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Original Article

Verification of exercise-induced transient postural tachycardia phenotype in Gulf War Illness

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Abstract: One third of Gulf War Illness (GWI) subjects in a recent study were found to develop transient postural tachycardia after submaximal exercise stress tests. Post-exercise postural tachycardia is a previously undescribed physiological finding. A new GWI cohort was studied to verify this novel finding and characterize this cardiovascular phenomenon. Subjects followed the same protocol as before. The change in heart rate between recumbent and standing postures (ΔHR) was measured before exercise, and after submaximal bicycle exercise. About one-fourth of the verification cohort (14/57) developed transient postural tachycardia after submaximal exercise. These subjects were the Stress Test Activated Reversible Tachycardia (START) phenotype. The largest change was observed between pre-exercise and time points 2 ± 1 (mean ± SD) hours post exercise (1st Peak Effect). Eleven subjects had Postural Tachycardia Syndrome (POTS) before and after exercise. The remaining subjects had normal ΔHR (12 ± 5 bpm) and no 1st Peak Effect, and were the Stress Test Originated Phantom Perception phenotype (STOPP). These findings indicate that about one-fourth of all Gulf War Illness study participants (24/90) developed transient postural tachycardia after the submaximal exercise stress test. The START phenotype was defined as being distinctly different from POTS. Additional studies are required to examine this phenomenon in other illnesses and to determine pathological mechanisms.

Keywords: Autonomic nervous system, exercise, postural tachycardia, chronic fatigue syndrome, Gulf War Illness

Introduction

Rayhan *et al* made the novel and unprecedented observation that exercise induced transient postural orthostatic tachycardia in one third of Gulf War Illness (GWI) study participants [1]. Prior to exercise, all control and GWI study participants had normal changes in heart rate (HR) when standing up from a recumbent position (12 ± 5 bpm, mean ± SD). However, after a submaximal exercise stress test, they developed transient orthostatic tachycardia with an increase in HR from recumbent to standing (ΔHR) of greater than 30 bpm at two or more time points. This subgroup was named the Stress Test Activated Reversible Tachycardia (START) phenotype. The remaining two thirds of GWI subjects maintained a normal ΔHR before and after exercise. This subset was named Stress Test Originated Phantom Perception (STOPP) phenotype because blood oxygen dependent level (BOLD) imaging during cognitive testing showed activation of basal ganglia and anterior insula that was not seen in control or START subjects [1].

The exercise-induced reversible tachycardia in START was distinctly different from Postural Tachycardia Syndrome (POTS). The consensus definition of POTS requires ΔHR ≥ 30 bpm at two or more time measurements and the absence of orthostatic hypotension (decrease ≥ 20 mmHg in systolic blood pressure) [2]. One healthy control veteran had asymptomatic POTS in the previous study and was excluded from those publication data.

Gulf War Illness has affected 25% to 32% of the 700,000 veterans who served in the Persian Gulf War from 1990-1991 [3-5]. Along with chronic fatigue, gastrointestinal complaints, total body pain, and cognitive impairment, a portion of GWI veterans were found to have altered heart rate variability due to blunted parasympathetic responses at night, measured by 24 hr Holter monitoring [6].

This replication study was conducted to 1) verify that a subset of GWI veterans would have no postural tachycardia before exercise and would develop transient postural tachycardia only after exercise (START), 2) detect POTS based on postural tachycardia before and after exercise (i.e., at every time point), and 3) determine the relationship between POTS and the START phenotype. We hypothesized that the START phenotype would be identified in one third of GWI subjects from the verification cohort (V). Data were compared to the original cohort (O).

Materials and methods

Ethics statement

The protocol was approved by the Georgetown University Institutional Review Board (IRB 2009-229, 2013-0943, and 2015-0579) and USAMRMC Human Research Protection Office (HRPO #A-15547 and A-18479), and listed in clinicaltrials.gov (NCT01291758 and NCT00-810225). Healthy and Gulf War Illness (GWI) veterans from the 1st Persian Gulf War, and healthy, non-military control subjects were recruited between 2009-2011 and 2015-2017 from websites, word of mouth, fliers, newspaper and online advertisements, and personal contacts in clinics and support groups.

Subjects

Interested participants responded via telephone or email. After obtaining verbal consent, each volunteer had an initial telephone screening with a clinical research associate who read a scripted outline of the study to assess inclusion and exclusion criteria. Candidates were screened for military service of at least 30 consecutive days between August 1, 1990 and July 31, 1991; service in the Gulf War Theater; Veterans Administration ratings of disabilities; Center for Disease Control criteria for GWI and Chronic Fatigue Syndrome (CFS) [7, 8]; current medications; chronic medical and psychiatric illnesses; and factors preventing functional magnetic resonance imaging (fMRI). After approval, subjects were asked to complete questionnaires using our online eZhengtricity data collection system [9-12]. GWI diagnosis was confirmed during history and physical on screening day by reporting moderate to severe scores in 3 out of 6 symptom domains of the Kansas criteria [4]. Exclusions included chronic medical illnesses that predated the onset of GWI symptoms or that could explain the full range of each individual's symptoms, and chronic psychiatric diseases with hospitalization in the past five years. Subjects with any history of cardiac illness or impairment were excluded except for those with controlled hypertension. Controlled Type II Diabetes and thyroid disease were allowed diseases.

Screening day

The first day of the protocol was considered an adjustment period, and included the patient's history and physical, blood work, 12-lead EKG including rhythm strip, and baseline studies.

Orthostatic measurements

Subjects lay supine and graded their symptoms. While recumbent, subjects relaxed and remained quiet for 5 minutes to prevent any confounding sympathetic nervous system activation. Continuous heart rates were acquired with a 3-lead EKG and ANSAR software (ANSAR, Philadelphia). Blood pressures were acquired with a calibrated, automated blood pressure cuff (Dinamap 300). Supine heart rate and blood pressures were measured at the end of every minute for the 5-minute supine period. Then, subjects stood up by themselves and remained 10 inches from the edge of the bed for five minutes. Heart rates and blood pressures were measured at the end of the first minute and each of the next 4 minutes. Symptoms were graded again at the end of the 5-minute standing period.

Orthostatic changes in heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded for each orthostatic measurement. ΔHR was calculated by subtracting the standing HR at the end of each minute minus the average supine HR. ΔSBP and ΔDBP were calculated in the same way. The average of the 5 ΔHR, ΔSBP, and ΔDBP measurements were calculated for each time point. Pre-exercise measurements were obtained on the screening day and the morning before exercise. After exercise, measurements were obtained approximately 1, 3, 8, 16, 24, and 36 hours after the first exercise stress test.

Bicycle stress test

The Schwinn AirDyne bicycle submaximal exercise protocol was adapted from Light *et al* [13].

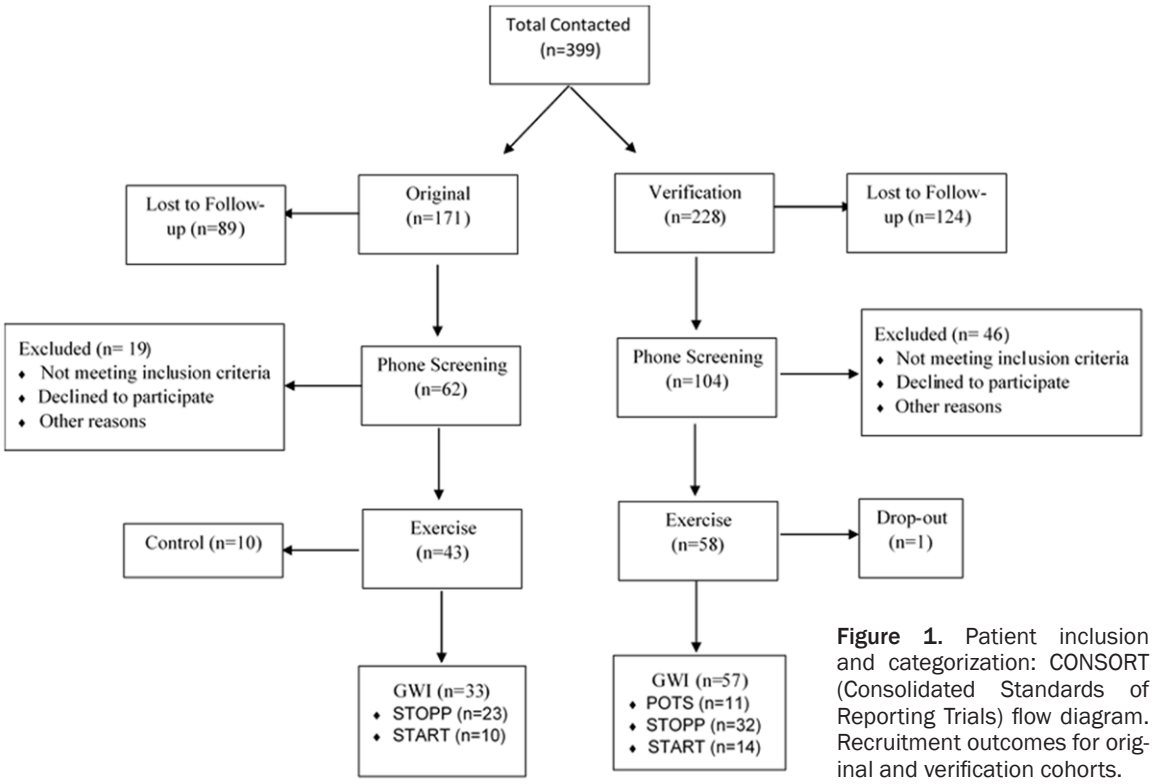

Figure 1. Patient inclusion and categorization: CONSORT (Consolidated Standards of Reporting Trials) flow diagram. Recruitment outcomes for original and verification cohorts.

Two tests were performed about 24 hours apart. Subjects cycled for 25 minutes at 70% predicted maximum heart rate (220-patient's age), followed by a climb to 85% maximum heart rate to reach anaerobic threshold.

Definitions

All subjects were assessed for POTS on the screening day. Subjects rested supine for 5 minutes and had HR measured from the continuous EKG monitor. Then, they stood up. POTS was defined as an increase in ΔHR ≥ 30 bpm at two or more measurements during the five minute standing period. ΔHR at the other 3 time points may have been less than 30 bpm leading to an average ΔHR of less than 30 bpm. Florid POTS was defined by a standing HR ≥ 120 bpm at two or more measurements while standing [2, 14, 15].

START was defined by having a normal ΔHR in the pre-exercise phase and post-exercise elevation in ΔHR to greater than 30 bpm at two or more measurements during the 5-minute standing periods [1].

STOPP was identified by a normal ΔHR (12 ± 5 bpm, mean ± SD) before and after exercise, and having ΔHR < 30 bpm at every time point [1].

The 1st peak effect in ΔHR was defined as the difference between the average ΔHR at the first post-exercise orthostatic measurement minus the average pre-exercise ΔHR (ΔΔHR).

Area under the curve (AUC) was calculated by the trapezoid method, and divided by the total duration of observations for each individual. This metric, AUC/duration, normalized differences the number of orthostatic measurements and total time in the study between individuals.

Postural systolic hypotension or hypertension were defined as a decrease or increase ≥ 20 mmHg in ΔSBP at two or more measurements during 5-minute standing periods. Postural diastolic hypotension was defined as a decrease in ΔDBP ≤ 10 mmHg at two or more measurements while standing [16]. We previously defined postural diastolic hypertension by Receiver Operating Characteristic (ROC) curve analysis as an increase in ΔDBP ≥ 18 mmHg at two or more measurements while standing [1].

Table 1. Subjects with hypertension and prescribed treatment

Group	Total	Hypertensive Subjects	Hydro-chlorothiazide	ACE Inhibitor	Beta blocker	Calcium channel blockers	Angiotensin II receptor antagonist	Alpha adrenergic blocker
O-HC	10	1	0	0	0	0	0	1
O-STOPP	23	10	7	4	1	1	2	0
O-START	10	4	2	1	0	1	0	2
V-POTS	11	3	0	1	0	2	0	0
V-STOPP	32	10	3	6	1	3	0	1
V-START	14	4	1	2	2	0	0	0
Total	100	32	13	14	4	7	2	4

32 subjects had a confirmed diagnosis of hypertension during history and physical examination. Eleven subjects were on a combination-drug regimen with the most common prescription being Hydrochlorothiazide/Lisinopril (n=6).

Table 2. Subject demographics and questionnaire data for control and all Gulf War Illness subgroups

Group	O-HC	O-STOPP	O-START	V-POTS	V-STOPP	V-START
N	10	23	10	11	32	14
Age	48.9 ± 6.1	46.8 ± 2.7	44.4 ± 5.2	45.7 ± 3.6	50.2 ± 2.3	46.6 ± 3.8
BMI	29.5 ± 3.7	31.7 ± 2.8	28.5 ± 3.7	30.4 ± 3.6	29.9 ± 2.1	28.1 ± 2.1
Sex						
Male	8	18	9	9	25	11
Female	2	5	1	2	7	3
Race						
White	9	18	8	9	25	13
Black	0	5	1	1	3	0
Other	1	0	1	1	4	1
CFSQ [10]	8.9 ± 4.4*	21.3 ± 2.1	24.7 ± 2.5	21.2 ± 3.3	21.1 ± 1.9	23.7 ± 2.0
GAD-7 [11]	3.7 ± 3.0	8.6 ± 2.3	14.6 ± 2.0†	11.2 ± 5.1†	9.5 ± 2.0	5.9 ± 2.3
SF-36 [12]						
Physical Function	83 ± 13.6*	46.8 ± 9.9	37.5 ± 17.7	45.5 ± 13.4	47.3 ± 8.6	46.9 ± 12.2
Limitations-Physical Health	67.5 ± 25.4*	15.9 ± 12.3	0	0	10.9 ± 8.5	9.6 ± 15.2
Limitations-Emotional problems	86.7 ± 17.4*	36.4 ± 17.1	3.3 ± 6.5	30.3 ± 24.1	29.2 ± 13.4	46.2 ± 22.8
Energy/Fatigue	50.5 ± 14.4*	15.7 ± 5.7	14.5 ± 6.8	20.5 ± 8.2	19.7 ± 6.2	11.2 ± 6.0
Emotional well being	70 ± 8.2	57.6 ± 7.1	39.2 ± 13.9	54.5 ± 14.0	54.9 ± 8.7	58.8 ± 8.1
Social functioning	71.3 ± 19.3*	31.3 ± 7.5	15 ± 9.5	33.0 ± 11.1	37.5 ± 10.6	30.8 ± 10.6
Pain	64 ± 14.4*	29.9 ± 7.3	17.2 ± 9.6	34.1 ± 8.8	30.4 ± 6.5	28.4 ± 9.3
General Health	65.9 ± 13.2*	27.6 ± 8.0	15.7 ± 8.2	23.4 ± 9.7	28.9 ± 7.3	25.2 ± 8.2

O-START and V-POTS had significantly higher GAD-7 anxiety scores than controls. All GWI subjects met CFS criteria and reported worse quality of life by SF-36 than controls, except for in the "Emotional Well Being" domain. *$P < 0.05$ for O-HC vs. all GWI groups by one way ANOVA followed by post-hoc Tukey's HSD. †$P < 0.05$ for O-HC vs. O-START and V-POTS by one way ANOVA followed by post-hoc Tukey's HSD. Mean ± 95% C.I.

Statistical analyses

The time courses for the average ΔHR, ΔSBP, and ΔDBP at each time point were inspected for each subject. First peak ΔHR effects and AUC/duration were evaluated by one way ANOVA followed by post-hoc Tukey's Honest Significant Difference (HSD) to account for multiple comparisons. All statistical analyses were calculated using IBM® SPSS® Statistics 25 for Windows and Microsoft Excel. Data were reported as mean ± SD or mean ± 95% confidence interval.

Results

Demographics and questionnaire outcomes

Recruitment outcomes for the two cohorts are displayed in **Figure 1**. Thirty-two subjects had a history of hypertension controlled with medicine (**Table 1**). Hypertensive subjects were randomly distributed between all subgroups, and so, hypertension and its treatment cannot explain the findings. There were no significant differences in demographic variables between the original and verification cohorts

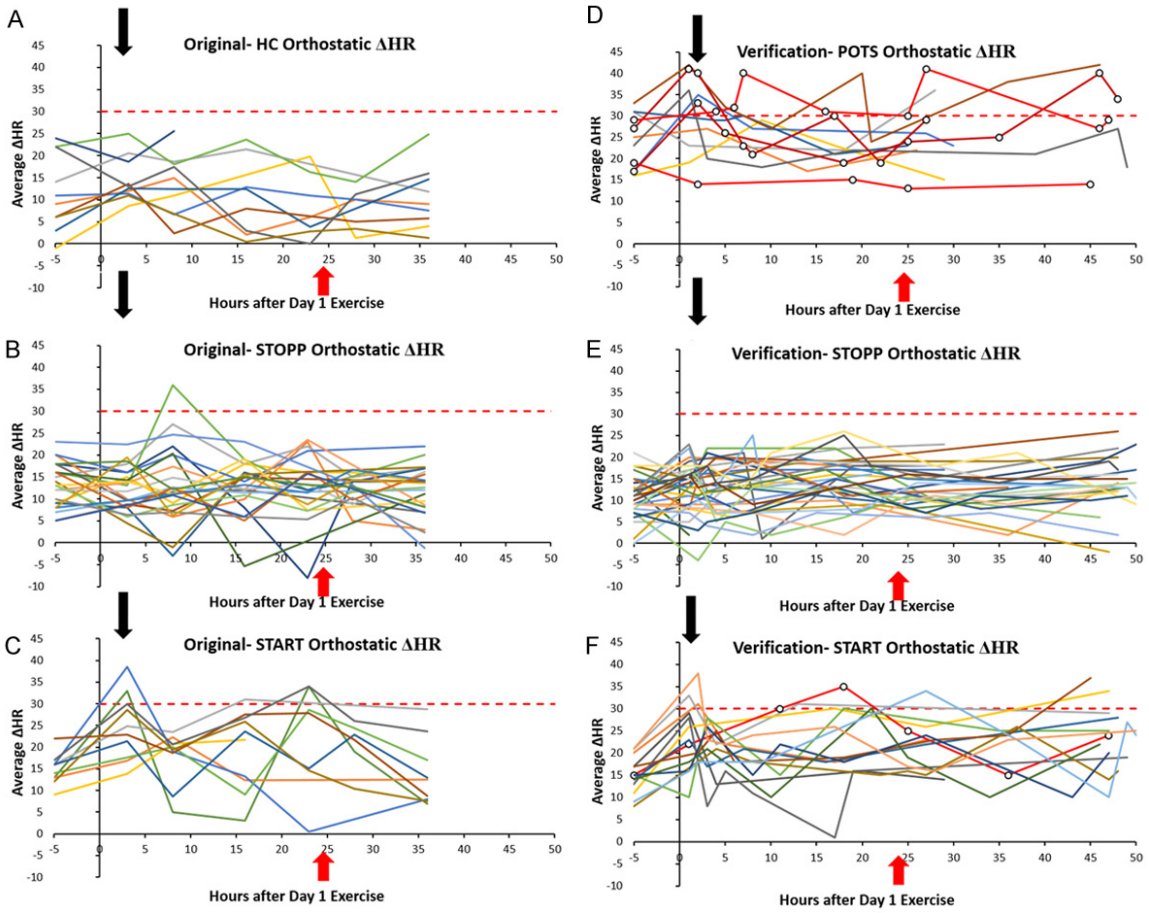

Figure 2. Individual time courses of average ΔHR before and after exercise. The time courses for average ΔHR changes before and after exercise were drawn for the Original Controls (A), Original STOPP (B), Original START (C), Verification POTS (D), Verification STOPP (E), and Verification START (F) groups. ΔHR was higher at the first time point after exercise (1st peak) in POTS, O-START, and V-START groups. Dotted red lines provide the reference point of ΔHR=30 bpm for POTS and START identification. Black arrows indicate average 1st peak time point. Red arrows indicate start of second exercise stress test. White circles indicate subjects with Florid POTS (n=4). Average pre-exercise ΔHR values were fixed to -5 hours.

(**Table 2**). GWI subjects from the two cohorts met criteria for CFS and scored significantly higher on the CFS questionnaire than controls [8, 10]. START subjects in the original study (O-START) and POTS subjects in the verification cohort (V-POTS) had significantly higher GAD-7 anxiety scores than controls [11]. All GWI subjects reported significantly worse quality of life using the SF-36, except for equivalent scores in the "Emotional Well Being" domain [12].

Prior to exercise, 11 GWI subjects from the verification cohort met criteria for POTS (V-POTS). After exercise, the 2:1 ratio of STOPP (32:14) was confirmed in the verification cohort by comparison to the original cohort (23:10); these were equivalent by Fisher's Exact Test.

The effect of exercise on ΔHR for each individual was graphed and inspected (**Figure 2**). Before exercise, supine HR, standing HR, and ΔHR were equivalent for controls, STOPP, and START subjects in both cohorts. Only V-POTS had significantly higher standing HR and ΔHR from all other groups ($P < 0.05$, Tukey's HSD) (**Table 3**). POTS was detected in the verification cohort, but was found in only one healthy control veteran in the original cohort.

After exercise, controls, O-STOPP, and V-STOPP were equivalent for supine HR, standing HR, and ΔHR. O-START and V-START groups had sig-

Table 3. Average vital signs before and after exercise

	O-HC (*n=10*)	O-STOPP (*n=23*)	O-START (*n=10*)	V-POTS (*n=11*)	V-STOPP (*n=32*)	V-START (*n=14*)
Pre-Exercise						
Supine HR	69.5 ± 3.0	67.8 ± 2.5	70.9 ± 4.1	71.9 ± 4.8	70.6 ± 2.4	68.2 ± 3.2
Standing HR	82.3 ± 2.6	80.4 ± 1.8	86.2 ± 1.9	96.4 ± 2.2*	81.1 ± 1.0	83.4 ± 1.2
ΔHR	11.6 ± 5.4	13.3 ± 2.1	14.8 ± 2.2	24.5 ± 3.7*	10.8 ± 1.6	15 ± 2.1
Supine SBP	128 ± 7.2	127 ± 4.7	128 ± 7.8	118 ± 6.1	122 ± 4.3	123 ± 6.4
Standing SBP	124 ± 7.7	125 ± 5.0	129 ± 8.7	120 ± 5.4	124 ± 4.2	126 ± 6.2
ΔSBP	-4 ± 2.4	-2 ± 2.7	0 ± 5.0.	2 ± 5.1	1 ± 2.2	3 ± 3.4
Supine DBP	73 ± 6.2	72 ± 3.1	74 ± 7.6	73 ± 5.2	76 ± 2.9	75 ± 5.7
Standing DBP	78 ± 5.4	78 ± 3.3	82 ± 7.5	80 ± 5.2	79 ± 3.4	80 ± 4.5
ΔDBP	5 ± 1.1	6 ± 1.6	8 ± 4.1	7 ± 4.1	4 ± 1.7	5 ± 3.3
Post-exercise						
Supine HR	72.3 ± 2.5	72.0 ± 2.0	70.5 ± 2.5	76.3 ± 3.3	72.7 ± 1.6	72.3 ± 2.6
Standing HR	83.8 ± 1.5	83.6 ± 1.3	91.0 ± 1.6†	104.0 ± 1.6*	85.7 ± 0.68	93.5 ± 1.1†
ΔHR	11.6 ± 1.0	12 ± 0.6	20.2 ± 1.2†	27.3 ± 1.0*	12.9 ± 0.4	21.7 ± 0.7†
Supine SBP	125 ± 5.6	122 ± 5.0	126 ± 9.0	117 ± 6.0	119 ± 3.9	118 ± 6.5
Standing SBP	124 ± 6.6	123 ± 5.2	129 ± 9.3	117 ± 4.0	120 ± 4.4	119 ± 6.9
ΔSBP	-1 ± 3.2	1 ± 2.5	3 ± 1.9	0 ± 2.6	2 ± 2.3	1 ± 3.2
Supine DBP	72 ± 4.6	70 ± 3.6	71 ± 6.4	71 ± 5.3	73 ± 2.9	72 ± 5.2
Standing DBP	77 ± 4.1	77 ± 4.2	80 ± 6.7	76 ± 4.3	78 ± 3.4	78 ± 5.2
ΔDBP	5 ± 2.0	6 ± 1.6	8 ± 1.9	5 ± 2.9	5 ± 1.4	6 ± 2.0

Before exercise, only V-POTS subjects had significantly higher standing HR and ΔHR than all other groups. After exercise, O-START and V-START had significantly higher standing HR and ΔHR than control and STOPP groups, while V-POTS was significantly higher than all other groups. Blood pressures did not differ. *$P < 0.05$ for V-POTS vs. all other groups by one way ANOVA followed by post-hoc Tukey's HSD. †$P < 0.05$ for O-START and V-START vs. O-HC, O-STOPP, and V-STOPP. Mean ± 95% C.I.

nificantly higher standing HR and ΔHR than O-HC, O-STOPP, and V-STOPP groups ($P < 0.05$, Tukey's HSD). V-POTS had significantly higher standing HR and ΔHR compared to all other groups ($P < 0.05$, Tukey's HSD).

Individual ΔHR time courses

O-HC, O-STOPP, and V-STOPP had equivalent ΔHR before and at each time point after exercise (**Figure 2A**, **2B**, **2E**). One O-STOPP subject had a single measurement of ΔHR > 30 bpm, and so did not meet START criteria. These constraints followed published consensus recommendations for POTS status [2].

O-START and V-START had normal ΔHR before exercise followed by a large significant increase in the post-exercise period ($P < 0.05$, Tukey's HSD) (**Figure 2C**, **2F**). The largest increase in ΔHR was observed in the immediate hours after the first exercise stress test (1st Peak Effect). ΔHR was more labile after exercise in the original and verification START groups. One V-START subject developed a standing HR ≥ 120 bpm during three of the orthostatic measurements.

By definition, V-POTS had orthostatic tachycardia before and after exercise. Four V-POTS subjects were identified as Florid POTS; three had recumbent tachycardia (≥ 100 bpm) and a standing HR ≥ 120 bpm. After exercise, V-POTS had orthostatic tachycardia at each time point and lability of ΔHR over time (**Figure 2D**). V-POTS subjects had significantly higher standing HR and ΔHR than all other groups for the entire post-exercise period ($P < 0.05$, Tukey's HSD). One Florid POTS subject had ΔHR in the normal range after exercise because of recumbent tachycardia, and standing HR between 120 to 125 bpm, resulting in ΔHR values that were ≤ 30 bpm.

First peak

The difference in ΔHR between the 1st time point after exercise and pre-exercise defined

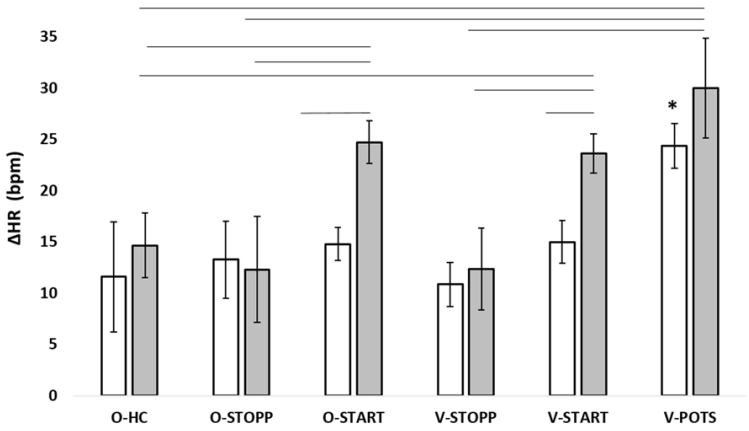

Figure 3. First Peak Effect. White bars indicate average pre-exercise ΔHR and grey bars indicate average ΔHR at the first post-exercise time point. O-HC, O-STOPP, and V-STOPP had equivalent ΔHR before and after exercise. Exercise induced 1st peak elevation of ΔHR in O-START and V-START. V-POTS had significantly higher ΔHR before and after exercise. Black lines indicate significance by Tukey's HSD ($P < 0.05$). *($P < 0.01$ for pre-exercise ΔHR in POTS vs. controls, STOPP, and START, Tukey's HSD). Mean ± 95% C.I.

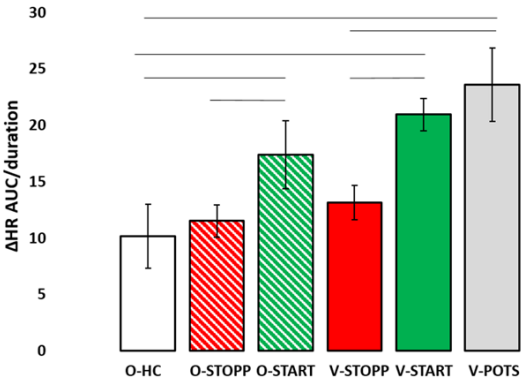

Figure 4. Area under the curve for ΔHR after exercise. START and POTS subjects had the largest increases in ΔHR after exercise relative to controls and STOPP subjects. Black lines indicate significance by Tukey's HSD ($P < 0.05$). Mean ± 95% C.I.

ΔΔHR and the 1st peak effect (**Figure 3**). The individual time courses revealed that O-START (9.9 ± 4.7) (ΔΔHR, mean ± SD), V-START (8.6 ± 3.3), and V-POTS (5.6 ± 5.2) groups appeared to have a consistent elevation in ΔHR between pre-exercise and their first post-exercise measurement. O-HC (3.0 ± 6.2), O-STOPP (-0.9 ± 5.4), and V-STOPP (1.5 ± 6.1) were equivalent and did not have any significant changes in ΔHR or ΔΔHR. Only O-START and V-START groups had significant increases in ΔΔHR at the first peak ($P < 0.05$, Tukey's HSD) (**Figure 3**). Before exercise, O-START and V-START had ΔHR of 14.8 ± 3.5 and 15.0 ± 4.0, respectively. After exercise, their first ΔHR were 24.7 ± 7.8 and 23.6 ± 7.6, respectively. O-START, V-START, and V-POTS groups had equivalent ΔHR at the first post-exercise time point. The average time for the 1st peak effect was 2.1 ± 1.0 hours (mean ± SD) after exercise.

Receiver operating characteristics (ROC) for ΔΔHR between O- and V-START and O-HC, O-STOPP, and V-STOPP had a threshold of 5 bpm, specificity of 0.72, sensitivity of 0.71, and AUC of 0.82. Cohen's d (mean difference/SD_{pooled}) for ΔΔHR was 1.14, indicating a strong effect size.

AUC/duration

Area under the curve (AUC) was measured to quantify the total increase in ΔHR after exercise (**Figure 4**). Once normalized by the total duration of observations for each subject, O-START and V-START groups had significantly higher AUC/duration than O-HC, O-STOPP, and V-STOPP groups ($P < 0.05$, Tukey's HSD). V-POTS subjects had the largest AUC/duration after exercise because orthostatic tachycardia was present at every time point (**Figure 2D**). V-POTS, O-START, and V-START had equivalent AUC/durations that were significantly higher than O-HC, O-STOPP, and V-STOPP groups. START and POTS could not be distinguished solely by post-exercise ΔHR.

Blood pressures

The individual time courses showed no consistent or persistent changes in systolic and diastolic blood pressure in any group (**Figures 5** and **6**). This confirmed that significant postural hypotension did not occur and was not a stimulus for orthostatic tachycardia.

Postural diastolic hypertension was previously described in the O-START group [1], but was found at only two isolated time points in two V-START subjects. Therefore, we did not confirm that postural diastolic hypertension was a component of the START phenotype.

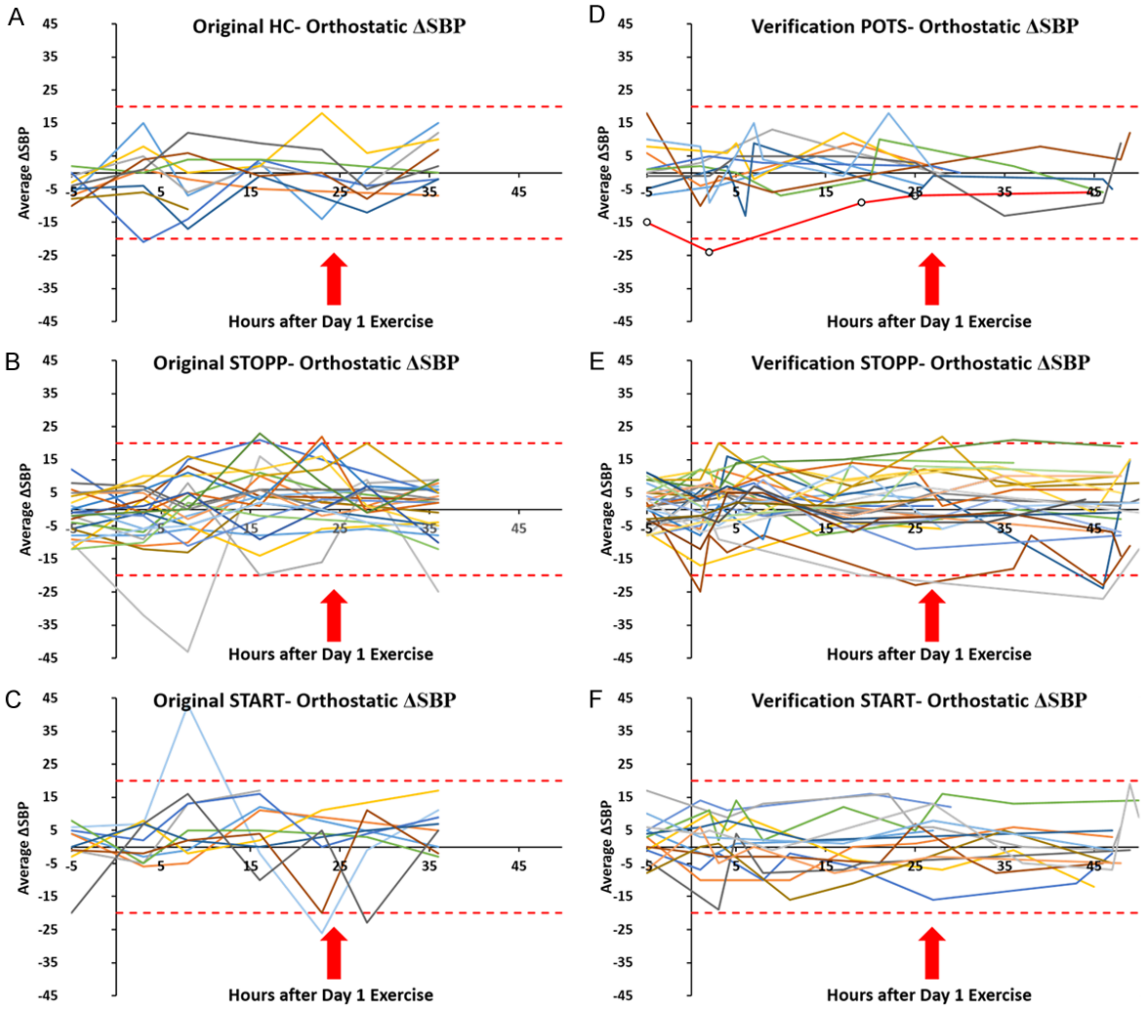

Figure 5. Time courses for ΔSBP before and after exercise. There were no significant differences in ΔSBP between groups. Red dotted lines provide reference points for postural systolic hypertension and hypotension (± 20 mmHg). Red arrows indicate start of second exercise stress test.

Discussion

The START and STOPP phenotypes were verified in GWI subjects by their responses to the submaximal exercise stress test. Prior to exercise, subjects had equivalent ΔHR, ΔSBP, and ΔDBP with the exception of the 11 V-POTS subjects. The O-HC, O-STOPP, and V-STOPP groups had equivalent ΔHR before and after exercise and had no 1st peak effect. Approximately one third of GWI subjects had normal ΔHR before exercise, but developed transient postural tachycardia after exercise with significant increases in 1st peak ΔΔHR and elevated AUC (START phenotype).

POTS subjects were found in the verification cohort. V-POTS subjects had postural tachycardia and large increases in ΔHR before and after exercise. START and POTS were not equivalent because START subjects have normal ΔHR before exercise and developed postural tachycardia as a transient, dynamic response to exertion.

New hypotheses to be explored include exercise-induced autonomic dysfunction and atrophy in the cardio-regulatory regions of the brainstem as seen in CFS and START [1, 17]. Upregulation of adrenergic and cholinergic receptors in peripheral blood leukocytes after exercise has been observed in CFS, but not examined in GWI [18]. Other hypotheses include disturbances in mitochondrial function after exercise or hypometabolic profiles as seen in CFS and GWI [19, 20].

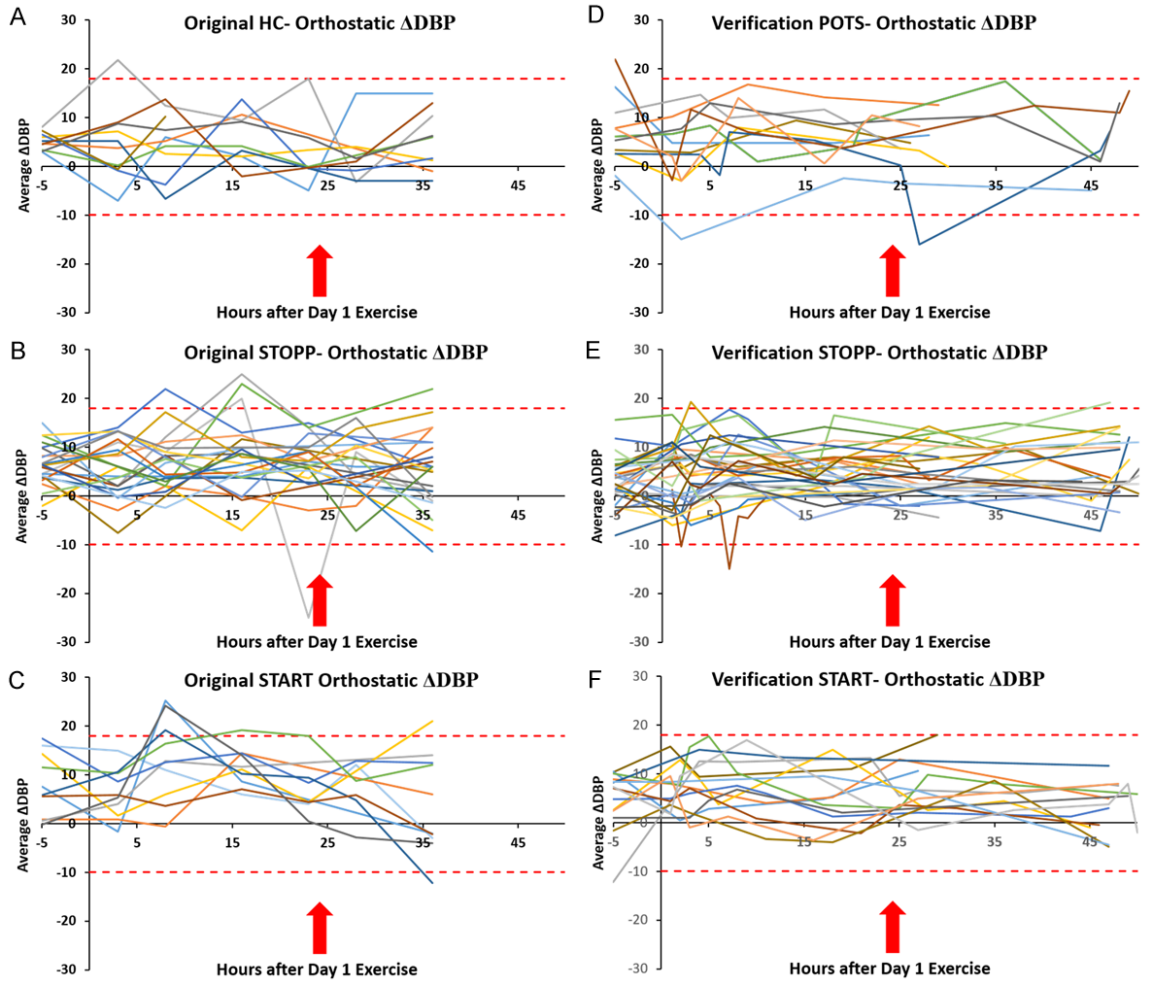

Figure 6. Time courses for ΔDBP before and after exercise. There were no significant differences in ΔDBP between groups. Red dotted lines provide reference points for postural diastolic hypertension (≥ 18 mmHg) and hypotension (≥ 10 mmHg). Red arrows indicate start of second exercise stress test.

We rejected the hypothesis that significant postural hypotension would be the stimulus for START physiology because postural systolic or diastolic hypotension did not develop in any group. There were isolated, spurious changes in ΔHR, ΔSBP, and ΔDBP in 6 out of 100 subjects, but these occurred at 15 out of 547 total time points and can be explained as the bounds of normal cardiovascular reactivity. Hypertension was present in 32 subjects, but there were no significant differences in the number of hypertensive subjects per group. A general linear model was constructed to detect START based on post-exercise ΔHR, medical history of hypertension, treatment type (ACE inhibitor, β-blocker, etc.), age, gender, and BMI. All variables regressed out of the model except for ΔHR for START detection, thus, hypertension or the prescribed medical treatment did not affect the detection of START status. Alternative explanations for the inability to detect significant hypotension that were addressed by standard clinical practice included use of the incorrect blood pressure cuff size and difficulties with oscillometric blood pressure measurements in patients with higher BMI [21, 22].

We rejected the hypothesis that START is the same condition as POTS because POTS subjects had postural tachycardia at every time point, but postural tachycardia in START only followed exercise.

Limitations

Other protocols and types of cognitive or emotional stressors were not examined. Genera-

lization to other illness groups is not yet possible. Patients with more severe symptoms did not volunteer and may have a different proportion of POTS and START phenotypes. Elevation of ΔHR was not consistently detected after the second exercise because subjects had other tasks to perform and ΔHR measurements had to be deferred. Future protocols may be redesigned to include additional measurements soon after the second exercise test. Hypertension was present in 32 subjects. β-blockers and ACE inhibitors were the most common antihypertensive drugs. In the original cohort, antihypertensive drugs were stopped before the screening day, but this led to rebound hypertension in 2 subjects who needed to have propranolol restarted. Thereafter, stable medication regimens were continued throughout the study. Hypertension, the type of drug, and discontinuation did not affect the detection of START status. Larger studies would be needed to study the interaction of START, hypertension, and its treatment.

Conclusions

We verified the discovery of the novel cardiovascular phenomenon that exercise causes transient postural tachycardia, with no changes in blood pressure, in one quarter (verification cohort) to one third (original cohort) of GWI subjects. START was different from POTS indicating a different pathophysiological response to exertion in the START phenotype compared to the constant postural effect in POTS. Criteria to define START status can now be independently verified by other groups and testing schemes. The START and STOPP phenotypes begins to explain heterogeneity in the pathophysiology of Gulf War Illness as previously shown by the different fMRI patterns seen during cognitive testing [1].

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Disclosure of conflict of interest

None.

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