Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Baroreceptor activity and sensitivity: normal values in children and young adults using the head up tilt test

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BACKGROUND: Baroreceptor function in children and adolescents has not been well studied in the current literature, with a lack of agreed upon normal values. The authors hypothesize that there is a significant increase in the baroreceptor activity with a decrease in the sensitivity during the upright phase in comparison to the supine phases of the head upright tilt test (HUTT) protocol.
METHODS: Baroreceptor evaluation was performed using the sequence method in 49 subjects ages 8–21 years, during the 3 phases of HUTT: supine, head up, and post-tilt supine positions. Baroreceptor Effectiveness Index (BEI) and the number and slope of baroreceptor events were recorded.
RESULTS: On study of the events and slope values, there was a significant difference between the three phases of the HUTT with regard to the baroreceptor activity and sensitivity. No significant difference was found in BEI.
CONCLUSIONS: Our study presents normal values of baroreceptor activity, sensitivity, and BEI in pediatric patients under controlled supine and head up position. We also present new data regarding delayed heart rate responses to pressure changes in the Lag 1 and Lag 2 parameters, which may be beneficial in diagnosis and management of pediatric patients with orthostatic intolerance.

Pediatric Research (2019) 85:841–847; https://doi.org/10.1038/s41390-019-0327-6

INTRODUCTION

The baroreceptor reflex is an intrinsic mechanism for controlling both acute and chronic changes in systemic blood pressure.[1] This reflex is vital in the adjustment of second to second variations in blood pressure to maintain homeostasis and stable perfusion to the vital organs. Dysfunction of this reflex has been shown to result in short- and long-term variations in systemic blood pressure. A decrease in baroreceptor activity has been demonstrated in patients with autonomic disorders, hypertension, and diabetes mellitus and is implicated in the increased morbidity and mortality of these disorders.[1–3]

The baroreceptor reflex offers a congregate measure of the overall sympathetic and parasympathetic input to the baroreceptors, which manifests as the heart rate response to blood pressure variation.[4] Historically, baroreceptors were assessed pharmacologically using invasive measurements of blood pressure and heart rate. This method has obvious drawbacks secondary to the risks of invasive measurement procedures and the side effects of pharmacological manipulation of multiple physiologic regulatory mechanisms outside of the arterial baroreceptors that were the focus of the studies.[5] Newer techniques have been developed to quantify the baroreceptor reflex, including the sequence and spectral methods, taking advantage of noninvasive methods of blood pressure and heart rate measurement. These non-invasive methods of measurement have been validated against the pharmacological methods with reliable results.[6–8]

The majority of research on baroreceptor reflex function has been performed in the adult population with established normal values.[2,9–12] The few published articles documenting baroreceptor sensitivity values in children and adolescents have variable definitions and protocols, and often incorporate special patient groups not generalizable to the greater population,[4,13–20] leaving a knowledge gap in regards to well-defined normal reference values and terminology, thus making comparison between studies difficult. To objectively describe the qualities of the carotid baroreceptors and use that information to help diagnose and identify variation between normal subjects and autonomic pathologies, further investigation into this topic is necessary to add to the literature. The head upright tilt test (HUTT) is a verified method to evaluate baroreceptor activity changes in both the supine and prone positions.[6,21]

This study aims to use the HUTT to discern the variations in the baroreceptor activity during the different phases of measurement and to establish robust normal reference values for the pediatric age group. This study also attempts to define the qualities of the baroreceptors to better describe terminology for future reference. We hypothesize that there will be a significant increase in the baroreceptor activity with a decrease in the sensitivity during the upright phase in comparison to the supine phases of the HUTT protocol as part of the normal autonomic response to the gravitational stress.

METHODS

Subjects

This was a prospective review of cataloged HUTT data obtained at the Children's Memorial Hermann Hospital and the McGovern

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Received: 26 September 2018 Revised: 16 January 2019 Accepted: 28 January 2019
Published online: 6 February 2019

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Table 1. Demographics

Age (median)	8–21 years (8)
Gender	43% Male
	57% Female
Ethnicity	49% Caucasian
	37% Hispanic
	14% African American
Weight (median)	25–104 Kg (54)

Medical School, The University of Texas Health Science Center at Houston, Houston, TX. Our study enrolled 60 healthy volunteer pediatric subjects between 2015 and 2017 following exclusion of subjects with any diagnosed neurologic or cardiovascular medical conditions. Eleven subjects were subsequently excluded for incomplete data records. The 49 subjects included in the study were aged 8–21 years, with 21 males and 28 females, with demographics as noted in Table 1. The subjects included in this cohort were not taking any prescription medications and the measured heart rate, respiratory rate, blood pressure, and body mass index were noted in the normal range for their age at the time of HUTT study. Blood pressure was monitored as part of the study and patients with blood pressures outside the normal range of the 10th–90th percentile for age, gender, and height were excluded from the study. No subjects suffered orthostatic intolerance during the HUTT procedure. Subjects aged <7 years were excluded owing to difficulty with compliance during the HUTT procedure. Consent was obtained from the subjects and/or parents, and this study was approved by McGovern Medical School, The University of Texas Health Science Center at Houston Institutional Review Board.

HUTT procedure

HUTT was performed according to a protocol divided into three phases. Phase 1 was the pre-tilt phase consisting of a 10-min supine period, followed by phase 2 defined as an upright head up tilt to 65–70 degrees for 30 min, followed by phase 3 consisting of another 10 min of recording while the subject was in a supine position. Vital signs in subjects were recorded using the Task Force Monitor by CNSystems® Graz, Austria and consisted of a continuous electrocardiogram, continuous heart rate, and non-invasive finger blood pressure measurements standardized with biceps cuff pressure measurements every minute. The HUTT procedure was performed while being monitored by a physician to ensure proper recording of goal measurements and manually validated at the time of testing. Patients were fasting from midnight prior to the HUTT procedure. In review of the literature, there is wide variation in HUTT procedures regarding time during each phase with no agreed upon standardized protocol. For our study, we conducted the HUTT according to our institutional protocol, in which the time and degree of the HUTT is within the range of what has been performed in the published literature.[21,22]

Goal measurements

The sequence method[23] was used to evaluate baroreceptor reflex function with the focus on three goal measurements. The first goal measurement is the overall activity of the baroreceptors, defined as the number of events per minute. A baroreceptor event is identified as a change in blood pressure >1 mm Hg per heart beat spanning over at least 3 heart beats, with an associated change in heart rate defined as a change in R-R interval ≥4 ms (Fig. 1). Lag between the change in systolic pressure and heart rate was defined at Lag 0 where the changes in the R-R interval and blood pressure were synchronized, Lag 1 where the change in heart rate was delayed by 1 R-R interval from the change in blood pressure,

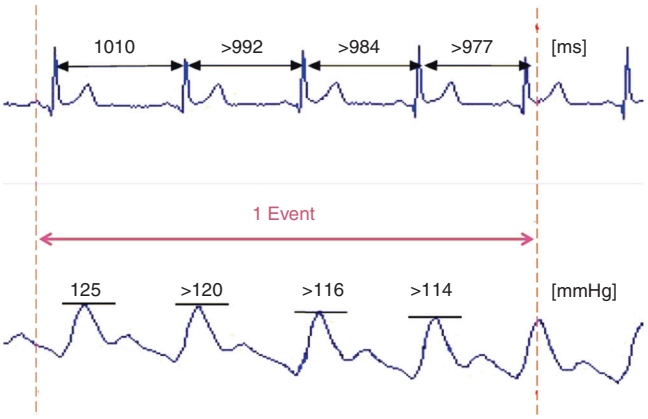

Fig. 1 Baroreceptor events. The figure shows an example of one event, where a blood pressure decrease spanning 5 heart beats from the initial 125 to 114 mm Hg (bottom tracing) resulted in an increase in the heart rate shown by a decrease of the R-R interval from 1010 to 977 ms (top tracing). An event was recorded when there was at least a 1 mm Hg change per heart beat, lasting at least 3 beats with an associated change in the R-R interval of at least 4 ms

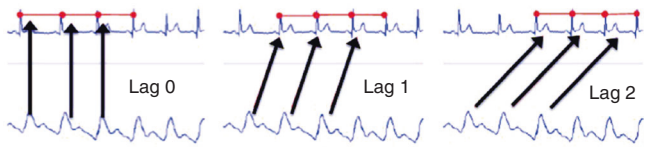

Fig. 2 Lag events. The figure shows the examples of Lag 0, 1, and 2 with the tracing on the bottom of the boxes representing the blood pressure and the tracing on the top of the boxes representing the heart rate. Box A depicts Lag 0 where the heart rate changes are synchronized with the blood pressure changes. Box B depicts Lag 1 where the heart rate changes are delayed by 1 R-R interval from the blood pressure change, and box C depicts Lag 2 where the heart rate change is delayed by 2 R-R intervals

and Lag 2 where the change in heart rate was delayed by 2 R-R intervals from the change in blood pressure (Fig. 2). Total numbers of events were tabulated throughout each phase of the HUTT and standardized based upon the length of the phase and reported as events per minute. The baroreceptor activity was chosen as a goal measurement because it provides information regarding the amount of input the baroreceptors have on the cardiac output. Measuring the activity also gives a general sense of the amount of blood pressure variations that the baroreceptors intervene on and adjust and how this varies in the different body positions of the HUTT.

The second goal measurement was the Baroreceptor Effectiveness Index (BEI) reported as the proportion of events that occurred divided by the total number of blood pressure changes that took place, including those instances with no associated heart rate change. This value provides information regarding how effective the baroreceptors are in responding to all the blood pressure changes. It also helps to identify if there is an amount or frequency of activity where the baroreceptors reach a point and are unable to continue to make adjustments for the blood pressure changes because the baroreceptors remain refractory to further stimuli. The BEI was reported as a percentage of total blood pressure changes using the equation:

$$\mathrm{BEI} = (\#\,\mathrm{events}/\mathrm{total}\,\#\,\mathrm{of\ blood\ pressure\ changes} > 1\ \mathrm{mmHg}) \times 100\%$$

The third goal measurement was the sensitivity of the baroreceptors, which was measured by the slope of the events and defined as the degree of heart rate change for each blood

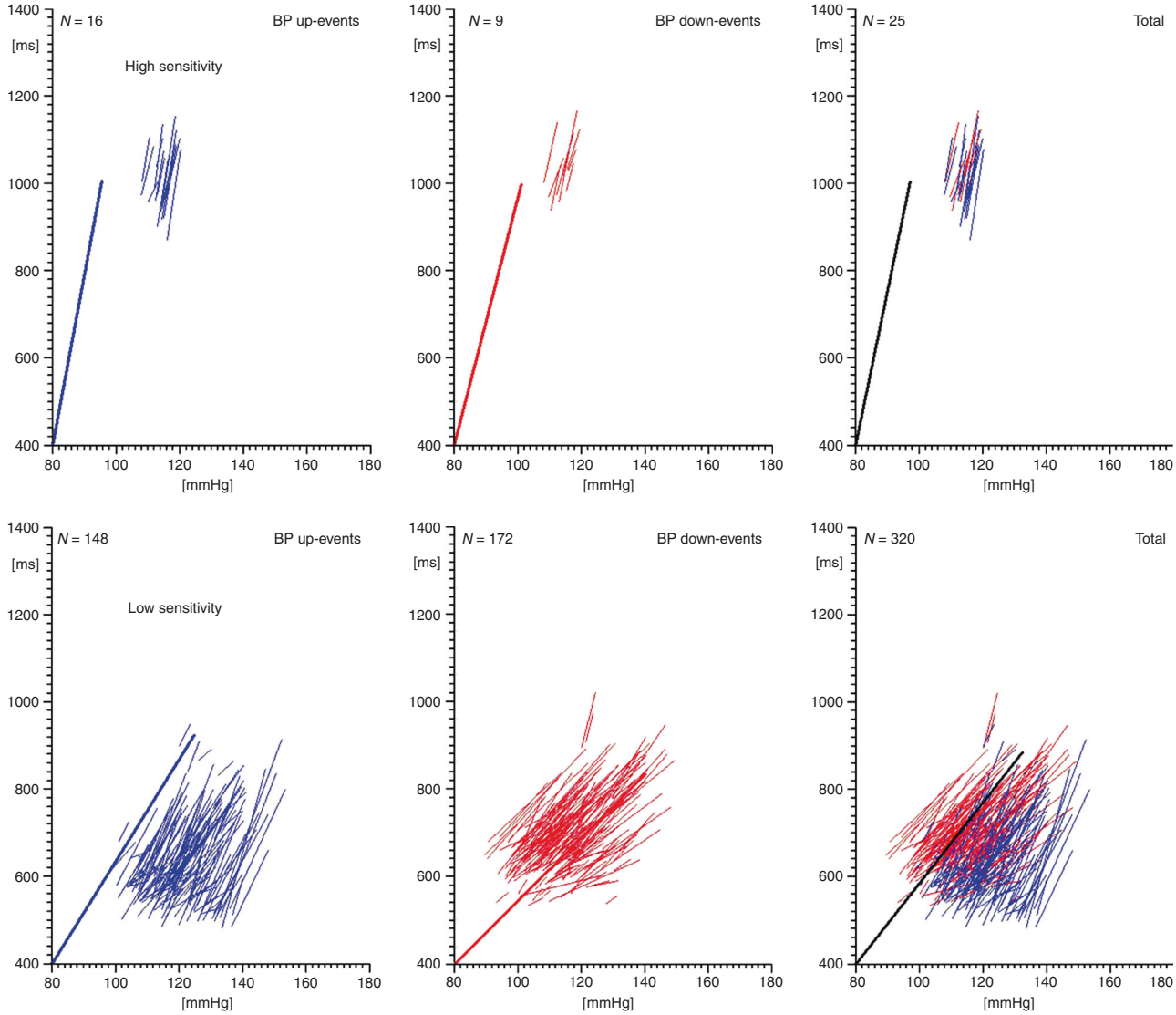

Fig. 3 Slope of baroreceptor events. The figure is a graphic representation of baroreceptor sensitivity defined by the slope, measured as ratio of change in heart rate/change in blood pressure. A steep slope indicates a large heart rate change in response to a blood pressure change representing a highly sensitive baroreceptor response (top graphs). Conversely, the low sensitivity baroreceptor response is shown by the graph with shallow slopes, which indicates a small heart rate change in response to a blood pressure change (bottom graphs)

pressure change. This was reported as ms/mm Hg using the equation:

$$\text{Slope} = \Delta R - R/\Delta BP,$$

with a steep slope indicating a high sensitivity and a shallow slope a low sensitivity (Fig. 3). The slope of events were also further identified based on the change of the blood pressure where an increase was defined an "up event" and a decrease was defined as a "down event." The sensitivity helps identify how effective the baroreceptor is at adjusting the heart rate to maintain cardiac output in a stable level. The sensitivity also helps identify how the baroreceptors change in response based on body position.

Data analysis

Descriptive statistics (mean, standard deviation) and box plots were provided for each Lag at each phase of events per minute, for each phase of BEI, and slope (Tables 2–4, Figs. 4–6). Comparisons among different Lags and phases of events per minute and comparisons among different phases of BEI and slope were conducted in a generalized linear mixed model with empirical estimators to account for the within-subject correlation robustly.[24] *P* values for post hoc comparisons were adjusted by the Tukey method for multiple comparisons and significance set at *P* value <0.05. All data analyses were performed in SAS 9.4 (Cary, NC).

RESULTS

Baroreceptor activity

In the baroreceptor activity values reported as events per minute in Table 2, there was a significant difference (all *P* values <0.05) in all the Lag groups on comparing phases 1 vs. 2 and 2 vs. 3 (Fig. 4). Furthermore, when comparing phase 1 vs. 3, there was a significant difference in Lag 0 and Lag 2 (*P* value = 0.02 and 0.004, respectively), but no significant difference was found in Lag 1 (*P* value = 0.39). On comparing different Lag values, there was a significant decrease in events/min from Lag 0 to Lag 1 to Lag 2 (all *P* values < 0.05).

Table 2. Events HUTT study results

	Phase 1—Baseline	Phase 2—HUTT	Phase 3—Post-tilt	Phase comparison	*P* value
Events (events/min) (mean ± SD)					
Lag 0	4.2 ± 3	7.2 ± 2.9	5.5 ± 2.9		
				Baseline vs. HUTT	<0.0001
				Baseline vs. Post-tilt	0.02
				HUTT vs. Post-tilt	<0.0001
Lag 1	2 ± 2.3	6.4 ± 2.8	2.4 ± 1.8		
				Baseline vs. HUTT	<0.0001
				Baseline vs. Post-tilt	0.39
				HUTT vs. Post-tilt	<0.0001
Lag 2	1 ± 0.8	4.3 ± 2.2	1.5 ± 1.2		
				Baseline vs. HUTT	<0.0001
				Baseline vs. Post-tilt	0.004
				HUTT vs. Post-tilt	<0.0001
P value					
Lag 0 vs. 1	<0.0001	0.03	<0.0001		
Lag 0 vs. 2	<0.0001	<0.0001	<0.0001		
Lag 1 vs. 2	0.001	<0.0001	0.04		

HUTT head upright tilt test

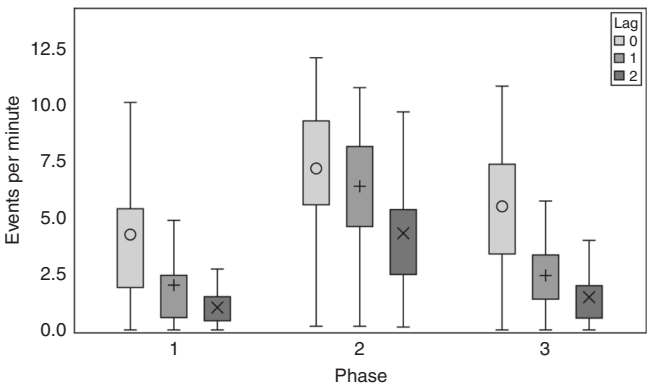

Fig. 4 Event comparison across different phases of the head upright tilt test (HUTT). The figure shows the box plot distribution of events/min in Lag 0, 1, and 2 across the 3 phases of the HUTT. Mean values depicted by circle, plus, and cross markings. Events/min significantly decrease from Lag 0 to 1 to 2 in the supine phases 1 and 3, with a significant increase in events/min during the head up phase 2 in comparison to the supine phases 1 and 3

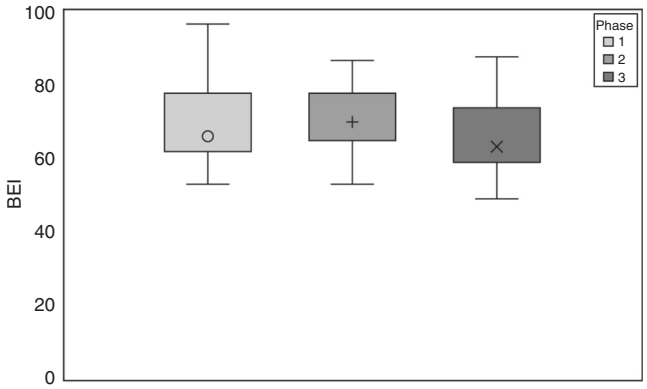

Fig. 5 Baroreceptor Effectiveness Index (BEI) comparison across the three phases of the head upright tilt test. The figure depicts a box plot of the BEI across the three phases of the head up tilt. Mean values depicted by circle, plus, and cross markings. There was no significant difference in BEI between the three phases of the head up tilt study

Baroreceptor Effectiveness Index

In regards to the BEI, the mean values were in the range of 63.3–70.1% across the 3 phases of the HUTT (Fig. 5). Statistical analysis did not show a significant difference when comparing the baseline and the other phases but did show a significant difference when comparing the HUTT to the post-tilt phase (*P* value 0.03), as shown in Table 3.

Baroreceptor sensitivity

In regards to the baroreceptor sensitivity, as shown in Table 4 on evaluating slope up events, slope down events, and net slope, defined as an absolute value of all up and down events, there was a significant difference in slope on comparing phase 1 to phase 2 and also phase 2 to phase 3 (all *P* values <0.05). There was no significant difference when comparing phase 1 to phase 3 (*P* values = 0.4, 0.07, and 0.11 for slope up, down, and net, respectively). The data show that, in all three analyses of slopes, there is a significantly higher slope in the supine phases in comparison to the HUTT phase (Fig. 6).

All subjects were able to complete the HUTT study, and none suffered orthostatic intolerance that required premature cessation of measurements.

DISCUSSION

The arterial baroreceptors provide a vital and constant input in the overall regulation of blood pressure homeostasis.[6] Multiple investigations have been performed regarding the normal functioning and activity of baroreceptors in adults,[25,26] but the total extent of their input and modulation remains to be investigated especially in pediatric populations. As baroreceptor dysfunction has been implicated in multiple disease processes, understanding the exact mechanism and normal functioning parameters of the baroreceptors will be an important tool to improve diagnosis and monitor therapies.[27]

Table 3. BEI HUTT study results

	Phase 1—Baseline	Phase 2—HUTT	Phase 3—Post-tilt	Phase comparison	*P* value
BEI (%) (mean ± SD)	66.2 ± 21.6	70.1 ± 10.2	63.3 ± 18.3		
				Baseline vs. HUTT	0.48
				Baseline vs. Post-tilt	0.65
				HUTT vs. Post-tilt	0.03

BEI Baroreceptor Effectiveness Index, *HUTT* head up tilt test

Table 4. BEI HUTT study results

	Phase 1—Baseline	Phase 2—HUTT	Phase 3—Post-tilt	Phase comparison	*P* value
Slope (ms/mm Hg) (Mean ± SD)					
Net	29.2 ± 18.2	13.1 ± 5.6	33.4 ± 17.4		
				Baseline vs. HUTT	<0.0001
				Baseline vs. Post-tilt	0.11
				HUTT vs. Post-tilt	<0.0001
Slope up	30.8 ± 20.8	13.9 ± 5.9	33.7 ± 18.2		
				Baseline vs. HUTT	<0.0001
				Baseline vs. Post-tilt	0.4
				HUTT vs. Post-tilt	<0.0001
Slope down	26.9 ± 17.1	12.5 ± 5.5	32 ± 18.5		
				Baseline vs. HUTT	<0.0001
				Baseline vs. Post-tilt	0.07
				HUTT vs. Post-tilt	<0.0001

BEI Baroreceptor Effectiveness Index, *HUTT* head up tilt test

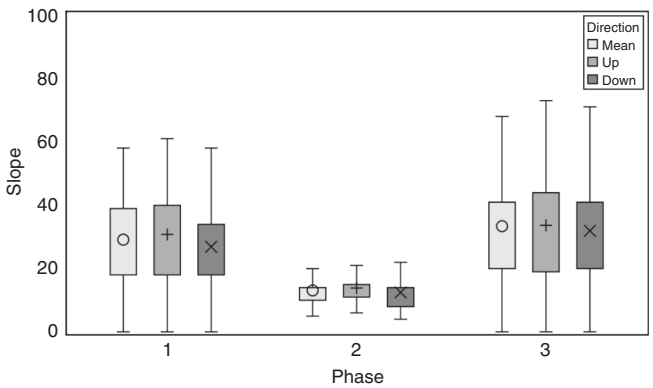

Fig. 6 Slope comparison across three phases of head up tilt test (HUTT). The figure depicts a box plot of the slope values across the three phases of the HUTT. The slopes are separated into slope up, where blood pressure increases; slope down where blood pressure decreases; and the net mean slope. Mean values depicted by circle, plus, and cross markings. There was a significant difference between each value between the supine phases 1 and 3 when compared to the head up tilt phase 2. There was no significant difference between phases 1 and 3. The decrease in slope values seen during phase 2 indicate that a larger change in slope is required to cause a change in heart rate, thus indicating a less sensitive baroreceptor

The few studies in the pediatric population that have been published to date do not provide a standardized investigation regarding the changes in baroreceptor activity under the stress of the HUTT.[4,17,20] The studies thus far also included patient populations with underlying disease processes that could possibly skew the values obtained, making it difficult to generalize the results to the normal population. Our study is one of the few to provide data regarding the baroreceptor reflex in a defined HUTT procedure in a pediatric population and the first study in pediatric subjects that analyzes the subdivision of Lag responses in the setting of the HUTT protocol.

Our decision to use noninvasive measurements arose from a concern for morbidity associated with invasive blood pressure measurements and difficulty in obtaining invasive access in the pediatric population. Pharmacologic means to modulate blood pressure in subjects were not utilized and thus avoided cross-reactions to receptors and resultant changes in the normal baroreceptor reflex physiology.[5]

The sequence and spectral method are both reliable and verified procedures for baroreceptor analysis.[18,28] The decision to use the sequence method for assessment of the baroreceptor reflex in this study was based on the advantage of the high specificity of this method stemming from its ability to correlate each change in blood pressure with heart rate. The spectral method was not used for this study as this method tabulates changes in pressure and heart rate as an average of the entire time of recording and only implies that pressure changes occur at the same time as the heart rate changes.[29] The sequence method not only avoids pharmacologic manipulation but also provides additional measurements as the ability to correlate the blood pressure with heart rate changes allows for assessment of the slope values of receptor activation and also allows for the assessment of the BEI.[5,23]

The first significant findings of this investigation are the values of the baroreceptor activity in normal subjects. As shown in Tables 2–4, our results are consistent with the current understanding of baroreceptors, in that activity does significantly increase in the head up position as venous blood pooling and

other stimuli occur more often while standing and thus stimulate the baroreceptors more frequently to intervene with a heart rate response to maintain a more constant blood pressure. A novel finding in our study is the subdivision of the heart rate responses into Lag 0, 1, and 2 values that further distinguish the 3 phases of HUTT and provides new information regarding the analysis of baroreceptor reflex function and the response of heart rate to blood pressure. The speed required for the heart rate to be coordinated with blood pressure changes in Lag 0 possibly indicates more rapid input from the carotid baroreceptor due to its proximity to the heart, while Lags 1 and 2 likely indicate more central input from the autonomic nervous system due to the resultant delay of heart rate changes. Further research into these mechanisms will be beneficial in clearly defining these measured differences. The mean number of events per minute significantly decreased from Lag 0, 1 to 2 in all phases. Further investigation into the HUTT phase and possibly an additional stress phase with even more baroreceptor activity may show more dependence on the Lag 2 phase and will help further characterize the baroreceptor activity. Another unique finding was the significant difference in activity in Lag 0 and Lag 2 when comparing phase 1 and 3. This could be due to an adaptive response to the supine phase where the baroreceptors have been very active and then remain overactive in the beginning part of phase 3 as the body is returning to homeostasis. Although this is a statistically significant finding, we do not have a clear clinical implication for the underlying cause and further investigation would be beneficial in further elucidating this finding.

The second significant finding reported in this investigation involves the normal values of the BEI. Until the present, only adult values have been reported and have ranged from 21 to 59%,[30,31] with the caveat that some of these studies included patients with other medical conditions that could affect the BEI values. In this study, the BEI values in our pediatric subjects ranged from 63.3 to 70.1%, and while there was no significant different when comparing the baseline phase to the HUTT or post-tilt phases, there was a significant decrease when comparing the HUTT to the post-tilt phase (*P* value 0.03). This could indicate a recovery phase in the baroreceptors where their overall activity decreases after being stressed during the HUTT before normalizing back to the previous baseline values. Further research in comparing the BEI of pediatric patient with longer periods of measurements will be beneficial in exploring this further. The higher BEI values in the pediatric patient may reflect the immaturity of the pediatric autonomic nervous system compared to that of the adult. It could also indicate a decreased ability of the baroreceptors in older patients to sense blood pressure changes, possibly due to aging of the nervous system or effects of increased cholesterol and/or increased blood sugar in some patients.[3] The wide variation in the values could also be due to confounding pathologies affecting the reported adult values. Nevertheless, further investigation can be useful to better determine the relationship between normal BEI values and age.

The third significant finding investigated in this project is the baroreceptor sensitivity. On our analysis of the net slope, in addition to the subdivisions of slope up and slope down, all values followed a similar pattern of lower slope during the HUTT in comparison with the supine phases, with no significant difference between the pre-tilt and post-tilt supine phases. The decrease in sensitivity during the HUTT phase in comparison to the supine phases is congruent with the trends reported in previous studies, although the protocols and conditions of measurements were different.[4,12] This is consistent with the theory that small pressure changes will naturally occur while standing and only the more significant pressure changes need to be acted upon by the baroreceptors to maintain blood pressure homeostasis.[4] This observation could also be in relation to the increased activity noted during the HUTT, where the decreased sensitivity is required to balance out the increased activity during the HUTT, or vice versa, to maintain a more stable cardiac output. It is, however, difficult to compare our results with other reported values for the baroreceptor sensitivity as the protocols and conditions of measurement differed between the studies, but the trends of the baroreceptor sensitivity are congruent.[4,13,20]

Study limitations

This study attempted to help establish normal values for the baroreceptor activity, sensitivity, and BEI. While normal references ranges cannot exclusively be established based on our study's sample size, the addition of our data to the literature can help identify trends and hopefully be used in the future in conjunction with further findings to establish a reliable set of normal values. Second, another limitation of this study was the inability to enroll infants and toddler subjects due to difficulty with compliance with the HUTT secondary to their stage of development. This resulted in a portion of the pediatric population left unstudied. Given some variability in the literature regarding the impact of age on the baroreceptor function,[3,15,32,33] further studies with larger sample sizes and consistent methods of measurement can help better establish normal values and the impact of development and specific age groups on the baroreceptor function. Finally, this study represents the findings at one academic institution. Although our institution does cover a large and diverse patient population, our experience may differ from other institutions and further investigation and correlation will be beneficial.

CONCLUSION

Our study provides well-defined terminology for the baroreceptor activity, sensitivity, and BEI and normal values in pediatric subjects under controlled supine and head up position phases. Our data trends correlate with previously reported values in adults but provide new data regarding delayed heart rate responses to pressure changes in the Lag 1 and Lag 2 values. The terminology and normal values presented in our study can be used in conjunction with other investigations involving normal subjects to further explore other disease processes involving blood pressure and autonomic system control mechanisms in order to improve diagnosis and management, including morbidity and mortality.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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