Author’s response to reviews

Title: Dynamic Cerebral Autoregulation Is an Independent Outcome Predictor of Acute Ischemic Stroke after Endovascular Therapy

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Author’s response to reviews:

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Dear Reviewers and Editors,

Thank you very much for your kind suggestions about our manuscript title as “Dynamic Cerebral Autoregulation Is an Independent Outcome Predictor of Acute Ischemic Stroke after Endovascular Therapy”. The paper has been revised according to your comments. Please kindly check them. Thank you for your attention.

Yours sincerely,

Prof. Yongming Wu

Reply to the reviewers and editors:

We thank our reviewers for the constructive comments and have revised the text accordingly. All of the corrected places in manuscript had been marked with red font. Please check them, thank you very much.

Reviewers' comments:

Reviewer #1.

Bilateral dCA abnormality has been shown in lacunar stroke but less reported in large vessel stroke. There is some novelty in this report.
1. However The treatment and control arms are not well matched especially the BP is different in a study looking at dCA. There are also large proportions of smokers and hypertension in the treatment patients.
Authors: Thanks for your support and kind suggestion. In our study, the aim of including healthy controls without cerebrovascular risk factors (such as hypertension, smoking and so on) was to set up completely healthy reference value of phase difference (PD), which was used to be comparable with patients. We have add more detailed description in “Methods” and “Discussion” sections, as “They were without cerebrovascular risk factors and also should meet the following inclusion criteria:” Please check them in P6, and “A PD of 0°indicates total absence of autoregulation, while a large positive PD of 40°-70°can be regarded as intact autoregulation. In our study, the PD obtained from oscillations in ABP and CBFV for MCA in healthy subjects were similar, which is consistent with previous studies. Comparing with healthy controls,” Please check them in P12.

2. Why was heparin given for a stroke thrombectomy? Please cite any references to show that it is beneficial.
Authors: Thank you for your comments. As far as we know, the specialized research to confirm benefit from using of full heparinization in emergency thrombectomy is very limited. And it may be an interesting field to study deeply in future. However, full heparinization is widely used in clinical practice. Most researchers and neurointerventionalists including us thought that most patients presented with hypercoagulable state during acute stage after ischemic stroke. Therefore if the patient had not received intravenous tPA, we proceeded with full heparinization to achieve an favourable coagulation time. In addition, up to now, no adverse events which was caused by heparinization have occurred in our institution. According to your suggestion, we performed some statement and add relative references in the part of Methods “if the patient had not received intravenous tPA, heparin infusion was started intravenously with a 2000-unit bolus, followed by an infusion of 450 units per hour during EVT, and was discontinued at the end of the procedure.” Please kindly check it in Methods (P6) and references 17,18 [17]. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, von Kummer R, Molina CA, Demaerschalk BM, Budzik R, Clark WM, Zaidat OO, Malisch TW, Goyal M, Schonewille WJ, Mazighi M, Engelert ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Martin RH, Foster LD, Tomsick TA. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med. 2013;368:893-903; [18]. Khatri P, Yeatts SD, Mazighi M, Broderick JP, Liebeskind DS, Demchuk AM, Amarenco P, Carrozzella J, Spilker J, Foster LD, Goyal M, Hill MD, Palesch YY, Jauch EC, Haley EC, Vagal A, Tomsick TA. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: An analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. Lancet Neurol. 2014;13:567-574, (P18).

3. Cerebral autoregulation has been reported to recover after 3-5 days post infarct, however the study seems to show there is persistent disability. The contralateral dCA is also persistently different.
Authors: Thank you for your comments. According to your suggestion, we performed some discussion and add relative references in the part of Discussion “Comparing with healthy controls, we found that dCA on both the ipsilateral hemisphere and the contralateral hemisphere were impaired in AIS patients. Consistently with our study, previous researches also reported bilateral impaired CA in the acute stroke29,30. The mechanism of this trans-hemispheric communication may be diaschisis where there is distant functional depression due to the effects of loss of axons (mainly facilitatory) arising at the site of the lesion and, in the case of the cerebral hemispheres, these may synapse with neurons in the contralateral hemisphere via the corpus callosum31. However, further basic research was needed to confirm it. In addition, Dawson et al, have indicated that dCA appeared impaired bilaterally
and remained so for at least 1 to 2 weeks over the subacute post-stroke period. In a follow-up study, CA was also abnormal on the affected side 2 months after stroke onset. All those were closely in keeping with our finding, that” Please kindly check it in Discussion (P12) and reference 31-33 (P19).

4. Looking at favourable outcomes, it appears that even the contralateral dCA shows a difference bordering on significance. The lack of significance is likely due to the small sample size, I am not sure if we can accept the conclusions of the author based on this analysis.

Authors: Thank you for your suggestion. In patient groups, t-test showed the contralateral dCA with a difference bordering on significance between favourable-outcome and unfavourable-outcome groups. But after adjusting confounding factors, the contralateral dCA showed no significance. However, the sample size of our study was small. Further research is needed. We have discussed the point as one limitation. Please check it “The t-test showed contralateral dCA with a difference bordering on significance between favourable-outcome and unfavourable-outcome groups. However after adjusting confounding factors, no significance of contralateral dCA was found. Larger sample size research is needed to explore it in future.” in P13.

5. What is the AUC of the ROC curve?

Authors: Thank you for your suggestion. “The area under the curve of the ROC curve was 0.781”. Please check it in Results (P10).

6. The thrombectomy images are not useful in this study and can be removed.

Authors: Thank you for your suggestion. The figures were used to demonstrate the dCA in patients with favourable outcome or unfavourable outcome. We respect reviewers’ and editors’ opinions on whether to remove the figures. Thank you very much!

7. I don't understand table 5- I assume it's the multivariate analysis for favourable outcomes? If so the title is wrong. I think a more interesting table would be what factors are associated with abnormal dCA in the patient cohort?

Authors: Thank you for your suggestion. We have modify the title of Table 5 to “Multivariate analysis of clinical characteristics and dynamic cerebral autoregulation for favorable long-term outcome”. Please check it in Table 5. Thank you very much!

Reviewer #2.

The investigators studied dynamic cerebral autoregulation (dCA) in patients with acute ischemic stroke (AIS) due to severe stenosis/occlusion of unilateral middle cerebral artery (MCA) or internal carotid artery (ICA) and treatment with endovascular therapy (EVT). They found that among 62 AIS patients after EVT and 77 non-stroke controls, dCA was impaired on both sides over the first 7 days in AIS patients. Phase difference (PD) <26.93°, one of indicator of dCA, on the ipsilateral side at 24h after onset is an independent unfavourable outcome predictor for AIS after EVT. This is a well designed and conducted study. However, there are few concerns.
1. The time intervals between completed EVT and dCA measurement should be presented. Authors: Thanks for your suggestion. We have added the time intervals between completed EVT and dCA measurement in different outcome groups in Table 3: 9.33 ± 3.57 hours vs 7.76 ± 3.75 hours, p=0.117. Please check it in Table 3.

2. In Table 1, what time point the blood pressure (SBP and DBP) was recorded at should be defined. Authors: Thank you for your suggestion. The time point of the SBP and DBP in Table 1 was recorded on admission for patients. We have added it in Table 1. Please check them in Table 1.

3. A recent published paper, Fixed Compared With Autoregulation-Oriented Blood Pressure Thresholds After Mechanical Thrombectomy for Ischemic Stroke. Stroke. 2020 Mar;51(3):914-921. could be referred and discussed. Authors: Thank you for your suggestion. That is an article worth learning from and provides many directions for future research. We have added it as a reference (reference 22) in discussion. And discussed it in Discussion “Consistent with our finding, although with a different dCA monitoring measurement, a recent research suggested that continuous estimation of autoregulation-based treatment strategies after EVT was feasible and could provide a BP range for individual patients tailored to their own physiology22. In future, larger sample size research is needed to observe dCA status when changing BP level.”. Please kindly check it in Discussion (P14) and Reference (P18).