Effects of Incentive Spirometry Breathing Exercise on Lung Function, C-Reactive Protein Level and Lipid Ratio in Individuals with Chronic Spinal Cord Injury

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Keywords: Chronic Spinal Cord Injury, Inflammation, Incentive Spirometry, Lung Function, Lipid Ratio, C-reactive Protein

Abstract: Spinal cord injury (SCI) is an inflammatory process caused by axon and cell membrane damages, cell death, leukocyte migration and degradation of the myelin layer. Inflammatory diseases are particularly associated with cardiovascular disease. The SCI patients can experience decreased sympathetic activity which influences carbohydrate and fat metabolisms. Decreased catecholamine release which plays a role in the process of lipolysis and glycogenolysis can increase levels of low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol. Since the SCI often causes respiratory problems due to reduced respiratory muscle conservation, the study was conducted to find out the impact of sustained maximum inspiration with Incentive Spirometer (IS) to CRP level and lipid ratio in chronic SCI patient. Methods: A quasi interventional design with a pre- and post-test approach was done to eleven patients with chronic phase of SCI. Conclusion: These findings show although incentive spirometry breathing exercise after 4 weeks can improve lung function and lipid ratio, it has not decreased the systemic inflammatory levels in individuals with chronic SCI. Improvement in lung function has not influenced the systemic inflammatory level (CRP), although a beneficial influence on LDL/HDL ratio was recorded.

1 INTRODUCTION

Spinal cord injury (SCI) referred to spinal cord damage due to trauma or particular diseases such as infections, neoplasms and degenerative processes. The Global prevalence of SCI demonstrated that 40 to 80 new cases had been discovered per one million populations every year (WHO, 2013). In worldwide, SCI patients had been reportedly increasing recently. Based on the data released by World Health Organization (WHO) 250,000 to 500,000 SCI patients were reported per year (WHO, 2013). Data published by the Fatmawati General Hospital in 2014 presented that there were 104 cases of new SCI (37 traumatic cases and 67 non-traumatic cases) (Tulaar, 2017).

The SCI has caused axon and cell membranes damages, cell deaths, leukocyte migration, and myelin deterioration. Damages in nerve cells can activate the immune system response and inflammation process (Alves, 2013). The continuous occurrence of inflammation process in SCI leads to chronic tissue damage. (Alves, 2013).

The inflammation process can be detected by increasing C-reactive protein (CRP) which is one of the cytokines that play roles in several inflammatory responses. The production of CRP from the liver is controlled by interleukin-6 (IL-6) (Pederson, 2006). Chronic SCI is commonly associated with increased CRP serum concentrations defining as an inflammatory marker of several phases such as

Ferryani, M., S, N., Biben, V., Arisanti, F., Tobing, I. and Pradanasari, R.
Effects of Incentive Spirometry Breathing Exercise on Lung Function, C-Reactive Protein Level and Lipid Ratio in Individuals with Chronic Spinal Cord Injury.
DOI: 10.5220/0009088402200226
In *Proceedings of the 11th National Congress and the 18th Annual Scientific Meeting of Indonesian Physical Medicine and Rehabilitation Association (KONAS XI and PIT XVIII PERDOSRI 2019)*, pages 220-226
ISBN: 978-989-758-409-1

acute and chronic inflammatory, and endothelial activation (Wang, 2007).

Inflammatory diseases are distinctively associated with cardiovascular diseases. An epidemiological study in normal population stated that high levels of CRP become a predictor of cardiovascular diseases. The CRP values in adults' chronic SCI were consistent with the AHA classification of high CVD risk, especially those of persons with tetraplegia (Gibson, 2008). Therefore cardiovascular disease has become one of many causes of deaths besides respiratory system disorders (Zonneveld, 2014).

The SCI patients can experience decreased sympathetic activity which influences carbohydrate and fat metabolisms. Decreased catecholamine release plays a role in the process of lipolysis and glycogenolysis that can increase levels of low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, and 8–18% fat mass which is higher than healthy people (Gibson, 2008). Dyslipidemia is observed in a large number of individuals with chronic SCI. The risk of dyslipidemia was seen to have increased in motor complete SCI patients and patients who could not be community ambulated (Koyunchu, 2017). The high percentage of dyslipidemia found in chronic SCI supports the increased risk of coronary heart disease (Vichiansiri, 2012). The LDL/HDL ratio is an indicator of sudden death risk due to cardiac abnormality (sudden cardiac death/SCD). A high LDL/HDL ratio (> 4,22) in blood is in accordance with an increased risk of SCD (Kunutsor, 2017).

Exercise is an important rehabilitation therapy for SCI patients because it can improve sympathetic response by increasing catecholamines, inducing the process of lipolysis and activation of immune cells in the blood (Alves, 2013). This condition leads to decreased body fat, especially visceral fat, and decreased inflammatory cytokines in the blood so that it will reduce the chronic inflammatory response in SCI patients (Alves, 2013).

Systemic inflammation has been associated with decreased lung function in individuals with or without chronic medical conditions. Individuals with chronic SCI have clinical characteristics that can cause systemic inflammation and decreased lung function. Plasma CRP and IL-6 in individuals with chronic SCI are inversely related to forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) (Hart, 2017). Systemic inflammation associated with chronic SCI can contribute to decreased lung function (Hart, 2017).

In patients with spinal cord injury (SCI), the respiratory function may be affected due to complete or partial paralysis of the respiratory muscles and abdominal muscles leading to a reduction in the ability to breathe (Kim, 2017). Improved inspiratory muscle strength and endurance could potentially improve cough and maximal exercise ventilation in addition to decreasing dyspnea (Sheel, 2007).

The advantages of using an incentive spirometer are: 1) it is easy to learn how to use the instrument; 2) it is economical, and 3) patients can be motivated to use it, as it produces a visible improvement. Its visual feedback helps to train patients to use the instrument independently and freely and it maximizes their respiratory motivation (Kim, 2017). Incentive spirometer can be used to maintain maximum inspiration by providing predetermined volume feedback (Restrepo, 2011). The IS enables the mobilization of large lung volumes and the increased intra-alveolar pressure at the end of inspiration. This condition improves breathing capacity, and challenges the patient with the visual stimulus generated by the device (Paiva, 2015).

The intervention of inspiratory muscle training (IMT) in chronic heart failure (CHF) patients have shown to reduce CRP levels (Adamopoulos, 2014). Giving IS exercise to patients with chronic obstructive lung disease (COPD) for 4 weeks also can reduce inflammatory cytokines of IL-6 and TNF-α. (Leelarungrayub, 2018).

The effect of IMT on CRP levels and lipid ratio in chronic SCI patients has not been clearly studied. Therefore, this study aimed to determine the effect of inspiratory muscle training with IS on CRP levels and lipid ratio in chronic SCI.

2 METHODS

This study used a quasi-interventional research design with a pre- and post-test approach. The population in the study was all chronic phase of SCI patients who occupied in the Social Care Center of Bina Daksa Pondok Bambu, West Jakarta, Indonesia.

The samples were recruited based on the inclusion criteria, that were chronic SCI, aged 18 – 59 years old, paraplegic, no acute infection, stable spinal structure, able to perform breathing muscle training inspiration procedure for 30 minutes, Hamilton Depression Score (HDS) less than 20, Mini Mental State Examination (MMSE) score between 22–30. Exclusion criteria unable to take a deep breath due to pain, taking analgesic opiates and patients with vital capacity <10 mL/kg. The subjects

signed an informed consent to be included in the study. After each set, a one-minute rest was allowed.

The IS training program was conducted after the subjects were given explanations of the exercise device, watched a video about the use of the exercise and familiarizing the device for 2 consecutive days. The subjects maintained a maximal inspiration for 3 to 5 seconds, and then performed maximal expiration. This exercise was performed for a total of five sets, with 10 repetitions making up one set. After each set, a one-minute rest was allowed (Kim, 2017).

The CRP levels and LDL/HDL ratio were examined 24 hours before the IS training begin and after the study ended. The study measured CRP levels by using hs-CRP which has sensitivity range 0.01 to 10 mg/L so that levels of lower systemic inflammations were able to be measured even in the absence of clear systemic inflammatory or immunological disorders (Kamath, 2015).

Lung function was measured with a computerized spirometer during maximal voluntary ventilation maneuvers. As the maneuvers were being measured, the subjects were asked to sit upright and make sure nothing was restricting chest movement or airflow. The subjects started the test by breathing normally through the mouthpiece, followed by breathing as deeply and rapidly possible for 20 seconds. At the end of the measurement interval, the subjects were asked to resume normal breathing and the mouthpiece was removed. Three trials of the maneuvers were performed, separated by a five-minute rest, and the average of the results was taken. The measured values included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), and the lung function indices were calculated automatically by the computer (Kim, 2017).

Continous data including age were presented with mean values and standard deviations (SD), maximum and minimum values. The subjects' characteristic data were presented in frequency distribution. Categorical variables were presented in percentage (%). Statistical analysis was carried out by performing a normality test to determine that the data were normally distributed or not normally distributed.

Data distribution was discovered using the Shapiro Wilks test since the samples were less than 50. Paired t test was used to compare numerical variables between before and after the intervention if the data were normally distributed and the Wilcoxon test if the data were not distributed normally. The study was conducted to find out the impact of sustained maximum inspiration with Incentive Spirometer (IS) in improving lung function and decreasing CRP level and lipid ratio in chronic SCI patients. Significance of the statistical test results was determined based on p-value (<0.05). All procedures were performed using the SPSS for Windows version 24.0.

The study was approved by the Ethics Committee of Padjadjaran University, Bandung, Indonesia with ethical numbers of 0318050786. All subjects signed an informed consent form. The subjects could leave the study at any time without giving any reason. All data and information of the subjects will be kept confidentially.

3 RESULTS

The study enrolled 11 chronic phase of SCI patients. The mean age of the subjects was 44 years old. The number of male subjects (90.9 %) was higher than female subjects. The subjects had SCI approximately 260 months (mean) due to trauma (90. 9%) (Table 1). Most of the subjects had complete SCI (81.8 %) with the body mass index (BMI), the subjects were mostly underweight, below 18,5, (63.6 %) without any other complications of chronic SCI. Occupation of the subjects was mostly as a craftsman. None of the subjects had smoking history. Also, the subjects did not consume medicines that could influence CRP levels such as statins, SSRI (selective serotonin uptake inhibitors), and aspirin.

The differences between pre- and post-test values for FVC (2.32 ±0.557 and 2.59 ±0.625) and FEV1 (2.16 ±0.596 and 2.40 ±0.654) was statistically significant increased (p=0.005 and p=0.007). However, there are no significant mean differences between CRP level (p=0.229), before and after practicing IS exercise (Table 2). The study also showed that there was a significant mean difference in LDL/HDL ratio (p=0.007) before and after IS exercise(Table2)

Table 1: Subject's Characteristics

Variables	Total (n=11)	Mean (SD)	Median
Age (Years old)		44.27±7.695	44
Sex			
Male	10 (90.9%)		
Female	1 (9.1%)		
Body mass index category			
Underweight (< 18,5)	7 (63.6%)		
Normal	3 (27.3%)		
Overweight (≥ 25)	1 (9.1%)		
Occupation			
Craftsman	10 (90.9%)		
Mechanic	1 (9.1%)		
Period of injury (months)*		259.63±104.375	228
Etiology			
Trauma	10 (90.9%)		
Spondylitis TB (inactive)	1 (9.1%)		
Pressure sores			
(+)	0 (0.0%)		
(-)	11 (100.0%)		
Medication			
Mecobalamin, yes	1 (9.1%)		
(-)	10 (90.9%)		
Smoking history			
Yes	9 (81.8%)		
Normal	2(18.2%)		
AIS classification			
Complete	10 (90.9%)		
Incomplete	1 (9.1%)		
MMSE Category			
Able (score 22-30)	11 (100.0%)		
Unable	0 (0.0%)		
HAMILTON Depression Rating Scale Category			
Yes	0 (0.0%)		
No	11(100.0%)		

Table 2 : C-reactive Protein (CRP), LDL/HDL Ratio, Total Leucocyte Comparison, FVC and FEV1 Before and After

Variables	Groups		p Value
	Before	After	
	n=11	n=11	
CRP (mg/dL)			0.229
Mean+SD	0.44±0.750	0.61±1.073	
Median	0.23	0.19	
LDL/HDL ratio			0.007**
Mean±SD	3.36 ±0.429	3.04 ±0.603	
Median	3.30	3.00	
Total leukocytes (/µL)			0.629
Mean±SD	7250.90±1716.347	7022.72±1645.849	
Median	6770.00	7360.00	
FVC			0.005**
Mean±SD	2.32 ±0.557	2.59 ±0.625	
Median	2.24	2.70	
FEV1			0.007**
Mean±SD	2.16 ±0.596	2.40 ±0.654	
Median	2.20	2.76	

the value presented is the mean value + SD. Numerical data the p value is tested by paired T test if the data is normally distributed with the alternative Wilcoxon test if the data is not normally distributed. Significance value based on the value of $p < 0.05$. Sign * indicates the value of $p < 0.05$ means significant or statistically significant.

4 DISCUSSIONS

The subjects of the study were mostly men (90,9%). Although women could have higher CRP levels than men due to hormonal factors (O'Connor, 2009), this condition may not significantly influence the CRP results.

CRP levels did not change significantly due to several factors, one of them is the high CRP level since the beginning, although there was no sign of infection during the study since the leucocyte count did not increase. The CRP level could be influenced by BMI, the level and severity of the lesion and smoking habits. Most of the subjects in this study were included in the underweight category with an average BMI was 18.72 ± 2.173 kg/m2. The BMI values are related to body fat composition. Low BMI could be caused by decreased fat-free muscle mass due to reduction in physical activity and atrophy caused by paralysis. Greater adipose tissue composition due to impaired fat and carbohydrate metabolisms can lead to increased CRP levels (Wang, 2007).

Lesion levels and severity of SCI itself can influence the CRP levels. The higher lesion levels and severe SCI indicate higher CRP levels. Those with tetraplegia have a greater risk of CVD compared to those with paraplegia in chronic SCI Gibson, 2008). SCI lesions of the subjects in this study were as high as the thoracic cord. Since most of the subjects had complete SCI, high CRP levels of the subjects were discovered since the beginning.

The smoking habits were not limited during the study, these may cause a high of CRP level. Smoking can increase the release of proinflammatory cytokines in the blood and lung circulation. It also can cause oxidative stress and vascular inflammation occurs marked by increased IL-6 and CRP levels. A previous study presented that higher CRP levels were mostly found in the subjects who smoked (O'Connor, 2009). Unfortunately, this study did not have any data to analyaze the correlation between the number of cigarettes (packs per year) and nicotine levels with distinctive measurements in each subject.

Exercise can decrease inflammatory cytokines in the blood (Alves, 2013). Muscle contractions can stimulate the release of IL-6 from muscle cells, namely muscle derived IL-6. IL-6 has important anti-inflammatory effects since it plays a role in the formation of anti-inflammatory cytokines such as interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10). The appearance of IL-10 and IL-1ra in the circulation contributes to mediating the

anti-inflammatory effects of exercise and induces a reduction in CRP levels and suggests that physical activity may suppress systemic low-grade inflammation.

The increased plasma IL-6 is related to exercise intensity, duration, the mass of muscle recruited and one's endurance capacity (Peterson, 2005). Physical activities with moderate intensity are recommended to reduce CRP levels (Zonneveld, 2014). IS exercise in this study counted as moderate intensity based on Borg scale 11-13. Most of the subjects had the same occupation as a craftsman and did their daily activities independently, but still there were no complete data and objective assessment of physical activities collected.

The IS exercise given in this study had not decreased the inflammation marker of CRP. This study given different result from the previous studies that after 4 weeks of physical training was associated with significantly improved plasma concentrations of adiponectin and CRP (Oberbach, 2006), IS exercise for 4 weeks (twice daily, 30 breaths a set for 30 days) in COPD patients was already showed a significant result in reducing IL-6 and TNF-α inflammatory cytokines (Leelarungrayub, 2017), IMT combined with aerobic training provides additional benefits in functional and serum biomarkers of inflammation (CRP) in patients with moderate CHF (Adamapoulos, 2014). The differences in the type of exercise, the mass of muscle recruited, the intensity and duration of exercise compared with the previous study, the markers of inflammation which had been examined may make the differences of the result.

The study has shown that IS exercise can improve lung function in an individual with chronic SCI. The similar results showed in another previous study (Kim, 2017). The study has not shown significant change in the circulating level of CRP however, a potential local effect of IS on diaphragmatic myocyte cytokine production cannot be excluded. Whether there was a reduction in local diaphragmatic muscle inflammation marker after IS was not tested in this study.

The IS exercise given in this study had influenced fat metabolism marked by the significant reduction of LDL/HDL ratio. IL-6 is the first cytokine released into the circulation during exercise, derived from the contracting muscle. This cytokine will activate lipolysis independently of elevations in Growth Hormone (GH) and/or cortisol and become a potent catalyst for fat oxidation in muscle cells (Peterson, 2005). The present study was given different result from the previous studies that IMT with low inspiratory loading fails to demonstrate any significant improvements in blood glucose levels, serum lipids, and/or HOMA-IR in female patients with type 2 diabetes (Ahmad, 2017) and after 7 days of IMT had not able to change metabolic variables (blood glucose and lipid profile) in women with metabolic syndrome (Feriani, 2017).

There are some limitations to this study that can be improved in future research. Firstly, the present study did not measure other cytokines, such as IL-10 and IL-1ra may be needed to confirm that the observed increase in IL-6 is muscle derived and not due to other factors, such as the existence of a catabolic/inflammatory state due to exercise training (Peterson, 2005). Secondly, this study did not have any data regarding the number of cigarettes (packs per year) and nicotine levels with distinctive measurements in each subject which can correlate with the inflammatory state. Thirdly, there was no complete data and objective assessment of physical activities and nutritional intake collected.

Further study can be conducted by giving longer-term IS exercise intervention or with other exercise combinations including aerobics. Assessment of detail physical activity level, other routine activity (such as smoking), nutritional status and other anti-inflammatory cytokine levels should be done in further study.

5 CONCLUSIONS

A 4 weeks incentive spirometry breathing exercise resulted in improvement in lung function and lipid ratio. Improvement in lung function has not influenced the systemic inflammatory level (CRP), although a beneficial influence on LDL/HDL ratio was recorded. Further follow up and studies are required to establish the role of inspiratory muscles in improving the systemic inflammatory status of patients with chronic spinal cord injury.

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