

## Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-20-7490>

Comment 1: There are numerous grammar errors in the text. For example, in the Introduction, the authors mention "Carotid artery disease is believed to be responsible for anywhere 10-20% of ischemic stroke". The word "between" is missing. Next sentence: "This criteria has been used..." The word "criteria" is the plural of the Greek word "criterion". Although many authors use the word "criteria" as a singular noun, I can assure you that this is completely wrong. This sentence should therefore read "These criteria have been used..."

Reply 1: We agree, we have modified the introduction section as proposed by the reviewer.

Changes in the text: "Carotid artery disease is believed to be responsible for anywhere between 10 and 20% of ischemic stroke." (see Page 3, lines 2-3)

"This criterion has been used to select patients in randomized clinical trials and is consequently considered when making treatment decisions in patients with carotid disease." (see Page 3, lines 4-5)

Comment 2. Page 5, The authors mention that "The cerebral blood flow (CBF) is about 50-57mL/100g/minutes" Are you sure about this number (50-57)?

Reply 2 : We agree. In most physiological studies, CBF is about 50mL/100g/min. We modified this point and changed the 16<sup>th</sup> reference for a more appropriate one.

Changes in the text : "The cerebral blood flow is about 50mL/100g/minutes" (see page 4, line 3)

Comment 3. Again, page 5, the authors write "This result were confirmed by two others studies". Please correct the grammar again here. It is either "This result was confirmed" or "these results were confirmed".

Reply 3: We agree, we have modified the sentence as proposed by the reviewer.

Changes in the text: "These results were confirmed by two other studies showing a decrease in vasoreactivity ipsilateral to carotid stenosis." (see Page 5, lines 23-24)

Comment 4. The hemodynamics in the section "Cerebrovascular reserve" needs to be explained better. As cerebral blood flow to the brains decreases in the side ipsilateral to a severe carotid artery stenosis, compensatory mechanisms take over, including increased blood flow from the contralateral hemisphere via collaterals and maximum cerebral

arteriole vasodilatation.. The authors need to describe this mechanism accurately as it is quite important for readers.

Reply 4: We agree, we tried to clarify it.

Changes in the text: “The cerebral blood flow (CBF) is about 50 mL/100g/minutes [16, 17]. Cerebral autoregulation maintains a constant CBF in case of increased brain functional activity or a significant drop of systemic blood pressure (from 50mmHg to 170mmHg) [18]. Cerebrovascular reserve is the ability of the brain to increase cerebral blood volume (CBV) via collateral network development to maintain a constant CBF. In case of severe decrease of CBF related to unilateral severe carotid artery stenosis, adaptative mechanisms are involved. First (grade I) a vasodilatation of arterioles occurs, which is traduced by an increase of mean transit time (MTT) and CBV while a normal OEF is maintain (OEF). If this mechanism is exhausted (grade II) OEF increases in order to maintain the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>). At the end, when these compensatory mechanisms are exhausted and CBF and CMRO<sub>2</sub> decrease, irreversible damage then takes place : this is ischemia (figure 2) [19].”  
(see page 4 lines 3-14)

Comment 5. The manuscript needs to be reviewed by a native English speaker.

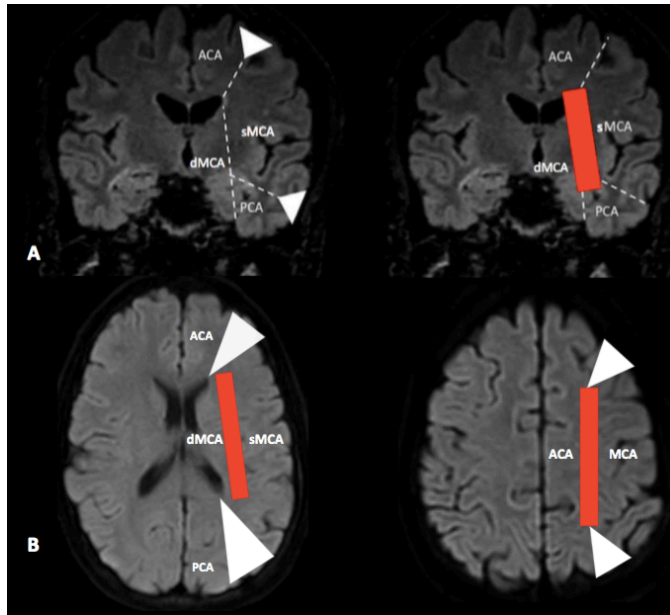
Reply 5: We agree, the manuscript has been reviewed by a Michelle Grange, a native English speaker.

Changes in the text: see revised manuscript

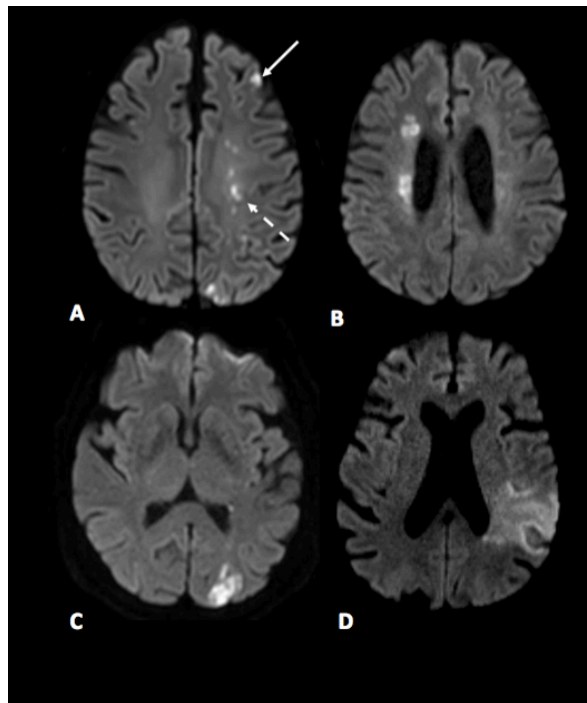
Comment 6. I would ask the authors to include some more figures highlighting watershed areas of the brain.

Reply 6: We agree, figures highlighting watershed areas of the brain have been added. We have completed the figure 1 with axial representation of cortical (white) and internal (red) watershed area and we have added the figure 3 showing axial diffusion weighted imaging-MRI slices of watershed infarcts.

Changes in the text: “Figure 3: Schematic representation of watershed area. Coronal (A) and axial (B) representation of cortical (white) and internal (red) watershed area (adapted from Zülch, 1985 [123]. (ACA : anterior cerebral artery; MCA : middle cerebral artery; dMCA: deep MCA; sMCA: superficial MCA; PCA : posterior cerebral artery)”



“Figure 4: Axial slices of diffusion-weighted MRI showing anterior cortical (full arrow) and internal (dotted arrow) watershed infarcts (A), internal (full arrow) watershed infarcts (B), posterior cortical watershed infarcts (C) and a territorial infarct in the middle cerebral artery territory (D).”



Comment 7. Section "Influence of degree of stenosis". The authors mention that " some studies reported a stronger association between altered CVR and risk of stroke for patients with carotid occlusion or with more severe stenosis." This sentence is un-referenced. Please provide these studies here.

Reply 7: It seems to be a mistake. We removed this sentence from the text.

Changes in the text: see page 8 line 10

Comment 8: The reference list needs to be reviewed and prepared properly. Please have a look at another article published in Annals of Translational Medicine to see how you should prepare the references.

Reply 8: We agree, as evoked in reply 5 of the reviewer 1, we have revised the reference style in our manuscript.

Changes in the text: (see Pages 15-24)

Comment 9. Section "Influence of collaterality": You probably mean "Influence of collateral circulation". Please amend.

Reply 9: We agree, we modified the sentence as proposed.

Changes in the text: "Influence of collateral circulation" (see Page 6, line 21)

### **Minor Revision**

Comment 1: The revised manuscript has improved considerably, the illustrations support the text quite well and the text is well-referenced. The authors need to work a bit on their Conclusions. Currently the Conclusions read "While some ischemic strokes associated with carotid artery disease may result from hypoperfusion, most of them are related to embolism from a vulnerable plaque. The contribution of these different pathways in patients with carotid plaque may be explored using routine and more advanced imaging techniques. A better understanding of ischemic stroke pathogenesis may support the therapeutic approach of symptomatic carotid stenosis." I do not understand what the authors mean when they say that "a better understanding of ischemic stroke pathogenesis may support the therapeutic approach of symptomatic carotid stenosis" This sentence is quite vague and not very helpful. How is a better understanding of ischemic stroke pathogenesis going to support the therapeutic approach of symptomatic carotid stenosis? Patients with symptomatic carotid stenosis (TIA or minor stroke) should be treated with carotid endarterectomy preferably within 2 weeks of symptoms. I am not sure how an understanding of ischemic stroke pathogenesis is going to support the therapeutic approach of these patients. Please address this comment and modify your conclusions in order to be in accordance with the messages of the main text.

Reply 1: We agree, the last sentence is unclear. A better understanding of ischemic stroke pathogenesis do not change indications for surgery but it may guide the technique. Using a shunt may be limited to patients with hemodynamic impairment, although there is no evidence. We have modified the conclusion section as follows.

Changes in the text:

*“A better understanding of ischemic stroke pathogenesis in carotid stenosis may limit the use of routine non-selective shunt, whose benefit-risk balance is debated, to patients with hemodynamic impairment (125).”* (see Page 13, lines 19-21)

We have added the following reference: *“125. Chongruksut W, Vaniyapong T, Rerkasem K. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database of Systematic Reviews 2014;6:CD000190.”* (see Page 21, lines 37-39)