치의과학석사 학위논문

Impacts of Shift Work Induced Chronic Circadian Disruption and Gender on Plasma Inflammatory Cytokine Levels

교대근무에 따른 만성적 생체주기의 변화 및 성별이 혈중 염증성 cytokine 농도에 미치는 영향

2013년 2월

서울대학교 대학원
치의과학과 구강내과진단학 전공
김 동 희

Impacts of shift work induced chronic circadian disruption and gender on plasma inflammatory cytokine levels

교대근무에 따른 만성적 생체주기의 변화 및
성별이 혈중 염증성 cytokine 농도에 미치는 영향

지도교수 정 진 우

이 논문을 치의과학석사 학위논문으로 제출함.

2013년 2월

서울대학교 대학원
치의과학과 구강내과진단학 전공
김 동 희

김동희의 치의과학석사 학위논문을 인준함.

2013년 2월

위 원 장 _____ (인)
부위원장 _____ (인)
위 원 _____ (인)

- ABSTRACT -

Impacts of shift work induced chronic circadian disruption and gender on plasma inflammatory cytokine levels

Dong-Hee, Kim, D.D.S.

Program in Oral Medicine and Oral Diagnosis

Dept. of Dental Science,

Graduate School Seoul National University

(*Directed by Professor* **Jin-Woo Chung**, D.D.S., M.S.D., Ph.D.)

Shift work can lead to disruption of the circadian rhythm which results in an irregular sleep pattern and subsequent alteration of plasma cytokine levels. And little is known about gender differences in plasma cytokine levels. The aims of this study were to investigate the impacts of shift work induced chronic circadian disruption and gender on plasma inflammatory cytokine levels.

Fifty-one healthy adults were recruited and divided into three age-matched groups

according to gender and shift work status; Group A- day time working men (39.7 ± 3.3 years), Group B- night shift working men (39.1 ± 4.5 years), and Group C- day time working women (35.3 ± 11.5 years). The Pittsburgh Sleep Quality Index (PSQI) was assessed of each subject and plasma concentrations of IL-1β, IL-6, IL-10, and TNF-α were measured.

Group B subjects reported higher PSQI scores than Group A and C subjects and PSQI score was significantly associated with shift work status ($\beta=0.372$, $p<0.05$). There were significant differences in plasma IL-1β, IL-6, IL-10, and TNF- α levels among the three groups with Group B showing the highest, and Group C showing the lowest values. Plasma IL-6 level was significantly associated with PSQI score ($\beta=0.317$, $p<0.05$) and plasma levels of IL-1β ($\beta=0.436$, $p<0.05$), IL-10 ($\beta=0.572$, $p<0.05$), and TNF-α ($\beta=0.630$, $p<0.05$) were significantly associated with gender.

These results suggest that shift work induced chronic circadian disruption can worsen sleep quality and poor sleep quality increases plasma IL-6 level. Men have higher plasma IL-1β, IL-10, and TNF-α levels compared to women.

Keywords: shift work, circadian rhythm, plasma, cytokine, sleep, gender difference

Student Number **:** 2011-22026

Impacts of shift work induced chronic circadian disruption and gender on plasma inflammatory cytokine levels

Dong-Hee, Kim, D.D.S.

Program in Oral Medicine and Oral Diagnosis

Dept. of Dental Science,

Graduate School Seoul National University

(*Directed by Professor* **Jin-Woo Chung**, D.D.S., M.S.D., Ph.D.)

-CONTENTS-

I. INTRODUCTION

The number of individuals working in shift work has increased recently. Shift work can lead to a disruption of circadian rhythm, which can cause internal instability and subsequent psychological and physiological disturbances.[1,2] In many cases, shift work induces recovery sleep (restorative sleep) reduction that can lead to systemic fatigue.[3] Physical fatigue and sleep quality loss will decrease individual's work satisfaction and efficacy.[4]

Recent research focuses on sleep disturbances caused by shift work influence on the immune system and such an activation of the immune system might be linked with cardiovascular disease risks. Irregular sleep pattern can alter plasma cytokine level.[5-7] Cytokines are initially classified into three broad categories: pro-inflammatory [such as tumor necrosis factor-a (TNF-a), interleukin (IL)-1 and IL-6), type 1 (such as IL-2 and interferon-c (IFN-c)] which promotes the development of antigen-specific cell-mediated immunity, and type 2 (such as IL-4 and IL-10) which facilitates the development of antibody-mediated immunity.

Previous studies demonstrated that acute sleep deprivation induces inflammatory response.[7-9] Plasma concentrations of inflammatory cytokines have a high correlation with chronic fatigue syndrome, myofascial pain syndrome and chronic diseases.[10,11] And high level of blood cytokine plays a major role in pathophysiology of cardiovascular diseases including atherosclerosis.[12-15] However, until recent days the influence on socio-economic aspects of sleep loss and subsequent immune responses due to shift works has not been well recognized.

Research about policemen indicates that police officers may have difficulties in coping with shift-related sleep loss. Police officers rotate from day shift to night shift in three or four days' term. Frequent repetition of sleep time changing causes poor sleep quality which imbalance body rhythms. Garbarino *et al*. reported that shift workers experienced more sleep disturbances than non-shift workers (35.7% vs. 26.3%).[16] Their findings also showed that the number of sleep-related accidents was significantly higher among shift workers than non-shifters. Moreover Phillips *et al*. demonstrated that sleep quality and sleep hygiene improved after changing from a rotating shift system to a permanent one.[17]

In recent years social and emotional quality of life has become more important as well as physical health. So the assessment of satisfaction and quality of life related to physical and social health is also required. In this study we used SF-36. The SF-36 questionnaire is designed to evaluate quality of life during the 4 weeks prior to the interview. The standard version of the SF-36 comprises eight areas: physical functioning, role limitations physical, physical pain, general medical health, vitality, social functioning, role limitations emotional and mental health. Higher scores indicate better health. Thus, 0 = worst state of health and 100 = ideal state of health.

The aim of this study was to examine the impact of shift work on the physical health by measuring blood cytokine levels. We further compared blood cytokine levels between men and women. The work loading of shift workers and normal workers assessed by health related quality of life questionnaires.

II. MATERIALS AND METHODS

Subjects

Fifty-one healthy adults were recruited and divided into three age-matched groups according to gender and shift work status; Group A- 17 day time working men (police officers who have been worked during day time for 5 years or longer, mean age 39.7 ± 3.3 years), Group B- 18 night shift working men (police officers who have been worked during night time for 5 years or longer, mean age 39.1 ± 4.5 years), and Group C- 16 day time working women (healthcare workers who have been worked during day time for 5 years or longer, mean age 35.3 ± 11.5 years).

The exclusion criteria were the presence of any disease or condition of hepatic or renal insufficiency, any medication known to affect on blood tests, the presence of trauma or pain, and the presence of acute or chronic inflammation.

The study protocol was approved by the Institutional Review Board of Seoul National University Dental Hospital (#CRI 11004). Each subject gave informed consent.

Collection of plasma

Plasma samples were collected from the antecubital vein of each subject and transferred to Lavender tubes (Becton Dickinson Vacutainer System, Rutherford, NJ, USA) with EDTA. Collecting was done between 9 a.m. and 12 noon, then immediately centrifuged (2000 rpm) for 10 minutes at 4℃ and stored at –70℃ before analysis.

Quantification of inflammatory cytokines

The human plasma concentrations of pro-inflammatory cytokines IL-1β, IL-6, TNF-α and the anti-inflammatory cytokine IL-10 were measured by means of the Procarta cytokine assays (Panomics, USA). The assays are multiplex immunoassays based on xMAP® technology developed by Luminex. The antibody specific to each cytokine was covalently coupled to microspheres, with each antibody coupled to a different microsphere uniquely labeled with a fluorescent dye. The microspheres were incubated with standards controls and samples in a 96-well microtiter filter plate at 500 rpm for 60 minutes at room temperature. After washing with assay wash buffer, diluted biotinylated secondary antibody was added to the appropriate wells and incubated at 500 rpm 30 minutes. After washing, steptavidin-phycoerythrin was added to each well and incubated for 30 minutes. After a final wash, the plate was analyzed using the Bio-Plex 200 analyzer (BIO-RAD Laboratories, Inc., USA) to determine the concentration of the cytokines.

Plasma samples were diluted a 3-fold with assay diluents. In each 96-well plate, the standards and a quality control pool were run in triplicate, and the 60 samples were run in duplicate.

The plasma concentrations of hs-CRP were measured by means of a highly sensitive immunoturbidimetric assay. Hitachi 7180 (Hitachi High-Technologies Corp., Tokyo, Japan) autoanalyzer, and automated blood test, was used for measurements. Polystyrene particles coated with monoclonal antibodies against CRP become agglutinated when mixed with samples containing CRP. The intensity of light scattering due to agglutination reaction was measured and directly related to the concentration of CRP.

The person conducting the measurements was blind to the identity and experimental group of the subjects.

Evaluation of quality of life

The Short Form Health Survey Instrument (SF-36) questionnaire is devised to evaluate general health related quality of life. The SF-36 is a questionnaire with 36 items consisted with eight components: physical functioning, physical role limitations, physical pain, general medical health, vitality, social functioning, emotional role limitations and mental health. Score were calculated from summation of all items. Higher scores indicate better health. Thus, 0 = worst state of health and 100 = ideal state of health. The Korean standard version of the SF-36 was validated in our population.

Evaluation of sleep quality

All participants were completed PSQI questionnaire for assessing sleep quality. The Pittsburgh Sleep Quality Index (PSQI) is an effective tool used to measure the quality and patterns of sleep. It differentiates “poor” from “good” sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The patient self rates each of these seven areas of sleep. Scoring of the answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale. A global sum of “5”or greater indicates a “poor” sleeper. Although there are several questions that request the evaluation of the patient’s bedmate or roommate, these are not scored, nor reflected in

the attached instrument. If an answer is not complete or the value is missing, it counts as a “0”.

Statistical analysis

Kruskal-Wallis test was applied to compare plasma IL-1β, IL-6, IL-10, and TNF-α levels among 3 groups. For comparing age, PSQI, and quality of life, One-way ANOVA was performed. Multivariate general linear models was used to evaluate the effect of shift work and gender on sleep quality- age, gender, and shift work as an independent variable and PSQI as dependent variables. And to evaluate the effect of sleep quality and gender on plasma cytokine levels- age, gender, and PSQI as an independent variable and IL-1, IL-6, IL-10, and TNF-α levels as dependent variables. Plasma IL-1β, IL-6, IL-10, and TNF-α levels were log-transformed to a normal distribution before entering into models. All the statistical analyses were performed by SPSS software program.

III. RESULTS

Evaluation of sleep quality

The mean PSQI scores are shown in Table 1. The mean PSQI score of day time working men group was 4.76, night shift working men group was 7.28, and day time working women group was 3.56.

Night shift working men reported the highest PSQI score among 3 groups. (Fig 1, Table 1)

Comparison of work loading among 3 groups

Work loading between shift work and daytime work was compared by quality of life questionnaire SF-36. SF-36 assesses the impact of general health on quality of life with 36 items across eight components: physical functioning, physical role limitations, physical pain, general medical health, vitality, social functioning, emotional role limitations and mental health. Higher scores indicate better health.

There were no significant differences in all eight components. So the working loading and quality of life differences are not exist among three groups. (Table 2)

Plasma cytokine level according to the working group

There were significant differences in plasma IL-1β, IL-6, IL-10, and TNF- α levels among the three groups with Group B showing the highest, and Group C showing the lowest values. (Fig. 2, Table 3)

Inflammatory cytokines and PSQI scores

Plasma IL-1β (ρ = 0.337), IL-6 (ρ = 0.458) and TNF-α (ρ = 0.293) levels were correlated with PSQI scores. Correlation coefficients were obtained by Spearman's correlation analysis.

When compared by multivariate general linear models IL-6 level was significantly associated with PSQI score (β=0.317, $p<0.05$). (Table 4)

Multivariate general linear models for PSQI scores according to the effect of age, gender and working status

PSQI score was significantly associated with shift work status (β=0.372, $p<0.05$). But age and gender made no significant differences in PSQI scores as a independent variable. (Table 5)

Multivariate general linear models for inflammatory cytokine levels according to the effect of age, gender, working status, and PSQI

Plasma IL-6 level was significantly associated with PSQI score (β=0.317, $p<0.05$) and plasma levels of IL-1β (β=0.436, $p<0.05$), IL-10 (β=0.572, $p<0.05$), and TNF-α (β=0.630, $p<0.05$) were significantly associated with gender. IL-10 were also significantly associated with age (β=-0.412, $p<0.05$). (Table 6)

IV. DISCUSSION

Shift work implies "any work organization of working hour that differs from the traditional diurnal work period"[18], accordingly, work that happens between 7 pm and 6 am. Shift work, particularly night work, forced to work and sleep against normal chronobiological rhythms and light-darkness rhythms.[16] These incongruent lifestyles induce various indispositions including sleep disturbances which can cause severe lack of sleep.[4,19] Physiologic sleep is mainly regulated by circadian and homeostatic cycle, which also regulates the levels of awakening and sleepiness during wakening, also in shift work. So shift workers could easily get to sleep disorders and chronic fatigue. In previous studies, shift workers reported significantly worsened sleep quality compared to daytime workers.[17,20] To investigate the relationship between shift work and sleep quality, we compared PSQI scores between normal and shift working groups. As a result, shift workers reported significantly worsened sleep quality rater than day workers. And PSQI score was significantly associated with shift work status (β=0.372, $p<0.05$). This is in line with many other studies that have described sleep disturbances and chronic fatigue caused by shift work.[21,22]

Vila *et al*. defined that fatigue is a mental and/or physical state resulting from insufficient good quality sleep or from prolonged or intense physical, emotional, or mental effort that tends to decrease alertness, impair performance potential, worsen mood, and interfere with decision making.[23] Chronically fatigued people tend to develop maladaptations that spill over into leisure time and after all make recuperation even more difficult.[24] Shift working police officers reported fatigue related accidents involving

patrol vehicles and having trouble staying awake while driving, eating meals engaging in a social activity more than once a week. Actually shift working police officers' PSQI scores were twice as higher than the normal, which means poorer sleep quality. 14% of the officers reported that they were always or usually tired at the beginning of their work shifts.[16,23] On the other hand, Sergio Gabarino *et el*. Showed that Shift-workers forced to sleep disorders and sleep-related accidents, but they do not influence ESS score. Maybe stressful conditions caused by shift work could induce sleepiness to be underestimated, so subjectively they might feel to overcome sleepiness.[16]

Shift-work, in particular night-shift disturbs the physiological circadian rhythm and has the potential to induce psycho-physiological and endocrine homeostasis alterations. Some studies report cytokines releasing after acute sleep disturbance which can lead to an induction of pro-inflammatory immune responses.[7,9,25] Cytokine levels correlate with fatigue and daytime sleepiness. Vgontzas *et al*. reported that one night sleep deprivation changed the circadian pattern of IL-6 secretion. And they observed similar effects in chronic insomnia patients. So they call IL-6 and TNF-a fatigue inducing cytokines.[26] Similar to acute sleep deprivation people with a chronic sleep debt due to obstructive sleep apnea show elevated cytokine activity.[12,27-29] In our study, there were significant differences in plasma IL-1β, IL-6, IL-10, and TNF- α levels among the three groups with night time shift working men showing the highest, and daytime working women showing the lowest values. And especially plasma IL-6 level was significantly associated with PSQI score ($\beta=0.317$, $p<0.05$). Shift working group showed higher score of PSQI which means poorer sleep quality. So the result emphasizes the fact that shift working people are prone to get inflammations. Patel et al. described a direct correlation of the length of sleep

and the increase of IL- 6 serum levels or the decline of TNF-a.[25] Similarly Prather et al. showed that self-reported higher sleep debt scores predict elevated cytokine levels of IL-1ß and IL-6.[7] Cytokines regulate cell proliferation and differentiation. Thereby pro-inflammatory cytokine activation induces the accumulation of lymphocyte and neutrophil cells. Liu *et al*. reported an increase of lymphocyte and neutrophil cells after acute sleep deprivation.[30] Recently inflammatory processes are recognized to play a major role in the systemic pathogenesis like atherosclerosis and metabolic disorders. Crispim *et al*. reported lower level of adiponectin and higher level of TNF-a in shift workers than day workers.[31] These findings might explain higher prevalence of metabolic disorders and insulin resistance observed in shift workers despite without BMI differences.

There were few studies about cytokine level differences between gender in normal conditions. In our study, male reported higher level of cytokine concentrations in spite of normal work status. Male control group was daytime working policemen and female group was daytime health care workers. There can be an estimation that cytokine level differences were because of job difference. To solve this question we compared work loading by Quality of life questionnaire SF-36. SF-36 is composed of 8 dimensions; Physical functioning, Role limitations due to physical health, Role limitations due to emotional problems, Energy/ fatigue, Emotional well being, Social functioning, Pain, General health. SF-36 summary scores are range from 0 to 100 and higher scores representing better self-reported health. No difference was observed in each dimension between two groups. Generally policeman is thought to be a hard working job. But in reality the quality of life because of working status showed no difference. Due to lack of normal blood cytokine level difference between genders, we can only assume the gender

difference by reactive cytokine level. One study compared endo-toxin-stimulated production of IL-6 and TNF-a in response to the Trier Social Stress Test among 18 women and 27 men. Results showed a pre- to 60min post- task decrease in stimulated production of IL-6 among males, but not on females.[11] Another study reported that responses to acute stress stimulated production of IL-6, TNF-a, and IL-1b immediately decreased in men but no change in women 30 min post-task. Thus, there were notable gender differences in the pattern of cytokine production responses to acute stress, with women showing no change from baseline to post-task, but a significant increase during the 30 min recovery period and men showing a more biphasic response, with a significant decrease from baseline to post-task and an increase during recovery. And post-menopausal women showed greater increases in cytokine production from baseline to immediately following the stressor than pre-menopausal women or men.[32] Macrophages release a number of cytokines/chemokines including IL-6 and TNF-a. Studies demonstrated that the alterations in macrophage functions following trauma-hemorrhage are gender specific. For example, males are shown to develop alteration in macrophage functions, whereas females in proestrus stage of estrus cycle do not. However, ovariectomized female mice exhibit altered macrophage function similar to those observed in male mice following trauma-hemorrhage.[33-35] So these findings suggest that in normal state and trauma/stress condition, cytokine levels in women are more stable than men. And men showed greater increasing in cytokine production from baseline to immediately following the stressor than women. That means women are more susceptible than men to a number of inflammatory or stress conditions. However the mechanism of these differences was poorly explained. Further investigations are required to assess the

cytokine level differences between genders in normal state.

V. CONCLUSIONS

Shift work can lead to disruption of the circadian rhythm which results in an irregular sleep pattern and subsequent alteration of plasma cytokine levels. The aims of this study were to investigate the impacts of shift work induced chronic circadian disruption and gender on plasma inflammatory cytokine levels.

In our study night shift working men reported higher PSQI scores than day time working men and women, and PSQI score was significantly associated with shift work status. Night shift working men showed the highest plasma IL-1β, IL-6, IL-10, and TNF- α levels among the three groups. Plasma IL-6 level was significantly associated with PSQI score and plasma levels of IL-1β, IL-10, and TNF-α were significantly associated with gender. In conclusion, shift work induced chronic circadian disruption can worsen sleep quality and poor sleep quality increases plasma IL-6 level. Men have higher plasma IL-1β, IL-10, and TNF-α levels compared to women.

VI. REFERENCES

1. Zucconi M. Article reviewed: Distribution of road accidents in policemen on shift-work on Italian highways: the contributing role of sleepiness. Sleep Med 2001;2:561-563.
2. Milton K, Erman RR. Modafinil shift work sleep disorder study group. Modafinil for excessive sleepiness associated with chronic shift work sleep disorder: effects on patient functioning and health-related quality of life. Prim Care Companion. J Clin Psychiatry 2007;9:188-194.
3. Owens JA. Sleep loss and fatigue in healthcare professionals. J Perinat Neonat Nurs 2007;21:92-100.
4. Å kerstedt T. Shift work and disturbed sleep/wakefulness. Sleep Med Rev 1998;2:117-128.
5. Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol 1997;158:4454-4464.
6. Dinges DF, Douglas SD, Zaugg L, *et al*. Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. J Clin Invest 1994;93:1930-1939.
7. Prather AA, Marsland AL, Hall M, Neumann SA, Muldoon MF, Manuck SB. Normative variation in self-reported sleep quality and sleep debt is associated with stimulated pro-inflammatory cytokine production. Biol Psychol 2009;82:12-17.
8. Martinez-Gomez D, Eisenmann JC, Gomez-Martinez S, *et al*. Sleep duration and emerging cardiometabolic risk markers in adolescents. The AFINOS study. Sleep Med

2011;12:997-1002.

9. Shearer WT, Reuben JM, Mullington JM, *et al*. Soluble TNF-α receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. J Allergy Clin Immunol 2001;107:165-170.
10. Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Cytokines play an aetiopathogenetic role in fibromyalgia : a hypothesis and pilot study. Rheumatology 2001;40:743-749.
11. Gaab J, Rohleder N, Heitz V, *et al*. Stress-induced changes in LPS-induced pro-inflammatory cytokine production in chronic fatigue syndrome. Psychoneuroendocrinology 2005;30:188-198.
12. Ryan S, McNicholas WT. Inflammatory cardiovascular risk markers in obstructive sleep apnoea syndrome. Cardiovasc Hematol Agents Med Chem 2009;7:76-81.
13. Mallon L, Broman JE, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. J Intern Med 2002;251:207-216.
14. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-843.
15. van Leeuwen WM, Lehto M, Karisola P, *et al*. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One 2009;4: e4589.
16. Garbarino S, Nobili L, Mascialino B, *et al*. Sleepiness and sleep disorders in shift workers: a study on a group of Italian police officers. Sleep 2002;25:642-647.

17. Phillips B, Magan L, Gerhardstein C, Cecil B. Shift work, sleep quality and disturbances. Moreover a third of the sample worker health: a study of policy officer. South Med J 1991;84:1176-1184.

18. Costa G. Factors influencing health of workers and tolerance to shift work. Theor Issues in Ergon Sci 2003;4:263-288.

19. Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. Sleep 2004;27:1453-1462.

20. Mark A, Weiler SW, Schroder M, *et al*. The impact of shift work induced chronic circadian disruption on IL-6 and TNF-alpha immune responses. J Occup Med Toxicol 2010;5:18-22.

21. Andlauer P, Reinberg A, Fourre L, Battle W, Duverneuil G. Amplitude of the oral-temperature circadian-rhythm and the tolerance to shift-work. J Physiol-Paris 1979;75:507-512.

22. Reinberg A, Ashkenazi I. Internal desynchronization of circadian rhythms and tolerance of shift work. Chronobiol Int 2008;16:21-34.

23. Vila B, Morrison GB, Kenney DJ. Improving shift schedule and work-hour policies and practices to increase police officer performance, health, and safety. Police Quarterly 2002;5:4-24.

24. Moore-Ede MC. The twenty-four hour society: understanding human limits in a world that never stops. The Wilson Quarterly. 1993.

25. Patel SR, Zhu X, Storfer-Isser A, *et a*l. Sleep duration and biomarkers of inflammation. Sleep 2009;32:200-204.

26. Vgontzas AN, Zoumakis M, Papanicolaou DA, *et al*. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. Metabolism 2002;51:887-892.

27. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax 2009;64:631-636.

28. Yokoe T. Elevated levels of c-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 2003;107:1129-1134.

29. Yue HJ, Mills PJ, Ancoli-Israel S, Loredo JS, Ziegler MG, Dimsdale JE. The roles of TNF-alpha and the soluble TNF receptor I on sleep architecture in OSA. Sleep Breath 2009;13:263-269.

30. Liu H, Wang G, Luan G, Liu Q. Effects of sleep and sleep deprivation on blood cell count and hemostasis parameters in healthy humans. J Thromb Thrombolysis 2009;28:46-49.

31. Crispim CA, Padilha HG, Zimberg IZ, *et al*. Adipokine levels are altered by shiftwork: a preliminary study. Chronobiol Int 2012;29:587-594.

32. Prather AA, Carroll JE, Fury JM, McDade KK, Ross D, Marsland AL. Gender differences in stimulated cytokine production following acute psychological stress. Brain Behav Immun 2009;23:622-628.

33. Angele MK, Ayala A, Cioffi WG, Bland KI, Chaudry IH. Testosterone: the culprit for producing splenocyte immune depression after trauma hemorrhage. Am J Physiol 1998;274:1530-1536.

34. Angele MK, Schwacha M, Ayala A, Chaudry IH. Effect of gender and sex hormones on immune responses following shock. Shock 2000;14:81-90.

35. Angele MK, Wichmann MW, Ayala A, Cioffi WG, Chaudry IH. Testosterone receptor blockade after hemorrhage in males. Restoration of the depressed immune functions and improved survival following subsequent sepsis. Arch Surg 1997;132:1207-1214.

Table 1. PSQI scores (mean ± SD) according to different types of working

Group	PSQI	Multiple comparisons
Day time working men (A)	4.76 ± 3.07	
Night shift working men (B)	7.28 ± 3.26	(A, B), (B, C)
Day time working women (C)	3.56 ± 2.12	
P-value	0.002	

P-value was obtained from one-way ANOVA
Multiple comparisons were performed by Scheffe test

Table 2. SF-36 scores according to different types of working

Dimension	Physical functioning			Role limitations due to physical health			Role limitations due to emotional problems			Energy/fatigue		
Group	A	B	C	A	B	C	A	B	C	A	B	C
Mean	95.0±5.6	89.7±10.1	85.9±14.1	91.2±21.5	87.5±23.1	78.1±28.7	84.3±35.6	83.3±23.6	79.2±34.2	63.5±23.6	53.9±16.4	47.5±17.7
P-value	0.051			0.299			0.883			0.068		

Dimension	Emotional well being			Social functioning			pain			General health		
Group	A	B	C	A	B	C	A	B	C	A	B	C
Mean	71.3±22.3	63.8±14.9	64.4±17.9	81.6±25.1	80.6±19.8	76.6±20.9	87.9±14.4	90.3±14.1	88.8±12.8	66.2±21.3	59.7±15.2	52.5±19.8
P-value	0.427			0.787			0.879			0.125		

Group A: day time working men, Group B: night shift working men, Group C: day time working women
P-values were obtained from one-way ANOVA

Table 3. Plasma cytokine level (pg/ml) according to different types of working

Group	IL-1β	IL-6	IL-10	TNF-α
Day time working men	0.66 ± 044	1.68 ± 1.93	2.12 ± 1.38	7.50 ± 8.22
Night shift working men	0.63 ± 0.41	3.36 ± 5.62	3.10 ± 3.72	19.36 ± 31.52
Day time working women	0.26 ± 0.31	0.29 ± 0.39	0.60 ± 0.43	1.75 ± 4.95
P-value	0.000	0.000	0.000	0.007

P-values were obtained from Kruskal-Wallis test

Table 4. Correlations among plasma levels of inflammatory cytokines and PSQI scores

Sleep index	IL-1β	IL-6	IL-10	TNF-α
PSQI	0.337*	0.458**	0.245	0.293*

*: P < 0.05, **: P < 0.01

The appearing values are Spearman's correlation coefficients.

Table 5. Multivariate general linear models for PSQI scores according to age, gender, and working status

Dependent variable	Independent variable	Coefficient	β-value	P-value
PSQI	Age	-0.023	-0.053	0.691
	Gender	-1.304	-0.189	0.219
	Working time	2.497	0.372	0.015

Working time: Day time working = 0, Night time working = 1
Gender: Men = 0, Women = 1

Table 6. Multivariate general linear models for inflammatory cytokine levels according to age, gender, working status, and PSQI

Dependent variable	Independent variable	Coefficient	β-value	P-value
IL-1β	Age	-0.021	-0.251	0.204
	Gender	-0.479	-0.436	0.044
	Working time	-0.170	-0.188	0.291
	PSQI	0.032	0.236	0.163
IL-6	Age	-0.008	-0.035	0.805
	Gender	-1.208	-0.316	0.058
	Working time	-0.490	-0.143	0.397
	PSQI	0.164	0.317	0.048
IL-10	Age	-0.054	-0.412	0.001
	Gender	-1.151	-0.572	0.000
	Working time	0.046	0.025	0.857
	PSQI	-0.005	-0.017	0.898
TNF-α	Age	-0.010	-0.033	0.798
	Gender	-2.850	-0.630	0.000
	Working time	-0.858	-0.202	0.245
	PSQI	0.126	0.198	0.211

Working time: Day time working = 0, Night time working = 1
Gender: Men = 0, Women = 1

Figure 1. Comparison of PSQI scores according to working types

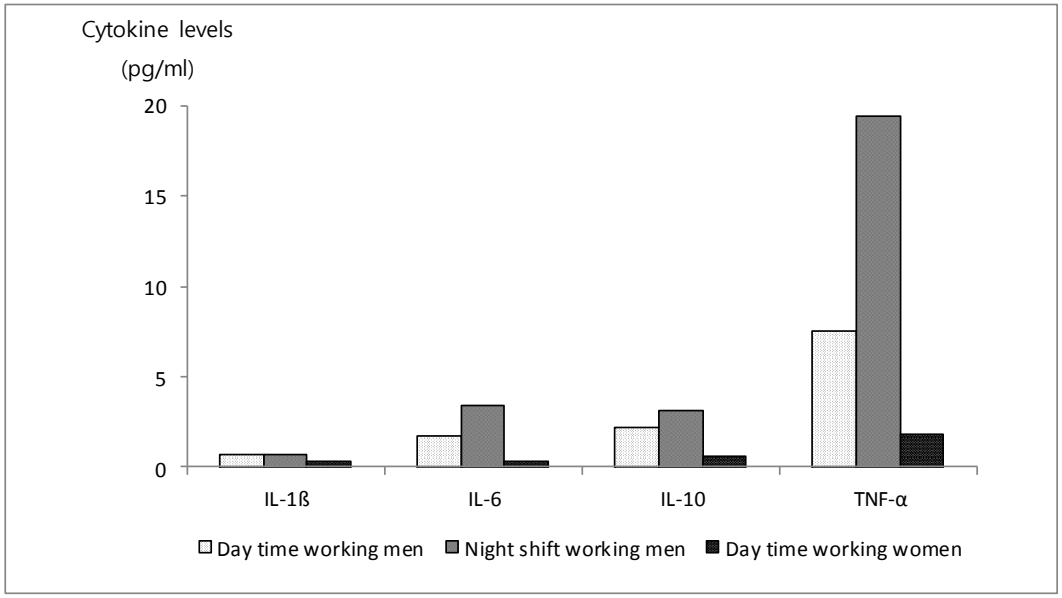

Figure 2. Comparison of plasma levels of IL-1β, IL-6, IL-10, and TNF-α according to working types

국문초록

교대근무에 따른 만성적 생체주기의 변화 및 성별이 혈중 염증성 cytokine 농도에 미치는 영향

서울대학교 대학원 치의과학과 구강내과진단학 전공

(지도교수 정 진 우)

김 동 희

1. 목 적

교대근무에 따른 생체주기리듬의 변화는 불규칙한 수면 패턴을 야기할 수 있으며, 이는 혈중 염증성 cytokine 농도의 변화를 가져올 수 있으리라 예상된다. 이번 논문의 목적은 교대근무에 따른 만성적인 생체주기의 변화 및 성별이 혈중 염증성 cytokine 농도에 미치는 영향에 관하여 알아보는데 있다.

2. 방 법

51 명의 건강한 성인을 성별 및 교대근무 여부에 따라 주간 근무 남성군 (평균 39.7 ± 3.3 세), 야간 교대근무 남성군 (평균 39.1 ± 4.5 세), 주간 근무 여성군 (평균 35.3 ± 11.5 세)의 평균 연령을 일치시킨 세

그룹으로 분류하였다. 모든 대상자들에게 Pittsburgh Sleep Quality Index (PSQI) 및 Short Form Health Survey Instrument (SF-36) 평가를 시행하였으며, 정맥혈을 채취하여 혈중 IL-1β, IL-6, IL-10, TNF-α 농도를 측정하였다.

3. 결 과

야간 교대근무 남성군은 PSQI 가 다른 그룹들에 비하여 높게 나타났으며, PSQI 점수는 야간 교대근무 여부와 높은 상관관계 (β=0.372, p<0.05)를 나타내었다. 또한 혈중 IL-1β, IL-6, IL-10, TNF-α 농도는 야간 교대근무 남성군에서 가장 높게 나타났으며, 주간 근무 여성군에서 가장 낮게 나타났다. 혈중 IL-6 농도는 PSQI 점수와 유의한 상관관계 (β=0.317, p<0.05)를 보였으며, IL-1β (β=0.436, p<0.05), IL-10 (β=0.572, p<0.05), TNF-α (β=0.630, p<0.05) 농도는 성별과 유의한 상관관계를 나타내었다.

결론적으로 교대근무에 따른 만성적 생체주기의 변화는 수면의 질을 저하시키며, 낮아진 수면의 질은 혈중 IL-6 농도의 증가에 영향을 주었다. 또한 남성은 여성에 비하여 혈중 IL-1β, IL-10, TNF-α 농도가 높은 것으로 나타났다.

주요어 : 교대근무, 생체주기, cytokine, 수면, 성별

학 번 : 2011-22026