CENTRAL ASIAN JOURNAL OF INNOVATIONS ON TOURISM MANAGEMENT AND FINANCE

https://cajitmf.centralasianstudies.org/index.php/CAJITMF
Volume: 07 Issue: 03 | July 2026 ISSN: 2660-454X

Article

State of the Autonomic Nervous System in Young Children With Congenital Heart Defects

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Abstract: Congenital heart defects in early childhood are frequently accompanied not only by structural and hemodynamic abnormalities but also by disturbances of autonomic cardiovascular regulation that may significantly influence adaptive capacity and functional stability of the growing organism. The present study aimed to evaluate the state of the autonomic nervous system in young children with congenital heart defects through analysis of heart rate variability parameters. A total of 80 children aged from 3 months to 5 years were included and divided into cyanotic and non-cyanotic groups according to the type of congenital cardiac pathology. Clinical examination, pulse oximetry, echocardiography, and electrocardiographic recording with subsequent heart rate variability assessment were performed in all patients. Children with cyanotic congenital heart defects demonstrated lower oxygen saturation together with significant reduction of parasympathetic activity and increased sympathetic predominance compared with non-cyanotic forms, indicating more pronounced autonomic imbalance associated with chronic systemic hypoxemia.

Keywords: Congenital heart defects, autonomic nervous system, heart rate variability, cyanotic heart disease, hypoxemia, pediatric cardiology.

Citation: Popenkov A. F. State of the Autonomic Nervous System in Young Children With Congenital Heart Defects. Central Asian Journal of Innovations on Tourism Management and Finance 2026, 7(3), 186-191.

Received: 10th Feb 2026
Revised: 11th Mar 2026
Accepted: 19th Apr 2026
Published: 19th May 2026

Introduction

The autonomic nervous system is crucial to cardiovascular stability in childhood, as the interactions between the sympathetic and parasympathetic control systems continuously modulate HR, myocardial contractility, vascular tone and adaptive hemodynamic responses during both physiological and pathological conditions. In early childhood, autonomic regulation is still in a very dynamic and still developing state, and is especially susceptible to disturbances that can change cardiovascular adaptation and metabolic balance. Congenital heart defects (CHD) in general, and particularly when accompanied by chronic hypoxemia and remarkable hemodynamic overload, can over time lead to gradual transition towards chronic sympathetic activity and quiescent vagal activity, which can set the stage for functional instability of cardiac regulation [1].

Heart rate variability analysis is one of the most informative noninvasive tools which can be used in pediatric cardiology to evaluate autonomic nervous system activity because the heart rate variability parameters provide information on dynamic interactions between the sympathetic and the parasympathetic influences on the sinoatrial node. A decrease in global HRV is seen as a sign of regulatory stress and loss of autonomic reserve, while an

increase of the ratio of LF/HF is often taken as a sign of sympathetic predominance and decreased adaptive capacity [2]. Multiple other international studies have shown that children with CHD may have reduced HRV values compared to healthy children, indicating that long-term circulatory disturbances can have a significant effect on neurocardiac regulation even prior to surgery [3].

In cyanotic congenital heart diseases, a long-term systemic hypoxia may exacerbate autonomic imbalance; the autonomic mechanisms that are activated in an attempt to maintain tissue perfusion and oxygen delivery become sustained. Cyanotic congenital heart defects are of particular clinical interest, because long-term systemic hypoxia can worsen autonomic imbalance due to persistent activation of compensatory neurohumoral mechanisms to maintain tissue perfusion and oxygen delivery. But adaption can become exhausted and cardiovascular control impaired over the long run due to the chronic sympathetic predominance. With the rising interest of science in the study of autonomic dysfunction in children, comparative studies between children with various hemodynamic types of CHD are still relatively scarce, particularly in children in their early years of life, at which time autonomic development is not fully complete [4]. Thus, monitoring the autonomic nervous system activity in children with CHD seems to be clinically relevant to better understand the functional cardiovascular adaptation and to provide other markers of severity and future prognosis.

Materials and methods

This prospective comparative clinical study was performed in the clinic of the Tashkent State Medical University, pediatric cardiac surgery department, and involved young children who had been diagnosed with congenital heart defects, who underwent full cardiovascular and functional assessment during the study period. The study population consisted of 80 children between the age of 3 months and 5 years, all of whom were examined under similar clinical conditions, thus reducing the possible influence of external physiological factors which could affect autonomic regulation and heart rate variability parameters. Informed consent was obtained from parents or legal guardians before enrolling the child and all aspects of the investigation were conducted in adherence to the internationally accepted ethical guidelines for Biomedical research in children [5].

Detailed clinical examination and transthoracic echocardiographic evaluation were performed by experienced pediatric cardiologists and a diagnosis of congenital heart defect was set. Children were divided into two comparative groups based on the hemodynamic characteristics and/or systemic hypoxemia. The first group comprised 30 children with cyanotic congenital heart defects and the second group comprised 50 children with non-cyanotic forms of cardiac malformations. The main defects in the cyanotic group were tetralogy of Fallot, transposition of great arteries, tricuspid valve atresia, and common arterial trunk, while those in the non-cyanotic group were mostly ventricular septal defect, atrial septal defect, patent ductus arteriosus, and coarctation of the aorta without clinically significant desaturation of systemic circulation [6].

All children were clinically assessed in accordance with standard pediatric practice, including heart rate, respiratory condition, peripheral oxygen saturation and cardiovascular insufficiency signs. Pulse oximetry was used to measure peripheral oxygen saturation at rest because chronic hypoxemia is considered as one of the main factors that can affect autonomic nervous system balance and adaptive cardiovascular responses in CHD [7].

ECG was then recorded in quiet rest, and the HRV indices analysed. Both frequency domain and time domain HRV parameters were examined to gain a wide perspective on the activity of the ANS. SDNN, RMSSD, and pNN50 indexes were used to assess overall variability and parasympathetic activity and LF, HF, and LF/HF indexes were used to assess sympathetic/parasympathetic interaction and autonomic balance, respectively, in time-domain analysis and spectral analysis. The HRV results obtained were further

compared between cyanotic and non-cyanotic groups to assess the extent of autonomic dysfunction in various hemodynamic forms of CHD [8].
The data collected were processed on the computer by statistical methods using SPSS software version 26.0. The data of quantitative variables were presented as mean value ± standard deviation and intergroup comparisons were carried out by applying suitable parametric statistical analysis after the normality of distribution was determined. Pearson correlation was also performed to assess the correlation between HRV parameters and oxygen saturation. A p value of < 0.05 was considered statistically significant.

Results

A final analysis included 80 children with CHD, and there were no statistically significant differences between age distribution or sex characteristics of the cyanotic and non-cyanotic groups, thereby making it possible to compare autonomic nervous system indicators as a more objective analysis without significant demographic imbalance. However, significant differences in clinically relevant parameters emerged when performing functional cardiovascular testing, including oxygen saturation, heart rate characteristics and heart rate variability parameters related to autonomic function. The peripheral oxygen saturation was significantly lower in children with cyanotic CHD than in those with non-cyanotic cardiac malformations, and autonomic imbalance and cardiovascular stress adaptation were more strongly present in children with CHDs. In the clinical examination, the children with cyanotic defects were more likely to have an abnormal exercise tolerance for their age, to be irritable, to have difficulties with feeding and to have recurrent peripheral cyanosis, while non-cyanotic defects were associated with comparatively more stable hemodynamic adaptation. Echocardiographic evaluation also showed that children with cyanotic CHD have more significant hemodynamic disturbances that may account for some of the more pronounced autonomic abnormalities seen with HRV analysis [9].

In children with cyanotic defects, there was significant decrease in SDNN, RMSSD, and pNN50 parameters of the time domain analysis of HRV. These results suggest that chronic hypoxemia and chronic cardiovascular overload can lead to persistent activation of stress-related regulatory pathways that are also linked to a decrease in overall autonomic flexibility. This tendency was also reflected in the results of the HRV analysis by the measurement of the HF component of the HRV spectrum, which represents vagal modulation, which was significantly decreased in the cyanotic group, and the LF/HF ratio which was significantly increased, suggesting an increase in sympathetic modulation over vagal modulation in cardiac rhythm regulation [10].

Table 1. Comparative HRV parameters in children with CHD.

Parameters	**Cyanotic CHD (n=30)**	**Non-cyanotic CHD (n=50)**	**Cyanotic CHD (n=30)** **p-value**
Heart Rate (beats/min)	128 ± 14	118 ± 12	0.002
SpO_2 (%)	82.6 ± 6.8	96.1 ± 1.9	<0.001
SDNN (ms)	32.4 ± 8.1	45.7 ± 10.3	<0.001
RMSSD (ms)	21.8 ± 6.5	34.2 ± 9.4	<0.001
pNN50 (%)	6.9 ± 3.2	14.8 ± 5.7	<0.001
HF (ms^2)	289 ± 105	510 ± 180	<0.001
LF/HF Ratio	2.31 ± 0.74	1.14 ± 0.39	<0.001

Table 1 shows that children with CHD (cyanotic) had significantly decreased parasympathetic regulatory activity and overall HRV when compared with children with non-cyanotic CHD. Of particular interest was the marked increase of the LF/HF ratio in cyanotic patients, which is indicative of increased sympathetic activity in chronic

hypoxemic states, and of higher cardiovascular stress. The results are consistent with the idea that early life chronic hypoxia could significantly impact the maturation of the autonomic nervous system, and functional cardiac adaptation. The moderate positive correlation between oxygen saturation and parasympathetic HRV parameters and the inverse correlation between oxygen saturation and the LF/HF ratio, showing increasing sympathetic activation with worsening systemic hypoxia, respectively, were also found by correlation analysis [11,12]. In the aggregate, the findings obtained indicate that the autonomic dysfunction in CHD is not only a secondary physiological process, but also a permanent adaptive physiological process in patients with chronic hemodynamic imbalance.

Discussion

The results of the present study suggest that children with CHD, especially those with cyanotic defects with chronic systemic hypoxemia, are already found to have significant abnormalities of autonomic control of the cardiovascular system as early as childhood, and that these abnormalities involve decreased overall HRV with a definite increase in sympathetic (decreased in parasympathetic) cardiac modulation. These changes could be clinically significant as autonomic dysfunction not only indicates functional adaptation to chronic hemodynamic stress but also progressive depletion of the physiological regulatory reserves, which may have negative effects on the long term cardiovascular stability and postoperative recovery potential [13].

The most important finding of this study was that the SDNN, RMSSD and HF parameters were significantly lower in cyanotic CHD children. These indices are considered to reflect parasympathetic function and autonomic flexibility and a decrease may reflect a suppression of vagal modulation to sinoatrial node function in the setting of chronic neurohumoral activation and persistent hypoxemia. Other recent studies in children with CHD have also found that decreased parasympathetic function is linked to greater cardiovascular stress, poorer adaptive function, and greater risk for arrhythmogenic risk in these patients [14]. The higher LF/HF ratio found in the cyanotic group is further evidence of sympathetic predominance and may be viewed as a compensatory process to sustain systemic perfusion and oxygen delivery, despite reduced arterial oxygen saturation. The correlation of peripheral oxygen saturation with HRV parameters is of special clinical interest, as it establishes the crucial role of chronic hypoxemia in autonomic dysfunction formation. As saturation fell, markers of vagal activity fell with each degree of drop in saturation, while markers of sympathetic activation rose with each drop. The pattern indicates that chronic hypoxia could directly affect the maturation of autonomic regulatory pathways at a developmental time when neurocardiac control mechanisms are physiologically immature and very responsive to chronic stress factors [15].

Therefore, autonomic imbalance in cyanotic congenital heart defects should not be considered as a sequential electrophysiological phenomenon, but rather as a multi-engagement adaptive response of cardiovascular, metabolic and neurohumoral system at the same time.

One clinically relevant finding of the present study is the relatively normal autonomic profile found in children with non-cyanotic defects despite their structural cardiac abnormalities and hemodynamic overload. Some parasympathetic impairment was still seen in this group, but it was not as marked as in cyanotic patients, demonstrating the significant effect of chronic systemic hypoxemia on autonomic nervous system impairment [16].

Overall, the results indicate the feasibility of using heart rate variability analysis as a potentially useful, noninvasive method for detecting functional cardiovascular abnormalities in early life in children with CHD. Therefore, autonomic balance may play a role in improving risk stratification, optimizing clinical follow-up and creating more

individual management strategies, which are all important to prevent progressive cardiovascular maladaptation in children.

Conclusion

The present study has shown that important disturbances of autonomic nervous system regulation develop in young children with congenital heart defects, that the severity of these alterations increases appreciably in cyanotic forms of cardiac defect with chronic systemic hypoxemia. In children with cyanotic congenital heart defects, the overall levels of HRV were significantly lower and parasympathetic components lower, with greater predominance of sympathetic autonomic components, indicative of high tension of heart adaptive mechanisms in the presence of chronic hemodynamic overload and oxygen deficiency. These results suggest that autonomic dysfunction is not only the secondary physiological reaction but also an important factor in pathological adaptation process occurring in the early childhood in CHD. An important finding of this research was that the decrease in arterial oxygen saturation was correlated with the increase in autonomic imbalance and sympathetic predominance as evidenced by heart rate variability parameters. This is that chronic hypoxemia is a key factor in the development of neurocardiac dysregulation and progressive exhaustion of autonomic reserve. Furthermore, the observed decrease in vagal activity could result in decreased functional flexibility of the cardiovascular system, which could lead to greater susceptibility to adverse clinical outcomes and poorer long-term adaptations. The results obtained also provide further evidence of the potential usefulness of the heart rate variability analysis as a non-invasive and informative approach to the assessment of functional autonomic status in pediatric cardiology. Prompt recognition of autonomic disturbances may help in clinical monitoring and help identify those children who are born with congenital heart disease who will benefit from more careful follow-up and more personalised treatment. In general, a complete evaluation of the autonomic nervous system activity with traditional clinical and echocardiographic cardiac evaluation can help to better understand cardiovascular adaptation mechanisms and contribute to the development of effective strategies to enhance the prognosis and quality of life of children with CHD.

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