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Original Article

# Fate of Patients with Chronic Cerebrovascular Steno-occlusive Disease According to Change of Cerebral Perfusion, Cerebrovascular Reserved, and Incidence of Recurrent Ischemic Stroke


## Abstract

**Objective:** The objective is to demonstrate change of cerebral perfusion and cerebrovascular reserve (CVR) in treating patients with cerebrovascular steno-occlusive disease stratified by change of cerebral perfusion and CVR. **Methods:** Retrospective review patients with radiographic proven major cerebrovascular steno-occlusive disease whom underwent cerebral perfusion imaging with vasoactive stimuli stress test in Siriraj Hospital and Bangkok General Hospital during 2010–2018. Medical records were also reviewed. Radiographic findings, cerebral perfusion parameters and signal change during the stress test were reviewed and used to categorize into three groups. **Results:** There were 40 patients sent to radiology department for the evaluation of CVR. One patient had airway problem during the procedure and was excluded. Remaining 39 patients were included in this study (32 males and 7 females, mean age of 54.55 years). In 42 sites involved, 28 (66%) were internal carotid artery, 14 (33%) were middle cerebral arteries. Laterality is left side in 20 cases, right side in 14 cases, and bilateral in 5 cases. Poor CVR response (increased cerebral blood flow <10%) was found in 9 patients (2 severe stenoses and 7 total occlusions). The mean follow-up time was 28.9 months. Eight cases (20.5%) underwent surgical treatment; surgical bypasses and endovascular interventions. Only one patient had subsequential ischemic symptom at immediate postoperative vascular bypass surgery. The remaining patients had no report of progressive or recurrent neurological deficit symptom. **Conclusion:** Poor CVR response is more often found in higher degree of steno-occlusion. Even inconclusive predicting incidence of recurrent ischemic stroke, CVR that reflects the capacity of neuro-autoregulation.


**Keywords:** *Cerebral perfusion, cerebrovascular steno-occlusive disease, functional magnetic resonance imaging, stimuli stress test*


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## Introduction

Chronic cerebrovascular disease from atherosclerotic disease is a major cause of ischemic strokes. Traditional imaging-based risk assessment of stroke, focused on defining the degree of arterial narrowing, has not taken into the effects of hemodynamics distal to the stenotic site. For example, when carotid stenosis is severe and reduces cerebral perfusion pressure (CPP), autoregulation of the vasculature will maximally dilate the cerebral arteries to maintain cerebral blood flow (CBF). With further reduction in CPP and exhausted compensatory autoregulation, the CBF will decrease and increase risk of stroke.

The integration of cerebral hemodynamics such as cerebrovascular reactivity (CVR) into assessment of stroke risk could help isolate a group of patients whom might be benefit from surgical revascularization or should be adhered to medical therapy because uncleared surgical indication.[1]

In the present day, two main standard approaches to measuring CVR, one attempts to direct measure CBF to the brain tissue (positron-emission tomography, computed tomography (CT) perfusion, and MR perfusion), and second approach is to measure flow velocity (transcranial Doppler ultrasound) both before and after giving vasodilatory stimulus. Vasodilatory stimuli mainly induced global hypercapnia; such stimuli include breath holding, inhalation of carbon dioxide ($CO_2$) gas mixture or



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pharmacologic challenge with acetazolamide (ACZ). Increased CBF is considered CVR.

## Methods

### Patients

Retrospective review of chart and radiographic studies of patients in Siriraj Hospital (SI) and Bangkok General Hospital (BGH) were conducted. All patients provided written informed consent.

For the inclusion criteria were patients with significant major cerebrovascular steno-occlusive disease defined as >50% luminal narrowing of carotid artery or middle cerebral artery (MCA) demonstrated in radiographic study and underwent perfusion study with vasoactive stimuli stress test during 2010–2018. Patients may either experienced ischemic symptom or not. Exclusion criteria were patient who had insufficient medical data record for analysis. There were total of 40 patients sent to radiology department for evaluation of CVR. One patient had airway problem during the procedure and was excluded from the study.

### Data acquisition

The patients underwent magnetic resonance imaging (MRI) perfusion with blood oxygenation level-dependent (BOLD) sequence using 3-Tesla MRI scanner. Vasoactive stimulus used was hypercarbic gas mixture (5%–10% $CO_2$ mix with room air). During 40-s breathing paradigm under standard nonrebreathing mask, patients were monitored for end-tidal carbon dioxide ($ETCO_2$) using capnography and adjust $CO_2$ concentration to increased $ETCO_2$ level about +8 to +10 mmHg for achieving vasodilatation effect. magnetic resonance perfusion (MRP) performed before and during hypercarbic gas inhalation [Figure 1].

BOLD signal changes derived from region of interests (ROIs) at gray matter of bilateral MCA territory. BOLD responses were expressed as percentage signal change which time-resolved indicated during breathing paradigm [Figure 2]. Individuals in BGH underwent either CT perfusion or MRI perfusion studies. Vasoactive stimulus used was intravenous ACZ (20 mg/kg/dose or about 1000 mg.) slowly injection. Perfusion imaging performed before and 15–30 min after injection.[2] The different vasoactive stimulus protocol in each institute was administered due to difference policy of the hospital.

### Data analysis and interpretation

The determination of ROI in T1-weighted images of each subject was manually placed in bilateral cerebral parenchyma at level of basal ganglia, centrum semiovale, and corona radiata. Arterial input function was chosen from MCA to quantify relative CBF by generating CBF maps. CBF values were obtained in these regions. Mean CBF values of each cerebral hemisphere were then calculated.

CVR is defined as percentage increased in CBF compared to baseline (resting) after introduction of vasoactive stimulus (stimulated). CVR can be calculated using formula shown.

$$CVR = \frac{(CBF_{stim} - CBF_{rest})}{CBF_{rest}} \times 100\%$$

We applied the criteria for categorizing stimuli stress test response from Eskey and Sanelli.[3] Normal healthy control would achieve 30%–60% increase in CBF after ACZ challenge and abnormal response defined as <10% increase in CBF. Patients were categorized into three groups based on the CVR response of the ipsilateral hemisphere.

- Good response (CVR >30%)
- Fair response (CVR 10%–30%)
- Poor response (CVR <10% or negative response).

## Results

Eligible 39 patients included in this study. There were 32 males and 7 females, mean age of 54.55 years. Demographic data of the subjects are shown in Table 1. In 42 steno-occlusive sites involved, 28 (66%) were

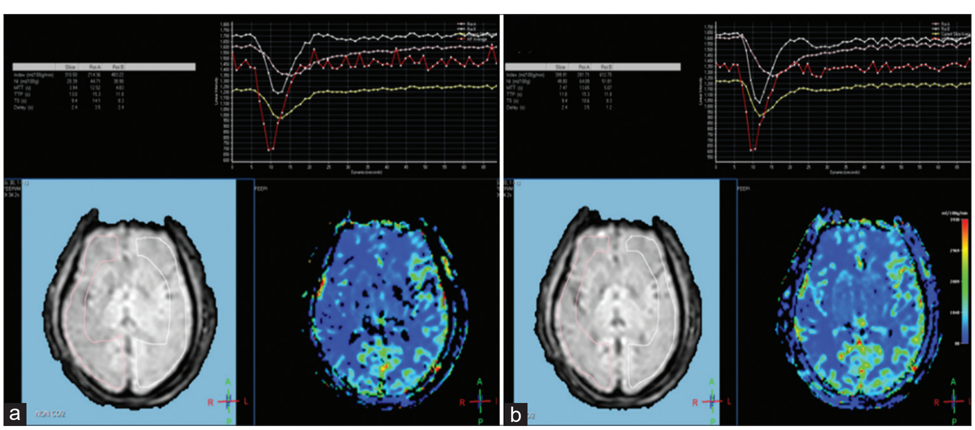


**Figure 1: The determination of region of interests at level of basal ganglia for cerebral blood flow measurement in subject with right internal carotid artery severe stenosis; Note decreased cerebral blood flow of the right cerebral hemisphere (a) and globally increased cerebral blood flow after carbon dioxide inhalation (b)**

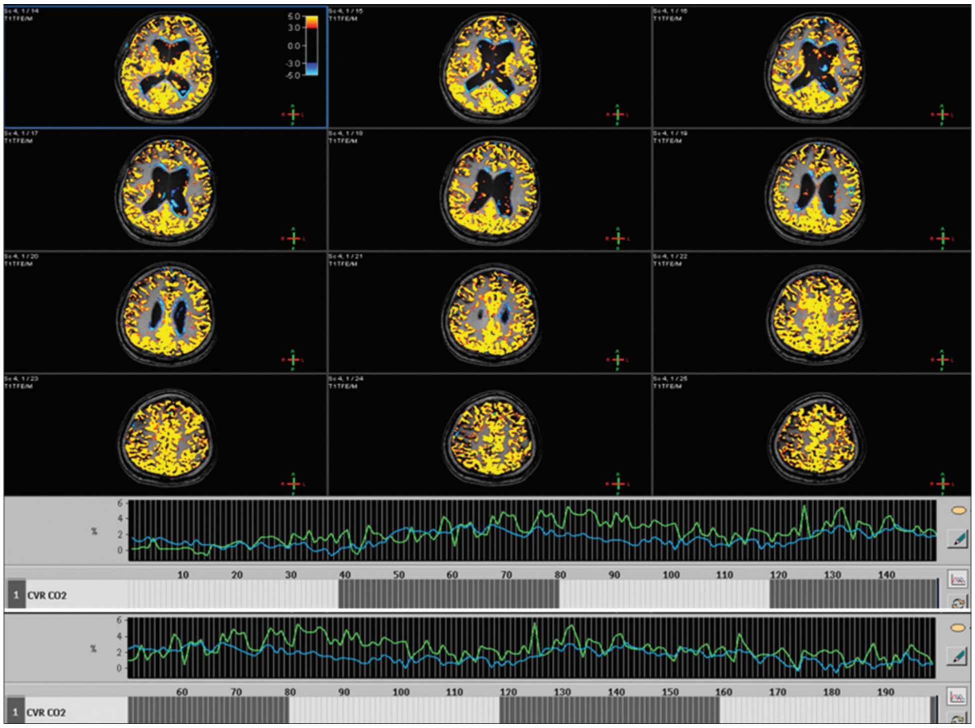

**Figure 2: Blood oxygenation level dependent sequence during carbon dioxide implementation; blood oxygenation level dependent signal change was color-mapped to anatomical images in correspond to time-resolved graph. Note the variation of blood oxygenation level dependent signal during the procedure (40-s breathing paradigm; white stripe-room air and black stripe-carbon dioxide mixed gas)**

internal carotid artery (ICAs), 14 (33%) were MCAs. Laterality is left side in 20 cases, right side in 14 cases, and bilateral in 5 cases. Poor CVR response (increased CBF <10%) was found in 9 patients (2 severe stenoses and 7 total occlusions). Mean follow-up time was 28.9 months. Patients with follow-up time <6 months or loss follow-up were rated at 20.5% (8 cases). Patients with moderate and severe arterial stenoses and arterial occlusion were not included in this group.

Stratification of each response type and variables (degree of stenosis, presented symptoms, and clinical treatment received) are presented in Tables 2-4.

Among cases we studied, we have shown the effect of vasoactive stimuli to the cerebral perfusion. For example, as shown in Figure 3, the test in a 56-year-old male with near-total occlusion of the left ICA, his MRP showed slightly decreased CBF at left parietal region and demonstrated increased CBF >30% which representing good positive CVR response after $CO_2$ inhalation test. It was noted in BOLD sequence that there was heterogeneous signal change of the left cerebral hemisphere at affected brain parenchyma (negative BOLD signal change at affected area differed from positive signal change at other area) which representing change in blood flow direction or steal phenomenon.

Our patients received the treatment either medication (such as antiplatelet and anti-hypertensive drugs) or surgical intervention. We followed clinical outcome of these patients to see whether there were significant different in treatment choices.

The treatments were mainly depending on clinical decision; however, due to many published studies that indicated beneficial of surgery in hemodynamically compromised occlusive disease, many subjects in our study were selected for such interventions.

There were 3 cases (SI) and 5 cases (BGH) whom received surgical intervention; 4 surgical bypasses, 2 carotid stentings, 1 carotid balloon angioplasty, and 1 carotid endarterectomy. They were all severe stenosed or totally occluded major cerebral vessels and also had fair or poor CVR responses. The two among them had follow-up MRI with stress test which showed improved CVR compared to preoperation. The example of these patients was a 43-year-old female diagnosed bleeding Moya-Moya like vessel (severe stenosis) at terminal right ICA who underwent STA-MCA surgical bypass in January 2014, her postoperative imaging in 2016 showed improved positive CVR response and positive BOLD signal change of the right cerebral hemisphere compared to preoperative imaging in 2013 [Figure 4] and a 70-year-old patient with acute ischemic stroke at right parieto-occipital region whose postoperative carotid arterial stenting showed the result in same fashion. Dramatically improved CBF to the affected right cerebral hemisphere in postoperative follow-up imaging was evident with unchanged of small area of perfusion defect represented core infarct [Figure 5].

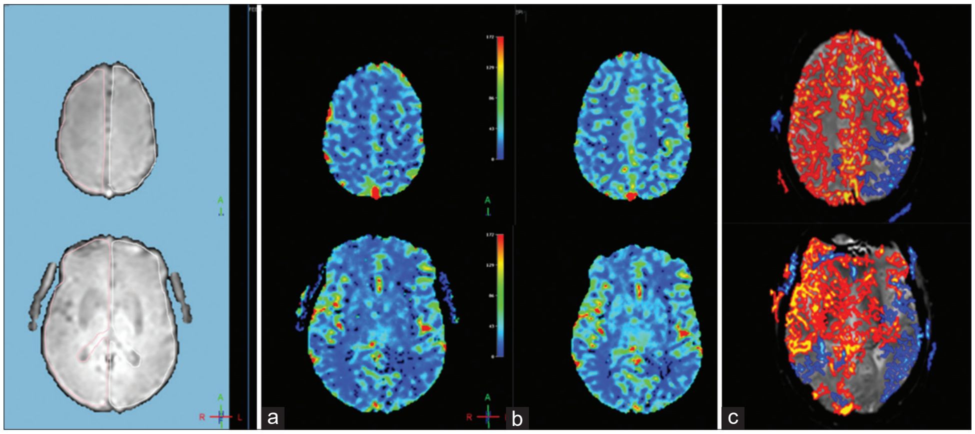

**Figure 3: A 56-year-old male with near-total occlusion of left internal carotid artery. Magnetic resonance imaging perfusion showed slightly decreased cerebral blood flow at left parietal region (a) with good positive CVR response after carbon dioxide inhalation test (b). Noted heterogeneous signal change of the left cerebral hemisphere (negative blood oxygenation level dependent signal change, shown in blue color, at affected area) which represent steal phenomenon (c)**

**Table 1: Demographic data of eligible patients**

| Demographic data | n(%) |
|---|---|
| Gender | |
| Male | 32 (82.1) |
| Female | 7 (17.9) |
| Age (year), mean | 52.8 (7-81) |
| Underlying disease | |
| Hypertension | 21 (53.8) |
| Diabetes mellitus | 10 (25.6) |
| Dyslipidemia | 18 (46.2) |
| Smoker | |
| Yes | 16 (42.1) |
| No/unknown | 23 (58.9) |
| Presenting symptoms | |
| TIA | 9 (23.1) |
| Ischemic stroke | 22 (56.4) |
| Other/asymptomatic | 8 (20.5) |
| Sit | |
| ICA | 28 (66) |
| MCA | 14 (33) |
| Laterality | |
| Left | 20 |
| Right | 14 |
| Bilateral | 5 |
| Degree of stenosis (*n* sites) | |
| Moderate | 5 |
| Severe | 20 |
| Total occlusion | 17 |
| Treatment | |
| Medication | 27 |
| Surgical intervention | 8 |
| Loss follow-up | 4 |
| Follow-up time (month, means) | |
| SI | 27.36 (0-69) |
| BGH | 30.45 (0-84) |

ICA – Internal carotid artery; MCA – Middle cerebral artery; TIA – Transient ischemic attack; SI – Siriraj Hospital; BGH – Bangkok General Hospital

However, surgical treatment was not the only option. Improvement of CVR is also demonstrated in 4 followed up cases who received only medication treatment. The evidence was possibly the result of controlled underlying condition that causes atherosclerotic disease and helpful in recovering vascular elasticity function.

Although we expected to determine the risk factors for recurrent ischemic event in the included groups but other than subject number 15, there was no such incident. Further follow-up period may be required to investigate the factors.

Only one patient had subsequential ischemic symptom, subject number 15, A 45-year-old male who presented SAH following BA tip aneurysmal rupture and found bilateral Moya-Moya vessels on diagnostic cerebral angiogram. He developed left hemiparesis, motor grade 4 upper and lower extremities, at immediate postoperative encephalo-duro-arterio-myo-synangiosis. No structural abnormality was found at plain CT, but CT perfusion suspected core infarction at right frontal lobe. He was fully recovered within 24 h.

The remaining patients had no report of progressive or recurrent neurologic-deficit symptom to present date.

## Discussion

CVR is the change in CBF to the brain in response to stimulus. In this study, we demonstrated CVR in two models, measuring CBF using dynamic susceptibility contrast (DSC)-MRI and perfusion mapping of BOLD functional MRI (fMRI). While DSC-MRI reflects direct CBF measurement by algorithmic calculation, the BOLD fMRI reflects visualization of cerebral metabolism by signal mapping.

### Pathophysiology of chronic cerebrovascular disease

Chronic cerebral hypoperfusion usually resulted from steno-occlusion of large arteries in the neck or circle of Willis. Clinical symptom may vary, developed consequently from either

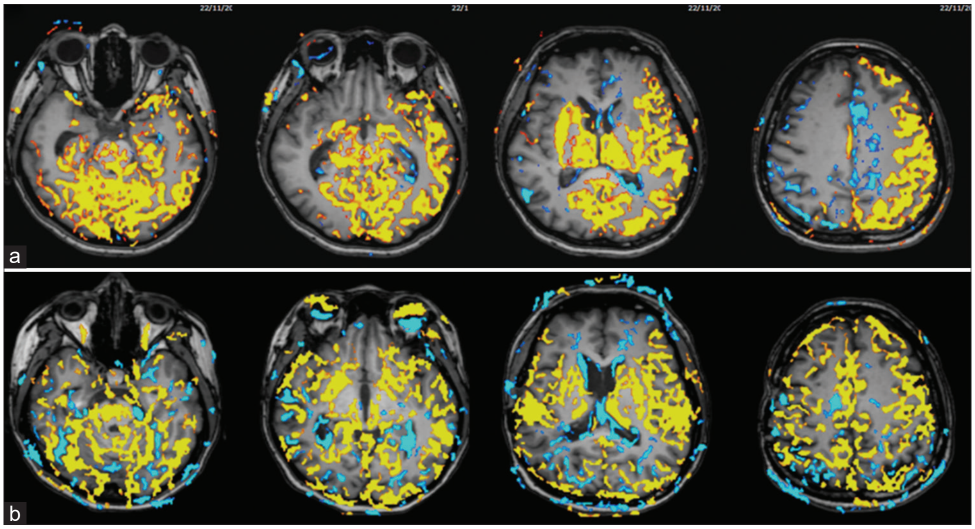


**Figure 4: Preoperative and postoperative blood oxygenation level dependent images of a 43-year-old female diagnosed bleeding Moya-Moya like vessel at terminal right internal carotid artery who underwent STA-MCA surgical bypass (a). Noted improved positive blood oxygenation level-dependent signal change of the right cerebral hemisphere postoperatively (b)**

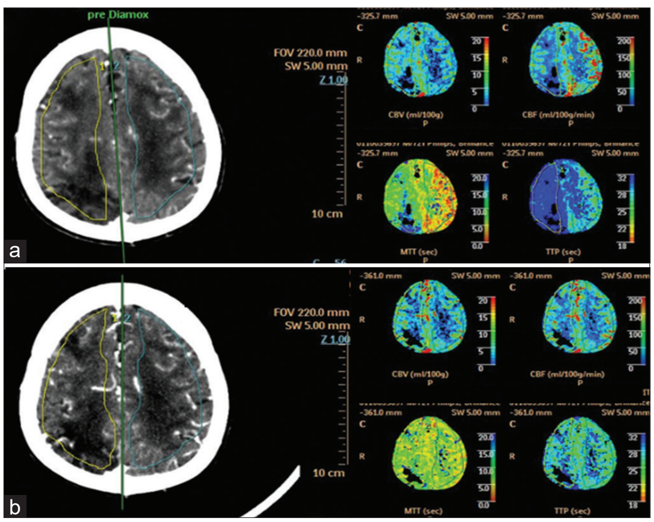


**Figure 5: A 70-year-old patient with acute ischemic stroke at right parieto-occipital region. The computed tomography angiography showed right carotid artery stenosis and poor cerebral blood flow to right cerebral hemisphere. The patient underwent carotid arterial stenting. The picture showed preoperative imaging (a) and dramatically improved cerebral blood flow to the right cerebral hemisphere in postoperative follow-up imaging (b). Noted the perfusion defect at affected area**

embolic event from atherosclerotic plaque or further reduction of systemic hemodynamics on already compromised cerebral perfusion state.[2,3] Powers[4] proposed 2-stage classification of hemodynamic impairment. Stage I, autoregulatory vasodilation, CBF, and oxygen extraction fraction (OEF) not affected but cerebral blood volume (CBV) and mean transit time are increased. Stage II, autoregulatory failure, CBF is decreased and OEF is increased to maintain normal cellular function. This latter stage is also termed "misery perfusion."

The evaluation of these compensatory mechanisms plays role in determinate the fate of disease, risk of future ischemic events and in-patient selection for therapeutic interventions.

**Table 2: The prevalence of degree of steno-occlusive disease stratified by cerebrovascular reactivity responses**

| Degree | CVR | | | Total |
|---|---|---|---|---|
| | Good response | Fair response | Poor response | |
| Moderate | 3 | 2 | 0 | 5 |
| Severe | 9 | 9 | 2 | 20 |
| Total | 8 | 3 | 7 | 17 |
| *n* | 20 | 14 | 9 | 42 |

Number of sites are shown Table 2. CVR – Cerebrovascular reactivity

**Table 3: Presenting symptoms stratified in relationship to cerebrovascular reactivity responses**

| Symptoms | CVR | | | Total |
|---|---|---|---|---|
| | Good response | Fair response | Poor response | |
| Asymptomatic | 5 | 2 | 2 | 9 |
| TIA | 4 | 3 | 2 | 9 |
| Ischemic stroke | 9 | 7 | 5 | 21 |

Number of cases are shown Table 3. CVR – Cerebrovascular reactivity; TIA – Transient ischemic attack

Rogg *et al*.[5] classified response of patient with chronic cerebrovascular disease into three types as follows: Type I: normal baseline CBF with increased CBF after ACZ challenge, Type II: Decreased baseline CBF that increased after ACZ challenge, and Type III: Decreased baseline CBF that continue to reduce after ACZ challenge. Type III response is related to steal phenomenon and most likely to benefit from surgical revascularization.

Paradoxical reduction in BOLD signal after vasodilatory stimulation called "steal" is associated with vascular pathology which representing change in blood flow direction, because of observed co-dependent territories that compete for the same total flow.[6] Steal phenomenon in

**Table 4: Treatment choices according to cerebrovascular reactivity responses**

| Treatment | CVR | | | Total |
|---|---|---|---|---|
| | Good response | Fair response | Poor response | |
| Medication | 17 | 8 | 6 | 31 |
| Surgery/intervention | 1 | 4 | 3 | 8 |

Number of cases are shown of Table 4. Surgical/intervention treatments included 2 cases of carotid stents (severe stenoses with fair CVR responses, 1 case of carotid endarterectomy (severe stenosis with fair CVR response). 1 case of carotid balloon angioplasty (severe stenosis with fair CVR response). Four cases of surgical bypasses (poor CVR responses in Moya-Moya disease, Moya-Moya like vessel, and total occlusion of ICA). CVR – Cerebrovascular reactivity; ICA – Internal carotid artery

BOLD sequence may represent mild-to-moderate ischemic brain tissue.

CT angiography or MR angiography is generally used as a frontline tool for evaluation of extracranial and intracranial arterial steno-occlusive disease. They are good in demonstrate arterial anatomy, variation, and site included percentage of stenosis and occlusion. However, they are known lack of ability to demonstrate compensatory arterial dilatation and evaluate change of flow toward brain when arterial stenosis or occlusion occurred. With that limitation sometimes it causes hesitation in prescribe further treatment to patient. As far as we know, no definite standard practice guideline of treatment for this group of patients has come out yet and tailor-made treatment for each patient is advised with unclear benefit of result.

We demonstrated series of cases those have occlusion of intracranial artery and results of management stratified by changes of cerebral perfusion and CVR. Almost all patients were recovered after one episode of ischemic symptoms by either given medication or surgical intervention to improve hemodynamic problem. Better understanding in hemodynamic change point out how to treat this group of patients in risks. It should be noted from our early experience, this strategy of treatment based on change of cerebral perfusion and CVR is effective enough for these high-risk groups of patients as only one patients in our study (subject number 15) developed clinical recurrent ischemic stroke that was transient and with uncertain cause (suspicious to be related to procedure). Our strategy may also help find patients in this group who are in need to get treatment and avoid risk that sometimes occurred on unnecessary treatment.

We would recommend to have further follow-up period for the evaluation of long-term outcome of these groups of patients considered mean follow-up time in this study is just <3 years while cumulative long-term risk of stroke recurrence is at 26.4% at 5 years and 39.2% at 10 years.[7]

### Limitation

Limitation of our study should be acknowledged. It is a retrospective study with small sample size. Various imaging techniques and nonuniform data processing are another technical consideration that may lead to imprecision of calculated data.

For example, CBFs are measured in global hemispheric ROI not specific to the area of negative BOLD signal change, thus correlation between CBF of specific region on CVR mappings may not be applied.

The patient selection and standardization of stress test protocol that is not a routine investigation require complicated equipment for stimulus delivery and monitoring. Clear definition of such protocol as a prospective study should be conducted to improved value of the future study.

## Conclusion

We found that degree of major cerebrovascular steno-occlusion may not directly reflect the CVR response as only a quarter of patients had poor CVR response, but among those with poor CVR response are likely to associate with higher degree severe stenosis or total occlusion of vessels. The rate of recurrent stroke risk in this group of patients was still impossible to determine due to there is only one patient developed indeterminate ischemic stroke during our relatively short follow-up period.

CT perfusion and DSC-MRP with vasoactive stimuli stress test for measuring CVR is interesting test for better detail in functional assessment of arterial adaptation and brain adaptation than degree of arterial steno-occlusion only. They help stratifies patient who need further revascularization.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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