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Long-term changes of blood pressure before cardiovascular mortality: A nested case-control study

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ABSTRACT

Background : Although many epidemiologic studies have assessed the association between changes of the blood pressure and cardiovascular disease (CVD), any information on the long-term blood pressure change before cardiovascular mortality, with performing repeated blood pressure measurements, is limited in Korea. The aim of this study was to investigate the association between the long-term changes of the blood pressure and the cardiovascular mortality of Korean adults. **Methods :** We performed a nested case-control study in the Korea Medical Insurance Corporation Study cohort. From 1990, we measured the blood pressure and major CVD risk factors every two years in 108,461 men and 64,119 women who were aged from 35 to 59 years. The causes and dates of death were obtained from the National Statistical Office of Korea. The cases consisted of 1,636 people who died from CVD between 1993 and 2004 and the controls were 3,272 survivors at the time of sampling. We sampled two controls per case using incidence-density sampling and matching for gender and age. **Results :** The people who died from CVD had higher blood pressure than did their controls. These differences were statistically significant from 14 years before death ($p<0.001$ for all examinations). During the 14 years, the systolic blood pressure significantly increased in the people who died from CVD ($p<0.001$) but not in their controls ($p=0.811$). The annual increase in systolic blood pressure among the cases was 0.60 mmHg 0-7 years before death and 0.22 mmHg 8-14 years before death. The diastolic blood pressure did not significantly increase in either the cases or in controls. **Conclusion :** These results support that both the long-term blood pressure history and recent increases in blood pressure are associated with the risk of cardiovascular mortality. **(Korean Hypertension J 2008;14(1):9-16)**

Key Words : Blood pressure changes, Cardiovascular disease, Long-term follow up, Cardiovascular mortality

INTRODUCTION

High blood pressure is the most important, treatable risk factor for cardiovascaulr disease (CVD).[1-5] Uncontrolled hypertension increases the risk of CVD and many clinical trials have shown that lowering the blood pressure through pharmacological or non-pharmacological intervention can decrease these patients' cardiovascular morbidity and mortality.[6-10] Most epidemiological studies have estimated the relationship between a single measurement of blood pressure and the development of cardiovascular events. However, performing repeated measurements of the risk factors for CVD has important advantages in epidemiological studies. On the one hand, repeated measurements of the blood pressure within short time intervals is likely to provide better classification of the individuals by reducing the intraindividual variations and the measurement errors of the blood pressure.[11,12] On the other hand, repeated measurements over longer intervals can provide more information about the duration of exposure to high blood pressure and about the changes of blood pressure. It has

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been reported that a change of the risk factora is associated with changes in the risk of incurring coronary heart disease.[13,14] The epidemiological data has suggested that an individual's blood pressure history can add increments to predicting the future cardiovascular morbidity and mortality, yet there is limited information on the long-term blood pressure changes, as determined by repeated blood pressure measurements, before these patients incur cardiovascular mortality.[15,16] There have not been any Korean studies concerned with the relationship of repeated measurements of blood pressure, with long-term follow up, and the cardiovascular mortality. The aim of this study was to investigate the association between the long-term changes of the blood pressure and the cardiovascular mortality of Korean adults.

METHODS

Cohort design and data collection

We performed a nested, case-control study in the Korea Medical Insurance Corporation Study cohort and the detailed methods of the KMIC Study have been previously reported.[17] The KMIC provided health insurance to the government and private school employees and their dependents until 1998, and later it merged with the National Health Insurance Corporation. In 1990, the corporation insured 1,213,594 workers and 3,389,767 dependents, which is about 11% of the total Korean population. The corporation required all insured employees to undergo a biannual physical examination, and 95% and 94% of the employees completed the examinations in 1990 and 1992, respectively. The KMIC Study cohort consisted of 108,461 men (a 25% random sample) and 64,119 women (a 100% sample) who were aged from 35 to 59 years in 1990 and who underwent health examinations. Major cardiovascular risk factors, including blood pressure, total serum cholesterol, fasting blood glucose and cigarette smoking, were repeatedly measured every two years until the year 2000. A registered nurse or blood pressure technician measured the blood pressures with using a standard mercury sphygmomanometer or automatic manometer when the subject was seated. If they were using manual manometers, they measured the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) as the first and fifth Korotkoff sounds, respectively.

Identification of cases and controls

We identified all deaths from January 1, 1993 to December 31, 2004 with computerized searches of the death certificate data from the National Statistical Office for each KMIC cohort member. We classified the causes of death according to the International Classification of Diseases, 10th revision. The cases included 1,636 people who died from disease of the circulatory system (ICD codes I00-I99) during the follow-up period. We sampled two controls per case with using incidence-density sampling. The controls were randomly sampled among the cohort members who were alive at the time that their matched cases died. The matched variables were gender and age, and the age difference between the cases and controls was less than six months.

Data analysis

We compared the characteristics noted at the baseline examination between the cases and controls with using Student's t-tests and χ^2-tests. The subjects' blood pressure could be measured one to six times for each case or control because the BP was repeatedly measured in the biannual physical examinations from 1990 to 2000. We defined an index year for the cases as the calendar year when they died and that for the controls as the calendar year when their matched cases died. The time of measuring the blood pressure was calculated as follows: Measuring time = index year − the calendar year of the health examination. For each case and control, their blood pressure was rearranged according to two-year intervals: 0-1, 2-3, 4-5, 6-7, 8-9, 10-11, 12-13 and 14 years before the index year. The blood pressure levels, according to the by different measuring times, were compared between the cases and controls using independent t-tests and paired t-tests. We calculated an annual increase of the SBP and the DBP according to the different periods: less than 7 years from death (the recent 7 years) and 8 to 14 years from death (the remote 7 years). In order to compare the blood pressure increases of the cases and controls, we performed repeated measurement analyses using Proc Mixed in SAS 9.1 (SAS Institute; Cary, NC, USA).

Table 1. Baseline Characteristics of the KMIC Cohort

Variables	Men (n=108,461)	Women (n=64,119)
Mean ± SD		
Age (year)	45.0 ± 6.7	42.5 ± 6.2
Body mass index (kg/m^2)	23.5 ± 2.4	22.3 ± 2.5
Systolic blood pressure (mmHg)	125.5 ± 14.2	116.5 ± 12.9
Diastolic blood pressure (mmHg)	82.1 ± 9.6	75.7 ± 9.1
Total cholesterol (mg/dL)	194.2 ± 33.2	189.5 ± 32.7
Fasting serum glucose (mg/dL)	93.5 ± 21.8	86.6 ± 13.7
Number (%)		
Hypertension (≥140/90 mmHg)	30,213 (27.9)	6,976 (10.9)
High total cholesterol (≥240 mg/dL)	9,371 (8.6)	4,598 (7.2)
High fasting glucose (≥126 mg/dL)	4,960 (4.6)	833 (1.3)
Cigarette smoking*		
Non-smoker	22,119 (21.2)	52,034 (99.1)
Past smoker	22,206 (21.3)	238 (0.5)
Current smoker	59,966 (57.5)	212 (0.4)
Alcohol consumption*		
Non-drinker	26,103 (24.8)	50,912 (89.3)
<50 g/day	69,289 (65.8)	4,939 (8.7)
≥50 g/day	9,900 (9.4)	1,177 (2.1)

*Baseline characteristics are the average of the examinations performed between 1990 and 1992, except for smoking and alcohol consumption, which were measured only in 1992.
KMIC: Korea Medical Insurance Corporation.

RESULTS

Table 1 shows the baseline characteristics of the KMIC cohort. The mean age was 45.0 years for the men and 42.5 years for the women and the mean body mass index was 23.5 kg/m^2 for the men and 22.3 kg/m^2 for the women. The mean SBP was 125.5 mmHg for the men and 116.5mmHg for the women and the mean DBP was 82.1 mmHg for the men and 75.7 mmHg for the women. The proportion of current smokers was approximately 58% for the men and 1% for the women. About 75% of the men and 11 % of the women were regular alcohol drinkers.

From 1993 through 2004, 8,756 deaths occurred among the KMIC cohort. Cancer was the most common cause of death (46.4%) and CVD was the second most common cause (18.7%) (Table 2).

Table 3 shows the characteristics of the cases and controls at the baseline examination. The cases and controls were matched for gender and age. At the baseline examination, the blood pressure and the total serum cholesterol and fasting blood glucose levels were higher in the cases than in the controls. Current smokers were more common in the cases than in the controls.

Table 4 shows the blood pressure distribution of the

Table 2. Deaths among the KMIC Cohort, 1993-2004

Cause of Death	Men	Women	Total
Cancer	3,366 (44.8)	692 (56.0)	4,058 (46.4)
Cardiovascular disease	1,416 (18.8)	220 (17.8)	1,636 (18.7)
Ischemic heart diseases	416 (29.4)	48 (21.8)	464 (28.4)
Cerebrovascular diseases	729 (51.5)	120 (54.5)	849 (51.9)
Other cardiovascular diseases	271 (19.1)	52 (23.6)	323 (19.7)
External causes	1,015 (13.5)	137 (11.1)	1,152 (13.2)
Digestive tract	666 (8.9)	50 (4.1)	716 (8.2)
Metabolic disorders	299 (4.0)	41 (3.3)	340 (3.9)
Respiratory tract	207 (2.8)	18 (1.5)	225 (2.6)
Infectious diseases	121 (1.6)	19 (1.5)	140 (1.6)
Others	431 (5.7)	58 (4.7)	489 (5.6)
Total	7,521 (100)	1,235 (100)	8,756 (100)

KMIC: Korea Medical Insurance Corporation.

Table 3. Characteristics of the Cases and Controls

Variables	Cases (n=1,636)	Controls (n=3,272)	*p*-value
Matched variables			
Gender (male)	1,416 (86.6%)	2,832 (86.6%)	1.000
Age at baseline (years)	49.5 ± 6.2	49.5 ± 6.2	0.987
Age at death (sampling, years)	58.9 ± 7.1	58.9 ± 7.1	1.000
Baseline characteristics			
Body mass index (kg/m^2)	23.6 ± 2.6	23.5 ± 2.4	0.053
Systolic blood pressure (mmHg)	137.4 ± 20.3	127.0 ± 15.7	<.001
Diastolic blood pressure (mmHg)	89.2 ± 13.1	82.8 ± 10.2	<.001
Total cholesterol (mg/dL)	202.3 ± 41.9	197.3 ± 33.8	<.001
Fasting serum glucose (mg/dL)	102.7 ± 37.1	94.5 ± 22.9	<.001
Cigarette smoking*			
Non-smoker	385 (25.4%)	954 (31.3%)	<.001
Past smoker	209 (13.8%)	651 (21.4%)	
Current smoker	920 (60.8%)	1,444 (47.4%)	
Alcohol consumption*			
Non-drinker	541 (34.9%)	1,111 (35.5%)	0.081
<50 g/day	869 (56.1%)	1,797 (57.4%)	
≥50 g/day	138 (8.9%)	221 (7.1%)	

*Baseline characteristics are the average of the examinations performed between 1990 and 1992 except for smoking and alcohol consumption, which were measured only in 1992.

Table 4. Blood Pressure of the Cases and Controls according to the Different Measuring Time Unit: mmHg

Measuring Time* (from case's death)	Cases	Controls	Difference (95% CI) †
Systolic blood pressure			
0-1 years	144.3 ± 26.4	129.5 ± 19.1	16.7 (11.8-21.6)
2-3 years	139.9 ± 23.6	127.4 ± 17.7	12.2 (10.5-14.0)
4-5 years	138.4 ± 21.8	126.9 ± 17.4	11.5 (10.3-12.8)
6-7 years	138.2 ± 22.2	126.9 ± 17.1	11.0 (9.7-12.2)
8-9 years	137.3 ± 21.6	127.3 ± 17.0	9.6 (8.4-10.8)
10-11 years	137.7 ± 22.6	126.6 ± 16.5	11.1 (9.9-12.4)
12-13 years	136.2 ± 22.9	127.2 ± 17.2	9.0 (7.5-10.4)
14 years	136.4 ± 21.4	127.8 ± 17.1	8.5 (6.6-10.5)
Diastolic blood pressure			
0-1 years	91.7 ± 16.9	83.3 ± 12.4	9.5 (6.5-12.6)
2-3 years	89.5 ± 15.4	82.2 ± 11.8	7.4 (6.3-8.5)
4-5 years	88.2 ± 13.8	82.5 ± 11.9	6.0 (5.2-6.9)
6-7 years	88.7 ± 13.9	82.5 ± 11.6	6.2 (5.4-7.0)
8-9 years	88.8 ± 13.8	83.0 ± 11.6	5.7 (4.9-6.5)
10-11 years	89.1 ± 14.6	82.6 ± 11.1	6.5 (5.7-7.4)
12-13 years	88.4 ± 15.2	83.0 ± 11.7	5.4 (4.4-6.4)
14 years	89.3 ± 14.6	83.1 ± 11.3	6.2 (4.9-7.5)

*Calendar year of the case's death- the calendar year of the blood pressure measurement.
†All the differences are statistically significant ($p<0.001$) on both independent t-tests and paired t-tests.

cases and controls according to the measurement time. The SBP and DBP in cases were significantly higher than those of the controls for all the measurements on both independent t-tests and paired t-tests. Among those cases who died from CVD, the mean SBP significantly increased from 136.4 mmHg (as measured 14 years before death) to 144.3 mmHg (as measured within 2 years from death, $p<0.001$), but among their gender and age-matched controls, the mean SBP increased from 127.8 mmHg to 129.5 mmHg ($p=0.811$). The diastolic blood pressure did not significantly change in either the cases ($p=0.811$) or in their controls ($p=0.065$).

We analyzed the change of blood pressureof the two different periods (the recent 7 years and the remote 7 years). The SBP of the cases increased by 0.22 mmHg per year during the remote 7 years ($p=0.260$) and by 0.60 mmHg per year during the recent 7 years ($p=0.012$). However, the SBP of the controls did not increase during

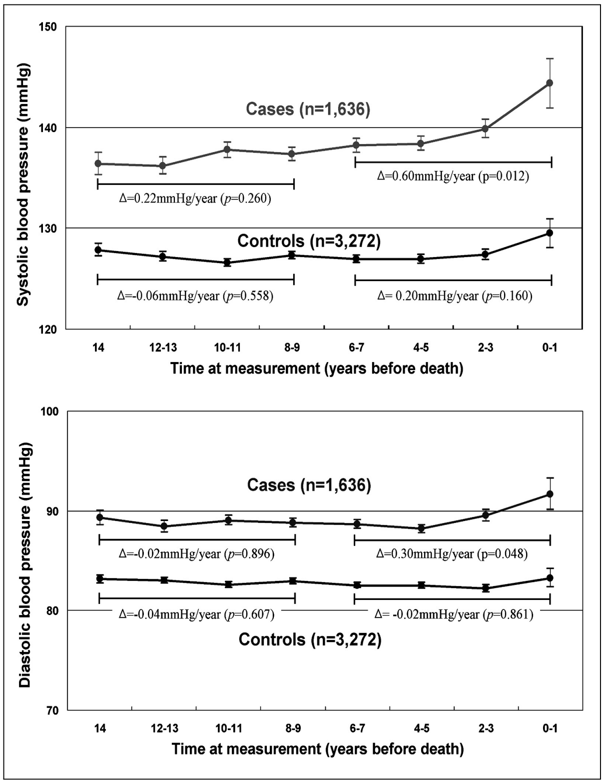

Fig. 1. Changes of the blood pressure before cardiovascular mortality.
The data is expressed as means (solid circles) and standard errors (vertical lines).

the same periods (p=0.558 and 0.160, respectively). The DBP increased only in the cases during the recent 7 years (0.30 mmHg per year, p=0.048) (Fig. 1).

DISCUSSION

In this nested case-control study, cardiovascular mortality was positively associated with both the past blood pressure levels and the recent increases in blood pressure. High blood pressure is an important cardiovascular risk factor and it has been associated with cardiovascular mortality.[1-5] The previous studies suggested that the past blood pressure history was also an independent predictor of the future risk for CVD.[15,16] In order to divide the effects of the absolute level and long-term changes of the blood pressure on cardiovascular mortality, the blood pressure should be repeatedly measured in cohort studies. With performing repeated measurements of blood pressure over 14 years and by conducting a nested case-control analysis, we compared the absolute level and changes of the blood pressure between those cases who died from CVD and their age and gender-matched controls. Our results suggested that both the long-term blood pressure history and a recent increase in blood pressure are associated with the risk of cardiovascular mortality.

The previous cohort studies reported that blood pressure change was an independent predictor of cardiovascular mortality.[18-22] Those studies mostly measured the change of blood pressure over the first several years and the outcome events were observed during the subsequent follow-up period. In order to assess the independent effects of the change of blood pressure, the previous studies controlled for the initial blood pressure level. We can expect a positive association between blood pressure and cardiovascular mortality with this approach because the changes of blood pressure determine the subsequent blood pressure, which affects the risk of incurring CVD. Other studies have used different approaches that examined the previous blood pressure change depending on the final attained blood pressure.[23,24] The second approach can assess the effects of past changes of the blood pressure on the cardiovascular mortality at a given level of blood pressure. Hofman reported that the increase of blood pressure predicts cardiovascular disease depending on the initial level of blood pressure, but this didn't depend on the final attained level.[19] The Seven Countries Study showed that increases in systolic blood pressure during the first 10 years of follow up were associated with increased cardiovascular and stroke mortality in the subsequent 10 or 25 years of follow up.[25,26] Witteman reported that a decline of the diastolic blood pressure indicates stiffening of the vessel wall, which is associated with the progression of atherosclerosis.[27] These various results of the previous studies and the wide range of relative risks in relation to incurring CVD may be the result of different study populations, outcome measurements and analytic approaches. The length of the baseline period, in which blood pressure change was measured, varied from 2 to 12 years and the follow-up period, which varied from 5 to 25 years, also contributed to the various findings in the previous studies.[19,23,25-28] Earlier increases of the blood pressure can prolong an individual's exposure to high blood pressure. More recent increases in blood pressure may accelerate the vascular wall stress.[29] According to our data, the people who died from CVD experienced significant increases of their SBP and DBP while their controls did not. This increase was confined to a few years before their deaths. Our data also showed that people who died from CVD had significantly higher SBPs and DBPs than did their their controls for a long period (at least 14 years before death). Our findings support that long-term exposure to high blood pressure and a recent increase in blood pressure may independently contribute to fatal cardiovascular events.

This study has several important strengths. First, the blood pressure levels were repeatedly measured for a long period before death. The biannual physical examinations measured the major cardiovascular risk factors, including blood pressure, independently from the outcome events. Thus, we could observe the absolute level and long-term changes of blood pressure before the cases death from CVD. Second, we used a nested case-control analysis within a large, established cohort. We had a large number of cases and controls that were well matched for their gender and age. With this approach, we could compare the blood pressure levels between people who died from CVD and their gender and age-matched controls. Third, the results of our study can be generalized to the Korean population as the KMIC Study cohort was recruited from across the Korean nation. To assess the generalizability of our results to the entire Korean population, we compared the characteristics of our subjects with the corresponding data from the 1998 Korean National Health and Nutrition Examination Survey. The populations were similar for several important health indices such as blood pressure, total cholesterol, the body mass index, the smoking status and alcohol intake.[30,31)]

This study also has several potential limitations. First, we had no objective information on the medical history of the study population. Various health behavior and various medications may have contributed to the changes of blood pressure, but we could not identify the subjects who were taking blood pressure-lowering drugs. Second, the blood pressure measurement was not well standardized because the health examinations were performed at hundreds of hospitals nationwide; thus, the blood pressure levels in this study were vulnerable to intraobserver and interobserver error. The misclassification bias, if any, is likely to be due to non-differential reduction of the association, and so it is unlikely the results were distorted by measurement error. Finally, cardiovascular mortality is subject to misclassification on death certificates. The limitations of the death certificate data have been characterized in several previous Korean studies.[32,33)] Chung and colleagues recently assessed the accuracy of the registered causes of death in a small county in Korea and they reported that the accuracy of death certificates was 76.6% for CVD in 1998.[34)] However, the accuracy in our study is likely to be much higher because the accuracy was higher for the younger, well-educated and employed deceased subjects in urban areas in Chung's study.[34)] The proportion of death certificates issued by physicians was also markedly increased from 53.9% in 1993 to 77.6% in 2002.[35,36)]

In conclusion, those people who die from CVD tend to have relatively higher blood pressure at least 14 years before death and they experience increases of their blood pressure for several years before their death. These findings also reaffirm the importance of repeated measurements of blood pressure and active blood pressure control to help prevent cardiovascular mortality.

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