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Effect of Cardiac Autonomic Axis Maturation on Heart Rate Variability Indices in Pediatric Population: Gender Based Study

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Abstract

Background: The HRV is a sensitive index in establishing the underlying cardiovascular derangements within the age. The study of cardiovascular autonomic function and its maturation in the pediatric age group has gained importance as there are no much data in the literature. *Objectives:* To assess the gender based differences on HRV during the period of puberty, the age at cardiac autonomic axis maturates. *Material & Methods:* The study was done on 145 children of both the genders of urban population categorized in two groups as Group I (7-9 years, n=65) & Group II (10-12 years, n= 80). Basal 5 minutes ECG was recorded and the standard time domain indices (mean RR, SDNN, PNN50 and RMSSD) and frequency domain indices (TP, LF, HF, and LFnu, HFnu and LF/HF ratio) of HRV were calculated and analyzed. *Results:* Time domain and frequency domain indices were significantly ($p<0.01$) more in females than males in younger group I and less in females in group II. *Conclusion:* The study proposed that there are established gender differences in the autonomic axis maturation due to the onset of puberty in females (preferably adrenarche) may result in profound decrease in the HRV parameters. A similar finding was not seen in boys because of the natural delay in the onset of puberty in comparison to their female counterparts.

Keywords: Autonomic Axis; Maturation; Heart Rate Variability; Gender.

Introduction

Autonomic control on cardiac function involvement is controversial [1]. Cardiovagal autonomic function is importantly related to baroreflex gain, which is in turn influenced by other mechanical and neural factors [2]. Baroreflex sensitivity is one of the early protective mechanism which is regulated by cranial nerves IX and X. Baroreceptors are stretch-sensitive receptors embedded in the barosensory vessel wall, and their response to pressure-induced stretch is importantly determined by the compliance of the vessel wall that too when there is any change in the blood pressure [3]. As there is change in the different endocrine secretion at different age the autonomic modulation and maturation occurs. In pediatric age group the influence of hormones on their autonomic regulation is very less. As the age advances and the children reach adolescent age group, the reproductive hormones play a vital role on cardiac autonomic and blood pressure regulation. Particularly in female age group the adrenal hormones produces much change in their cardiac axis regulation at the time of their puberty [7]. Cardiovagal autonomic function declines with age during the adult years, which is partly because of gradual impairment of baroreflex function. Time domain analysis of heart rate variability uses statistical methods to quantify the variation of the standard deviation or the differences between successive RR intervals [8]. Frequency domain analysis of heart rate variability enables us to calculate the respiratory dependent high frequency and the low frequency power. High frequency power is mediated by vagal activity, while low frequency power has been

suggested to represent predominantly sympathetic modulation [10,11]. There are no much data in the literature about the cardiac autonomic function and its maturation in the pediatric age group, because it is this age, children are exposed to various physical and mental challenges which makes them to undergo enormous anxiety and stress along with their daily activities. This lacking of normative data on autonomic function and maturation and its gender differences potentiates the purpose of research in this field particularly in south Indian population.

Materials and Methods

The present study was conducted on 145 children of age 7to 12 years of urban population. The children were categorized in two groups as Group I (7-9 years, n=65) and Group II (10-12 years, n= 80) of both the genders. All were free of overt autonomic and systemic diseases like cardiovascular disease, Diabetes mellitus, Thyroid disorders and any previous syncopal attacks. No history of intake of any other medications. All subjects or relatives of the subject gave informed consent, and the local ethics committee approved the study. Written Informed consent and assent was obtained for recruiting the children by sending a consent form to parents through their children explaining them about the non invasiveness of the procedures done, the importance of the study and the benefits attained. The consent forms have been issued to the children in person through random selection in the respective age groups. The concerned teachers were informed in detail about the procedures done. They were requested to collect the consent forms which have been brought by the children after getting signed from their parents. The children were allowed to participate in this study only if they are free from any medical, surgical, congenital disorders. They do not have any previous history of syncopal and pre-syncopal attacks, epilepsy and any neurological illness. Preliminary systemic and neurological examinations were done prior to the study.

Parameters Recorded

Basal physiological parameters such as Heart rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) were recorded to show the variations among the children of both the age groups. The subjects were allowed to lie down on a couch in supine posture for 10 minutes and HR and BP were recorded along with Lead II ECG recording for five minutes with Bio-harness HRV monitoring system which is tied at the level of fourth intercostals space. HRV parameters like time domain & frequency domain indices were analyzed.

Statistical Analysis

Data were analyzed using Student t test and Mann Whitney U test according to the normality of the distribution of data for cross sectional comparison of two age groups. For all measurements, Mean with SD was calculated. All statistical procedures were performed using SPSS 19.0 version. The P value of <0.05 was considered to denote statistical significance.

Results

The standard deviation of normal to normal RR intervals (SDANN) which reflects the long term heart rate variability is found to be less in the older group though the statistical significant is marginally lost. However the standard deviation of the heart rates (Bpm) is found to be significantly more in the younger group though their heart rates are not significantly different. The root mean square of successive standard deviations of normal to normal intervals (RMSSD) is found to be more in the younger group as compared to older group. This is the powerful time domain parameter which reflects short term heart rate variability and in our study is found to be significantly different across the groups (p=0.0373). Similarly the other time domain indices like PNN50 and NN50 are significantly more in the younger group as compared to the older group and found to be significant (p= 0.0467) The Geometric indices i.e. RRTI (p=0.0422) and TINN (P=0.0218) are found to be significantly more in younger group as compared to the older group (Table 1).

Total power (TP) is significantly reduced in older age group when compared to younger age group. (p= 0.0017). The low frequency power (LF) is found to be more in the younger age group when compared to the older age group with significance of (p=0.0459). This is the power which indicates the sympathetic activity is statistically significant when comparing the younger and older age group. However, it is interpreted with caution rather than to superfluously conclude the high sympathetic activity in younger age group. The details of it are discussed in discussion section. The high frequency power (HF) is more in younger age with significant difference between two

groups (p=0.0002). When the absolute powers expressed in normalized units as LF nu and HF nu, they were not found to be significantly different. Though the LF/HF ratio found to be more in older age group there is no statistical significance (Table 2).

SDNN is found to be less in the older group and there is no significant difference. However, the standard deviation of the heart rates is found to be more in females though their heart rates are not significantly different. RMSSD is found to be more in females as compared to males and found to be significantly different across the groups (p=0.0359). Similarly the other time domain parameter like PNN50 is significantly more in females and found to be significant (p= 0.0258) and NN50 is also more in females with a significant difference of P=0.003. The Geometric indices i.e. RRTI (p=0.4831) and TINN (p=0.1754) are not found to be significantly between the genders (Table 3).

The Low frequency power is significantly more in females when compared to males (p=0.0338). The HF is also is significantly more in females when compared to males (p=0.0023). The total power TP is more in females when compared to males with a significant difference of p=0.0105. The LF: HF ratio is found to be increased in males when compared to females with no significant difference. The LFnu and HFnu are not found to be significantly different between males and females (Table 4).

The standard deviation of normal to normal RR intervals (SDNN) is found to be more or less equal in both males and females and there is no significant difference. There is only marginal difference in standard deviation of the heart rates

Table 1: Time domain statistical measures of HRV in two age groups of 7-9 years and 10-12 years

Variables	Group I (n=65) Mean ± SD	Group II (n=80) Mean ± SD	P – Value
Mean RR	0.6749±0.07696	0.6881 ±0.09865	0.529
SD RR	0.055±0.02146	0.05188±0.02836	0.0714
Mean HR	89.77±10.232	88.998±11.651	0.7354
SD HR	7.43±2.769	7.1598±4.237	0.0277
RMSSD	57.6292±26.265	48.14±25.584	0.0373
NN50	128.553±68.973	106.18±89.95	0.0183
PNN50	30.363±17.824	25.755±20.338	0.0467
RRINDEX	0.10927±0.09119	0.08733 ±0.03466	0.0422
TINN	288.23±96.531	255.775±109.45	0.0218

The p values < 0.05 was considered significant

Table 2: Frequency domain (Non-parametric) measures of HRV in two age groups of 7-9 years and 10-12 years

Variables	Group I (n=65) Mean ± SD	Group II (n=80) Mean ± SD	P – Value
LF	344.153±210.35	280.29±171.58	0.0459
HF	479.77±297.59	316.1625±218.093	0.0002
VLF	162.85±85.23	142.24±99.14	0.1874
TP	986.77±453.49	756.04±415.24	0.0017
LF:HF	1.0115±0.6561	1.14746 ±0.7443	0.3271
LF nu	46.10±14.196	48.98 ±14.343	0.2279
HF nu	53.92±14.27	51.42±14.68	0.3047

The p values < 0.05 was considered significant.

Table 3: Time domain statistical measures of HRV between males and females in 7-9 age groups

Variables	Males (n = 35) Mean ± SD	Females (n=30) Mean ± SD	P – Value
Mean RR	0.674±0.074	0.6724±0.08	0.6546
SD RR	0.051±0.02	0.06±0.022	0.0925
Mean HR	90.532±9.933	88.88±10.67	0.2719
SD HR	7.029±2.190	7.90±3.298	0.2042
RMSSD	49.262±20.556	61.21±23.37	0.0359
NN50	104.657±67.577	156.90±68.397	0.003
PNN50	25.011±17.717	35.713±17.536	0.0258
RRINDEX	0.116±0.120	0.1004±0.033	0.4831
TINN	270.3±102.16	304.5±98.079	0.1754

The p values < 0.05 was considered significant

Table 5: Time domain statistical measures of HRV between males and females in 10-12 age groups

Variables	Males (n = 35) Mean± SD	Females (n=30) Mean ± SD	P – value
LF	301.91±101.28	393.43±224.45	0.0338
HF	378.69±240.82	593.7±305.22	0.0023
VLF	167.6±84.89	157.3±81.83	0.6218
TP	844.28±413.25	1144.43±504.12	0.0105
LF:HF	1.072±0.548	0.9398±0.7662	0.119
LF nu	48.49±13.11	43.33±15.11	0.1454
HF nu	51.58±13.23	56.65±15.17	0.1548

The p values < 0.05 was considered significant.

Table 6: Frequency domain (Non-Parametric) measures of HRV between males and females in 10-12 age groups

Variables	Males (n = 40) Mean ± SD	Females (n=40) Mean ± SD	P – Value
LF	366.9±143.88	211.52±103.28	0.0001
HF	373.1±140.51	223.7±111.18	0.0001
VLF	156.22±77.35	125.25±53.77	0.0408
TP	896.23±436.05	543.9±308.34	0.0001
LF:HF	1.107±0.710	1.1872±0.7841	0.6615
LF nu	48.25±15.22	49.72±13.56	0.6507
HF nu	52.39±15.81	50.46±13.59	0.5589

The p values < 0.05 was considered significant.

(Bpm) between males and females. RMSSD is found to be more in males as compared to females which do not show any significant difference. PNN50 and NN50 are more in males with no significant difference. The Geometric indices i.e. RRTI is not found to be significantly different between the genders. TINN is significantly more in males than females (p= 0.036) (Table 5).

The Low frequency power, HF power and Total Power also significantly more in males when compared to females (p=0.0001). The LF: HF ratio is found to be increased in females when compared to males with no significant difference. The LFnu and Fun are not found to be significantly different between males and females (Table 6) .

Discussion

From the findings of our study, we would like to propose that the sympathetic output steadily increases by ageing. In addition to this normal phenomenon, we would like to put forward the exaggerated reduction in the HRV as a key tool in establishing the underlying latent and evolving cardiovascular derangements. Within the age,among the genders, there is a very high heterogeneity in the magnitude of HRV [8]. The HRV is a sensitive tool and index in establishing the underlying cardiovascular derangements [11]. Data mining in our study reveals the presence of high HRV in children with favorable body habitués in the same age group [21]. As per the data, the younger half of the study group i.e. 7-9 years did show statistical differences in many of the time domain parameters like RMSSD, NN50 and PNN50 are significantly higher in females. We would like to propose that there are established gender differences in the autonomic maturation and functioning right from the embryogenesis [5]. We believe in good hope that the sex hormones modulate and only widen these differences rather than initiating it. As there are no appreciable differences in the heart rates between the genders in old and young groups, we would like to state that the parasympathetic tone is equal in both the boys and girls. This excludes the major argument against the rule of inherent heart rate differences inducing HRV changes [12]. However, in the younger children group as reflected by the RMSSD, the girl children have more parasympathetic modulation of the heart rates in comparison with their male counterparts. Taking the understanding that there are other contributory components to the HRV, we would like to express the aforementioned conclusion with caution and analyzed the frequency domain parameters [15]. The frequency domain parameters in the 7-9 years group very clearly stated that the girl children had statistically significant higher values of HF than their male counterparts. This clearly states that, girl children in the 7-9 years group have more parasympathetic modulation than their male counterparts. Since there are no significant differences in body mass

index, waist circumference and WHR in both the genders in the younger age group we strongly admit that by removing all the confounders, the only factor among the plausible parameters inducing the HRV changes is the gender. In the older age group, the condition is totally reversed. The time domain parameters like RMSSD, PNN50 and NN50 though not statistically significant found to be higher in the male group in comparison with the females. The triangular index is higher in the male counterparts and found to be statistically significant. This compulses us to say in the older children group the males had higher HRV than the females. In addition the HF component is found to be significantly higher in the male group as compared to females. The total power (TP) is found to be extremely less in the female counterparts in the older children group and the statistical significance of this difference is extreme. Thus, with utmost clarity our study reflects that the parasympathetic modulation, but not the tone is lower in females than the male counterparts in the older children group. In the previous studies it is very clearly stated that the reduction in the HF component is well associated with underlying cardiovascular strain or stress [22]. The HRV parameters which partly reflect the sympathetic modulation is the LF power [10, 12]. The LF power also significantly reduced in females children. It is seen that the girls have lower LFnu in younger age group. Therefore in younger children resting sympathetic tone and modulation is higher in the males than females which is proved with the corroborative evidence of mean arterial pressure which is also higher in boys than girls. Interestingly, we observed high diastolic pressures in the females in the older age group. There is hardly any scientific documentation so far in this aspect. Thus we would like to appreciate and consider as an increase in the sympathetic modulation in girls rather than to merely conclude that boys & girls of this age group show equal sympathetic modulation. An immediate evidence for this statement would be a decrement in the male LFnu projecting as the reason for a higher sympathetic modulation in girls as age advances since LFnu of the girls changes drastically from 43.3 to 49.7 in the younger & older age groups respectively. Therefore, we would like to suggest that it is the absolute increment in the sympathetic modulation in the older girls and merely a decrement in the LFnu of males. We would like to propose that the decrease in HRV parameters is due to the onset of puberty in females preferably adrenarche. A similar finding is not seen in the boys because of the natural delay in the onset of puberty in comparison to their female counterparts [16,17]. The present understanding in the medical literature is that the females who have the vasodilator sex hormones are found to have lower vasomotor tone and vasoreactivity in comparison with their male counterparts [18]. However, in this study, in the older children age group the presence of high vasomotor tone in the females compulses us to state that the perimenarcheal period profoundly alters the vasomotor milieu. This reflects that basal sympathetic tone is higher in girls as compared to boys in the older age group. The literature says that the resting diastolic values reflect the vasomotor tone that is the resting sympathetic output [13]. The resting parasympathetic output can be studied by analyzing the resting heart rates [15]. We infer that girls in the older group have some undefined cardiovascular strain in comparison to their male counterparts. So, finally we would conclude that sympathetic tone and modulation is higher in older age group girls with decreased HRV parameters as compared to boys in that age group. The rise in the sympathetic tone and modulation needs an established mechanism for its explanation and we have proposed certain mechanisms like atherosclerosis in the vessels feeding the sensors, altered dynamics in the sensor transducing mechanisms by ageing, permissive and inhibitory role of other hormonal mediators, altered integrator activity, evolutionary remnant and external plausible psycho- social factors [5,10].

Conclusion

From our study we infer that Gender influences the cardiovascular autonomic modulation at rest as well as the autonomic reactivity to various challenges. In our study we conclude that girls of group I were found to have lower sympathetic reactivity and tone and higher parasympathetic modulation than boys. The onset of puberty in girls during the pre and perimenarcheal period definitely changes the cardiovascular autonomic milieu and found to have higher cardiovascular strain or stress [5,13, 20] with profound decrease in HRV parameters which is preferably due to adrenarche. Thus the underlying cardiovascular milieu explains the later onset of many cardiovascular morbidity and mortality. So, it becomes a very difficult task to consider HRV like other biological parameters and to evolve normative data though the very intention of the study was to get a yardstick in this highly unexplored domain. However, accepting and aware of the situation we proposed a normative data as created from our sample for reference purposes which would be refined in time taking the aforementioned scientific arguments into considerations as the study demands a huge sample size.

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