

Original Article

A new rodent model of cerebral hyperperfusion

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Abstract: Background: Most studies of hyperperfusion and hyperperfusion syndrome after carotid endarterectomy or carotid stenting are based on clinical observation or meta-analyses in patients, whereas there is little corresponding fundamental research since proper animal model that can reproduce phenotype stably is not available. Therefore, we developed a rat model in which the pathophysiologic process of hyperperfusion can be mimicked. Methods: Global ischemia was induced by occluding bilateral common carotid arteries (BCAO) for 2 weeks. After that, the ligature was loosened to allow reperfusion. Phenylephrine was administered at concentrations of 10, 20, 30, 40, 50, 80, and 120 $\mu\text{g/mL}$ for rapidly elevating blood pressure. Relative cerebral blood flow in relation to mean arterial pressure (MAP) was measured with Laser Doppler techniques. Sham animals underwent the same surgical operation but without artery-occlusion and received the same concentrations of phenylephrine. Results: Mild hypertension rapidly increased cerebral blood flow. Phenylephrine at different concentrations produced different effects on blood pressure. Hyperperfusion can be induced by phenylephrine at around 30 $\mu\text{g/mL}$, whereas phenylephrine at 80 $\mu\text{g/mL}$ or higher induced arrhythmia and further cardiac dysfunction thus failed to induce hyperperfusion. Conclusions: Our data suggest that 30-50 $\mu\text{g/mL}$ phenylephrine mildly elevated MAP and cerebral blood flow to the level exceeding 100% of baseline. This hyperperfusion model possesses several advantages including high phenotype reproducibility, low experimental failure rate and low animal mortality rate. It can be applied to study carotid stenosis or ischemia/reperfusion injury in rats.

Keywords: Bilateral carotid artery occlusion, hyperperfusion, hyperperfusion syndrome, carotid endarterectomy, carotid stenting, cerebral blood flow, phenylephrine

Introduction

Carotid endarterectomy (CEA) is the gold standard therapy for primary and secondary carotid artery disease and carotid stenting (CAS) has emerged as a potential alternative to CEA in certain cases. Although rare, cerebral hyperperfusion and cerebral hyperperfusion syndrome (CHS) after carotid surgery have been well documented [1-4]. The potentially devastating consequences make it extremely important to studies its underlying mechanism for exploring proper diagnosis and treatment against CHS.

Hyperperfusion following CEA is thought to be resulted from alterations of cerebral blood flow (CBF). The incidence of hyperperfusion following CEA is 0.2-18.9% in patients [5, 6]. In series studies [7-9], 16.7-28.6% of patients with an

increase of CBF >100% above baseline developed CHS. Various studies supported the definition of hyperperfusion as an increase in CBF compared to preoperative or baseline values, representing a parameter of cerebral-circulation hemodynamics [10-12]. However, the emergence of clinical symptoms is essential for the definite diagnosis of CHS beside hyperperfusion *per se*. Such syndrome is characterized by ipsilateral migraine-like headaches, seizures, and transient focal neurologic defects after CEA, that sometime occur without evidence of ischemic infarction [7, 10].

The exact mechanism leading to hyperperfusion or CHS is unknown because recent studies are based on clinical observation or meta-analyses in patients [13, 14]. There is no appropriate animal model for elucidating the mechanism underlying pathogenesis of CHS.

Table 1. Mean arterial pressure of rats before and after phenylephrine administration

Phenylephrine concentration	Phenylephrine bolus	Sham group	HP group
10 µg/ml	Before	81.19±2.33	78.40±2.60
	After	104.51±2.65	105.61±7.81
20 µg/ml	Before	77.03±2.89	80.54±3.43
	After	101.67±2.58	109.78±3.94
30 µg/ml	Before	82.44±3.43	82.78±5.36
	After	117.79±3.46	124.40±7.87
40 µg/ml	Before	79.94±2.65	79.37±2.90
	After	143.71±3.48	138.94±4.11
50 µg/ml	Before	78.70±3.10	80.19±3.00
	After	138.87±6.09	142.30±2.68
80 µg/ml	Before	80.21±4.48	76.52±3.45
	After	136.54±5.27	138.50±2.74
120 µg/ml	Before	74.33±3.20	80.95±2.60
	After	139.00±3.23	142.34±3.23

Data are represented as mean ± S.E. (10-50 µg/ml groups, n=6; 80 and 120 µg/ml groups n=4). HP: hyperperfusion.

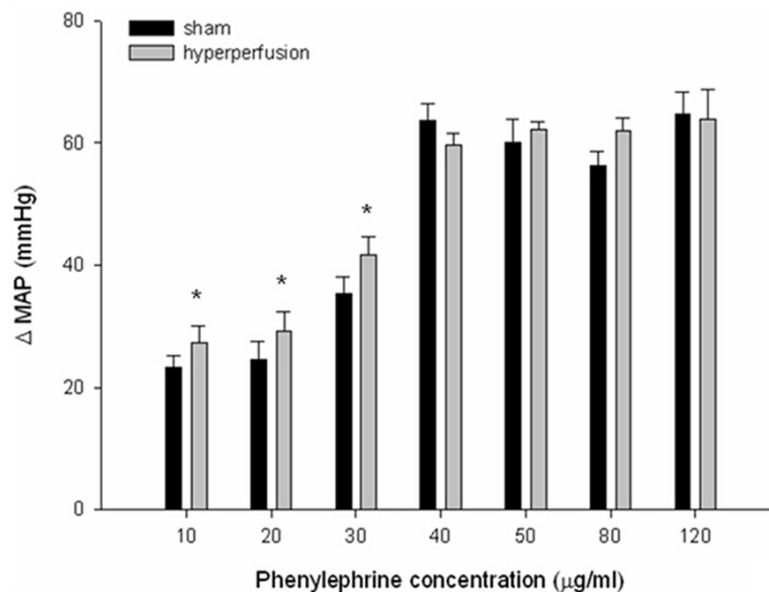


Figure 1. Mean arterial pressure (MAP) in the hyperperfusion and sham groups. Data are represented as mean ± S.E. *P<0.05 versus 50 µg/ml hyperperfusion group (10-50 µg/ml groups, n=6; 80 and 120 µg/ml groups, n=4).

Bilateral common carotid artery occlusion (BCAO) is a well-established model for studying chronic cerebral hypoperfusion, which produces global hypoperfusion, induces less dramatic damage in nervous tissue and does not lead to obvious motor dysfunction or seizures. In this

and vagus nerve. In rats assigned to hyperperfusion groups, each artery was ligated with a 5-0 silk suture. At the end of the occlusion, the midline incision was sutured. Rats in sham-operated control groups underwent the same operation except carotid occlusion.

study, we develop a new stable hyperperfusion rat model based on BCAO manipulation for further research on hyperperfusion.

Materials and methods

Experimental animals

This study was approved by the Capital Medical University of China Animal Care and Use Committee. Male Wistar rats weighing 250-350 g were housed under a 12-h/12-h light/dark cycle in a conventional animal facility in which the environmental temperature and relative humidity were monitored and controlled. Animals had free access to food and water. All experimental protocols were approved by the Animal Care and Use Committee of Capital Medical University and they are also in consistent with the NIH Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23).

First surgical procedures (chronic hypoperfusion model)

Rats were anesthetized with chloral hydrate (360 mg/kg) via intraperitoneal injection. A ventral midline incision was then made in head, and bilateral common carotid arteries were exposed and gently separated from carotid sheath

Table 2. Blood gas content of rats 5 min after HP

Phenylephrine concentration	Groups	PaO ₂	PaCO ₂	pH
10 µg/ml	sham	121±3.1	39.8±1.7	7.39±0.01
	HP	120±4.6	39.0±1.4	7.41±0.01
20 µg/ml	sham	129±2.8	40.2±1.2	7.39±0.01
	HP	122±2.1	38.8±1.0	7.40±0.01
30 µg/ml	sham	123±4.4	41.4±1.3	7.38±0.01
	HP	124±3.7	38.2±1.6	7.41±0.02
40 µg/ml	sham	128±1.5	38.2±1.0	7.40±0.01
	HP	121±3.3	41.4±1.9	7.38±0.02
50 µg/ml	sham	126±2.7	42.6±1.5	7.37±0.01
	HP	124±2.8	41.8±3.5	7.40±0.01

Data are represented as mean ± S.E. (n=5 for each group). HP: hyperperfusion.

was registered according to two standard leads with isolated steel needles continuously throughout the experimental period. All data were collected with the Biopac MP150 (American) acquisition system. During surgical procedures, body temperature of each rat was maintained within 37.5±0.5°C using a surgical warming platform.

Regional CBF measurements

Animal preparation and surgical procedures (hyperperfusion model)

BCAO rats were anesthetized with the same concentration of chloral hydrate (360 mg/kg). Then, the animals were maintained on a ventilator. Ventilation was supplemented with oxygen adjusted to maintain PaCO₂ readings within physiological range, i.e., 37-40 mmHg. Tail artery was cannulated with a PE-50 tube for continuous measurement of physiological parameters. Lateral tail vein was cannulated with a 24-gauge intravenous catheter for phenylephrine injection. After assessing CBF as basic value, the ligation of bilateral common arteries was loosened under a microscope to allow reperfusion.

Animal groups

Initially, we defined the BCAO and sham groups based on whether ligation of the common bilateral arteries was performed. After 2 weeks, the BCAO group underwent a second surgery to allow reperfusion, and this group was named as hyperperfusion group (HP group). Animals in sham and HP groups all received a single bolus injection of phenylephrine at concentrations of 10, 20, 30, 40, 50, 80, or 120 µg/ml, respectively. In total, BCAO and sham groups include 126 rats respectively.

Measurements of physiological parameters

Blood PaCO₂, pH, HCO₃⁻, and PaO₂ saturation were measured before assessing CBF. Tail arterial mean blood pressure (MAP) readings were collected. Electrocardiograph (ECG) in animals

A non-penetrating burr hole (2 mm in diameter) was drilled into the cranium over right parietal cortex 2 mm posterior to the bregma and 2 mm to the right of the midline. A flexible fiber-optic probe was glued to the hole and connected to a laser-Doppler flowmeter to measure relative CBF (probe 407, Periflux System 5010, Perimed, Sweden). CBF was continuously recorded using a computer-based data acquisition system. Mean blood flow during the 10-s recording was used for each measurement when CBF was stable and percentage of the baseline level was calculated. In addition, we defined CBF value before loosening the bilateral common arteries as baseline in HP group.

Assessment of neurological scores

After hyperperfusion, animals were assessed for neurobehavioral activity after came back to consciousness. Performance was scored on a 25-point scale modified from the previous literature [15]. Rats were scored again at 6, 24, and 48 h after hyperperfusion. The score was determined by an investigator blinded to the treatment of animals.

Statistical analysis

Values are represented as mean ± SE. Statistical analysis was conducted with one-way ANOVA followed by pairwise multiple comparison procedures using Bonferroni's test. The significance of differences in neurologic scores was analyzed by the Kruskal-Wallis test followed by multiple comparison procedures using Dunn's procedure. Differences were considered significant if P<0.05.

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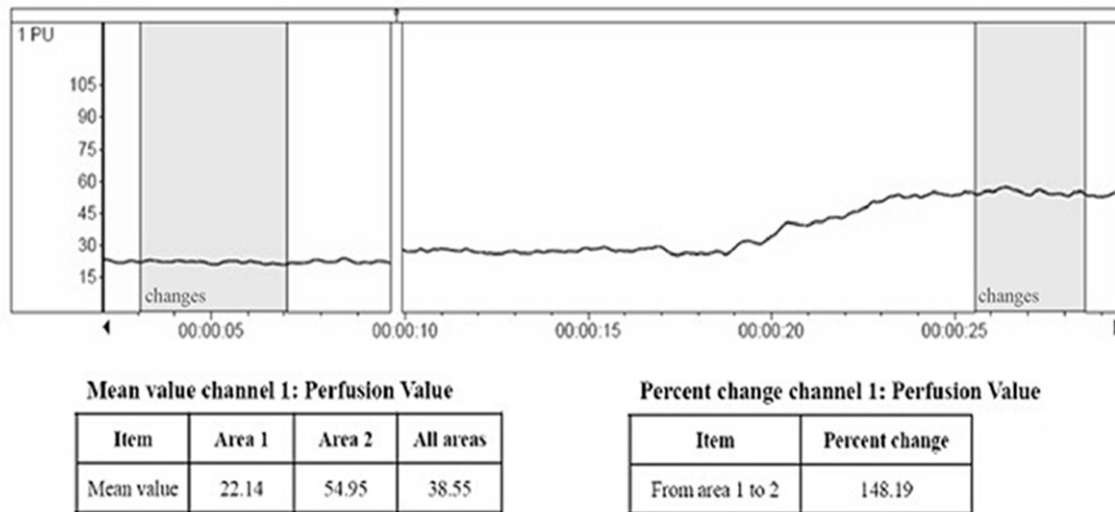


Figure 2. Change of cerebral blood flow (CBF) after phenylephrine administration. The left part of the curve (before 00:00:10) indicates the CBF baseline value. The right part of the curve (after 00:00:10) includes two components. The front part (from 00:00:10 to 00:00:20) indicates the CBF value after reperfusion, and the latter part (after 00:00:20) indicates the sudden increase after the elevation of mean arterial pressure. The mean value represents the absolute value of CBF. The percent change represents CBF values normalized to baseline. The phenylephrine concentration was 50 µg/mL.

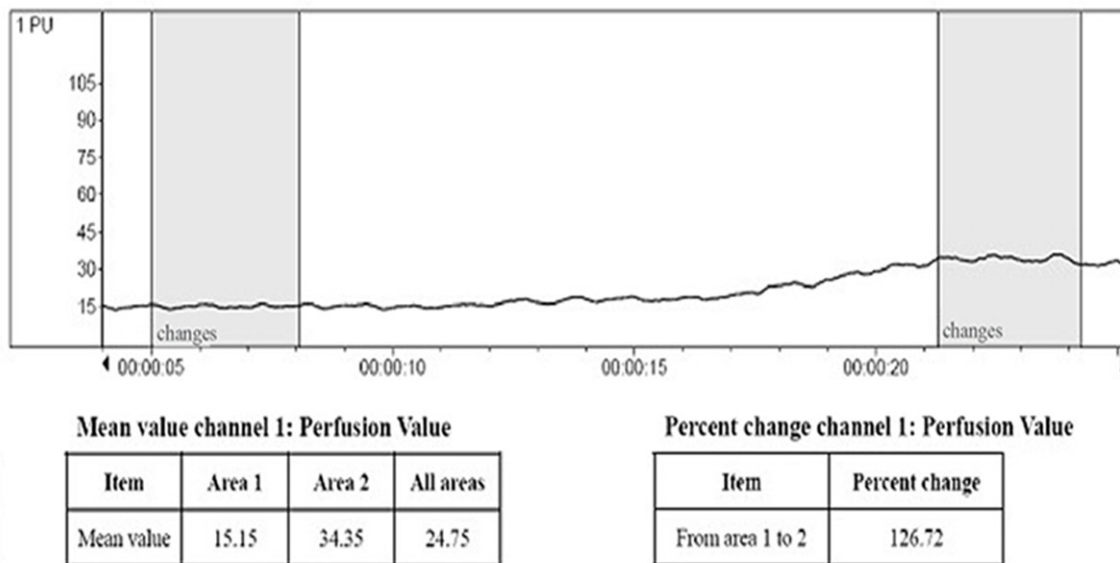


Figure 3. In typical rats, after the ligature was loosen, cerebral blood flow elevates to the level exceeding 100% of baseline after the bolus injection of 50 µg/ml phenylephrine.

Results

Effects on mean arterial pressure and blood gas content

After measuring mean arterial pressure (MAP), blood samples were taken from the tail artery of rats for analyzing blood gas content, including PaO₂, PaCO₂ and pH. **Table 1** shows the MAP of rats before and after phenylephrine injection. **Figure 1** is the histogram-summary

for **Table 1**. Phenylephrine increased MAP in both HP and sham rats. The absolute values and changes of MAP after phenylephrine injection did not show significant differences between HP and sham groups. **Table 2** shows the blood gas content of rats 5 min after hyperperfusion. All measured parameters were within normal physiological limits, and no significant differences were observed between groups.

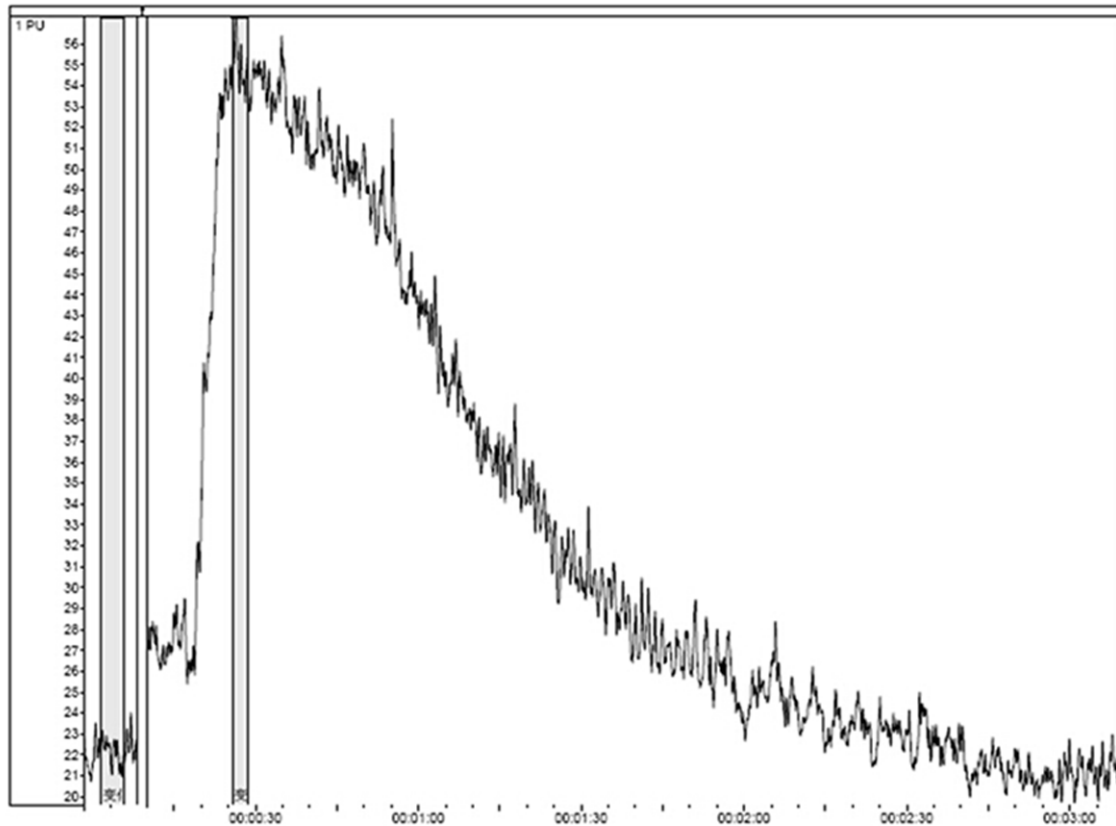


Figure 4. Original cerebral blood flow diagram. CBF increased only in the peak period, can exceed 100% of the baseline value. Meanwhile, CBF is maintained for only a few seconds, after which it decreases even below the baseline. Hyperperfusion rats received 50 $\mu\text{g/mL}$ phenylephrine.

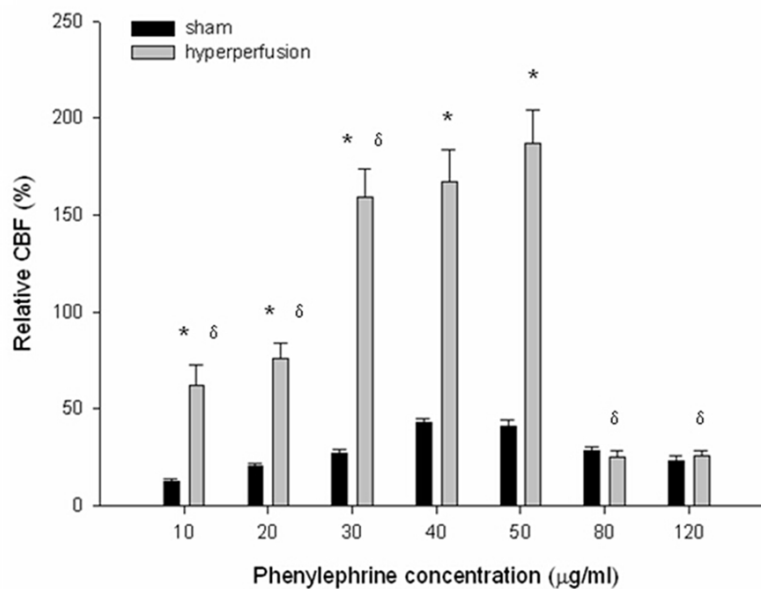
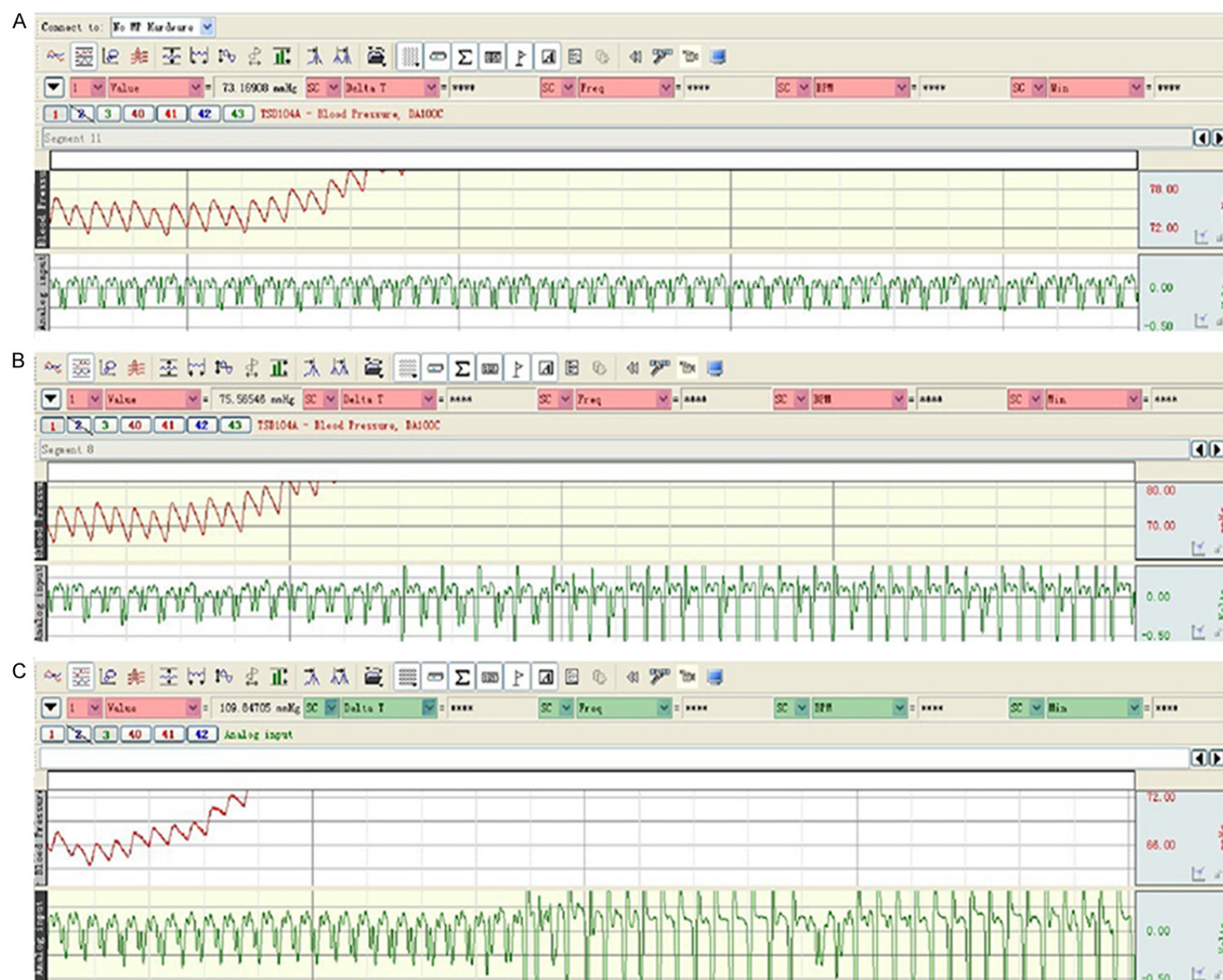


Figure 5. Relative CBF after phenylephrine injection, values were normalized to respective baseline CBF values. * $P < 0.05$ versus the sham group; $\delta P < 0.05$ versus the 50 $\mu\text{g/ml}$ phenylephrine group.

Effects on regional CBF

We defined the CBF value before ligature-loosening as baseline (**Figure 2**, upper panel, before 00:00:10, shadowed) and successful cerebral hyperperfusion as CBF exceeds 100% of basal level. In most rats in the HP group (15/18), when reperfusion occurred, CBF increased by some extent (**Figure 2**, upper panel, from 00:00:10 to 00:00:20). After phenylephrine injection, CBF increased and exceeded 100% of basal level as MAP increased (**Figure 2**, upper panel, after 00:00:20, shadowed, and lower two panels show absolute values of CBF and

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Figure 6. HP group rats received 30 µg/mL (A), 80 µg/mL (B) and 120 µg/mL (C) phenylephrine. Red, MAP; Green, ECG. There was no obvious change of ECG in A after MAP elevation, while changes are obvious in (B) and (C).

Table 3. Neurological deficit scores

Phenylephrine concentration	Groups	Consciousness	Six hours after	Twenty-four hours after	Forty-eight hours after
10 µg/mL	sham	1.4±0.2	0.6±0.2	0.2±0.2	0
	HP	7.2±0.4 [#]	4.6±0.5	3.8±0.5	0 [#]
20 µg/mL	sham	1.8±0.4	0.8±0.4	0.2±0.2	0
	HP	7.6±0.5 [#]	5.2±0.4	4.2±0.5	1.6±0.2 [*]
30 µg/mL	sham	2.2±0.5	0.6±0.2	0.4±0.2	0
	HP	8.6±0.8 [#]	7.4±0.9	4.8±0.5	1.8±0.4 [*]
40 µg/mL	sham	2.6±0.4	1.0±0.3	0.4±0.2	0
	HP	9.6±0.5 ^{#,δ}	7.8±0.7 ^{#,δ}	5.0±0.5 ^δ	1.6±0.6 ^{*,δ}
50 µg/mL	sham	2.6±0.5	1.0±0.5	0.4±0.2	0
	HP	10.2±0.7 ^{#,ε}	7.4±0.9 ^{#,ε}	4.8±0.7 ^ε	1.8±0.4 ^{*,ε}

Data are represented as mean ± S.E (n=5). HP: hyperperfusion. ^{*}P<0.05 versus sham group, [#]P<0.05 versus twenty-four hours after administration HP group, ^δP<0.05 versus 40 µg/ml sham group, ^εP<0.05 versus 50 µg/ml sham group.

fold-change relative to baseline, also see **Figure 3** for another typical case). Such high level of CBF was maintained for only a few seconds, after which it decreased even below the baseline (**Figure 4**).

Figure 5 is the histogram summary of CBF changes relative to baseline CBF. Only after reperfusion in HP rats, phenylephrine at different concentrations produces different effects on CBF. At 30, 40, and 50 µg/ml, phenylephrine induced cerebral hyperperfusion (CBF exceeds 100% of basal level), whereas at concentrations of 80 µg/ml or higher, it lead to arrhythmia or heart failure and failed to elevating CBF to the level exceeding 100% of basal level. Such effect cannot be observed in sham rats.

Effects on ECG

As phenylephrine at 50 µg/ml induced highest level of hyperperfusion (**Figure 6**), we treated rats with phenylephrine at 50 µg/ml in following experiments. HP-rats receiving 50 µg/ml phenylephrine displayed normal ECG patterns (green trace in **Figure 6A**), whereas those receiving 80 or 120 µg/ml phenylephrine exhibited arrhythmia and heart failure (green traces in **Figure 6B** and **6C**).

Effect on neurological defects scores

Neurological defects scores were assessed when animal came back to consciousness 6,

24 and 48 h after phenylephrine administration. There were significant differences in neurological defects scores at 48 h between the sham and HP groups except the 10 µg/ml phenylephrine group (**Table 3**).

Reproducibility and animal mortality rate

Phenylephrine at 10, 20, 80, and 120 µg/mL did not increase CBF to the level exceeding 100% of the baseline. However, when phenylephrine was injected

at 30, 40, and 50 µg/mL, percentages of rats showing 100% CBF increment were 33.3 (6/18), 40.0 (6/15), and 42.9% (6/14), respectively. Mortality was never observed except when the common carotid arteries were broken during loosening the ligation in HP rats.

Discussion

In summary, we established a hyperperfusion model based BCAA in rat with 30-50 µg/mL phenylephrine. This hyperperfusion model possesses several advantages including high phenotype reproducibility, low experimental failure rate and low animal mortality rate. It can be applied to study carotid stenosis or ischemia/reperfusion injury in rats.

At present, rodent models of chronic cerebral hypoperfusion were established via bilateral common carotid artery occlusion (BCAO). This strategy aims to produce various degrees of ischemia or oligemia in the brains. BCAO models are mainly carried out in two strategies. The first involves occlusion of both carotid arteries using vascular clamps for a few minutes to produce transient ischemia, after which the clamps are removed for reperfusion [16-18]. The second involves permanent ligation of both carotid arteries to prevent reperfusion [19-21]. These two strategies are widely applied for studying brain ischemia. Otori and colleagues adopt a permanent ligation model and found that CBF

decreased significantly after 2 days and gradually recovered after 1 week, except that CBF in the frontal cortex remained significantly lower than the control values even 4 weeks after BCAO [22]. However, there is little research focusing the effects of reperfusion after 2 weeks of ligature, and thus, we introduced cerebral hypoperfusion to mimic the clinical progression of carotid artery stenosis and allowed reperfusion before CBF-recovery to establish a rat model of hyperperfusion.

After maintaining cerebral hypoperfusion for the desired duration, we loosened the ligature and applied phenylephrine to elevate MAP. Phenylephrine is a selective agonist of α -1 adrenergic receptor, which is lack in cerebral vessels that increases arterial blood pressure via peripheral vasoconstriction and does not impair cerebrovascular function [23, 24]. At present, phenylephrine is used in patients and animal models for increasing blood pressure [26-29]. In our experiment, we found that phenylephrine at different concentrations produces different effects on MAP and CBF after reperfusion. Phenylephrine at 10 or 20 $\mu\text{g/mL}$ cannot elevate MAP and CBF, thus precluding hyperperfusion, but phenylephrine at 30-50 $\mu\text{g/mL}$ elevate CBF to the level exceeding 100% of baseline. Although MAP in rats tends to increase as phenylephrine concentrations increases, no difference in the change of CBF was noted between phenylephrine concentrations of 40 and 50 $\mu\text{g/mL}$ because the changes of MAP was not significantly different at these concentrations ($P>0.05$). This result suggests that the extent by which MAP changes plays a key role in this process, especially when concentration of phenylephrine exceeds 30 $\mu\text{g/mL}$. During this process, ischemia or reperfusion could impair cerebral autoregulation. Under physiological conditions, cerebral autoregulation maintains CBF within constant range when a change in MAP occurs. The primary autoregulatory mechanism involves cerebrovascular reactivity, i.e., the ability of the arterioles to constrict or dilate in response to alterations of blood flow. Under ischemia, hypoperfusion may lead to cerebrovascular changes that initiate leukocyte and platelet adhesion. The severity of such changes depends on the duration of hypoperfusion-exposure. With the development of ischemia, resistance arteries and arterioles under the chronic stimulation of athero-

sclerosis gradually dilate for maintaining sufficient cerebral blood supply. Over time, long-term dilation results in maximal vasodilatation even in the resting state [30]. When this intrinsic autoregulation is impaired or lost, CBF in patients or experimental animals will be vulnerable to blood pressure fluctuations. In our experiments, we believe that two-week hypoperfusion provoked changes in cerebral vascular pathophysiology of rats as mentioned previously, and thus, after reperfusion, the vasculature cannot contract, ultimately resulting in hyperperfusion [31]. In normal rats, the autoregulation of CBF occurs over the MAP range of 60-145 mmHg [32, 33]. In our study, at a phenylephrine concentration of 30 $\mu\text{g/mL}$, although the blood pressure of several rats did not exceed 145 mmHg, hyperperfusion was still observed. In addition to impaired cerebral autoregulation, ischemia/reperfusion state also may shift the upper limits of autoregulatory range. Although this hypothesis does not have substantial experimental supports, several studies reported that pathological states such as subarachnoid hemorrhage or hypertension shift the upper limit of autoregulation in the opposing direction [34, 35]. However, it is possible that different pathophysiologic mechanisms exist between hemorrhagic and progressive ischemic stages.

The results of the present study revealed that phenylephrine at 80 $\mu\text{g/mL}$ or higher concentrations lead to arrhythmia and failed to elevate CBF to the level exceeding 100% of baseline. Even after recovery from arrhythmia, CBF did not exceed 100% of baseline at any phenylephrine concentration. We hypothesized that the arrhythmia affected hemodynamic control and resulted in subsequent acute cardiac dysfunction. Therefore, we did not assess the neurological deficit scores of the 80 and 120 $\mu\text{g/mL}$ phenylephrine groups.

Our results indicated that phenylephrine-induced hypertension results in increased CBF whose value can exceed 100% of the baseline during the peak period. Such high level CBF can be maintained for only a few seconds, and decreases even below the baseline after that. Although there are substantial research on hyperperfusion and CHS, there is little characterization on the time-course of hyperperfusion after vascular recanalization. As there is no

definition of hyperperfusion concerning the exact value and duration of CBF, we strictly followed the definition of hyperperfusion in other literatures and neglected the duration of CBF elevation. Moreover, our data also illustrated that after a few minutes of hyperperfusion, CBF will decrease even below the baseline level. We believe this observation is accounted for by the use of higher phenylephrine concentrations [25, 36] and the way for phenylephrine delivering. In preliminary experiments, we failed to elevate CBF to the level exceeding 100% of baseline by elevating blood pressure, this indicates that in addition to differences in rat models, the effect autoregulation is another important target for elevating CBF. Effect of phenylephrine on cerebrovasculature autoregulation needs further research.

Conclusion

Taken together, we established a novel rat model of cerebral hyperperfusion. This model possesses several advantages, including high reproducibility, low experimental failure rate and easy recovery for recirculation and sufficient reperfusion. Therefore, this model can be widely used for studying both the mechanism of hyperperfusion and the effect of pharmacological manipulations on ischemic brain damage in patients receiving carotid-stenosis manipulation in future.

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Disclosure of conflict of interest

None.

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