

Pre-anesthesia systolic blood pressure increases with age regardless of sex

Ju Mizuno · Shinya Kato · Tomoko Sato · Shigehito Sawamura

Received: 11 August 2011 / Accepted: 16 March 2012 / Published online: 15 June 2012
© Japanese Society of Anesthesiologists 2012

Abstract

Purpose Pre-anesthesia hypertension (PAH) is the temporary elevation of blood pressure (BP), compared with normal ambulatory recorded BP or self-measured BP at home, in patients waiting for operation in the operating room (OR) before anesthesia induction. In general, the incidence of sustained hypertension (SH) increases progressively with age and the increase is greater in males than in females. In this study, we investigated the influence of age and sex on PAH. **Methods** Sampling data on consecutive patients who were more than 20 years old and who had undergone surgery under general, intrathecal, or epidural anesthesia were retrospectively collected from hospital records and anesthesia records. Patients with SH, which was defined as a past history of hypertension and taking oral antihypertensive medications, were excluded from the analyses, and the data of 231 patients, 102 males and 129 females, were used for the analyses.

Results The proportions of male and female patients with a systolic BP (sBP) of more than 140 mmHg in the OR before anesthesia induction were 55.9 and 42.6 %, respectively. The proportions of male and female patients with a diastolic BP (dBP) of more than 90 mmHg were 34.3 and 23.3 %, respectively. There was no difference in the proportions of male and female patients with PAH. The

differences in sBP between measurements in the hospital room (HR) before the operation and those in the OR (Δ sBP) in males and females were 22.9 ± 25.6 and 19.0 ± 24.0 mmHg, respectively. The differences in dBP between measurements in the HR and those in the OR (Δ dBP) in males and females were 12.7 ± 16.5 and 8.4 ± 17.9 mmHg, respectively. There were no differences in Δ sBP and Δ dBP between males and females. The sBP in the OR and the Δ sBP increased significantly with age in both males and females.

Conclusion Age is an important clinical factor related to PAH. Pre-anesthesia sBP and the change in pre-anesthesia sBP increase progressively with age regardless of sex. These findings suggest that the higher BP seen in the elderly in the OR before anesthesia induction, as reported previously, might be explained in part by a greater impact of PAH in older people.

Keywords Pre-anesthesia hypertension · Before anesthesia induction · Operating room · Age · Male and female

Introduction

Clinically, we often find that blood pressure (BP) in patients awaiting operation in the operating room (OR) before anesthesia induction is temporarily elevated regardless of the patient's normal ambulatory recorded BP or self-measured BP at home. This phenomenon is called pre-anesthesia hypertension (PAH) or pre-induction hypertension [1].

A pre-operative history of sustained hypertension (SH) causes perioperative cardiac events such as myocardial ischemia, arrhythmias, cardiovascular lability [2], cerebrovascular events, and death [3]. For example, it is reported that

J. Mizuno (✉) · S. Kato · S. Sawamura
Department of Anesthesiology and the Intensive Care Unit,
Teikyo University School of Medicine, 2-11-1 Kaga,
Itabashi-ku, Tokyo 173-8605, Japan
e-mail: mizuno_ju8@yahoo.co.jp

T. Sato
Center for Integrated Medical Research, School of Medicine,
Keio University, 35 Shinanomachi, Shinjuku-ku,
Tokyo 160-8582, Japan

isolated systolic hypertension is associated with a 40 % increase in the likelihood of perioperative cardiovascular morbidity in coronary artery bypass grafting surgery patients [4]. In addition, acute intra-operative hypertension and BP lability are associated with a higher incidence of perioperative myocardial ischemia, infarction, and stroke [5]. Therefore, the presence of PAH may increase the risk of cardiac and cerebrovascular complications in the perioperative period. It is reported that the incidence of adverse outcomes (i.e., elevated troponin and in-hospital mortality) is 1.3 % for PAH overall and 2.8 % for the subset of PAH patients with baseline systolic BP (sBP) greater than 200 mmHg [1].

Clinically, SH in the elderly is characterized by a significant increase in sBP and a slight decrease in diastolic BP (dBP), and then by a significant increase in pulse pressure [6]. Arterial walls stiffen with age due to arteriosclerosis [7]. The most consistent and well-reported changes are luminal enlargement with wall thickening and a reduction in elastic properties at the level of large elastic arteries. Longstanding arterial pulsation in the central artery causes elastin fiber fatigue and fracture. Increased vascular calcification and endothelial dysfunction are also characteristic of arterial aging.

Females in the reproductive age range are less likely to develop hypertension and hypertension-related diseases than males and postmenopausal females [8]. A study using 24-h ambulatory BP monitoring has shown that BP is lower in females than in males at similar ages [6]. The epidemiological evidence suggests that females receive the anti-atherogenic effects of estrogen [9], and that there is a regulatory role for estrogens in maintaining vascular function and structure [10]. Moreover, it is known that plasma renin activity is lower in females than in age-matched males [11].

It is useful to interpret the factors affecting PAH. It is suspected that the vascular changes that occur with aging and the different hormone and enzyme concentrations in males and females may affect PAH. Therefore, in this study, we investigated the influence of age and sex on PAH.

Methods

Study population

Sampling data on consecutive patients aged more than 20 years old who underwent surgery under general, intrathecal, or epidural anesthesia were retrospectively collected from hospital records and anesthesia records in the OR at Teikyo University Hospital in May and June 2008. The sBP, dBP, and heart rate values of the patients while they rested in a hospital room (HR) of the medical

ward before entering the OR were measured once with an automatic blood pressure machine. The measurements were performed by a nurse and were documented in increments of 1 mmHg and 1 beat/min in the hospital records.

The duration of nothing per os (NPO) before elective operation in the patient cohort was more than 8 h. The patients did not have any premedication, and they walked into the OR or entered the OR on a stretcher or in a wheelchair. Electrocardiogram (ECG) patches were placed on the patient's chests and an arterial pressure cuff was positioned on the patient's upper arm by an anesthesiologist. After the patients had rested on the operating table for 3 min, the sBP and dBP values were measured with an automatic blood pressure machine and the heart rate value was measured with an ECG monitor. The sBP and dBP values were documented in increments of 5 mmHg and the heart rate value was documented in increments of 5 beats/min in the anesthetic records. Patients with a pre-operative history of SH; those taking oral antihypertensive medications such as calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, α -blockers, β -blockers, or diuretics; and those showing arrhythmias on the pre-operative 12-lead ECG were excluded from the analyses.

Statistical analysis

The statistical software we used was SPSS 16.0vJ (SPSS, Chicago, IL, USA) and Deltagraph 5.4.5v J (Deltapoint, Monterey, CA, USA). The unpaired Student's *t*-test was used for comparisons of age, height, weight, body mass index (BMI), sBP, dBP, and heart rate between males and females. The paired Student's *t*-test was used for comparisons of sBP, dBP, and heart rate between the measurements in the HR and those in the OR. The χ^2 test was used for comparisons of the proportions of hypertensive patients between males and females. Simple linear regression analyses between the sBP values in the HR and age, the sBP values in the OR and age, the difference in sBP between the HR and OR (Δ sBP) and age, and the difference in dBP between the HR and OR (Δ dBP) and age were performed. The values are expressed as the mean \pm standard deviation (SD) unless otherwise noted. A *P* value of <0.05 was considered to indicate statistical significance.

Results

Sampling items

The total data of 365 patients were collected; they had no cardiac or cerebrovascular events in the perioperative

periods. Seven patients had atrial fibrillation on pre-operative 12-lead ECG and were omitted from the analyses. Also, the pre-operative medical history of 1 patient, the sBP values of 2 patients in the HR, and the sBP values of 3 patients in the OR were missed or not completely noted in hospital records and anesthesia records. The incomplete data of these 6 patients were also omitted from the analyses. Further, 112 patients had a pre-operative history of SH and 109 patients were taking oral antihypertensive drugs. Thus, 121 patients were excluded from the analyses.

Therefore, the data of 231 patients, 102 males and 129 females, were used for the analyses. Table 1 shows the demographic characteristics of this patient cohort. The patients were from the departments of orthopedic surgery (59), general surgery (38), otorhinolaryngology (28), urology (26), gynecology (25), plastic surgery (18), obstetric surgery (12), oromaxillofacial surgery (6), neurosurgery (4), ophthalmology (4), psychiatry (3), emergency (3), dermatology (2), cardiac surgery (1), thoracic surgery (1), and anesthesiology (1).

Table 2 shows the hemodynamic data in the HR and OR. The sBP in both the HR and OR were higher in males than in females. However, there was no difference in Δ sBP between males and females. There was no difference in dBP in the HR between males and females, but dBP in the OR was higher in males than in females. However, there was no difference in Δ dBP between males and females. There were no differences between males and females in the heart rate values in the HR and OR, and there was also no difference between males and females in changes in the heart rate between the HR and OR (Δ heart rate).

Age and sex differences

In the total population, the proportion of patients who had an sBP of more than 140 mmHg in the HR was 8.7 % (20/231 patients), and the proportions of male and female patients who had an sBP of more than 140 mmHg in the HR were 10.8 % (11/102 patients) and 7.0 % (9/129 patients), respectively. There was no difference between males and females in the

Table 1 Demographic characteristics

Characteristics	Total (<i>n</i> = 231)	Male (<i>n</i> = 102)	Female (<i>n</i> = 129)	<i>P</i> value (male vs. female)
Age (years)	50.4 ± 16.4	52.8 ± 18.3	48.5 ± 14.5	0.04
Height (cm)	161.9 ± 9.1 (<i>n</i> = 227)	168.4 ± 7.0 (<i>n</i> = 101)	156.7 ± 6.9 (<i>n</i> = 126)	<0.001
Weight (kg)	59.5 ± 12.5 (<i>n</i> = 229)	65.4 ± 11.5 (<i>n</i> = 101)	54.8 ± 11.3 (<i>n</i> = 128)	<0.001
BMI (kg/m ²)	22.6 ± 3.9 (<i>n</i> = 227)	23.0 ± 3.7 (<i>n</i> = 101)	22.3 ± 4.0 (<i>n</i> = 126)	0.16

Values are means ± standard deviation (SD)

BMI body mass index

Table 2 Hemodynamic data in the hospital room (HR) and operating room (OR)

Measurements	Total (<i>n</i> = 231)	Male (<i>n</i> = 102)	Female (<i>n</i> = 129)	<i>P</i> value (male vs. female)
sBP in HR (mmHg)	119.1 ± 14.1	122.3 ± 13.5	116.5 ± 14.2	0.002
sBP in OR (mmHg)	139.8 ± 27.9	145.2 ± 28.2	135.6 ± 27.0	0.009
Δ sBP	20.7 ± 24.7	22.9 ± 25.6	19.0 ± 24.0	0.24
<i>P</i> value (HR vs. OR)	<0.001	<0.001	<0.001	
dBP in HR (mmHg)	69.6 ± 11.6	70.7 ± 11.2	68.8 ± 11.8	0.20
dBP in OR (mmHg)	79.9 ± 17.0	83.4 ± 17.1	77.1 ± 16.5	0.005
Δ dBP	10.3 ± 17.4	12.7 ± 16.5	8.4 ± 17.9	0.06
<i>P</i> value (HR vs. OR)	<0.001	<0.001	<0.001	
Heart rate in HR (beats/min)	74.9 ± 10.8 (<i>n</i> = 222)	75.9 ± 10.0 (<i>n</i> = 97)	74.2 ± 11.3 (<i>n</i> = 125)	0.24
Heart rate in OR (beats/min)	78.1 ± 14.4 (<i>n</i> = 225)	77.6 ± 13.1 (<i>n</i> = 97)	78.6 ± 15.3 (<i>n</i> = 128)	0.67
Δ Heart rate	4.1 ± 26.3	1.6 ± 30.2	6.1 ± 22.8	0.20
<i>P</i> value (HR vs. OR)	0.006	0.35	0.006	

Values are means ± SD

sBP systolic blood pressure, Δ sBP difference in sBP between the HR and OR, dBP diastolic blood pressure, Δ dBP difference in dBP between the HR and OR, Δ Heart rate difference in heart rate between the HR and OR

proportion of patients with an sBP of more than 140 mmHg in the HR. Simple linear regression lines drawn between the sBP values in the HR and the age of the total population; the sBP values in the HR and the age of the males, and the sBP values in the HR and the age of the females are shown in Fig. 1. The sBP in the HR of the total population and that of the females increased significantly with age.

In the total population, the proportion of patients with a dBP of more than 90 mmHg in the HR was 5.2 % (12/231 patients) and the proportions of male and female patients who had a dBP of more than 90 mmHg in the HR were 3.9 % (4/102 patients) and 6.2 % (8/129 patients), respectively. There was no difference between males and females in the proportion of patients with a dBP of more than 90 mmHg in the HR. The dBP in the HR of the total population and these values in the males and females did not increase significantly with age.

In the total population, the proportion of patients with an sBP of more than 140 mmHg in the OR was 48.5 % (112/231 patients) and the proportions of male and female patients were 55.9 % (57/102 patients) and 42.6 % (55/129 patients), respectively. There was no difference between males and females in the proportion of patients with an sBP of more than 140 mmHg in the OR. Simple linear regression lines drawn between the sBP values in the OR and the age of the total population, the sBP values in the OR and the age of the males, and the sBP values in the OR and the age of the females are shown in Fig. 2. The sBP in the OR

of the total population and the values in the males and females increased significantly with age.

In the total population, the proportion of patients with a dBP of more than 90 mmHg in the OR was 28.1 % (65/231 patients) and the proportions of male and female patients were 34.3 % (35/102 patients) and 23.3 % (30/129 patients), respectively. There was no difference between males and females in the proportions of patients with a dBP of more than 90 mmHg in the OR. The dBP in the OR of the total population increased significantly with age ($P = 0.004$), but the dBP in the OR of males and that of females did not increase significantly with age.

The sBP values in the OR of the total population and the values in male and female patients were significantly higher than those in the HR, as shown in Table 2. Simple linear regression lines drawn between the Δ sBP values and the age of the total population and the ages of the males and females are shown in Fig. 3. The Δ sBP values of the total population and the values of the males and females increased significantly with age.

The dBP values in the OR of the total population and the values in male and female patients were significantly higher than those in the HR, as shown in Table 2. Simple linear regression lines drawn between the Δ dBP values and the age of the total population and the ages of the males and females are shown in Fig. 4. The Δ dBP of the total population and that of the males increased significantly with age.

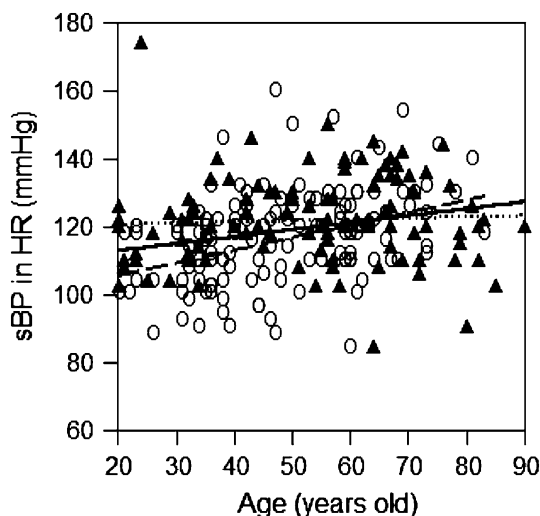


Fig. 1 Systolic blood pressure (sBP) in the hospital room (HR) related to age. *Solid line* linear regression line for total population ($n = 231$). $sBP = 0.206 \times \text{age} + 108.724$ ($r = 0.239$, $P < 0.001$). *Dotted line* linear regression line for males (*closed triangles*, $n = 102$). $sBP = 0.037 \times \text{age} + 120.355$ ($r = 0.051$, $P = 0.611$). *Dashed line* linear regression line for females (*open circles*, $n = 129$). $sBP = 0.372 \times \text{age} + 98.517$ ($r = 0.382$, $P < 0.001$)

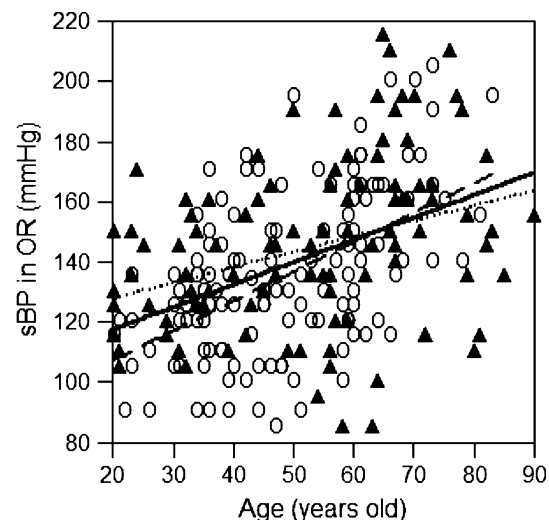


Fig. 2 sBP before anesthesia induction in the operating room (OR) related to age. *Solid line* linear regression line for total population ($n = 231$). $sBP = 0.745 \times \text{age} + 102.323$ ($r = 0.438$, $P < 0.001$). *Dotted line* linear regression line for males (*closed triangles*, $n = 102$). $sBP = 0.509 \times \text{age} + 118.277$ ($r = 0.331$, $P = 0.001$). *Dashed line* linear regression line for females (*open circles*, $n = 129$). $sBP = 0.982 \times \text{age} + 88.056$ ($r = 0.527$, $P < 0.001$)

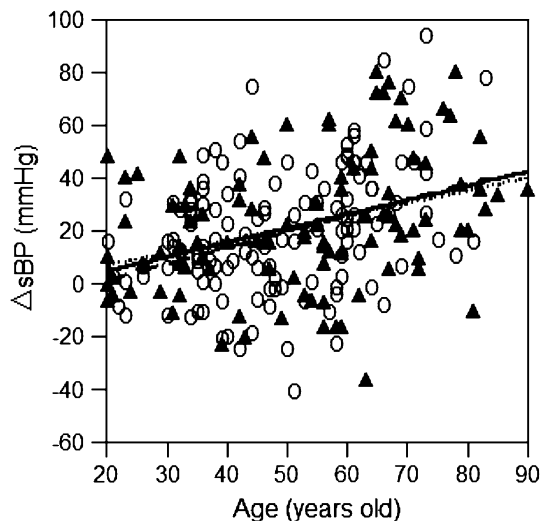


Fig. 3 Difference in sBP between the HR and OR (Δ sBP) with age. *Solid line* linear regression line for total population ($n = 231$). Δ sBP = $0.539 \times \text{age} - 6.400$ ($r = 0.358$, $P < 0.001$). *Dotted line* linear regression line for males (*closed triangles*, $n = 102$). Δ sBP = $0.472 \times \text{age} - 2.077$ ($r = 0.338$, $P = 0.001$). *Dashed line* linear regression line for females (*open circles*, $n = 129$). Δ sBP = $0.610 \times \text{age} - 10.461$ ($r = 0.369$, $P < 0.001$)

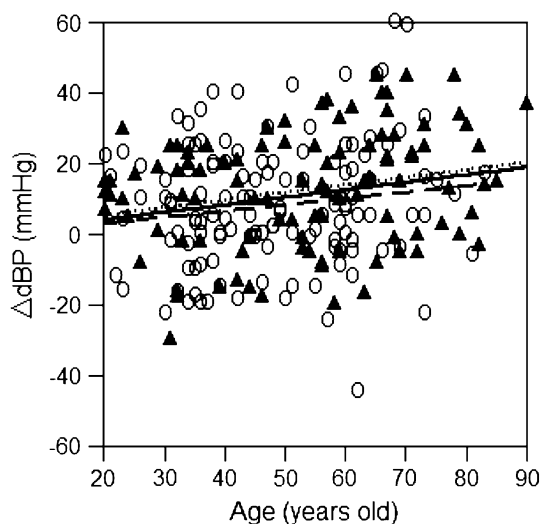


Fig. 4 Difference in diastolic BP (*dBp*) between the HR and OR (Δ dBp) with age. *Solid line* linear regression line for total population ($n = 231$). Δ dBp = $0.212 \times \text{age} - 0.402$ ($r = 0.201$, $P = 0.002$). *Dotted line* linear regression line for males (*closed triangles*, $n = 102$). Δ dBp = $0.214 \times \text{age} + 1.391$ ($r = 0.239$, $P = 0.016$). *Dashed line* linear regression line for females (*open circles*, $n = 129$). Δ dBp = $0.178 \times \text{age} - 0.225$ ($r = 0.144$, $P = 0.103$)

The heart rate values in the OR of the total population and the values in the females were significantly higher than those in the HR, but in the males, the heart rate value in the OR did not increase more significantly compared with that in the HR, as shown in Table 2.

Discussion

Pre-anesthesia sBP in the OR and the Δ sBP increased significantly with age in both males and females. The mean Δ sBP and Δ dBp in males were as same as the values in females. These results suggest that age, but not sex, may be an important factor affecting PAH related to the increase in sBP before anesthesia induction.

White coat hypertension

Temporarily high BP in the doctor's office, compared with normal ambulatory recorded BP or self-measured BP at home, is called white coat hypertension (WCH) [12, 13], and this phenomenon is also called isolated office hypertension or isolated clinic hypertension. The main criteria of WCH are an sBP of more than 140 mmHg and/or a dBp of more than 90 mmHg in the doctor's office. The rises in sBP and dBp during the visit to the doctor are, on average, 27 and 14 mmHg, respectively [14]. WCH persists during the first 4 min during the doctor's visit, and disappears within about 10 min, and rarely diminishes even after several visits [14]. It is reported that, in different subjects, and as determined by different methods and criteria, WCH is present in 6.6 % [15], 10.4 % [16], 29.9 % [17], 32.6 % [18], and 33.9 % [19] of patients. WCH responds poorly to antihypertensive therapy.

Some studies report that WCH is associated with high reactivity to mental stress [20, 21] and standing stress [21], and sympathetic nervous system activity [22]. Because mental stress [23], time urgency, impatience, and hostility [24] have been reported to be independent risk factors for the development of SH, it is possible that a higher reactivity to stress in medical environments leads to WCH. Therefore, mental and physical activities and emotional factors, such as defensive responses to the medical staff or medical circumstances, and conditioned reflexes may affect WCH.

Similarly, situations in the OR and anxiety about anesthesia and an impending operation may influence PAH. It is reported that PAH, in which mean sBP is 167 mmHg, is present in 10 % of patients [1]. In our present study, the condition in the hypertensive patients in the HR might have corresponded to WCH. We found that the sBP and dBp in the OR were significantly higher than those in the HR regardless of sex. We speculate that PAH in the OR is caused by a greater degree of mental and physical stress than that in the HR. We should examine the changes and abnormalities in the organs, and their function, in the cardiovascular and cerebrovascular systems in patients with PAH.

PAH and aging

White coat hypertension is commonly seen in the elderly, and the degree of WCH increases with age [6]. The

ambulatory white coat effect is higher in subjects who are more than 65 years old [15]. The prevalences of WCH in the third, fourth, fifth, sixth, seventh, and eighth decades of life are 23.2, 24.2, 33.3, 44.5, 40.7, and 25.2 %, respectively [18].

Independent predictors of adverse outcomes in PAH include increased baseline sBP and increased age [1]. Thus, in the clinical evaluation of PAH, the potential for target organ damage should be considered, although, fortunately, in the present study none of our study cohort experienced any cardiac or cerebrovascular events in the perioperative period. However, we might need to perform further physical examinations in elderly patients with PAH and control their sBP to prevent cardiac and cerebrovascular events.

The mechanism of increased variability of sBP differs depending on the age of individuals. An increased responsiveness of α -adrenergic receptors in resistance vessels and depressed baroreflex function are likely to be related to sBP variability in elderly subjects. On the other hand, the hyperactivity of β -adrenergic receptors is potentially involved in sBP variability in young subjects. Therefore, we need to study the function of the sympathetic nervous system in patients with PAH.

Sex

White coat hypertension is more often seen in females than in males. It is reported that in subjects with WCH at dBp values between 90 and 104 mmHg, female sex is an independent predictor of WCH [25]. In another study, the diagnosis of WCH is independently associated with female sex [26], and multivariate logistic regression in another study shows that female sex is the sole independent predictor of WCH [16]. A statistically significant association of the white-coat effect and sex has been observed, and the prevalence of this effect is greater among females (30 vs. 20 %) [27]. Of patients with the white-coat effect, 74 % are females and 26 % are males [27].

However, in the present study, the proportion of males with PAH was as same as that for females, and Δ sBP and Δ dBp in males were the same as the values in females. Therefore, the occurrence of PAH may be independent of sex.

Study limitations

First, the patients whose data we analyzed in the present retrospective study may have included some with untreated hypertension. The BP in the HR and OR was measured only once. We should have measured home BP or 24-h ambulatory BP [25] multiple times to obtain the appropriate data; also, to exclude subjects with untreated hypertension, we should have measured BP a number of

times after patients had entered the OR. Second, the BP data in the HR and OR were obtained by different members of the medical staff. It is known that the increase in sBP during measurement is less when measurement is done by a nurse than when measurement is done by a doctor [14]. Third, automatic blood pressure measurement may be inaccurate [28]. We should perform BP measurements with mercury sphygmomanometers to obtain more accurate data. Fourth, this study included emergency operations carried out during the day or at night. The serum hormone and catecholamine concentrations in the patients submitted for an emergency operation might be different from the usual levels. The hemodynamics of these molecules would differ between daytime and night-time [22], and circadian variation should be considered. Fifth, the long duration of NPO for elective operations may induce dehydration in elderly subjects, and dehydration may be associated with PAH. Sixth, the patients in this study did not have any premedication. The lack of premedication may be a risk factor for patients with ischemic heart disease and those with brain infarction. We plan to investigate elective surgery during the day time in a prospective study.

Age is one factor which affects PAH, but it is not the only factor. We speculate that some other factors, such as obesity, dyslipidemia, and non-smoking would lead to differences in the incidence of PAH. Furthermore, we need to investigate the influence of medication and coexisting disease before anesthesia and operation, and to investigate in detail the association between PAH and cardiac and cerebrovascular risk in the perioperative period.

Conclusion

Age is an important clinical factor related to PAH. Pre-anesthesia sBP and the change in this parameter increase progressively with age regardless of sex. These findings suggest that the previously observed higher BP seen in the elderly in the OR before anesthesia induction might be explained, in part, by a greater impact of PAH in older people.

References

1. Wax DB, Porter SB, Lin HM, Hossain S, Reich DL. Association of preanesthesia hypertension with adverse outcomes. *J Cardiothorac Vasc Anesth*. 2010;24:927–30.
2. Howell SJ, Sear JW, Foëx P. Hypertension, hypertensive heart disease and perioperative cardiac risk. *Br J Anaesth*. 2004;92:570–83.
3. Howell SJ, Sear YM, Yeates D, Goldacre M, Sear JW, Foëx P. Hypertension, admission blood pressure and perioperative cardiovascular risk. *Anaesthesia*. 1996;51:1000–4.

4. Aronson S, Boisvert D, Lapp W. Isolated systolic hypertension is associated with adverse outcomes from coronary artery bypass grafting surgery. *Anesth Analg*. 2002;94:1079–84.
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–52.
6. Wiinberg N, Høegholm A, Christensen HR, Bang LE, Mikkelsen KL, Nielsen PE, Svendsen TL, Kampmann JP, Madsen NH, Bentzon MW. 24-h ambulatory blood pressure in 352 normal Danish subjects, related to age and gender. *Am J Hypertens*. 1995;8:978–86.
7. Lee HY, Oh BH. Aging and arterial stiffness. *Circ J*. 2010;74:2257–62.
8. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986;111:383–90.
9. Rubanyi GM, Johns A, Kauer K. Effect of estrogen on endothelial function and angiogenesis. *Vascul Pharmacol*. 2002;38:89–98.
10. Oparil S, Chen SJ, Chen YF, Durand JN, Allen L, Thompson JA. Estrogen attenuates the adventitial contribution to neointima formation in injured rat carotid arteries. *Cardiovasc Res*. 1999;44:608–14.
11. Kaplan NM, Kem DC, Holland OB, Kramer NJ, Higgins J, Gomez-Sanchez C. The intravenous furosemide test: a simple way to evaluate renin responsiveness. *Ann Intern Med*. 1976;84:639–45.
12. Angeli F, Verdecchia P, Gattobigio R, Sardone M, Reboldi G. White-coat hypertension in adults. *Blood Press Monit*. 2005;10:301–5.
13. Celis H, Fagard RH. White-coat hypertension: a clinical review. *Eur J Intern Med*. 2004;15:348–57.
14. Mancina G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension*. 1987;9:209–15.
15. Den Hond E, Celis H, Vandenhoven G, O'Brien E, Staessen JA, THOP investigators. Determinants of white-coat syndrome assessed by ambulatory blood pressure or self-measured home blood pressure. *Blood Press Monit*. 2003;8:37–40.
16. Verdecchia P, Palatini P, Schillaci G, Mormino P, Porcellati C, Pessina AC. Independent predictors of isolated clinic ('white-coat') hypertension. *J Hypertens*. 2001;19:1015–20.
17. Puchades R, Ruiz-Nodar JM, Blanco F, Rodríguez F, Gabriel R, Suárez C. White-coat hypertension in the elderly. Echocardiographic analysis. A substudy of the EPICARDIAN project. *Rev Esp Cardiol*. 2010;63:1377–81.
18. Helvaci MR, Kaya H, Seyhanli M, Yalcin A. White coat hypertension in definition of metabolic syndrome. *Int Heart J*. 2008;49:449–57.
19. Helvaci MR, Kaya H, Duru M, Yalcin A. What is the relationship between white coat hypertension and dyslipidemia? *Int Heart J*. 2008;49:87–93.
20. Munakata M, Saito Y, Nunokawa T, Ito N, Fukudo S, Yoshinaga K. Clinical significance of blood pressure response triggered by a doctor's visit in patients with essential hypertension. *Hypertens Res*. 2002;25:343–9.
21. Lantelme P, Milon H, Gharib C, Gayet C, Fortrat JO. White coat effect and reactivity to stress: cardiovascular and autonomic nervous system responses. *Hypertension*. 1998;31:1021–9.
22. Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DASG. Sympathetic neural mechanisms in white-coat hypertension. *J Am Coll Cardiol*. 2002;40:126–32.
23. Armario P, del Rey RH, Martin-Baranera M, Almendros MC, Ceresuela LM, Pardell H. Blood pressure reactivity to mental stress task as a determinant of sustained hypertension after 5 years of follow-up. *J Hum Hypertens*. 2003;17:181–6.
24. Yan LL, Liu K, Matthews KA, Daviglus ML, Ferguson TF, Kiefe CI. Psychosocial factors and risk of hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *JAMA*. 2003;290:2138–48.
25. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA*. 1988;259:225–8.
26. Martínez MA, García-Puig J, Martín JC, Guallar-Castillón P, Aguirre de Cárcer A, Torre A, Armada E, Nevado A, Madero RS. Frequency and determinants of white coat hypertension in mild to moderate hypertension: a primary care-based study. Monitorización Ambulatoria de la Presión Arterial (MAPA)-Area 5 Working Group. *Am J Hypertens*. 1999;12:251–9.
27. Segre CA, Ueno RK, Warde KRJ, Accorsi TAD, Miname MH, Chi CK, Pierin AMG, Mion Júnior D. White-coat hypertension and normotension in the League of Hypertension of the Hospital das Clínicas, FMUSP: prevalence, clinical and demographic characteristics. *Arq Bras Cardiol*. 2003;80:117–26.
28. O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *BMJ*. 2001;322:531–6.