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Original Article

Association of frailty with morning blood pressure and blood pressure variability in elderly patients with hypertension

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Abstract: This study aims to investigate the association of frailty with morning blood pressure and blood pressure variability in elderly patients with hypertension. 156 elderly patients with hypertension were divided into control group (non-frail group), pre-frail group and frail group according to the results of frail scale. Data on patients' gender, age, history of smoking, hypertension duration and anti-hypertensive drug usage were collected, their blood lipid, fasting blood glucose and blood uric acid were detected. The morning hypertension and variation of blood pressure were evaluated by monitoring the 24-hour ambulatory blood pressure in elderly patients with hypertension. Results showed that there were no significant differences in gender, age, history of smoking, hypertension duration, anti-hypertensive drug usage, Triglycerides, Total cholesterol, Low density lipoprotein cholesterol, High density lipoprotein cholesterol, Fasting glucose and Uric acid among the three groups ($P>0.05$). Morning SBP gradually decreased among control group, pre-frail group and frail group ($P<0.01$). However, no significant difference in morning DBP was observed among the three groups. 24 h SBP, daytime SBP, nighttime SBP, 24 h DBP, daytime DBP, night time DBP did not differ among the three groups ($P>0.05$). 24 h SBPV gradually increased among control group, pre-frail group, frail group ($P<0.05$). Daytime SBPV gradually increased among control group, pre-frail group, frail group ($P<0.05$). The nighttime SBPV, 24 h DBPV, daytime DBPV, nighttime DBPV did not differ among the three groups ($P>0.05$). The ordinal regression analyses showed that frailty was influenced negatively by morning SBP but had no effect on 24 h SBPV and Daytime SBPV. In conclusion, frailty is closely related to morning SBP, but not associated with blood pressure variability.

Keywords: Frailty, morning blood pressure, blood pressure variability, hypertension

Introduction

With the aging trend of the global population, the prevalence of hypertension in the elderly population is increasing, accompanied by the rising risk of cardiovascular events in the elderly. The blood pressure continuously changes in 24 hours, it is usually high in daytime and low in nighttime, and there is a substantial increase in blood pressure in the morning. Previous studies have reported that that rising rate of morning blood pressure in most hypertensive patients is significantly higher than those with normal blood pressure [1]. It belongs to pathological status that morning blood pressure rises too much, which is not only closely related to cardiovascular risks, but also reduces antihypertensive benefit significantly. Blood pressure variability indicates the degree of blood pressure fluctuation within a certain time. Blood pressure variability significantly increases in hypertensive patients and directly affects the severity and prognosis of target organ damage. It is independent of the average blood pressure in reflecting cardiovascular activity [2, 3]. Blood pressure variability is an independent predictor of mortality, cardiovascular mortality, and non cardiovascular mortality in patients with hypertension [4-6].

Aging cardiovascular system has a series of changes in morphology and function, which is

the trigger of high incidence of diseases. The prevalence of cardiovascular accidents increases significantly after the patients reach 60. At the same time, the aging of other systems will also influence the occurrence and development of cardiovascular diseases, among which the frailty effect on cardiovascular disease outcomes is paid more and more attention. Frailty is a syndrome involving multiple systems. The symptoms include physical degradation which is not commensurate with age, decrease of functional reserve, or decrease of resisting acute or chronic trigger events such as various types of cardiovascular diseases [7]. Because frailty and hypertension are common in the elderly and they are promoting each other, it is undoubtedly of great significance in improving the level of treatment and the health of the elderly by illustrating the relationship between frailty and hypertension accurately. Nevertheless, there are few reports about the effect of frailty on morning blood pressure and blood pressure of elderly patients with hypertension. This study aims to investigate the effect of frailty on morning blood pressure and blood pressure variability in elderly hypertensive patients, so as to provide the scientific basis for further optimization of the management of blood pressure in elderly hypertensive patients.

Subjects and methods

Research subjects

156 cases of II or III grades elderly hypertensive patients were selected from July 2015 to November 2016 in the Third Affiliated Hospital of Anhui Medical University. According to the frail scale score (CFS) [8], these patients were divided into 3 groups, including 62 cases of prefrail group, 44 cases of frail group, non-frail elderly patients with hypertension in 50 cases as control group. Inclusion criteria were as follows: patients of 65 years or older with hypertension, sustained blood pressure or 3 times measuring systolic blood pressure of different days were greater than 160 mmHg (1 mmHg = 0.133 kPa) and (or) diastolic blood pressure greater than 100 mmHg; elderly patients, with a previous history of II, III grades hypertension and currently taking antihypertensive drugs, their blood pressure less than 160/100 mmHg, with a diagnosis of hypertension, were also selected. Exclusion criteria were as follows: secondary hypertension, acute cardiovascular patients, severe cardiac insufficiency, severe infection, elevated alanine aminotransferase or aspartate aminotransferase of liver, elevated creatinine, end-stage of malignant tumor, gout, patients refusing to accept screening of frailty and unable to communicate or present available clinical data to obtain valid information to determine whether a patient is frail. This study was conducted in line with the Declaration of Helsinki, and was approved by the ethics committee of the Third Affiliated Hospital of Anhui Medical University. All participants in the study have signed an informed consent.

Clinical evaluation of frailty

The clinical data were collected by using blind method, adopting the frail scale from International Society for nutrition and aging [8], which is a simple and rapid method in clinical evaluation. It includes the following 5 items: (1) Fatigue: in the previous week, the patients often felt tired in doing everything; (2) Resistance: it is very difficult to go upstairs, even one floor; (3) Less activity: it is impossible to walk to another block (500 meters); (4) Coexistence of diseases >5 diseases; (5) Decrease of body weight: weight decrease >5% in one year. In accordance with a score of 1 point, the total score of 5 points. 0 points: strong (no frailty); 1-2 points: prefrailty; 3-5 points: frailty.

Morning blood pressure and dynamic blood pressure monitoring

24-hour-monitoring of the ambulatory blood pressure of all the enrolled patients were conducted using MGY-ABP1 automatic portable ambulatory blood pressure monitor. The blood pressure was measured every 30 minutes from 6 a.m. to 10 p.m., and every 60 minutes from 10 p.m. to 6 a.m. The blood pressure were recorded automatically every time, and also the following parameters in 24 h, daytime and nighttime: (1) The average systolic blood pressure (SBP) and systolic blood pressure standard deviation (SBPSD), the average diastolic blood pressure (DBP) and diastolic blood pressure standard deviation (DBPSD); (2) Morning blood pressure (morning BP): it refers to the ambulatory blood pressure recorded before treatment, early in the morning before breakfast, two hours after getting up. Systolic blood pressure variability (SBPV) and diastolic blood

Table 1. Comparison of general features, clinical and laboratory characteristics among the three groups

	Control group (n = 50)	Prefrailty group (n = 62)	Frailty group (n = 44)	*P*-value
Male/Female (%)	39 (78.0)/11 (22.0)	50 (80.1)/12 (19.9)	32 (72.7)/12 (27.3)	0.627
Age (years)	80.5±8.0	79.1±6.7	78.3±7.2	0.321
Smoker (%)	22 (44.0)	24 (38.7)	24 (43.2)	0.828
Hypertension duration (years)	17.1±9.7	15.7±8.4	15.3±7.4	0.534
Triglycerides, mmol/L	1.2±0.9	1.0±0.5	1.2±0.9	0.179
Total cholesterol, mmol/L	4.1±1.1	4.1±1.0	4.0±1.2	0.932
LDL cholesterol, mmol/L	2.3±0.9	2.3±0.8	2.1±0.9	0.479
HDL cholesterol, mmol/L	1.3±0.3	1.4±0.4	1.3±0.3	0.597
Fasting glucose, mmol/L	5.9±1.2	5.8±1.7	6.0±1.9	0.789
Uric acid, μmol/L	326.4±99.3	327.8±89.1	328.0±90.4	0.996
Antihypertensive drugs				
Calcium channel blocker, n	48	60	43	0.894
ACEI, n	19	27	18	0.838
ARB, n	30	33	24	0.759
Diuretics, n	10	14	7	0.698
Beta blocker, n	18	22	12	0.602
α blocker, n	10	14	9	0.938
Compound hypotensive tablets, n	4	5	2	0.746
Aldosterone antagonists, n	4	6	4	0.953

All values are presented as the mean ± SD. LDL low density lipoprotein, HDL high density lipoprotein, ACEI angiotensin converting enzyme inhibitors, ARB angiotensin receptor blockers.

pressure variability (DBPV) were calculated according to the recording parameters. Formula of calculating BPV: the blood pressure standard deviation was divided by the average blood pressure, for example 24 h systolic blood pressure variability (24 h SBPV) = 24 h SBPSD/24 h SBP*100%.

Collection of baseline data and the checking of related indicators

Before inclusion, the information of all the elderly patients with hypertension as to their gender, age and whether they smoke (smoking is defined as daily smoking more than one cigarette, smoking for one year or more) were collected, the course of hypertension and medication were also recorded, the morning fasting venous blood samples were collected, and the laboratory examination indexes including total the cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), fasting blood glucose (FPG) and blood uric acid (UA) were detected.

Data processing and statistical analysis

The measurement data in line with the normal distribution were expressed as mean ± standard deviation. One way ANOVA was used to compare the differences among multiple groups of quantitative data. Qualitative data were compared by using chi-square test. Significant variables in the univariate analysis were included in the ordinal regression analyses. All statistical analyses were conducted by SPSS 16.0, *P* value of less than 0.05 was considered to be statistically significant.

Results

Basic conditions

There were no significant differences in gender, age, smoking, hypertension, TG, TC, LDL-C, HDL-C, FPG and UA among control group, prefrail group and frail group (all *P*>0.05). No significant difference in the use of antihypertensive drugs were observed among the three groups (*P*>0.05) (**Table 1**).

Table 2. Comparison of morning blood pressure and average blood pressure among the three groups ($\bar{x}$±s, mmHg)

	Control group (n = 50)	Pre-frailty group (n = 62)	Frailty group (n = 44)	F-value	*P*-value (ANOVA)
Morning SBP	135.5±12.0	130.8±14.3[a]	127.4±10.9[a,b]	4.848	0.009
24-hour SBP	124.3±9.7	122.5±10.2	125.7±12.4	1.175	0.312
Daytime SBP	125.2±10.1	123.8±10.5	125.9±12.7	0.526	0.592
Nighttime SBP	120.7±10.8	119.5±12.1	124.9±16.3	2.286	0.105
Morning DBP	72.2±6.2	71.8±9.8	70.6±6.4	0.511	0.601
24-hour DBP	69.8±7.2	68.1±8.2	69.2±7.9	0.656	0.520
Daytime DBP	71.5±7.2	69.4±8.2	69.3±8.6	1.188	0.308
Nighttime DBP	67.4±7.1	66.1±9.4	68.2±8.7	0.826	0.440

All values are presented as the mean ± SD. SBP systolic blood pressure, DBP diastolic blood pressure. [a]versus control group, $P<0.05$. [b]versus prefrail group, $P<0.05$.

Table 3. Comparison of blood pressure variability among the three groups ($\bar{x}$±s, %)

	Control group (n = 50)	Pre-frailty group (n = 62)	Frailty group (n = 44)	F-value	*P*-value (ANOVA)
24-hour SBPV	10.3±2.6	11.2±2.6[a]	11.8±2.3[a,b]	3.963	0.021
Daytime SBPV	10.0±2.7	10.9±2.7[a]	11.3±2.3[a,b]	3.150	0.046
Nighttime SBPV	8.9±2.9	8.6±3.3	9.7±4.0	1.372	0.257
24-hour DBPV	14.0±3.6	14.2±3.6	15.5±4.7	2.013	0.137
Daytime DBPV	13.9±3.9	13.7±3.9	14.6±4.6	0.648	0.524
Nighttime DBPV	11.4±4.4	11.4±4.5	13.2±6.9	2.033	0.135

All values are presented as the mean ± SD. SBPV systolic blood pressure variability, DBPV diastolic blood pressure variability. [a]versus control group, $P<0.05$. [b]versus prefrail group, $P<0.05$.

Comparison of blood pressure and morning blood pressure

There were significant differences in morning SBP among three groups ($P<0.01$), while there was no significant difference in morning DBP among three groups ($P>0.05$). The 24 h SBP, daytime SBP, nighttime SBP, 24 h DBP, daytime DBP and nighttime DBP did not differ significant among control group, prefrail group and frail group (all $P>0.05$) (**Table 2** and Supplementary Data).

Comparison of BPV

There were significant differences in 24 h SBPV and daytime SBPV among three groups (all $P<0.05$). Nighttime SBPV, 24 h DBPV, daytime DBPV and nighttime DBPV showed no significant difference among the three groups (all $P>0.05$) (**Table 3** and Supplementary Data).

Ordinal regression analysis of independent variables that were associated with frailty

The ordinal regression analyses were used to identify independent variables that were associated with frailty. Frailty seemed to be influenced negatively by morning SBP. However, no significant influence of 24 h SBPV and daytime SBPV on frailty were observed (**Table 4**).

Discussion

Frailty is a clinical syndrome which is due to increased vulnerability and the decline of individual ability to maintain internal balance. The risk of having a variety of adverse health outcomes among elderly people increases. It has a serious impact on the health status, functional integrity and life quality of the elderly and causes a heavy burden for the family and society [9]. It has been shown that 10% of people over 65 years old have the problem of frailty; for people over 85, it is about 25%-50% [10]. The elderly frail syndrome often associates with hypertension; the detection rate of frailty is 7% among people between 65 and 85 years old. The detection rate was 32% among people over 80 years old. In 2016, ESH/EUGMS published expert hypertension management of elderly frail elderly suggesting that elderly hypertensive patients have many particularities [11]. Therefore, the strategy of blood pressure management is different from young hypertensive patients, and is also different from the elderly population who is physically healthy. We should pay attention to evaluate the degree of frailty of old people. For patients having a higher degree of frailty, having a variety of diseases, having poor tolerance of antihypertensive treatment, their blood pressure control should be moderately loose. HYVET test indicated that keeping the target value of blood pressure control is under 150/80 mmHg can

Table 4. Variables independently associated with frailty by ordinal regression

	Estimate	*Wald*	*P* value	95% CI
Dependent variable: frailty				
Independent variables				
Morning SBP	-.031	6.899	.009	-.055~-.008
24-hour SBPV	16.781	1.627	.202	-9.008~42.571
Daytime SBPV	-1.744	.019	.891	-26.618~23.129

reduce all-cause mortality in the elderly frailty patients with hypertension [12]. Muller et al [13] found that strict antihypertensive treatment is related to falling incidence and mortality in the elderly. If blood pressure level is higher than 160/90 mmHg, the initial drug therapy is recommended for elderly patients with frailty, and the blood pressure target value is 140-150/70-90 mmHg. This result shows that the prognosis of patients with hypertension is closely related to frailty. Longitudinal Aging Study Amsterdam (LASA) [14] showed for the healthy older adults, when DBP exceeds 90 mmHg, their risk of death increases 50%. If diastolic blood pressure does not exceed 70 mmHg, the risk of death does not increase significantly. But in the frail elderly group, lower DBP increases the patients' risk of death to 50%, while patients whose diastolic blood pressure is over 90 mmHg have no increased risk of death. The study suggests that the biological age (decline or not) is an important factor influencing the benefit of antihypertensive treatment.

Previous study showed that for patients with hypertension, due to activation of the sympathetic nervous system, RAS activation, and the increase of endocrine humoral factors such as endothelin, their morning blood pressure is significantly higher than those of normal blood pressure. The excessive elevation of morning blood pressure is closely related to the risk of cardiovascular events [15]. This study shows that if the blood pressure of the elderly patients is under control and there is no significant differences in the application of antihypertensive drugs and the average blood pressure in elderly patients with hypertension, their morning blood pressure is significantly lower than the non-frail patients, and the patients' morning blood pressure decreased with the decline of the trend of gradual frailty no matter they are prefrail or frail patients. These results indicate that frailty and hypertension are not only common in the elderly, but also closely related to each other. (1) Frailty is a geriatric syndrome involving the loss of reserve capacity in multiple physiological systems, and the ability to cope with acute or chronic trigger events such as various types of cardiovascular disease decreases. According to the findings of this study, it is estimated that frail hypertensive patients' stress ability tends to reduce in the morning, which leads to the decrease of the degree of sympathetic nervous system activation, RAS activation and the level of endocrine humoral factors compared with those of the non-frail patients, resulting in a gradual decline in the morning blood pressure. (2) The effects of aging on left ventricular function are obvious during exercise, when the elderly people's cardiac output is significantly lower than that of the young people. At the same time, most of the patients who are frail may reduce the amount and time of activities, the speed, and intensity, which causes the rising of morning blood pressure relatively low. This may also be one of the reasons. (3) The rising of morning blood pressure is an important factor causing cardiovascular and cerebrovascular events. However, the morning blood pressure of frail patients has a downward trend, which may be a protective reaction in elderly patients with frailty. Its specific mechanism needs further study.

Blood pressure variability is one of the most basic physiological characteristics of human. Therefore, it is significant to control both blood pressure and blood pressure variability in order to further reduce the damage of target organs. ASCOT- BPLA study [16] showed that BPV is closely associated with the risk of stroke or coronary heart diseases. BPV increases patients' risk of cardiovascular events. BPV is more predictive of cardiovascular events compared with the average of blood pressure. After the cross section of 77 Brazilian old people who are over 60 years with the average age of 74.5 years, Bastos-Barbosa et al [17] found that there is no significant difference in family blood pressure and office blood pressure between the frail group and the non-frail group. But the 24 hour ambulatory blood pressure shows that the blood pressure of the frail group is higher

than that of the control group, and the difference is significant. It is concluded that there are many risk factors for patients with frailty such as cardiovascular diseases. Yano et al [18] studied 148 patients who are over 60 years old with the average age of 75.5 years. Take pace <1.5 m/s as the frail index. Through 24 hours ambulatory blood pressure monitoring, it is found that there is a relationship between low speed and nocturnal hypertension. Koizumi et al [19] found that there is a correlation between frailty and the prevalence of hypertension and uncontrolled hypertension. The mutual effect between frail syndrome and hypertension exists. For the elderly patients with uncontrolled hypertension, the incidence of the disease increases. Early active antihypertensive treatment would help to prevent or slow down the decline of its progress. For patients with frailty syndrome but without hypertension, the incidence of hypertension can be reduced through walking exercise. We found that although the average blood pressure of 24 hours reached the target value in the elderly patients with hypertension, and there was no significant difference in the average blood pressure among three groups, with the increasing of the degree of frailty, there was no significant change in SBPV and DBPV. It is speculated that as the frailty gradually aggravated, rest time gradually extended and activity gradually reduced in the elderly patients, thus the fluctuation of blood pressure did not increase with the increase of frailty. Second, it may have even more complex relationship between frailty and blood pressure variability. Therefore, further studies are still needed to confirm these results.

Conclusion

To summarize, frailty is closely related to morning SBP, but not associated with blood pressure variability. This finding will be helpful for carrying out screening, early prevention, multidimensional intervention among the early stage of frailty in high-risk population. However, the sample size of this study is relatively limited, further studies with larger sample size are needed to accurately describe the frailty status of elderly hypertensive patients. Additionally, related mechanisms among frailty, morning blood pressure and blood pressure variability remain to be further explored.

Disclosure of conflict of interest

None.

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