When Sinus Tachycardia Becomes Too Much: Negative Effects of Excessive Upright Tachycardia on Cardiac Output in Vasovagal Syncope, Postural Tachycardia Syndrome, and Inappropriate Sinus Tachycardia

Running title: *Stewart et al.; Reduced cardiac output during upright tachycardia*

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Abstract:

Background - Upright posture reduces venous return, stroke volume and cardiac output (CO) while causing reflex sinus rate (HR) increase. Yet, in inappropriate sinus tachycardia (IST), postural tachycardia syndrome (POTS), and vasovagal syncope (VVS) symptomatic excessive HR occurs. We hypothesized CO reaches maximum as function of HR in all.

Methods - We recruited 12 healthy controls, 9 IST, 30 VVS and 30 POTS patients (13-23years) selected randomly by disorder not by HR, each fulfilled appropriate diagnostic criteria. Subjects were instrumented for electrocardiography, beat-to-beat blood pressure, respiratory rate, CO-Modelflow algorithm, and central blood volume (CBV) from impedance cardiography; 10min data was collected supine; subjects were tilted head-up for =/<10min. We computed phase differences, ΔΦ, between fluctuations of HR (ΔHR) and CO (ΔCO) tabulating data when phases were synchronized, determined by a squared nonlinear phase synchronization index (PhSI) >0.5, describing extent/validity of CO/HR coupling. We graphed results supine, 1min-post-tilt-up, mid-tilt, and pre-tilt-down using polar coordinates (HR - radius, ΔΦ – angle) plotting cos(ΔΦ) vs HR to determine if transition HR exists at which in-phase shifts to anti-phase above which CO decreases when HR further increases.

Results - At baseline HR, diastolic and mean arterial pressure in IST and POTS were higher vs controls. Upright HR increased most in POTS then IST and VVS, with diverse changes in CO, SVR, and CBV. Each patient grouping was separately and collectively analyzed for HR change showing transition from in-phase to anti-phase (ΔΦ) as HR increased: $HR_{transition}$ =115±6(IST),123±8(POTS),124±7(VVS), p=ns. Controls never reached transitional HR.

Conclusions - Excessive HR independently and equivalently reduces upright CO, in IST, POTS and VVS.

Key words: tachycardia; phase analysis; orthostatic; phase synchronization; in-phase; anti-phase

Non-standard Abbreviations and Acronyms

BP: blood pressure in mmHg

bpm: beats per minute

CO: cardiac output

HR: heart rate in beats per minute

$HR_{transition}$: The HR at which CO falls with increasing HR

HUT: head-up tilt

IST: inappropriate sinus tachycardia

OI: orthostatic intolerance

POTS: postural tachycardia syndrome

VVS: Vasovagal syncope

Introduction

Standing upright (orthostasis) translocates 500–700 ml from central stores into the legs and abdominal vascular beds producing central hypovolemia and reflex tachycardia [1]. Upright tachycardia is excessive in postural tachycardia (POTS) [2], in inappropriate sinus tachycardia (IST) [3], and in some with vasovagal syncope (VVS) in whom excessive tachycardia precedes hypotension with/without bradycardia [4, 5]. Indeed, selective treatment of tachycardia with ivabradine improves patient well-being and orthostatic tolerance [6-8].

An "inverted U-shape" dependence of cardiac output (CO) on heart rate (HR) in which CO increases to a maximum with increasing HR and then declines with further HR increase has been demonstrated under experimental conditions in which reflex adjustments were controlled [9, 10]. For example, Guyton et al showed that a maximum CO occurred with increasing HR, but that the HR at which maximum CO occurred declined with reduced venous return [10] as a consequence of reduced stroke volume [9].

Orthostasis decreases venous return and stroke volume in humans [11]and therefore excessive HR could importantly limit cardiac output at achievable heart rates. However, the specific effects of HR on CO are difficult to ascertain in unanesthetized, unpaced humans because of respiratory and cardiovascular control mechanisms acting on cardiac filling, vascular responses, and cardiac contractility. These would tend to obscure specific HR-CO dependencies.

We hypothesized that using a fluctuation analysis approach during orthostasis, below a certain transitional HR ($HR_{transition}$), CO is independently increased by further HR increments, while above that HR, CO is decreased by further HR increments. Thus, we considered fluctuations in HR and CO using variability and nonlinear phase synchronization methods to determine $HR_{transition}$ in IST, POTS and VVS using head-up tilt (HUT) as an orthostatic challenge

to increase HR. To test that hypothesis, we employed the following perspective in the consideration of the data collected during orthostatic challenge from control subjects and patients with IST, VVS and POTS.

Computational Rationale

HR-CO Relationship and Phase Synchronization

Our research question was whether a change in HR produces a directionally similar change in CO as HR increases. This is equivalent to considering the phase difference between CO and HR when they are demonstrably linked, i.e. at times of "phase synchronization" defined as "the operation of oscillatory systems in unison such that their phases and frequencies closely relate" [12]. Systems can be phase synchronized at any difference in phase, $\Delta\Phi$, as long as that difference remains unchanged over a period of time. When synchronization occurs, the systems are said to be "phase locked" or "frequency entrained." Referring to **Figure 1** adapted from [13], there is a peak in the CO-HR relationship. At HR less than the peak, increasing HR increases CO. At HR greater than the peak, increasing HR decreases CO. We define these states respectively as "in-phase" and "anti-phase" coupling. In the absence of noise and intrusive factors, one might propose a perfect "in-phase" coupling of HR to CO (**Figure 2, Panel A**) below the CO peak such that fluctuations of HR would lead to directionally similar fluctuations in CO. This contrasts with "anti-phase" coupling of HR to CO (**Figure 2, Panel B**, also known as completely out of phase) above the CO peak such that fluctuations of HR would lead to directionally opposite fluctuations in CO. The phase difference in perfectly in-phase signals is 0^o (alternately 0 radians). The phase difference in perfectly anti-phase signals is 180^o (alternately π radians). In both cases one can say that HR and CO are phase synchronized implying a fixed difference in phase.

Another depiction is to graph ΔΦ on the unit circle (**Figure 3**) where in-phase denotes the right half, and anti-phase denotes the left half plane. One could render this more conveniently for numerical statistics by taking the cosine of ΔΦ. Cos(ΔΦ)>0 is in the right hand plane, and cos(ΔΦ)<0 in the left hand plane. A transition from in-phase to anti-phase would correspond to a zero-crossing of cos(ΔΦ).

Other Dependencies of CO and HR

The change in CO with changing HR not only depends on HR but may depend on the state of regional blood volumes, vascular resistances and capacitances, respiration etc. The functional relationship of **Figure 1** can be achieved experimentally by controlling these quantities, which is unfeasible in humans. Using data from experimental dogs, Melbin [14] summarized these as changes in preload (P), afterload (A), and contractility (C) and applied the chain rule of differential calculus [15].

$$\frac{dCO}{dHR} = \frac{\partial CO}{\partial HR}|_{P,A,C} + \frac{\partial CO}{\partial P}\frac{dP}{dHR} + \frac{\partial CO}{\partial A}\frac{dA}{dHR} + \frac{\partial CO}{\partial C}\frac{dC}{dHR} + other \cdot terms$$

Where the first term is the change of CO with HR when P, A, C are held constant, and additional terms represent the effect of P, A and C as functions of changing HR on CO.

To effectively measure $\frac{\partial CO}{\partial HR}|_{P,A,C}$ we examined small fluctuations in HR that cause small fluctuations in CO. Small and short-lived fluctuations then then P, A and C, may be regarded as quasi-stable or slowly changing with respect to HR-CO fluctuations. Under these conditions $\frac{dCO}{dHR} = \frac{\partial CO}{\partial HR}|_{P,A,C}$. This has the form of a variability method and uses the same assumptions of approximating a multiple-input transfer function model by a single input analysis [16]. Because HR and CO cyclically change during each breath [17] we calculated the means of CO and HR over

consecutive respiratory cycles as shown in **Figure 4A**, and used a band pass filter from 0.02 Hz to 0.2 Hz to smooth out respiratory related changes and to remove very low frequency trends (**Figure 4B**). Such an approach has formal similarity to Detrended Functional Analysis (DFA)[18]. The resultant signals contained fluctuations near 0.1Hz where HR and CO are known to synchronize [19]. One approach to analysis uses Fourier transform methods to calculate coherence, gain and phase over quasi-stationary time periods (transfer function analysis) [20]. Our concern with such analyses is that they are strictly applicable to linearly related, stationary, time-independent signals. During orthostasis hemodynamic quantities are nonlinear, time-dependent, non-stationary, and poorly amenable to such analyses [21]. Instead, we employed phase synchronization methods as in previous work [22, 23].

Phase Synchronization Methods

"Phase synchronization", or "phase-locking" is a well-established concept in nonlinear dynamics. Two or more oscillators, each potentially having their own dominant frequency, become entrained or synchronous causing the difference in phase, $\Delta\Phi(t)$, between the oscillators to become nearly constant over some period of time [12]. A non-zero constant difference in phase is equivalent to a time lag in the time domain. Phase synchronization methods are time independent and are well-suited to nonlinear analyses of phase [24].

The degree of synchronization can be quantified by several methods [24, 25]. In all, phase makes intuitive sense when the fluctuations oscillate around zero. Thus, preprocessing after respiratory averaging (**Figure 4-A**) involved band pass filtering HR and CO signals from 0.02 to 0.2 Hz so that signal phase trajectories encircle the origin, and very low frequency contributions are detrended (removed), **Figure 4-B**. The filter we used was a forward and backward 8-pole Butterworth band pass filter which leaves phase unchanged. Each filtered time domain signal

was examined and oscillated around zero. We then calculated phase using the Hilbert transform, took phase differences ΔΦ in HR and CO, and defined the coefficient of synchronization, γ^2 [12] (see on-line supplement).

HR and CO phase relationships can be reliably obtained during periods of phase synchronization when ΔΦ(t) is approximately constant. We examined ΔΦ and cos(ΔΦ) during these periods in the supine and tilted position [12]. Analogous to transfer function methods in which signals are taken to be reliable for a squared coherence>0.5, CO and HR signals were regarded as adequately synchronized when γ^2 exceeded 0.5.

Methods

In accordance with the AHA journals' Transparency and Openness Promotion Guidelines, the data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

We studied 30 subjects with a history of recurrent vasovagal syncope (VVS, mean age 17 ± 1 years, 18 females), 30 patients with Postural Tachycardia (POTS, mean age 18 ± 1 years, 28 females), 9 patients with inappropriate sinus tachycardia (IST, mean age 17 ± 1 years, 7 females) and 12 healthy control subjects (mean age 18 ± 1 years, 8 females). Subjects ranged in age from 13-23 years. All patients were selected on the basis of diagnosis made prior to study enrollment, and not based on any heart rate measurements. VVS patients were diagnosed by typical history and absence of cardiac disease [26]. POTS patients exhibited age-stratified excessive upright tachycardia (>30 bpm in patients >19 years, >40 bpm in those <19years) in absence of hypotension during a 10min upright tilt with symptoms of orthostatic intolerance [27, 28]. IST

patients were diagnosed by complaints of tachycardia/palpitations, mean resting sinus heart rate >100bpm, and mean sinus rate >90 bpm on 24 hour Holter monitor [29]. Control subjects were healthy volunteers who responded to advertisements and had no previous history of orthostatic intolerance.

Subjects with systemic or cardiac illness or other forms of orthostatic intolerance, competitive athletic training, nicotine use, pregnancy in the last year, or prolonged periods of bed rest were excluded from this study. No subjects were taking medications at the time of study. All subjects refrained from caffeine or xanthine-containing substances for 72 hours prior to the test. The study was approved by the Institutional Review Board of the New York Medical College. Each subject received a detailed description of all protocols and was given an opportunity to have their questions answered. Signed informed consent was obtained from all adult participants; those younger than 18 assented to participate and their parent of legal guardian signed an informed consent.

Prolonged upright tilt may invoke a fainting response in young healthy subjects or POTS patients. We limited HUT testing to 10min. We have previously demonstrated that this is sufficient tilt time for comparison of orthostatic changes between control and VVS subjects [30, 31]. VVS subjects were only included if they fainted during the 10min HUT without pharmacologic provocation. No subjects in POTS, IST or control groups fainted during tilt testing.

Tilt and Measurement Protocol

Testing began at 9:30 AM in a climate-controlled room at 20°C following a 3 hour fast. Subjects were familiarized with the procedure and instrumented for ECG, photoplethysmograph for continuous blood pressure monitoring, respiratory plethysmography, and impedance

cardiography using methods and analyses previously employed, as detailed in the *on-line supplement.*

Data Analysis and Statistics

Measurements were made at 4 stages:

-Baseline supine: data analyzed as mean during 10min rest prior to tilt

-Early at 1min after start of HUT (these data were unused because of rapid change due to mechanical disequilibrium (initial orthostatic hypotension) [32];

-Late either at end-tilt or just prior to rapid hypotension-bradycardia in VVS;

-Mid at midway between early and late.

Times of sampling were approximate because phase synchronization index had to exceed 0.5 for valid measurement. This was not generally problematic and values of BP, HR, CO, SVR, respiratory rate (in breaths per minute), CBV, $\Delta\Phi$, and $\cos(\Delta\Phi)$, were obtained by averaging signals over at least 15s at times of sampling. Baseline measurements were analyzed using independent t-tests between Control vs POTS, VVS and IST with Bonferroni correction for multiple comparisons.

Extremum changes (maximum or minimum depending on the measured quantity) from baseline in POTS, VVS, and IST patients ΔHR, ΔSAP, ΔDAP, ΔMAP, ΔCO, ΔSVR, ΔRespiratory Rate, Δ%CBV were compared to control using multiple t-tests for each group with correction for multiple comparisons.

We used "circular statistics" because the usual methods for computing means and variances for continuous linear data do not apply to circular data. We measured a key outcome measure, the relationship of $\Delta\Phi$ to HR, using polar (circular) coordinates r, Θ, replacing the radius r by HR and Θ by $\Delta\Phi$ for each group. Groups were then analyzed separately, using

circular statistics33 to estimate the relationship between HR and ΔΦ for each group. A circular variant of ANOVA was used to detect group differences where ANOVA is applied to the phase angles which are presumed to be drawn from the circular analogue of a linear normal distribution. The Watson-Williams multi-sample test is a circular analogue of the one-factor ANOVA.

A transformed analysis was obtained by plotting cos(ΔΦ) vs HR, applying multiple regression methods to detect $HR_{transition}$. This facilitated detection of the in-phase to anti-phase breakpoint at $HR_{transition}$ using two-segment linear regression for each group [33],[34]. Groups were compared for difference in $HR_{transition}$. Since we were only interested in comparing the three patient groups to the control group, we did not conduct an omnibus test of hypothesis using ANOVA. Rather, to control for the family-wise error in these situations, we applied Bonferroni's adjustment to the p-values for the three pairwise comparisons of interest. As such, significance testing was conducted at $p < 0.0167$. Since correlations are descriptive, significance testing for correlations was conducted at $p < 0.05$. We also correlated cos(ΔΦ) to HR, BP, CO, SVR, Δ%CBV, and respiratory rate by calculating the Pearson linear correlation coefficients between cos(ΔΦ) for each patient group independently.

Results

Anthropometrics

POTS patients weighed less than control with commensurate reduction in BMI. This has been previously reported [32].

Supine Hemodynamics

Baseline measurements are presented in Table 1. Resting HR, DAP, and MAP were higher in POTS patients and in IST patients compared to controls. Respiratory Rate (Resp Rate), systolic arterial pressure (SAP), CO, and SVR were similar.

Upright Hemodynamics

Referring to Table 2, HR increased the most in POTS, and similarly in VVS and IST. All patient group HR increments exceeded control increments. The increase in SAP was larger in control than in any group and was reduced in VVS patients compared to baseline. Diastolic arterial pressure (DAP) was increased most in POTS compared to Control but did not reach significance in this analysis. DAP was significantly decreased in IST, and was negative in VVS. Respiratory rate was slightly increased for all groups by paired statistics.

CO was significantly decreased in POTS and IST, and significantly increased in VVS compared to Control. SVR increased initially in all groups but was larger than control in POTS. SVR decreased throughout tilt in VVS. %CBV decreased in all subjects, was lowest in POTS and also significantly different from Control for IST.

Figure 5. Relationship of ΔΦ to HR

A polar coordinates representation of the relationship between ΔΦ and HR when phase synchronized is shown in Figure 5. The Figure includes baseline and tilted HR. HR was significant increased ($P<0.001$) in the left half plane compared with the right half plane for patient groups. Excepting controls, points were similarly distributed by angle for given HR and were independent of group. With HR as the independent variable one can also show $HR_{transition}$ (shift from right half-plane to left half-plane) occurred at HR of approximately 120bpm independent of patient group.

Figure 6. Relationship of cos(ΔΦ) to HR

The use of the cosine transform may make the HR- ΔΦ relationship more apparent (Figure 6) where cos(ΔΦ) is graphed as a function of HR. The percentage of points with cos(ΔΦ)<0 greatest in IST, followed by POTS, and smallest in VVS, because the HRs were more often higher in IST and POTS than VVS. The few IST points with cos>0 represent only baseline values that were in the range of 100 bpm. $HR_{transition}$ =115±6(IST), 123±8(POTS), 124±7(VVS), p=ns. There was no effect of order (baseline, early, mid or late) on the cosine value which depended exclusively on HR. Control points appear in the left upper quadrant because all HR's were >0.

Table 3 Correlations of cos(ΔΦ) to HR, BP, CO, SVR, Δ%CBV, and respiratory rate

We calculated linear correlation coefficients between cos(ΔΦ) for each patient group independently. After correcting for multiple comparisons, only HR correlated with cos(ΔΦ) (P<0.001).

Discussion

Our study demonstrated a maladaptive change in the relationship between cardiac output and heart rate while upright in Postural orthostatic tachycardia, inappropriate sinus tachycardia and vasovagal syncope in comparison to controls. HR in orthostatic intolerance has, however, been consistently regarded as compensatory in maintaining orthostatic tolerance [35]. Those experiments employed lower body negative pressure without orthostasis in healthy individuals showing orthostatic tolerance was favored by higher heart rates; but heart rates did not exceed 120bpm for any subject. Stroke volume and cardiac output decrease due to orthostatic positioning [36] and decline steadily as a function of HR once upright [13]. Since CO = stroke volume x HR, rise in HR

must exceed fall in stroke volume for CO to continue to rise with HR but animal experiments have shown that there is a maximum in the single-valued relationship of CO as a function of HR.

We have denoted $HR_{transition}$ as the HR at that maximum CO. Below $HR_{transition}$ CO increases with HR. Above $HR_{transition}$ CO decreases with HR. If CO decreases above $HR_{transition}$ then SV decreases more than HR rises when HR exceeds $HR_{transition}$ [9, 10, 13, 14, 37]. Therefore, increasing HR during orthostatic stress compensates for the fall in stroke volume within limits, up to the $HR_{transition}$ threshold, beyond which further increase in HR decreases CO. Conversely, our findings predict that lowering HR would improve CO if upright HR has already exceeded $HR_{transition}$. This phenomenon is common to patients with POTS, VVS, and IST. Each demonstrated a threshold $HR_{transition.}$ Also, despite possibly different illness mechanisms, $HR_{transition}$ for patient groups were not statistically different, implying the essential role of excessive heart rate *per se*, in the presence of intact ventricular function and regardless of pathophysiology, to compromise cardiac output. This finding suggests the utility of agents such as ivabradine as primary therapy in forms of orthostatic tachycardia.

The importance of HR is further evidenced by the significant and exclusive correlation of $\cos(\Delta\Phi)$ with HR alone but not respiratory rate, SVR, CO. CBV or MAP. Thus, while there can be relationships of HR to BP (e.g. cardiovagal baroreflex) or to SVR, the "phase transition" depends solely on HR. This work comprises the only experiments in which a $HR_{transition}$ has been established in humans without using pharmacological interventions that perturb the system. However, experiments employing pharmacologic perturbations in humans support our findings. Thus, Weissler et al using postural change and atropine in healthy young humans showed that cardiac output is enhanced by atropine-induced tachycardia when supine, but not when upright [38]. However, these findings were likely influenced by the additional effects of atropine including

hemodynamic changes, dysregulation of cardiac sympathetic actions, respiratory effects, gastrointestinal effects and central nervous system actions [39]. Elstad et al used combinations of atropine and propranolol to achieve vagal or total sinus node blockade in the supine and upright position in healthy humans [20]. They used a transfer function approach applied under quasi-static, near-linear conditions to study the buffering effects of oscillations of HR and CO on BP and showed that CO and HR were in-phase at rest supine and anti-phase when upright with induced sinus tachycardia. Their steady state time invariant analysis therefore confirmed anti-phase of HR and CO in excessively tachycardic upright healthy subjects. Results contrast with the work of Segerson et al who showed that in patients with preserved ejection fraction, diastolic and mean BP increased and sympathetic nerve activity decreased with HR up to 140 bpm [40]. The rhythm was paced but the key difference in experimental design was their studying supine patients. Standing (or upright tilt) without moving or exercising produces a large reduction in venous return in otherwise normal subjects which makes patients particularly vulnerable to hemodynamic fluctuations and causes changes in physiologic blood flow and HR relationships. It is expected that CO, BP and HR interrelationships should differ during supine vs upright testing [41].

In the current investigation, we measured $\Delta\Phi$ during times of phase synchronization such that HR and CO were phase locked. The time course of HR-CO phase interactions defines the integrity but not the sensitivity of the relationship. Entrainment between HR and CO is present when we can distinguish their relationship from noise. Phase synchronization is a necessary condition for the existence of intact functional relationship between HR and CO. For there to be any relationship between HR and CO depends on phase synchronization between the signals. Insufficient synchronization results in loss of ability to discern a relationship. Coupling does not

extend to causality although it seems apparent that HR drives CO; whether CO drives HR is less clear. The effects of HR on CO could be investigated by open loop analyses: fixing HR such that HR becomes the controlling, or independent variable, and CO becomes the controlled, or dependent variable. But the use of partial differential expression implies contributions of preload, afterload, and contractility in establishing direct causality. Multivariate analysis could be performed using multiple input single output relationships augmented by, for example, Granger causality. This would require a huge, multivariate dataset and is beyond the scope of the present paper.

Limitations

There are several limitations to our current data that deserve attention. Our VVS patients were only included if they fainted within 10 minutes. Our prior work did not indicate much variation in physiology when comparing similar phases of fainting in patients with different times to faint [42].

Only a relatively small number of IST patients were studied. This is counterbalanced to an extent by their consistency of high heart rates when upright.

None of the control subjects and a lower percentage of VVS patients underwent the phase transition compared to POTS or IST. The reason is that none of the control subjects and fewer syncope patients reached the transitional HR which was, at least for VVS, similar to $HR_{transition}$ for IST and POTS. As stated we did not recruit patients on the basis of HR criteria.

Sex may also be a potential limitation. POTS and IST patients were almost entirely female which matches our prior observations of the sex distribution of these disorders. We chose controls as 2/3 female and VVS patients were similarly distributed. We only had two male POTS subjects and 1 male IST patient. Comparing sex across disorders suggested that the phase

relationship depended on HR regardless of sex but was not well powered. Future investigations can be conducted using phase synchronization methods to further probe for differences between men and women.

Also, we did not control for menstrual cycle in our female subjects. Hormone fluctuations in women may play a role in orthostatic intolerance [43, 44], could affect maximum upright heart rate or venous return, and venous return affects the CO-HR maximum [10, 13].

The controls failed to reach transition. This was simply because they did not experience the heart rate rise common to other groups. In principle, another control group could be devised from healthy volunteers where the heart rate is increased by atropine or by atrial pacing. Atropine was used in Elstad et al [20] found that CO and HR were in-phase at rest supine and anti-phase when upright with induced sinus tachycardia. Their work confirmed anti-phase of HR and CO in excessively tachycardic upright healthy subjects. Pacing was not performed for ethical reasons.

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References:

1. Sheriff DD, Nadland IH, Toska K. Hemodynamic consequences of rapid changes in posture in humans. *J Appl Physiol.* 2007;103:452-8.

2. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology.* 1993;43:132-7.

3. Shen WK, Low PA, Jahangir A, Munger TM, FriedmanPA, Osborn MJ, Stanton MS, Packer DL, Rea RF, Hammill SC. Is sinus node modification appropriate for inappropriate sinus

tachycardia with features of postural orthostatic tachycardia syndrome? *Pacing Clin Electrophysiol.* 2001;24:217-30.

4. Medow MS, Merchant S, Suggs M, Terilli C, O'Donnell-Smith B, Stewart JM. Postural Heart Rate Changes in Young Patients With Vasovagal Syncope. *Pediatrics.* 2017;139.

5. Sutton R, Petersen M, Brignole M, Raviele A, Menozzi C, Gianni P. Proposed classification for tilt induced vasovagal syncope. *Eur J Card Pacing Electrophysiol.* 1992;2:180-3.

6. Barzilai M, Jacob G. The Effect of Ivabradine on the Heart Rate and Sympathovagal Balance in Postural Tachycardia Syndrome Patients. *Rambam Maimonides Med J.* 2015;6.

7. Cappato R, CastelvecchioS, Erlinger P, Sanghera R, ScheckD, Ostroff A, Rissmann W, Gropper C, Bardy GH. Clinical efficacy of ivabradine in patients with inappropriate sinus tachycardia: a prospective, randomized, placebo-controlled, double-blind, crossover evaluation. *J Am Coll Cardiol.* 2012;60:1323-9.

8. Sutton R, Salukhe TV, Franzen-McManus AC, Collins A, Lim PB, Francis DP. Ivabradine in treatment of sinus tachycardia mediated vasovagal syncope. *Europace.* 2014;16:284-8.

9. Noble MIM, Trenchord D, Guz A. Effect of changing heart rate on cardiovascular function in the conscious dog. *Circ Res.* 1966;XIX:206-13.

10. Sugimoto T, Sagawa K, Guyton AC. Effect of tachycardia on cardiac output during normal and increased venous return. *Am J Physiol.* 1966;211:288-92.

11. Rowell LB. *Human cardiovascular control*. New York, NY: Oxford University Press; 1993.

12. Rosenblum M, Pikovsky A, Kurths J. Synchronization Approach to Analysis of Biological Systems. *Fluctuation and Noise Letters.* 2004;4:L53-L62.

13. Kumada M, Azuma T, Matsuda K. The cardiac output-heart rate relationship under different conditions. *Jpn J Physiol.* 1967;17:538-55.

14. Melbin J, Detweiler DK, Riffle RA, Noordergraaf A. Coherence of cardiac output with rate changes. *Am J Physiol.* 1982;243:H499-H504.

15. Anton H. The Chain Rule. *Calculus with Analytic Geometry*. 2 ed. New York: Wiley; 1999. p. 165-71.

16. Bendat JS, Piersol AG. *Random Data: Analysis and Measurement Procedures* . 3 ed. New York: Wiley-Interscience, John Wiley & Sons, Inc.; 2000. p. 437-41.

17. Toska K, Eriksen M. Respiration-synchronous fluctuations in stroke volume, heart rate and arterial pressure in humans. *J Physiol.* 1993;472:501-12.

18. Peng CK, Buldyrev SV, Havlin S, Simons M, Stanley HE, Goldberger AL. Mosaic organization of DNA nucleotides *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics.* 1994;49:1685-9.

19. Karavaev AS, Prokhorov MD, PonomarenkoVI, Kiselev AR, Gridnev VI, Ruban EI, Bezruchko BP. Synchronization of low-frequency oscillations in the human cardiovascular system. *Chaos.* 2009;19:033112.

20. Elstad M, Walloe L, Chon KH, Toska K. Low-frequency fluctuations in heart rate, cardiac output and mean arterial pressure in humans: what are the physiological relationships? *J Hypertens.* 2011;29:1327-36.

21. Latka M, Turalska M, Glaubic-Latka M, Kolodziej W, Latka D, West BJ. Phase dynamics in cerebral autoregulation. *Am J Physiol Heart Circ Physiol.* 2005;289:H2272-H2279.

22. Ocon AJ, Kulesa J, Clarke D, Taneja I, Medow MS, Stewart JM. Increased phase synchronization and decreased cerebral autoregulation during fainting in the young. *Am J Physiol Heart Circ Physiol.* 2009;297:H2084-H2095.

23. Ocon AJ, Medow MS, Taneja I, Stewart JM. Respiration drives phase synchronization between blood pressure and RR interval following loss of cardiovagal baroreflex during vasovagal syncope. *Am J Physiol Heart Circ Physiol.* 2011;300:H527-H540.

24. Quian QR, Kraskov A, Kreuz T, Grassberger P. Performance of different synchronization measures in real data: a case study on electroencephalographic signals. Phys Rev E Stat Nonlin Soft Matter Phys. 2002;65:1-12.

25. Lo MT, Hu K, Liu Y, Peng CK, Novak V. Multimodal Pressure Flow Analysis: Application of Hilbert Huang Transform in Cerebral Blood Flow Regulation. *EURASIP J Adv Signal Process.* 2008;2008:785243.

26. Wieling W, van Dijk N, de Lange FJ, Olde Nordkamp LR, Thijs RD, van Dijk JG, Linzer M, SuttonR. History taking as a diagnostic test in patients with syncope: developing expertise in syncope. *Eur Heart J.* 2015;36:277-80.

27. Low PA, Opfer-Gehrking TL, Textor SC, Schondorf R, Suarez GA, Fealey RD, Camilleri M. Postural tachycardia syndrome (POTS). *Neurology.* 1995;45:S19-S25.

28. Singer W, Sletten DM, Opfer-Gehrking TL, Brands CK, Fischer PR, Low PA. Postural Tachycardia in Children and Adolescents: What is Abnormal? *J Pediatr.* 2011 October 11.

29, Sheldon RS, Grubb BP, Olshansky B, Shen WK, Calkins H, Brignole M, Raj SR, Krahn AD, Morillo CA, Stewart JM, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm.* 2015;12:e41-e63.

30. Nowak JA, Ocon A, Taneja I, Medow MS, Stewart JM. Multiresolution wavelet analysis of time-dependent physiological responses in syncopal youths. *Am J Physiol Heart Circ Physiol.* 2009;296:H171-H179.

31. Taneja I, Medow MS, Glover JL, Raghunath NK, Stewart JM. Increased vasoconstriction predisposes to hyperpnea and postural faint. *Am J Physiol Heart Circ Physiol.* 2008;295:H372-H381.

32. Stewart JM, Taneja I, Medow MS. Reduced body mass index is associated with increased angiotensin II in young women with postural tachycardia syndrome. *Clin Sci (Lond).* 2007;113:449-57.

33. Neuhauser M, Ruxton GD. Comparing Two or More Samples of Circular Data. *Circular Statistics in R*. Oxford University Press; 2013. p. 131-48.

34. Kuchenhoff H, Carroll RJ. Segmented regression with errors in predictors: semi-parametric and parametric methods. *Stat Med.* 1997;16:169-88.

35. Convertino VA. Neurohumoral mechanisms associated with orthostasis: reaffirmation of the significant contribution of the heart rate response. *Front Physiol.* 2014;5:236.

36. van Lieshout JJ, Harms MP, Pott F, Jenstrup M, Secher NH. Stroke volume of the heart and thoracic fluid content during head-up and head-down tilt in humans. *Acta Anaesthesiol Scand.* 2005;49:1287-92.

37. Vatner SF, Boettcher DH. Regulation of cardiac output by stroke volume and heart rate in conscious dogs. *Circ Res.* 1978;42:557-61.

38. Weissler AM, Leonard JJ, Warren JV. Effects of posture and atropine on the cardiac output. *Circ Res.* 1957;36:1656-62.

39. Montano N, Cogliati C, Porta A, Pagani M, Malliani A, Narkiewicz K, Abboud FM, Birkett C, Somers VK. Central vagotonic effects of atropine modulate spectral oscillations of sympathetic nerve activity. *Circulation.* 1998;98:1394-9.

40. Segerson NM, Wasmund SL, Daccarett M, Fabela ML, Hammond CH, Stoddard G, Smith ML, Hamdan MH. The acute effect of atrioventricular pacing on sympathetic nerve activity in patients with normal and depressed left ventricular function. *Am J Physiol Heart Circ Physiol.* 2008;295:H1076-H1080.

41. Stead EA, WARREN JV, Merrill AJ, Brannon ES. The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization Normal Values with observations on the Effect of Anxiety and Tilting. *J Clin Invest.* 1945;24:326-31.

42. Jardine DL, Wieling W, Brignole M, Lenders JW, Sutton R, Stewart JM. The pathophysiology of the vasovagal response. *Heart Rhythm.* 2018;15:921-9.

43. Carter JR, Lawrence JE, Klein JC. Menstrual cycle alters sympathetic neural responses to orthostatic stress in young, eumenorrheic women. *Am J Physiol Endocrinol Metab.* 2009;297:E85-E91.

44. Fu Q, Vangundy TB, Shibata S, Auchus RJ, Williams AJ, Levine BD. Menstrual cycle affects renal-adrenal and hemodynamic responses during prolonged standing in the postural orthostatic tachycardia syndrome. *Hypertension.* 201;56:82-90.

Table 1. Subject anthropometrics and supine resting baseline measurements in Control, POTS, VVS and IST

	Control (N=12)	POTS (N=30)	VVS (N=30)	IST (N=9)
Age (yrs)	17 ± 1	17± 1	18 ± 1	18 ± 1
Height (cm)	171 ± 2	166 ± 2	164 ±4	165 ± 4
Weight (kg)	68 ± 2	59 ± 2*	68 ± 5	64 ± 2
BMI (kg/m2)	23.5 ± 0.7	21.0 ±0.5*	24.5 ± 0.9	22.6 ±0.6
HR (bpm)	65 ± 2	79 ± 3*	69 ± 4	100 ± 4*
Resp Rate (breaths/min)	13.6 ± 2.4	14.6 ± 1.2	15.0 ± 1.0	14.7 ± 1.9
SAP (mmHg)	112 ± 4	114 ± 2	116 ± 3	114 ± 4
DAP (mmHg)	58 ± 4	66 ± 2*	60 ± 3	69 ± 4*
MAP (mmHg)	72 ± 4	82 ± 1*	77 ± 3	84 ± 3*
CO (L/min)	5.3 ± 0.3	5.2 ± 0.3	4.8 ± 0.3	5.5 ± 0.8
SVR (mmHg/L/min)	14 ± 2	16 ± 1	16 ± 1	16 ± 2

POTS, postural tachycardia syndrome; VVS, vasovagal syncope; IST, inappropriate sinus tachycardia; BMI, body mass index; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CO cardiac output; SVR, systemic vascular resistance. all values ± SE. * $P < 0.01$

Table 2. Change in Hemodynamic Variables during HUT

	Control (N=12)	***POTS (N=30)***	***VVS (N=30)***	***IST (N=9)***
ΔHR (bpm)	20 ± 2	55 ± 4*	40 ± 4*	40 ± 4*
ΔResp Rate (breaths/min)	2.0 ± 2.2	2.1 ± 2.6	1.0 ± 1.2	0.8 ± 1.4
ΔSAP (mmHg)	20 ± 2	8 ± 2*	-17 ± 3*	8 ± 4*
ΔDAP (mmHg)	10 ± 4	14 ± 2	-6 ± 3*	6 ± 2*
ΔMAP (mmHg)	12 ± 3	14 ± 2	-10 ± 3	6 ± 3*
ΔCO (L/min)	-0.29± 0.13	-0.95 ± 0.13	1.00 ± 1.51	-0.92 ± 0.31
ΔSVR (mmHg/L/min)	4 ± 1	8 ± 1‡	-2 ± 1*	5 ± 1
Δ%CBV	-7 ± 3	-14 ± 2*	-9 ± 2	-11 ± 3
Tilt Duration (seconds)	600	535 ± 35	559 ± 51	545 ± 31

* P < 0.01 and ‡ P < 0.0167

Table 3. Correlation of Hemodynamic Variables with Cos(Δϕ)

	CONTROL (N=12)	***POTS (N=30)***	***VVS (N=30)***	***IST (N=9)***
HR (bpm)	0.017	-0.743*	-0.686*	-0.704*
MAP (mmHg)	0.001	-0.076	-0.018	-0.098
CO (L/min)	0.001	0.118	0.116	0.149
SVR (mmHg/L/min)	0.002	0.101	0.075	-0.108
Δ%CBV	0.001	0.006	-0.126	0.131
Resp Rate (breaths/min)	0.001	0.004	0.028	0.015

*P < 0.001

Figure Legends

Figure 1 shows a CO-HR relationship in which loading conditions are controlled. There is a peak in the relationship. At HR less than the peak, increasing HR increases CO. At HR greater than the peak increasing HR decreases CO. We will define these states respectively as “in-phase” and “anti-phase” coupling.

Figure 2: Panel A shows perfect “in-phase” coupling of HR to CO below the CO peak such that fluctuations of HR would lead to directionally similar fluctuations in CO. This state of perfect phase alignment might exist in the absence of noise or external forces. This contrasts with Panel B which shows “anti-phase” coupling of HR to CO (also known as completely out of phase) above the CO peak such that fluctuations of HR would lead to directionally opposite fluctuations in CO. The phase difference in perfectly in-phase signals is 0^o (alternately 0 radians). The phase difference in perfectly anti-phase signals is 180^o (alternately π radians).

Figure 3 depicts a natural way to examine the relation between $\Delta\Phi$ and HR is to graph $\Delta\Phi$ on the unit circle where in-phase comprises the right half, and anti-phase comprises the left half plane. This can be rendered this statistically amenable by taking the cosine of $\Delta\Phi$. $\text{Cos}(\Delta\Phi)>0$ in the right hand plane, and $\cos(\Delta\Phi)<0$ in the left hand plane. A transition from in-phase to anti-phase would correspond to zero-crossing of $\cos(\Delta\Phi)$.

Figure 4 showed preprocessing performed on the original and CO signals, the means of which were calculated over respirations, then band passed to obtain signals that oscillated around 0.

Figure 5 shows a polar coordinates representation of the relationship between ΔΦ and HR when phase synchronized. Baseline and tilted HR are included. HR was significant increased ($P<0.001$) in the left half plane compared with the right half plane for patient groups. Excepting the controls, points were similarly distributed by angle for given HR and were independent of group.

Figure 6 uses a cosine transform to compute statistics of $HR_{transition}$ for IST, POTS and VVS and to make HR and phase relationships more apparent. cos(ΔΦ) is graphed as a function of HR. The percentage of points which were negative (antiphase) was greatest in IST > POTS > VVS, because HR's were more often higher in IST and POTS than VVS. Nevertheless, no difference among groups for $HR_{transition}$ was found.

What is known:

- Venous return and thus cardiac output (CO) decrease during orthostasis. An upright increase in heart rate (HR) is generally regarded as compensatory support of CO. However, animal work indicates that HR increases CO up to a maximum above which CO falls with rising HR.
- The maximum depends directly on central blood volume, which is reduced during orthostasis. Very high heart rates may be achieved during orthostasis in postural tachycardia syndrome, inappropriate sinus tachycardia and vasovagal syncope (VVS).

What the study adds:

- Our study demonstrated an "inverted U-shape" dependence of CO on HR when upright in which CO increases to a maximum with increasing HR and then declines with further heart rate increases.
- This occurs at a similar HR between 120-130 beats/minute for all forms of orthostatic intolerance investigated. Excessive upright tachycardia critically reduces stroke volume independent of specific disease pathophysiology.
- Lowering HR to less than compromising heart rates could improve CO independent of other forms of therapy.