Hypertension associated with unhealthy lifestyle and marked by serum cortisol levels

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Abstract

There are more and more individuals with hypertension due to major risk factors (mRFs) related to unhealthy lifestyle. Here, we report that a new type of hypertension associates with unhealthy lifestyle and marks by serum cortisol levels, which is termed C-type hypertension (CtH). All subjects collected at random at outpatient department between 2012 and 2017, with or without family history of hypertension, with or without unhealthy “environment-sleep-emotion-exercise-diet” intervention [E(e)SEEDi] related mRFs, were screened and measured serum cortisol levels (8:00 AM and 4:00 PM) and blood pressure. Typical cases with CtH have unhealthy E(e)SEEDi related mRFs, such as stay up later or OSA (+++), psychological pressure or bad emotion, lack of physical exercise or sitting for a long time, heavy smoking and/or liquor drinking. Day serum cortisol levels (8:00 AM and 4:00 PM) in this group were significantly elevated (vs control group, $P < 0.01$). Follow-up analysis showed that the outcomes were closely linked to these individuals’ lifestyle and adherence to treatment. In conclusion, this study suggested that there is indeed CtH. Most are young and middle-aged individuals and easy to suffer from major adverse cardiovascular events (MACEs).

Introduction

Hypertension has become one of the common major non-communicable diseases (mNCDs) that endanger human health, and it brings heavy burden to global public health. Currently, the total number of hypertensive patients in China has exceeded 330 million. One in every three adults suffers from hypertension, while another 130 million patients do not know that they have hypertension. Even among the patients receiving treatment, up to 75% of them have uncontrolled blood pressure. That is to say, the “three rates” (awareness rate, treatment rate and control rate) of hypertension in China are still low. Almost 50% of Chinese adults over 35 years have hypertension¹. According to the revised diagnostic criteria for hypertension ($> 130/80$ mmHg) in the US in 2017², the prevalence of hypertension in China has exceeded 60% and the number of patients is estimated to exceed 600 millions³. Therefore, paying attention to early screening, early diagnosis, early treatment and prevention of hypertension is of great significance for reducing target organs damage and high mortality and disability rate, and for global economic and social development.

Although we already knew in 1970s that there is a linkage between stress and cardiovascular disease⁴, there were a few reviews on cortisol-induced hypertension as a hypothesis⁵, and the effects of cortisol on targeted organs such as brain, heart, kidneys, and blood vessels as well as its related mechanisms remain unclear^{6,7}. In this study, we reported a novel type of secondary hypertension associated with unhealthy lifestyle as new stress factors and marked by serum cortisol levels, and termed it as “C-type hypertension (CtH)”.

Results

Brief introduction of clinical presentation of four typical cases of CtH as follows: Table 1 (Case 1, Case 2, Case 3, and Case 4).

The results of blood pressure elevation and cortisol level of peripheral blood in 15 patients with typical CtH (6 males and 6 females) were as follows (Table 2, Table 3). There was a significant difference between patients in

Table 1 or Table 2 and 3 healthy controls (Table 4, 2 males and 1 females) ($P < 0.01$).

Cortisol levels in CtH patients during the day (8:00 Am and 4:00 Pm) was significantly higher than that in healthy controls ($P < 0.01$), but there was no significant difference between male and female patients ($P > 0.05$). It accorded with the main clinical characteristics of temporarily sharply or sustained slowly increase of cortisol levels, and improved lifestyle and antihypertensive therapy can keep cortisol levels in normal range. The outcome of follow-up analysis was also related to the improvement of patients' lifestyle and adherence to treatment (Fig 1). In addition, preliminary clinical data of elderly patients with hypertension or diabetes mellitus showed that cortisol levels were basically within the normal range (Table 5), which may also be related to the number of samples.

Discussion

As we known, mNCDs including hypertension share one or more modifiable lifestyle risk factors⁸, such as abnormal internal environment (hypertension, hyperglycemia, dyslipidemia, obesity, and chronic infection and inflammation), sedentary lifestyle or physical inactivity, alcohol consumption, cigarette smoking, and poor nutrition. Lifestyle modification may lower BP in the population⁹, or prevention and control of hypertension can be achieved through targeted and/or population-based unhealthy lifestyle strategies¹⁰. The combination of reduced sodium intake and the DASH (Dietary Approaches to Stop Hypertension) diet may lower systolic blood pressure¹¹. Both American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC)/European Society of Hypertension (ESH) blood pressure guidelines recommended healthy lifestyle including exercise, body weight reduction, low to moderate alcohol intake, a low-sodium diet, and adequate potassium intake for prevention of elevated blood pressure¹².

Since long-term working at department of cardiovascular disease (CVD), Dr. Hu has to face to face with hypertensive patients. In the process of careful inquiry and consultation according to the previously creatively established by five core elements of health, that is, "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi]¹³⁻¹⁵, and teaching the curriculum "Health Assessment" for medical students, Dr. Hu paid special attention to the association of unhealthy lifestyle related major risk factors with hypertension or coronary heart disease, and expected assessing these cardiovascular risk factors due to applying for "Grand Challenges Explorations" projects (unfortunately, not funded).

Hypertension caused by unhealthy lifestyle (a secondary hypertension) is deeply impressed, especially, after participated in medical students and postgraduates' physical examination for many times. It was found that many young students were long-term staying up late to study, not enough sleep and psychological pressure during their professional examinations, Most of these young adults have elevated blood pressure due to sedentary lifestyle, physical inactivity and coffee drinking. After literature search and in-depth thinking and analysis, it is found that this kind of hypertension related to "new typical stress" caused by unhealthy lifestyle is mainly characterized by temporary sharp increase or sustained slow increase of serum cortisol levels as a

biomarker, and has been confirmed by reliable data in this paper. Therefore, this new type of hypertension discovered have been named as “C-type Hypertension (CtH)”¹⁶⁻¹⁸.

It is well known that hypertension includes essential hypertension (about 95%) and secondary hypertension (about 5%). In addition to renal diseases, the latter is mainly caused by unhealthy lifestyle, and also known as “lifestyle disease” or “wealth disease”. Due to the prevalence of modern unhealthy lifestyle, such as e-life related e-noise¹⁹, CtH has become more and more common in clinical practice among young and middle-aged individuals. For example, moderate or severe OSA (apnea hypopnea index $\geq 20/h$ or even $\geq 30/h$) during rapid eye movement sleep was significantly associated with prevalent hypertension²⁰.

The so-called “new typical stress” caused by unhealthy lifestyle mainly refers to those related to five core factors of health. For example, major depression is associated with an increased risk of hypertension and coronary artery disease as well as acute cardiovascular events²¹, such as myocardial infarction and chronic heart failure. Not only emotional and psychological stress, but also stress from abnormal environment (for example, external environment, water-air-soil-sound pollution; Or internal environment, chronic inflammation, vascular injury and other diseases), stress from sleep disorders (OSA, staying up late, shifting, insomnia, etc.), stress from exercise linked disorders (sedentary lifestyle, lack of physical activity, and obesity; Or intense exercise, physical overload, etc.); And stress from dietary disorders (excessive salt, cigarette smoking, drinking, or inadequate water and fresh fruit intake)²². For example, high salt intake increased blood pressure in chimpanzees²³, cigarette smoking among women was associated with an increased risk of developing hypertension²⁴. These “new typical pressures” were found to link with the change of biomarker cortisol levels in serum, which ultimately induced CtH.

However, several studies found that improved diet quality could attenuate genetic risk for obesity and reduce risk of incident hypertension^{25,26}, and was consistently associated with a decreased risk of death²⁷. In fact, lifestyle modification, such as adequate sleep, aerobic exercise, healthy diet habits can lower the risk of not only CVD but also diabetes, cancer, and related CDC strips or Re-CDC strips²⁸.

A recent work confirmed that unhealthy lifestyle linked with high serum cortisol levels²⁹. There were also high [cortisol levels in pregnancy induced hypertension patients](#)³⁰. Hence, whether is high blood pressure during pregnancy a special CtH due to “internal environment changing” among younger women or not, it needs further investigation, but we already known that women with hypertensive disorders of pregnancy in their first pregnancy had increased rates of chronic hypertension and development of risk factors for CVD³¹, and these women may also benefit from lifestyle intervention.

Previous studies showed that hypertensive and normotensive individuals who adhere multiple lifestyle modifications (e.g., Aerobic exercise or the DASH diet plus physical activity and weight control) could improve control of blood pressure and reduce the risk for CVD³²⁻³⁴. In recent years, healthy lifestyle is widely recommended for hypertension and CVD^{35,36}. However, lifestyle changes to treat hypertension needs to improve the adherence since younger individuals and those with lower educational attainment and lower income were, in general, less likely to adhere lifestyle behaviors for blood pressure control^{37,38}. In addition, since impaired vascular function may contribute to exaggerated blood pressure responses during daily living³⁹, hence, aerobic exercise as a part of the ideal lifestyle is very suitable for patients with CtH, and exercise-testing (Bruce protocol)⁴⁰ may be a useful tool to evaluate these patients.

Thus, early lifestyle modifications should be recommended not only for preventing atherosclerotic CVD and diabetes⁴¹⁻⁴³, but also for hypertension according to this study. In fact, one year of lifestyle intervention may lower hypertension⁵¹. Lifestyle modifications by regular exercise and weight reduction had already been recommended for the first time with class I, level of evidence A for the management of hypertension by ESH and ESC guidelines in 2013^{12,45}. Obviously, the guideline-based management was beneficial for hypertension control⁴⁶.

All in all, CtH was discovered in our clinical practice. It is characterized by a temporary sharp or sustained slow increase of the serum biomarker cortisol level. Cortisol's first letter is C, so it is called "C-type hypertension". CtH is worth establishing and screening animal models and conducting in-depth basic research so as to disclose the pathogenesis and vital pathogenic genes. Whether the levels of urinary cortisol⁴⁷ is also a biological biomarker, it still waits for our study. The pro-inflammatory role and adverse effects of cortisol dysregulation is an alarm clock of MACEs⁴⁸ since increased cortisol levels were predictive of acute mortality⁴⁹.

There are several limitations of this study. First, it was only a preliminary report from a clinical observational study. Second, as a new discovery in clinical practice, it was restricted by scientific research funds for further basic and translational development. Hence, further large-scale clinical trials which based on current study is highly recommended confirming the role of unhealthy and/or healthy E(e)SEEDi lifestyle on CtH. In addition, it needs to further explore which cortisol levels in serum, saliva, hair, and urine is better as a biomarker of CtH.

In conclusion, there is indeed a new type of hypertension termed CtH which is associated with unhealthy lifestyle and marked by temporarily sharply or continuously slowly rising serum cortisol levels. Most are young and middle-aged individuals and are easy to suffer from MACEs. Since healthy E(e)SEEDi can lower the risk of CVD, diabetes, and cancer, it should be prescribed to all hypertensive individuals, especially CtH.

Methods

Data Collection

Patients were randomly enrolled at outpatients department with hypertension from 2012 to 2017, those with or without family history of hypertension, with or without unhealthy lifestyles, including abnormal home or work environment (air pollution, radiation, all kinds of noise), abnormal internal environment (chronic inflammation, high blood sugar or dyslipidemia); Abnormal sleep quality (OSA, staying up late, shifting, insomnia, etc.); Long-term stress, anxiety or depression; Physical inactivity or obesity; And unscientific and non-rational diet, unbalanced nutrition (excessive salt, heavy smoking and drinks), excessive intake of red meat, inadequate water, fruits and vegetables intake not enough.

Clinical investigations

Patients were examined by physical examination and biochemical examination (including routine blood and urine, liver and kidney function, fasting blood glucose, blood lipid, blood viscosity, uric acid, myocardial enzymes, troponin I, oral administrative glucose tolerance test or postprandial 2-hour blood sugar), hepatitis virus examination, four items of tumors, carbohydrate antigen, prostatic antigen and other related auxiliary examinations (including chest X-ray, routine electrocardiogram and exercise test and 24-hour ambulatory electrocardiogram, ambulatory blood pressure monitoring, color Doppler ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI), coronary angiography, mammography, etc). Relevant data were retained for analysis.

Serum cortisol assay

Cortisol levels in serum^{50,51}, saliva^{52,53}, hair⁵⁴, and urine^{55,56} had been measured successfully. In this study, we assayed serum cortisol levels at 8:00 AM and 16:00 PM with previously documented methods. The samples for serum cortisol (0.5 ml) were transported to the laboratory either immediately or the next morning after being stored in a refrigerator at 4 °C overnight. Serum cortisol levels were measured using commercial kits by [radioimmunoassay](#) (Northern Biotechnology Institute, Beijing, China) or chemiluminescent immunoassay (Di'anhuaixing Medical Laboratory, Jiangxi, China). Interassay and intraassay coefficients of cortisol variations were 4.7% and 10.4%, respectively. Detection limit for cortisol was 14 nmol/L.

Informed consent

Data collection was followed by a study protocol that was approved by the local ethics committee with reference numbers 0312/2012. It was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000, and all enrolled patients gave written informed consent. No potential sources of bias.

Statistical analysis

The results of original records were used. Data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS version 17.0, SPSS Inc., Chicago, IL, USA) with t-test for comparisons between two groups. A *P*-value of <0.05 was considered statistically significant.

Declarations

Ethics statement

This work was approved by Human Research Ethics Committee of the Nanchang University, Hospital of Nanchang University, Jiangxi Academy of Medical Science (approval 20120312).

Role of the funding source

No funding was received for this study. All authors had full access to all study data, and the corresponding author had final responsibility for the decision to submit for publication.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data that support the findings of this study are not publicly available but are available upon reasonable request from the corresponding author.

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Contributions

C.H. designed the study, collected and analyzed all data, performed statistical analyses, wrote original draft and revised the final manuscript, and contributed to writing-review & editing; Y.W., J.L., M.W., Y.G. and T.T. contributed to interpretation of data and data evaluation, writing-review & editing; Q.W. contributed to supervision, interpretation of data and data evaluation, writing-review & editing. All authors discussed the results, critically reviewed the paper, and approved the manuscript for submission.

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Ethics declarations

Competing interests

The authors declare no competing interests.

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Tables

Table 1. Clinical characteristics of cases with C-type hypertension (CtH).

Items	Case 1. CtH with arteriosclerosis and coronary heart disease	Case 2. CtH with asymptomatic but with genetic history	Case 3. CtH with symptomatic and genetic history	Case 4. CtH with symptomatic but no genetic history
General information	Male, 45 yrs, married, construction contractor	Male, 51 yrs, married, elevator maintenance worker	Female, 47 yrs, married, financial staff	Female, 34yrs, married, laid-off workers
Chief complaint	Chest tightness at night and palpitation for half a month	No discomfort, physical examination for annual qualification certificate	Chest tightness, dizziness for 2-3 years, syncope with palpitation and cold sweat for one day	Palpitation, tremor and insomnia for a month
Past history	First visit doctor	Physical examination every four years, first twice results are unknown, Never see a doctor or take medicine	Physical examination found "high blood pressure", has not been treated with agents	No records
Family history	Two brothers died of lung cancer and liver cancer, respectively	His father has hypertension, arrhythmia, chronic heart failure, his mother has hypertension, rheumatism	Her father died of cardiovascular disease and her mother was healthy	Both her father and mother are healthy
Environment	Rural life	City life, has hypertension with genetic history	City life	City life
Sleep	OSA (+++), don't stay up later	His sleep is good, OSA (-), Often stay up later until 24:00 PM	Sleep at 23:00-24:00, sometimes OSA (+)	Often stay up later (sleep at 24:00-2:00), and her sleep was not so good, OSA (-)
Emotion	Work under great pressure	Less psychological pressure	Work under little pressure	Bad emotion
Exercise	Physical inactivity	Physical inactivity, repair work, go to work by electric vehicle, take the elevator to the eighth floor when getting home, watching TV often	Physical inactivity, sitting and using computers for a long time (more than 10 hrs a day), do housework	Physical inactivity, do housework
Diet	80-100 cigarettes per day for 2 years, liquor drinking (quarter a kilogram a week)	30 cigarettes per day for 30 years, liquor drinking once a night (2 to 3 drinks at a time), drink strong tea	Non-smoking and alcohol addiction, but have passive smoking	Non-smoking and alcohol addiction, passive smoking (her husband smoking, 20 cigarettes per day)
Blood pressure	136/110 mmHg (Right), 136/106 mmHg (Left)	210/140 mmHg (Right), 214/140 mmHg (Left)	156/114 mmHg (Right), 158/122 mmHg (Left)	166/116 mmHg (Right), 166/116 mmHg (Left)

BMI	80+kg/1.68m(2)	78kg/1.67m(2)	56kg/1.60m(2)	55kg/1.56m(2)
Others	-	-	-	Premature pulse, thyroid function (-)

Table 2.

Preliminary clinical data of patients with CtH: Blood pressure and cortisol levels.

Gender	Age	BMI	Bp (R) (mmHg)	Bp (L) (mmHg)	Cortisol(ng/mL) F8:00AM	Cortisol(ng/mL F4:00PM)
Male	49	27.68	154.00/112.00	146.00/106.00	No record	312.09
	52	31.14	116.00/96.00	116.00/96.00	257.01	168.62
	55	29.05	No record	136.00/96.00	426.35	308.55
	59	34.60	162.00/106.00	146.00/96.00	342.18	No record
Female	42	32.05	122.00/82.00	126.00/86.00	No record	280.09
	25	20.08	126.00/92.00	122.00/88.00	320.00	632.00
	49	No record	156.00/110.00	156.00/112.00	385.67	467.85
	49	23.44	152.00/96.00	166.00/98.00	386.72	168.29
	52	33.46	146.00/116.00	No record	301.72	156.64

Notes 1: The standard of normal blood pressure can be found in the relevant guidelines, and the normal range of cortisol levels can be found in the instructions of the corresponding test kit.

Notes 2: Cortisol levels were determined by radioimmunoassay kits of Northern Institute of Biotechnology in Beijing. Normal reference values of plasma cortisol levels were 7:00-9:00 (F8:00AM) 66-286 ng/dL, 15:00-17:00 (F4:00PM) 22-154 ng/dL (Data at 24:00 time point were not measured because all the subjects were outpatients).

Table 3.

Clinical data of patients with CtH by modified lifestyle and antihypertensive agents: Blood pressure and cortisol levels.

Gender	Cases	Age	BMI	Bp (R) (mmHg)	Bp (L) (mmHg)	Cortisol(ng/mL) F8:00AM	Cortisol(ng/mL) F4:00PM
Male	No. 1	40	28.16	128.00/102.00	116.00/90.00	214.00	No record
	No. 2	50	24.65	176.00/128.00	178.00/118.00	124.85	126.53
Female	No. 3	28	24.65	106.00/92.00	112.00/86.00	75.80	34.00

Notes: Cortisol levels in male patients were measured by radioimmunoassay and in female patients by chemiluminescence.

Table 4.

Clinical data of healthy population controlled with CtH: Blood pressure and cortisol levels.

Gender	Cases	Age	BMI	Bp (R) (mmHg)	Bp (L) (mmHg)	Cortisol(ng/mL) F8:00AM	Cortisol(ng/mL) F4:00PM
Male	No. 1	50	21.26	112.00/72.00	115.00/76.00	102.80	62.70
	No. 2	40	22.49	120.00/76.00	102.00/72.00	107.50	64.80
Female	No. 3	20	17.31	86.00/62.00	96.00/66.00	86.20	79.30

Notes 1: The standard of normal blood pressure can be found in the relevant guidelines, and the normal range of cortisol level can be found in the instructions of the corresponding test kit.

Notes 2: Cortisol levels of healthy population samples in this study was measured by the Chemiluminescence Kit of Di'anhuaxing Medical Laboratory in Jiangxi Province. Normal reference values of plasma cortisol level were 7:00-9:00 (F8:00AM) 67-226 ng/dL, 15:00-17:00 (F4:00PM) less than 100.00 ng/dL (No data at 24:00 time point were measured).

Table 5.

Preliminary clinical data of elderly patients with hypertension or and diabetes mellitus: Blood pressure and cortisol levels.

Gender	Cases	Age	BMI	Bp (R) (mmHg)	Bp (L) (mmHg)	Cortisol(ng/mL) F8:00AM	Cortisol(ng/mL) F4:00PM
Male	No. 1	73	30.07	152.00/90.00	No record	212.29	No record
	No. 2	64	24.22	No record	174.00/114.00	229.92	142.90
	No. 3	62	26.30	150.00/92.00	122.00/92.00	173.70	80.20
	No. 4	62	No record	156.00/112.00	146.00/106.00	102.00	82.30
Female	No. 5	57	28.58	150.00/116.00	No record	140.20	101.50

Notes 1: The standard of normal blood pressure can be found in the relevant guidelines, and the normal range of cortisol levels can be found in the instructions of the corresponding test kit.

Notes 2: Cortisol levels were measured by radioimmunoassay in patients 1 and 2, and chemiluminescence in patients 3-5.

Figures

Figure 1

E(e)SEEDi “closures” arterial vessels for adverse outcomes of C-type hypertension (CtH).