
Study design

This randomized, double-blind, crossover, active- and placebo-controlled clinical trial was conducted in the spring period (March-April) at fixed and repeated intervals. This study had a 3 × 4 within-subjects design: treatment (modafinil, galantamine, placebo) × test time (T = 8:00 PM, T = 8:00 AM, T = 11:30 AM, T = 2:00 PM). The entire study consisted of three experiments, two consecutive trial days each (Fig. 1), during which (1) Vigil® (100 mg modafinil), (2) Nivalin® (10 mg galantamine), or (3) placebo pill was administered once just at 10.30 AM. As a result, each participant took part in three experimental sessions, differing only in the type of orally administered drug.

Each experiment started at 07:00 PM after a full day of the participants regular daily activities, and ended at 04:00 PM the following day. On the first day of the experiment, the median wake time of the participants was 07:00 AM. Consequently, at the time of drug administration (10:30 AM the following day), the participants had a median period of wakefulness of 27 h (range: 25.5–29.0 h).

During each two-day experiment, the participant underwent the following measurements and tests (Fig. 1):

- heart rate (HR), blood pressure (BP), body core temperature (Tc), and the state of hydration of the body (every 3 hours at night, starting at 7:00 PM, every 2 hours the next day after a sleepless night). Body temperature was measured in the external auditory canal. Hydration status control included three assessments: a skin turgor test (evaluation of skin elasticity after pinching the back of the hand), assessment of urine color, and the sensation of dryness in the oral cavity.
- measurements of body mass and temperature, blood pressure, and energy expenditure were conducted at 8:00 PM, 8:00 AM, 11:30 AM, and 2:00 PM. During these tests (Fig. 1, TEST A-D), participants also performed tasks such as detecting a light stimulus using the CFFT (critical flicker fusion threshold) test, carrying out pilot tasks in a flight simulator, and completing tasks assessing psychomotor efficiency and attention concentration (psychological tests). The results of these tests were not included in the analysis and were not evaluated as part of the present study. The presented analysis focused solely on the impact of pharmacological stimulation (using psychostimulants) on heart rate.



Type of test:

a) BP, Tc, weight, energy expenditure, CFFT, psychomotor performance and attention tests

b) Flight simulator test

Fig. 1. Scheme of the study design of the influence of psychostimulants (modafinil, galantamine) in the condition of the prolonged wakefulness in association with the +3 Gz exposure. HR- heart rate, BP – blood pressure, Tc – body core temperature.

The sequence of pharmaceutical agents (modafinil, galantamine) and the control trial (placebo) was randomized. Measurements in the tests were always carried out strictly according to the specified research protocol (Fig. 1). Meals were consumed in the evening at 10:00 PM and in the morning at 9:30 AM.

In each of the three experimental conditions, the participant was exposed to linear acceleration of +3 Gz between 12:30 PM and 2:00 PM (the period of peak effect of the administered drugs) in the centrifuge (Fig. 2). The profile generated in the human centrifuge is shown in Fig. 3. In order to reduce the level of situational stress prior to the examination, all participants were acquainted with the course of the examination, +Gz exposure and the physiological consequences of acceleration on the body by an aviation medicine physician conducting trainings in the conditions of human centrifuge. The entire centrifuge test was supervised by an instructor. Prior to the start of the overload exposure, the instructor familiarized the participants with the test and outlined the safety conditions.

Psychostimulants and dosage

Two psychoactive substances, modafinil and galantamine, were selected for the study, both of which have been approved within the European Union. The pharmaceutical products containing these substances were: Vigil® (100 mg of modafinil) by Torres Chiesi Polska Sp. z o.o., and Nivalin® (10 mg of galantamine) by Janssen-Cilag Polska Sp. z o.o. The drugs were administered in a single dose. The modafinil dose (100 mg) is considered an effective dose for combating fatigue in military aviation [6,9]. Research findings [8,19] have shown that the optimal modafinil dose is between 100 and 200 mg, administered at 4-5 hour intervals. Its positive effects were observed within 30-60 minutes after administration [60], with optimal benefits occurring after 2-4 hours [62] and a half-life of 12–15 hours [43]. The dose of galantamine (10 mg) is considered a medium-range but effective dose, for which the maximum operating time is within the range of 0.5-2 h with an elimination half-life of 5.5 h [46]. Therefore, in order to maximize the benefits of the administered substances in our study, medication intake was specified to be taken 2 hours before the start of the +3Gz acceleration simulation tests.

The psychostimulants were similar in appearance, smell and consistency to the placebo pill (control), which contained powdered lactose. The participants swallowed the tablets whole (without chewing) at the same time each day, in accordance with the pre-established research protocol (Fig. 1), accompanied by a glass of still mineral water. The order of administering the psychostimulants and placebo to each participant was randomized. The properties of these pharmacological agents are described in detail in the publication [41].

Research device

To generate the acceleration stimulus, the human centrifuge (Fig. 2) (Military Institute of Aviation Medicine in Warsaw, Poland) was used. The centrifuge cabin is mounted at the end of a 9-meter arm. It is equipped with an aviation seat (19° tilt back) with a harness to secure the participant, as well as a 42-inch monitor designed to display flight scenery or graphic markers that allow for the assessment of peripheral vision disturbance.

The acceleration was generated by a computer according to a defined acceleration profile (Fig. 3). The centrifuge's system for recording physiological parameters allowed for the measurement and recording of electrocardiography (ECG) signals, heart rate (HR), pulse oximetry (SpO2 from the ear lobe), breathing pattern (thermistor sensor in the nostril of the test person), and a light bar to assess peripheral vision (time and accuracy of the simple response).

The participants were exposed to an acceleration profile that included a peak of +3Gz in three consecutive stages:

- Stage 1 – a linear program with a gradual onset rate (GOR), in which the acceleration was increased linearly at 0.1 G/s from the baseline start point (+1.4 Gz) up to maximum +3Gz,
- Stage 2 – a program of gradually increasing overload to 2, 2.5 and +3Gz. During this stage, the acceleration was increased and decreased linearly at 0.1 G/s,
- Stage 3 – rapid onset rate (ROR) program, in which the acceleration was increased linearly at 3.5 G/s from the baseline up to maximum +3Gz.

Return to baseline in the first and second stages occurred at a speed of 0.1 G/s. In phase three, the decrease in acceleration was 3.5 G/s. The protocol consisted of three stages, as presented in Fig. 3.

To maximize detection of variability in physiological response, the testing protocol (Fig. 3) was performed without standard G-suit protection and without anti-G straining maneuvers.

Fig. 2. The Military Institute of Aviation Medicine in Warsaw centrifuge (produced in the 1960s, after modernization).

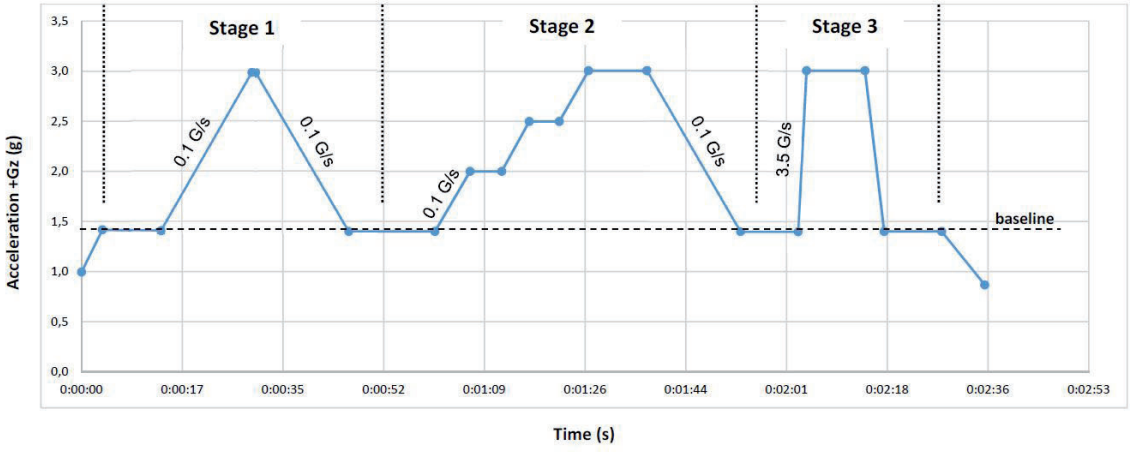


Fig. 3. A profile of the acceleration generated in the human centrifuge.

Measurements

A series of standard physiological parameters were measured and recorded continuously during the experiment in the human training centrifuge. These parameters included ECG, HR, ear lobe pulse pressure, SpO2, breathing pattern, the reaction time to visual stimuli presented in the peripheral vision, and acceleration value.

A NATO-standard light bar (comprising a central red lamp and two green lamps positioned at an angle of approx. 60° to a participant) was used to assess impairment of central and peripheral vision. During each stage of acceleration, participants reported peripheral light loss (PLL) by pressing a button on a control stick in response to light stimuli presented on the light bar. All experimental runs were videotaped.

As a method of assessing the cardiovascular load, the average heart rate (HR) over a ten-second time period was taken, starting from the point of reaching the peak overload value in the first, second, and third stages of the acceleration profile (Fig. 3).

Procedure

Prior to the study, each participant was acquainted with study methods and safety conditions. All participants were instructed not to drink any caffeinated beverage during testing sessions or alcoholic beverages in the 24 hours prior to the study. They were also informed of the known side effects of each stimulant. All participants performed the same tests in the same order and with the same breaks maintained in between (Fig. 2).

To reduce the level of situational stress prior to the study, all participants were also made aware of the exposure to +Gz and the physiological consequences of acceleration. A debriefing was conducted by an aviation medical specialist (flight surgeon) who was also responsible for the supervision of the human centrifuge tests.

The centrifugation was terminated following the criteria set out by Whinnery and Gillingham [59], and in particular when:

- the acceleration profile ended (acceleration profile duration 210 seconds, Fig. 3),
- heart rate > 200 bpm,
- 100% loss of peripheral vision (100% PLL) (blackout),
- arrhythmias occurred, such as ventricular bigeminy/trigeminy, supraventricular tachycardia, ventricular tachycardia, or bradycardia,
- lack of blood flow in the ear lobe occurred for more than 4 seconds,
- the subject reported pain or other concerning symptoms,
- the test was terminated by the subject (releasing the button on the control stick, which automatically stops the centrifuge's rotational motion).

A physician (flight surgeon) was available for consultation at all centrifuge runs.

Statistical analysis

The averaged HR values for each of the 3 stages of the acceleration profile, as well as for all phases combined, were subjected to statistical analysis (Fig. 3). In case of violation of the normality assumption, non-parametric Friedman's ANOVA (test statistic = $\chi 2$) followed by Wilcoxon signed-rank test with a Holm-Bonferroni correction (test statistic = Z) were used. All statistical analyses were performed using IBM SPSS version 17.0 (IBM Corporation, US). The significance of differences was assumed to be $p<0.05$.

RESULTS

During the study, all acceleration exposures were completed as planned, i.e., after reaching the end of the program. None of the participants reached the medical criteria for centrifuge termination, and no episodes of G-LOC occurred in any participant. The mean HR values for the individual experimental conditions (modafinil, galantamine, placebo) and stages of the acceleration profile (Fig. 3) are presented in Tab. 1.

In stage 1 of the acceleration profile (Fig. 3, GOR), a statistically significant reduction in HR was observed after the administration of galantamine compared to the values recorded with placebo (Tab. 1, Fig. 4), as well as in comparison to the HR values after the administration of modafinil. The latter drug also reduced HR, but this change was not statistically significant (Tab. 1).

Tab. 1. The mean HR values for each experimental condition (modafinil, galantamine, placebo) at each stage of the acceleration profile.

Acceleration stage	Heart rate (bpm) (M / SD)			p-value
	Modafinil (a)	Galantamine (b)	Placebo (c)	
Stage 1	107 / 14.20	99 / 12.55	113 / 9.43	a vs c = 0.107 **a vs b = 0.018** **b vs c = 0.010**
Stage 2	101 / 13.74	92 / 14.72	100 / 12.62	a vs c = 0.666 a vs b = 0.113 **b vs c = 0.010**
Stage 3	102 / 13.88	95 / 14.50	102 / 11.08	a vs c = 1.000 a vs b = 0.119 **b vs c = 0.047**
All stages	103 / 13.04	95 / 13.43	105 / 9.85	a vs c = 0.624 a vs b = 0.059 **b vs c = 0.015**

Note. M – mean, SD – standard deviation

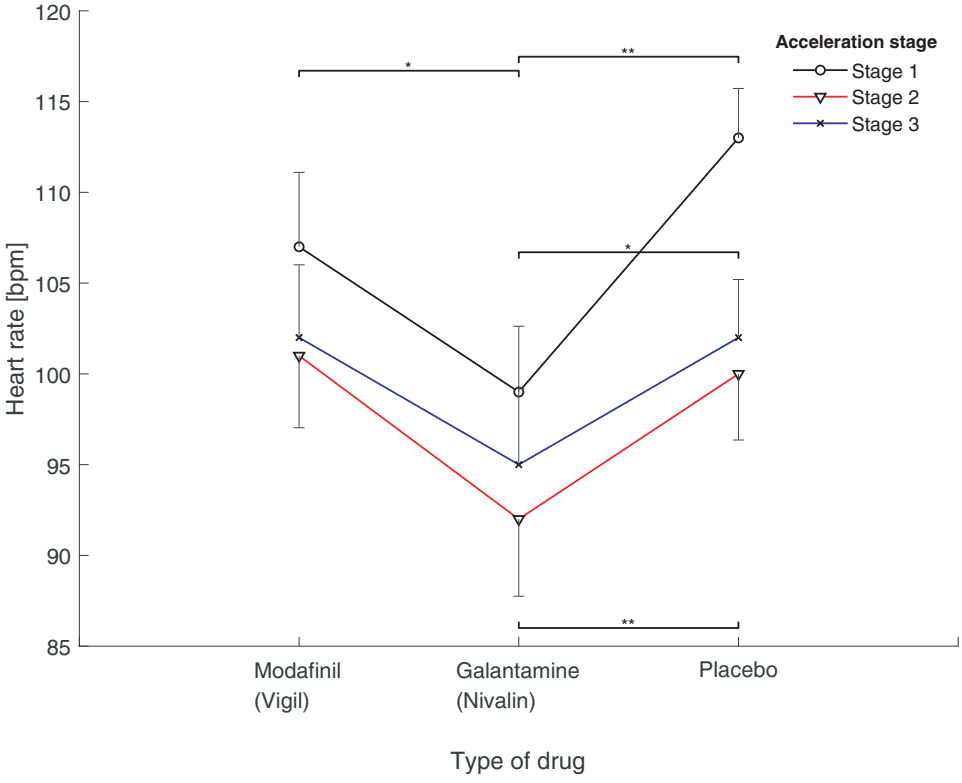


Fig. 4. Changes in heart rate during exposure to three different acceleration programmes (stages) after taking different drugs (modafinil, galantamine and placebo). Error bars represent the standard error of the mean (SEM); **p ≤ 0.01, *p ≤ 0.05.

Fig. 5. Changes in heart rate during exposure to the acceleration profile (all stages) after taking different drugs (modafinil, galantamine and placebo). Error bars represent the standard error of the mean (SEM); **p ≤ 0.01, *p≤0.05.

In stages 2 and 3 (Fig. 3), a statistically significant reduction in HR was observed only after the administration of galantamine (Tab. 1, Fig. 4). In other cases, the effect of modafinil on HR values was not statistically significant.

The statistical analysis also included the mean HR values averaged across all three stages of the acceleration profile. The results of the mean values from these three stages are presented in Tab. 1. Analysis of these results showed a statistically significant advantage of galantamine over placebo (Tab. 1, Fig. 5). After the administration of galantamine, HR was significantly lower ($p=0.015$) compared to placebo (95 vs 105 bpm). The result for galantamine was also lower than the mean HR value for modafinil, but this difference was not statistically significant.

In all stages of the acceleration profile, a significant advantage of galantamine over modafinil was observed in the reduction of HR (HR after the administration of galantamine was lower than after the administration of modafinil).

DISCUSSION

The negative side effects after modafinil or galantamine administration were mild and affected approximately one of five study participants. This result is consistent with previous reports, showing a very low side effect rate after these stimulants use [16,38,62].

In all three stages of centrifugation (Fig. 3), which differed in the profile of Gz/s acceleration change (linear, GOR, ROR), a statistically significant effect of galantamine (active ingredient of Nivalin®) vs. placebo was observed on reducing HR (Tab. 1, Fig. 4). This drug significantly affects the reduction of cardiovascular load and thus may positively influence the increase in tolerance to acceleration forces. A possible explanation for these results is that galantamine, by increasing the activity of the cholinergic system, facilitates the conduction of impulses in neuromuscular junctions, which leads to vasodilation and, consequently, a decrease in blood pressure and HR [46].

A statistically significant difference in HR reduction was also observed between galantamine and modafinil, but only in stage 1. The latter drug also lowered HR compared to placebo, but this change was not statistically significant (Tab. 1, Fig. 4). In the remaining cases (stages 2, 3, and averaged HR), no significant effect of modafinil on HR was observed. It is also important to note that modafinil did not increase cardiovascular load compared to placebo in conditions of fatigue resulting from prolonged wakefulness.

The analysis conducted for the averaged HR values from all three stages of the acceleration profile (Fig. 5) showed a favorable effect of both psychostimulant substances on limiting the increase of this parameter. However, a statistically significantly better effect appeared after galantamine was administered compared to placebo, in comparison to the effect obtained after modafinil relative to placebo. The reduction of HR after modafinil administration compared to placebo was assessed as a trend ($p<0.059$), without statistical significance. Despite the significant drop in HR after galantamine administration, it was assessed as having no impact on tolerance to acceleration forces.

The statistically significant advantage of galantamine over modafinil, measured by a smaller increase in HR under the same acceleration profile, suggests a priority for the use of galantamine. However, it should be emphasized that statistical confirmation of modafinil's effectiveness in reducing HR compared to placebo in two out of three stages of the acceleration profile was not achieved. Therefore, it can be assumed that the use of a single dose of modafinil does not increase tolerance to +Gz acceleration forces, nor does it reduce it. This assumption, however, requires confirmation in further studies.

Finally, it is worth noting that although psychostimulants may, in some cases, ensure the maintenance of alertness in extreme conditions where high levels of vigilance are required, it should be remembered that artificially maintaining alertness likely comes at a physiological cost regarding recovery, which is still not fully understood. Although the impact of modafinil on restorative sleep was not assessed in our study, the results of other authors' studies [62] suggest that administering modafinil in doses of 2x100mg does not affect the duration or quality of subsequent sleep. Although reports from other studies [27,56,57,61] indicate that taking modafinil (200 mg) after more than 20 hours of wakefulness may significantly shorten the duration of restorative sleep, it did not worsen its quality.

Study limitation

The participants were asked to stop taking caffeine during the experimental sessions. While this helps to eliminate the effect of caffeine on the study results, it does not reflect the typical practice of military aircrew members, the majority of whom consume caffeine regularly. The effect of

modafinil or galantamine combined with caffeine on the physiological response during positive acceleration may be different from that observed in the present study.

We conducted our study under controlled laboratory conditions using relatively simple tasks in a flight simulator. In real military operations, the shift workload and stressors including the complex nature of cockpit tasks performed under time pressure are more exhausting for the pilot's psychophysical condition [16]. It therefore seems necessary to repeat the study under actual flight conditions to verify whether the demonstrated benefits of stimulants can be replicated during flight operation [60].

Although the obtained study results highlight the importance of stimulant countermeasures in developing and strengthening strategies for managing alertness and fatigue levels in military aviation, they should be interpreted with caution due to the relatively small sample size. In future research, the evaluation of objective physiological parameters after the administration of modafinil or galantamine to a larger group of participants could provide more reliable evidence for the development of guidelines regarding the use of fatigue countermeasures.

CONCLUSIONS

In conclusion, the results of this study showed that none of the drugs tested (modafinil or galantamine), given in a single dose after a 27-hour wakefulness period, had a negative effect on the physiological response (HR) to variable acceleration reaching +3Gz. It can therefore be assumed that, if there are no contraindications to their use, they may be useful in alleviating the symptoms of fatigue (maintaining alertness and cognitive performance) in flying personnel exposed to low G-forces (≤ +3Gz). Furthermore, these drugs do not cause a significant increase in HR, which, with high G forces, could result in a decrease in cardiac performance (reduction in stroke volume). It is worth noting that our findings have been tailored to the specific airframe and mission profiles, as helicopter operations differ from those of high-performance aircraft [60].

When operating conditions require the use of stimulants among aircrews, it should be remembered that this is a solution away from the body's physiological recovery mechanisms and should not be abused. Although the psychostimulants tested do not produce euphoria, they may have a low potential for addiction. Therefore, the development of addiction should not be completely excluded, especially during prolonged use. The preferred solution is to provide aircraft crews with the opportunity for normal rest.

AUTHORS' DECLARATION:

Study Design: Joanna Łaszczyńska, Krzysztof Kowalczuk. **Data Collection:** Anna Przewodzka, Anna Czerwińska, Krzysztof Kowalczuk, Marcin Biernacki, Rafał Lewkowicz. **Manuscript Preparation:** Anna Przewodzka, Marcin Biernacki, Rafał Lewkowicz. The Authors declare that there is no conflict of interest.

REFERENCES

1. Battleday RM, Brem A-K. Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review. Eur Neuropsychopharmacol. 2015; 25(11):1865–81.
2. Biernacki MP, Tarnowski A, Lengsfeld K, Lewkowicz R, Kowalczuk K, Dereń M. +Gz load and executive functions. Aviat Space Environ Med. 2013; 84(5):511–5.
3. Bisagno V, González B, Urbano FJ. Cognitive enhancers versus addictive psychostimulants: The good and bad side of dopamine on prefrontal cortical circuits. Pharmacol Res. 2016; 109:108–18.
4. Bonnet MH, Arand DL. Clinical effects of sleep fragmentation versus sleep deprivation. Sleep Med Rev. 2003; 7(4):297–310.

5. Cabon P, Coblentz A, Mollard R, Fouillot JP. Human vigilance in railway and long-haul flight operation. Ergonomics. 1993; 36(9):1019–33.
6. Caldwell JAJ, Caldwell JL, Smythe NK 3rd, Hall KK. A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. Psychopharmacology (Berl). 2000; 150(3):272–82.
7. Caldwell JA. Efficacy of stimulants for fatigue management: the effects of Provigil® and Dexedrine® on sleep-deprived aviators. Transp Res Part F Traffic Psychol Behav. 2001; 4(1):19–37.
8. Caldwell JA, Caldwell JL, Smith JK, Brown DL. Modafinil's effects on simulator performance and mood in pilots during 37 h without sleep. Aviat Space Environ Med. 2004; 75(9):777–84.
9. Caldwell JA, Mallis MM, Caldwell JL, Paul MA, Miller JC, Neri DF. Fatigue countermeasures in aviation. Aviat Space Environ Med. 2009; 80(1):29–59.
10. Cornum R, Caldwell JA, Cornum KG. Stimulant use in extended flight operations. Airpower J. 1997; 11(1):53–58.
11. Daubner J, Arshaad MI, Henseler C, Hescheler J, Ehninger D, Broich K, et al. Pharmacological Neuroenhancement: Current Aspects of Categorization, Epidemiology, Pharmacology, Drug Development, Ethics, and Future Perspectives. Neural Plast. 2021; 2021:8823383.
12. Dias FL da C, Silva RMFL da, Moraes EN de, Caramelli P. Cholinesterase Inhibitors Modulate Autonomic Function in Patients with Alzheimer's Disease and Mixed Dementia. Curr Alzheimer Res. 2013; 10(5):476–81.
13. Diaz-Piedra C, Rieiro H, Suárez J, Rios-Tejada F, Catena A, Di Stasi LL. Fatigue in the military: towards a fatigue detection test based on the saccadic velocity. Physiol Meas. 2016; 37(9):N62-75.
14. Dziuk Z, Sulejnis H, Wojtkowiak M. Ocena współzależności między znoszeniem przyspieszeń w osi +Gz, wynikami prób czynnościowych a rozwojem wybranych cech motorycznych. Postępy Astronaut. 1969; 4:49–56.
15. Edelwejn Z, Kwarecki K, Wojtkowiak M. Wpływ ekstremalnych przyspieszeń na czynność bioelektryczną ośrodkowego układu nerwowego i serca oraz zmiany morfologiczne narządów wewnętrznych u małp. Med Lotnicza. 1973; 43:125–37.
16. Ehlert AM, Wilson PB. Stimulant Use as a Fatigue Countermeasure in Aviation. Aerosp Med Hum Perform. 2021; 92(3):190–200.
17. Emonson DL, Vanderbeek RD. The use of amphetamines in U.S. Air Force tactical operations during Desert Shield and Storm. Aviat Space Environ Med. 1995; 66(3):260–3.
18. Ercan E, Gunduz SH. The Effects of Acceleration Forces on Cognitive Functions. Microgravity Sci Technol. 2020; 32(4):681–6.
19. Estrada A, Kelley AM, Webb CM, Athy JR, Crowley JS. Modafinil as a replacement for dextroamphetamine for sustaining alertness in military helicopter pilots. Aviat Space Environ Med. 2012; 83(6):556–64.
20. Florence G, Riondet L, Serra A, Etienne X, Huart B, Van Beers P, et al. Psychostimulants and G tolerance in rhesus monkeys: Effects of oral modafinil and injected caffeine. Aviat Sp Environ Med. 2005; 76(2):121–6.
21. Gardiner C, Weakley J, Burke LM, Roach GD, Sargent C, Maniar N, et al. The effect of caffeine on subsequent sleep: A systematic review and meta-analysis. Sleep Med Rev. 2023; 69:101764.
22. Grgic J, Pickering C, Bishop DJ, Del Coso J, Schoenfeld BJ, Tinsley GM, et al. ADOR2A C Allele Carriers Exhibit Ergogenic Responses to Caffeine Supplementation. Nutrients. 2020; 12(3).
23. Howes LG. Cardiovascular effects of drugs used to treat Alzheimer's disease. Drug Saf. 2014; 37(6):391–5.
24. Kandera B, Škultéty F, Mesárošová K. Consequences of flight crew fatigue on the safety of civil aviation. Transp Res Procedia. 2019; 43:278–89.
25. Kelley AM, Feltman KA, Curry IP. A Survey of Fatigue in Army Aviators. Aerosp Med Hum Perform. 2018; 89(5):464–8.
26. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. Aviat Space Environ Med. 2012; 83(7):685–90.
27. Killgore WDS, Rupp TL, Grugle NL, Reichardt RM, Lipizzi EL, Balkin TJ. Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness. J Sleep Res. 2008; 17(3):309–21.
28. Kim D. Practical use and risk of modafinil, a novel waking drug. Environ Health Toxicol. 2012; 27:e2012007.
29. Klöpping W, Jonkman A, Valk P, Simons M. Efficacy of modafinil and caffeine to counteract hypnotic induced sleepiness during sustained operations. In: Strategies to Maintain Combat Readiness during Extended Deployments – A Human Systems Approach Meeting Proceedings RTO-MP-HFM-124. Neuilly-Sur-Seine, France: NATO Science and Technology Organization; 2005. p. 32–1 – 32–6.
30. Kożuchowska I, Wojtkowiak M. Assessment of intraocular pressure abnormalities in pilots after exposure to acceleration in a human centrifuge. [Ocena zaburzeń ciśnienia śródgałkowego w następstwie działania przyspieszeń u pilotów poddawanych badaniom w wirówce przeciążeniowej]. Med Lotnicza. 1978; 58:7-16 (in Polish).

31. Łaszczyńska J, Janusińska A, Biernacki M. Enhance the psychophysical state of the soldier during combat sentences through pharmacological stimulation. [Poprawa stanu psychofizycznego żołnierza w czasie zdań bojowych przez stymulację farmakologiczną]. In: Kocik J, editor. Żołnierz jako broń precyzyjna – pakiety i zestawy: ochrona przed NBC i zagrożeniami środowiskowymi; żywienie i farmakoterapia – przetrwanie w trudnych warunkach i optymalizacja wydolności psychofizycznej; medyczny – opatrunki aktywne biologicznie. Warszawa: WIHE; 2012. p. (in Polish).
32. LeDuc P, Rowe T, Martin C, Curry I, Wildzunas R, Schmeisser E, et al. Performance Sustainment of Two Man Crews during 87 Hours of Extended Wakefulness with Stimulants and Napping. Fort Rucker (AL); 2009.
33. Matysek-Nawrocka M, Cyrankiewicz P. Substancje biologicznie aktywne pozyskiwane z herbaty, kawy i kakao oraz ich zastosowanie w kosmetykach. Postępy Fitoter. 2026; 17(2):139–44.
34. Military Aviation Authority. Medicatie En Luchtvaart. Soesterberg, The Netherlands: Royal Netherlands Air Force; 2021.
35. Miller JC, Melfi M. Causes and Effects of Fatigue in Experienced Military Aircrew. AFRL-HE-BRTR- 2006-0071. Brooks City--Base, TX; 2006.
36. Mitler MM, Aldrich MS. Stimulants: efficacy and adverse effects. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 3rd ed. Philadelphia, PA: W.B. Saunders Company; 2000. p. 429–40.
37. Nehlig A. Interindividual Differences in Caffeine Metabolism and Factors Driving Caffeine Consumption. Pharmacol Rev. 2018; 70(2):384–411.
38. Ooi T, Wong SH, See B. Modafinil as a Stimulant for Military Aviators. Aerosp Med Hum Perform. 2019; 90(5):480–3.
39. Pickering C, Grgic J. Caffeine and Exercise: What Next? Sports Med. 2019; 49(7):1007–30.
40. Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, et al. Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. J Sleep Res. 1995; 4(4):212–28.
41. Przewodzka A, Czerwińska A, Łaszczyńska J. Influence of Selected Pharmacological Agents on the Psychophysical Efficiency of a Human in Conditions of the Extended Alert Period in Association with the Hypoxia Stimulus at High Altitude. Polish J Aviat Med Bioeng Psychol. 2018; 24(4):5–19.
42. Ramsey CS, Werchan PM, Isdahl WM, Fischer J, Gibbons JA. Acceleration tolerance at night with acute fatigue and stimulants. Aviat Space Environ Med. 2008; 79(8):769–73.
43. Robertson PJ, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet. 2003; 42(2):123–37.
44. Rodak K, Kokot I, Kratz EM. Caffeine as a Factor Influencing the Functioning of the Human Body-Friend or Foe? Nutrients. 2021; 13(9).
45. Schallhorn CS. Vigilance Aid Use and Aircraft Carrier Landing Performance in Pilots of Tactical Aircraft. Aerosp Med Hum Perform. 2020; 91(6):518–24.
46. Scott LJ, Goa KL. Galantamine. Drugs. 2000; 60(5):1095–122.
47. Senechal PK. Flight surgeon support of combat operations at RAF Upper Heyford. Aviat Space Environ Med. 1988; 59(8):776–7.
48. Shender BS. Human tolerance to Gz acceleration loads generated in high-performance helicopters. Aviat Space Environ Med. 2001; 72(8):693–703.
49. Sinha B. Effect of Modafinil on Autonomic Cardiovascular Function during Isometric Hand Grip Strength Test. Indian J Aerosp Med. 2016; 60(2):23–30.
50. Sinha B, Nataraja M, Harshavardhan G. The Effect of Modafinil on +Gz Tolerance in Healthy Male Aircrew. Indian J Aerosp Med. 2018; 62(1):19–23.
51. Stojiljković MP, Škrbić R, Maksimović ŽM. Cardiovascular Effects of Acetylcholinesterase Inhibitors. In: Djuric, D.M. Agrawal DK, editor. Environmental Factors in the Pathogenesis of Cardiovascular Diseases Advances in Biochemistry in Health and Disease, vol 30. Springer, Cham.; 2024. p. 233–57.
52. Taneja I, Diedrich A, Black BK, Byrne DW, Paranjape SY, Robertson D. Modafinil elicits sympathomedullary activation. Hypertens (Dallas, Tex 1979). 2005; 45(4):612–8.
53. Truszczyński O, Lewkowicz R, Wojtkowiak M, Biernacki MP. Reaction time in pilots during intervals of high sustained G. Aviat Sp Environ Med. 2014; 85(11):1114–20.
54. Truszczyński O, Wojtkowiak M, Biernacki MP, Kowalczuk K, Lewkowicz R. Effect of high acceleration exposure on visual perception in Polish pilots measured with Critical Fusion Frequency Test (CFFT). Polish J Aviat Med Psychol. 2012; 1(1):19–27.
55. Truszczyński O, Wojtkowiak M, Lewkowicz R, Biernacki MP, Kowalczuk K. Reaction time in pilots at sustained acceleration of +4.5 Gz. Aviat Space Environ Med. 2013; 84(8):845–9.
56. Walsh JK, Randazzo AC, Stone KL, Schweitzer PK. Modafinil improves alertness, vigilance, and executive function during simulated night shifts. Sleep. 2004; 27(3):434–9.

57. Wesensten NJ, Killgore WDS, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. J Sleep Res. 2005; 14(3):255–66.

58. Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. Psychopharmacology (Berl). 2002; 159(3):238–47.

59. Whinnery JE, Gillingham KK. Medical standards for experimental human use in acceleration stress research. Aviat Space Environ Med. 1983; 54(3):241–5.

60. Wingelaar-Jagt YQ, Wingelaar TT, Riedel WJ, Ramaekers JG. Fatigue in Aviation: Safety Risks, Preventive Strategies and Pharmacological Interventions. Front Physiol. 2021; 12:712628.

61. Wingelaar-Jagt YQ, Wingelaar TT, Riedel WJ, Ramaekers JG. Modafinil Subjectively Does Not Impair Sleep in Aviators After a Period of Extended Wakefulness. Aerosp Med Hum Perform. 2024; 95(6):290–6.

62. Wingelaar-Jagt Y, Wingelaar T, Riedel W, Ramaekers J. Subjective Effects of Modafinil in Military Fighter Pilots During Deployment. Aerosp Med Hum Perform. 2022; 93(10):823.

63. Wojtkowiak M, Domaszuk J, Zawitkowski J. An intraocular pressure in pilots exposed to +Gz accelerations. [Zachowanie się ciśnienia śródgałkowego u pilotów poddawanych działaniu przyspieszeń w osi +Gz]. Med Lotnicza. 1975; 47:39-45 (in Polish).

64. Wright N, McGown A. Vigilance on the civil flight deck: incidence of sleepiness and sleep during long-haul flights and associated changes in physiological parameters. Ergonomics. 2001; 44(1):82–106.

Cite this article as: Przewodzka A, Łaszczyńska J, Czerwińska A, Kowalczuk K, Biernacki M, Lewkowicz R. How Do Modafinil And Galantamine Affect Heart Rate During +Gz Stress. Pol J Aviat Med Bioeng Psychol 2021; 27(4): 5-18. DOI: 10.13174/pjambp.17.12.2024.01