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Short communication

Normal versus abnormal: What normative data tells us about the utility of heart rate in postural tachycardia

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1. Introduction

The autonomic reflex screen (ARS) has been established as an important clinical tool in the evaluation and diagnosis of autonomic disorders (Low, 2003). Specifically, passive Head-up Tilt (HUT) to a minimum 60° angle from the horizontal provides an orthostatic challenge that is sensitive in diagnosing disorders of orthostatic intolerance, including but not limited to, neurogenic orthostatic hypotension, autonomic failure, postural orthostatic tachycardia syndrome, syncope, etc. (Low and Benarroch, 2008). While various pathologies can adversely affect normal autonomic functioning, age also plays a significant role in the responsiveness and integrity of the autonomic nervous system. Therefore, from a clinical perspective it is important to acquire and maintain normative data across various age groups to more clearly pars out the effects of normal aging versus a pathological state. For example, the current clinical definition of postural orthostatic tachycardia syndrome (POTS) is a heart rate (HR) increment ≥30 bpm on HUT or active standing and the absence of orthostatic hypotension (Low et al., 2008). However, in children and adolescents, previous reports demonstrate considerable overlap between patients and controls with 42% of the controls meeting or exceeding the HR criteria for POTS (Singer et al., 2012). Moreover, in 2015 the Heart Rhythm Society released an expert consensus statement observing a HR increment ≥40 bpm should be considered in individuals aged 12–19 years (Sheldon et al., 2015). However, a growing source of literature has begun to accumulate to suggest that these findings have expanded such that even young adults frequently manifest benign postural tachycardia at levels ≥30 bpm on HUT without any associated orthostatic symptoms (Baker and Kimpinski, 2015). To better understand 'normal' values, and to accurately assess the presence or absence of disease, clinicians require the most up-to-date and representative sample that can be acquired. As such, it is important for individual clinics to generate their own normative dataset to account for differences between different geographical regions, populations and laboratories (Low and Benarroch, 2008). Therefore, the objective of the current report was to provide normative hemodynamic values with a specific focus on heart rate and blood pressure changes during Head-up Tilt that is representative of young, middle aged and older individuals from Ontario, Canada.

2. Methods

2.1. Participants

All healthy participants were recruited from the general population. Recruitment strategies included: poster and newspaper advertisements, as well as in person from activity centers. All study participants were examined to confirm the absence of any neurological conditions including any autonomic and orthostatic dysfunction. Additionally, due to the potential influence on the autonomic nervous system, healthy participants were excluded if they fell under any one of the following categories: i) pregnant or lactating females, ii) clinically significant coronary artery disease, iii) concomitant therapy with anticholinergic, alpha- and beta-adrenergic antagonists or other medications which could interfere with autonomic functioning, and iv) failure of other organ systems or systemic illness that could affect autonomic function or participants' ability to cooperate. Ethical approval for this study was obtained from the Health Sciences Research Ethics Board at Western University and written informed consent was obtained from all study participants.

2.2. Autonomic testing

All study participants underwent a standard Head-up Tilt (HUT) test as previously described (Low, 2003). In brief, following a minimum 15-minute baseline in the supine position, participants were passively tilted to a 70° angle from the horizontal for 5 min, followed by a 5-minute recovery period back in the supine position. Heart rate (HR) and blood pressure (BP) changes during HUT were captured between the 3rd and 5th minute of HUT. Maximum HR was calculated as a peak average, maintained for a minimum of 10 s to ensure an aberrant/transient HR spike was not captured. This peak average was subtracted

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from the average supine HR to calculate a heart rate change in response to HUT. Similar methods were taken to obtain average BP changes. HR and BP were continuously recorded using an electrocardiography (ECG) device (Model 3000 Cardiac Trigger Monitor, IVY Biomedical Systems, Inc., Branford, CT) and Nexfin hemodynamic monitoring system (BMEYE Cardiovascular, Amsterdam, Netherlands), respectively. All data were recorded and analyzed using WR Testworks™ software. In addition, all participants were asked to complete the Autonomic Symptom Profile (ASP) to provide a self-reported measure of orthostatic intolerance (Suarez et al., 1999). The ASP is a validated self-report questionnaire comprised of 169 questions pertaining to various domain of autonomic health. For the current study, we evaluated the Orthostatic Index of the ASP, to provide a measure of orthostatic intolerance with a maximum obtainable score of 40.

2.3. Statistical analysis

Orthostatic Index scores are presented as mean ± standard deviation. Hemodynamics (heart rate and blood pressure) are presented percentiles (2.5th, 5th, median, 95th, 97.5th). To evaluate the effect of age and sex, a multiple stepwise regression analysis was performed. A one-way ANOVA was used to evaluate differences between age groups (young vs. middle-aged vs. old) with a Bonferroni correction for multiple comparisons. An alpha level of 0.05 was used to denote significance. The procedures for setting normative values were completed according to the methods outlined by O'Brien and Dyck (1995). All statistical analyses were performed using SPSS® statistical software version 21 for Windows (SPSS, Inc., Chicago, IL).

3. Results

A total of 252 participants (age: 42 ± 21; range: 18–94 years) were including in the current study. Participant were grouped as young (18–29 years; $n = 123$) middle aged (30–59 years; $n = 59$) and old (60–94 years; $n = 70$). Resting heart rate (RHR) regressed significantly with age ($p < 0.047$) and sex ($p < 0.001$). RHR as a function of age can be expressed as $Y = 0.06X + 59.8$, where Y = RHR (bpm) and X = age (years). Due to the significant effect of sex, RHR data for males and females were separated. Subsequent regressions demonstrated that females maintained a significant effect of age on RHR ($Y = 0.12X + 59.1$) ($p < 0.005$) (Fig. 1A), while males did not ($p = 0.80$) (Fig. 1B). Median and percentile data (2.5th, 5th, 95th, and 97.5th) for RHR in males and females are presented in Table 1. In contrast, heart rate change (ΔHR) during HUT regressed significantly with age ($p < 0.001$), but not sex ($p = 0.187$). The ΔHR (Y) can be expressed as: $Y = -0.37X + 42.2$, where X = age (years) (Fig. 1C). Similarly, there was a significant effect of age on resting systolic BP ($p < 0.001$) and ΔSBP ($p = 0.02$) during HUT (Fig. 2A and B). The RSBP and ΔSBP (Y) can be expressed as $Y = 0.45X + 105.2$ and $Y = -0.08X - 3.3$, respectively, where X = age (years). Median and percentile data (2.5th, 5th, 95th, and 97.5th) for ΔHR and ΔSBP in young, middle aged and older groups during HUT are presented in Table 2.

3.1. Orthostatic index

Young individuals scored significantly higher than older individual on the orthostatic index of the Autonomic Symptom Profile (ASP) (7.57 ± 7.38 versus 3.62 ± 5.26, respectively). No other significant differences were found. Despite the significance between young and older individuals, the mean score in our young population is clinically unremarkable compared to patients diagnosed with orthostatic intolerance. For example, our laboratory recently reported an average orthostatic symptom score of 27.8 ± 9.6 in patients diagnosed with orthostatic intolerance (Baker et al., 2019). These results are congruent with other clinics that have reported Orthostatic Intolerance scores of 30.2 and 21.6 for patients with postural tachycardia and neurogenic autonomic failure, respectively (Kimpinski et al., 2012; Suarez et al., 1999).

4. Discussion

The objective of the current study was to investigate normal hemodynamic parameters in response to a standardized orthostatic challenge. The results are consistent with data previously reported (Ives and Kimpinski, 2013; Low et al., 1997). Importantly, our results demonstrate that all hemodynamic parameters associated with HUT regressed significantly with age. The effects of natural aging play a critical role in the normal functioning of the autonomic nervous system (Ingall et al., 1990). In the current study we see that with progressive aging, HR and BP changes in response to HUT are reduced and resting SBP tend to increase. The BP data are consistent with many previously reported studies showing an increased prevalence of both hyper- and orthostatic hypotension with age, particularly among adults aged 65 years and older (Low, 2008; McDonald et al., 2009). Importantly, the most prevalent forms of orthostatic hypotension associated with normal aging (i.e. hypotension due to endocrine issues, generalized low pressure, hypovolemia) can be parsed out from any underlying neurodegenerative causes with appropriate standardized tests. In contrast, the relationship between aging and HR response remains controversial. In the current study, there was a significant reduction in the HR responses associated with normal aging. However, the controversy lies at the other end of the spectrum, when this relationship is viewed in reverse in that young to middle aged individuals manifest larger HR responses to HUT despite smaller BP drops. Given this significant relationship and the lack of any clinically significant orthostatic symptomatology, we would argue that the current hemodynamic values represent normal orthostatic responses, despite meeting the physiological criterion for POTS. Previous studies suggested that the current HR criterion for the diagnosis of POTS be reconsidered in adolescent patient populations (< 18 years) (Singer et al., 2012), an issue that was address in a 2015 consensus statement by the Heart Rhythm Society (Sheldon et al., 2015). We would argue this point further to suggest that even among young healthy adults the current HR increment of 30 bpm is a normal response, warranting reconsideration in age groups beyond pediatric patient populations. Our young adult population (18–29 years) attained an average HR response of 33.7 bpm on HUT, with ΔHR's > 40 bpm for individuals in the 95th percentile. So why is this important? The age range for most POTS patients is 15–40 years (Low et al., 2008). Given the high propensity for young healthy adults to express higher HR increments on orthostatic challenges, it is reasonable to question whether younger individuals who present with, arguably a normal HR response, along with some constitutional symptoms such as generalized lightheadedness, dizziness, fatigue, etc. that aren't appropriately interpreted, may be over diagnosed with POTS. For example, if you take generalized non-specific symptomatology such as fatigue, dizziness, and lightheadedness, but do not appropriately discriminate these symptoms as postural versus non-postural, then you are likely to overdiagnose POTS. The issue of over diagnosis also becomes relevant in syndromes such as chronic fatigue syndrome, chronic pain and fibromyalgia, where orthostatic intolerance is a common impression (Joyner and Masuki, 2008). However, in such conditions where issues like deconditioning are highly prevalent, benign orthostatic tachycardia combined with physical deconditioning could be misconstrued as POTS, creating addition, yet unnecessary, complicating treatments. Overall, more work is needed to better understand the pathophysiology of POTS, and the multitude of underlying factors that may contribute to heart rate increments and symptomatology. It is also important to emphasize that despite the name, “postural orthostatic *tachycardia* syndrome”, heart rate increments are not and should not be the whole criteria for diagnosis. This point becomes even more evident as studies have shown that heart rate changes do not correlate with symptoms (Baker and

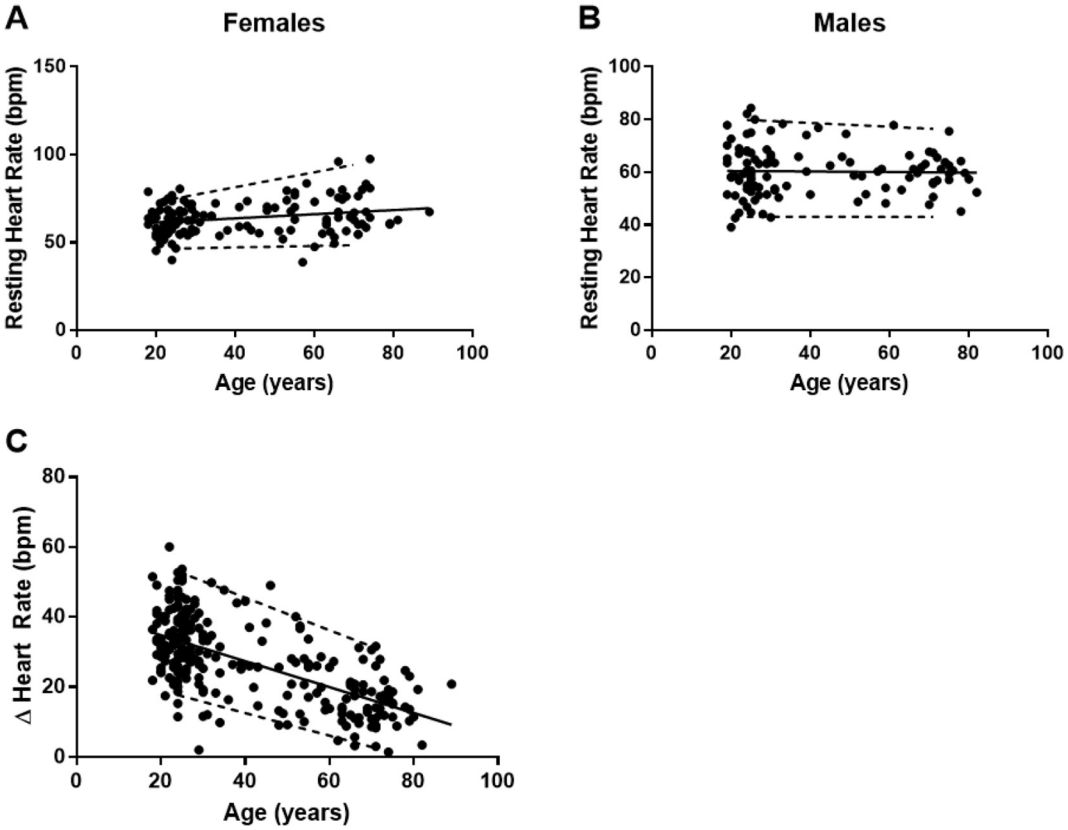

Fig. 1. Resting heart rates regressed significantly with age in females (A), but not males (B). There was a significant effect of age on delta heart rates (C) during head-up tilt ($p < 0.001$). Dashed lines represent the 5th and 95th percentiles, solid line represents the linear regression. Abbreviations: bpm, beats per minute; Δ, change.

Table 1
Female and male percentile values (2.5, 5, Median, 95, and 97.5) for resting heart rates.

Age	RHR percentile (female; male) (bpm)				
	2.5	5	Median	95	97.5
18–29 years	43.3; 40.4	47.3; 43.7	62; 58.7	76.4; 80.6	79.5; 86.6
30–59 years	38.8; 42.9	46.0; 42.3	65.4; 60.8	81.4; 77.7	–
60–94 years	47.5; 45.1	49.3; 43.3	64.2; 60.2	96.1; 76.8	–

ΔHR; heart rate change; bpm, beats per minute.

Kimpinski, 2015), and the ability to lower a patient's heart rate, does not result in significant improvements in symptomatology. Nonetheless, in the context of the current study, it is important to understand normative hemodynamic data and how these data may change with aging, to be able to apply this knowledge within a clinical setting.

4.1. Study limitations

It is important to note that the current study is limited to the population of Ontario, Canada. As a result, these data may not be representative of all populations across different geographical regions. Therefore, as previously noted, it is important for individual clinics to generate their own normative dataset to account for differences between geographical regions, populations and laboratories. However,

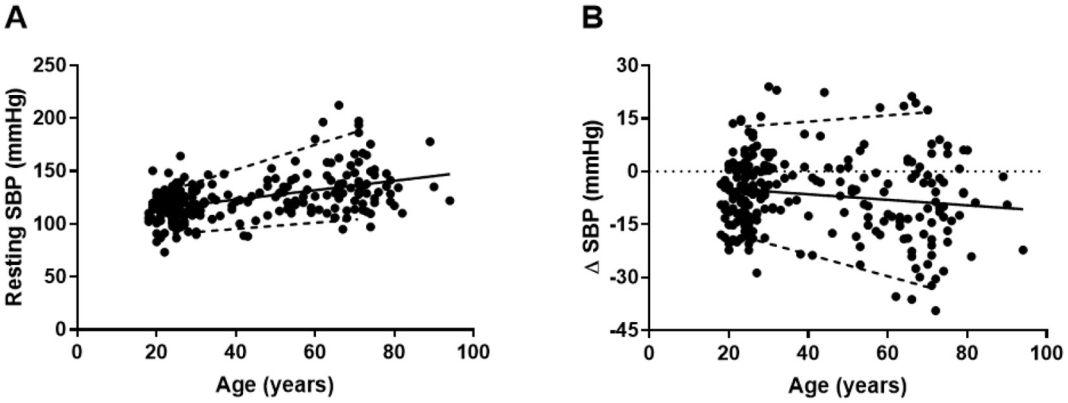

Fig. 2. Resting systolic (A) and Δsystolic (B) blood pressures regressed significantly with age ($p < 0.001$; $p = 0.02$, respectively). Dashed lines represent the 5th and 95th percentiles, solid line represents the linear regression. Abbreviations: SBP, systolic blood pressure; mmHg, millimeters of mercury.

Table 2
Percentile Values (2.5, 5, Median, 95, and 97.5) for resting/supine systolic blood pressure and heart rate and blood pressure responses to Head-up Tilt.

Age	2.5	5	Median	95	97.5
Percentile (ΔHR) (bpm)					
18–29 years	15.4	18.8	33.7	50.9	52.7
30–59 years	9.2	9.8	26.0	47.7	49.4
60–94 years	2.5	3.3	15.6	29.7	31.3
Percentile (RSBP) (mmHg)					
18–29 years	87	93	116	137	141
30–59 years	89	92	122	147	150
60–94 years	99	106	135	191	197
Percentile (ΔSBP) (mmHg)					
18–29 years	−21	−20	−6	10	14
30–59 years	−24	−22	−3	19	23
60–94 years	−37	−34	−10	15	19

ΔHR, heart rate change; RSBP, resting systolic blood pressure; ΔSBP, systolic blood pressure change; bpm, beats per minute; mmHg, millimeters of mercury.

the current data are still important, particularly for laboratories/clinics that have not or cannot generate their own normative data. Additionally, 5-min of tilt was used instead of 10 min, with the latter time window typically used for POTS. However, the current results are still valid as it is unlikely that the HR would have decreased between 5 and 10 min suggesting the current HR data may actually be modest compared to HR responses to a longer tilt. Finally, participants were not tested at any particular time of day and diet was not controlled. Participants were not instructed to alter their normal daily routines as we wanted to be able to collect data that are the most representative of a normal population on any given day. We believe these data provide a truer presentation of 'normal' to have available for comparison with clinical populations.

5. Conclusion

The current study supports previous reports surrounding the age-related effects on heart rate and blood pressure in response to a standard orthostatic challenge. Furthermore, there continues to be a growing number of studies questioning the diagnostic criteria used for POTS and the current study adds further evidence to support the argument for modification of the current criteria in younger adult populations.

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