Capacity to Compensate for Central Hypovolemia and Effects of Menstrual Cycle Phases

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BACKGROUND: Tolerance to central hypovolemia is dictated by exhaustion of the physiological capacity to compensate called the compensatory reserve. Such physiological compromise can have detrimental impact on performance in aerospace environments as well as survival from hemorrhage on the battlefield. We induced central hypovolemia using progressively stepwise lower body negative pressure (LBNP) in women during various phases of the menstrual cycle to test the hypothesis that similar tolerance across all menstrual cycle phases would be reflected by similar changes in compensatory reserve.

METHODS: Based on self-reporting of the last menstrual period, 40 healthy women, matched by demographics, were classified into 1 of 5 menstrual cycle phases: early follicular (EF, Days 1–7; $N = 10$), late follicular and ovulatory (LF, Days 9–15, $N = 6$), early luteal (EL, Days 16–18, $N = 6$), midluteal (ML, Days 19–25, $N = 8$), and late luteal (LL, Days 26–30, $N = 10$). All subjects had a 28–30 d menstrual cycle and were not taking oral contraceptives. Tolerance to central hypovolemia was measured as time (seconds) from baseline to the onset of presyncopal symptoms induced by LBNP.

RESULTS: Time to presyncope as well as hemodynamic and compensatory reserve responses were statistically indistinguishable across all menstrual cycle phases.

DISCUSSION: Consistent with our hypothesis, compensatory reserve with associated hemodynamic responses and tolerance to central hypovolemia was not affected by menstrual cycle phases. Our findings indicate experimental comparisons of responses to central hypovolemia involving the participation of healthy women with normal menstrual cycles and not taking oral contraceptives can be conducted independent of menstrual cycle phase.

KEYWORDS: women, compensatory reserve, lower body negative pressure tolerance, hemodynamics.

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It is well known that women as a population display lower tolerance to central hypovolemia compared to men, as evident by an earlier presentation of hemodynamic instability (e.g., hypotension) and clinical symptoms (e.g., syncope) with reductions in central blood volume.[7,16,25] Such physiological compromise can have detrimental impact on performance in aerospace environments (e.g., $+G_z$ intolerance, post spaceflight orthostatic intolerance) as well as survival from hemorrhage on the battlefield. Specific to gender differences in blood pressure regulation during progressive reductions in central blood volume, healthy young women not on birth control pills have been reported to have: 1) lower stroke volume, cardiac output, and mean arterial blood pressure;[7] 2) less relationship between sympathetic nerve activity (SNA) and peripheral vasoconstriction or cardiac output;[14] 3) reduced cardiac baroreflex response;[7] 4) lower levels of circulating norepinephrine;[7] 5) less coherence in baroreflex-mediated SNA activation by diastolic blood pressure oscillatory patterns;[33] and 6) increased pooling of blood in the pelvic region[32] compared with men.

The interpretation of compromised tolerance to central hypovolemia in women may be complicated by female sex hormones (e.g., estradiol, progesterone) that are known to fluctuate during the menstrual cycle and exert changes to vasculature smooth muscle and SNA.[4,31] As a result, experimental designs

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of previous investigations have been driven to limit female subjects to those in their earlier follicular phase of the menstrual cycle to minimize or eliminate potential confounding hormonal influences.[7,14,20] However, it has been reported that the menstrual cycle does not affect tolerance to central hypovolemia and carotid baroreflex control of heart rate or peripheral vascular resistance despite significant variations in estradiol and progesterone.[6]

Low tolerance to central hypovolemia has been associated with reduced responsiveness in a variety of compensatory mechanisms related to blood pressure regulation, including low circulating blood volume,[7,24] impaired baroreflex function,[7,8,12] and decreased cardiac filling pressure[22] with lower stroke volume and cardiac output.[7,22] However, the total integration of compensation to hypovolemia has been shown to be variable and complex, as indicated by the observation that individuals with similar tolerances to reduced central blood volume can display completely different combinations of compensatory responses.[2] As such, there is evidence to support the notion that tolerance to central hypovolemia is ultimately dictated by the exhaustion of the sum total of all compensatory mechanisms (e.g., tachycardia, vasoconstriction, deep inspiration) that contribute to sustaining adequate tissue oxygenation in the face of reduced systemic circulation.[9,11] Taken together, this capacity to compensate is called the compensatory reserve, which can be accurately quantified by analyzing subtle changes in photoplethysmographic arterial waveform characteristics using feature extraction techniques with machine learning.[10,11]

In this study, we extracted existing data from laboratory archives and conducted a retrospective cross-sectional comparison of tolerance and compensatory reserve to progressive central hypovolemia using lower body negative pressure (LBNP) to induce presyncopal endpoints in women representing all phases of the menstrual cycle: 1) early follicular (EF), 2) late follicular and ovulatory (LF), 3) early luteal (EL), 4) midluteal (ML), and 5) late luteal (LL). We hypothesized that if tolerance to central hypovolemia was unaffected by the menstrual cycle, then the rate and absolute reductions to lowest values of compensatory reserve would be similar across all menstrual cycle phases.

METHODS

Subjects

All experimental procedures were conducted in accordance with a protocol approved by the Institutional Review Board of the Office of Human Research Protection under the U.S. Army Medical Research and Material Command, Fort Detrick, MD. All experiments were conducted in the laboratory of the Center for Human Integrative Physiology at the U.S. Army Institute of Surgical Research, JBSA Fort Sam Houston, TX.

From a total database of 87 women, we were able to obtain menstrual cycle data on 40 healthy nonsmoking female subjects (mean ± 95% CI, age of 25 ± 2 yr; weight of 63 ± 3 kg; mean height 164 ± 3 cm) who volunteered to participate in this study (**Table I**). The subjects were subsequently classified into one of five menstrual cycle phases based on self-reporting of regular 28–30 d menstrual cycles and confirmed by identification of the last start of menses: EF (Days 1–7, $N = 10$), LF (Days 9–15, $N = 6$), EL (Days 16–18, $N = 6$), ML (Days 19–25, $N = 8$), LL (Days 26–30, $N = 10$). Subjects were screened using a standard preoperative screening tool (American Heart Association/American College of Cardiology assessment of cardiovascular risk) to ensure subjects had no chronic systemic diseases including any history of anemia. Subjects were instructed to refrain from exercise, maintain normal sleep patterns, and avoid caffeine intake and other autonomic stimulants at least 24 h prior to commencement of the experiment. All subjects were asked to complete a medical history questionnaire to confirm that they were not taking oral contraceptives, did not report irregular menstrual cycles, and to provide the date of their last menstrual period. Cycle day on the day of the LBNP study was determined based on the self-reported date of the onset of last menstrual period being defined as Day 1. The subjects also confirmed that they were not pregnant as verified by a standard urine test taken prior to each experiment. A written informed consent was obtained from each subject prior to participation in the study.

Protocol Design

Following entry to the laboratory and their clinical assessment for participation, subjects assumed a supine position for at least 30 min prior to the initiation of the LNBP protocol in an effort to assure a minimal level of anxiety as reflected by normal blood pressures and heart rates. Subjects underwent a progressive stepwise LBNP protocol to induce hypovolemia until they demonstrated characteristics of presyncope, which was verified by a drop in mean blood pressure <80 mmHg with various combinations of symptoms such as nausea, sweating, dizziness, or loss of peripheral vision. The LBNP protocol began with a 5-min baseline period (0 mmHg LBNP), followed by 5 min with chamber pressures set at −15, −30, −45, and −60 mmHg, with additional decreases of −10 mmHg every 5 min until either the onset of hemodynamic decompensation or the completion of 5 min at −100 mmHg, at which time the chamber vacuum was immediately released to ambient pressure, resulting in the return to baseline physiological status as a result of rapid restoration of the central circulation. An ACLS-certified caregiver was present in the laboratory during all LBNP experiments to assure subject safety. Time to presyncope was measured in seconds from start of baseline to termination of LBNP.

Measurement of Hemodynamics

Noninvasive hemodynamic measurements were recorded at baseline and at the point of presyncope. Heart rate was measured from a standard lead-II electrocardiogram. Beat-to-beat systolic and diastolic blood pressures were measured noninvasively using an infrared finger photoplethysmograph (Finometer® Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). The Finometer® blood pressure cuff was placed on the middle finger of the left hand, which was

Table I. Demographics and Baseline Hemodynamics and Compensatory Reserve for Subjects in Each Phase of the Menstrual Cycle.

	MENSTRUAL CYCLE PHASE					
	EF	LF	EL	ML	LL	*P*-VALUE
Age (yr)	27 ± 5	27 ± 6	22 ± 3	26 ± 4	23 ± 2	0.26
Weight (kg)	64 ± 6	72 ± 12	62 ± 6	63 ± 6	58 ± 5	0.10
Height (cm)	161 ± 7	167 ± 7	166 ± 4	164 ± 5	165 ± 5	0.76
Mean arterial pressure, mmHg	94 ± 6	92 ± 7	91 ± 9	90 ± 5	91 ± 5	0.92
Systolic arterial pressure, mmHg	130 ± 8	125 ± 12	126 ± 12	122 ± 7	127 ± 7	0.70
Diastolic arterial pressure, mmHg	75 ± 6	75 ± 6	73 ± 9	72 ± 5	73 ± 5	0.96
Heart rate, bpm	68 ± 6	68 ± 9	69 ± 5	71 ± 8	72 ± 8	0.89
Stroke volume, mL	88 ± 11	93 ± 15	81 ± 14	86 ± 7	85 ± 8	0.69
Cardiac Output, mL · min^{-1}	6.0 ± 0.4	6.0 ± 0.8	6.0 ± 0.8	6.0 ± 1.0	6.0 ± 1.0	0.75
Pulse pressure, mmHg	56 ± 5	50 ± 9	52 ± 7	50 ± 6	54 ± 5	0.55
Total peripheral resistance	18 ± 2	15 ± 2	18 ± 3	16 ± 2	16 ± 2	0.47
Compensatory reserve	95 ± 2	92 ± 4	95 ± 2	93 ± 4	89 ± 4	0.16

Values are means ± 95% CI. EF, early follicular; LF, late follicular and ovulatory; EL, early luteal (EL); ML, midluteal; LL, late luteal.

laid at heart level. Accurate estimates of directly measured intra-arterial pressures during various physiological maneuvers have been demonstrated with this device.[26] Mean arterial pressure was calculated by dividing the sum of systolic blood pressure and twice diastolic blood pressure by three. Using the arterial pressure waveform as input, stroke volume was estimated on a beat-by-beat basis using the pulse contour method.[19] Cardiac output was calculated by multiplying heart rate and stroke volume, and total peripheral resistance was calculated by dividing mean arterial pressure by cardiac outpust.

Hemodynamic data were sampled at 500 Hz and recorded directly to data acquisition software (WINDAQ, Dataq Instruments, Akron, OH). Data analysis was subsequently accomplished using commercially-available software (WinCPRS, Absolute Aliens, Turku, Finland).

Compensatory Reserve Measurement

Noninvasive compensatory reserve measures were recorded during LBNP at baseline and at the point of presyncope as previously detailed and validated.[9,17,18] Arterial waveforms were collected in real time from a Finometer blood pressure cuff and processed using an algorithm which uses feature-extraction of the entire waveform with machine-learning techniques. The algorithm estimates the remaining physiological reserve available to compensate for changes in effective circulating blood volume by comparing waveforms over a 30-heartbeat window to an extensive database of reference waveforms used to create the algorithm. This estimate of the remaining physiological reserve is represented by a 0–100% value, where 100% reflects the maximum capacity of all physiological mechanisms (baroreflexes, respiration) to compensate for reduced central blood volume and 0% implies the depletion of compensatory reserve mechanisms and imminent cardiovascular instability or collapse (presyncope). The estimated compensatory reserve value corresponds to the compensatory reserve value of the most similar reference waveform in the training set. This technique has consistently produced area under the curve receiver operator characteristic values ≥0.90 for sensitivity and specificity of predicting LBNP tolerance.[17,18,29]

Data Analysis

All data are presented as means ± 95% confidence interval (95% CI). Comparisons of all variables between the groups were assessed using one-way analysis of variance followed by Tukey post hoc tests. Paired *t*-tests were used to compare hemodynamic and compensatory reserve values between baseline and presyncope time points for each phase. Data were analyzed using the Graphpad Prism 7 software for Windows (GraphPad Software, Inc., La Jolla, CA). The probability that any differences between menstrual cycle phase groups were not due to chance was expressed as exact *P*-values.

RESULTS

Subjects were similar in age, weight, and height between menstrual cycle phase groups (Table I). Additionally, there were no discernable differences in the hemodynamic responses at baseline ($P \geq 0.16$; Table I) or at the time of presyncope ($P \geq 0.16$; **Table II**) between menstrual cycle phase groups. **Fig. 1** displays the results in box plot format showing the median and individual data points for the time to presyncope (panel A; seconds), absolute change in compensatory reserve (panel B; %Δ), and rate of change in compensatory reserve (panel C; %Δ · s^{-1}). Average times to presyncope for EF (1586 ± 176 s), LF (1449 ± 116 s), EL (1428 ± 144 s), ML (1583 ± 204 s) and LL (1452 ± 106 s) were indistinguishable between menstrual cycle phase groups, with large individual variability ($P = 0.462$). Likewise, average absolute (%Δ) and rate of change (%Δ · s^{-1}) in compensatory reserve from baseline to presyncope were statistically similar (Table II).

DISCUSSION

While numerous investigations have revealed an effect of changing menstrual cycle hormones on specific mechanisms associated with blood pressure regulation,[1,3,5] there is evidence that these hormonal influences do not translate to a lower tolerance to reduced central blood volume.[6] In an attempt to bridge this knowledge gap, the present retrospective cross-sectional analysis of data collected from 40 women is the first designed to investigate the compensatory reserve as it relates to tolerance to central hypovolemia across five phases of the menstrual cycle. In the presence of well-documented alterations in estrogen that have been associated with blood pressure controlling mechanisms,[1,27,31] we hypothesized that if tolerance to central hypovolemia was not influenced during various phases of the

Table II. Hemodynamics and Compensatory Reserve at Presyncope for Subjects in Each Phase of the Menstrual Cycle.

	MENSTRUAL CYCLE PHASE					
	EF	**LF**	**EL**	**ML**	**LL**	***P*-VALUE**
Mean arterial pressure, mmHg	77 ± 8	83 ± 8	73 ± 6	76 ± 5	79 ± 6	0.55
Systolic arterial pressure, mmHg	96 ± 8	100 ± 11	93 ± 7	95 ± 8	100 ± 7	0.70
Diastolic arterial pressure, mmHg	67 ± 8	74 ± 8	63 ± 6	68 ± 5	68 ± 5	0.46
Heart rate, bpm	118 ± 13	107 ± 22	110 ± 8	119 ± 14	112 ± 10	0.73
Stroke volume, mL	36 ± 5	39 ± 13	39 ± 4	39 ± 4	42 ± 5	0.69
Cardiac Output, mL · min^{-1}	4.0 ± 0.6	4.0 ± 0.8	4.0 ± 0.6	5.0 ± 0.6	5.0 ± 0.7	0.39
Pulse pressure, mmHg	29 ± 3	27 ± 9	29 ± 3	27 ± 5	31 ± 3	0.67
Total peripheral resistance	20 ± 3	24 ± 7	18 ± 3	17 ± 3	18 ± 2	0.16
Compensatory reserve, %	14 ± 9	13 ± 8	12 ± 4	11 ± 6	11 ± 3	0.98
Absolute change in Compensatory Reserve, % **Δ**	−81 ± 1	−79 ± 2	−83 ± 2	−82 ± 1	−78 ± 1	0.85
Rate of change Compensatory Reserve, %**Δ** · s^{-1}	0.052 ± 0.007	0.054 ± 0.007	0.059 ± 0.011	0.053 ± 0.016	0.055 ± 0.007	0.79

Values are means ± 95% CI. EF, early follicular; LF, late follicular and ovulatory; EL, early luteal (EL); ML, midluteal; LL, late luteal.

menstrual cycle,[6] then maximal changes in compensatory reserve would be similar across all menstrual cycle phases. To test our hypothesis, the change in compensatory reserve was measured during a progressive LBNP protocol designed to systematically and safely induce a presyncopal endpoint in all our female subjects who represented all phases of the menstrual cycle. Our results corroborate earlier findings that phase of the menstrual cycle does not affect tolerance to central hypovolemia,[6] but extend our understanding to five rather than three menstrual phases and are the first to support the notion that the total integration of all compensatory mechanisms is also not influenced by the menstrual cycle. Consistent with this interpretation, we also found no differences in hemodynamic responses at baseline and presyncope. Our findings are also consistent with previous observations that heart rate and blood pressure responses were not correlated to or influenced by changes in estrogen during the EF and ML phases.[3]

In the present study, we investigated for the first time the menstrual cycle effect on the total integrated physiological capacity to compensate for central hypovolemia. Compensatory reserve is gradually reduced during progressive reductions in central blood volume as the capacity of various compensatory mechanisms (e.g., tachycardia, vasoconstriction, respiration) is reduced. Consistent with previous observations,[9,10,18] we observed reductions in compensatory reserve from 90–95% at baseline to 11–14% at presyncope independent of the menstrual cycle phase. Using this measurement as an indicator of impending physiological collapse, we observed no difference in maximal compensatory response across menstrual cycle phases, consistent with the absence of differences in tolerance to central hypovolemia. These results corroborate the validity of compensatory reserve as a highly sensitive and specific predictor of time to presyncope in individuals.[17,18,29]

In an effort to identify the effects of the menstrual cycle on mechanisms that might be associated with tolerance to central hypovolemia in women, numerous previous investigations have focused on comparing the effects of various conditions of central hypovolemia on the early follicular phase (low hormones) with the midluteal phase (high hormones),[1,3,21] or comparing women on oral contraceptives during the low and high hormone phases.[15,27,30] Although results from these studies have yielded conflicting information about the impact of the menstrual cycle on central hypovolemia, some have revealed that elevated estrogen can be associated with increased SNA,[1,13,30] the transduction of SNA into elevated blood pressure,[1,13] less vasoconstriction,[5,31] and baroreflex-mediated heart rate elevations.[31] On the other hand, others have shown no difference in SNA response between low (EF) and high (ML) hormone phases.[3,21] It is therefore noteworthy that the interindividual variability in responses to different phases of the menstrual cycle reported across numerous studies were not reflected in differences in tolerance to central hypovolemia in our female subjects. To the contrary, despite well-documented fluctuations in menstrual cycle hormones associated with alterations in blood pressure, volumes and flows,[13,28,30] our results suggest that any influence of changes in menstrual hormones on blood pressure regulation are too negligible to impact the overall integration of compensatory mechanisms (i.e., the compensatory reserve) during central hypovolemia. Our findings are consistent with previously published observations that there exists variability and uniqueness in individual human physiological strategies designed to compensate for progressive reductions in central blood volume.[2] The data of the present investigation also confirm that the sum total of these integrated strategies is accurately reflected by measures of the compensatory reserve, which was also unaltered by the menstrual cycle.

Our investigation is not without limitation. As a result of the retrospective nature of our study, we did not have blood samples from our subjects to verify menstrual hormone levels. As such, we relied on self-reported record-keeping of our subjects as commonly used by other investigators[15,28,32] to assess their classification into the five phases of the menstrual cycle. However, the statistical outcomes and individual overlap in LBNP tolerance across menstrual cycle phases (Fig. 1) in the present study make it unlikely that our interpretation is incorrect that menstrual cycle does not influence tolerance to central hypovolemia. Our interpretation is also validated by the absence of menstrual cycle influence on similar compensatory reserve values and hemodynamic responses at the point of presyncope. Although our experimental approach was limited to cross-sectional comparisons of independent subject groups, it corroborates similar findings from a longitudinal study that verified menstrual cycle phase

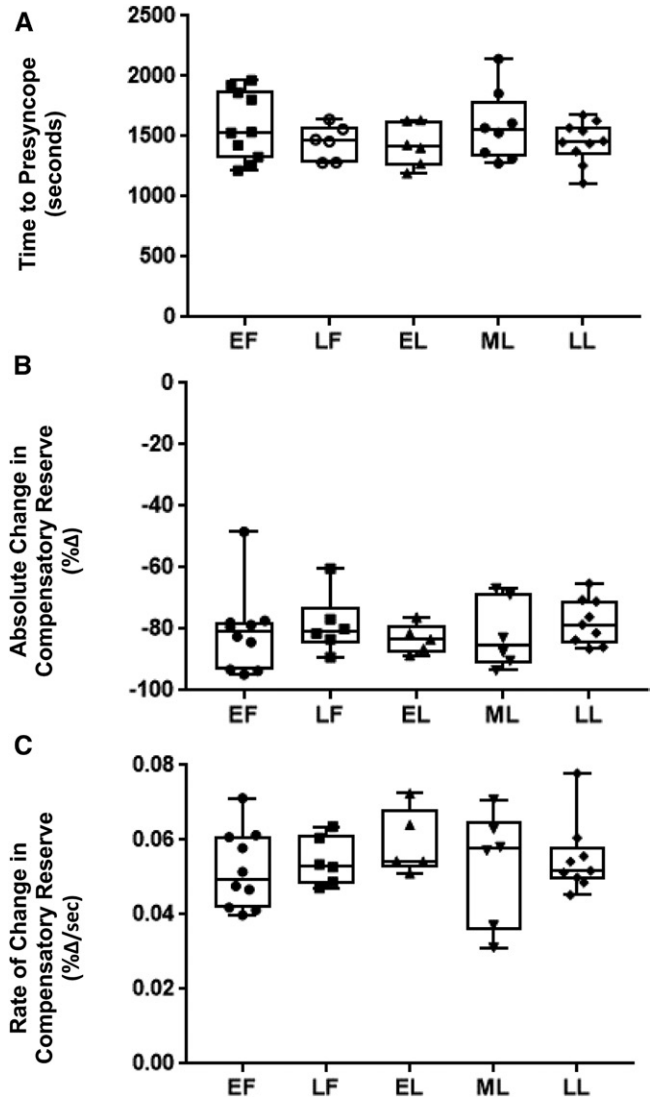

Fig. 1. Box plot comparisons of A) the time to presyncope, B) change in compensatory reserve, and C) rate of change in compensatory reserve in the early follicular (EF), late follicular, and ovulatory (LF), early luteal (EL), midluteal (ML), and late luteal (LL) phases of the menstrual cycle ($P \geq 0.462$ for all comparisons).

with direct hormone measurements.[6] Further, our approach not to conduct a prospective study with LBNP tolerance tests on repeated comparisons in the same subjects avoided the possibility that any differences observed in tolerance across menstrual cycle phases might be the result of a physiological training effect.[23] Finally, the exclusion of women using oral contraceptives and postmenopausal women strengthens our specific design and conclusions, but limits the generalizability of our findings to a narrow subset of healthy young women who are not taking contraceptives and do not have other clinical complexities (e.g., various medications, pregnancy, postmenopausal, postpartum, birth control, abnormal hemoglobin). The 'bridge' needed to allow for application of measuring the compensatory reserve to a more general female population during low circulating blood volume states will be accomplished in time with data collected in civilian prehospital and emergency department settings on various women in various states of physiology and pathophysiology, and comparison of such data with survival outcomes in men. Because the machine-learning technology developed to measure the compensatory reserve allows the monitor to recognize patient status based on changing features of hundreds of thousands of arterial waveforms that occur with central hypovolemia (e.g., hemorrhage, orthostatic challenge), we hypothesize accurate assessment of an individual patient independent of the patient's clinical condition.

Confusion regarding the impact of the menstrual cycle on female tolerance to central hypovolemia has been perpetuated by investigations that have been designed to compare effects of high and low hormones (e.g., estrogen) on mechanisms associated with blood pressure regulation.[15,27,30] Although insightful for understanding the variability of female menstrual cycle physiology, the trajectory of results from such investigations are limited because of the failure to incorporate measures of tolerance and integrated compensatory mechanisms. Due to the complex nature of changes and effects of menstrual cycle hormones, previous investigations of physiological responses to central hypovolemia have been mostly limited to participation of women during their early follicular phase when hormones are low.[14,20,33] The findings of the present investigation are scientifically relevant and unique because they provide evidence for the first time that recruitment and participation of female subjects in experiments designed to identify mechanisms underlying blood pressure regulation need not be limited since total integrated compensatory response associated with tolerance to central hypovolemia is not affected by menstrual cycle phase. As such, our results are consistent with the notion that the most sensitive and specific physiological assessment of tolerance status in conditions of central hypovolemia is the measurement of compensatory reserve. Operationally, the results of the present investigation support the notion that readiness and performance of women for combat operations (e.g., hemorrhagic injuries, dehydration, hyperthermia, altitude) or execution of tasks in aerospace environments (e.g., orthostatic hypotension after spaceflight, high G acceleration in high performance aircraft) that may be affected by low circulating blood volume will not be influenced by the menstrual cycle.

Our findings suggest that any physiological variations across the menstrual cycle are not significant enough to impact the overall integrated compensatory response, and subsequently tolerance, to central hypovolemia. This interpretation is substantiated by similar responses of the compensatory reserve and hemodynamic responses across all menstrual phases in our subjects. As such, the results of the present investigation suggest that experimental comparisons of responses to central hypovolemia involving the participation of women with normal menstrual cycles can be conducted independent of menstrual cycle phase.

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