IMPACT OF RESPIRATORY PHYSICAL THERAPY ON HEART RATE AUTONOMIC CONTROL IN CHILDREN WITH LEUKEMIA

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ABSTRACT

Introduction: Considering that heart rate (HR) autonomic control is impaired in cancer and subsequent respiratory effort may overload the heart, we aimed to evaluate the effect of a respiratory physical therapy session on HR autonomic regulation in children with leukemia so as to confirm its safety. **Methods:** We selected children with leukemia (n=10) and healthy children (n=11), which were submitted to a session of respiratory physical therapy. We used Spiron Kids (NCS, Brazil), Children's Voldyne (HUDSON RCI, USA) and Shaker (NCS, Brazil) as respiratory devices. The respiratory exercise protocols were founded on three standardized protocols. HR variability (HRV) was analyzed before, in the first minute and 5 to 10 minutes after intervention. **Results:** We recognized no change between rest and recovery from intervention in HRV (rMSSD- square root mean square of the differences between adjacent normal R-R intervals) - Control: p=0.8111, Leukemia: p=0.1197, among groups: p=0.6574; SD1- standard deviation from instantaneous beat-to-beat variability - Control: p=0.8111, Leukemia: p=0.131, among groups: p=0.6556; 0V- with no variation [3 equal symbols, for example (2,2,2)- Control: p=0.3679, Leukemia: p=0.3553, among groups: p=0.7421; 2UV- with two variations to the contrary [the three symbols form a peak or a valley, for instance (3,5,3)- Control: p=0.3679, Leukemia: p=0.2359, among groups: p=0.4007). HF - high frequency component, range 0.15 to 0.4Hz - decreased 0 to 1 minute after intervention in the leukemia group (p=0.0303) and no change was observed in the control group between rest versus recovery from intervention (p=0.9761). No significant change was reported in HF between groups (p=0.8700). Two Leukemia subjects treated with Vincristine presented different HRV responses to the intervention group. **Conclusion:** A respiratory physical therapy session did not significantly change autonomic control of HR in children with leukemia. Yet, clinicians should be mindful of subjects undergoing treatment with Vincristine.

Keywords: Autonomic Nervous System; Cardiovascular system; Physiotherapy; Heart Rate; Leukemia.

INTRODUCTION

Leukemia is a malignant hematological disease that affects the formation of blood cells in bone marrow. It is characterized by white bone marrow cell proliferation and decrease of red blood cells and platelets (1). Leukemia may be classified as acute if there is a change in the maturation process of young cells, specifically, blast cells with fast progression and, as chronic when mature cells or clasts are unable to halt proliferation; its progression is typically slower (1,2). The principal signs and symptoms are fatigue, weight loss, bleeding, weakness, joint pain, fever, infections, leukopenia, anemia, dyspnea and cardiovascular impairments (2,3).

Accordingly, the cardiovascular system may be assessed via heart rate (HR) variability (HRV), which assesses the fluctuations of the intervals between successive heart beats (R-R intervals) and is intrinsically interrelated to the ability of the heart to adapt to stimulus. HRV is influenced by the autonomic nervous systems' (ANS) activity on the sinus node and is necessary to identify the influence of diseases, physical exercise and medications on the ANS (4–6). HRV is a simple and non-invasive measure of cardiac health; high HRV is an indicator of decent physiological health whilst low HRV is a warning of maladaptation and could be an indicator of a pathological state (4,6–9).

In patients with leukemia, HRV is reduced during treatment (10,11) and in surviving patients (12). Extensive treatment, cumulative doses of anti-neoplastic medication and the disease itself can result in cardiac autonomic dysfunction (11). Although, Hirvonen *et al*. (13) stated HRV recovery after cessation of anti-neoplastic medication, further studies are required to better comprehend this cardiac autonomic dysfunction in leukemia.

Patients with leukemia undergo lengthy treatments allied to symptoms such as fatigue, dyspnea, apathy, pain, which can initiate decreased physical activities and activities of daily living. During this scenario, a physical rehabilitation program is vital to circumvent sarcopenia, muscle weakness and overall loss of functionality (14). It was previously demonstrated that a five-day hospital stay can impair the muscular and pulmonary systems (15).

In this way, physical therapy acts in the prevention, maintenance and restoration of functional disorders prompted by cancer treatment (16). San Juan *et al*. (14) coordinated a study with a 16-week in-hospital intervention, presenting significant gains in muscle strength, mobility and peak oxygen consumption (VO_2 peak), supporting this intervention as an important technique. A study in children with leukemia presenting strength training exercise associated with aerobic exercise for 12 weeks reported a beneficial impact and no substantial adverse effects. Participants had a substantial gain in muscle strength and quality of life (17).

Likewise, Kim *et al*, (18) established feasibility of cardiopulmonary exercise monitoring in patients with hematologic cancer after undertaking chemotherapy.

Review articles recommend that exercise and respiratory physical therapy agendas are safe and central for maintenance and cardiorespiratory gain, body composition, flexibility, muscle strength and quality of life in subjects with cancer during and after treatment. Yet, there is no agreement on the protocol to be followed because of the diverse methodologies applied and the small cohort of participants (19,20). In this manner, we should be wary of contraindications for rehabilitation based on biochemical assessments, low platelets, hemoglobin and hematocrit analysis (16).

Accordingly, we were unable to locate studies assessing the safety of respiratory physical therapy in children undergoing leukemia treatment. Consequently, we raise the question: Considering that patients with leukemia have impaired HRV, could a protocol of respiratory physical therapy cause autonomic overload in this group? Or rather, is respiratory physical therapy safe for children presenting with leukemia? We hypothesized that autonomic overload would be related to the exaggerated response of the sympathetic tone or depression of the parasympathetic system.

In order to resolve the question, we proposed to confirm the acute effects of a respiratory physical therapy protocol on the autonomic control of HR in children with leukemia.

METHODS

CONSORT Statement

Our study is in agreement with the CONSORT (Consolidated Standards of Reporting Trials) statement. Our investigation comprises details of the study population and settings; subject selection (eligibility criteria); efficacy and safety procedures. The study design and statistical procedures have been described. We provided details concerning trial design, participants, interventions, outcomes, sample size and statistical methods. It was impossible to blind the intervention as the physical therapy protocol was founded on voluntary respiratory effort.

Trial Design

This is a prospective case-control study. We included children and adolescents undertaking leukemia treatment and healthy children and adolescents selected from February 2018 to July 2018. The project was registered with the Brazilian Registry of Clinical Trials

(http://www.ensaiosclinicos.gov.br/rg/RBR-9cvrrs/ Protocol number: RBR-9d5cr6. The study was completed at the Onco-hematology outpatient clinic, Marilia, SP, Brazil.

Participants

We designated children with leukemia and healthy children from Marilia, SP, Brazil. The leukemia group (LG) was composed by 10 children and adolescents (3 boys, 4 to 11 years old) with leukemia of either gender under treatment at the Onco-hematology outpatient clinic, Marilia, SP, Brazil. All children and adolescents who progressed through the outpatient clinic were invited to participate. As eligibility criteria, the subjects could not have neurological, musculoskeletal, renal, metabolic, endocrine and other reported disorders that prevented them performing the procedures; use of medications other than those for leukemia.

The control group (CG) consisted of 11 healthy children and adolescents (6 boys, 4 to 14 years old) of either gender. A request was made to their parents and, if the child agreed, they would partake in the study. Subjects from the CG were excluded under the following circumstances: cardiorespiratory, neurological, musculoskeletal, renal, metabolic, endocrine and other reported disorders that prohibited the successful completion of the protocols, those subjects undergoing pharmacotherapies.

Ethical approval and informed consent

This study was agreed by the Research Ethics Committee in Research of UNESP/Marilia (Number 007686/2017). All participants' responsible signed a confidential informed letter of consent. All actions were achieved in accordance with the 466/2012 resolution of the National Health Council of December 12th 2012.

Initial Assessment

The initial review was finalized to obtain characterization information of the individuals and their eligibility criteria. An anamnesis was commenced to authorize the absence of reported disorders, the use of medications, to measure cardiovascular variables and to evaluate the suitability of participating in the experimental protocol.

The LG evaluation was completed on the day of consultation at the reference outpatient clinic, in advance of the medical appointment and chemotherapy session. All subjects were pierced for blood collection and left venous access for chemotherapy administration before medical consultation and prior to participation in the study. Subjects were identified and the following information was collected: age, type of chemotherapy, gender, mass, height, HR, respiratory rate (RR), systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI), respiratory muscle strength, peripheral oxygen saturation (SpO_2), blood count.

Anthropometric measurements were obtained consistent with the recommendations described by Lohman *et al.* (21). Body mass was recorded via a digital scale and height with a stadiometer (Welmy, Brazil) with precisions of 0.1 kg and 0.1 cm, respectively. BMI was computed via the mathematical formula: mass (kg) / height $(m)^2$.

The dimensions of waist, circumference, hip and abdominal were achieved whilst in the standing position, with abdomen relaxed, arms extended at their sides, feet together and weight equally supported by both legs. Waist circumference was measured with a measuring tape positioned at the smallest curvature located between the ribs and the iliac crest. The hip boundary was taken with the tape situated in the greater trochanter zone, in the location of greatest bulge.

To evaluate the respiratory muscle strength, we used a manometer (Indumed, Brazil). First, maximal inspiratory pressure (MIP) was taken from residual volume and after that maximal expiratory pressure (MEP) was taken from total lung capacity. In the sitting position, a nasal clip was placed and the subject was instructed to release all the air and intake as if drinking juice with a straw. Then, the subject was instructed to draw all the air and blow as if filling a balloon. Each technique was undertaken three times and we logged the highest attained value. (22,23) To facilitate familiarization of the equipment, prior to starting the evaluation, the procedure was described and performed once.

SpO_2 was assessed using an oximeter with ± 2% accuracy (Elera, Brazil). The assessment was performed by a single researcher during the entire experiment.

Outcomes

Cardiorespiratory variables:

HR was evaluated with the Polar RS800cx HR monitor (Polar Electro, Finland). SBP and DBP were attained indirectly by auscultation with a stethoscope (Premium, Barueri, SP, Brazil) and calibrated via an aneroid sphygmomanometer (Premium, Barueri, SP, Brazil) on the subjects' left arm (24). Respiratory rate (RR) was achieved by counting the respiratory cycles during one minute whilst the subject was unaware; to avoid potential influences and changes in the subjects' respiratory patterns.

HRV analysis:

For analysis of HRV indices, beat-to-beat was recorded during the experimental protocol by a heart rate monitor (Polar RS800cx, Finland) with a sampling rate of 1 kHz. The R-R intervals recorded by the portable HR monitor were transferred to the Polar program. Precision Performance (v. 3.0, Polar Electro, Finland) enables HR viewing and a period of signal stability visualization. A five-minute interval was carefully chosen and saved to a "txt" file.

Subsequently, digital filtering was completed by the Polar Precision Performance program (v. 3.0, Polar Electro, Finland) accompanied with manual filtering for artifact elimination, and for data analysis a 256 R-R interval stable series was selected (25). Only series with over 95% of sinus beats were included in the study (26,27). The electrical signals of the heartbeat are detected by the Polar´s chest belt and logged. These data are transmitted via infrared and the software enabled the visualization of the HR and the extraction of a cardiac period file (R-R interval) in the "txt" format. The Polar devices are more accessible in terms of cost and usage. The Polar S810 demonstrated decent accuracy during the recordings in exercise and at rest, when compared to those of the ambulatory electrocardiogram (28,29).

For HRV analysis in the frequency domain, we included the high frequency component (HF, range 0.15 to 0.4 Hz, corresponding to respiratory and vagal modulation indicators) used in absolute units (ms^2). Spectral analysis was calculated using the Fast Fourier Transform (FFT) (6,25). Time domain analysis was achieved using the rMSSD index representing the vagal predominance (square root mean square of the differences between adjacent normal R-R intervals) (6,25).

The geometric domain analysis was completed via the Poincaré plot (SD1). For the construction of the Poincaré Plot, each R-R interval was characterized as a function of the previous interval and for quantitative analysis we calculated the SD1 (standard deviation from instantaneous beat-to-beat variability) (6,25). The rMSSD, SD1 and HF indices correspond to the parasympathetic HR regulation and are enforced for data using recordings of 10 minutes or less. (25–27,30).

The first inferences concerning the impact of the ANS on heart rate were achieved in anesthetized animals. They understood that the heart rhythm is related to sympathetic and parasympathetic activity and in the same period observed that inspiration leads to an inhibition of the cardiac vagal tone. The parasympathetic parameters of HRV are related to a better adaptation and response to external disturbances (30).

For the linear indices computations, Kubios HRV® software (Kubios HRV v.1.1, Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) was required (31).

The HRV symbolic analysis was completed by distributing the R-R interval series in six levels (0 to 5), which converts it to a symbolic sequence, from which patterns are created (three symbol sequence). All possible patterns were grouped into families according to the number and type of variations between successive symbols: 1) 0V with no variation [3 equal symbols,

e.g. (2, 2, 2) or (4, 4, 4)] and; 2) 2UV with two variations to the contrary [the three symbols form a peak or a valley, for instance (3, 5, 3) or (4, 1, 2)] (32).

Previous studies involving pharmacological blockade and autonomic tests indicated that the 0V index is characteristic of heart rhythm sympathetic modulation and, 2UV are linked to HR vagal modulation (6). For symbolic analysis the CardioSeries v2.4®, (Ribeirao Preto, SP, Brazil) software was enforced.

Interventions

Initial Assessment:

With the purpose of controlling potential sources of bias, data collection was achieved individually between 7:00 AM and 11:00 AM in a silent room with humidity between 40% and 70% and temperature between 20°C and 26°C. The subjects were instructed to remain at rest, avoiding conversations during the entire experimental period.

The descriptive profile of the individuals was defined to describe the sample, reduce the unpredictability of the variables, improve reproducibility and physiological interpretation. We standardized age, SBP, DBP, mass, hip, abdominal, waist circumferences, waist-hip ratio, fat percentage, height and body mass index (BMI) with the objective of controlling their physiological variability.

Following the initial evaluation, the HR Polar RS800cx capture belt (Polar Electro, Finland) was located on the subjects' chest at the distal third of the sternum. Then, a respiratory physical therapy procedure was completed.

We monitored respiratory rate, which extended between 10 and 17 cpm.

Respiratory physical therapy protocol:

We enforced Spiron Kids (NCS, Brazil), Children's Voldyne (HUDSON RCI, USA) and Shaker (NCS, Brazil) as respiratory devices. The respiratory exercise protocols were founded on the three protocols designated below.

I- Spiron Kids: This is an exerciser and respiratory incentive used to strengthen the respiratory muscles and increase lung volumes and capacities. It is widely enforced in public hospitals by reason of affordability. The subject was instructed to release all their breath (complete exhalation), fit the mouthpiece and perform a quick inhalation so that the colored balls rise. The technique was undertaken on one occasion so that the subject was acquainted with the equipment and recognized the procedure. Next, the subject was instructed to perform 3 sets of 10 repetitions with a 1-minute interval between them.

II- Children's Voldyne: This is a Volumetric Incentive Spirometer Breathing Exerciser necessary for prevention of atelectasis. The subject was instructed to emit all air (full exhalation) and fit the mouthpiece and perform a slow inhalation so that the "Kite" was between the clouds and trees. The technique was completed once to facilitate the subject being acquainted with the equipment and recognized the procedure. Later, the subject was instructed to start 3 sets of 10 repetitions with a 1-minute interval amid them.

III- Shaker: This is another respiratory exerciser and promotes a high frequency of oral oscillation recognized to mobilize pulmonary secretions by enabling and stimulating the expectoration (ejecting phlegm or mucus from the throat or lungs by coughing). The subject was told to apply the mouthpiece, take a deep breath through the nose and release via the mouth. The technique was performed on one occasion so that the subject was accustomed to the equipment and recognized the procedure. Then, the subject was told to complete 3 sets of 10 repetitions with a 1-minute interval between them.

HRV analysis was performed 10 minutes at rest before the physical therapy session, 0 to 1 minute and 5 to 10 minutes after the respiratory physical therapy protocol. In the LG, HRV analysis was completed separately with two children who received Vincristine as an anti-neoplastic drug and with eight children who did not have the drug administered.

Sample Size

The sample size calculation was achieved based on a pilot study, which provided additional data for the present study. We applied the online software from the website (www.leedante.com.br) and calculated the RMSSD index as a reference. We accepted a standard deviation of 13.8 ms and the extent of the difference was 15.23 ms, with alpha risk of 5% and beta risk of 80%. The sample size provided was a minimum of 10 subjects per group.

Statistical analysis

Considering that all distributions were non-parametric, we executed the Mann-Whitney test to compare variables between groups (33). For comparisons of HRV between before vs. 0 to 1 min after the intervention vs. 5 to 10 min after intervention and for analysis of points in time (rest vs. 0 to 1 min recovery vs. 5 to 10 min recovery) we implemented the repeated Friedman test followed by Dunn's post-test (33).

For significant differences, the effect size was calculated by Cohen's *d*. Large effect size was considered for values greater than 0.9, while moderate effect size was considered for values between 0.9 and 0.5 (34).

Spearman's correlation test was completed in order to examine the relationship between HRV and blood parameters, chemotherapy period and initial evaluation. Strong correlation was considered for $r > 0.75$ and moderate correlation was considered for r between 0.5 and 0.75. Significant differences were considered for $p<0.05$, (or, <5%).

We implemented the software Biostat® 2009 Professional 5.8.4 for Windows.

RESULTS

According to Table 1, we detected no significant differences for age, mass, height, BMI, WHR, MIP, MEP, SpO_2, SBP and DBP between groups. Yet, RR was higher in the leukemia group (large effect size).

Table 2 indicates that the leukemia group presented normal laboratory tests.

Table 3 presents correlations between: HRV vs. BMI, WHR, MIP, MEP, SpO_2, HB, HT, leukocytes and chemotherapy period in children with leukemia. We observed moderate negative correlation between BMI and 0V and moderate positive correlation between BMI and 2UV. Chemotherapy period was positively correlated with 2UV.

Founded on Table 4, we were unable to find significant correlation between HRV vs. BMI, WHR, MIP, MEP and SpO_2 in the control group.

We observed no significant differences between rest and recovery from intervention in rMSSD (Control: p=0.8111, Leukemia: p=0.1197, among groups: p=0.6574) and SD1 (Control: p=0.8111, Leukemia: p=0.131, among groups: p=0.6556) in the leukemia and control groups. Yet, HF decreased 0 to 1 minute after intervention in the leukemia group (p=0.0303) while no change was detected in the control group between rest vs. recovery from intervention (p=0.9761). No significant difference was detected in HF between groups (p=0.8700) (Figure 1).

In Figure 2 we observe HRV symbolic analysis before and during recovery from respiratory physical therapy. We revealed no significant differences between rest and recovery from intervention in 0V (Control: p=0.3679, Leukemia: p=0.3553, among groups: p=0.7421) and 2UV (Control: p=0.3679, Leukemia: p=0.2359, among groups: p=0.4007).

Similarly, we investigated two children with leukemia treated with Vincristine. While it did not attain statistical significance as a consequence of the small sample size, we observed

different recovery patterns in rMSSD (p=0.1767), HF (p=0.5), SD1 (p=0.1667) (Figure 3) and symbolic analysis (0V: p=0.1667; 2UV: p=0.1561) (Figure 4).

DISCUSSION

This study was originated to evaluate the effects of a respiratory physical therapy session on the autonomic control of heart rhythm in children with leukemia. Our key results indicate that:

1) There was no difference of resting HR autonomic control amongst children with and without leukemia;

2) The respiratory physical therapy protocol triggered a *slight* HR autonomic overload in children with leukemia, but there was no significant change in the control group;

3) Chemotherapy period was related with autonomic HR control;

4) Children with leukemia treated with Vincristine had different autonomic responses induced by the physical therapy protocol.

Regarding the association between HRV and the variables in leukemia group, we detected significant correlations for 0V vs BMI, 2UV vs BMI, SD1 vs WHR and rMSSD vs WHR. The correlation between the 2UV index and chemotherapy period was positive, suggesting that the longer the chemotherapy period, the greater the parasympathetic HR modulation. It has been previously documented that the accumulation of chemotherapy doses has a negative impact on cardiac fitness (11,18) and HRV can be used to detect autonomic dysfunction and forecast survival rates (35). A previous study indicated the effectiveness of cardioprotective strategies. The number of premature cardiovascular deaths in patients receiving chemotherapy was reduced and the number of patients that had any symptoms related to the cardiovascular system was diminished (36). A further study conducted with 203 patients demonstrated positive effects of cardioprotective medications (11). So, we considered the estimation of HRV vital during the treatment of these patients since, when presented with indications of autonomic dysfunction the clinical team can apply cardioprotective strategies.

One hypothesis to explain the positive correlation between 2UV vs chemotherapy time is that the ANS supported the chemotherapy to manage the disease. The study by Kim *et al*. (18) revealed that the level of chemotherapy received may significantly influence resting HR, signifying that higher resting HR is linked with the progression of cancer and damage to cardiac tissue.

Thus, two review studies presented evidence that higher vagal activity is a protective aspect, since it was related to better prognosis and extended survival in patients with cancer.

Instead, decreased HRV is related to higher mortality (35,36). A study with pancreatic cancer patients indicated that low HRV and high inflammatory index, represented by blood analysis of C-reactive protein, had a smaller amount of survival time. Consequently, the authors considered HRV as a predictor of cancer diagnosis (37–39).

Lígia *et al*. (40) accepted that increased sympathetic control in patients undergoing cancer treatment may precede heart failure signals. This idea is reinforced by Caru *et al.* (11) who make known that initially the body attempts to compensate, inducing subclinical cardiovascular changes, yet in the long term it can promote heart failure. Equally, our results revealed no difference in the 0V parameter amongst children with leukemia and the control group.

In this context, respiratory physical therapy uses therapeutic resources as inspiratory motivators, which while there is no consensus on its effectiveness (41–43), it is applied extensively in clinical practice with cancer patients. Its effectiveness is questioned, as the studies assessed are of poor quality, with diverse methodology and protocol, making their analysis and conclusions problematic.

The research literature highlighted complications when studying children because of the difficulties keeping them quiet. Kemper *et al* (44) evaluated the impact of music on HRV in children with cancer. These authors emphasized effort in maintaining children silent during the protocol. Based on this understanding, we enforced a procedure that was attractive and included some playful aspects.

The recovery pattern between the groups was analogous, suggesting safety in applying the devices for respiratory physical therapy. Even so, it is vital to realize that children with leukemia had greater autonomic sensitivity to stimuli from the physical therapy protocol.

Moreira *et al*. conducted a study in 33 healthy subjects and evaluated HRV during the use of respiratory supporters (and volume flow). The authors detected increased rMSSD and pNN50 during use of both boosters (45). Instead, the instability of R-R intervals oscillations is a bias. Another study evaluated the influence of the Shaker on HRV in 20 healthy participants. There was a decrease in rMSSD and pNN50 indices and an increase in HF and LF indices. Hitherto, the authors used a metronome (inspiration/expiration: ratio 2/3), which may have influenced HRV patterns (46). Thus, we cannot compare the results owing to different protocols.

Two children administered Vincristine presented different HR autonomic recovery from physical therapy compared to the other groups. Immediately after the therapy session, there was an increase in rMSSD, HF, SD1 and decrease in 0V when compared to rest. Approximately five minutes after the physical therapy intervention, a decrease in the same rates was observed

when compared to before intervention. We accept that the cardiotoxicity of Vincristine (47,48), coupled with the respiratory physical therapy interacts with the autonomic control of HR. Previous studies in leukemia patients who were administered Vincristine have documented autonomic alterations and could progress with HRV neuropathy (12,13).

Some points need highlighting. The metronome was superfluous during the execution of the protocol, as we accept that slow and controlled breathing influences HRV (49–51) and blood pressure (52). Besides, findings suggest that children undergoing leukemia treatment may have nerve damage that may lead to a deficit between a respiratory modulation (here represented by the HF index) and the heart (13).

Though, few studies have evaluated the use of motivators in HRV. While respiratory devices are not specific to separate muscles, a study in 2014 suggested increased respiratory muscle strength when 3 sets of 15 repetitions were performed (53). Thus, we accept that these strategies when enforced weekly during cancer treatment could be advantageous in sustaining respiratory muscle strength and preventing pulmonary complications.

With the increasing survival of cancer patients, it is important to understand the effects of respiratory physical therapy on autonomic control so that we can provide an improved quality of life. Considering that respiratory stimulatory devices are extensively used in clinical practice; we accept the requirement for additional studies (multicenter and longitudinal) to better understand their effect on the ANS during and after treatment. In this study, children who took Vincristine demonstrated an exaggerated autonomic response, yet, owing to the small sample, we cannot claim that the use of these respiratory devices is safe for those who use this medication, then depending on the drug administered this protocol may not be appropriate. Also, during the treatment of leukemia, children may attain pulmonary infections, reinforcing the necessity of respiratory physical therapy (16).

The study undertaken presented limitations regarding the analysis of acute effects. We have confidence in the importance of additional heart rate assessments, so that we can understand the long-term effects. Age impacts HRV (54) and is an extra limitation in our study. Another constraint is the single session of physiotherapy; a suggestion is that a greater number of sessions could convey more significant results.

Our results improve knowledge concerning the treatment of children with leukemia, since at present we are unaware of studies in the research literature that evaluated the effects of respiratory devices on ANS in children with leukemia.

CONCLUSION

A respiratory physical therapy session did not cause clinical or substantial overload in the autonomic control of HR in children with leukemia. Our results emphasize the safety of this protocol for subjects with this illness. Yet, care is recommended in children treated with Vincristine.

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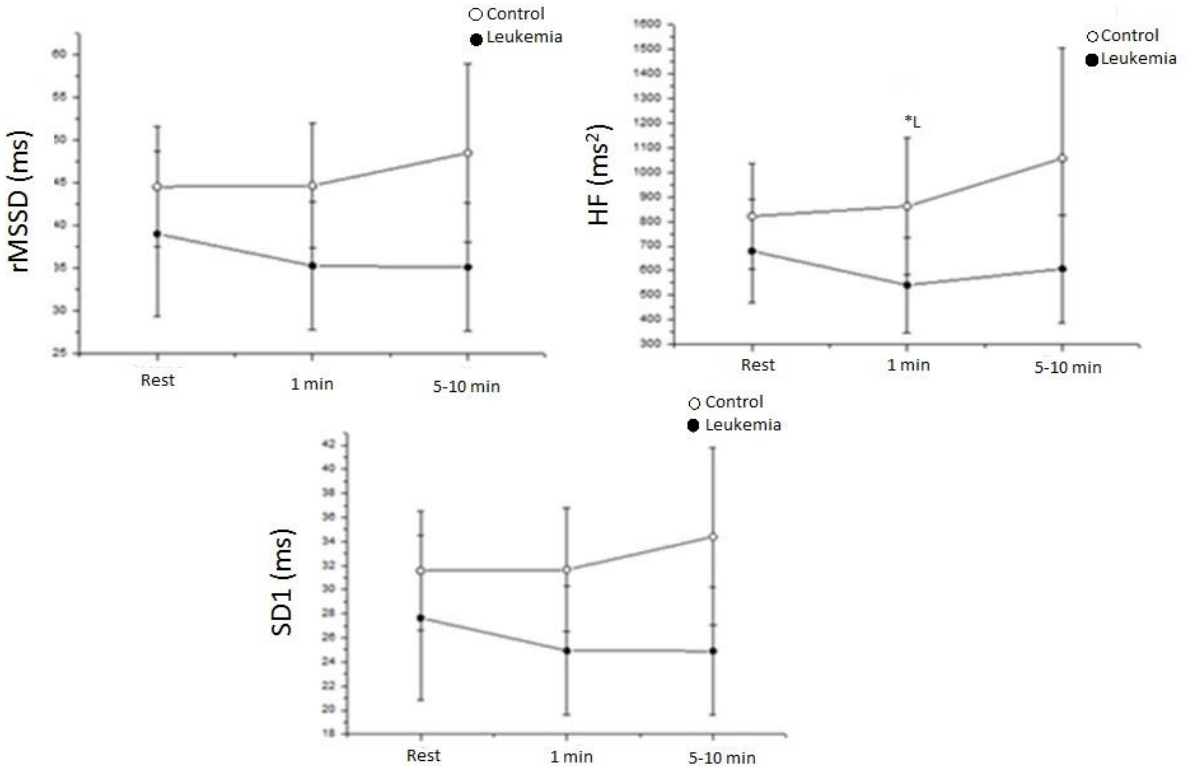

Figure 1. Mean values and respective standard deviations of rMSSD, HF and SD1 indexes obtained at rest and during recovery from the intervention. rMSSD: square root mean square of the differences between adjacent normal RR intervals; HF: high frequency; SD1: standard deviation of instantaneous beat-to-beat variability; ms: milliseconds; *L $p < 0.05$ vs. Rest in the leukemia group.

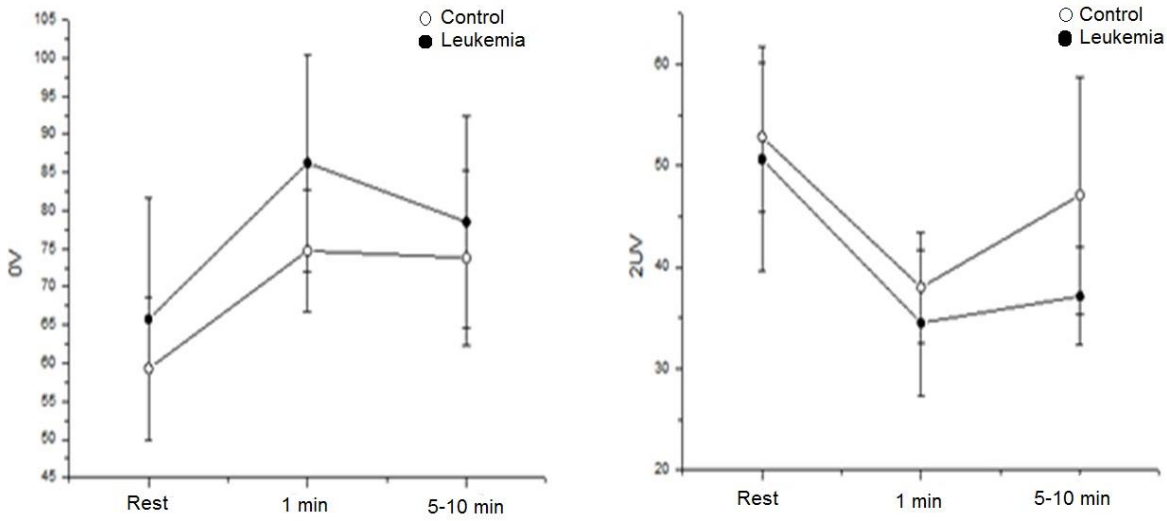

Figure 2. Mean values and respective standard deviations of 0V and 2ULV obtained at rest and during recovery from the intervention.

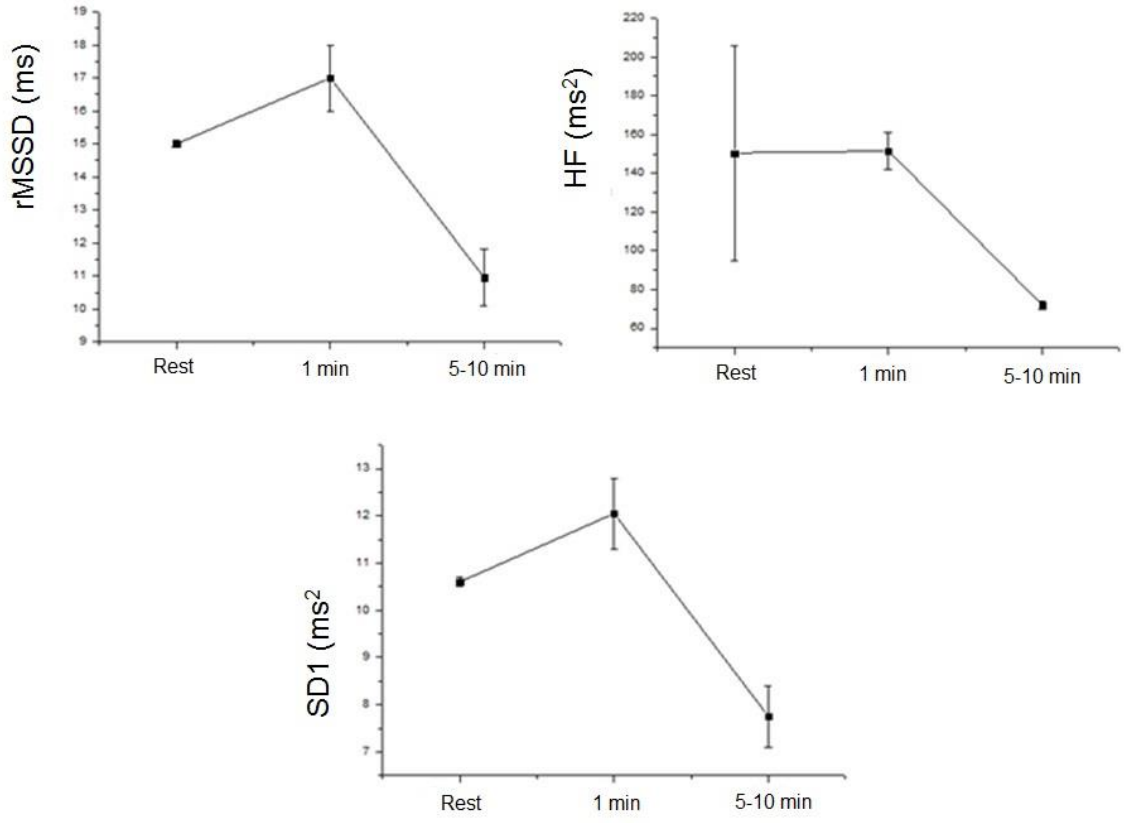

Figure 3. Mean values and respective standard deviations of rMSSD, HF and SD1 indexes obtained at rest and during recovery from the intervention in two leukemia children treated with Vincristine. rMSSD: square root mean square of the differences between adjacent normal RR intervals; HF: high frequency; SD1: standard deviation of instantaneous beat-to-beat variability; ms: milliseconds.

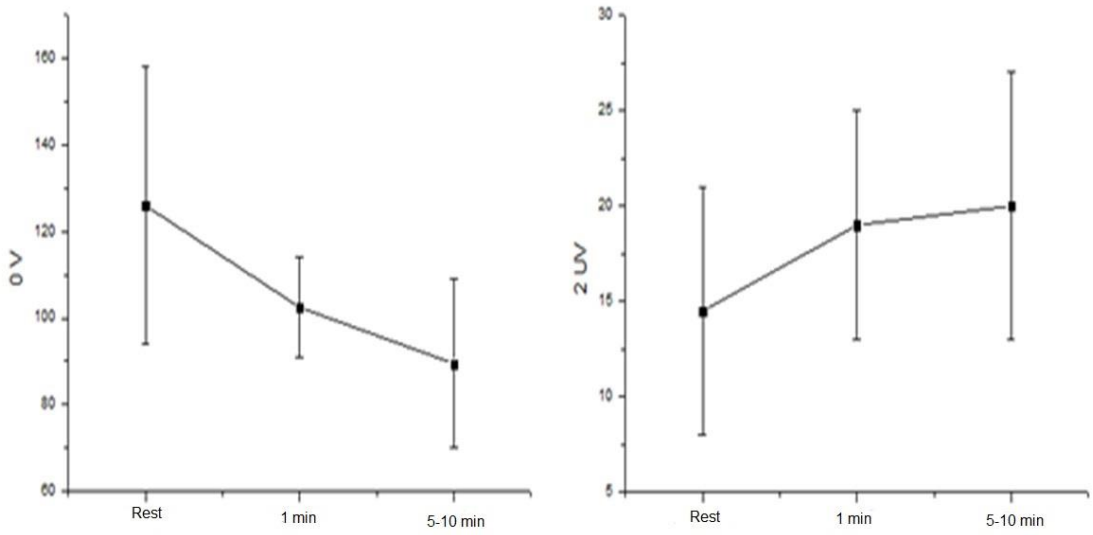

Figure 4. Mean values and respective standard deviations of 0V and 2ULV obtained at rest and during recovery from the intervention in two leukemia children treated with Vincristine.

Table 1. Mean values followed by their respective standard deviations, minimum and maximum of age, mass, height, BMI, WHR, MIP, MEP, SpO_2. RR, SBP and DBP.

Variable	Control	Leukemia	P	Cohen's d
Age (years)	8 ± 3.13 [4 - 14]	7.5 ± 2.59 [4 - 11]	0.9719	-
Mass (kg)	30.94 ± 13.38 [15 - 64]	26.87 ± 6.58 [18.6 –39.6]	0.6047	-
Height (m)	1.31 ± 0.18 [1.09 - 1.66]	1.2 ± 0.12 [0.99 - 1.33]	0.1734	-
BMI (kg/m^2)	17.12 ± 3.28 [12.20 - 23.20]	18.69 ± 3.95 [14.50 - 27.90]	0.3597	-
WHR (m)	0.86 ± 0.04 [0.81 - 0.93]	0.89 ± 0.03 [0.85 - 0.96]	0.4167	-
MIP (CmH_2O)	111.36 ± 14.50 [75 - 120]	98.5 ± 28.67 [40 - 120]	0.3914	-
MEP (CmH_2O)	57.27 ± 11.90 [40 - 80]	49 ± 17.76 [20 - 80]	0.2892	-
SpO_2 (%)	97 ± 1.78 [94 - 99]	95.9 ± 1.66 [93 - 99]	0.2033	-
RR (cpm)	18.54 ± 3.53 [12 - 24]	22 ± 3.09 [18 - 28]	0.0484	1.04
SBP (mmHg)	97.72 ± 6.06 [90 - 110]	97.5 ± 9.78 [85 - 110]	0.8315	-
DBP (mmHg)	56.81 ± 5.6 [45 - 60]	59.5 ± 5.98 [50 - 70]	0.3682	-

Legend: BMI: body mass index; WHR: waist-hip ratio; MIP: maximum inspiratory pressure; MEP: maximal expiratory pressure; RR: respiratory rate; SpO_2: peripheral oxygen saturation; cpm: cycles per minute; cm: centimeters; mmHg: millimeters of mercury; kg: kilograms.

Table 2: Mean values followed by their respective standard deviations, minimum and maximum of hemoglobin, hematocrit, leukocytes, platelets and chemotherapy time.

HB (millions/mm^3)	**HT (millions/mm^3)**	**Leukocytes (millions/mm^3)**	**Platelets (millions/mm^3)**	**T. Qtx (months)**
11.98 ± 1.23	34.05 ± 2.04	3749 ± 1359	217600 ± 60877	12 ± 7.88
[10.20 - 14.50]	[30.50 - 36.10]	[1500 - 5590]	[76000 - 28100]	[2 - 24]

Legend: HB: hemoglobin; HT: hematocrit; mm: millimeters.

Table 3. Correlation between HRV vs. BMI, WHR, MIP, MEP, SpO_2, HB, HT, leukocytes and chemotherapy time in children with leukemia.

Variable	r	P
BMI		
rMSSD	0.3769	0.2788
SD1	0.3769	0.2788
HF	0.4802	0.1663
0V	-0.8146	0.0058
2UV	0.6991	0.0306
WHR		
rMSSD	-0.6566	0.0438
SD1	-0.6566	0.0438
HF	-0.5315	0.1139
0V	0.3252	0.3487
2UV	-0.3127	0.3679
MIP		
rMSSD	-0.1103	0.7589
SD1	-0.1103	0.7589
HF	-0.04541	0.9184
0V	0.3373	0.3304
2UV	-0.5255	0.1231
MEP		
rMSSD	0.5427	0.1049
SD1	0.5427	0.1049
HF	0.4573	0.1912
0V	-0.2744	0.4483
2UV	0.06707	0.8651
SpO_2		
rMSSD	0.3548	0.3129
SD1	0.3548	0.3129
HF	0.4688	0.1786

0V	-0.4878	0.1548
2UV	0.3928	0.2632
HB		
rMSSD	0.4424	0.2044
SD1	0.4424	0.2044
HF	0.4424	0.2044
0V	0.3769	0.2788
2UV	0.1879	0.6073
HT		
rMSSD	0.6	0.2417
SD1	0.6000	0.2417
HF	0.4802	0.1663
0V	-0.2571	0.6583
2UV	0.7714	0.1028
Leukocytes		
rMSSD	-0.3697	0.2957
SD1	-0.3697	0.2957
HF	-0.3818	0.2788
0V	0.1152	0.7589
2UV	-0.2485	0.4918
T. Qtx		
rMSSD	0.3659	0.2957
SD1	0.3359	0.2957
HF	0.4634	0.1786
0V	-0.6281	0.0544
2UV	0.6585	0.0438

Legend: BMI: body mass index; WHR: waist-hip ratio; MIP: maximum inspiratory pressure; MEP: maximal expiratory pressure; SpO_2: peripheral oxygen saturation; HB: hemoglobin; HT: hematocrit.

Table 4. Correlation between HRV vs. BMI, WHR, MIP, MEP and SpO_2 in the control group.

Variable	r	P
BMI		
rMSSD	0.1367	0.6937
SD1	0.1367	0.6937
HF	0.2050	0.5393
0V	-0.5103	0.1142
2UV	0.2968	0.3713
WHR		
rMSSD	0.0228	0.9462
SD1	0.0228	0.9462
HF	0.0549	0.8812
0V	-0.3066	0.3560
2UV	0.2087	0.5393
MIP		
rMSSD	-0.1426	0.6731
SD1	-0.1426	0.6731
HF	-0.2588	0.4348
0V	0.3961	0.2250
2UV	-0.3493	0.2862
MEP		
rMSSD	-0.0431	0.9033
SD1	-0.0431	0.9033
HF	-0.0527	0.8812
0V	0.5127	0.1072
2UV	-0.3626	0.2731
SpO_2		
rMSSD	0.2171	0.5208
SD1	0.2171	0.5208
HF	0.1986	0.5574
0V	0.1663	0.6147

2UV	-0.0254	0.9462

Legend: BMI: body mass index; WHR: waist-hip ratio; MIP: maximum inspiratory pressure; MEP: maximal expiratory pressure; SpO_2: peripheral oxygen saturation.