



Case report

Improving cerebral oxygenation, cognition and autonomic nervous system control of a chronic alcohol abuser through a three-month running program



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ABSTRACT

The abusive use of alcohol has shown to be associated to cerebral damage, impaired cognition, poor autonomic nervous control, impaired cardiovascular health, increased levels of stress and anxiety, depression symptoms and poor quality of life. Aerobic exercise has shown to be an efficient tool to reduce and overcome these issues. In this case report, a patient (forty-four years old, male) under treatment in public psychiatric hospital, classified as having a substance use disorder, underwent a three-month running program. The maximal oxygen consumption increased from 24.2 ml/kg/min to 30.1 ml/kg/min, running time increased from 6 min to 45 min (650%) and distance covered from 765 m to 8700 m (1037.2%). In prefrontal cortex oxygenation, oxyhemoglobin levels improved by 76.1%, deoxyhemoglobin decreased 96.9% and total hemoglobin increased 78.8% during exercise. Reaction time in the cognitive test during rest decreased 23%, and the number of correct answers increased by 266.6%. Parasympathetic cardiac parameters increased in several heart rate variability indices. Thus, we conclude that running exercise performed by an alcoholic patient hospitalized in a psychiatric hospital improves cerebral function, cognition and cardiovascular health.

1. Introduction

According to the fifth edition of the Statistical Manual of Mental Illness (American Psychiatric Association, 2013), disorders related to alcohol abuse are defined as a set of psychosocial problems that occur repeatedly due to chronic use of a substance. In this integrative approach, the severity of the disorder varies according to the number of criteria that the subject fits, and may be classified as mild, moderate or severe. Currently, excessive consumption of alcohol is a serious public health problem worldwide with approximately 3.3 million deaths per year (Alcohol Facts and Statistics | National Institute on Alcohol Abuse and Alcoholism (NIAAA), n.d.). Moreover, it has been widely shown to causes liver diseases and cancer (Alcohol Consumption | Cancer Trends Progress Report, n.d.). In the brain, deterioration of prosencephalic regions caused by alcohol abuse has been reported (Asensio et al., 2016; Pahng, McGinn, Paulsen, & Edwards, 2017), with decreased oxygenation (Schecklmann et al., 2007) and reductions of gray matter volume in the anterior cingulate and in the medial, orbitofrontal and prefrontal cortices (Wang et al., 2016). Impairment in these structures has been accompanied by decreases in cognition (Volkow, Koob, & McLellan, 2016) with lower control of impulsivity and emotional regulation,

leading to inappropriate decision-making with further alcohol seeking behavior (Goldstein & Volkow, 2011). Also, consuming alcohol can lead to withdrawal in vagal control of the sinoatrial node, increasing the sympathetic nervous system in the organism (Reed, Porges, & Newlin, 1999), and thus increasing the risk of cardiovascular and cerebrovascular events (Melillo et al., 2015; Süfke, Fiedler, Djonlagić, & Kibbel, 2009). In addition, abusive alcohol ingestion can cause several psychological and social problems, such as anxiety, depression, antisocial and suicidal behaviors (Blanco-Gandía et al., 2015), as well as aggressiveness (Beck & Heinz, 2013). Pharmacotherapy has been indicated as the main option for treating these patients; however, there are inconsistencies in this practice (Thompson, Owens, Pushpakom, Faizal, & Pirmohamed, 2015), including side effects such as gastrointestinal distress, dizziness, drowsiness, altered libido, peripheral neuropathy and addiction (Connor, Haber, & Hall, 2016). Therefore, it is necessary to elaborate alternative strategies which are effective in rehabilitating and treating this multifactorial disorder, especially in public psychiatric hospitals in low income countries that have limited space and limited financial resources to treat a wide range of mental illnesses.

The practice of regular physical activity has been widely

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demonstrated as an effective tool for treating several physiological disorders (Galioto, Fedor, & Gunstad, 2015; Jeng, Chang, Liu, Hou, & Lin, 2016; O'Brien, Tynan, Nixon, & Glazier, 2016; Stephen, Hongisto, Solomon, & Lönnroos, 2017; Wilson, 2017). It has also been shown to improve self-esteem, well-being, emotions and mood (Bahrke & Morgan, 1978; Driver & Taylor, 2000). Physical activity has also been shown to benefit the autonomic nervous system (ANS) (Fu & Levine, 2013), cognitive functions (Hillman, Erickson, & Kramer, 2008), in addition to promote neuroplasticity and improve efficiency of some cerebral structures (Burzynska et al., 2016; Chaddock et al., 2010; Davis et al., 2011; Dishman et al., 2006). Furthermore, studies have shown that aerobic exercise performed by healthy individuals acutely increases prefrontal cortex (PFC) oxygenation (Bediz et al., 2016; Chang et al., 2013; G. Tempest & Parfitt, 2016), however, it is unclear if individuals with an impaired PFC, such as in alcoholics, will have similar benefits. As a matter of fact, some studies have suggested physical exercise as treatment and rehabilitation of alcoholics (Georgakouli et al., 2017; Jamurtas et al., 2014; Manthou et al., 2016), but not using a neurobiological marker such as brain oxygenation. Moreover, the long-term effects of exercise on cerebral hemodynamics, either in healthy or pathological individuals, remain unclear. Thus, in the present study a male alcohol abuser admitted to a public psychiatric hospital completed a three-month running program and we measured its effects on running performance, cerebral oxygenation, cognition, ANS control and psychosocial parameters.

2. Methods

2.1. Subject

The subject is a forty-six years old public psychiatric hospital male patient, who has been alcohol and cigarette dependent for about thirty-three years, and has been hospitalized for twenty-two years. The subject was classified as having a substance use disorder (SUD) according to criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Moreover, the patient was given 10 mg/day of Diazepam. Also, the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was used to investigate the patient's preferred drug. In this questionnaire, the subject scored thirty-four points for alcohol, which means severe need for treatment intervention. It is worth mentioning that the evaluated person was allowed to go out of the hospital every weekend, so he could access alcoholic beverages. Additionally, he smoked cigarettes every day in the hospital. Besides alcohol and cigarettes, the individual had no other addictive behaviors. The study followed the guidelines of the Helsinki Declaration and it was properly accepted by the Federal University of Rio Grande do Norte local ethics committee (number: 51836215.3.0000.5537). The patient signed the informed consent term before the start of the first evaluation.

2.2. Experimental design

After the physician approved participation of the patient in this running program, he underwent an initial screening to evaluate his physical conditions to exercise. Blood pressure and questionnaires for physical activity readiness and the mini mental status exam were applied, as well as resting heart rate variability (HRV) recordings. Then, the patient performed an incremental cycling test with continuous measures of cardiorespiratory (heart rate and oxygen uptake) and PFC oxygenation. Moreover, the subject performed a cognitive test (short version of the Stroop test) every 2 min in this incremental test which rated his perceived exertion. This testing protocol was done before the running program (pre), after the 18th session (forty-five days) and after the 36th session (ninety days).

2.3. Running program

The proposed training program consisted of three weekly sessions in a space provided by the public psychiatric hospital. In the first training session, the subject was instructed to run between 3 and 6 min and the distance was recorded. In the next session, the task was to repeat the distance from the previous running and the duration was recorded. Finally, on the third day of training of the week, the subject ran the distance of the previous training in the shortest possible time. Lastly, with the week completed, the running time was increased between 3 and 5 min to start a new week. This progression procedure was applied throughout the running program. Furthermore, the training intensity was controlled by self-selected running method. It was chosen to use this method to prioritize a psychobiological perspective with higher involvement of the brain in regulating the patient's physical activity, and to develop the subject's autonomy to continue practicing running after the proposed program. Moreover, affect and perceived exertion scales were used. These scales were presented in every training session for self-monitoring. Internal conversations such as: "I can't do anymore", "I'm going to give up", "it's very difficult" were also used to discuss the emotions that arise during physical exercise and how to tolerate them to stay active (Hardy, Hall, & Alexander, 2001; St Clair Gibson et al., 2006). Always respecting biological individuality, the program sought to allow the individual to achieve between 40 and 50 min of continuous running at the end of the program. The protocol lasted for about 1 h. The running time was increased along the weeks.

2.4. Incremental protocol test

As a form of physical and cognitive evaluation, we performed a maximal incremental test on a cycle ergometer with the subject completing the Stroop test at every exercise intensity. Initially, the patient was familiarized with the cycle ergometer and with the Stroop Test. Then, he rested for 6 min followed by baseline physiological and cognitive measurements. The cycling test started with an intensity of 25 watts (W) and had 25 W increases every 2 min. The subject performed the incremental protocol until exhaustion.

2.5. Ergospirometry

Ergospirometry was performed during the incremental maximal exercise test performed on a bicycle ergometer (model CG04, Inbrasport, Porto Alegre, Brazil). The initial intensity was 25 W with increments of 25 W every 2 min, and cadence was maintained between 60 and 70 r/min. Minute ventilation (VE), oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were measured by a metabolic analyzer (Metalyzer® 3B). Threshold determination and maximal oxygen consumption (VO₂max) was performed using software (Ergo PC Elite®) supplied by the manufacturer. Ventilatory threshold (VT) was determined by the equivalent method when the VE/VO₂ ratio presented its minimum value before presenting progressive increases. Respiration compensation point (RCP) was performed by the V-slope (Dafoe, 2007). The equipment for gas exchange analysis was calibrated prior to each analysis. Calibration was performed with ambient gas samples (20.9% O₂ and 0.04% CO₂) and samples obtained from a cylinder with a known concentration of O₂ (17%) and CO₂ (5%). In addition, the gas flow of the apparatus was calibrated using a three-liter syringe. All procedures were performed according to the manufacturer's standardization.

2.6. Stroop test

The test was applied through the Testinpac® software, for which the volunteer had to make choices on a set of tasks (arrows: right and left) as fast as possible. The tests were viewed on a computer screen 90 cm away and in front of the patient during the exercise. The answers were given through two buttons attached on the bike handlebar. The

Stroop test has been used as a psychometric test to evaluate cognition, and is related to the executive functions of decision making and inhibitory control, for which the PFC plays an important role. The Stroop effect is based on task situations in which color names are written in different colors (Schack, Chen, Mescha, & Witte, 1999). The individual should inhibit the meaning of the word and choose the correct answer corresponding to the color of the word which is written. The reaction time (ms), number of correct answers and errors were recorded and automatically transferred to an Excel sheet.

2.7. Near infrared spectroscopy (NIRS)

Cerebral oxygenation was analyzed using Near Infrared Spectroscopy (NIRS) (Imagent, ISS, Champaign, IL, USA) which allows absolute quantification of oxyhemoglobin (O₂Hb), deoxyhemoglobin (HbH) and total hemoglobin ([HbT] = [O₂Hb] + [HbH]) according to absorbance at specific wavelengths using the modified Beer-Lambert law (Ekkekakis, 2009). Each one of the two optodes contained one detector and four pairs of sources, with each pair consisting of two wavelengths (690 and 830 nm) and positioned at different distances from the detector (1.5; 2.5; 3.5 and 4.5 cm). The optodes were placed on the PFC of the participant on the Fp1, Fp2 and Fp3 regions and were tied with a dark bandage to prevent any light entering the PFC, according to the international EEG 10–20 distribution system. The equipment was calibrated before each evaluation (pre, 45 days and 90 days) using a calibration phantom and a check phantom that have specific absorption and dispersion coefficients. Data were analyzed by a specific routine in Matlab and Homer two, provided by the National Institutes of Health (P41-RR14075, R01-EB006385). Data from the six minute rest were exported and normalized to express the magnitude of the changes (Δ), and thus we were able to analyze the exercise changes in the cortex.

2.8. Heart rate variability (HRV)

For HRV measurements, the volunteer was told to relax in the dorsal decubitus position without becoming drowsy. R-R interval recording was performed for 10 min in this position, and was only initiated when the respiratory rate was below 20 breaths/min. A heart rate monitor (RS800CX training computer, Polar®, Finland) was used with a recording interval every 5 s. The most stable 5 min was used to record the time domain mean R-R interval, root mean square of successive differences (RMSSD) and frequency domain high frequency power (HF) for HRV analysis (Berntson et al., 1997; Malik, 1996). The Kubius HRV program was used in the Matlab platform to calculate statistical indexes of time and frequency domains.

3. Results

3.1. Running performance and fitness level

Fig. 1 shows the physical and motor performance of the subject, as well as his VO₂max. It is observed that the patient increased his running time from 6 min to 45 min ninety days after beginning the protocol, corresponding to a total increase of 650%. In addition, there was an increase in the distance covered from 765 m to 8700 m 90 days after starting the program, indicating a total increase of 1037.2%. Finally, there was an increase in VO₂max from 24.2 ml/(kg·min) to 30.1 ml/(kg·min) 90 days after beginning the running program, corresponding to a total increase of 24.4%.

3.2. Cognitive performance (Stroop test)

Fig. 2 shows the performance in the third phase of the cognitive test. An increase during exercise in the number of correct answers is shown from the first evaluation for the subsequent ninety days, being from two

to eleven (266.6%). At rest, the patient increased the number of correct answers comparing pre-protocol and ninety days after from nine to eleven (33.3%). In reaction time, there was a decrease at rest from 3316 ms to 2553.3 ms (23%) in comparing pre-protocol and ninety days. During exercise, the reaction time went to from 2560.1 ms to 2560.2 ms (0.003%) after ninety days from the beginning of the running program.

3.3. Pre frontal cortex oxygenation

Fig. 3 presents the PFC oxygenation data during the incremental exercise evaluated before, 45 days and 90 days after the running program. The O₂Hb levels at the ventilatory threshold (VT) went from 0.1 μ M to 1.9 μ M (921%). In the respiratory compensation point (RCP), the levels of O₂Hb went from 1.4 μ M to 0.9 μ M (604.2%); and in the VO₂max peak, O₂Hb levels went from 6.8 μ M to 11.9 μ M (76.1%). The levels of HbH in VT went from 0.2 μ M to -1.74 μ M (728.5%), in RCP they went from 0.9 μ M to -3.6 μ M (294.5%), and in VO₂max peak they went from -1.9 μ M to -3.8 μ M (96.9%). THb went from 0.14 μ M to 0.22 μ M (57.1%) in VT, from -0.55 μ M to 5.28 μ M (1060%) in RCP, and from 4.82 μ M to 8.62 μ M (78.8%) in VO₂max. All parameters described were compared pre and 90 days after the running protocol.

3.4. Heart rate variability

Fig. 4 shows the R-R interval, RMSSD and HF indexes. R-R interval went from 811.9 ms to 1086 ms (33.7%), RMSSD went to from 23.8 ms to 55.3 ms (132.3%), and HF went to 186 ms² to 1029 ms² (453.2%). All indexes were comparing pre and 90 days after the running program.

3.5. Alcohol, smoking and substance involvement screening test (ASSIST)

The ASSIST questionnaire was answered before and after the running program. The patient had a decreased score on the questionnaire from 34 to 26, corresponding to a score reduction of 23%. Thus, the subject went from “sever need for intervention” to “need of a brief intervention”.

4. Discussion

The main findings of the present study indicate that a three-month running program performed by a patient under treatment for alcohol addiction in a psychiatric hospital classified as “severe need of intervention” resulted in improvements in running performance, cardiovascular function, cerebral oxygenation with concomitant enhancement in cognitive functions (inhibitory control) and in autonomic nervous control. In addition, psychosocial parameters also improved.

It is well known aerobic exercise improves cardiovascular health through a range of adaptations in the body (Warburton, Nicol, & Bredin, 2006). In this perspective, VO₂max is a variable that represents an individual's ability to consume the maximum amount of oxygen per unit of body mass and time (Robinson, Edwards, & Dill, 1937; Saltin & Astrand, 1967), and can be used as a measurement for cardiovascular health (Nes et al., 2011). Also, it is worth mentioning that alcoholic individuals have increased risk of cardiovascular diseases such as atrial fibrillation, myocardium infarction and congestive heart failure (Whitman et al., 2017). The results here show that the patient increased his VO₂max with a concomitant increase of running time and distance. The evaluated patient had cardiovascular improvement and was able to perform aerobic physical activity for a longer time. Therefore, the efficacy of the proposed protocol based on self-selected intensity as a complement for treating an alcoholic patient hospitalized in a psychiatric hospital may be confirmed.

Studies have shown that alcoholic individuals have lower PFC volume, activity and oxygenation, with consequent impairment in cognitive functions (Asensio et al., 2016; Pahng et al., 2017; Schecklmann

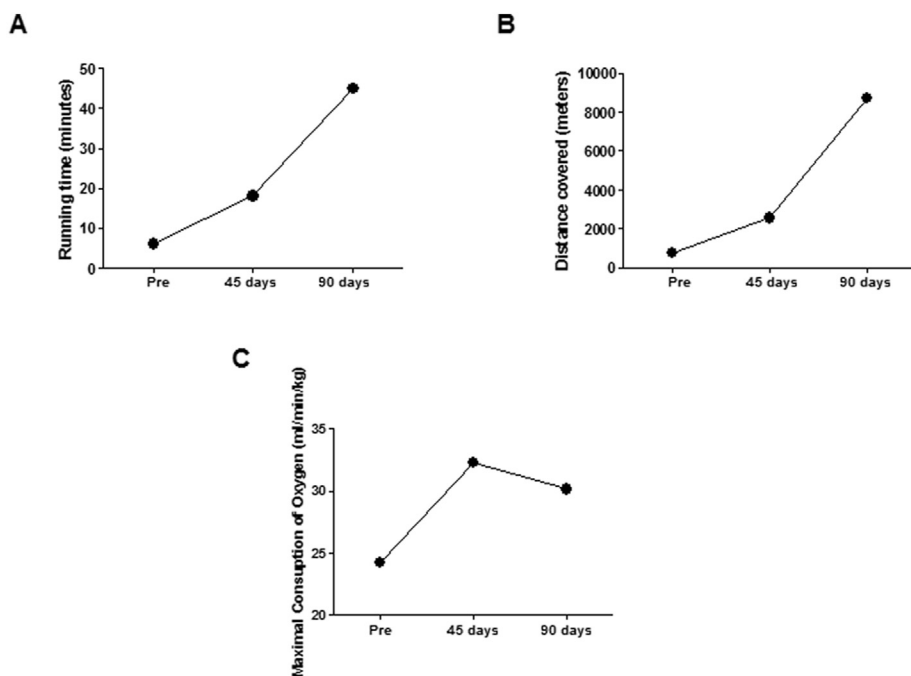


Fig. 1. Running performance and fitness level of an alcoholic under treatment in a psychiatric hospital in the three evaluations. Panel A: running time. Panel B: distance covered. Panel C: measurement of maximum oxygen uptake (VO₂max).

et al., 2007; Wang et al., 2016). This condition has been associated to compulsive behavior and greater chance for relapse (Volkow et al., 2016). Our results demonstrated that PFC oxygenation of the alcoholic patient increased (increased oxyhemoglobin and decreased deoxyhemoglobin) after ninety days of the exercise program (Fig. 4). These hemodynamic changes are in accordance with other studies that show the same pattern in PFC oxygenation during exercise (Bediz et al., 2016; Chang et al., 2013; G. Tempest & Parfitt, 2016). However, the present study is the first to show this in an individual with impaired PFC function, as in alcoholics. This augmented oxygenation in PFC during incremental exercise with concomitant cognitive test has been associated to physiological and cognitive demand while interpreting afferent signaling from working muscles (G. D. Tempest, Davranche, Brisswalter, Perrey, & Radel, 2017). Moreover, no studies have shown long-term effects of physical activity on PFC hemodynamics as we have shown here, where the patient increased oxygenation and blood flow (Fig. 3). These longitudinal changes in cerebral metabolism after a running program can also be related to increments in the number of angiogenic factors with a consequent increment in the brain capillaries (Ding et al., 2006; Swain et al., 2003). These findings are relevant to this patient since increased cerebral oxygenation might be related to higher cognitive functions, which may lead to higher impulsive control over substance consumption (Volkow et al., 2016). Thus, we believe that such an increase in PFC oxygenation acutely and chronically contributes to the maintenance of alcohol abstinence, thus helping the

rehabilitation.

The lower PFC oxygenation of alcoholic individuals has been associated with poor cognitive performance (Schecklmann et al., 2007). Deficits in cognitive mechanisms may promote a decrease in self-regulating behaviors, which may lead to using the substance again (Hillman & Drobos, 2012), creating a compulsive behavior/vicious cycle. Therefore, the neural activation of PFC associated with cognitive control is necessary to counterbalance the activation of cerebral subcortical regions, which are considered more active in the process of drug consumption (Kalivas & Volkow, 2005). After the running program implemented in the present study, the patient decreased his reaction time on the cognitive test at rest, and kept the reaction time unchanged during exercise. In addition, there was an increase in the number of correct answers on the test during both exercise and rest. This improvement seems to be matched with increased cerebral oxygenation and may characterize an important contribution for the treatment of alcohol abuse. Interestingly, the applied cognitive test (the Stroop test), is widely known to access inhibitory cognitive control since it is required to ignore the automatic response of reading a word (e.g., blue), and instead respond to its font color (red). Studies have shown that alcoholic patients usually show impairments in inhibitory control measured by the Stroop test (Hillman & Drobos, 2012). Hence, improving inhibitory cognitive performance may promote higher control over impulsivity and facilitate maintaining abstinence, thus decreasing the deleterious effects on cognitive functions caused by chronic use of

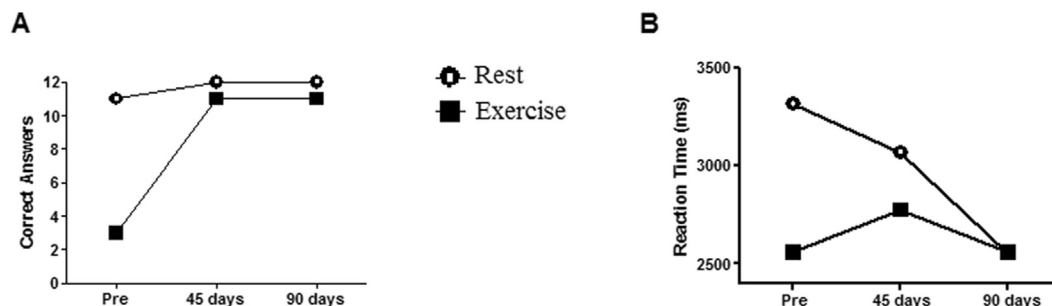


Fig. 2. Cognitive performance before, during and after the running program, performed by an alcoholic under treatment in a psychiatric hospital. Panel (A) Number of correct answers on the third phase of the cognitive test at rest and during exercise on the cycle ergometer. (B) Reaction time in the third phase of the cognitive test at rest and during exercise.

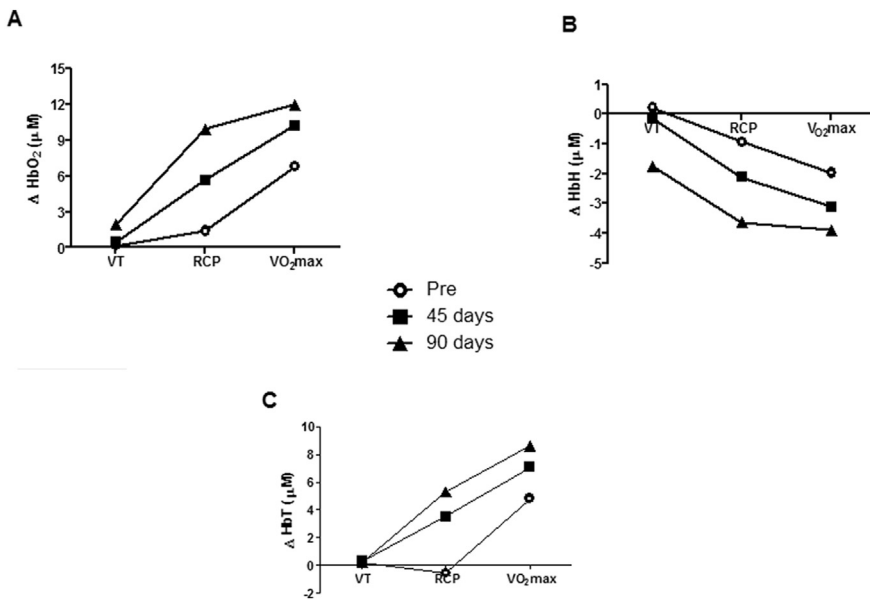


Fig. 3. Prefrontal cortex oxygenation of an alcoholic under treatment in a psychiatric hospital while performing incremental cycling test during a three months running program. Panel A: oxyhemoglobin. Panel B: deoxyhemoglobin. Panel C: total hemoglobin. Legend: VT: ventilatory threshold; RCP: respiratory compensation point; VO₂max: maximal oxygen consumption.

alcohol.

The functionality of ANS and vagal tone predominance has been shown to be related to greater cardiovascular health (Berntson et al., 1997). This is because high levels of sympathetic activity are related to increased oxygen demand by the myocardium, triggering arrhythmia and vascular oxidative stress (Caetano & Delgado Alves, 2015). It is well known that chronic alcohol ingestion can have negative effects on sympathovagal balance (de Zambotti et al., 2014; Ingjaldsson, Laberg, & Thayer, 2003), leading to greater chances of cardiovascular and cerebrovascular events (Melillo et al., 2015). Therefore, we have measured ANS control through HRV in response to the running program, which is widely shown to improve cardiovascular health (Fu & Levine, 2013). A low HRV is commonly related to insufficient ANS control with increased sympathetic activation (Berntson et al., 1997; Malik, 1996), which is associated to deficiency of the cognitive processes (Julian F. Thayer & Lane, 2009). Additionally, lower parasympathetic activation is related to a greater susceptibility to stress and anxiety (J. F. Thayer, Friedman, & Borkovec, 1996), leading the individual to seek a way out of these undesirable sensations through the use of drugs (Volkow et al., 2016). However, physical exercise has been

widely shown to be a useful tool in improving ANS efficiency by increasing vagal tone (Cole, Blackstone, Pashkow, Snader, & Lauer, 1999; Fu & Levine, 2013). After the present exercise intervention, the patient improved ANS control, reflected by the HRV indices of R-R interval, RMSSD and HF (Fig. 4). Moreover, functionality of the prefrontal cerebral structures has been related to parasympathetic (vagal) control in the sinoatrial node (Hansen, Johnsen, Sollers, Stenvik, & Thayer, 2004; Julian F. Thayer & Lane, 2009). These autonomic improvements may reflect and confirm actual improvements in PFC oxygenation, since it is also associated with lower sympathetic activation (Julian F. Thayer & Lane, 2009). Furthermore, the ANS results are also related to favoring better responses to negative situations imposed by the environment (Porges, 1995), leading to improved decision making related to the use of alcohol consumption.

It is well known that psychosocial responses are important for treating alcohol dependence. In this work, we have also identified that the running program promoted benefits in quality of life and sleep, as well as decreased stress, anxiety and depression levels. We believe that the improvements in physiological and cognitive aspects, as well as in the psychosocial aspects, may facilitate better relationships with nurses

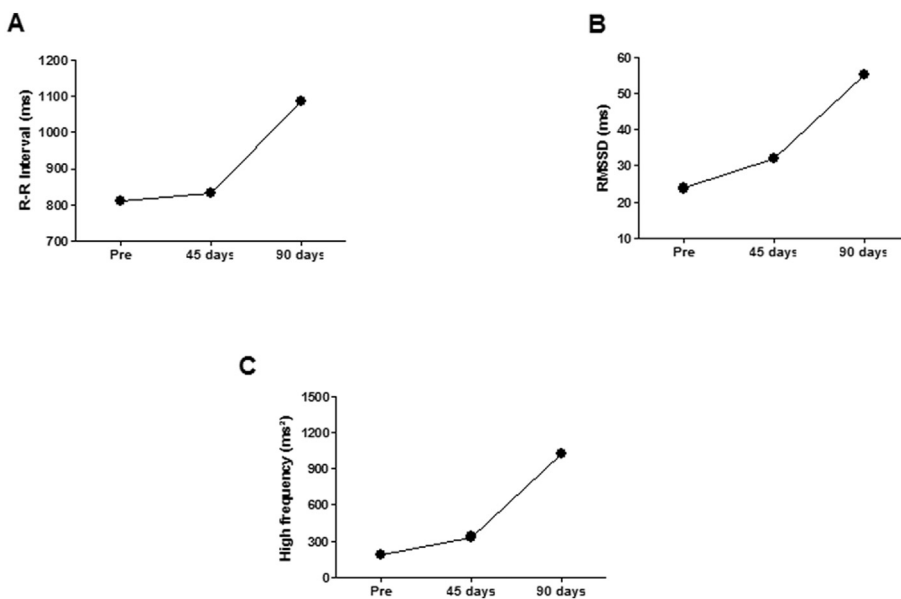


Fig. 4. Heart rate variability parameters before, during and after three months running program performed by an alcoholic under treatment in a psychiatric hospital. Panel A: R-R heart rate intervals; Panel B: root mean square of successive differences (RMSSD) in R-R intervals; Panel C: high frequency power.

and other patients, contributing to a higher quality of life. In addition, although the subject is allowed to visit his family on the weekends, the public psychiatric hospital is a very difficult environment to live since locomotion inside the building is limited, with few leisure opportunities. Furthermore, the increased interaction with other patients with different and severe mental illnesses may complicate the alcoholic patient rehabilitation. Living in this negative hospital setting for twenty years, as in the case of the present patient, may have hindered his rehabilitation of alcohol addiction. However, it is worth mentioning that the patient currently continues to run and participates in local races and he affirmed, through informal conversations, that he decreased alcohol consumption on his free weekends, corroborating with the autonomy proposed by the self-regulating running program.

5. Conclusion

In summary, we conclude that a running exercise program performed in a self-regulating way, organized and respecting the biological individuality of a chronic alcoholic patient hospitalized in a public psychiatric hospital improves several physiological, cognitive and psychosocial factors. The increase in cerebral oxygenation and cognitive functions are important for impulsive and inhibitory control, being essential requirements to prevent the subject returning to alcohol use and even to reduce the damage caused by excessive use of the substance. In addition, the results were positively reflected in cardiovascular health related to the hospitalized patient in a public psychiatric hospital. These preliminary findings have strong public health implications since alcohol abuse is a worldwide problem. Thus, it is possible to visualize the use of a running exercise as an important alternative tool in treating chronic alcohol user patients who are hospitalized for treatment.

Disclosure of interest

None.

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