The association of employment status and blood pressure dipping patterns in a Korean cohort: cardiovascular and metabolic diseases etiology research center – high risk study

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ABSTRACT

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Cardiovascular disease (CVD) is prevalent in the general population, affecting majority of people over 60 years old. There are several well-established risk factors for CVD, and better control of these modifiable risk factors are very important to prevent further complications from CVD. Psychosocial status is one of the important modifiable risk factors and are getting more attention regarding its potential role in the early development and progression of CVD. Employment status can significantly affect the psychosocial status of each individual, and recent findings show that unemployment can adversely affect the incidence of CVD and its complication. However, the underlying mechanism of how employment status can affect cardiovascular outcome in patients with CVD are largely unknown. Using a cohort study called, Cardiovascular and Metabolic Diseases Etiology Research Center – High Risk (CMERC–HI, NCT02003781), we investigated the association of employment status with surrogate cardiovascular markers collected by various ways of blood pressure measurement and pulse wave velocity. Among the total of 1,915 participants, 449 (23.5%) were unemployed and 1,466 (76.5%) were employed. Unemployment group had higher frequency of reverse-dipping pattern compared to employment group [81 (18.0 %) vs. 167 (11.4 %), $P < 0.001$]. Multiple logistic regression showed significant association between unemployment status and reverse BP dipping pattern even after adjustment of multiple confounding factors (Odds ratio, 1.577; 95% CI, 1.124 – 2.202; P = 0.008). Our study suggests that unemployment can adversely affect cardiovascular outcome by disrupting normal hemodynamic circadian rhythm.

Key words : employment status, unemployment, reverse dipping pattern, ambulatory blood pressure monitoring, cardiovascular disease

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I. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide. Globally, 17.6 million deaths were attributed to CVD in 2016, and more than 23.6 million deaths are expected by 2030.[1] The global incidence and prevalence of CVD and its related complications are increasing with an aging society, obesity, and other factors including tobacco and alcohol use. Hypercholesterolemia, diabetes, hypertension, obesity, and smoking are the five leading modifiable causes of CVD, and more than 90 percent of CVD events occur in patients with at least one of these risk factors.[2] Prevention and early management of these major risk factors are the key strategies to reduce the burden of CVD worldwide.

Recently, psychosocial and socioeconomic status have received lots of attention as non-traditional risk factors in the development and progression of CVD.[3,4] The effect of psychosocial factor on CVD is considered to be both direct, via endothelial damage and inflammation,[5-7] and indirect, via exacerbating pre-disposed risk factors such as hypertension and hyperlipidemia.[8,9] A longitudinal study of 1,055 males showed that those with the highest level of anger had a significantly increased risk of premature CVD, especially myocardial infarction, compared to those with lower levels.[10] Another study on the coronary heart disease patients showed that depression was associated with higher frequency of angina events, more physical limitation, and a lower quality of life.[11] Employment status is an important aspect of psychosocial status and there are several studies indicating that unemployment can negatively affect people by worsening their health status and causing higher mortality.[12,13] Unemployed people showed higher susceptibility to cardiovascular disease, anxiety disorders, depression, and suicide.[14-22] Also, those individuals were associated with more frequent medication use, poor diet, smoking and alcohol consumption, and less exercise.[23-26]

It is controversial whether the employment status affects health outcome directly or by modifying other CVD risk factors. Some studies suggested that unemployment could cause bias due to 'health selection effects', saying that those who do not have jobs tend to have less healthy lifestyle and more frequent emotional problems.[23,25,26] However, more recent studies are showing that employment status per se has independent implications on the adverse cardiovascular outcomes.[19,27] A prospective cohort study by Meneton *et al.*, showed that unemployment is associated with the development of CVD even after the adjustment of demographic/biologic/socio-economic variables.[19] However, there is nothing much known about the underlying mechanism how unemployment negatively affects cardiovascular outcomes.

The Cardiovascular and Metabolic Diseases Etiology Research Center – High Risk (CMERC–HI, NCT02003781) study is an ongoing, nationwide, prospective cohort study in South Korea, including individuals with high risks of cardiovascular or metabolic diseases. This cohort study intends to investigate the individualized risk factors of cardiovascular and cerebrovascular diseases and to establish personalized preventive strategy. This cohort data includes demographic information such as age, gender, employment status, economical status, educational status, past medical histories, and biochemical information, as well as cardiovascular parameters. Cardiovascular parameters were collected in multiple ways including office-based blood pressure (BP), central BP, and 24-hour ambulatory blood pressure monitoring (ABPM).

24-hour ABPM is known to be a better indicator of morbidity and mortality than office-based BP.[28,29-31] Also, the circadian variation pattern of BP monitored by ABPM shows strong association with CVD risks.[32,33] Especially, reverse dipping BP pattern, which means higher systolic BP during the nighttime than in the daytime, is associated with increased risks of CVD and cardiovascular complications[34-36], and some of the studies indicated that psychosocial factors as potential contributors.[37-41]

In this study, we investigated whether employment status is related to any cardiovascular surrogates collected from various BP measurement modalities and considered whether this finding can potentially explain the negative effects of unemployment on CVD risks.

II. MATERIALS AND METHODS

1. Study population

The participants of this cross-sectional analysis were recruited from the CMERC–HI cohort study ranging from November 2013 to December 2018. The inclusion criteria of the CMERC-HI were as follows: patients with high-risk hypertension, diabetes mellitus with albuminuria, anuric end-stage renal disease, and use of dialysis (urine output < 200 ml/d); relatives of acute myocardial infarction patients who were younger than 55 years (for men) or 65 years (for women); patients with asymptomatic atherosclerotic CVD (abdominal aorta diameter ≥3 cm or ankle-brachial index <0.9, carotid plaque or carotid intima-media thickness ≥0.9 mm, asymptomatic old cerebrovascular accident, or 30% stenosis in at least 1 major coronary artery); rheumatic arthritis patients aged older than 40 years with use of methotrexate or corticosteroids; atrial fibrillation patients with a CHA2DS2-VASc score ≥1; and kidney transplant recipients who underwent transplantation more than 3 months ago. The exclusion criteria were as follows: history of acute coronary syndrome, symptomatic coronary artery disease, symptomatic peripheral artery disease, or heart failure; less than 6 months life expectancy because of a non-cardiovascular disease; pregnant or breastfeeding status; history of contrast allergy and related adverse effects; or kidney transplantation within the last 3 months or acute rejection after transplantation. According to the criteria, 3,270 participants were enrolled in the cohort study from November 2013 to December 2018. After initial screening, any subjects with no complete socioeconomic questionnaire, missing data on BP or PWV measurements, incomplete biochemical studies, and end-stage renal disease were excluded. Consequently, 1,915 subjects were selected for this study (**Figure 1**).

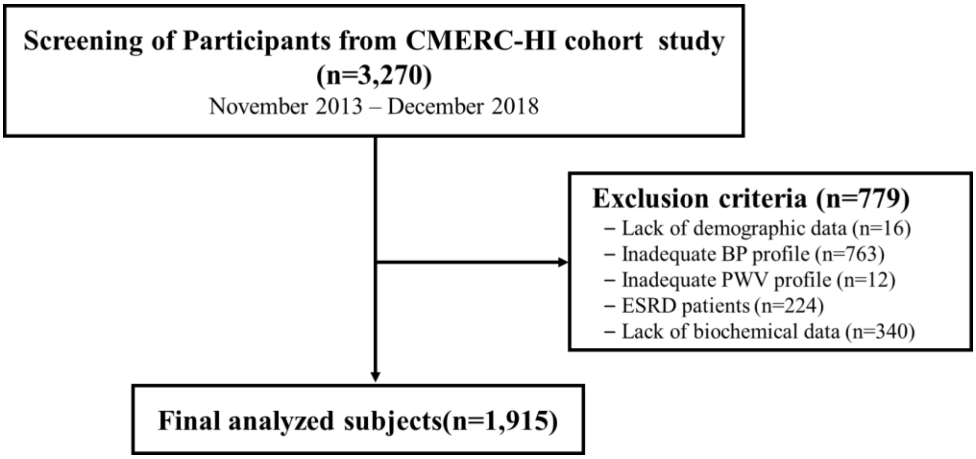

Figure 1. Flow chart of the study participants.

Abbreviations: CMERC-HI, Cardiovascular and Metabolic Diseases Etiology Research Center – High Risk Cohort; BP, blood pressure; PWV, peak wave velocity; ESRD, end-stage renal disease.

2. Clinical and biochemical data collection

All the demographic and clinical data of CMERC–HI cohort study were collected by experienced and specialized nurses, and these data include age, sex, history/status of smoking and alcohol, intensity of exercise, sleep problem, the number of housemate, the presence of solitary life and marital problem, education status, income from the participating subjects, and past medical histories. Weight, height, and biochemical data were assessed at the time of enrollment. Body mass index was calculated as the ratio of weight/height^2 (kg/m^2). Diabetic and hypertensive patients were defined as previously described,[42,43] and the history of cardiovascular disease was defined as a composite of previous coronary artery disease, cerebrovascular accident, ischemic heart disease, and congestive heart failure. The severity of depression was interpreted as following criteria; none or minimal depression, < 10; mild-to-moderate depression, 10–18; moderate-to-severe depression, 19–29; and severe depression, 30-63.[44] In present analysis, each subjects were considered to have depression if the person belongs to the moderate-to-severe or severe depression groups.

A blood test was performed after 12-hour overnight fasting. Plasma was separated within 30 to 60 minutes after centrifugation at 1,000 *g* for 10 minutes and stored in a -70˚C deep freezer until analysis. 30-40 ml of mid-stream urine samples were collected and stored in the standard refrigerator immediately after collection. Hemoglobin, glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum albumin, calcium, phosphate, blood urea nitrogen, creatinine, urinary albumin-to-creatinine ratio, and high-sensitivity C-reactive protein were measured. The estimated glomerular filtration rate (eGFR) was calculated by using the chronic kidney disease epidemiology collaboration equation.[45]

3. Labor force participation

The participants were required to complete the socio-demographic questionnaires at enrollment. The data about occupation and present work status were determined based on these self-reported records. CMERC–HI cohort study defined participants as employed when they were engaged in any paid work, self-employed, or was involved in unpaid family work. Unemployment was defined when someone is out of work since their loss of last occupation or who has never been employed. The details regarding occupational classification was obtained from Korean standard industrial classification provided by Statistics Korea (http://kostat.go.kr/ portal/eng/ index.action).

4. Measurement of BP and pulse wave velocity

The automated office BP (AOBP) was measured by trained nurses in an examination room with patients in the sitting position and their right arm supported at heart level. After a minimum of five-minute rest in the sitting position, AOBP was obtained using a validated automatic device (HEM–7080, Omron Corporation, Kyoto, Japan), which was programmed to automatically measure the BP of a person at 5, 7, and 9 minutes. The mean of the three BP values was used as AOBP. Central BP was measured noninvasively by mathematically transforming radial artery pulse waveform that was acquired from a high-fidelity micromanometer (Millar Instruments, Houston, TX, USA) to aortic pulse waveform using a Millar transducer and customized software (SphygmoCor, AtCor Medical, Sydney, Australia).[46] ABPM was assessed by automatic ABPM device (Takeda TM–2430, A&D Company, Tokyo, Japan) recording BP and pulse rate on the left arm of participating individuals by oscillometric method every 30 minutes for 24 hours. Adequacy of ABPM recording was defined as completing at least 70% of the expected measurements, and at least 14 measurements during the daytime and 7 measurements during the nighttime. Daytime and nighttime periods were defined according to the information provided in patients' diaries. Ambulatory BP readings were averaged for 24-hour, daytime, and nighttime values. Patterns of diurnal BP variation were defined as follows: dippers (nighttime BP decrease ≥ 10% and ≤ 20%), non-dippers (nighttime BP decrease < 10% and ≥ 0%), extreme dippers (nighttime BP decrease > 20%), and reverse dippers (nighttime BP > daytime BP).[33] Pulse pressure was determined as the difference between systolic and diastolic BP. Pulse wave velocity (PWV) was estimated by using SphygmoCor® with respect to the electrocardiogram wave. PWV was measured using 'foot-to-foot method' by recording pulse waveforms at carotid area and femoral area and the time delay between each pressure waveforms. The distance between the two measurement points were divided by the time difference, which provided PWV value in each participant.

5. Statistical analysis

Continuous variables with normal distribution were expressed as the mean ± standard deviation, and median with interquartile range was used for nonparametric continuous variables. Categorical variables were expressed as total numbers with their percentages. The Shapiro-Wilk test was used to analyze the normality of the distribution of parameters. Comparisons between employed and unemployed subjects were performed by using Student's *t*-tests or Mann-Whitney *U*-tests for continuous variables, and chi-square tests were used for categorical variables. Univariate and multiple logistic regression analyses were performed to find the association between employment status and reverse-dipping BP pattern. All results were expressed in odds ratio (OR) with their 95% confidence interval (CI). All statistical analyses were performed using R (version 3.4.3; www.r-project.org; R Foundation for Statistical Computing, Vienna) with a *P* value <0.05 considered significant.

III. RESULTS

1. Baseline characteristics of participants based on their employment status

The demographic and laboratory baseline characteristics of study populations are presented in **Table 1**. Mean age of the 1,915 participants was 61.1 ± 10.6 years and 1,009 (52.7%) were men. The subjects with smoking or alcohol history were 849 (44.3%) and 1,213 (63.3%), respectively. There were 861 (45.0%) patients with diabetes, 1,607 (83.9%) with hypertension, and 686 (35.8%) with chronic kidney disease ≥ stage 3.

Table 1. Baseline characteristics of subjects

Variables	Total (n=1,915)	Unemployment (n=449, 23.5%)	Employment (n=1,466, 76.5%)	P
Age (years)	61.1 ± 10.6	66.9 ± 9.1	59.3 ± 10.3	< 0.001
Male (%)	1,009 (52.7%)	334 (74.4%)	675 (46.0%)	< 0.001
Body mass index (kg/m^2)	26.5 ± 64.4	24.6 ± 3.3	27.1 ± 73.5	0.182
Socio-economic factors				
Smoking (yes)	849 (44.3%)	275 (61.2%)	574 (39.2%)	< 0.001
Alcohol (yes)	1,213 (63.3%)	303 (67.5%)	910 (62.1%)	0.043
Exercise (yes)	1,552 (81.2%)	369 (82.4%)	1,183 (80.9%)	0.519
Sleep problem (yes)	684 (35.8%)	157 (35.0%)	527 (36.0%)	0.748

Housemate number	2.9 ± 1.4	2.6 ± 1.5	3.0 ± 1.3	< 0.001
Solitary life (%)	125 (6.5%)	43 (9.6%)	82 (5.6%)	0.004
Marital problem (%)	291 (15.2%)	89 (19.8%)	202 (13.8%)	0.002
Low education (%)	574 (30.0%)	143 (31.8%)	431 (29.4%)	0.351
Low income (%)	341 (17.8%)	108 (24.1%)	233 (15.9%)	< 0.001
Comorbidities (%)				
Diabetes mellitus	861 (45.0%)	247 (55.0%)	614 (41.9%)	< 0.001
Hypertension	1,607 (83.9%)	387 (86.2%)	1,220 (83.2%)	0.154
Hyperlipidemia	1,155 (60.3%)	256 (57.0%)	899 (61.4%)	0.111
History of CVD [a]	375 (19.6%)	105 (23.4%)	270 (18.4%)	0.024
Cancer	92 (4.8%)	26 (5.8%)	66 (4.5%)	0.322
CKD (≥ stage 3)	686 (35.8%)	208 (46.3%)	478 (32.6%)	< 0.001
Depression [b]	233 (12.2%)	67 (14.9%)	166 (11.3%)	0.050
Laboratory findings				
Hemoglobin (g/dl)	13.1 ± 2.1	13.0 ± 2.2	13.2 ± 2.0	0.095
Glucose (mg/dl)	114.0 ± 32.6	118.5 ± 36.2	112.7 ± 31.4	0.002
Cholesterol (mg/dl)	172.8 ± 40.8	166.0 ± 39.7	174.8 ± 40.9	< 0.001
Triglyceride (mg/dl)	141.5 ± 97.5	131.2 ± 71.8	144.7 ± 104.0	0.003
HDL-C (mg/dl)	48.9 ± 13.8	46.8 ± 13.8	49.5 ± 13.7	0.001
LDL-C (mg/dl)	94.5 ± 33.3	91.2 ± 33.1	95.6 ± 33.3	0.018
Serum albumin (g/dl)	4.2 ± 0.4	4.1 ± 0.4	4.2 ± 0.4	0.003
Calcium (mg/dl)	9.1 ± 0.5	9.1 ± 0.6	9.1 ± 0.5	0.245
Phosphate (mg/dl)	3.8 ± 0.7	3.7 ± 0.8	3.8 ± 0.7	0.351
BUN (mg/dl)	25.2 ± 17.8	28.2 ± 20.0	24.5 ± 17.0	< 0.001
Creatinine (mg/dl)	1.0 (0.8-1.6)	1.1 (0.9-2.1)	1.0 (0.7-1.5)	< 0.001[c]
eGFR (ml/min/1.73 m^2)	61.6 ± 30.6	55.4 ± 31.3	63.5 ± 30.1	< 0.001
UACR (mg/g Cr)	74.7 (12.9-624.1)	96.2 (17.2-715.3)	70.3 (12.2-621.9)	0.090[c]
hs-CRP (mg/l)	0.8 (0.5-1.7)	0.9 (0.5-1.8)	0.8 (0.5-1.6)	0.306[c]

Note: [a] History of cardiovascular disease is defined as a composite of previous coronary artery disease, cerebrovascular accident, ischemic heart disease, and congestive heart failure; [b] Moderate to severe or severe depression groups were included; [c] Mann-Whitney`s U-test

Abbreviations: CVD, cardiovascular disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; hs-CRP, high sensitivity C-reactive protein

The participants were divided into two groups according to their employment status - 1,466 (76.5%) were employed and 449 (23.5%) were unemployed. Unemployment group were significantly different than employment group including older age (66.9 ± 9.1 vs. 59.3 ± 10.3 years, P < 0.001), higher percentage of male [334 (74.4%) vs. 675 (46.0%), P < 0.001], and higher frequency of smoking and alcohol history [275 (61.2%) vs. 574 (39.2%), P < 0.001 and 303 (67.5%) vs. 910 (62.1%), P = 0.043, respectively]. Unemployment group also had lower number of housemates (2.6 ± 1.5 vs. 3.0 ± 1.3, P < 0.001], showed higher frequency of solitary life [43 (9.6%) vs. 82 (5.6%), P = 0.004], experienced more marital problems [89 (19.8%) vs. 202 (13.8%), P = 0.002], and had lower income [108 (24.1%) vs. 233 (15.9%), P < 0.001]. Unemployment group had more diabetes [247 (55.0%) vs. 614 (41.9%), P < 0.001], history of CVD [105 (23.4%) vs. 270 (18.4%), P = 0.024], and chronic kidney disease (≥ stage 3) [208 (46.3%) vs. 478 (32.6%), P < 0.001] compared to the employment group. Further comparison using biochemical parameters showed significantly lower cholesterol profiles including triglyceride, HDL-C, and LDL-C, as well as serum albumin, and decreased kidney function showing higher blood urea nitrogen (BUN), creatinine, lower eGFR in the unemployment group compared to the employment group.

2. Reverse-dipper is more frequently observed in unemployment group

The detailed comparative data on the parameters of BP and PWV between the groups are described in **Table 2**.

Table 2. Baseline blood pressure and pulse wave velocity of participating subjects

Variables	Total (n=1,915)	Unemployment (n=449, 23.5%)	Employment (n=1,466, 76.5%)	P
Systolic BP (mmHg)				
Office	128.9 ± 17.9	131.5 ± 18.5	128.0 ± 17.6	<0.001
Central	119.7 ± 19.4	122.6 ± 20.5	118.8 ± 19.0	0.001
24-h (total)	131.4 ± 16.1	134.1 ± 16.8	130.5 ± 15.7	<0.001
24-h (day)	135.9 ± 15.9	137.9 ± 16.1	135.2 ± 15.8	0.002
24-h (night)	123.2 ± 19.0	127.5 ± 20.1	121.9 ± 18.4	<0.001
Diastolic BP (mmHg)				
Office	75.9 ± 10.4	73.4 ± 9.9	76.6 ± 10.4	<0.001
Central	75.3 ± 10.5	74.0 ± 10.0	75.7 ± 10.6	0.003
24-h (total)	78.1 ± 8.6	76.9 ± 8.1	78.5 ± 8.7	0.001
24-h (day)	81.0 ± 9.0	79.5 ± 8.3	81.5 ± 9.1	<0.001
24-h (night)	72.7 ± 9.7	72.5 ± 9.6	72.7 ± 9.8	0.700
Pulse pressure (mmHg)				
Office	53.0 ± 14.8	58.1 ± 16.2	51.4 ± 14.0	<0.001
Central	44.4 ± 14.7	48.6 ± 16.6	43.1 ± 13.8	<0.001
24-h (total)	53.3 ± 11.7	57.2 ± 12.6	52.0 ± 11.1	<0.001
24-h (day)	54.8 ± 11.9	58.4 ± 12.4	53.7 ± 11.6	<0.001
24-h (night)	50.6 ± 12.9	55.0 ± 14.2	49.2 ± 12.2	<0.001
Pulse rate (beats/min)	69.6 ± 11.4	69.7 ± 12.1	69.6 ± 11.1	0.921
Dipping patterns (%)				
Extreme-dipper	171 (8.9%)	29 (6.5%)	142 (9.7%)	0.045
Dipper	783 (40.9%)	159 (35.4%)	624 (42.6%)	0.008
Non-dipper	713 (37.2%)	180 (40.1%)	533 (36.4%)	0.169
Reverse-dipper	248 (13.0%)	81 (18.0%)	167 (11.4%)	<0.001

Cardiovascular markers				
hc-PWV (cm/s)	981.4 ± 363.3	1084.7 ± 452.5	949.9 ± 325.1	<0.001
hf-PWV (cm/s)	1,059.1 ± 346.3	1,138.2 ± 427.9	1,035.0 ± 313.5	<0.001
cf-PWV (central, m/s)	9.6 ± 2.4	10.4 ± 2.6	9.4 ± 2.3	<0.001

Abbreviations: BP, blood pressure; hc-PWV, heart-carotid pulse wave velocity; hf-PWV, heart-femoral pulse wave velocity; cf-PWV, carotid-femoral pulse wave velocity

Unemployment group showed higher systolic BP on all different modalities of BP measurement than employment group (AOBP, 131.5 ± 18.5 vs. 128.0 ± 17.6 mmHg, P < 0.001; central BP, 122.6 ± 20.5 vs. 118.8 ± 19.0 mmHg, P = 0.001; total ABPM, 134.1 ± 16.8 vs. 130.5 ± 15.7 mmHg, P < 0.001; daytime ABPM, 137.9 ± 16.1 vs. 135.2 ± 15.8 mmHg, P = 0.002; nighttime ABPM, 127.5 ± 20.1 vs. 121.9 ± 18.4 mmHg, P < 0.001); and this difference was largest in the nighttime ABPM between these two groups. Unemployment group had lower diastolic BP across all the modalities of BP measurement except nighttime ABPM (AOBP, 73.4 ± 9.9 vs. 76.6 ± 10.4 mmHg, P < 0.001; central BP, 74.0 ± 10.0 vs. 75.7 ± 10.6 mmHg, P = 0.003; total ABPM, 76.9 ± 8.1 vs. 78.5 ± 8.7 mmHg, P = 0.001; daytime ABPM, 79.5 ± 8.3 vs. 81.5 ± 9.1 mmHg, P < 0.001; nighttime ABPM, 72.5 ± 9.6 vs. 72.7 ± 9.8 mmHg, P = 0.700). Those differences mentioned above resulted in significantly higher pulse pressure in unemployment group compared to employment group on all BP measurement modalities (AOBP, 58.1 ± 16.2 vs. 51.4 ± 14.0 mmHg, P < 0.001; central BP, 48.6 ± 16.6 vs. 43.1 ± 13.8 mmHg, P < 0.001; total ABPM, 57.2 ± 12.6 vs. 52.0 ± 11.1 mmHg, P < 0.001; daytime ABPM, 58.4 ± 12.4 vs. 53.7 ± 11.6 mmHg, P < 0.001; nighttime ABPM, 55.0 ± 14.2 vs. 49.2 ± 12.2 mmHg, P < 0.001). There was no difference in pulse rate depending on the employment status.

Further analysis on BP dipping patterns using ABPM data showed that unemployment group had lower frequency of normal dipping pattern [159 (35.4 %)

vs. 624 (42.6 %), *P* = 0.008] and rather had higher frequency of reverse-dipping pattern [81 (18.0 %) vs. 167 (11.4 %), P < 0.001] (**Figure 2**).

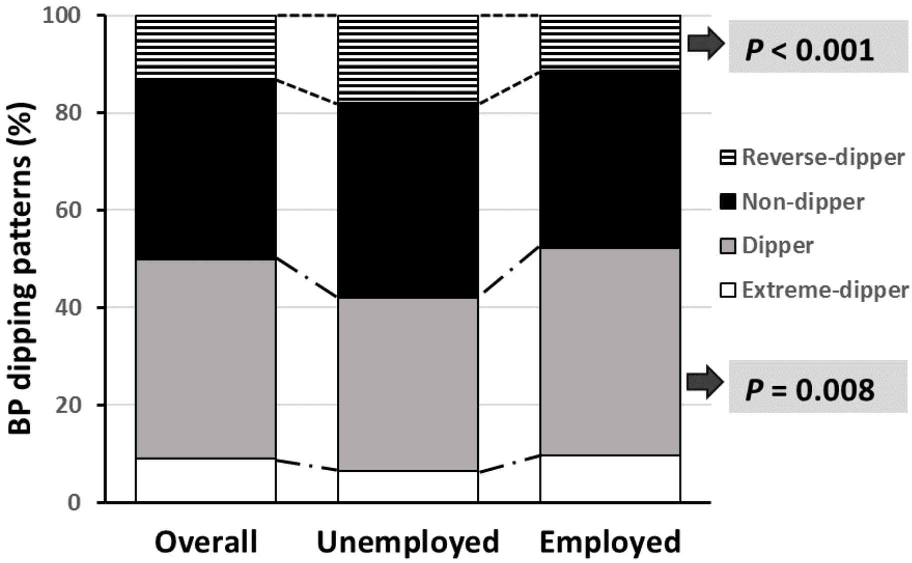

Figure 2. Distribution of extreme-dipper, dipper, non-dipper, and reverse dipper according to employment status. The frequency of reverse-dipper was significantly higher in the unemployed population.
Abbreviations: BP, blood pressure

In addition, PWV was significantly higher in unemployment group (heart-carotid, 1,084.7 ± 452.5 vs. 949.9 ± 325.1 cm/s, *P* < 0.001; heart-femoral, 1,138.2 ± 427.9 vs. 1,035.0 ± 313.5 cm/s, *P* < 0.001; carotid-femoral, 10.4 ± 2.6 vs. 9.4 ± 2.3 m/s, *P* < 0.001) compared to employment group.

When we regrouped the participants based on the presence of reverse-dipping pattern, there were no significant differences in their socio-economic status or underlying medical conditions except employment status and presence of CKD. The reverse-dipper group had higher unemployment rate (32.7% vs. 22.1%, P < 0.001) and had of higher frequency of CKD (≥ stage 3) (50.8% vs. 33.6%, *P* < 0.001) compared to those having other dipping patterns such as extreme-dipper, dipper, or non-dipper.

3. Unemployment is significantly associated with reverse-dipper

To investigate whether there is any independent association between reverse-dipper and occupational status, multiple logistic regression analysis was performed. The unadjusted OR (95% CI) of unemployment for being reverse-dipper was 1.712 (95% CI, 1.277 – 2.280, $P < 0.001$). When the multiple logistic regression analysis were performed, unemployment was independently associated with an increased risk of being reverse-dipper (OR, 1.577; 95% CI, 1.124 – 2.202; $P = 0.008$) after adjustment for age, gender, body mass index, smoking and alcohol history, housemate number, marital problem, economic status, history of diabetes, hypertension, and depression, cholesterol, phosphate, eGFR, and serum albumin concentrations (**Table 3**). We further evaluated whether this significant association can be found in each subgroup categorized based on age, gender, body mass index, marital problem, economic status, diabetes, hypertension, eGFR, and depression (**Table 4, Figure 3**).

Table 3. Multiple logistic regression analysis for the association of unemployment condition with reverse dipper

	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Unemployment	1.819 (1.311-2.513)	<0.001	1.763 (1.265-2.445)	0.001	1.577 (1.124-2.202)	0.008
Age	0.997 (0.984-1.011)	0.713	0.995 (0.981-1.009)	0.464	1.003 (0.988-1.018)	0.739
Male	0.820 (0.618-1.088)	0.169	0.948 (0.612-1.453)	0.809	1.000 (0.639-1.550)	1.000
Body mass index	0.974 (0.936-0.998)	0.194	0.969 (0.931-1.001)	0.123	0.978 (0.939-1.001)	0.275
Smoking			0.797 (0.532-1.206)	0.277	0.738 (0.489-1.124)	0.152
Alcohol			1.120 (0.811-1.551)	0.493	1.197 (0.864-1.664)	0.283
Housemate number (> 3)			0.704 (0.353-1.361)	0.305	0.725 (0.360-1.415)	0.353
Marital problem			1.248 (0.782-1.935)	0.337	1.158 (0.720-1.811)	0.531
Low income			1.190 (0.834-1.676)	0.327	1.081 (0.753-1.531)	0.668
Diabetes mellitus			1.250 (0.945-1.655)	0.118	1.240 (0.930-1.653)	0.143
Hypertension			1.175 (0.811-1.746)	0.408	0.967 (0.661-1.447)	0.867
Depression			1.103 (0.703-1.627)	0.632	0.925 (0.605-1.381)	0.711
Cholesterol (per 10 mg/dl)					1.006 (0.973-1.038)	0.699
Phosphate					1.157 (0.962-1.386)	0.117
eGFR (per 10 ml/min/1.73 m^2)					0.900 (0.853-0.949)	<0.001
Serum albumin					0.734 (0.520-1.039)	0.079

Abbreviations: OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate

Table 4. Subgroup analyses for reverse dipper-pattern according to the unemployment status

Subgroups		[a] Model 3; OR (95% CI)	
		Unemployment	P
Age	< 65 years	1.902 (1.147-3.100)	0.011
	≥ 65 years	1.281 (0.798-2.047)	0.302
Sex	Male	1.774 (1.131-2.787)	0.013
	Female	1.019 (0.548-1.812)	0.950
BMI	< 25.0 kg/m^2	1.775 (1.134-2.764)	0.011
	≥ 25.0 kg/m^2	1.329 (0.775-2.243)	0.293
Marital problem	Yes	1.575 (0.739-3.309)	0.232
	No	1.551 (1.055-2.266)	0.024
Low income	Yes	1.086 (0.498-2.331)	0.833
	No	1.734 (1.184-2.526)	0.004
Diabetes mellitus	Yes	1.071 (0.668-1.700)	0.773
	No	2.604 (1.582-4.268)	<0.001
Hypertension	Yes	1.570 (1.087-2.257)	0.015
	No	1.365 (0.518-3.440)	0.517
Depression	Normal to mild	1.565 (1.082-2.252)	0.017
	Moderate to severe	1.595 (0.620-4.054)	0.326
eGFR	eGFR ≥ 60 ml/min/1.73 m^2	1.352 (0.795-2.260)	0.257
	eGFR < 60 ml/min/1.73 m^2	1.727 (1.093-2.723)	0.019

Note: [a] Model 3 was adjusted for age, sex, BMI, smoking and alcohol consumption, housemate, marital problem, economic status, diabetes, hypertension, depression, cholesterol, phosphate, eGFR, and serum albumin

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate

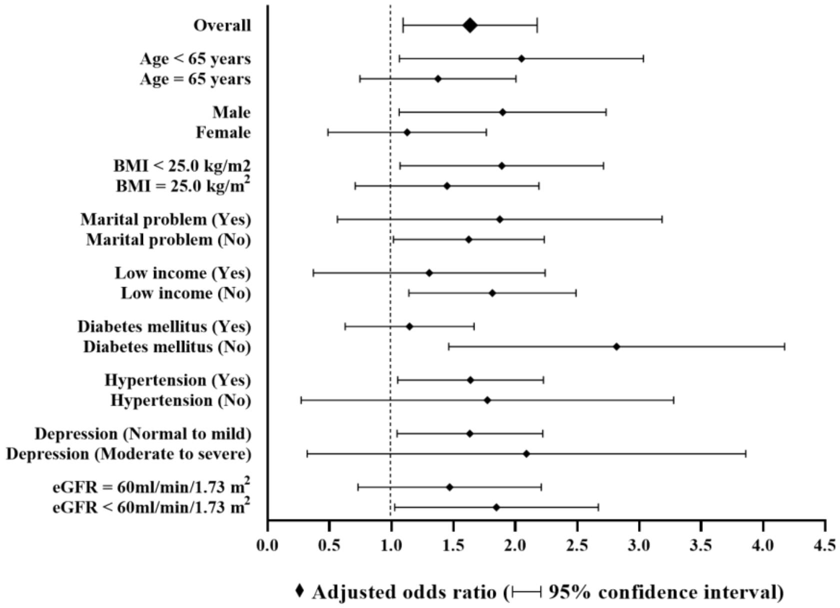

Figure 4. Forest plot displaying the adjusted odds ratio of reverse-dipping patterns in regard to different subgroups. All the data was adjusted for age, sex, BMI, smoking and alcohol consumption, housemate, marital problem, economic status, diabetes, cholesterol, phosphate, eGFR, and serum albumin; cholesterol, per 10 mg/dl; eGFR, per 10 ml/min/1.73 m^2. This plot contains the subgroup analysis data in different groups according to their age, sex, BMI, marital problem, low income, diabetes mellitus, hypertension, depression, and renal function.
Abbreviations: OR, odds ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate

The significant ORs between unemployment and reverse-dipper were only remained valid in the population who were younger (age < 65 years; OR, 1.902; 95% CI, 1.147 – 3.100; P = 0.011), male (OR, 1.774; 95% CI, 1.131 – 2.787; P = 0.013), non-obese (body mass index < 25.0 kg/m^2; OR, 1.775; 95% CI, 1.134 – 2.764; P = 0.011), with no marital problem (OR, 1.551; 95% CI, 1.055 – 2.266; P = 0.024), with normal income level (OR, 1.734; 95% CI, 1.184 – 2.526;

P = 0.004), non-diabetic (OR, 2.604; 95% CI, 1.582 – 4.268; *P* < 0.001), hypertensive (OR, 1.570; 95% CI, 1.087 – 2.257; *P* = 0.015), without depression (OR, 1.565; 95% CI, 1.082 – 2.252; *P* = 0.017), and decreased renal function (OR, 1.727; 95% CI, 1.093 – 2.723; *P* = 0.019).

IV. DISCUSSION

In this study, we investigated how employment status would relate to the various cardiovascular surrogate parameters derived from AOBP, central BP, ABPM, and PWV. We found that the unemployed participants were having more frequent reverse-dipping patterns, higher pulse pressure, and higher PWV than employment group, suggesting higher arterial stiffness in unemployment group. Furthermore, unemployment status was independently associated with the presence of reverse-dipping pattern even after adjustment for demographic variables, biochemical variables, comorbidities, and socio-economic factors. These findings suggest that unemployment status can detrimentally affect the development and progression of CVD by disrupting normal hemodynamic circadian rhythm or autonomic nervous system, which can cause arterial stiffness and higher oxidative stress leading to chronic organ damage.[47,48] To our knowledge, this study is the first to explore the potential mechanisms contributing to work-related health disparities in cardiovascular risks.

Socioeconomic disparities including education, income, and occupational status, have been recognized as the notable factors on cardiovascular events in many industrialized countries. Among them, unemployment has a significant impact on individual's health condition by causing profound mental/emotional stress, limiting their access to health care systems, and inducing unhealthy life style.[49] These relationships between unemployment and the unfavorable clinical outcomes are well-established in multiple studies in the past.[14-22,24-26] Moreover, repeated job loss seems to have more detrimental effect on acute cardiovascular events.[20] However, the plausible explanation on why and how unemployment contributes to cardiovascular health status beyond their association has not been sufficiently studied. Our study shows that unemployment is significantly associated with reverse dipping pattern, wider pulse pressure, and higher PWV, which are the surrogate markers of cardiovascular risks, providing insightful information to understand the mechanism underlying unemployment and cardiovascular disease. With emergence of the 4th industrial revolution and potential substitution of human workforce with technology, further investigations regarding the effects of unemployment on health outcome and its underlying mechanism would be helpful to identify patients at risk of CVD and consider early medical intervention.

Subgroup analysis from our study showed that the stronger association between unemployment and reverse-dipping patterns were only found in the younger, non-obese patients with no history of diabetes, depression, nor any problems in their marriage or income. This analysis provides us interesting insight suggesting that the detrimental cardiovascular effects of unemployment work more independently rather than through other well-known cardiovascular risk factors. This result implies that more careful medical attention is required for unemployed population even without any clinical or socioeconomical risk factors.

24-hour ABPM is widely applied these days for more accurate assessment of BP status in both clinical and research settings.[50] ABPM can provide more benefit over office BP or home BP by recording much larger number of BP readings over 24 hours, which makes it possible to evaluate BP variability.[51] In an individual with normal circadian rhythm, nocturnal BP drops 10-20% compared to daytime due to reduction in sympathetic tone and the increase in vagal activity during the sleep period. A blunted or absent BP drop during nighttime can be caused by multiple factors including autonomic dysfunction, obstructive sleep apnea, kidney disease, severe hypertension or diabetes.[52-54] Reverse dipping pattern is associated with multiple subclinical organ damages including left ventricular hypertrophy, proteinuria, carotid plaques, and arterial stiffness.[55-57] Many studies have also shown that patients with reverse dipping pattern is at risk of higher mortality and cardiovascular events than patients with preserved circadian BP pattern.[58,59] Even though there is yet no strong evidence that restoring normal circadian BP pattern has significant clinical benefit, 24-hr ABPM can be used for early detection of individuals with high risk of cardiovascular disease, including individuals with socioeconomical problems – unemployment, low income, marital problems etc.

Our study has several limitations. First, this data is based on cross-sectional analysis, limiting our potential to interpret the temporal relationship between the employment status and cardiovascular surrogate markers. Even though we assumed the causal relationship of employment status on cardiovascular outcomes based on the multiple previous longitudinal studies, further prospective studies following the changes in employment status with repetitive measurement of cardiovascular surrogates will provide us more useful information regarding the mechanism of employment status on cardiovascular outcome. Second, our cohort study population is limited to South Koreans, which can limit the capacity to extrapolate our finding to people in other socio-economical background, because the influence from unemployment can be fairly different according to their culture, politics, or economic status of the country. However, higher unemployment rate and wage inequalities are now a global issue affecting many peoples' lives. Considering these international processes, our findings may have meaningful point to consider about the potential effect of job status and health outcome, and proper medical attention and intervention in the unemployed group.

V. CONCLUSION

In conclusion, we demonstrate that unemployed individuals have higher rate of reverse-dipping pattern on ABPM and higher PWV compared with employed population, and the association between unemployment and reverse dipping pattern persisted even after adjusting for several demographic/ socioeconomic/biochemical confounders. These findings suggest that previously known association between unemployment and cardiovascular events might be mediated by abnormal diurnal hemodynamics. Further studies to elucidate the underlying mechanisms of unemployment on cardiovascular disease are needed, and subsequent assessment of the beneficial effects of medical interventions to normalize circadian BP patterns on cardiovascular prognosis should be followed.

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ABSTRACT (IN KOREAN)

CMERC-HI 코호트를 이용한 취업이 24시간 주기 혈압 패턴에 미치는 영향 분석

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이 슬 아

심혈관 질환은 일반 인구 내에 상대적으로 흔한 질환으로, 특히 60 대 이상의 노인층에서 흔히 진단된다. 심혈관 질환의 발생에 영향을 미치는 위험 요소들을 잘 관리하는 것은 그로 인한 추가 합병증을 예방하는데 있어 굉장히 중요하다. 최근 개인의 사회심리 상태가 심혈관 질환의 발달과 진행에 상당한 영향을 미치는 것으로 알려져 주목을 받고 있다. 취업 유무는 개인의 사회 심리 상태에 중대한 영향을 미치는 요인으로서, 최근 연구들에 따르면 무직 상태가 심혈관 질환 및 그 합병증 발생 여부에 악영향을 미치는 것으로 보인다. 하지만 취업 상태가 어떤 기전을 통해 심혈관 질환의 발생 및 진행에 영향을 미치는지에 대해서는 현재까지 연구된 바가 없다. 이에 본 연구는 뇌심혈관 질환 고위험군 대상자에 특화된 코호트를 이용하여 (CMERC-HI) 취업 여부가 진료실 측정 혈압, 24 시간 혈압, 중심동맥혈압, 맥파 속도 등 다양한 방법으로 측정된 심혈관계 생체 표시자와 어떤 상관 관계를 갖는지 분석하였다. 총 1,915 명의 코호트 대상 중 449 명 (23.5%)의 환자가 무직인 상태였으며 1,466 명 (76.5%)은 취업 상태였다. 무직 군은 취업군에 비해 야간 혈압이 주간 혈압보다 올라간 환자군 (reverse dipper)이 상대적으로 많았다 [81

(18.0%) vs. 167 (11.4%), $P < 0.001$]. 다항 로지스틱 회귀 분석에 따르면 다양한 교란 변수를 보정한 이후에도 무직 여부와 reverse dipper의 빈도는 유의미한 연관성을 보여주었다 (Odds ratio, 1.577; 95% CI, 1.124 – 2.202; $P = 0.008$). 따라서, 본 연구는 무직 상태가 혈역학적 생체주기에 지장을 미침으로써 심혈관계에 악영향을 미칠 수 있음을 시사하였다.

핵심되는 말 : 취업 상태, 무직, 역강하, 24 시간 혈압 측정 검사, 심혈관 질환

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