Ann Med Res 2021;28(10):1902-7

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.12.1161

Original Article

Sympatho-vagal activity in the mothers of pediatric cancer and non-cancer patients

Pinar Cakan[1], Sedat Yildiz[2]

[1]Department of Physiology, Faculty of Medicine, Health Sciences University, Istanbul, Turkey
[2]Department of Physiology, Faculty of Medicine, Inonu University, Malatya, Turkey

Abstract

Aim: Pediatric diseases affect both the children and their families psychologically. Parents may experience stress with the development of these diseases. The autonomic nervous system is one of the systems activated in response to stress. The current study aimed to investigate the activity of sympatho-vagal axis in mothers of children with pediatric diseases.

Materials and Methods: Following ethical consent, the study was carried out on the mothers of healthy children (healthy, n=25) and children with cancer (cancer, n=25), and children with non-cancer disease (non-cancer, n=25). Heart rate variability was used to assess autonomic nervous system's activity by taking a 5 min electrocardiogram recording. Heart rate variability (HRV) parameters such as standard deviation of RR intervals, mean square of successive RR interval differences, and low frequency/high frequency band were calculated by special software.

Results: Standard deviation of NN intervals (healthy 37±2, non-cancer 35±2, cancer 35±3), root mean square of successive RR interval differences (healthy 33±3, non-cancer 30±3, cancer36±5), LF/HF (healthy 1.69±0.21, non-cancer 1.40±0.17, cancer 1.30±0.16) and other HRV findings (p>0.05) were not different among the mothers. Systolic blood pressures were higher (p=0.000) in the mothers of healthy children (115±2) than in mothers of children with non-cancer diseases (102±2) and with cancer (109±2). Diastolic blood pressures were higher (p=0.022) in mothers of healthy children (79±2) compared to mothers of children with non-cancer disease (73±1), but not from those mothers of children with cancer (78±2).

Conclusion: Mothers did not differ in terms of HRV parameters, suggesting that children, whether healthy or sick, are always perceived as a great responsibility by the mothers.

Keywords: Cancer; heart rate variability; mother; sympatho-vagal tonus

INTRODUCTION

Cancer incidence is increasing in people of all ages and social groups all over the World (1). The number of malignancies, and deaths caused by them, are increasing in whole world (1). In the developed countries cancer is the second most common cause of death in children (2). Treatment of childhood cancer takes place over a period of 2 to 3 years, with the first intensive stages of chemotherapy followed by less severe treatment periods (3). Families of children diagnosed with cancer begin to experience intense anxiety and depression immediately after their children are diagnosed with cancer (1). This type of psychological trauma causes post traumatic stress response (4). Problems experienced by families due to children's chronic problems might be associated with genetic factors, socio-economic status, social support, nutrition, child factors and coping strategies (5).

Pediatric diseases have dramtic effects both on children and their families (6). For example, the pain and fatigue experienced by the sick child affects not only himself/herself but also his/her parents and siblings (6). There are differences between fathers and mothers in dealing with existing problems (7). Studies have shown that mothers of children with pervasive developmental disorders experience more stress and depressions than fathers (5). Families of pediatric patients with cancer reported to have more trauma than that of children having chronic diseases (8). Psychological distress is common among the parents of children during cancer treatment (9). However, non-cancer diseases in children can lead to depression and anxiety in parents (10).

The autonomic nervous system (ANS) is activated by stress response (11). ANS activity or sympatho-vagal balance can be determined by heart rate variability (HRV) by non-invasive means (12). HRV means to variation of heart

Received: 23.12.2020 **Accepted:** 03.02.2021 **Available online:** 18.10.2021
Corresponding Author: Pinar Cakan, Department of Physiology, Faculty of Medicine, Health Sciences University, Istanbul, Turkey
E-mail: pinar.cakan@sbu.edu.tr

rate in beat-to-beat intervals. Sympatho-vagal balance can reflect mental health related to stress, depression, or anxiety (13). This study evaluated sympatho-vagal activity, as measured by HRV, in mothers of children with malignant disease.

MATERIALS and METHODS

Ethical consent and participants

The study was carried out following ethical approval from the local ethics committee (Malatya Clinical Ethics Committee, No: 2019/43). The mothers were informed about the experiment and they signed written consent form. The study was conducted during the hospitalization of the disease children. Mothers of healthy children (n=25) and of children with non-cancer diseases (n=25, average diagnosis time (day) =19) and with cancer (n=25, average diagnosis time (day) =56) were included. They were included into study if they were healthy at the ages between 18 and 45 and if they were not using any drugs. Menstrual cycles of the experimental groups were adjusted so that similar numbers of women had follicular and luteal phases. For that purpose, self-reported length of the last three cycles was taken into consideration. Follicular and luteal phases were confirmed in the individuals by the length of the last cycle. Mothers were non-smokers and had regular cycles. Demographic characteristics of the mothers are represented in Table 1. Body mass indexes [BMI; (weight in kilograms/height in meter^2)] of the subjects were also calculated.

The State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) questionnaire was used in this study. The participants filled in STAI at the time immediately before ECG recording. STAI was developed in 1970 by Speilberger et al. and Öner and Le Comte in 1983 (14) adapted it Turkish. The STAI is a self-assessment questionnaire that uses to find out how participants felt at a particular time or under a specific condition. We used the State Anxiety Scale (S-Anxiety) in our study. The STAI-S helps professionals differentiate between feelings of anxiety and depression by making a clear distinction between the transient state of anxiety and the more general and prolonged persistent anxiety (15).

Table 1. Demographic data of the study population. Values represent mean ± standard error. P<0.05 was considered as level of significance

Subject characteristic	Mother (healthy)	Mother (non-cancer)	Mother (cancer)	P value
n	25	25	25	
Age (years)	36±1	33±1	34±1	0.077
BMI (kg/m^2)	27±1	27±1	25±2	0.864
Average diagnosis time (day)		19	56	
Average number of children	3	3	3	
Job				
Housewife	24	25	25	
Teacher	1			
		n	n	
Disease				
Lower respiratory tract infection		5		
Upper respiratory tract infection		3		
Diabetes		3		
Urinary tract infection		4		
Encephalitis		1		
Hematological disease (undefined)		1		
ChroniC renal failure		2		
Hydrocephalus		1		
Nephrotic syndrome		1		
Meningitis		1		
Neurological bladder		1		
Liver disease		1		
Allergy		1		
Acute Lymphoblastic Leukemia		10	10	
Acute Myeloblastic Leukemia		5	5	
Hodgkin Lymphoma		3	5	
Non Hodgkin Lymphoma		2	4	
Osteosacoma		3	1	

*Mother (healthy): Mother with healthy child; Mother (non-cancer): Mother of the child diagnosed with a disease other than cancer; Mother (cancer): Mother of a child diagnosed with cancer; *BMI: Body mass index

Heart Rate Variability and Arterial Blood Pressure

All participants were asked not to consume tea or coffee for approximately 2 hours before heart rate variability was measured. In order to assess HRV, electrocardiogram (ECG) recording was taken for 5 minutes in supine positions with eyes open. ECG recordings were taken once between 4:00 pm and 8:00 pm. Poly-Spectrum 8-E was used for ECG recording and HRV analysis was made with the HRV software program of the same device (Neurosoft, Ivanovo, Russia). All inter-beat intervals were visually checked to make sure that the program recognized them correctly. Time domain parameters (HR, SDNN, RMSSD and pNN50) and frequency domain parameters (TP, LF, HF and LF/HF) were evaluated. Time domain parameters: Heart rate, HR (bpm); standard deviation of NN intervals, SDNN (ms); root mean square of successive RR interval differences, RMSSD(ms); percentage of successive RR intervals that differ by more than 50 ms, pNN50(%) and total power, TP(ms²) (16). Frequency domain parameters: High-frequency, HF (ms²) (synchronous with respiration, generally in the band 0.2–0.45 Hz); low-frequency, LF (ms²) (band 0.03–0.15 Hz) and ratio of LF-to-HF power, LF/HF (17). Systolic and diastolic pressures were measured by a digital blood pressure device (Omron, M6 comfort, China).

Statistical Analyses

Statistics were analysed by Minitab statistical package (USA). The data was was analysed for normality by the Anderson-Darling test. Data that did not have normal distribution was log transformed. If the data had normal distribution, GLM (generalized linear model) was used followed by post-hoc Tukey's t-test. The data which had non-normal distribution were analyzed by Kruskall-Wallis test followed by post-hoc Mann-Whithney. The data were presentedas mean ± standard error and signicance level was set to $p<0.05$.

RESULTS

Arterial Blood Pressure

Blood pressure of the groups is shown in Table 2. Mean systolic blood pressure was higher in the mothers of healthy children (115±2 mm Hg, p=0.000) compared to the mother of children with non-cancer disease (102±2 mm Hg). Mean diastolic blood pressure was higher in the mothers of healthy children (79±2 mmHg, p=0.022) compared to the mothers of the children with non-cancer disease (73±1 mm Hg).

Table 2. Heart rate variability parameters in mothers of children hospitalized for malignant or non-malignant diseases. The data are expressed as mean ± standard error. P<0.05 was considered as level of significance

Variable	Mother (healthy) 25	Mother (non-cancer) 25	Mother (cancer) 25	P value
Blood pressure indicates				
Systole (mm/Hg)	118±3	104±2	110±2	0.000
Diastole (mm/Hg)	80±2	73±2	78±2	0.022
Time domain parameters				
HR (bpm)	75±1	76±1	75±2	0.679
SDNN (ms)*	37±2	35±2	37±4	0.766
RMSSD (ms)	33±3	30±3	36±5	0.599
pNN50 (%)	13±2	10±3	15±4	0.634
Frequency domain parameters				
VLF (ms²)	495±57	513±62	455±58	0.790
TP (ms²)	1848±160	1244±157	1424±266	0.813
LF (ms²)*	457±62	356±57	396±76	0.289
HF (ms²)	351±71	375±72	494±125	0.982
LF/HF (ms²)	1.95±0.27	1.4±0.17	1.79±0.40	0.440
%VLF	40±3	46±4	41±3	0.394
%LF	34±2	28±2	31±2	0.095
%HF	25±3	27±3	28±3	0.866

*Mother (healthy): Mother with healthy child; Mother (non-cancer): Mother of the child diagnosed with a disease other than cancer; Mother (cancer): Mother of a child diagnosed with cancer

*HR, heart rate; SDNN, standard deviation of NN intervals; RMSSD, root mean square of successive RR interval differences; pNN50, percentage of successive RR intervals that differ by more than 50 ms; TP, total power; VLF, absolute power of the very-low-frequency band; LF, absolute power of the low-frequency band; HF, absolute power of the high-frequency band; LF/HF, ratio of LF-to-HF power (Shaffer and Ginsberg, 2017). *p<0.05 Tukey test

The State-Trait Anxiety Inventory (STAI)

STAI was not different in the mothers of children with cancer (43±1 points, p=0.327) compared to the mothers of children with non-cancer disease (41±1 points) and to the mothers of healthy children (44±1 points).

Time Domain Parameters of HRV

Time domain parameters of the HRV are shown in Table 2. HR was not different in the mothers of children with cancer (75±2, p=0.679) compared to the mothers of children with non-cancer disease (76±1) and to the mothers of healthy children (75±1 mm Hg). SDNN was not different in the mothers of children with cancer (35±3, p=0.766) compared to the mothers of children with non-cancer disease (35±2) and to the mothers of healthy children (37±2 mm Hg). RMSSD was not different in the mothers of children with cancer (36±5, p=0.599) compared to the mothers of children with non-cancer disease (30±3) and to the mothers of healthy children (33±3). pNN50 was not different in the mothers of children with cancer (15±4, P=0.634) compared to the mother of children with non-cancer (10±3) and to the mothers of healthy children (13±2).

HRV Frequency domain parameters

Frequency domain parameters of the HRV are shown in Table 2. VLF was not different in the mothers of children with cancer (455±58, p=0.790) compared to the mothers of children with non-cancer (513±62) and to the mothers of healthy children (495±57). TP was not different in the mothers of children with cancer (1424±266, p=0.813) compared to the mothers of children with non-cancer diseases (1244±157) and to the mothers of healthy children (1848±160). LF was not different in the mothers of children with cancer (396±76, p=0.289) compared to the mothers of children with non-cancer disease (356±57) and to the mothers of healthy children (457±62). HF was not different in the mothers of children with cancer (494±125, p=0.982) compared to the mothers of children with non-cancer diseases (375±72) and to the mothers of healthy children (351±71). LF/HF was not different in the mothers of children with cancer (1.30±0.16, P>0.05) compared to the mothers of non-cancer disease (1.40±0.17) and to the mothers of healthy children (1.69±0.21). %VLF was not different in the mothers of children with cancer (41±3, P=0.394) compared to the mothers of children with non-cancer disease (46±4) and to the mothers of healthy children (40±3). % LF was not different in the mothers of children with cancer (31±2, p=0.095) compared to the mothers of children with non-cancer diseases (28±2) and the mother (healthy) group (34±2). % HF was not different in the mothers of children with cancer (28±3, p=0.866) compared to the mothers of children with non-cancer disease (27±3) and to the mothers of healthy children (25±3).

DISCUSSION

HRV is a reliable reflection of many physiological factors that regulate the normal rhythm of the heart (18). HRV provides a powerful tool to observe the interaction between the sympathetic and parasympathetic nervous systems (18). Also, low heart rate variability has been correlated with deterioration of health (19). In this study, we evaluated time and frequency dependent HRV parameters in mothers of healthy children and children with non-cancer disease and children with cancer. In the current study, no statistical difference was observed between the mothers in terms of HRV parameters.

Arterial Blood Pressure

Mean systolic blood pressure (SBS) and diastolic blood pressures (DBP) were found to be higher in the mothers of healthy children than the mothers of children hospitalized for non-cancer reasons. However, SBP and DBP were within the normal range in both groups. Hospitalization of the child can cause serious anxiety and stress for the parents, especially for the mother (20). Studies show that low blood pressure levels have been associated with sleep disturbance, anxiety and depression (21). However, in chronic stress situations, more stabilized and limited behaviors can be seen (22). Because behavioral and structural adaptation, blood pressure can develop against chronic stress (22. The average diagnosis time for children staying in hospital for reasons other than cancer is 19 days, while the average diagnosis time for children staying in hospital for cancer is 56 days. Therefore, the lack of a statistically significant difference between the mothers might be associated with adaptation to stress.

Heart Rate Variability

ANS, through its sympathetic and parasympathetic branches, acts as the line of communication between the central nervous system and the rest of the body (23). ANS responds to physiological and environmental challenges and regulates internal processes such as HR and blood pressure (23). HR parameter is used as a health indicator (24). Groups did not differ for HR values. In literature search, we found very few studies investigating HRV in mothers of children with diseases. Hospitalization for children is a stressful and upsetting experience not only for children but also for their parents (25). Studies have shown that HR increases in acute stress, but decreases in chronic stress (26). The reason why the HR value did not cause a significant difference between the mothers may be due to the fact that the sick children have been diagnosed for at least 19 days. During this time, adaptation to stress may have also developed. In fact, no differences in STAI scores support this situation.

There was no difference between the mothers in terms of SDNN value. A similar trend was also observed for STAI scoring and this supports the result. SDNN reflects an overall measure of autonomic nervous system balance (27). Low SDNN finding has been correlated with both morbidity and mortality (16). High SDNN value has been associated with better health (de Castilho et al., 2018). Hernando et al. applied mental stress to healthy volunteers in their study and it did not cause a significant difference in SDNN value (12).

The groups did not differ for RMSSD and pNN50. It is reported that RMSSD and pNN50 are parasympathetic components of HRV (28). Wekenborg et al. emphasized that vagal dysfunction is predictive and specific for burnout symptoms (Wekenborg et al., 2019). Hernando et al. were applied mental stress to healthy volunteers in their study. The stress they applied in their study did not make a significant difference in RMSSD and pNN50 values (12). While HF is predominantly modulated by the parasympathetic nervous system, LF is a product of the parasympathetic and sympathetic systems (16). VLF mostly reflects the sympathetic tone and normal VLF value is an indicator of healthy function (16). The groups did not differ for LF, HF and VLF. The LF / HF ratio reported to represent the balance between sympathetic and parasympathetic systems (28). Autonomic imbalance has been reported to be a risk factor for diseases of cardiovascular system (29). TP reflects autonomic nervous system activity (30). The groups did not differfor LF/HF and TP. Normalized LF (%LF) reflects the sympathetic tone (30). Normalized HF (% HF) reflects the inhibition of the sympathetic system (30). The groups did differ for % LF, % HF and % VLF.

In our literature review, we did not find any study evaluating HRV in mothers of children with cancer. Having cancer in the child has significant effects on the parents (31). Parents of pediatric cancer patients have financial difficulties as it might be difficult for them to attend work as required (complying with work hours, having sick leave, ability to work etc.) (31). Studies have shown that after pediatric cancer diagnosis, parents experience symptoms such as anxiety, difficulty in concentrating, feeling guilty, post-traumatic stress symptoms (PTSS), sadness, pessimism, and sleep disorders (31). Severity of the disease, the intensity of the treatment, and being a mother (32) all are risk factors. Stress is a risk factor for cardiovascular disease (33). HRV analysis is a tool used to predict cardiac autonomic regulation in humans and animal models (34). In our study, HRV parameters were not found statistically different between the groups.

Several studies have been conducted in rats investigating the short-term and long-term effects of repetitive stress exposure on cardiac autonomious regulation. Subchronic stress has been shown to reduce heart rate through in vagal activation in rats (35) After stress-induced sympathetic hyperactivity, which is commonly observed initially in stress situations, vagal activation can be seen in repeated exposure to stress (34, 35). This situation is a sign of adaptation (34, 35). Chronic stress may provide a constant resilience that allows the stress response and perception of stress to continue to adapt to environmental challenges throughout life (22). However, this adaptation may fail in situations of longer exposure to stress or more severe stress (36). This condition is maladaptive and is seen as vagal retraction and sympathetic dominance (36). However, the groups did not differ for HRV and STAI in our study and this strengthens the possibility of adaptation.

CONCLUSION

Parents of children with cancer may experience problems such as physical, psychological and social problems (37). The groups did not differ for HRV and STAI. The data of the current study suggest that the mothers can adapt to a very serious disease of the child such as cancer in about two months. Alternatively, it seems that children, whether healthy or sick, are always perceived as a great responsibility by the mothers.

Acknowledgements: I wold like to thank everyone contributed to this study.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Malatya Klinik Etik Kurul, no: 2019/43

REFERENCES

1. Kloter E, Barrueto K, Klein SD, et al. Heart rate variability as a prognostic factor for cancer survival–a systematic review. Front Physiol 2018;9:623.
2. Kaatsch, P. Epidemiology of childhood cancer. Cancer Treat Rev 2010;36:277-85.
3. Earle EA, Clarke SA, Eiser C, et al. 'Building a new normality': mothers' experiences of caring for a child with acute lymphoblastic leukaemia. Child Care Health Dev 2007;33:155-60.
4. Best M, Streisand R, Catania L, et al. Parental distress during pediatric leukemia and posttraumatic stress symptoms (PTSS) after treatment ends. J Pediatr Psychol 2001;26:299-307.
5. Mugno D, Ruta L, D'Arrigo VG, et al. Impairment of quality of life in parents of children and adolescents with pervasive developmental disorder. Health Qual Life Outcomes 2007;5:22.
6. Barlow JH & Ellard DR. The psychosocial well-being of children with chronic disease, their parents and siblings: an overview of the research evidence base. Child Care Health Dev 2006;32:19-31.
7. Goldbeck L. Parental coping with the diagnosis of childhood cancer: gender effects, dissimilarity within couples, and quality of life. Psychooncology 2001;10: 325-35.
8. Bruce M. A systematic and conceptual review of posttraumatic stress in childhood cancer survivors and their parents. Clin Psychol Rev 2006;26:233-56.
9. Rosenberg AR, Bradford MC, Junkins CC, et al. Effect of the Promoting Resilience in Stress Management Intervention for Parents of Children with Cancer (PRISM-P): A Randomized Clinical Trial. JAMA network open 2019;2:e1911578.
10. Ata N, Bulbul T, Gokcen C, et al. Depression and anxiety levels in mothers of children with epistaxis: A controlled study. Acta Otorrinolaringol Esp 2019;70: 286-9.

11. Won E & Kim YK. Stress, the autonomic nervous system, and the immune-kynurenine pathway in the etiology of depression. Curr Neuropharmacol 2016;14:665-73.
12. Hernando D, Hernando A, Casajús JA, et al. Methodological framework for heart rate variability analysis during exercise: application to running and cycling stress testing. Med Biol Eng Comput 2018;56:781-94.
13. Zou L, Sasaki JE, Wei GX, et a. Effects of mind–body exercises (Tai Chi/Yoga) on heart rate variability parameters and perceived stress: A systematic review with meta-analysis of randomized controlled trials. J Clin Med 2018;7:404.
14. Gümüş AB, Yardımcı H, Keser A. Evaluation of the nutritional status of students preparing for the exam according to their anxiety scores. J Duzce University Institute of Health Sciences 2018; 8:22-8.
15. Özkaraman A, Dügüm Ö, Yılmaz HÖ, et al. Aromatherapy: The effect of lavender on anxiety and sleep quality in patients treated with chemotherapy. Clin J Oncol Nurs 2018;22:203-10.
16. Shaffer F & Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017;5:258.
17. Mainardi LT. On the quantification of heart rate variability spectral parameters using time–frequency and time-varying methods. Philos Trans A Math Phys Eng Sci 2009;367:255-75.
18. Acharya UR, Joseph KP, Kannathal N, et al. Heart rate variability: a review. Med Biol Eng Comput 2006;44:1031-51.
19. Wagner J, Keuky L, Lampert R, et al. Socioeconomic status, waist-to-hip ratio, and short-term heart rate variability in Cambodians with type 2 diabetes. Int J Behav Med 2015;22:786-91.
20. Tehrani TH, Haghighi, M & Bazmamoun H. Effects of stress on mothers of hospitalized children in a hospital in Iran. Iran J Child Neurol 2012;6:39-45.
21. Hildrum B, Mykletun A, Stordal E, et al. Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study. J Epidemiol Community Health 2007;61:53-8.
22. Cameron HA & Schoenfeld TJ. Behavioral and structural adaptations to stress. Front Neuroendocrinol 2018;49:106-13.
23. Speer KE, Semple S, Naumovskiet al. Heart rate variability for determining autonomic nervous system effects of lifestyle behaviors in early life: A systematic review. Physiol Behav 2020;217:112806.
24. Jensen MT. Resting heart rate and relation to disease and longevity: past, present and future. Scand J Clin Lab Invest 2020;79:108-16.
25. Doupnik SK, Hill D, Palakshappa D, et al. Parent coping support interventions during acute pediatric hospitalizations: a meta-analysis. Pediatrics 2017;140:e20164171.
26. Schubert C, Lambertz M, Nelesen RA, et al. Effects of stress on heart rate complexity—a comparison between short-term and chronic stress. Biol Psychol 2009;80:325-32.
27. Evrengul H, Tanriverdi H, Dursunoglu D, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. Epilepsy Res 2005;63:131-9.
28. Yang Z, Liu H, Meng F, et al. The analysis of circadian rhythm of heart rate variability in patients with drug-resistant epilepsy. Epilepsy Res 2018;146:151-9.
29. Koenig J & Thayer JF. Sex differences in healthy human heart rate variability: a meta-analysis. Neurosci Biobehav Rev 2016;64:288-310.
30. Wei CY, Kung WM, Chou YS, et al. Cardiac autonomic function in patients with ankylosing spondylitis: a case-control study. Med 2016;95:e3749.
31. Wikman A, Hovén E, Cernvall M, et al. Parents of children diagnosed with cancer: work situation and sick leave, a five-year post end-of-treatment or a child's death follow-up study. Acta Oncol 2016;55:1152-7.
32. Sultan S, Leclair T, Rondeau E, et al. A systematic review on factors and consequences of parental distress as related to childhood cancer. Eur J Cancer Care (Engl) 2016;25:616-37.
33. Jarczewski J, Furgała A, Winiarska A, et al. Cardiovascular response to different types of acute stress stimulations. Folia Med Cracov 2019;59:95-110.
34. Carnevali L & Sgoifo A. Vagal modulation of resting heart rate in rats: the role of stress, psychosocial factors, and physical exercise. Front Physiol 2014;5:118.
35. Carnevali L, Bondarenko E, Sgoifo A, et al. Metyrapone and fluoxetine suppress enduring behavioral but not cardiac effects of subchronic stress in rats. Am J Physiol Regul Integr Comp Physiol 2011;301:1123-31.
36. Sgoifo A, Carnevali L & Grippo AJ. The socially stressed heart. Insights from studies in rodents. Neurosci Biobehav Rev 2014;39:51-60.
37. Carlsson T, Kukkola L, Ljungman L, et al. Psychological distress in parents of children treated for cancer: An explorative study. PloS one 2019;14:e0218860.