High Pulse Pressure Decreases Cardiopulmonary Ability among Older Chinese Patients with Primary Hypertension

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Summary

There is limited information regarding the reference values for cardiopulmonary exercise testing (CPX) variables in patients with primary hypertension. Our aim was to provide such values. In this single-center, retrospective study, we included 635 patients (male, 53.7%; mean ± standard deviation age, 62.1 ± 12.6 years) who completed maximal ramp incremental CPX using cycle ergometry at the Rui An Hospital of Traditional Chinese Medicine from August 1, 2018, to December 31, 2021. The patients were classified into two groups based on pulse pressure (PP): (1) patients with a low PP ≤ 60 mmHg (n = 324) and (2) patients with a high PP > 60 mmHg (n = 311). Stepwise linear regression was used to fit the equations of the key CPX variables. CPX was self-interrupted owing to fatigue by 64.5% (low PP) and 72.0% (high PP) of patients ($\chi^2$ analysis, $P = 0.05$). The anaerobic threshold (AT) could not be determined in 3.7% and 7.7%, respectively ($\chi^2$ analysis, $P = 0.038$). Peak oxygen consumption ($VO_2$), carbon dioxide production, ventilation/minute, work rate, and $VO_2$ at the AT were associated with age, weight, and sex. Moreover, a high PP was associated with impaired anaerobic exercise ability, as indicated by the reduced peak $VO_2$, peak VE, and absolute peak work rate. Compared with prior research of a healthy population, patients with primary hypertension in this study exhibited impaired cardiopulmonary ability both at rest and during exercise, especially in the high PP group. The reference values and predictive equations for CPX variables provide a framework for interpreting the response to maximal ramp incremental cycle ergometry among older Chinese patients with primary hypertension.

Key words: Cardiorespiratory fitness, Cardiopulmonary exercise testing, Elderly

Hypertension is highly prevalent around the world and is the leading cause of cardiovascular diseases and premature death. One of the reasons for its rising prevalence is exposure to lifestyle-related risk factors (e.g., high sodium intake, low potassium intake, and the lack of physical activity).1,2 Increasing physical activity with a structured exercise program is an important nonpharmacological intervention to lower blood pressure (evidence level: I [A]).3,4 Indeed, a recent network meta-analysis demonstrated that, although first-line antihypertensive medication has a greater effect in reducing the blood pressure of patients with hypertension, there is insufficient evidence to suggest a statistically significant difference with the effect of exercise interventions.5-7 Although regular exercise is recognized as a concurrent treatment option for primary hypertension, detailed guidance of exercise prescription is lacking.

As an independent predictor of disease progression and all-cause mortality in patients with hypertension, pulse pressure (PP) was defined as systolic minus diastolic blood pressure and a high PP was defined as a PP > 60 mmHg. In elderly individuals, an elevated PP was demonstrated to be associated with an increased risk of cardiovascular mortality, stroke, and cognitive decline both among the general population and in patients with hypertension.8-9 The role of a high PP as a risk factor for cardiovascular disease was recognized in the 2013 European Society of Hypertension/European Society of Cardiology guidelines, where it was included among the indexes of asymptomatic organ damage.9 However, how the elevated PP would influence the exercise ability among the elderly is unknown. Moreover, although an elevated PP among older individuals is related to an increased risk of cardiovascular mortality and stroke, most guidelines focus on systolic and diastolic blood pressure as the treatment goals.
In terms of exercise recommendations, the frequency, intensity, time, and type principle has been widely used. Among the diverse kinds of exercises for individuals with hypertension, aerobic exercise is universally recommended as initial lifestyle therapy, with moderate intensity, i.e., 40% - < 60% peak oxygen uptake (VO2) or heart rate (HR) reserve. In fact, exercise intensity is considered the most important element in lowering blood pressure. Cardiopulmonary exercise testing (CPX) is an examination technique that provides reproducible variables for the accurate assessment of the global exercise responses of the respiratory, cardiovascular, and musculoskeletal systems. The European Association of Preventive Cardiology recommended peak exercise capacity assessment with CPX as the gold standard for all clinical conditions. It is used to precisely define exercise capacity through the measurement of peak VO2, ventilatory efficiency, and the ventilation/carbon dioxide production (VE/VCO2) slope. It can also be used to predict mortality among patients with a variety of conditions, such as cardiovascular and respiratory disease, and for the preoperative assessment of the need for surgery and exercise. Thus, the physiological response to CPX among patients with primary hypertension may provide essential reference information for the formulation of exercise prescriptions.

Considering the lack of detailed guidance for exercise prescription and CPX characteristics among patients with primary hypertension, in the present study, we aimed to determine the CPX characteristics of such patients using a cycle ergometer. We also compared CPX variables between patients with a low PP and those with a high PP. The overarching goal was to collect data for future guidance of exercise prescription among patients with primary hypertension.

**Methods**

**Study design and participants:** This was a single-center, retrospective cohort study. We screened 3,258 consecutive CPXs performed at the Rui An Hospital of Traditional Chinese Medicine, China, from August 1, 2018, to December 31, 2021. The study included adult patients with primary hypertension (age ≥ 18 years) and a left ventricular ejection fraction > 50% who were referred for and completed cycle ergometry-based CPX. Only the first test was used for this analysis if a patient underwent multiple tests. Patients were excluded from further analysis if any of their predictors or outcome values were missing. Patients were divided into two groups based on their PP: (1) patients with a low PP (≤ 60 mmHg) and (2) patients with a high PP (> 60 mmHg). The study enrollment flowchart of the participants is shown in Figure 1. This study was approved by the Ethics Committee of the Rui An Hospital of Traditional Chinese Medicine (approval number: RAZYEC-2022-03-P008), and it conformed with the Declaration of Helsinki guidelines.

**Procedures and interpretation of CPX:** Preliminary CPXs were performed using a Quark PFT Ergo testing...
system (Cosmed Srl, Rome, Italy). The patients underwent maximal symptom-limited metabolic exercise testing with a cycle ergometer and the ramp protocol. The ramp protocol was used to estimate the patient’s exercise capacity. Workloads were gradually increased each minute by the predicted maximal workload divided by 10 according to the individual’s self-reported daily activity to allow the patient to undergo fatigue-limited exercise for 8-12 minutes. Blood pressure, HR, respiratory rate, changes in electrocardiogram characteristics, symptoms, and any arrhythmias were also recorded at baseline and during each stage of exercise and recovery.

The ramp protocol comprised four stages: an inactive stage lasting 3 minutes to determine the baseline HR, a 3-minute warm-up stage, the exercise stage, and the recovery stage, starting when the patient had reached exhaustion, lasting for 5 minutes. The test was ended if (1) the termination criteria defined in the American College of Sports Medicine guidelines were met or (2) the patient stopped the exercise.

The following data were collected on a breath-by-breath basis and averaged over 10-second intervals: VO₂, VCO₂, and minute VE. The peak VO₂ was reported as absolute (mL/minute) or relative (mL/kg/minute) and the peak work rate as absolute (watt [W]) or relative (W/kg). The VE/VCO₂ slope was calculated as the slope of the linear relationship between VE and VCO₂ from 1 minute after the beginning of the exercise until the end of the isocapnic-buffering period. The anaerobic threshold (AT) was measured using the V-slope method.

Breathing reserve (%) was calculated using the following equation: breathing reserve = 100 × (maximal voluntary ventilation – peak VE)/maximal voluntary ventilation.

**Data collection:** Datasets were created using data extracted from patients’ medical history and the CPX system. All data were separated from personal identifiers using a code to preserve patients’ privacy.

**Statistical analysis:** The statistical software package IBM SPSS, version 26.0 (IBM Corp., Armonk, NY, USA), was used for all analyses. All continuous data were reported as means ± standard deviations or medians (25th-75th percentiles), depending on the normality of the data distribution, whereas all categorical variables were reported as counts (percentages). Continuous variables were compared between the groups with the unpaired t-test, and χ² analysis was used to assess the differences in categorical variables. The Shapiro-Wilk test was used to assess normality. Stepwise linear regression was used to establish equations for absolute peak VO₂, VO₂ at the AT, peak VCO₂, peak VE, and peak work rate. The adjusted r² was used to assess the goodness of fit of the equations. Statistical differences with a two-tailed P value of < 0.05 were considered significant.

**Results**

**Anthropometric characteristics:** A total of 635 adult patients were included in this study. A summary of the baseline demographics and therapy is presented in Table I. The two groups had a comparable left ventricular ejection fraction, grip force, hypertension stage, and beta-blocker use. Patients with a low PP (< 60 mmHg) were younger, tended to be male, were taller, weighed more, and had a larger body mass index than patients with a high PP. Moreover, patients with a low PP had a higher prevalence of smoking and a higher distance in the 6-minute walking test. The carotid-femoral pulse-wave velocity was higher in the high PP group. Patients with a high PP had a high prevalence of coronary heart disease.

**Primary CPX variables of participants:** Most of the cardiopulmonary variables at rest, exercise capacity variables, gas exchange response to maximal exercise, and cardiovascular response to maximal exercise exhibited significant statistical differences between the groups. The only exceptions were the peak work rate (W/kg), reason for termination of exercise (n, %), breathing reserve (%),...
In the absence of clinical events, CPX was self-interrupted by the patients when they stated that they were exhausted, and the proportions were 64.5% and 72.0% in the low and high PP groups, respectively. The AT could not be determined in 3.7% and 7.7% of patients in each group, respectively (Table II).

Predictive equations for the primary CPX variables for patients with hypertension: The stepwise linear regression analysis showed that height was only significantly predictive of VO₂ at the AT (β = −0.06) and PP was significantly predictive of peak VO₂ (β = −51.95), peak VE (β = −3.84), and absolute peak work rate (β = −7.32). Age, weight, and sex were significantly predictive of all five CPX variables. The values of five CPX variables declined with age (with all β < 0), increased with a higher weight (with all β > 0), and were higher in men than in women.

The predictive equations for absolute peak VO₂ (adjusted \( r^2 = 0.595, P < 0.001 \)), VO₂ at the AT (adjusted \( r^2 = 0.114, P < 0.001 \)), peak VO₂ (adjusted \( r^2 = 0.491, P < 0.001 \)), peak VE (adjusted \( r^2 = 0.446, P < 0.001 \)), and absolute peak work rate (adjusted \( r^2 = 0.623, P < 0.001 \)) exhibited good linear fits (Table III).

Discussion

To our knowledge, this is the first study in which the primary CPX variables in patients with primary hypertension were described. The study demonstrated the following: (1) patients with primary hypertension with a high PP had impaired cardiopulmonary ability both at rest and during exercise and had impaired submaximal exercise capacity; (2) the AT could not be determined in 7.7% of patients with a high PP, compared with 3.7% among patients with a low PP, which indicated that they could not reach...
anaerobic metabolism during incremental exercise; (3) among patients with primary hypertension, a high PP was associated with a lower peak VO2, peak VE, and absolute peak work rate; and (4) the reason for the decreased exercise ability may be low skeletal muscle mass rather than low cardiopulmonary function. Our results may aid in the guidance regarding CPX for patients with primary hypertension, which is currently lacking.

As race-related differences may account for the observed differences in CPX variables, we compared the results in the present study with those of a healthy Chinese cohort.13) Regarding the CPX results among the total cohort in the present study, the mean value of the peak voluntary VE was 26.4% lower, forced vital capacity was 15.8% lower, forced expiratory volume in the first second was 15.8% lower, the peak work rate was 50.3% lower, and the HR recovery 1 minute after exercise was 46.3% lower than those in the healthy Chinese cohort. The lower values indicated that our patient cohort had an impaired cardiopulmonary ability at rest and during exercise, which was more serious among patients with a high PP.

In the present study, patients without clinical events stopped the CPX when they were exhausted, which was the most common reason for stopping the exercise (64.5% and 72.0% in the low and high PP groups, respectively), with a mean value of 68.2%. Peripheral muscle dysfunction seemed to contribute to exercise intolerance, similar to what we have observed (unpublished data) regarding the CPX characteristics of patients with heart failure and atrial fibrillation.

The AT was unidentified in 7.7% of patients with a high PP and 3.7% of patients with a low PP. The rate was much lower compared with 27% in patients with heart failure and atrial fibrillation,14) which is probably due to a greater perfusion/contraction mismatch in the working muscles of patients among HF that implies an intramuscular uneven onset of anaerobic metabolism.14) Among the 121 patients with coronary heart diseases, the numbers of patients with unidentified AT in the high and low PP groups were only 2 and 11. It revealed that the cardiopulmonary ability per se could not explain the decreased exercise ability in the current cohort. Combined with the result that the most common reason for stopping exercise is fatigue, the reason for the decreased exercise ability might be low skeletal muscle mass rather than low cardiopulmonary function.

In terms of the cardiovascular and metabolic responses during CPX, the low peak VO2, VO2 during the AT, dVO2/dWork rate, peak HR, and peak O2 pulse reflected an impaired circulatory response in patients with a high PP.

The mean HR recovery was 17 in the present study, which is lower than that of 32 in the healthy Chinese cohort.13) A slower HR recovery in the first minute post exercise (≤ 18 beats/minute) is reportedly correlated with a reduced peak VO2, VO2/peak work rate, and O2 pulse among patients with pulmonary arterial hypertension.15) However, the prognostic value of HR recovery in patients with primary hypertension may differ from that of such patients, and it would be an interesting topic for further investigation.

Although ventilatory efficiency was normal, as indicated by the VE/VCO2 slope, patients with a high PP had a higher value. The mechanism of the effect of primary hypertension on ventilatory efficiency is unknown, but recent data from the FRIEND study revealed that the VE/VCO2 slope is correlated with age, body mass index, and sex (equation: 26.4 + 0.09 [age] − 0.08 [body mass index in kg/m2] + 0.83 [sex: male = 0, female = 1]).16) The fact that the patients in the high PP group were older and were more likely to be female may have partially contributed to the slightly higher VE/VCO2 slope than that of the low PP group. The effect of a high PP on ventilatory efficiency warrants further investigation.

This study demonstrated that an elevated PP among patients with primary hypertension was associated with an impaired submaximal exercise capacity, reflected in impairments in most CPX variables.

On the basis of the stepwise linear regression results, among the five covariates used to establish the predictive equations, the equations with height were only significantly predictive of VO2 at the AT. PP was significantly predictive of peak VO2, peak VE, and absolute peak work rate. The predicted peak VO2 value declined with age at a yearly rate of 12.5 mL/minute and increased with weight at a rate of 11.88 mL/minute/kg. The tendency was similar for the peak VCO2. All five CPX variables exhibited higher values in men than those in women. Moreover, the peak VO2, peak VE, and absolute peak work rate were lower with a high PP, and VO2 at the AT decreased with height. After adjustment for age, weight, height, and sex, the PP was only significantly predictive of peak VO2, peak VE, and absolute peak work rate. Hence, a high PP was associated with reduced anaerobic exercise ability. The

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**Table III. Predictive Equations of the Primary CPX Variables for Cycle Ergometry**

| Dependent variables | Constant | Age (years) | Weight (kg) | Height (cm) | Sex | PP | P value | Adjusted r2 | SEE |
|---------------------|----------|-------------|-------------|-------------|-----|----|---------|------------|-----|
| Peak VO2 (mL/minute) | 1280.83  | −12.50      | 11.88       | -           | 210.58 | −51.95 | < 0.001 | 0.595      | 262.543 |
| VO2/AT (mL/minute)  | 32.38    | −0.06       | 0.09        | −0.06       | 1.89  | -   | < 0.001 | 0.114      | 2.803   |
| Peak VCO2 (L/minute)| 1814.73  | −18.65      | 10.45       | -           | 240.10 | -    | < 0.001 | 0.491      | 372.647 |
| Peak VE (L/minute)  | 50.47    | −0.43       | 0.29        | -           | 10.25 | −3.84 | < 0.001 | 0.446      | 12.701  |
| Peak work rate (watts) | 137.70  | −1.41       | 0.76        | -           | 20.03 | −7.32 | < 0.001 | 0.623      | 23.097  |

AT indicates anaerobic threshold; CO2, production of carbon dioxide; CPX, cardiopulmonary exercise; PP, pulse pressure; SEE, standard error of the estimate; VE, ventilation per minute; VO2, oxygen consumption; -, variables were considered in the analysis but had no significant effect on the prediction (P > 0.05). Stepwise linear regression analysis was used to establish the equations. *Sex as a binary variable: female = 1 and male = 2. †PP as a binary variable: low PP = 1 and high PP = 2.
prediction of height with \( VO_2 \) contrasted with results among Westerners [17,18] and Asians, [19] which may be attributable to differences in the methodology of testing, patient health, and population selection bias because of race-related differences.

We divided the cohort with PP level because of several reasons. Data from the Framingham Heart Study and other studies indicate that SBP increases continuously across all age groups whereas DBP increases until age 60 years and then begins to decrease steadily. As a result, PP may become a more important blood pressure measure associated with CVD in older individuals. This could be confirmed from the research results that owing to arterial stiffening with increasing age, PP markedly rises after the fifth decade of life. [20,21] Thus, in consideration of patient’s characteristics, we choose PP instead of other measures of blood pressure (e.g., SBP) as the grouping factor and predictor for primary CPX variables.

This study had certain limitations. Owing to its retrospective, single-center design, the patients’ muscle mass and exercise habits were not considered. Moreover, we could not confirm the duration of the hypertension. The impacts of these factors on the CPX results require further investigation. Nevertheless, we provided the first reference values for Chinese patients with primary hypertension based on CPX using a cycle ergometer. Combined with the normal reference values for the Chinese population, CPX variables could provide more information regarding the diagnosis, prognosis, and therapeutic benefits in hypertension.

This study demonstrated markedly different values for primary CPX variables and established predictive equations for peak \( VO_2 \), \( VO_2 \) at the AT, peak \( VCO_2 \), peak VE, and peak work rate, with a good linear fit in Chinese patients with primary hypertension. It also demonstrated that patients with primary hypertension had impaired submaximal exercise capacity, especially those with a high PP. The reason for the decreased exercise ability among older Chinese patients with primary hypertension may be low skeletal muscle mass rather than a decrease in cardio-pulmonary function.

The results of the present study may find application in the interpretation of the performance of patients during CPX using cycle ergometry. The results also provided a valuable opportunity to rethink how the low skeletal muscle mass would affect exercise ability among patients with cardiopulmonary disability (e.g., coronary heart disease and heart failure). This may further improve the guidance of exercise prescription among Chinese patients with primary hypertension and other cardiopulmonary diseases.

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Disclosure

Conflicts of interest: None.

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