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Cerebral Oxygen Desaturation Occurs Frequently in Patients with Hypertension Undergoing Major Abdominal Surgery

Hongyi Li [1], Qiaochu Fu [2], Zongfang Wu [2], Jiaoli Sun [2], Anne Manyande [3], Hui Yang [2], Peng Wang [2]*

[1]Department of Anesthesiology, Peking Union Medical College Hospital, CAMS & PUMC, Beijing, China

[2] Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030,China.

[3] School of Human and Social Sciences, University of West London, London, UK

Running Title: observing rSO_2 in hypertensive patients

***Corresponding author:** Peng Wang, Department of Anesthesiology, Tongji Hospital, Tongji Medical College

College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, 430030 Wuhan, People's Republic of China.

Tel: 86-027-83663282 Fax: 86-027-83663282 E-mail: chj@medmail.com.cn

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Abstract:

Hypertensive patients are more likely to experience decreased regional cerebral oxygen saturation (rSO_2) during general anesthesia caused by latent cerebral ischemia. . The aim of this prospective observational study was to assess the incidence of decreased rSO_2 in hypertensive patients scheduled to undergo major abdominal surgery and the perioperative factors affecting this change in rSO_2. A convenience sample of 41 patients with hypertension were enrolled in this study. The intraoperative rSO_2 and physiological data were routinely collected. The Mini-Mental State Exam (MMSE) was used to assess cognitive function before surgery and 4 days postoperatively. Cerebral desaturation was defined as a decrease in rSO_2 of more than 20% of the baseline value. After surgery 20 patients (49%) who suffered cerebral desaturation were assigned into the cerebral desaturation group (group D) and 21 without desaturation into the normal group (group N). The number of patients in the uncontrolled hypertensive group D (12/20) was significantly higher than in group N (4/21) ($P = 0.007$). A significant positive correlation was observed between relative decrease in MAP and relative decrease in rSO_2 (r^2=0.495, $P < 0.001$). Moreover, 9 patients (45%) in group D had early postoperative decline in cognitive function as measured by MMSE in comparison to 3 patients (14.3%) in the normal group (P=0.031). The extent of the decrease in MMSE score was also significantly related to the $AUC_{rSO2 <80\% \text{ of baseline}}$ in the D group (r^2=0.28, $P = 0.016$). This pilot study showed that a large proportion of hypertensive patients experienced cerebral desaturation during major abdominal surgery. This decrease in rSO_2 was associated with the control of hypertension and this decrease might be responsible for the decline in postoperative cognitive function.

Keywords： general surgery； hypertension; postoperative cognitive dysfunction； regional cerebral oxygen saturation；

Clinical trial registration: NCT02147275 (registered at http://www.clinicaltrials.gov).

Introduction

Near-infrared spectroscopy (NIRS) has been used to continuously and noninvasively monitor regional cerebral oxygen saturation (rSO_2)[1, 2], which provides information about the equilibrium between cerebral oxygen supply and consumption[3]. This monitoring technology has been used extensively in cardiac and vascular surgery due to the high incidence of intraoperative brain hypoperfusion and cerebral vascular accidents [4-7]. However, because the association between desaturation and poor outcomes remains controversial, non-cardiovascular surgery has had little effect in controlling the cerebral blood flow. Besides, since this technology is hardly routinely applied, the monitoring of rSO2 continues to be neglected. . Recent studies have shown a high incidence of rSO_2 decrease as measured with NIRS during thoracic surgery [8-10] and abdominal surgery [11, 12]and this decrease is significantly related to clinical symptoms of postoperative cognitive dysfunction (POCD), and prolonged hospital stay.

However, very few studies have demonstrated the impact of co-morbidity, such as hypertension, on rSO2 in anaesthetized patients. Hypertension, a common but serious long term medical condition, causes both cerebrovascular structural and functional changes that can impair cerebrovascular autoregulation and result in cerebral ischemia and anoxia during periods of low arterial pressure[16]. Intraoperative patients with hypertension are prone to encounter labile hemodynamics [17, 18]. For these reasons, it was hypothesized that hypertensive patients under general anesthesia may have a high risk of latent cerebral ischemia and decreased rSO2.

Therefore, this prospective pilot study aimed to assess the incidence of decreased rSO_2 in hypertensive patients scheduled to undergo major abdominal surgery and explore factors related to hypertension, such as preoperative medical history, complications and intraoperative vital signs, and whether they have any effect on changes in rSO_2.The secondary research aim was to assess whether early postoperative cognitive function is influenced by the variation in rSO_2 during surgery in hypertensive patients.

Methods

Ethical approval for this prospective pilot study was obtained from the Ethics Committee of Tongji Hospital affiliated Huazhong University of Science and Technology (HUST), Wuhan, China on 10 January 2014 and registered with ClinicalTrials.gov (ref: NCT02147275).

From March to November 2014, we consecutively included patients over the age of 18 years with sustained hypertension for more than 3 years and scheduled for major abdominal, non-vascular surgery for at least 2 hours under general anesthesia. This study excluded subjects with pre-existing cerebral malfunctions such as episodes of cerebral ischemia or stroke, American Society of Anesthesiologists physical status (ASA) ≥ IV, hepatic failure, renal failure, preoperative Mini-Mental State Examination (MMSE) score less than 24, or a history of cardiovascular surgery or craniotomy. All patients who participated in this study signed written informed consent.

The characteristics of patients' hypertension were assessed according to the guidelines [19-21]. Hypertension was graded into three different stages and the stratification of risk to quantify prognosis, based on the presence of other cardiovascular risk factors, target organ damage, and associated clinical conditions, was also used The control hypertension was estimated using the patient's blood pressure measurement, in the family and on admission. If the measurement met the target of hypertension control, it was regarded as well controlled. Details of the above criteria are shown in the supplement tables. Throughout the study, standard monitoring variables including electrocardiography (ECG), heart rate

(HR), invasive blood pressure (IBP), pulse oximetry (SpO2), end-tidal carbon dioxide (ETCO2), and nasopharyngeal temperature were used to assess changes. Additionally, arterial blood gas analysis was measured at the discretion of the anesthesiologists. A spatially-resolved NIRS device (FORESIGHT cerebral oximeter, CASMED, USA) was used to measure rSO2. Before induction of general anesthesia, the sensors of rSO2 were placed bilaterally on the patient's forehead. To avoid ambient light from affecting the measurements, an opaque plastic patch was applied to cover the sensors. The rSO2 values were concealed from the anesthetist so that all the anesthetic management was not influenced by the values. Baseline rSO2 was considered as the average rSO2 value of awake patients in breathing room air 5 min after the sensors were positioned. A decrease in rSO2 values of more than 20% of the baseline value was regarded as cerebral desaturation. Standard monitoring variables and rSO2 values were recorded every 5 minutes based on the time interval of the electronic patients' data management system. The amount of decreased rSO_2 was reported as $AUC_{rSO2\ <90\%\ of\ baseline}$ and $AUC_{rSO2\ <80\%\ of\ baseline}$ for comparison between patients. After surgery, patients were assigned into two groups; those with cerebral desaturation were in the cerebral desaturation group (group D) and those without cerebral desaturation were in the normal cerebral saturation group (group N).

Anesthesia was induced with propofol 1.5 – 2.0 mg kg -1, sufentanyl 0.4 – 0.5μg kg -1, and rocuronium 0.6 μg kg -1. Mechanical ventilation controlled with 40% oxygen mixture was regulated to sustain ETCO2 ranging from 35 to 40 mmHg (tidal volume 8 ml kg -1; respiratory rate 12 breaths min -1; inspiratory to expiratory time 1: 2). Anesthesia was maintained with propofol 3mg kg -1 h -1, remifentanly 0.1μg kg -1 h -1 and 1.0 minimum alveolar concentration (MAC) sevoflurane to keep Narcotrend index (Narcotrend®-Compact, MT MonitorTechnik GmbH und Co. KG, Germany) between

D1 and E1. Transient hypotension, of at least a 25% decrease in mean arterial blood pressure (MAP) or MAP <60 mm Hg, was treated with ephedrine bolus 5-10 mg and the depth of anesthesia and vascular volume was regulated to remain stable in hemodynamics with a decrease less than 25% of the MAP baseline value. Muscle relaxation was achieved with intermittent infusion of rocuronium. In the event that hemorrhage exceeded 20% of the whole circulating volume, homologous blood was transfused to maintain the hemoglobin concentration above the threshold of ≥ 8 g dL -1.

The Mini-Mental State Exam (MMSE) assessed cognitive function including orientation, registration, attention, calculation, recall, and language [22]. The test combines high degree of validity and reliability with brevity and ease of application and suggests monitoring decline in cognitive function with repeated tests [23, 24]. Patient cognitive function was tested by a research assistant, not aware of intraoperative rSO2 values, using MMSE on the day before surgery (baseline) and then repeated 4 days postoperatively. A decrease in MMSE score ≥ 2 points from baseline was considered as an indication of postoperative cognitive function impairment [10-12, 14, 15].

Due to lack of published literature that evaluate the incidence of decreased rSO2 in hypertensive patient, we could not perform sample size calculations for this pilot study. A sample size of 45 patients was adopted for the exploratory study based on the literature that suggests that there is decreased rSO2 in older patients undergoing prolonged major abdominal surgery[25]. Patient characteristic data and intraoperative physiological data were expressed as mean ± standard deviation (SD), or as number (%) appropriately. Statistical analysis was performed using SPSS (v. 18.0, SPSS Inc., Chicago, IL, USA). Student's-test or the Mann-Whitney U-tests was appropriately adopted to compare continuous data.

Categorical variables were analyzed utilizing the Pearson Chi-Square test or the Fisher's exact test where appropriate. The correlations between decrease in rSO2 and standard monitoring parameters or the severity of cognitive decline were analyzed using linear regression analysis. Significance was indicated by $P < 0.05$.

Results

Forty-five hypertension patients undergoing major abdominal surgery were consecutively enrolled in the study. Three patients were excluded as surgery was canceled and one because of failure of the FORE-SIGHT monitor. A total of 41 patients (male: 24 and female: 17, aged 48 to 72 yrs.) remained for data analysis. Twenty (49%) had cerebral desaturation (defined as a decrease in rSO2 values more than 20% of the baseline value) during surgery and were assigned to group D (cerebral desaturation group). The remaining 21 patients without intraoperative cerebral desaturation were allocated to group N (normal cerebral saturation group).

The operations included partial hepatectomy (group D=6, group N=7), radical prostatectomy (group D=2, group N=1), pancreaticoduodenectomy (group D=6, group N=7), colorectal resection (group D=4, group N=3) and others (group D=2, group N=3). All surgeries but two were uneventful and no patient experienced serious intraoperative complications. Two patients received 6U of red blood cell transfusion due to excessive blood loss.

Groups did not differ in terms of age, weight, height, gender and the ASA. Neither did they differ in intraoperative data, including duration of surgery, infusion, urine, blood loss, the start Hb or the lowest Hb, (Table 1). In addition, the groups, were similar in the intraoperative HR, SpO2, ETCO2, temperature and Narcotrend index (Table 1).

Table 1 about here

According to the comprehensive clinical history and clinic or ambulatory blood pressure measurement, the mean duration of hypertension in group D was longer than that in group N (group D=9.1±3.1, group N=7.0±2.4; P=0.017) and group D had more patients with poorly controlled hypertension than in group N (group D=12, group N=4; P=0.007). Groups differed in the systolic blood pressure (SBP) and mean arterial pressure (MAP) on admission. Although there was no difference in the distribution of patients based on classification of blood pressure levels, differences were found based on stratification of risk to quantify prognosis (Table 2).

Table 2 about here

Groups did not differ in baseline rSO2 values which have a large patient-to-patient variability. However, differences were observed in the changes of intraoperative rSO2 (Table3, Fig. 2). The mean rSO_2 and minimum rSO_2 values of group D fell significantly. The degree of decrease in rSO_2 represented as $AUC_{rSO2 <90\% \text{ of baseline}}$ or $AUC_{rSO2 <80\% \text{ of baseline}}$ was more profound in group D than in group N. The groups were similar in baseline values of blood pressure and MAP changes throughout surgery (Table3 and Fig. 1)

Table 3 and Figure 1 about here

Figure 2 about here

In selected clinical parameters (age, operation time, haemoglobin, SpO2 or ETCO2) of group D, the maximum relative decrease in MAP was moderately correlated with maximum relative decrease in rSO2 (r^2=0.558, P < 0.001). A moderate positive correlation was also observed between relative MAP decrease and relative rSO2 decrease during surgery (r^2=0.495, P < 0.001) (Fig. 3).

Figure 3 about here

Patients in group D had a baseline MMSE value of 28.3±1.0 points (26–30) and those in group N 28.3±1.1 points (26–30), which fell to 26.5±3.0 points (21–30) and 27.7±2.0 points (21–30) respectively 4 days after surgery. Early decline in postoperative cognitive function (decrease in MMSE score ⩾2 points 4 days after surgery as compared to baseline value) was observed in 9 patients (45%) in group D and 3 patients (14.3%) in group N (P=0.031) (Table 4). For patients in group D there were positive correlations between the $AUC_{rSO2 <80\% \text{ of baseline}}$ and postoperative decrease in MMSE scores before surgery and 4 days postoperatively. (r^2=0.28, P = 0.016; Supplement Figure 1). When patients were divided into those with controlled hypertension and those with uncontrolled hypertension there were more patients with impaired postoperative cognitive function in the uncontrolled hypertension group (n = 16 (56.3%) than in the controlled hypertension group (n = 9 (12%) (P = 0.002; Supplement Figure 5).

Table 4 about here

Figure 5 about here

Discussion

The most important finding was that a significant proportion of the hypertensive patients (49%) experienced cerebral oxygen desaturation (more than 20% from their baseline) when undergoing major abdominal surgery. The duration, control and the stratification of risk to quantify prognosis with regards to hypertension may be the risk factors for cerebral desaturation. We also found that there was a moderate but significant correlation between relative MAP decrease and relative rSO2 decrease. Once the cerebral desaturation occurred in these patients, it increased the likelihood of early postoperative cognitive decline 4 days after surgery. The severity of the cognitive decline was also related to the degree of desaturation and this impaired cognitive function was more likely to occur in uncontrolled hypertension patients.

The association between desaturation and poor outcomes remains controversial. Studies which used cerebral oximetry in cardiac anesthesia showed that a decrease of 20% from the rSO2 baseline value increased the likelihood of postoperative complications, the length of postoperative mechanical ventilation time, and the total hospital stay [4, 5]. In the carotid endarterectomy, Samra and colleagues found that a threshold of 20% relative decrease in the pre-clamp rSO2 can predict an increased incidence of neurological complications with 80% specificity and sensitivity [7]. Likewise, in the patients who experienced thoracic surgery with single-lung ventilation (SLV), Hemmerling and colleagues [9, 10] reported that a significant proportion (56%) of the patients had a reduction of more than 20% from baseline values of rSO2. Therefore， the current study also defined more than 20% relative decrease of rSO2 baseline as criterion of cerebral oxygen desaturation. We found that a large proportion (49%) of patients with persistent hypertension experienced cerebral desaturation. The results were in accord with our hypothesis that patients with hypertension undergoing general anesthesia may have a high incidence of decreased rSO_2 as hypertension impacts on cerebral autoregulation.

When comparing the preoperative characteristics between the groups, the patients in the cerebral saturation group had longer duration of hypertension and more poorly controlled blood pressure than those in the normal cerebral saturation group. This could be due to the fact that the control and duration of hypertension may have an effect on the changes in the cerebral artery structure and function[16]. An unexpected finding is the distribution of patients in stratification of risk to quantify prognosis for hypertension which was different between the groups rather than the classification of blood pressure levels or the number of diabetic patients. To our knowledge, the stratification of risk to quantify prognosis is not just based on the blood pressure level, but on risk factors for cardiovascular diseases, such as age, gender, smoking, diabetes and cholesterol. plus also the presence of target-organ damage and associated clinical conditions such as cardiovascular or renal disease[26] . Our results indicate that it may be better for hypertensive patients to be estimated using risk stratification to predict the risk of cerebral desaturation than by simple classification of the blood pressure levels or some concomitant diseases.

This study has also shown that relative MAP decrease is moderately associated with relative rSO_2 decrease during the surgery This finding, to some extent, is in agreement with Moerman and colleagues' study that indicated that rSO2 seems to reflect acute haemodynamic alterations during off-pump coronary artery bypass grafting [27]. The rSO_2 can be affected by some vasopressor agents through regulating MAP and cardiac output, whereas phenylephrine decreased the rSO_2 when it increased the MAP [28]. To avoid the "false" low rSO_2 caused by the vasopressors, the transient hypotension during operation was treated with ephedrine which increased both MAP and rSO_2 [28]. In major abdominal surgery of elderly patients, Casati and colleagues [11] reported no correlation between decrease in rSO2 and variations in MAP. The main reason for this difference may be that in their study, patients were relatively healthy but in our study all patients had sustained hypertension. The hypertensive patients may be more sensitive to the MAP alterations because the cerebral autoregulatory curve is affected especially with the presence of pre-existing hypertension [29].

Intraoperative blood pressure is often managed empirically on the basis of cerebral autoregulation, patient medical history, and preoperative blood pressure. According to the cerebral autoregulatory curve, intraoperative hypotension somewhat arbitrarily defined as absolute values, or relative values, is deficient in individualization and lacks precision to reflect tissue perfusion [30, 31]. The cerebral autoregulatory curve, however, is derived from patients who have fewer comorbidities and generally younger than patients in current practices [32, 33]. This is also demonstrated by Joshi and colleagues who reported that there was large variability in the lower threshold (43 to 90 mmHg) for cerebral autoregulation in patients during CPB, which indicates that the lower threshold of MAP, based on the preoperative history and blood pressure, was inaccurate[34]. In our study, even though we maintained the intraoperative mean decrease in MAP of less than about 21% from baseline, cerebral desaturation also occurred and was correlated with changes in MAP. This result suggests that cerebral desaturation is sensitive to the change of MAP and applying NIRS to monitor cerebral saturation could provide guidance for intraoperative blood pressure management. In addition, our findings showed that the reduction in rSO_2 of more than 20% from baseline might contribute to early decline in cognitive function 4 days after surgery and the decreased score of MMSE was slightly correlated with the degree of $AUC_{rSO2\ <80\%\ of\ baseline}$, which is consistent with results of previous studies [10, 12].In patients without cerebral desaturation, however, there were three patients who had decreased measurement of postoperative cognitive function. In these patients, rSO_2 decreased by more than 10% of baseline, According to a recent study [35], cerebral desaturation below 10% relative to baseline is required during high-risk cardiac surgery. The prolonged reduced rSO_2, even of less than 20% at baseline, may also be related to adverse events. Therefore, both the degree and duration of cerebral desaturation need to be considered as the threshold.

To the best of our knowledge, the current study was the first to investigate the incidence of rSO2 decrease in hypertensive patients and the possible factors causing this change. However, the limitations of the study should be considered. Firstly, the sample size of this pilot study was small. Nevertheless, we found that a large proportion of hypertensive patients experienced cerebral desaturation. The findings of this pilot study are novel and provide a rationale to justify conducting a larger randomized controlled trial. Secondly, the study was mainly observational which might reflect as a limitation. It will be for further studies to investigate the potential benefits of the outcome caused by using rSO2 to manage blood pressure using an intervention trial [31]. Finally, only the MMSE was used to assess the decline of early postoperative cognitive function. To our knowledge, there are other more sensitive and specific tests that can be used to exam each element of cognitive function precisely [36, 37]. Nonetheless, the simple MMSE is extensively used to measure cognitive impairment in clinical settings and was easily completed by patients who failed to take complex tests 4 days after surgery.

In conclusion, a large proportion of patients with persistent hypertension experienced cerebral desaturation during major abdominal surgery. This decrease in rSO2 was significantly correlated with the alternations in MAP and may have led to early decline in cognitive function on the fourth day after surgery. If this argument is correct, our results suggest that blood pressure management based on individualized estimates and monitoring the target-organ balance between oxygen demand and supply may be beneficial for hypertensive patient.

Compliance with ethical standards

Conflict of interest none.

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Table 1. Patient characteristics and intraoperative data.

	D group (n=20)	N group (n=21)	*P*-value
Age (yr)	62.8 ± 7.1	61.6 ± 6.4	0.551
Weight (kg)	67.4 ± 8.7	65.8 ± 10.1	0.583
Height (cm)	167.8 ± 8.4	164.3 ± 10.7	0.251
Gender (Male/Female)	12/8	12/9	0.852
ASA (Ⅱ/Ⅲ)	13/7	15/6	0.658
NYHA (Ⅰ/Ⅱ/Ⅲ/Ⅳ)	11/8/1/0	16/5/0/0	0.273
Surgery duration (h)	5.4 ± 2.3	5.5 ± 1.2	0.975
Infusion (ml)	4556 ± 764	4688 ± 680	0.568
Urine (ml)	648 ± 256	621 ± 241	0.735
Blood loss (ml)	1050 ± 536	1038 ± 498	0.427
Start Hb (g dl^{-1})	13.1 ± 1.7	13.0 ± 1.8	0.805
Lowest Hb (g dl^{-1})	8.4 ± 1.6	8.2 ± 1.5	0.355

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as the number of patients. ASA, American Society of Anesthesiologists; NYHA, New York Heart Association.

Table 2. Preoperative condition of hypertensive patients

	D group (n=20)	N group (n=21)	*P*-value
Length of hypertension (yr)	9.1 ± 3.1	7.0 ± 2.4	0.017
Classification of blood pressure levels:			
Grade 1/Grade 2/Grade 3 (cases)	5/9/6	8/10/3	0.423
Stratification of risk to hypertension:			
Low risk / Med risk (cases)	0/1	0/9	
High risk / Very high risk (cases)	12/7	10/2	0.009
Whether controlled (Y/N)	8/12	17/4	0.007
Whether diabetic (Y/N)	12/8	7/14	0.087
Blood pressure on admission (mmHg)			
SBP	150 ± 18	134 ± 11	0.001
DBP	80 ± 9	77 ± 6	0.292
MAP	103 ± 11	96 ± 7	0.015

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as number of patients. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Table 3. Cerebral oxygen saturation and intraoperative blood pressure in both groups.

	D group (n=20)	N group (n=21)	*P*-value
Baseline rSO_2 (%)	70 ± 7	69 ± 8	0.848
Mean rSO_2 (%)	56 ± 5	60 ± 3	＜0.0001
Minimum rSO_2 (%)	51 ± 4	58 ± 4	＜0.0001
Mean relative rSO_2 decrease (%)	18 ± 6	13 ± 5	＜0.0001
Max relative rSO_2 decrease (%)	27 ± 4	15 ± 3	＜0.0001
$AUC_{rSO2\ <90\%\ of\ baseline}$ (min%)	6264.9 ±1832.3	2752.4 ±1453.3	＜0.0001
$AUC_{rSO2\ <80\%\ of\ baseline}$ (min%)	4486.5 ± 1664.9	0.0	
Baseline blood pressure before surgery (mmHg)			
SBP	134 ± 11	133 ± 9	0.323
DBP	75 ± 7	76 ± 7	0.304
MAP	102 ± 8	102 ± 7	0.264
Mean intraoperative MAP (mmHg)	82 ± 7	80 ± 6	0.215
Minimum intraoperative MAP (mmHg)	75 ± 9	74 ± 8	0.124
Mean relative MAP decrease (%)	21 ± 4	21 ± 3	0.188
Max relative MAP decrease (%)	25 ± 3	26 ± 2	0.153

Data are presented as mean ± standard deviation according data distribution. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Table 4. Mini mental state examination (MMSE) score and postoperative cognitive function decline in both groups.

	D group (n=20)	N group (n=21)	*P*-value
MMSE baseline	28.3±1.0(26～30)	28.3±1.1(26～30)	0.960
MMSE at 4th day	26.5±3(21～30)	27.7±2(21～30)	0.098
Early Postoperative cognitive function impaired (cases)	9	3	0.031

Data are presented as mean ± SD (range) and categorical variables are presented as numbers of patients.

MMSE, mini mental state examination score.

Supplement table1 Definition and classification of hypertension by office blood pressure measurement.

Staging	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	160-179	or	100-109
Stage 3 hypertension	≥180	or	≥110
Isolated systolic hypertension	≥140	and	<90

Systolic BP ≥130 mmHg or diastolic BP≥80 mmHg are considered high blood pressure in special patient groups (coronary heart disease, diabetes, and proteinuric chronic kidney disease), and also in patients who receive antithrombotics for stroke prevention. (Modified from Chiang et al. with permission.)

Supplement table 2 Factors influencing prognosis

Risk factors for cardiovascular disease	Target-organ damage (TOD)	Associated clinical conditions (ACC)
• Levels of systolic and diastolic blood pressure (grades 1–3) • Males > 55 years; Females > 65 years • Smoking • Abnormal glucose tolerance (2h Postload plasma glucose 7.8–11.0 mmol/L) and (or) abnormal fasting plasma glucose (6.1–6.9 mmol/L) • Dyslipidemia TC ≥ 5.7 mmol/l (220 mg/dL) or LDL-C > 3.3 mmol/l (130 mg/dL) or HDL-C <1.0 mmol/l (40 mg/dL) • Family history of premature CV disease (M at age <55 years; W at age < 65 years) • Abdominal obesity (waist circumference ≥ 90 cm(M), ≥85 cm(W)) or Obesity (BMI ≥ 28 kg/m^2) • Plasma homocysteine increase (≥10 μmol/L)	• Left ventricular hypertrophy electrocardiogram: Sokolow-Lyon >38mm or Cornell >2440 mm• ms; echocardiography: (LVMI: M ≥125 g/m^2, W ≥120 g/m^2) • Carotid wall thickening (IMT ≥ 0.9 mm) or plaque • Carotid-femoral pulse wave velocity ≥12 m/s • Ankle/brachial BP index < 0.9 • eGFR decrease (eGFR< 60ml• min^{-1} • 1.73m^{-2}) or Slight increase in plasma creatinine : M: 115–133 μmol/L (1.3–1.5 mg/dL), W: 107–124 μmol/L (1.2–1.4 mg/dL) • Microalbuminuria 30–300 mg/24 hr or albumin-creatinine ratio ≥ 30mg/g (3.5mg/mmol)	• Cerebrovascular disease ischemic stroke; cerebral hemorrhage; transient ischemic attack • Heart disease myocardial infarction; angina; coronary revascularization; heart failure • Renal disease diabetic nephropathy; renal impairment (Serum creatinine M ≥133 μmol/L, W ≥124 μmol/L); proteinuria (≥300 mg/24 hr) • Peripheral vascular disease • Retinopathy hemorrhages or exudates, papilloedema • Diabetes mellitus Fasting plasma glucose ≥7.0 mmol/L (126 mg/dl), 2h Postload plasma glucose ≥ 11.1 mmol/L (200 mg/dL), glycosylated hemoglobin ≥ 6.5%

TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; CV, cardiovascular disease; M, men; W, women; LVMI, left ventricular mass index; IMT, h, hour; intima-media thickness; eGFR: estimated glomerular filtration rate; BMI, body mass index.

Supplement table 3 Stratification of risk to quantify prognosis

Other risk factors and disease history	Blood pressure (mmHg)		
	Grade 1 (SBP 140–159 or DBP 90–99)	Grade 2 (SBP 160–179 or DBP 100–109)	Grade 3 (SBP ≥ 180 or DBP ≥ 110)
No other risk factors	Low risk	Medium risk	High risk
1–2 risk factors	Medium risk	Medium risk	Very high risk
3 or more risk factors, or TOD	High risk	High risk	Very high risk
Clinical complications or Diabetes	Very high risk	Very high risk	Very high risk

SBP, systolic blood pressure; DBP, diastolic blood pressure; TOD, target-organ damage.

Supplement table 4 Blood pressure targets.

Categories	Targets (mmHg)
Primary prevention	<140/90
Secondary prevention	
diabetes mellitus	<130/80
chronic kidney disease	<130/80
coronary heart disease	<130/80
stroke	<140/90
Very elderly (age ≥ 65 years)	<150/90

Figure legends

Fig.1 Comparison of mean arterial pressure (MAP) values throughout surgery between D group and N group: MAP awake state (D group=20, N group=21), surgery after 40 (D group=20, N group=21), 80 (D group=20, N group=21), 120 (D group=20, N group=21), 160 (D group=20, N group=21), 200 (D group=20, N group=21), 240 (D group=20, N group=20), 280 (D group=15, N group=18), 320 (D group=10, N group=12), 360 (D group=8, N group=8), 400 (D group=7, N group=5), 440 (D group=1, N group=2) min. Data shown as mean, bars represent standard deviation.

Fig.2 Comparison of regional cerebral oxygen saturation (rSO2) values throughout surgery between D group and N group: rSO2 awake state (D group=20, N group=21), surgery after 40 (D group=20, N group=21), 80 (D group=20, N group=21), 120 (D group=20, N group=21), 160 (D group=20, N group=21), 200 (D group=20, N group=21), 240 (D group=20, N group=20), 280 (D group=15, N group=18), 320 (D group=10, N group=12), 360 (D group=8, N group=8), 400 (D group=7, N group=5), 440 (D group=1, N group=2) min. Data shown as mean, bars represent standard deviation.

Fig.3 (a) Correlation between Max relative rSO2 decrease and Max relative MAP decrease in D group.

(b) Correlation between relative rSO2 decrease and relative MAP decrease throughout surgery in D group.