

## Association of Resting Heart Rate with Infrarenal Aortic Diameter: A Cross Sectional Study in Chinese Hypertensive Adults

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### WHAT THIS PAPER ADDS

The association between resting heart rate (RHR) and aortic diameter has rarely been studied. In the current study, results showed a negative association between RHR and maximum infrarenal aortic diameter, and that in females, such an association may be potentially exaggerated by smoking. These results suggest that RHR may affect aortic diameter, and that RHR should be taken into consideration in further epidemiological investigations. This is the first report of the prevalence of AAA in Chinese hypertensive adults, which differs significantly from the incidence in Western countries.

**Objective:** Elevated resting heart rate (RHR) has been shown to be a risk marker for cardiovascular disease. Results from studies on the effects of RHR in large arteries are limited to the functional changes of those arteries, while the association between RHR and aortic diameter remains largely understudied.

**Methods:** This was a cross sectional study of hypertensive Chinese adults from rural areas. The maximum infrarenal aortic diameter (maxIAD) from renal arteries to the iliac bifurcation was obtained by ultrasound. MaxIADs in different RHR groups were compared in males and females separately because of the significant differences between sexes. Multiple regression analysis was used to determinate the correlation between RHR and maxIAD. Further interactions between three factors (BMI, smoking, and anti-hypertensive regimens) and RHR for maxIAD were examined using subgroup analysis.

**Results:** 19,200 subjects were enrolled in the study, with an average age of  $64.8 \pm 7.4$  years and 61.6% females. Only 22 cases (0.11%) were detected with AAA, with males ( $n = 17$ ) presenting a higher AAA incidence than females ( $n = 5$ ). In subjects  $\geq 65$  years, there were 18 (0.19%) AAA, and 15 (83.3%) had a history of smoking. In the total subjects, the mean maxIAD ranged from  $15.7 \pm 2.1$  mm to  $15.2 \pm 2.2$  mm as RHR changed from the lowest quartile to the highest ( $\geq 84$  bpm) in males, with a similar tendency observed in females. The correlation coefficient of RHR on maxIAD was  $-0.17$  in males and  $-0.12$  in females. Further subgroup analysis revealed that smoking exaggerated the correlation between RHR and maxIAD, but only in females.

**Conclusions:** A low AAA incidence was observed in this hypertensive Chinese population. There was a negative association between RHR and maxIAD, potentially exaggerated by smoking, especially in females.

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### INTRODUCTION

Numerous clinical trials and epidemiological studies have demonstrated an association between resting heart rate (RHR) and cardiovascular disease, and have concluded that elevated RHR is a risk marker for cardiovascular disease,<sup>1–3</sup> and an independent marker for predicting all cause and cardiovascular death.<sup>4–7</sup> Further studies have revealed the potential mechanisms of RHR on the coronary artery and cardiac muscle. For the coronary artery, elevated HR affects

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the vascular endothelium,<sup>8,9</sup> catalyzes the atherosclerotic process,<sup>10,11</sup> increases the arterial stiffness,<sup>12</sup> causes atherosclerotic plaques prone to rupture,<sup>13</sup> and finally leads to its stenosis or occlusion. For the cardiac muscle, elevated HR augments ventricular wall stiffness,<sup>14</sup> reduces diastolic time and myocardial blood supply and simultaneously increases the myocardial oxygen consumption, and finally exacerbates myocardial ischemia and arrhythmias.<sup>15</sup>

An important part of the cardiovascular system, the aorta has a similarly complex physical structure as the heart. Aortic smooth muscle cells (SMCs) have elasticity of relaxation and contraction, while the endothelial layer also participates in many physiological and pathological processes, such as atherosclerosis and necrosis.<sup>16,17</sup> Thus, the aorta is subject to the influence of the RHR. Some clinical studies have shown a significant correlation between RHR and the functional changes of large arteries, mainly pulse wave velocity.<sup>18,19</sup> However, the correlation between RHR and a change in arterial diameter has not been carefully studied.

The infrarenal aorta is the weakest segment of the aorta because of its thin middle layer, which mainly consists of elastic fibers and smooth muscle cells.<sup>20</sup> Hence, it is prone to pathological changes compared with other parts of the aorta, including aneurysmal dilatation and atherosclerotic stenosis (AS), which eventually cause a change in the infrarenal aortic diameter (IAD). The current study investigated the correlation between RHR and maximal IAD (maxIAD), which may offer important clues about the effect of RHR on the aorta. To the authors' knowledge, there has been no other published work on this topic.

## METHODS

### *Study design and study participants*

The study participants were taken from a population based study which began in 2008 and aimed to investigate whether a combination of lowering blood pressure (BP) and homocysteine was more effective than lowering BP alone in reducing of the risk of stroke in hypertensive patients. All of the voluntary participants were "relatively healthy hypertensives" from rural areas in Lianyungang, Jiangsu province and Anqing, Anhui province, China, and met the inclusion criteria as follows: 1. aged 45–75 years; and 2. resting systolic blood pressure (SBP)  $\geq 140$  mmHg and/or resting diastolic blood pressure (DBP)  $\geq 90$  mmHg on two screening visits (with at least 24 hours between each visit) or who were currently undergoing anti-hypertensive treatment. Participants were excluded if they had a history of myocardial infarction, stroke, heart failure, cancer, and/or serious mental disorders; or if they were unwilling to participate in the survey. Participants were scheduled for follow up every 3 months. Each visit included an assessment of RHR, BP, trial medication compliance, concomitant use of other medications, and adverse events.

At the last follow up visit, which was carried out between July and August 2013, aortic diameters were measured for all study participants, with the aim of investigating abdominal aortic diameter and the prevalence of abdominal

aortic aneurysm (AAA) in this hypertensive Chinese population. At the visit, basic information, BP, RHR, electrocardiograms, and blood tests were all re-collected, and the data were used for the final analysis. Written informed consent was obtained from each participant before data collection. Approval for this study was obtained from the human subject committee at the Biomedical Institute of the Anhui Medical University (clinical trials.gov identifier: NCT00794885).

In the current study, subjects were excluded if they: 1. had been using  $\beta$  blockers (such as metoprolol, esmolol) which have an effect on RHR; 2. had a severe spinal malformation or were severely obese (BMI  $\geq 35$  kg/m<sup>2</sup>) because in these circumstances the aorta cannot be adequately or accurately measured with ultrasound; or 3. had severe hypertension (SBP  $\geq 180$  mmHg and/or DBP  $\geq 110$  mmHg), because in this condition the aorta would potentially be injured.

### *Data collection*

Baseline information was collected through questionnaires that were specifically designed and conducted by trained research staff.<sup>21</sup> Height, weight, waist circumference, and resting blood pressure (BP) were measured according to the standard procedure. Body mass index (BMI) was calculated by weight in kilograms divided by height in meters squared. RHR was measured by palpating the radial pulse for 30 seconds after resting quietly for 10 minutes, and this was repeated twice. Mean RHR was determined by calculating the average of the three values.

Blood samples were obtained from each subject after 12–15 hours of fasting. Serum or plasma samples were separated within 30 minutes and stored at  $-70^{\circ}\text{C}$ . Laboratory indicators (including fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC) and homocysteine) were measured in the normal way.<sup>21</sup>

### *Abdominal aorta evaluation*

A professional ultrasound machine (SonoScape Technologies, Shenzhen, China), with a 3.5 MHz real time sector scanner, was used for screening and measurement. Ultrasound examinations were performed by specially trained technicians from the Vascular and Endovascular Surgery Department of PLA General Hospital in Beijing, China. An examination of each subject was scheduled for approximately 15 minutes. The procedure was as follows: Participants lay on a bed in the supine position with their abdomen exposed. First, a longitudinal scan of the aorta from the level of the renal arteries to the aortic bifurcation was conducted to see whether obvious dilation or stenosis could be identified. Next, the diameter of the abdominal aorta was measured between two points, the first point just inferior to the level of the renal arteries and the second point at the aortic bifurcation. If an obvious dilation existed in the middle of the abdominal aorta, the diameter of its widest point was also taken. Each point was measured antero-posteriorly and

transversely according to the “leading edge to leading edge” principle. The mean value was calculated. The largest diameter of these two or three points was defined as the maxIAD.

Inter- and intra-observer measurement reliability were also assessed. In total, 100 cases were sampled in random from the whole study population, with approximately equal numbers of males and females, and approximately equal numbers from each age group (<60 years, 60–69 years, ≥70 years). To evaluate inter-observer reliability, five trained technicians performed independent measurements of the 100 case sample in random order. Then one of the observers repeated these same measurements 1 week later in random order to assess intra-observer reliability. Finally, inter- and intra-observer agreement was assessed based on the method proposed by Bland and Altman.<sup>22</sup> The results (Appendix I) showed that intra-observer difference was 0.13 mm, 95% limits of agreement –2.03–2.29 mm. Four inter-observer (observer 1 versus others) differences were also calculated, they were between 0.16 and 0.27mm, the widest limits of agreement were –3.40–3.72mm. Bland-Altman plots revealed no significant differences within or between observers.

### Statistical analysis

Descriptive statistics of the study population by sex were summarized by means of frequencies, as appropriate. The differences between sexes were compared using a *t* test or chi-square test. The distribution of maxIAD is presented by quartiles of RHR (defined as groups 1 to 4 from the lowest quartile to the highest) based on its distribution in the population, and a one way analysis was used for testing the differences. In view of the significant differences in maxIAD between males and females, all of the analyses in the current study were conducted in males and females separately. The effects of RHR (as a continuous variable and a categorical variable, respectively) on maxIAD were estimated using linear regression models. Model 1 was adjusted for age; model 2 was adjusted for centers, age, BMI, waist circumference, anti-hypertensive regimens, SBP, DBP, FPG, TG, TC, smoking and drinking conditions. Furthermore, considering that BMI, smoking and antihypertensive drugs may potentially influence both RHR and aortic diameter according to published papers,<sup>26,28–30</sup> subgroup analysis was performed to examine the potential interactions between RHR and these factors separately. For the subgroup analysis, with RHR as a continuous

**Table 1.** Characteristics of study population by sex.

| Characteristic                        | Overall<br>( <i>n</i> = 19,200) | Male<br>( <i>n</i> = 7377) | Female<br>( <i>n</i> = 11,823) | <i>p</i> |
|---------------------------------------|---------------------------------|----------------------------|--------------------------------|----------|
| Center <sup>a</sup>                   |                                 |                            |                                | <.001    |
| Lianyungang                           | 14,022 (73.0%)                  | 5,194 (70.4%)              | 8,828 (74.7%)                  |          |
| Anqing                                | 5,178 (27.0%)                   | 2,183 (29.6%)              | 2,995 (25.3%)                  |          |
| Age (years) <sup>b</sup>              | 64.8 ± 7.4                      | 65.9 ± 7.4                 | 64.1 ± 7.3                     | <.001    |
| RHR (bpm) <sup>b</sup>                | 76.8 ± 11.4                     | 75.8 ± 11.7                | 77.5 ± 11.2                    | <.001    |
| BMI (kg/m <sup>2</sup> ) <sup>b</sup> | 24.7 ± 3.6                      | 23.9 ± 3.5                 | 25.2 ± 3.6                     | <.001    |
| Waist circumference (cm) <sup>b</sup> | 84.9 ± 10.4                     | 84.2 ± 10.7                | 85.3 ± 10.2                    | <.001    |
| SBP (mmHg) <sup>b</sup>               | 135.7 ± 16.3                    | 133.2 ± 16.1               | 137.3 ± 16.2                   | <.001    |
| DBP (mmHg) <sup>b</sup>               | 81.5 ± 10.3                     | 81.8 ± 10.8                | 81.3 ± 10.0                    | .001     |
| FPG (mmol/L) <sup>b</sup>             | 6.2 ± 2.2                       | 6.2 ± 2.1                  | 6.2 ± 2.2                      | .99      |
| TC (mmol/L) <sup>b</sup>              | 5.3 ± 1.3                       | 5.0 ± 1.3                  | 5.4 ± 1.3                      | <.001    |
| Triglycerides (mmol/L) <sup>b</sup>   | 1.8 ± 1.4                       | 1.6 ± 1.4                  | 1.9 ± 1.4                      | <.001    |
| Homocysteine (mmol/L) <sup>b</sup>    | 13.7 ± 7.5                      | 15.8 ± 9.7                 | 12.4 ± 5.3                     | <.001    |
| Antihypertensive drugs <sup>a</sup>   |                                 |                            |                                | <.001    |
| No anti-hypertensive treatment        | 1688 (8.8%)                     | 538 (7.3%)                 | 1,150 (9.7%)                   |          |
| ACEI+CCB+diuretics                    | 4,162 (21.7%)                   | 1,846 (25.0%)              | 2,316 (19.6%)                  |          |
| ACEI+CCB                              | 4,038 (21.0%)                   | 1,800 (24.4%)              | 2,238 (18.9%)                  |          |
| ACEI                                  | 3,077 (16.0%)                   | 1,132 (15.3%)              | 1,945 (16.5%)                  |          |
| ACEI+diuretics                        | 1,935 (10.1%)                   | 745 (10.1%)                | 1,190 (10.1%)                  |          |
| Others                                | 4,300(22.4%)                    | 1,316 (17.8%)              | 2,984 (25.2%)                  |          |
| Smoking <sup>a</sup>                  |                                 |                            |                                | <.001    |
| Never                                 | 13,152 (68.5%)                  | 1,864 (25.3%)              | 11,288 (95.5%)                 |          |
| Past smoking                          | 2,113 (11.0%)                   | 1,899 (25.7%)              | 214 (1.8%)                     |          |
| Current smoking                       | 3,935 (20.5%)                   | 3,614 (49.0%)              | 321 (2.7%)                     |          |
| Drinking <sup>a</sup>                 |                                 |                            |                                | <.001    |
| Never                                 | 13,286 (69.2%)                  | 2,310 (31.3%)              | 10,976 (92.8%)                 |          |
| Past drinking                         | 1,945 (10.1%)                   | 1,633 (22.1%)              | 312 (2.6%)                     |          |
| Current drinking                      | 3,969 (20.7%)                   | 3,434 (46.6%)              | 535 (4.5%)                     |          |
| AAA <sup>a</sup>                      | 22 (0.11%)                      | 17 (0.23%)                 | 5 (0.04%)                      | <.001    |

ACEI = angiotensin converting enzyme inhibitors; CCB = calcium channel blockers; AAA = abdominal aortic aneurysm.

<sup>a</sup> Frequency (%).

<sup>b</sup> Mean ± SD.

variable, BMI was stratified to four categories (<19 kg/m<sup>2</sup>, 19–22.9 kg/m<sup>2</sup>, 23–26.9 kg/m<sup>2</sup>, and ≥27 kg/m<sup>2</sup>) according to the cutoff points for overweight and obesity in an Asian population,<sup>23</sup> while smoking conditions were stratified to three groups (never, past smoking, and current smoking). Current smoking was defined as having smoked at least one cigarette every day or no less than 18 packs in the last year.

All of the analyses were performed using R software (version 2.15.1). A two sided *p* value <.05 was considered to be statistically significant.

**RESULTS**

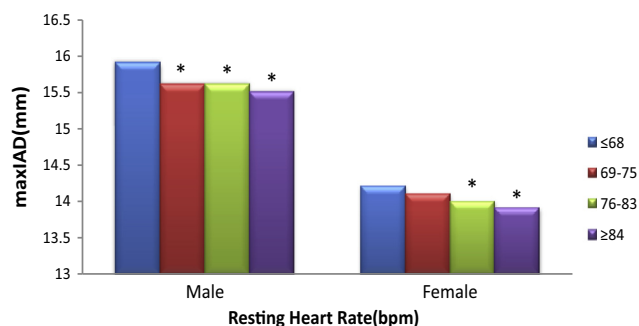
A total of 20,884 subjects underwent aortic diameter measurement. After excluding those with missing covariates (*n* = 903), use of β blockers (*n* = 43), severe obesity (BMI ≥35 kg/m<sup>2</sup>) (*n* = 198), and severe hypertension (*n* = 540), a total of 19,200 subjects were analyzed. The characteristics of the study population are shown in Table 1. Of the whole population, females comprised 61.6% (*n* = 11,823) and 73.0% (*n* = 14,022) were from Lianyungang, Jiangsu province. The average age of all participants was 64.8±7.4 years, and males were older than females. The mean RHR of males was faster than that of females. DBP and homocysteine in males were higher than in females, while BMI, waist circumference, SBP, TC, and TG were higher in females than males. Males reported a higher frequency of smoking and drinking. In all, 91.2% of participants were taking anti-hypertensives. In general, 21.7% of the population used angiotensin converting enzyme inhibitors (ACEIs) combined with calcium channel blockers (CCBs) and diuretics, 21% used ACEIs combined with CCBs, 16% used ACEIs alone, and 10.1% used ACEIs combined with diuretics. The rest of the population used other anti-hypertensive regimens, such as CCBs alone, diuretics alone, or CCBs combined with diuretics. Intriguingly, of the 19,200 subjects, only 22 cases (0.11%), with a mean age of 71.9±5.6 years, were detected with abdominal aortic aneurysm (AAA) according to the definition of having at least a 50% increase of abdominal aortic diameter compared with the adjacent normal artery, and males (*n* = 17) had a higher AAA incidence than females (*n* = 5). The mean AAA size was 29.0±7.7 mm. As Table 2 shows, 18 cases (0.19%) with AAA were present in subjects aged ≥65 years, and 77.8% were males. Fifteen cases had a history of

smoking, including 13 current smokers. In the group aged <65 years, three males and one female had an AAA, but only one case had a history of smoking.

Of the total subjects, the mean maxIAD of males ranged from 15.7±2.1 mm to 15.2±2.1 mm with elevation of RHR from the lowest quartile (≤68 bpm) to the highest quartile (≥84 bpm) (Fig. 1 and Table 3). Meanwhile, compared with group 1, the changes of maxIAD in the other RHR groups were all significant. Similarly, in females the mean maxIAD also decreased significantly with elevation of RHR.

In the analysis of the association between RHR and maxIAD, negative correlation trends were observed in both sexes (Table 4). The correlation coefficient was -0.17 mm (95% CI -0.22 to -0.13mm per 10 bpm) in males and -0.12 mm (95% CI -0.15 to -0.09 mm per 10 bpm) in females, with RHR as a continuous variable in the full adjustment model. By quartering the RHR, group 4 showed the most obvious maxIAD decrease compared with group 1, especially in males (β -0.53, 95% CI -0.67 to -0.38 mm). All of the correlation coefficients changed slightly with full adjustment, indicating an independent and reliable association between RHR and maxIAD.

Further subgroup analysis of maxIAD with RHR according to BMI groups and different anti-hypertensive drug groups indicated that both the RHR and anti-hypertensive drugs had little influence on the correlation between maxIAD and RHR. Intriguingly, smoking presented an interaction effect (Table 5). The correlation coefficient of RHR with maxIAD in females with current smoking was nearly fourfold greater



**Figure 1.** Distribution of MaxIAD in different RHR groups by sex. \* indicates *p* <.01 vs. group 1.

**Table 2.** Characteristics of subjects with and without abdominal aortic aneurysm by age.

| Characteristics               | <65 years                   |                                | <i>p</i> | ≥65 years                    |                                | <i>p</i> |
|-------------------------------|-----------------------------|--------------------------------|----------|------------------------------|--------------------------------|----------|
|                               | AAA present<br><i>n</i> = 4 | AAA absent<br><i>n</i> = 9,813 |          | AAA present<br><i>n</i> = 18 | AAA absent<br><i>n</i> = 9,365 |          |
| Male sex <sup>a</sup>         | 3 (75.0%)                   | 3,258 (33.2%)                  | 0.110    | 14 (77.8%)                   | 4,102 (43.8%)                  | .007     |
| Mean age(years) <sup>b</sup>  | 61.7 ± 2.5                  | 58.8 ± 4.2                     | 0.140    | 74.1 ± 2.8                   | 71.1 ± 3.9                     | .001     |
| Mean maxIAD (mm) <sup>b</sup> | 31.2 ± 13.9                 | 14.3 ± 2.1                     | <.001    | 28.5 ± 6.1                   | 14.6 ± 2.2                     | <.001    |
| Smoking <sup>a</sup>          |                             |                                | .702     |                              |                                | <.001    |
| Never                         | 3 (75.0%)                   | 7,251 (73.9%)                  |          | 3 (16.7%)                    | 5,895 (62.9%)                  |          |
| Past smoking                  | 0                           | 844 (8.6%)                     |          | 2 (11.1%)                    | 1,267 (13.5%)                  |          |
| Current smoking               | 1 (25.0%)                   | 1,718 (17.5%)                  |          | 13 (72.2%)                   | 2,203 (23.5%)                  |          |

<sup>a</sup> Frequency (%).

<sup>b</sup> Mean ± SD.

**Table 3.** Distribution of MaxIAD in different RHR groups by sex.

|               | Group 1<br>( $\leq 68$ bpm) | Group 2<br>(69–75 bpm)      | Group 3<br>(76–83 bpm)      | Group 4<br>( $\geq 84$ bpm) |
|---------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| <b>Male</b>   |                             |                             |                             |                             |
| N             | 2,145                       | 1,684                       | 1,805                       | 1,743                       |
| Diameter(mm)  | 15.7 $\pm$ 2.1              | 15.5 $\pm$ 2.1 <sup>a</sup> | 15.4 $\pm$ 2.3 <sup>a</sup> | 15.2 $\pm$ 2.1 <sup>a</sup> |
| <b>Female</b> |                             |                             |                             |                             |
| N             | 2,599                       | 2,678                       | 3,235                       | 3,311                       |
| Diameter(mm)  | 14.0 $\pm$ 2.0              | 13.9 $\pm$ 2.0              | 13.8 $\pm$ 2.0 <sup>a</sup> | 13.7 $\pm$ 1.9 <sup>a</sup> |

<sup>a</sup> Indicates  $p < .01$  vs. group 1.

**Table 4.** Regression analysis of maxIAD with HR groups by sex.

| RHR (bpm)          | N      | Model I<br>$\beta$ (95% CI), mm | $p$   | Model $\alpha$<br>$\beta$ (95% CI), mm | $p$   |
|--------------------|--------|---------------------------------|-------|----------------------------------------|-------|
| <b>Male</b>        |        |                                 |       |                                        |       |
| RHR, per 10 bpm    | 7,377  | -0.16 (-0.20, -0.11)            | <.001 | -0.17(-0.22, -0.13)                    | <.001 |
| RHR quartiles, bpm |        |                                 |       |                                        |       |
| Quartile 1         | 2,145  | Ref                             |       | Ref                                    |       |
| Quartile 2         | 1,684  | -0.17 (-0.30, -0.03)            | .02   | -0.20 (-0.33, -0.06)                   | .005  |
| Quartile 3         | 1,805  | -0.24(-0.38, -0.09)             | .001  | -0.28 (-0.42, -0.14)                   | <.001 |
| Quartile 4         | 1,743  | -0.47 (-0.61, -0.32)            | <.001 | -0.52 (-0.67, -0.37)                   | <.001 |
| $p$ for trend      |        |                                 | <.001 |                                        | <.001 |
| <b>Female</b>      |        |                                 |       |                                        |       |
| RHR, per 10 bpm    | 11,823 | -0.10 (-0.13, -0.07)            | <.001 | -0.12 (-0.15, -0.09)                   | <.001 |
| RHR quartiles, bpm |        |                                 |       |                                        |       |
| Quartile 1         | 2,599  | Ref                             |       | Ref                                    |       |
| Quartile 2         | 2,678  | -0.15 (-0.26, -0.04)            | .008  | -0.17 (-0.28, -0.06)                   | .002  |
| Quartile 3         | 3,235  | -0.24 (-0.35, -0.13)            | <.001 | -0.30 (-0.41, -0.19)                   | <.001 |
| Quartile 4         | 3,311  | -0.30 (-0.41, -0.19)            | <.001 | -0.36 (-0.47, -0.24)                   | <.001 |
| $p$ for trend      |        |                                 | <.001 |                                        | <.001 |

Model I was adjusted for age. Model II was adjusted for centers, age, BMI, waist circumference, SBP, DBP, FPG, TC, triglycerides, anti-hypertensive regimens, smoking and drinking conditions.

**Table 5.** Subgroup analysis of maxIAD with RHR according to smoking status by sex.

| Smoking status      | Male          |                      |       | Female         |                      |       |
|---------------------|---------------|----------------------|-------|----------------|----------------------|-------|
|                     | N             | $\beta$ (95% CI), mm | $p$   | N              | $\beta$ (95% CI), mm | $p$   |
| Never               | 1,864 (25.3%) | -0.18 (-0.27, -0.10) | <.001 | 11,288 (95.5%) | -0.11 (-0.14, -0.08) | <.001 |
| Past smoking        | 1,899 (25.7%) | -0.22 (-0.30, -0.14) | <.001 | 214 (1.8%)     | -0.20 (-0.44, 0.04)  | .11   |
| Current smoking     | 3,614 (49.0%) | -0.15 (-0.21, 0.09)  | <.001 | 321 (2.7%)     | -0.43 (-0.63, -0.23) | .001  |
| $p$ for trend       |               |                      | <.001 |                |                      | <.001 |
| $p$ for interaction |               |                      | .40   |                |                      | <.01  |

Adjusted for centers, age, waist circumference, BMI, SBP, DBP, FPG, TC, triglycerides, anti-hypertensive regimens, drinking conditions.

than that in females without smoking (-0.43 vs. -0.11,  $p < .01$ ), indicating that smoking exaggerated the correlation between RHR and maxIAD in females. However, such an interaction was not observed in males.

## DISCUSSION

Several published papers<sup>24–27</sup> have investigated the factors correlating with the aortic diameter based on cross sectional measurement, but RHR has rarely been included. The data reported here reveal an independent correlation between RHR and maxIAD, and demonstrate that people with elevated RHR tend to have smaller IAD measurement detected by ultrasound.

Vascular ultrasonography has long been used as an effective method to diagnose aneurysmal dilatation and atherosclerotic stenosis by measuring the diameter of the

vessel. The frame frequency of the ultrasound machine used for the current study was about 30–40 fps, which allowed image capture of the aorta in real time. Meanwhile, during detection, ultrasound images of the aorta were frequently captured and recorded in at least two periods of the cardiac cycle, after which the maximum diameter was identified and measured by reviewing the recorded images. Such a procedure ensured an accurate and highly reproducible measurement of maxIAD.

Although maxIAD in females was smaller than in males, the inverse relationship between RHR and maxIAD was consistent in both sexes. As both RHR and IAD correlate with several traditional cardiovascular disease risk factors, their association may be confounded by those factors. This hypothesis was explored by examining the effect of each individual risk factor on the association between RHR and



maxIAD. However, the addition of each individual factor to the model containing RHR and age did not materially affect the coefficient for maxIAD. The result indicated an independent relationship between maxIAD and RHR.

Previous studies have revealed an association between smoking and elevated RHR,<sup>28</sup> and have found that smokers tend to have increased aortic diameter.<sup>26</sup> Similarly, BMI has been positively associated with RHR, potentially because of increased sympathetic nervous system activation,<sup>29</sup> and BMI is also significantly associated with increased aortic diameter.<sup>30</sup> Given these previous associations, subgroup analyses of RHR with both smoking and BMI were performed to test the potential interactions. Intriguingly, a significant interaction between smoking and RHR for maxIAD was found among females in the present study, and smoking exaggerated the decrease in maxIAD with elevation of RHR. However, such an interaction was not observed in males. The potential mechanisms underlying these results need to be further investigated. In addition, the subgroup analysis of BMI eliminated the possibility of an interaction between BMI and RHR for maxIAD, but demonstrated a persistent relationship between RHR and maxIAD in both the obese and the non-obese populations.

The effect of RHR on the carotid and coronary arteries may provide some clues to help explain the present results. Experimental studies in animal models showed that elevated HR was associated with enhanced atherosclerotic plaque formation in the carotid and coronary arteries.<sup>9,10</sup> Further studies revealed that elevated RHR increased the magnitude and frequency of the tensile stress imposed on the arterial wall, which enhances the expression of pro-atherosclerotic genes by the endothelial cells and leads to endothelial dysfunction that then accelerates lipid deposition and atherogenesis.<sup>8,31</sup> Meanwhile, oscillatory shear stress enhanced by elevated RHR has also been shown to stimulate smooth muscle cells to proliferate and migrate from the media to the intima, with the production of metalloproteinase, leading to impairment of the organizational structure of the arterial wall,<sup>32</sup> and aggravating atherogenesis. Such potential effects of elevated RHR may cause the intima-media membranes to be thicker and the aortic lumen to be smaller. In other words, given such a mechanism, elevated HR may be prone to cause the aortic wall to develop atherosclerosis rather than dilation in the long term.

The prevalence of AAA was another interesting finding in the present population. Considering the mean maxIAD of the studied population was smaller than in a Caucasian population,<sup>30</sup> the criterion of "having at least a 50% increase of abdominal aortic diameter compared with the adjacent normal artery" was chosen as the AAA definition, rather than the diameter definition of >29 mm or >39 mm. The present results revealed that only 0.11% of the enrolled population had an AAA (0.23% in males and 0.04% in females). Even in the population aged >65 years, the incidence was only 0.19%, which was significantly less than incidences in Western countries. Recent population based prevalence in the general population in Europe has shown

falling incidences, thought to be a result of decreased smoking rates in the elderly population.<sup>33</sup> Yet, the prevalences are approximately 10 times higher than in this Chinese population: 1.5–1.7% among 65 year old men<sup>34,35</sup> and 0.4% among 70 year old women,<sup>36</sup> despite the fact that a more strict definition of AAA (diameter >29 mm) was chosen in those studies. Such results suggest that Chinese people may be less susceptible to AAA, probably as a result of genetic and/or lifestyle differences. In addition, the present results also showed that 68.2% (15/22) of AAA cases had a history of smoking, indicating a potential association between AAA and smoking, but further analysis must be performed to eliminate other interferences.

## CONCLUSIONS

The present study showed a negative correlation between RHR and maxIAD, and that such correlation may be exaggerated by smoking, especially in females. In view of this, RHR should be taken into account when aortic diameter related research is conducted. In addition, the prevalence of AAA may be significantly lower in China than in Western countries, and the potential causes need to be further investigated.

## LIMITATIONS

This study has several limitations. First, the study population was not a representative sample but one with a history of hypertension; hence, selection bias should be kept in mind in generalizing the present findings. Second, the study was cross sectional, and the effect of elevated RHR on aortic diameter cannot be certain. At the beginning of the trial, because the initial objective was to investigate the prevalence of AAA in regional areas of China, the maximum diameter of the infrarenal abdominal aorta was set as the main endpoint. Measuring the atherosclerotic plaques in the abdominal aorta, as well as the intima-media thickness and the diameter of the smallest point in the infrarenal abdominal aorta, would offer more information regarding the potential influence of RHR on the aortic wall. However, based on such a large population, the results were reliable and persuasive, and prompted further investigation of the internal mechanisms. Third, when the aortic diameter was measured, ultrasonic images of the aorta were recorded for at least one period of the cardiac cycle, after which the maximum diameter was deemed to be the systolic diameter by reviewing the recorded images. Hence, potential systematic error caused by technicians in identifying the maximum diameter should be noted. Fourth, the participants were all given different kinds of antihypertensive drugs. The potential influence of these drugs on the results should be carefully considered, although no interaction effect of the drugs was found in this study.

## CONFLICT OF INTEREST

None.

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## APPENDIX I. MEASURE OF INTRA- AND INTER-OBSERVER REPEATABILITY

|                               | Mean $\pm$ SD (mm) | 95% limits of agreement (mm) |
|-------------------------------|--------------------|------------------------------|
| Observer 1–1 (intra-observer) | 0.13 $\pm$ 1.08    | –2.03 ~ 2.29                 |
| Observer 2–1 (inter-observer) | 0.21 $\pm$ 1.47    | –2.73 ~ 3.14                 |
| Observer 3–1 (inter-observer) | 0.27 $\pm$ 1.25    | –2.24 ~ 2.77                 |
| Observer 4–1 (inter-observer) | 0.18 $\pm$ 1.26    | –2.35 ~ 2.70                 |
| Observer 5–1 (inter-observer) | 0.16 $\pm$ 1.78    | –3.40 ~ 3.72                 |

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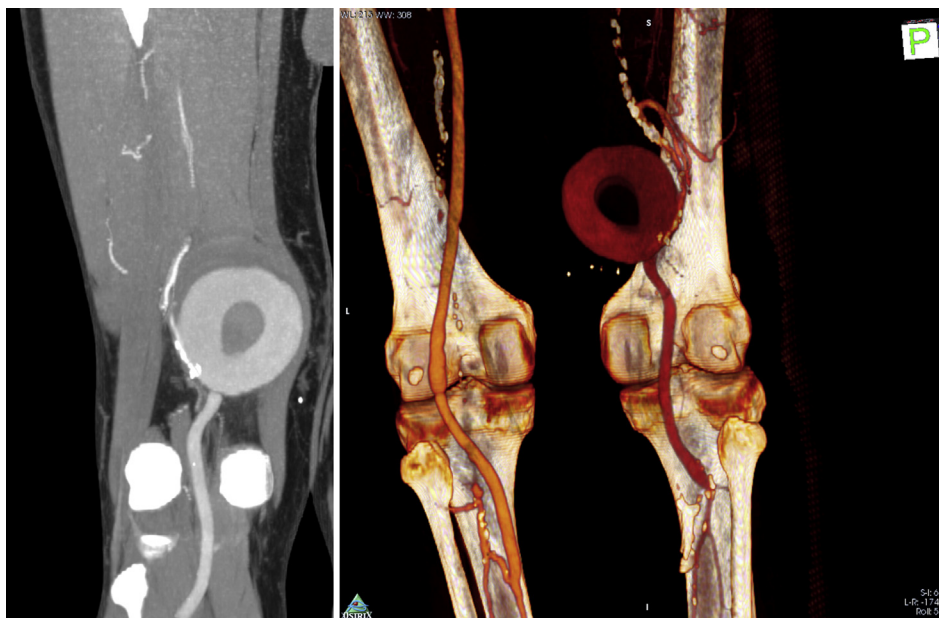
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## COUP D'OEIL

# O-shaped, Non-pulsatile Distal Superficial Femoral Artery Pseudoaneurysm in the Presence of Proximal Occlusion

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A 69 year old patient who, 10 years previously, had undergone popliteal artery aneurysm exclusion with a distal superficial femoral (SFA) to below knee popliteal artery bypass using the great saphenous vein presented with a non-pulsatile mass in the lower thigh. Computed tomography angiography revealed a “contrast ring” or “O” shaped 6.5 cm pseudoaneurysm at the proximal anastomosis fed through a large collateral via the profunda, in the presence of SFA occlusion. Pressurization of this unique pseudoaneurysm was considered low and thus it was non-pulsatile, thereby obscuring clinical evaluation. The pseudoaneurysm was resected and a bypass from the proximal SFA to the previous venous conduit below the knee was performed.

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