Fluid Loading Effects on Temporal Profiles of Cardiovascular Responses to Head-Down Tilt

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BACKGROUND: Susceptibility of healthy astronauts to orthostatic hypotension and presyncope is exacerbated upon return from spaceflight. Up to 64% of astronauts experience postflight orthostatic intolerance. A promising countermeasure for postflight orthostatic intolerance is fluid loading by giving crew salt tablets and water prior to re-entry. The primary goal of the current study was to determine the optimal time window prior to re-entry when individual crewpersons would initiate fluid loading.

METHODS: There were 16 subjects who were given two 6-h exposures, with and without fluid loading (conditions), to head-down tilt (HDT) to simulate the effects of microgravity. Pre- and post-HDT stand tests of orthostatic tolerance were given. Physiological measurements recorded included heart rate, blood pressure, peripheral blood volume, total peripheral resistance, and impedance cardiography. Echocardiography measures of stroke volume and cardiac output were also recorded.

RESULTS: Data were analyzed with three-way repeated measures ANOVA (gender × condition × time). Only the condition × time interaction was significant for mean arterial pressure. Post hoc multiple comparison tests revealed significant increases in mean arterial pressure occurred between hours 1 and 3 of HDT after fluid loading (10 mmHg higher than no fluid).

DISCUSSION: These findings indicate that the optimal time for crew to begin fluid loading is within 1 to 3 h prior to re-entry. Nonsignificant trends of multiple cardiovascular responses showed similar time profiles. The large amount of individual variability suggests that fluid loading alone may be an inadequate countermeasure for all crewmembers. Further research is needed on possible adjunct methods of tailoring countermeasures for individuals.

KEYWORDS: orthostatic intolerance, autonomic responses, simulated microgravity.

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NASA's Human Research Program has identified several risks related to crew health and safety during extended duration spaceflight. Further, the program has identified important gaps in our knowledge on the effectiveness of specific countermeasures for mitigating these risks.[7,11] Specifically, there is a risk of orthostatic intolerance during re-exposure to gravity and a knowledge gap (CV3): is orthostatic intolerance a potential hazard for International Space Station and other long-duration missions? Buckey et al.[2] reported that up to 64% of astronauts experience postflight orthostatic hypotension. Meck et al.[12] found that 14-d flights resulted in 20% of astronauts experiencing presyncope, whereas the rate rises to 83% following longer duration missions (129-190 d). Hypovolemia is suspected to play an important role in cardiovascular deconditioning following exposure to spaceflight, which may lead to increased peripheral resistance, attenuated arterial baroreflex, and changes in cardiac function. A promising countermeasure for postflight orthostatic intolerance is fluid loading, used to restore lost plasma volume by giving crew salt tablets and water prior to re-entry. Ground-based countermeasure tests use six-degree head-down bed rest as an analogue to spaceflight because it removes the gravity vector directed from the head to the feet and induces a similar cephalad fluid shift as seen in spaceflight.[4,8,14]

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To counteract orthostatic hypotension during re-exposure to gravitational stress following spaceflight, astronauts ingest salt tablets and drink water to expand the extracellular fluid volume.[13] This is done shortly before re-entry into the atmosphere. To insure that the fluid load is isotonic with the extracellular fluid, portions of approximately 9 g of salt combined with about 1 L of water are administered. This procedure was originally developed by Bungo et al.,[3] who showed that it improved postflight orthostatic tolerance in astronauts after shuttle flights by damping the increase in heart rate during a stand test. The fluid loading procedure combined with other countermeasures such as an antigravity garment immediately after landing have had a positive effect in mitigating postflight orthostatic intolerance. The mechanism of the fluid load is thought to be an expansion of extracellular fluid volume and thus plasma volume, thereby increasing cardiac preload and stroke volume.[6,9] What is not known, however, is the temporal profile and magnitude of the fluid load induced increase in plasma volume and cardiac preload, and whether the uptake of ingested salt and water occurs in equal proportion so that the fluid volume expansion is isotonic with the extracellular fluid.

It is known that the effectiveness of these countermeasures can vary considerably across individuals and may not be effective following long-duration spaceflight.[7] Understanding individual variability in multiple physiological responses should be a priority for any countermeasure investigation. Several principles have been developed in the field of psychophysiology that help the investigator to interpret these data. The principle of "individual response stereotypy" reflects the observation that specific physiological parameters produce larger magnitude or more prolonged responses to stimuli in some individuals but not in others. A hierarchy of response levels can be generated to "profile" a given individual's most sensitive responses to stimuli.[5,10] The principle of "stimulus-response specificity" states that there are general classifications of responses to a given stimulus. For example, an exciting event produces a different class of responses (e.g., faster heart beat) than a boring event (e.g., drowsiness or slowing heart rate). This study used psychophysiological methods and principles in examining the effects of the fluid loading countermeasure for orthostatic intolerance.

The primary goal of the current study was to determine the optimal time window prior to re-entry when crew would begin the fluid loading protocol. Specific objectives were: 1) to define the temporal profile of cardiovascular responses to simulated microgravity: 6-h exposures to 6° head-down tilt (HDT); 2) to examine individual differences in cardiovascular and other physiological responses to HDT and the fluid loading countermeasure; and 3) to examine fluid loading effects on orthostatic intolerance and symptom mitigation following HDT.

METHODS

Subjects

Eight men and eight women, ages ranging between 21 and 56 (mean = 36.7), participated in this study. All subjects were recruited from the NASA Ames workforce (civil servants and contractors) and received no compensation for their participation. Exclusion criteria for this study were: 1) pregnant women, 2) unable to stand comfortably for 3 min, 3) history of fainting, 4) coronary heart disease, 5) uncontrolled hypertension, and 6) significant renal problems (e.g., kidney stones). Qualified subjects were briefed on all participation requirements as well as the anticipated risks and discomforts by the principal investigator and the NASA medical monitor before providing their voluntary consent. After reviewing medical records of candidate subjects the NASA medical monitor determined if they were healthy enough to participate. Each participant signed a study consent form approved by the NASA Ames Human Research Institutional Review Board.

Apparatus

Physiological measures 1-6 listed below were recorded with a Flexcomp data encoder (Thought Technology, Inc., Montreal, Quebec, Canada), a portable, battery-operated commercial instrument. Blood pressure was measured beat-to-beat with an inflatable cuff on the finger (Finapres, Inc., Amsterdam, The Netherlands), and measures of cardiac function were obtained with both an impedance cardiograph instrument (HIC–2000, Bioimpedance Technology, Inc., Chapel Hill, NC) and an echocardiograph system (Biosound MyLab Alpha, Esaote North America, Indianapolis, IN).

1) Electrocardiography: measured with three disposable electrodes at precordial locations.
2) Respiration rate: obtained with a strain gauge wrapped around the upper chest.
3) Finger pulse volume: infrared plethysmograph transducers were attached to the index fingers of both hands and on the second toe of each foot to measure relative changes in peripheral vasomotor activity.
4) Skin temperature: a thermistor was taped on the small finger of the right hand.
5) Skin conductance: electrodes attached to the distal phalanges of the middle and ring fingers on the left hand provided noninvasive measures of sympathetic nervous system activity.
6) Electromyography: electrodes were applied to the left and right forearm extensor muscles and gastrocnemius muscles of the leg.
7) Blood pressure: an inflatable cuff and an infrared plethysmograph placed on the middle finger of the right hand provided beat-to-beat measures of systolic and diastolic blood pressure. A manual cuff placed over the brachial artery was

Table I. NASA Standard Fluid Loading Protocol for Flight Crew.

PARTICIPANT WEIGHT (kg)	QUANTITY OF WATER (L)	NUMBER OF SALT TABLETS (1 g)
<54.43	0.71	6
54.43-70.31	0.95	8
70.31-86.18	1.18	10
>86.18	1.42	12

Table II. Water and Salt Tablets Consumed and Volume of Urine Voided by Each Participant During 6-h HDT Tests.

				HDT - NO FLUID LOADING		HDT - FLUID LOADING		
I.D.	GENDER	AGE	WGT. (kg)	WATER INGESTED (ml)	VOL. URINE VOIDED (ml)	WATER INGESTED (ml)	SALT (g)	VOL. URINE VOIDED (ml)
Y02	M	43	77	0	0	1185	10	750
Y03	M	54	61	0	0	948	8	800
Y05	M	56	75	0	0	1185	10	355
Y09	M	54	87	0	590	1422	12	1840
Y10	M	24	83	120	0	1185	10	1700
Y12	M	35	94	237	0	1422	12	750
Y14	M	21	74	237	690	1185	10	865
Y17	M	29	78	573	0	1185	10	520
Y01	F	23	73	0	0	1185	10	0
Y04	F	31	59	30	0	948	8	0
Y06	F	54	68	15	0	948	8	0
Y07	F	28	68	325	0	948	8	490
Y08	F	38	59	503	0	948	8	0
Y13	F	50	51	0	-	711	6	450
Y15	F	22	87	117	0	1422	12	0
Y16	F	25	53	0	0	711	6	547

used to calibrate the finger cuff. The right hand with the finger cuff was placed at heart level during HDT and stand tests. The instrument was programmed to deflate the finger cuff for 60 s every 20 min during HDT to relieve finger discomfort.

8) Impedance cardiography: two pairs of electrodes placed on the lateral sides of the neck (at the level of the lower jaw) and thorax (at the xyphoid process) measured changes in electrical impedance as a function of the amount of fluid in the thoracic segment. Thoracic impedance was used to calculate measures of stroke volume and cardiac output using the Kubicek and Sramek equations.[1]
9) Echocardiography: an ultrasound transducer was used to image two-dimensional slices of the heart and provide measures of cardiac function, e.g., stroke volume, cardiac output, and ejection fraction.

Procedures

Subjects were instructed to limit their dietary intake of salt to 2300 mg per day for 3 d before each test day. They reported to the laboratory at 0800 on test days, and electrodes and transducers were attached to the chest, arms, and legs. Urine samples were collected to measure sodium intake levels before and after each HDT test. During HDT tests men wore external latex catheters and women wore disposable diapers for urine collection and were not permitted to use the rest room during testing. The volume of urine voided by each participant during and after HDT was measured.

Subjects were given two 6-h exposures to 6° HDT; one test with fluid loading and a second test without fluid loading. Each test was separated by 7 d and the order of the tests was counterbalanced. On each test day physiological measurements were collected continuously during the following conditions: 10 min sitting, 3 min standing (orthostatic challenge), 6 h HDT, and 3 min standing. Physiological data were edited off-line to remove movement artifacts and interruptions in blood pressure measurements (60-s rest periods) when the finger cuff was deflated. Physiological data collected during HDT tests were reduced to 30-min means and data collected during stand test data were reduced to 3-min means for subsequent analyses.

Echocardiography measurements were recorded for 30-s periods during pretest sitting, during stand tests, and at 30-min intervals during HDT tests. These data were manually processed and 30-s means were calculated for stroke volume and cardiac output. The standard fluid loading protocol[13] used with astronauts consisted of salt tablets and water where quantities of each were determined by bodyweight as shown in **Table I**. On test days when the countermeasure was given, subjects were asked to begin fluid loading immediately after HDT and to consume the required quantity within 1 h.

Table III. Symptoms Reported by Subjects During Post-HDT Stand-Tests.

I.D.	GENDER	NO FLUID LOADING	FLUID LOADING
Y02	M	none	none
Y03	M	light-headed	light-headed
Y05	M	light-headed	light-headed
Y09	M	none	none
Y10	M	none	none
Y12	M	none	none
Y14	M	light-headed	light-headed
Y17	M	none	none
Y01	F	syncope	light-headed
Y04	F	light-headed	none
Y06	F	light-headed	none
Y07	F	none	none
Y08	F	none	light-headed
Y13	F	presyncope	none
Y15	F	light-headed	light-headed
Y16	F	light-headed	none

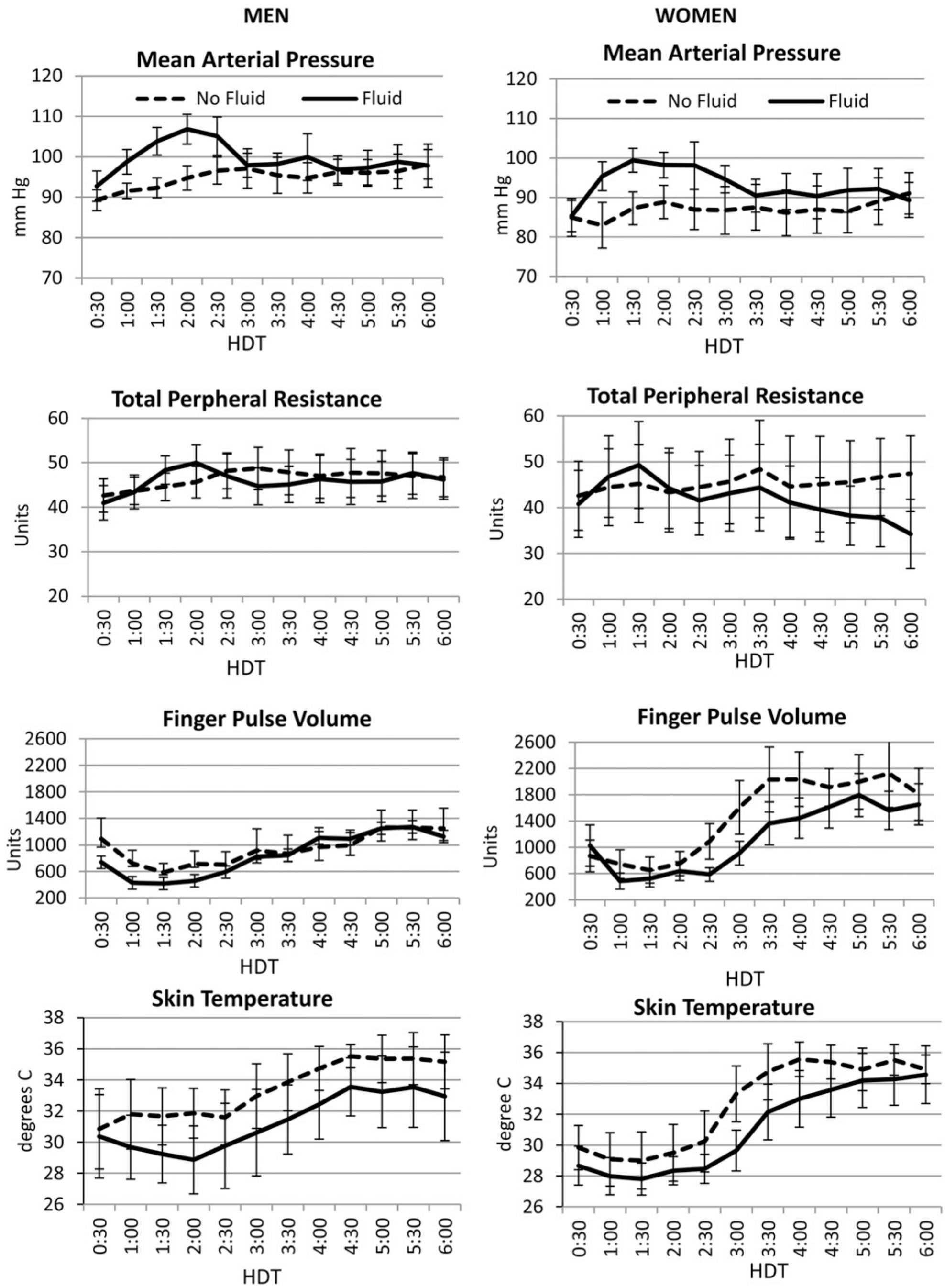

Fig. 1. Physiological data in 30-min means during 6 h of HDT.

Statistical Analysis

A three-way repeated measures ANOVA was used for analyzing physiological measurements collected during HDT tests with gender as a between subject factor, and condition (no fluid HDT and fluid HDT) and time (30-min increments during HDT) as within subject factors. Physiological measurements collected during stand tests were also analyzed with three-way repeated measures ANOVA: gender × condition (no fluid HDT and fluid HDT) × stand (pre-HDT and post-HDT). Probability levels for *F* tests were adjusted using the Geisser-Greenhouse epsilon. Significant interactions were further examined with the Tukey-Kramer multiple comparisons test. Statistical significance was set at $P < 0.05$.

RESULTS

Table II shows quantities of water (ml) and number of 1-g salt tablets consumed by each participant during HDT tests. On test days with no fluid loading 9 of 16 subjects requested water and only 2 subjects voided during HDT. On test days when fluid loading was given, all eight men voided and three women voided during HDT. All subjects reported some bladder discomfort during HDT and most had difficulty urinating while supine.

On the no-fluid HDT test day mean sodium intake for men was 118 mmol (pre) and 117 mmol (post), and on the fluid loading HDT test day sodium intake was 100 mmol (pre) and 130 mmol (post). Mean sodium intake for women on the no fluid HDT test day was 78 mmol (pre) and 79 mmol (post), and on the fluid loading HDT test day sodium levels were 53 mmol (pre) and 87 mmol (post). All sodium intake levels were below the daily average for adult Americans of 150 mmol.

Table III lists the symptoms reported by all subjects during post-HDT stand tests. Only one woman (Y01) experienced syncope following no fluid HDT and reported light-headiness following fluid loading HDT. Another woman (Y13) experienced presyncope following no fluid HDT and reported no symptoms after fluid loading HDT. Eight subjects reported feeling light headed on one or both stand tests and six subjects reported no symptoms on either test. These data suggest that a 6-h exposure to HDT was not adequate for reliably inducing orthostatic intolerance.

Physiological Measurements (30-min Means)

There were no significant gender effects for any of the measurements. The main effect of condition was significant for finger pulse

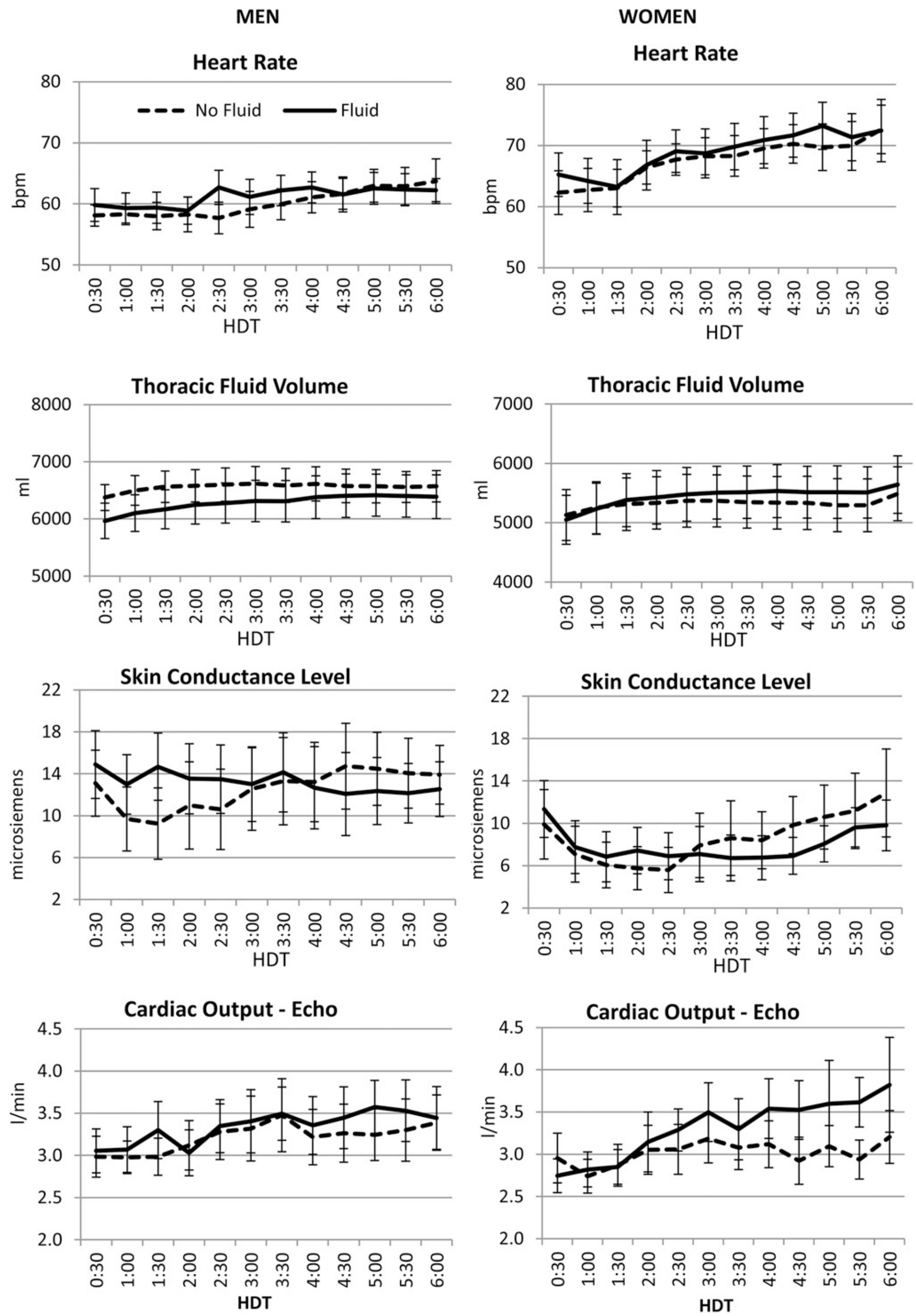

Fig. 2. Physiological data in 30-min means during 6 h of HDT. Cardiac output = 30 s.

volume and mean arterial pressure, and there was a significant time effect for all measurements. A significant two-way interaction, condition × time, was found for mean arterial pressure [$F_{(11,154)} = 4.81, P = 0.001$], skin conductance [$F_{(11,154)} = 4.96, P = 0.004$], thoracic fluid volume [$F_{(11,154)} = 11.0, P = 0.00002$], and total peripheral resistance [$F_{(11,154)} = 3.10, P = 0.02$]. Tukey-Kramer tests revealed significantly higher mean arterial pressures ($P < 0.05$) at 60, 90, 120, and 150 min following fluid loading HDT when compared to no fluid HDT. None of the other variables showed significant differences at these time-points.

Echocardiography Measurements (30-s Means)

The main effects of gender and condition were not significant for either stroke volume or cardiac output, while the time effect was significant only for cardiac output [$F_{(11,143)} = 8.52, P = 0.001$]. However, there were no significant two or three-way interactions for either measurement.

Fig. 1 and **Fig. 2** show the physiological responses (30-min means and SEMs) of men (left) and women (right) during 6-h exposures to HDT with and without fluid loading. Although there were no significant effects for the three-way interaction of gender × conditions × time, the graphs show physiological trends and how the measurements vary over time. In Fig. 1 mean arterial pressure increased during the first 3 h of HDT with fluid loading for both men and women. Total peripheral resistance increased only slightly during HDT fluid loading for both men and women. Right finger pulse volume and left finger skin temperature of men and women, both measures of peripheral blood flow, show vasoconstriction in the first 3 h of HDT when mean arterial pressure was high, which was followed by vasodilation as mean arterial pressure decreased. These changes in peripheral blood flow were compensatory responses to HDT, which is an example of stimulus-response stereotypy. The effect of fluid loading resulted in greater vasoconstriction as mean arterial pressure was even higher in this condition. The finger pulse volume of women was higher than men after 3 h of HDT.

Fig. 2 shows the trends for heart rate, thoracic fluid volume, skin conductance level, and cardiac output derived from echocardiography. Although not significant, women had higher heart rates than men for both conditions, and both men and women showed a gradual increase in heart rate during HDT. The effect of

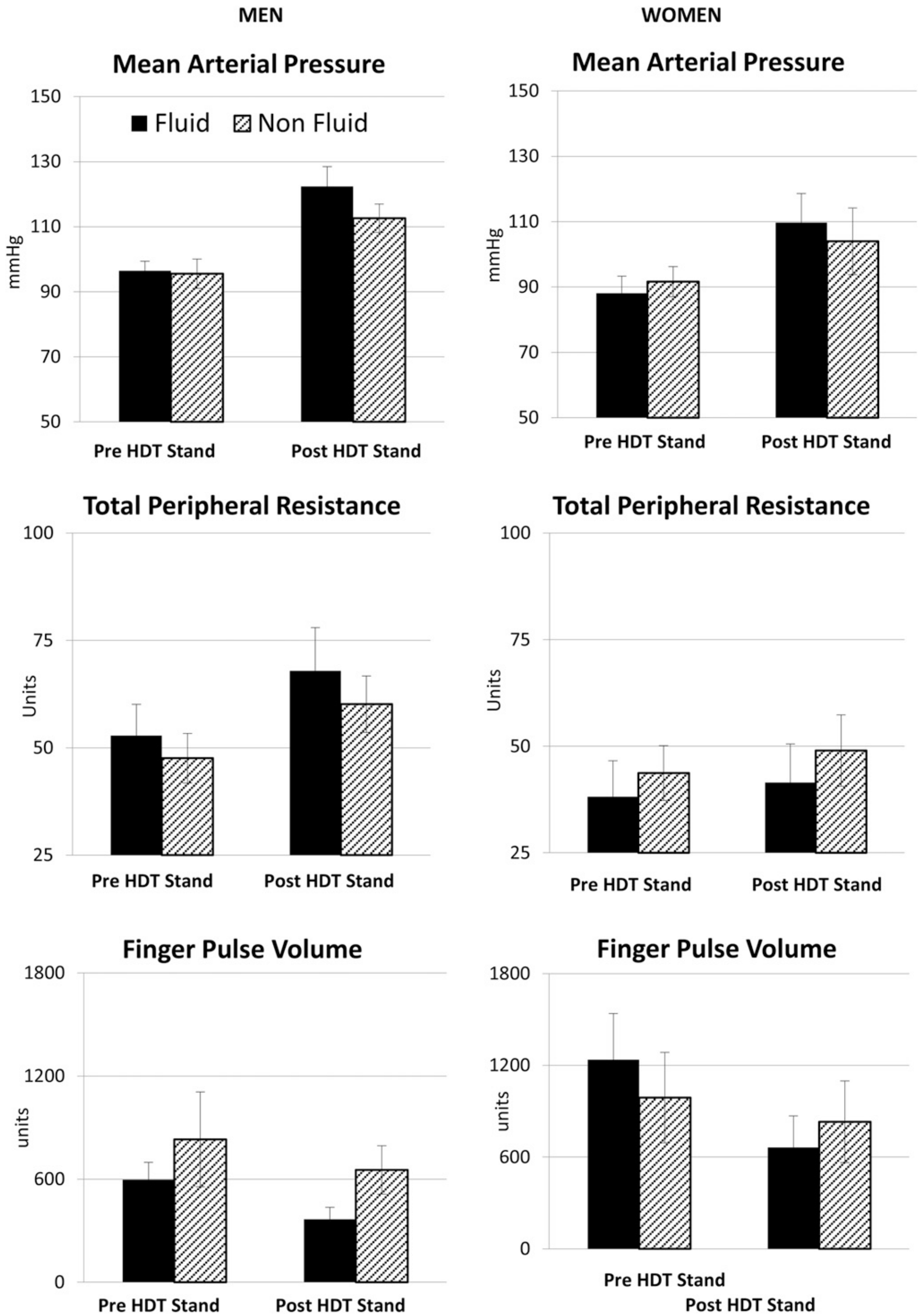

Fig. 3. Cardiovascular responses to pre-HDT stand tests and post-HDT stand tests (3-min. means). Note: no fluid was consumed prior to the pre-test of the fluid loading condition.

fluid loading condition for both men and women, which may have been related to reported increases in discomfort. During fluid loading men initially showed higher skin conductance (more discomfort) than women and, after 3 h, a gradual decrease to levels below that observed during the no fluid loading condition (men reported less discomfort after voiding). Women showed similar trends, but overall their skin conductance levels were lower. For both men and women small increases in cardiac output were observed after fluid loading between hours 1 and 3; however, during the remaining 3 h of HDT, cardiac output for women continued to increase while men showed a plateau for this response.

fluid loading produced small increases in heart rate for both men and women. Thoracic fluid volume, derived from impedance cardiography, was higher for women with fluid loading, while men produced the opposite response. One possible explanation for this observation is that five of eight women retained water after fluid loading (i.e., did not void), while all men voided after fluid loading. Skin conductance levels, an indicator of sympathetic nervous system activation, increased over time in the no

Stand Tests

The main effects of gender and condition were not significant for any of the measurements, while the main effect of stand (pre- vs. post-HDT) was significant for all measures except skin temperature, skin conductance, and stroke volume. There was no significant gender × stand interaction or three-way interaction for any of the measurements. The gender × condition interaction was significant for mean arterial pressure [$F_{(1, 13)} = 4.82$, $P = 0.04$], cardiac output measured with impedance cardiography [$F_{(1, 13)} = 5.12$, $P = 0.04$], and total peripheral resistance [$F_{(1, 13)} = 6.25$, $P = 0.004$] with men generally higher, although not significantly than women after fluid loading. The condition × stand interaction was only significant for mean arterial pressure [$F_{(1, 13)} = 6.88$, $P = 0.02$]. Tukey-Kramer tests for mean arterial pressure of all subjects revealed significant increases from pre- to post-stand tests for both conditions; however, there was no difference between the posttest following fluid loading and no fluid loading. **Fig. 3** and **Fig. 4** illustrate trends in men and women observed in pre- vs. post-stand tests for six measures.

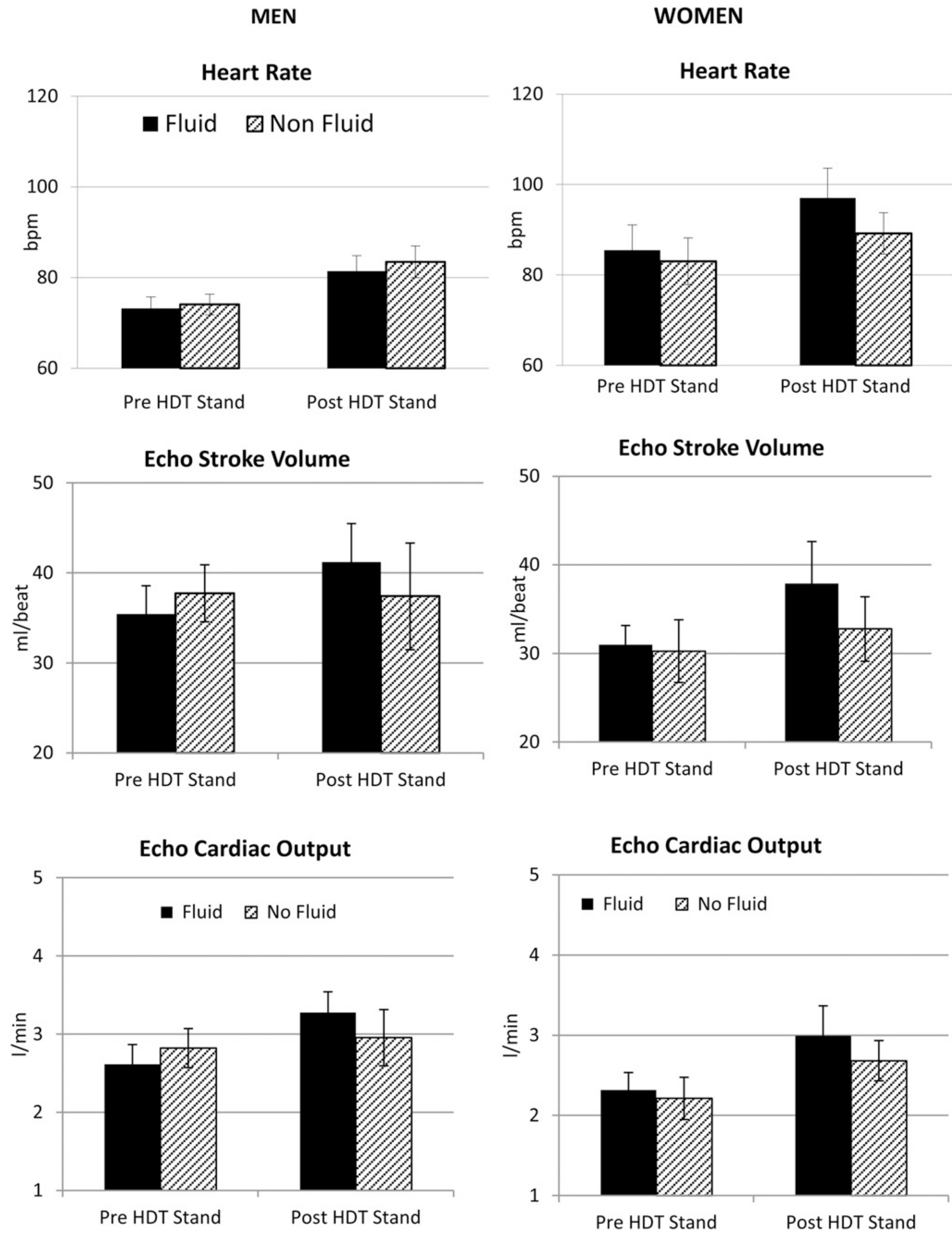

Fig. 4. Cardiovascular responses to pre-HDT stand tets and post-HDT stand tests (3-min means). Echocardiography measures are 30-s means. Note: no fluid was consumed prior to the pre-test of the fluid loading condition.

Individual Response Profiles

Because the analyses of these data indicated that there remained a great deal of individual variability for both fluid and nonfluid loading tests, how might these observed differences point to an optimal treatment for any given individual? **Fig. 5** shows physiological data (3-min means) of subject Y01, who experienced syncope after the nonfluid loading HDT and reported feeling light headed following the fluid loading test. Her data are compared to another woman, Y07, who was similar in age and weight, but reported no symptoms in either condition.

Y01 had a higher heart rate than Y07. Both showed the expected increase in mean arterial pressure following fluid loading, but Y01's increase was smaller and of shorter duration. Both women had comparable mean arterial pressures at the end of 6 h HDT in both conditions. They differed considerably when looking at peripheral circulation (i.e., skin temperature) responses to HDT and fluid loading. Although most subjects initially produced vasoconstriction during HDT (even more so after fluid loading) followed by vasodilation, Y01 did not. Lastly, the graphs of total peripheral resistance also show differences between the two subjects. In response to HDT only and HDT with fluid loading, Y07 showed increased total peripheral resistance when peripheral skin temperature reflected constriction, which corresponds in time to increases in blood pressure. Subject Y01, however, showed no distinctive response in either condition.

DISCUSSION

The primary contribution of this study to researchers investigating physiological responses to HDT, exposure to microgravity, and the effectiveness of countermeasures like fluid loading were the use of noninvasive methods for continuously monitoring several different parameters simultaneously. These real-time measurements allowed investigators to observe how these responses changed in relationship to each other. For example, the reliability of skin temperature of the hands and feet as a measurement of peripheral vascular changes can be validated by comparing it to plethysmography measures at the same sites and its relationship to total peripheral resistance. The advantage of skin temperature is that it is easier to measure and less subject to movement artifact than plethysmography. Unlike echocardiography, impedance cardiography provides a measure of thoracic fluid volume (as body position changes and as fluid loading occurs) and it can be used to

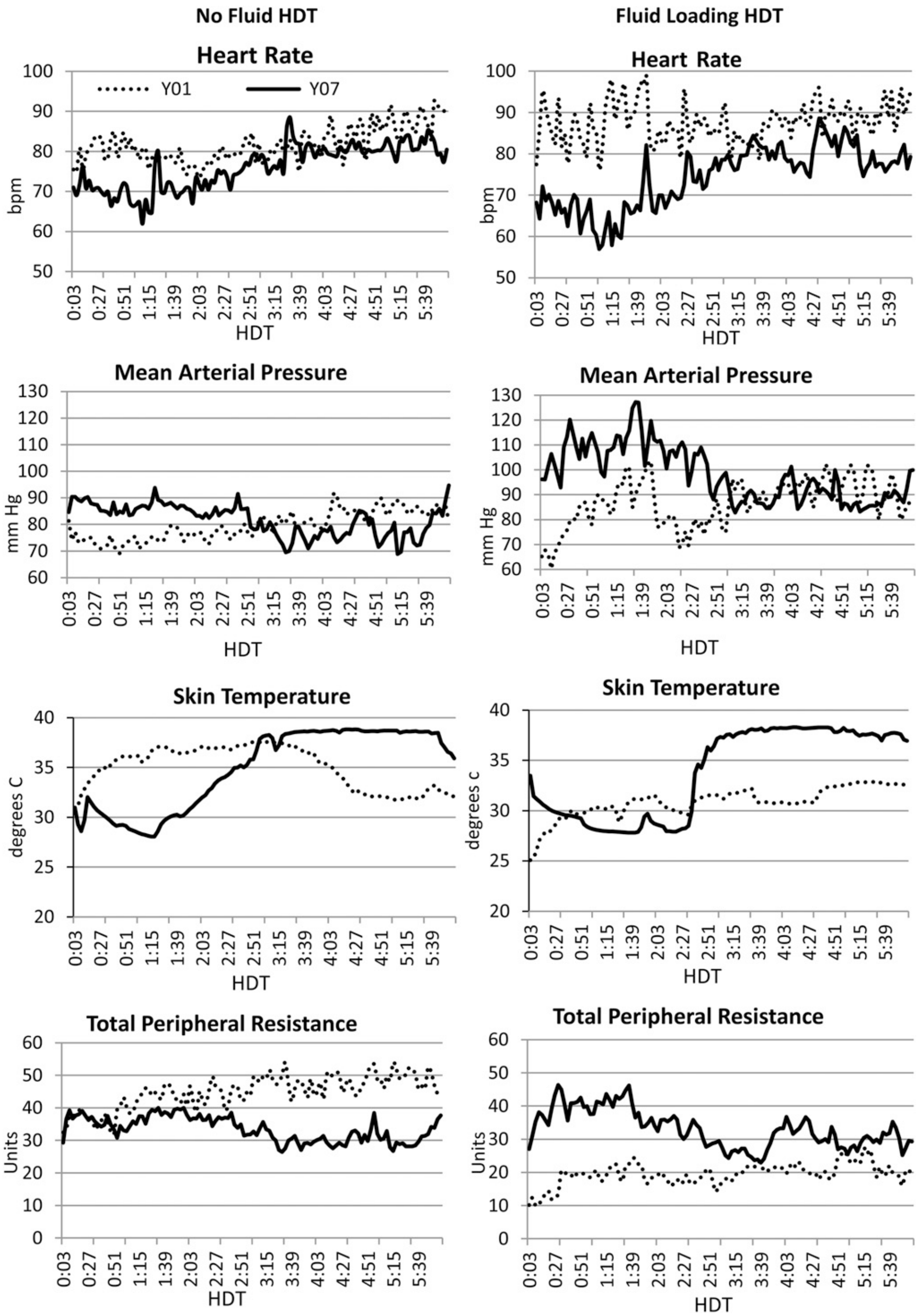

Fig. 5. Physiological responses (3-min means) of Y01—syncope after no fluid HDT and light headed after fluid loading—and Y07, who had no symptoms after either test.

calculate stroke volume beat-to-beat. Using stroke volume and heart rate, we can observe continuous changes in cardiac output. Mean arterial pressure measured beat-to-beat and cardiac output provide a continuous record of total peripheral resistance. By measuring skin conductance level and calculating an estimate of vagal tone (frequency analysis of heart rate variability, not shown), the investigator can assess both sympathetic and parasympathetic tone. This capability makes it easier for physicians and researchers to see individual differences in the time-course and magnitude of response changes and thereby enables more accurate diagnoses of a given individual's condition or countermeasure effectiveness.

This study showed in multiple physiological indicators that the peak effects are observed at 2 to 3 h after fluid loading in both men and women. This result indicates that crewmembers should use this countermeasure no more than 3 h before returning to Earth. Cardiac dynamics alone of stroke volume or cardiac output, whether derived from echocardiography or impedance cardiography, may not be the most sensitive indicators of countermeasure effectiveness. Continuous measurements of mean arterial pressure and peripheral blood flow should also be examined.

Clearly, 6 h of HDT was insufficient for producing cardiovascular deconditioning and hypervolemia leading to orthostatic intolerance as seen in longer HDT bed-rest studies or in long-duration spaceflight. Consequently, the adequacy of fluid loading as a countermeasure cannot be determined by this study. However, the large amount of individual variability suggests that fluid loading alone may be an inadequate countermeasure for all crewmembers and further research is needed on possible adjunct methods of tailoring countermeasures to suit the needs of the individual. A longer duration bed-rest study is recommended using the same monitoring techniques.

The use of operant conditioning to train individuals to both increase and decrease physiological response levels is referred to as "exercising smooth muscle." This approach should also be considered as an adjunct countermeasure. Once the best measures for a specific crewmember are determined, continuous monitoring would allow him or her to self-detect and correct off-nominal physiological responses while in space by adding "exercising of smooth muscles" to existing onboard exercise regimens. In a MIR flight experiment, one cosmonaut received preflight training to control blood pressure and other autonomic responses. During flight, he practiced self-regulation of his own responses for 15 min/d, one day per month on a 190-d mission and had no orthostatic intolerance after returning to Earth.[10]

The psychophysiological principle of "individual response stereotypy" states that that individuals vary in terms of which physiological measures are most sensitive in response to a stimulus. This accounts for the large amount of individual variability between subjects where Y01 was an extreme case. The principle of "stimulus-response specificity" exists if a stimulus brings about a similar pattern of physiological response among most subjects. This explains why most people responded to HDT and fluid loading in a similar manner. A possible explanation for the syncope in Y01 was that she lacked sufficient homeostatic control of peripheral circulation. If she had been given a vasoconstrictor medication along with fluid loading, she might not have experienced symptoms. Alternatively, training her to voluntarily control peripheral constriction and vasodilation[5,10] could have been applied when needed, with no side-effects caused by medications and may have been a more efficacious treatment.

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