

Effects of Moderate Strength Cold Air Activity on Hypertensive Patients

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Abstract: Objective: The mechanism underlying the effects of cold air on hypertensive disorders was investigated in an experimental study examining blood pressure and biochemical indicators. **Methods:** Zhangye, a city in Gansu Province, China, was selected as the experimental site. Health screening and blood tests were conducted, and 30 cardiovascular disease patients and 30 healthy subjects were recruited. The experiment was performed during a cold event during April 26–April 29, 2013. Blood pressure, norepinephrine (NE), epinephrine (E) and angiotensin II (ANG-II) levels of the 60 subjects were evaluated 24 h before cold air activity (April 26, morning), during cold air activity (at minimum temperature, between 7:00 and 8:00 on April 28), and 24 h after cold air activity (morning of April 29). The change before, during, and after the cold air activity were analyzed. **Results:** Cold air exposure can cause significant metabolism and secretion of norepinephrine (NE), epinephrine (E) and angiotensin II (ANG-II) in subjects; take the patient group as an example, NE, E, ANG II and systolic blood pressure was 306.86, 78.65, 34.2ng/L and 136.3mmHg, respectively, during the cold air exposure, respectively increased by 148.13, 1.34, 39.1ng/L and 11.6mmHg, compared with that before the cold air exposure. Furthermore, the mean value of NE, E, ANG II and the systolic blood pressure was still maintained at a high level one hour after the end of the cold air exposure, which was 363.39, 81.3, 67.3ng/L and 131.7mmHg respectively, increased by 204.66, 3.99, 26.1ng/L and 7.1mmHg, respectively, compared with before the cold air exposure. The impact of cold air exposure on the change of blood pressure was shown in both cardiovascular patients and healthy people, and the

effect on the cardiovascular patients lasted longer. **Conclusions:** Cold air exposure increases blood pressure in cardiovascular disease patients and healthy subjects via the sympathetic nervous system (SNS) that is activated first and which augments ANG-II levels accelerating the release of the norepinephrine and stimulates the renin-angiotensin system (RAS). The combined effect of these factors leads to a rise in blood pressure. This paper discusses preliminarily the possible mechanism for increasing in human blood pressure leaded by cold air.

Keywords: cold air; NE; ANG–II; Hypertension disorders; mechanism

1 Introduction

With the worldwide concern and study of cardiovascular disease caused by low temperatures, cold air activity has been acknowledged as an important weather risk factor, which affects the increase in morbidity and mortality of cardiovascular disease¹⁻¹¹. A study by the World Health Organization showed that incidence of hypertensive disorders and related cardiovascular diseases in colder northern China is significantly higher than that in warmer southern China¹². Cold weather can aggravate hypertension disease, and increase the incidence of hypertension associated cardiovascular diseases such as stroke and myocardial infarction¹³⁻¹⁵. Cold air stimulation can result in blood pressure increase; the mechanism of impact has been previously studied in animal experiments¹⁶⁻¹⁸. We wanted to determine whether a similar mechanism was present in cardiovascular disease patients. In this paper, cold air of moderate intensity in Zhangye City of Gansu Province was used as the experimental example to study. Zhangye City in Gansu Province, northern China, has a complex climate, changeable weather, and large temperature differences. It is the choke point through which cold air from China's northwest must pass to the southeast. Each year approximately 95% of the cold air affecting China passes through Gansu Province. Adverse weather conditions have a strong impact on the local residents' lives and health, especially cardiovascular disease patients.

In our studies, the effects of moderate-intensity cold air observed in April 2013 in cardiovascular and cerebrovascular disease patients was evaluated based on a previous studies in healthy and hypertensive rats. Blood pressure, NE, AD and angiotensin II (ANG-II) levels of both cardiovascular disease patients and healthy subjects were measured before, during, and after

cold air activity with the aim of investigating the effects on cardiovascular and cerebrovascular diseases induced by changes in catecholamine.

2 Experimental Section

2.1 Study Site

Zhangye City, Gansu Province was chosen as the study site. Zhangye is a city in northwestern China with no chemical pollution. Air quality meets the set ambient air standards; there is good air cleanliness, highly variable weather, and large temperature variations. Cold air flowing to the south must pass through this location.

2.2 Study Subjects

A random cluster sampling method was used, and the Zhangye City People's Hospital was selected as a monitoring point. Health records of residents living within 1000 m of the monitoring point and between the ages of 40 and 70 years were examined, and cardiovascular and cerebrovascular disease patients without organic disease were selected according to health screening and blood tests.

Before the on-site study, 30 cardiovascular disease patients (15 males and 15 females) with an average age of 59 years, none with alcohol addiction, and none having taken medication for at least 3 days, were selected to form the patient group. Eligible patients included six cases of cerebral thrombosis, two cases of cerebral hemorrhage, 12 cases of coronary heart disease, and 10 cases of hypertension. At the same time, 30 healthy subjects (15 males and 15 females) chosen on the same inclusion criteria with an average age of 55 years were selected to form the control group. The difference in sex and age composition between the patient and control groups was not statistically significant ($P > 0.05$). The study was reviewed and approved by the Medical Ethics Committee of Zhangye City People's Hospital before the experiment began. All the volunteers provided their written informed consent to participate in this experiment. This consent procedure was approved by the Medical Ethics Committee of Zhangye City People's Hospital and all the written informed consent was archived by the Committee.

2.3 Data Acquisition

Questionnaire: In the period of April 26–April 29, 2013, a questionnaire survey was administered to the study groups. The questionnaire included questions on physical condition, diet, medication, activities, etc. in the preceding 4 days. The purpose of the questionnaire was to rule out confounding factors and ensure the same exposure history between the patient and control groups.

Determination: The measurement indicators were blood pressure, NE, E and ANG-II levels.

Sample collection: Samples of 5 ml fasting venous blood were collected from each volunteer 24 h before cold air activity (April 26, morning), during cold air activity (at minimum temperature, between 7:00 and 8:00 on April 28), and 24 h after cold air activity (morning of April 29). Samples were collected in vacuum blood collection tubes without anticoagulant. After centrifugation at 3000 rpm, the serum was frozen at -80 °C.

Determination: The enzyme-linked immunosorbent assay (ELISA) double antibody sandwich method was used to determine catecholamine level. The steps were as follows: (1) a microtiter plate was coated with purified antibody to make a solid-phase antibody; (2) a test sample and the enzyme reagent were added to form an antibody–antigen–enzyme–antibody complex; (3) a chromogenic agent was added after washing; (4) the absorbance was measured at 450 nm; and (5) the concentration of the test sample was calculated.

The ELISA kit was produced by an American R&D Company and packaged by Xi'an Kehao Biological Engineering Co., Ltd., and the microplate reader was produced by the Austrian Tecan Company. Detection was performed by the Medical Research Center, Lanzhou University.

Meteorological data: The crowd experimental study in Zhangye City, Gansu Province was conducted on April 26–April 28, 2013 during the onset of cold air. Cold air data including temperature, pressure, and other hourly monitoring data were provided by the Lanzhou Central Meteorological Observatory. Cold air activity was determined according to China's Cold Air Level National Standard (GB/T20484-2006) developed by the Central Meteorological Observatory in 2006¹⁹.

2.4 Statistical Methods

SPSS13.0 software was used for statistical analysis of data. The chi-square test was used to compare the sex and age composition of the patient and control groups. A randomized block design two-factor variance analysis was used for different times, groups, and gender rheology data; the Mann-Whitney U test for comparing two independent samples was used to compare the case and control groups; the multiple-related-sample Kendall's W test was used to compare the indicators before, during, and after cold air activity; and Wilcoxon two-related sample tests were used to compare the two groups. These test standards were based on $\alpha = 0.05$.

3 Results

3.1 Analysis of changes in cold air

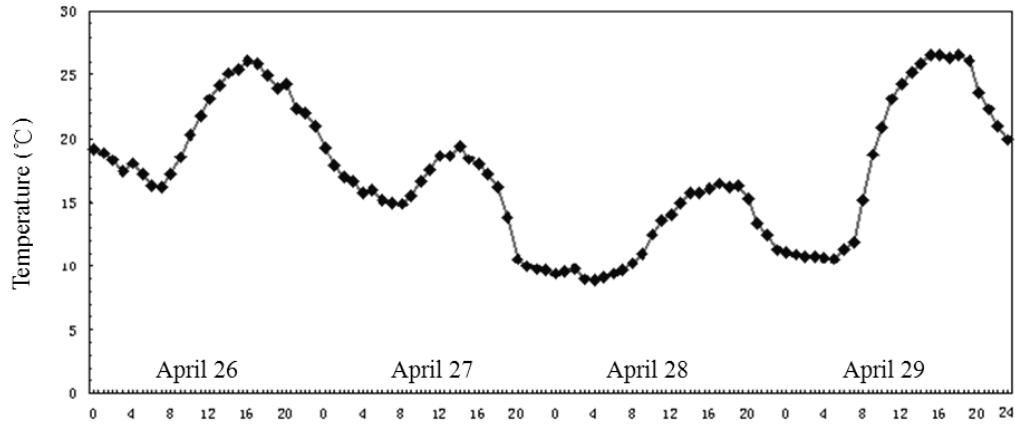


Fig. 1 Temperature chart for Zhangye City, April 26–April 29, 2013.

Figure 1 showed that in Zhangye City, the minimum temperature on April 26, 2013 was 16.2 °C and that on April 28 it was 8.8 °C. Thus, the minimum temperature dropped by 7.4 °C in 48 h. China's national cold air level standards (GB/T20484-2006)¹⁹ confirms that cold air showing a daily minimum temperature drop greater than or equal to 6 °C but less than 8 °C is moderate strength cold air.

3.2 Analysis of NE and E detection

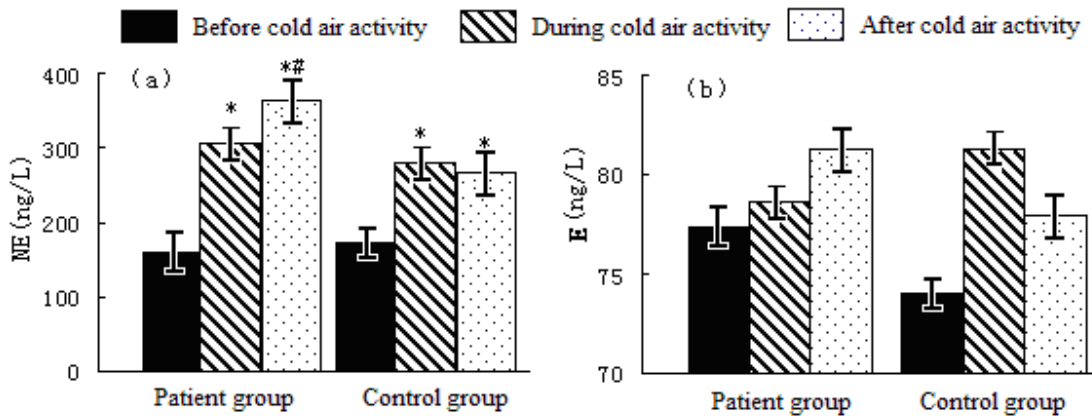


Fig. 2 The trend of average NE (a) and E (b) levels during a cold air event. *compared with the indicators before the cold air activity, $P < 0.05$; #comparison with the indicators during the cold air activity, $P < 0.05$.

As shown in Figure 2, when comparing before, during, and after cold air activity groups, the smaller change was in E levels, and the change in NE levels was bigger, with both NE and E showing a growth trend. During the cold air activity, E and NE levels in the control group showed varying degrees of elevation relative to the time before cold air activity. E and NE levels

in the during cold air activity patient group were elevated compared to levels before cold air activity, but neither showed a significant difference ($P > 0.05$). After the cold air activity, E levels dropped but were higher than the levels before cold activity, and NE levels dropped to levels lower than those during cold activity but still higher than those before cold activity. Both indicators showed significant differences when compared to before cold air activity groups ($P < 0.05$). NE levels continued to rise and were significantly different compared with those before cold air activity ($P < 0.05$). When comparing the indicators during and after cold air activity, NE levels in the patient group were significantly different ($P < 0.05$).

3.3 Analysis of ANG-II test results

As shown in Figure 3, ANG-II levels in both the patient and control groups before, during, and after cold air activity increased compared with levels before the cold air activity. ANG-II elevated by 39.1 ng/L and 46.7 ng/L during the cold air activity in the patient and control groups, respectively; the difference was significant ($P < 0.001$). ANG-II levels in both the patient and control groups dropped significantly ($P < 0.005$). To the levels lower than those observed during cold air activity but they were still higher than those before cold air activity (26.1 ng/L and 34.7 ng/L higher, respectively). There were no significant changes to ANG-II levels during the same cold air activity periods in both the patient and control groups ($P > 0.05$).

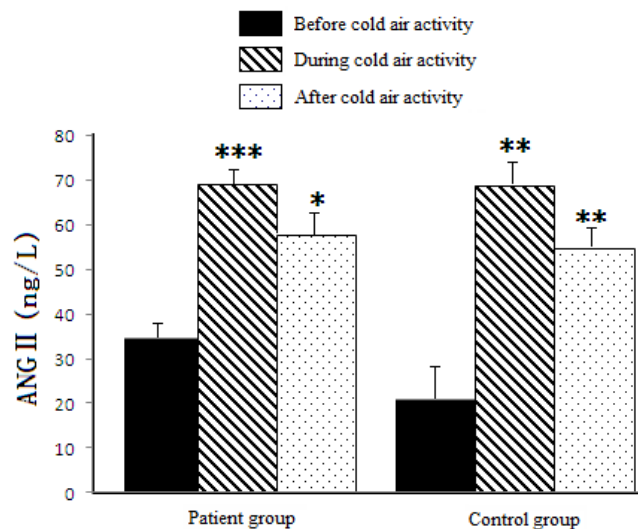


Fig. 3 Average ANG-II levels in the patient and control groups during a cold air event. ***compared with the indicators before the cold air activity, $P < 0.001$; **compared with the indicators before the cold air activity, $P < 0.001$; *compared with the indicators before the cold air activity, $P < 0.005$.

3.4 Analysis of blood pressure test results

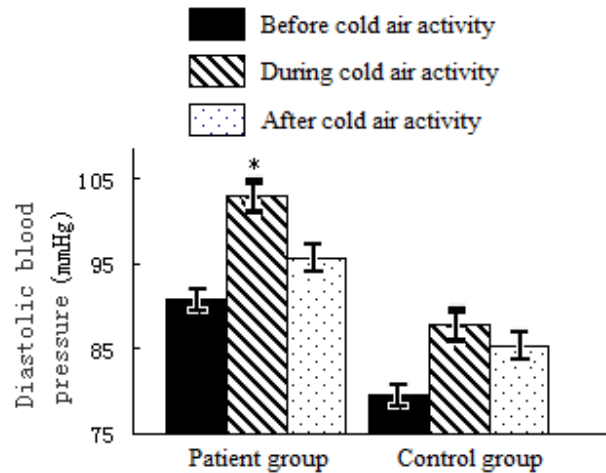


Fig. 4 Average diastolic blood pressure levels in the patient and control groups during a cold air event. *compared with the indicators before the cold air activity, $P < 0.05$

As shown in Figure 4, diastolic blood pressure levels in both the patient and control groups increased during and after the cold air activity compared with those before the cold air activity. Diastolic blood pressure levels reached the maximum value during cold air activity. After cold air activity, it dropped to levels lower than those during cold air activity but still higher than those before cold air activity. Diastolic blood pressure levels after cold air activity in the patient group significantly changed compared to the before cold air activity group ($P < 0.05$); there was no significant difference in the control group ($P > 0.05$). There was a significant difference in diastolic blood pressure levels during the same period of cold air activity between patient and control groups ($P > 0.05$). These results show that the cold air activity significantly influences both the health of cardiovascular and cerebrovascular patients.

4 Discussion

To study the effect of moderately cold air on blood pressure, we examined blood E, NE, and ANG-II plasma concentration levels in both patient and control groups. NE concentration in plasma showed a trend; in the patient group, the concentration was high during and after cold air activity. After cold air activity, blood pressure decreased slightly, but remained at a high level. However, in the control group, it was high during cold air activity and recovered soon after the cold air activity. Blood pressure in the control group recovered faster than in the patient group, which also indicates that the effects of cold air on blood pressure in the patient group were longer lasting than in the healthy control group.

Elevated NE and ANG-II plasma concentrations suggest that the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) were activated, respectively. Activation of these two systems will inevitably lead to elevated blood pressure. NE and ANG-II are vasoconstrictors thus they narrow the blood vessel. The combination of NE and adrenergic α receptors causes extensive vascular contraction. In vascular smooth muscle, ANG-II induces systemic arterial contraction. The effect of these two substances likely caused systemic vasoconstriction, thereby elevating the blood pressure. Many studies have fully demonstrated that an increase in blood pressure following cold air stimulation is caused by activation of the SNS and RAS²⁰⁻²¹. Cold air stimulation in this study differed from previous studies, in this study, temperature dropped gradually, which in itself was a stimulation and this also led to NE and ANG-II increases in plasma. Therefore, we concluded that the cold air that lead to a rise in blood pressure also excited the SNS and the RAS. In addition, we found that E plasma concentration which has a strong effect on the SNS did not change significantly before, during, and after cold air activity. Scriven *et al.* also found that NE increased in subject groups, and E did not change significantly after cold stimulation for 30 min at 4 °C²². In our experiment, we also showed that NE levels increased in plasma, and there was no significant change in E levels. This means that the NE in the plasma was not secreted by the adrenal medulla, but by other factors. Blood NE can also be released from adrenal glands and nerve endings, in addition to the adrenal medulla; ANG-II can be released from the adrenal glands and nerve endings as well²³. Therefore, the increase in NE we demonstrated with the cold air activity was due to an increase in ANG-II. As mentioned above, cold air activity led to an increase in blood pressure in both the patient and control groups. This was mainly due to activation of the RAS, which caused ANG-II increase and NE release, and excited the SNS. A combination of these two systems causes blood pressure to rise.

Based on our results, we can draw the following conclusions: (1) Considering the influence of cold air on cardiovascular and cerebrovascular diseases, NE and ANG-II are the most sensitive indices, and have the greatest impact. (2) Cold air led to an increase in blood pressure in cardiovascular disease patients and healthy subjects, activated the RAS system, raised ANG-II levels, accelerated the release of NE, and excited the SNS. The combined effect of these systems led to a rise in blood pressure. The impact of cold air on the change of blood pressure in cardiovascular patients was more significant than in healthy people, and the effect on the cardiovascular patients lasted longer.

Acknowledgments

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