Author's response to reviews

Title: Retrospective evaluation of the effect of carotid artery stenosis on cerebral oxygen saturation during off-pump coronary artery bypasses grafting in adult patients

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Author's response to reviews: see over
RE: MS 9534909721709918
Title: Cerebral oxygen saturation during off-pump coronary artery bypass grafting in patients with carotid artery stenosis: a retrospective review
(New title: Retrospective evaluation of the effect of carotid artery stenosis on cerebral oxygen saturation during off-pump coronary artery bypasses grafting in adult patients)

We are submitting a revised version of the above manuscript. We have carefully considered and attempted to address each of the comments of the referees. As suggested by the referees, we revised the manuscript so that the aim of our study is more clearly defined and shortened the discussion by removing parts that discuss speculations on cerebral circulation. In addition, we have changed the title of the manuscript to better represent the results of the study. In separate pages, we present a point by point response to each of the referees’ comments.

All the authors of the revised manuscript have read the paper, attest the validity of its contents, and agree to its resubmission in BMC Anesthesiology.

We thank the referees for their helpful comments in improving the manuscript and hope that this revised manuscript is now acceptable for publication.

Sincerely yours,

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Response to the Comments of Referee 1

We found your comments given to our manuscript most helpful. We have revised the manuscript in accordance with your comments. Responses to your comments are as follows:

Comment:
The authors should refocus the main objective of their study or specify some important information in the study introduction: cerebral NIRS simply does not measure FLOW! It measures regional microcirculatory (?) saturation, which might be also affected by flow (other than, as correctly stated, by anesthesia, anemia, surgery, low cardiac output, hypotension, hypocapnia, micro and macro emboli and finally monitor errors). That is why all the paper is a huge speculation of something that could happen at a cerebral level as measured by NIRS monitoring.

Response:
It is controversial whether CAS is an independent risk factor of strokes following cardiac surgery or non-cardiac surgery. However, despite hemodynamic depression due to cardiac displacement during anastomosis can lead to a decrease in cerebral oxygenation more frequently during off-pump CABG than on-pump CABG, little information is available for cerebral oxygenation itself in patients with CAS undergoing off-pump CABG. As the referee pointed out, rSO$_2$ values derived from NIRS might be affected by several factors. However, under the same anesthetic and surgical management in both patients with and without CAS, the effect of CAS on cerebral oxygenation in adult patients could be estimated by using rSO$_2$ values derived from NIRS even if several factors affect rSO$_2$ values. Thus, we have focused the main objective of our study on assessing cerebral oxygenation by rSO$_2$ values derived from NIRS during off-pump surgery in patients with and without CAS and evaluating the effect of CAS on cerebral oxygenation during off-pump CABG in adult patients. The goal of our study was rewritten in the background section (Page 5, Line 9–10).

Comment:
In particular the authors might have “validated” their findings by cerebral Doppler (correlation with NIRS) or by clinical outcomes (neurological outcomes): the authors have addressed neither of these aspects.

Response:
We did not perform Doppler ultrasonography monitoring of cerebral blood flow. However, neurological complications, which were defined as focal neurologic deficits persisting ≥ 24 h and confirmed by brain CT or MRI, were examined. There were no neurological complications in both patients with and without CAS. This result was added to the results section (Page 12, Line 11–13 and revised Table 3).

**Comment:**
Apart from clearly stating these biases in the limitation section, the authors should retune their article starting from the title: “Retrospective evaluation of carotid stenosis effect on cerebral oxygen saturation during off-pump coronary artery bypass grafting in adult patients”. The subjects of your study are CABG adult patients and NOT patients with CAS.

**Response:**
As the referee pointed out, we have revised the title of our study.

**Comment:**
Methodology: it is not clear if the authors addressed the duration of intraoperative cerebral NIRS desaturation and if they compared it in the two groups. This is a MANDATORY ASPECT TO BE observed in such a small cohort.

**Response:**
The duration of rSO\(_2\) values < 90% of baseline and 80% of baseline during anastomosis were examined, and those in each frontal lobe of patients with and without CAS were analyzed by one-way ANOVA. There were no significant differences in these data between patients with and without CAS. These were added to the methods section (Page 9, Line 17–21) and results section (Page 13, Line 3–13 and revised Table 4 and 5).

**Comment:**
“The rSO2 values from the right and left frontal lobes were averaged to represent regional cerebral oxygenation”: why? Can the authors provide some of these data separated per each lobe? Was the drift from the two sensors significantly different? Was it different in patients with unilateral CAS?

**Response:**
Since the rSO\(_2\) values from the right and left frontal lobes showed a similar time course in most patients, they were averaged in an initial manuscript. However, as the referee pointed out, it is thought to be inappropriate for patients with CAS, especially patients without a good compensation of the intracerebral circulation, to average the rSO\(_2\) values from the right and left frontal lobes. Thus, we have omitted the sentence in the methods section and revised
the results on rSO$_2$ values by separating per each lobe (Page 12, Line 14–Page 13, Line 13 and revised Table 4 and 5). Separating per each probe, there were no significant differences in changes in rSO$_2$ values during anastomosis between patients with bilateral and unilateral CAS and those without CAS, suggesting that cerebral bi-hemispheric perfusion by Willis circle was working properly in patients with all of the study patients (Page 16, Line 9–16).

**Comment:**
I do not seem to have identified in the paper what NIRS device you used: please specify.

**Response:**
Cerebral oxygenation was monitored by using an INVOS 5100C cerebral oximeter (INVOS, Covidien, Mansfield, MA). We have added it in the methods section (Page 6, Line 24–Page 7, Line 1).

**Comment:**
Sample size: the authors’ calculation is wrong since they focused the whole study on CAS vs non CAS comparison. As is, it appears as significantly underpowered. However, by following my suggestion of changing the subject, sample size power still might work as you presented.

**Response:**
As the referee pointed out, we have revised the title of our study and exchanged the subjects of our study from “patients with CAS undergoing off-pump CABG” to “adult patients undergoing off-pump CABG”. Thus, since the main objective of our study became the effect of CAS on cerebral oxygenation during off-pump CABG in adult patients, not the comparison of cerebral oxygenation between patients with and without CAS, we think the calculation of sample size is appropriate.

**Comment:**
Results: specify the number of studied patients (beyond referring to flowchart).

**Response:**
As the referee pointed out, we have added the number of studied patients in the results section (Page 11, Line 2–7).

**Comment:**
Differently from what done by the authors I would have analyzed the cohort as a whole, secondarily providing a quick comparison between CAS and non CAS patients (as theoretically stated in the objectives).
Response:
As the referee pointed out, we have revised the title of our study. Thus, as the main objective of our study, changes in rSO$_2$ values during off-pump CABG in patients with and without CAS were assessed, and the effect of CAS on cerebral oxygenation during off-pump CABG in adult patients was evaluated by multiple logistic regression analysis. The comparisons of patient characteristics and perioperative data between patients with and without CAS were performed as the secondary objective of our study.

Comment:
In this line I would have analyzed intraoperative desaturation in the multivariable regression by putting a dichotomous variable "CAS yes/no" into the model in order to assess its effect. In the same line, in my opinion, comparing the results coming from two populations is barely meaningful. Also, this might better highlight the effect of MAP/vasoactive drugs/CI on the overall model.

Response:
As the referee pointed out, we have reanalyzed intraoperative cerebral desaturation in the multiple logistic regression analysis by putting a dichotomous variable "CAS yes/no" into the model, and the odds ratio of the presence of CAS for cerebral desaturation (a decrease in rSO$_2$ $> 10\%$ from baseline) was adjusted by hemodynamic data and the doses of vasoactive drugs. In re-multiple logistic regression analysis, CAS was not associated with an increased risk of cerebral desaturation. These were added to the methods section (Page 9, Line 21–Page 10, Line 1) and results section (Page 13, Line 20–Page 14, Line 4 and revised Table 6).

Comment:
Furthermore, as the authors correctly stated in the introduction, surgery/heart manipulation length is a fundamental aspect that should be included in the multivariable model.

Response:
In our multiple logistic regression analysis, the relationships between a decrease in rSO$_2$ $\geq 10\%$ from baseline during anastomosis and hemodynamic parameters (MAP $< 60$ mmHg, cardiac index $< 2.0$ l/min/m$^2$, and CVP $> 10$ mmHg) and the presence of CAS were evaluated. For example, if the relationships between intraoperative factors and the incidence of neurological complications following off-pump CABG are evaluated, the duration of hypotension and low cardiac output, the presence of CAS, and surgery/heart manipulation length should be included in multiple logistic regression analysis. Thus, we think that surgery/heart manipulation length is unnecessary to be included in our multiple
logistic regression analysis.

**Comment:**
no data are presented on neurologic outcomes in the text.

**Response:**
In our study, neurological complication was defined as focal neurologic deficit persisting \( \geq \) 24 h and confirmed by brain CT or magnetic resonance imaging, and there were no neurological complications in both patients with and without CAS. This result was added to the results section (Page 12, Line 11–13 and revised Table 3).

**Comment:**
It might be rather hard to evaluate neurologic outcomes of patient with stroke/TIA in anamnesis. The study should have had to enroll only patients without neurologic issues. Add this in the long limitations section.

**Response:**
In our study, neurological complication was defined as as focal neurologic deficit persisting \( \geq \) 24 h. As the referee pointed out, it might be difficult to evaluate neurological outcomes correctly in patients with preoperative stroke/TIA. We have added this limitation in the discussion section (Page 18, Line 22–Page 19, Line 1).

**Comment:**
Discussion: please significantly shorten it especially all the part with pathophysiological speculations that cannot simply be confirmed by your data. Also comment on the fact that decreases were not that significant form a clinical standpoint (absolute values never really appeared to decrease below the critical level of 40%).

**Response:**
As the referee pointed out, many speculations about cerebral circulation, especially in patients with CAS, which could not be confirmed by our results, were included in an initial manuscript. We have omitted several parts with pathophysiological speculations in the discussion section. In addition, we have added the fact that absolute \( rSO_2 \) values did not decrease \(< 40\% \) in revised Table 5.

**Comment:**
Furthermore what is totally missing in the discussion is the acknowledgment that, if your results actually showed an insignificant desaturation secondary to CAS, it may simply mean that cerebral bi-hemispheric perfusion by Willis circle was working properly in all patients.
Response:
In our study, there were no significant differences in changes in rSO₂ values during anastomosis between patients with bilateral and unilateral CAS and those without CAS. In addition, multiple logistic regression analysis showed that bilateral CAS was not an independent risk factor of a decrease in rSO₂ ≥ 10% from baseline. As the referee pointed out, our results may suggest that cerebral bi-hemispheric perfusion by Willis circle was working properly in all of the study patients. We have added this result in the results section (Page 13, Line 3–13 and revised Table 4, 5, and 6) and discussion section (Page 16, Line 10–16).

Comment:
The authors stated that “In patients with CAS, the OR for a decrease in rSO₂ > 10% from preoperative value was 0.711 (95% CI 0.547–0.925; p=0.011) for every 0.1 l/min/m² increase in cardiac index above 2.0 l/min/m²”: this finding is not reported in the main text of the article. Please revise.

Response:
This result was presented in Table, but not in the main text of the manuscript. In re-multiple logistic regression analysis, cardiac index < 2.0 l/min/m² was associated with an increased risk of cerebral desaturation (OR 3.773, 95%CI 2.451–5.809, p < 0.001). We have added the reanalyzed result in the results section (Page 13, Line 25–Page 14, Line 1 and revised Table 6), and the abstract was revised (Page 3, Line 1–2).
Response to the Comments of Referee 2

We found your comments given to our manuscript most helpful. We have revised the manuscript in accordance with your comments. Responses to your comments are as follows:

Comment:
The method used for CI estimation should be indicated (PAC – Thd).
Response:
Cardiac output was measured by thermodilution technique with a pulmonary artery catheter, and the cardiac index was calculated. This was added to the methods section (Page 7, Line 13–15).

Comment:
The number of patients included in the analysis should be indicated in the “results” section.
Response:
As the referee pointed out, we have added the number of studied patients in results section (Page 11, Line 2–7).

Comment:
The degree of the stenosis MUST be indicated in the summary.
Response:
The demographic data in patients with CAS, including the degree of the stenosis, was added to the results section (revised Table 2).

Comment:
The values of blood pressure during the most challenging phases (e.g. marginal, posterior revascularization) has to be considered in the results. Blood pressure could as important as blood flow in decreasing tissue oxygen saturation.
Response:
As the referee pointed out, we have reanalyzed hemodynamic data and rSO$_2$ values at specific points including the beginning of grafting the left circumflex coronary artery, right coronary artery, and left anterior descending artery. Significant changes in cardiac index, CVP, and rSO$_2$ were observed at the beginning of grafting the left circumflex coronary artery and/or right coronary artery, but changes in blood pressure were not significant. These were added to the methods (Page 8, Line 8–14) and results section (Page 12, Line 14–Page 13, Line 2, Page 13, Line 14–19, and revised Figure 2, 3, and 4).
Comment:
the author stated that: “… NIRS devices assume that the hemoglobin content of the cerebral cortex is distributed 75% in the venous and 25% in the arterial district …” … and this is true… In fact, a reduction in rSO2 can derive from a reduction in arterial supply (as occurs during OPCAB), a decrease in venous drainage (as also occurs during OPCAB), or a combination of them (as clearly occurs during OPCAB) … For example, a patients with cardiac tamponade may has a still good “antegrade-arterial” flow with acceptable perfusion but limited venous drainage with consequent venous congestion. This condition may be associated with reduction in rSO2…. this aspect should be considered in the discussion. In addition, in order to identify any possible correlation between venous congestion and drop in rSO2, central venous pressure values should be considered. It is my opinion that a graph showing the relationship between CVP and sSO2 could be important.

Response:
As the referee pointed out, an increase in CVP may be associated with a decrease in cerebral oxygenation. Thus, we have added data on CVP in the results section (Page 13, Line 14–Page 14, Line 4, revised Figure 4, and revised Table 6). In our study, CVP increased during grafting the right coronary artery or left circumflex coronary artery. However, multiple logistic regression analysis demonstrated that increased CVP was not associated with an increased risk of cerebral desaturation, inconsistent with the referee’s opinion and a previously reported study (Moritz S, et al. Eur J Anaesthesiol 2012; 29: 82–7). In our study, patients were usually positioned in a Trendelenburg position during grafting the LCX and/or RCA. Several studies have shown no relationship between the Trendelenburg position and a change in rSO2 value since an increase in CBF due to the Trendelenburg position increases oxygen delivery (Harrison GR. Anaesthesia 2001; 56: 1181–1184 and Park EY, et al. Acta Anaesthesiol Scand 2009; 53: 895–899). Thus, in our study, increased CVP might not be an independent risk factor of a decrease in rSO2 > 10% from baseline value. The reason of no relationship between increased CVP and cerebral desaturation in our study was discussed in the discussion section (Page 17, Line 23–Page 18, Line 5).

Comment:
When “aortic no-touch technique” is used, major hemodynamic instability do not occur during revascularization. Moreover, venous congestion, due to heart dislocation, do not occur. This sub-group of patients should be separated from the others.

Response:
In our patients, gastroepiploic artery was usually used for grafting the right coronary artery if
aortic no-touch technique was performed, and thus heart displacement was also performed during this anastomosis. In addition, hemodynamic status was not impaired severely by partial ascending aortic clamping for anastomosis of saphenous vein to ascending aorta. Thus, patients who received aortic no-touch technique were not separated from the others.

Comment:
The use of the “pulmonary artery catheter” is almost unusual in modern NON-combined cardiac surgery (e.g. CABG or OPCAB). Please provide a comment.

Response:
In our hospital, pulmonary artery catheter is used routinely in cardiac surgery because pulmonary catheter is educational devise to understand hemodynamic status for residents (Page 7, Line 10–12). Although most of Japanese anesthesiologists know a recent opinion on the use of pulmonary artery catheter during cardiac surgery well, pulmonary artery catheter is usually used in non-combined cardiac surgery in many Japanese university hospitals.

Comment:
In many cardiac centers, carotid and coronary artery revascularization are performed during the same intervention in order to limit the neurological consequences due to hemodynamic instability. Please, provide a comment on this.

Response:
In our hospital, simultaneous carotid endarterectomy and CABG are not performed routinely in patients with CAS, irrespectively of symptomatic or asymptomatic. This was added to the methods section (Page 6, Line 15–16). In addition, simultaneous carotid endarterectomy and CABG are rare in Japanese hospitals.

Comment:
Page 10 – line 9: “3 patients received carotid artery stenting prior to CABG”. Did you include these patients into the group with stenosis? Please specify.

Response:
In our study, 3 patients with CAS received carotid artery stenting preoperatively. However, carotid artery stenting was unsuccessful in 1 patient. In addition, in patients with CAS, baseline rSO2 correlated with both preoperative LVEF and baseline MAP. Even if 2 patients, who received successful carotid artery stenting preoperatively, were excluded, baseline rSO2 correlated with both preoperative LVEF and baseline MAP. The correlation coefficients between baseline rSO2 and preoperative LVEF or baseline MAP in patients with CAS were
not affected by including the 2 patients who received successful carotid artery stenting preoperatively. Meanwhile, in patients without CAS, baseline rSO<sub>2</sub> correlated with neither preoperative LVEF nor baseline MAP. Thus, perioperative data in 2 patients with CAS, who received successful carotid artery stenting preoperatively, were not excluded from those in patients with CAS. Thus, we included these 3 patients in patients with CAS. This was added to the results section (Page 11, Line 19–Page 12, Line 6). Moreover, hemodynamic data and rSO<sub>2</sub> values did not differ between patients with and without these 3 patients (data are not shown).

Comment:
Page 10 – lines 11-12: “Aortic not-touch technique was used more frequently in the stenosis group than the normal group (p = 0.026).” Please provide the numbers a see the comment above.

Response:
As the referee pointed out, we have added the number of patients with aortic no-touch technique in the results section (Page 12, Line 7–11).

Comment:
The technique used for CI estimation must be described. Moreover, thermodilution is imprecise in presence of tricuspid regurgitation (TR) and cannot be used for flow calculation. How did the authors exclude TR during ALL the phases of surgery? Once the heart is dislocated to perform posterior and lateral anastomosis, TEE cannot be used because the contact between the esophagus and the pericardium is interrupted by air. Please provide a comment.

Response:
Cardiac output was measured by thermodilution technique with a pulmonary artery catheter, and the cardiac index was calculated. This was added to the methods section (Page 7, Line 13–15). As the referee pointed out, cardiac index estimation by pulmonary artery catheter may be inaccurate in the presence of TR. We have added the limitation of cardiac index estimated by thermodilution technique with a pulmonary artery catheter in the discussion section (Page 19, Line 1–6).

Comment:
Neurological outcome of the studied patients should be highlighted.

Response:
In our study, neurological complication was defined as focal neurologic deficit persisting >
24 h and confirmed by brain CT or MRI, and there were no neurological complications in both patients with and without CAS. This result was added to the results section (Page 12, Line 11–13 and revised Table 3).

**Comment:**
Page 8 – lines 7-8: “The rSO2 values from the right and left frontal lobes were averaged to represent regional cerebral oxygenation.” In case of stenosis of a single carotid artery (more common condition) and without a good compensation of the intracerebral circulation, a major desaturation of a single side would be expected. Since the authors did the average of the two sides, a comment on this could be useful for the reader.

**Response:**
Since the rSO2 values from the right and left frontal lobes showed a similar time course in most patients, they were averaged in an initial manuscript. However, it is likely to be inappropriate for patients with CAS, especially patients without a good compensation of the intracerebral circulation, to average the rSO2 values from the right and left frontal lobes. Thus, we have revised the results on rSO2 values by separating per each lobe. Moreover, there were no significant differences in changes in rSO2 values during anastomosis between patients with bilateral and unilateral CAS and those without CAS. In addition, multiple logistic regression analysis showed that bilateral CAS was not an independent risk factor of a decrease in rSO2 ≥ 10% from baseline value. These results may suggest that cerebral bi-hemispheric perfusion by Willis circle was working properly in patients with all of the study patients. These were added to the results section (Page 13, Line 3–13 and revised Table 4 and 5) and discussion (Page 16, Line 9–16).

**Comment:**
Page 8 – lines 10-12: “a decrease in rSO2 > 20% from baseline value indicates a critical reduction in cerebral oxygenation and perfusion” ... (AGAIN) a reduction in rSO2 can derive from a reduction in arterial supply (as may occur during OPCAB), a decrease in venous drainage (as usually occurs during OPCAB), or a combination of them (as clearly occurs during OPCAB) ... For example, a patients with cardiac tamponade may have a still good “antegrade” flow with acceptable perfusion but limited venous drainage with consequent venous congestion. This condition may be associated with reduction in rSO2.... this aspect should be considered in the discussion. In addition, in order to identify any possible correlation between venous congestion and drop in rSO2, central venous pressure values should be considered. It is my opinion that a graph showing the relationship between CVP and sSO2 could be important.
Response:
As the referee pointed out, an increase in CVP may be associated with a decrease in cerebral oxygenation. Thus, we have added data on CVP in the results section (Page 13, Line 14–Page 14, Line 4, revised Figure 4, and revised Table 6). In our study, increased CVP was observed during grafting the right coronary artery or left circumflex coronary artery, but multiple logistic regression analysis demonstrated that increased CVP was not associated with an increased risk of cerebral hypoxia. As mentioned above, increased CVP might not be an independent risk factor of a decrease in rSO₂ ≥ 10% from baseline value in patients with Trendelenburg position because of an increase in oxygen delivery (Page 17, Line 11–Page 18, Line 5).

Comment:
Page 10 – lines 4-7: “In the stenosis group, 4 patients had a unilateral high-grade (> 70%) CAS, 1 patient had a unilateral high-grade (>70%) CAS with a contralateral occlusion, 4 patients had bilateral high-grade CAS and 2 patients had bilateral moderate-grade (> 50%) CAS”. The CAS group shows a very high heterogeneity. A stenosis > 70% may have, depending on adopted guidelines and recommendations (and the presence or absence of symptoms) surgical indication while 50-60 usually not. This variability is a strong limitation of the study and need a dedicated comment.

Response:
As the referee pointed out, the variability of the degree of CAS is a strong limitation in our study. However, in our study, there was no significant correlation between the degree of CAS and changes in rSO₂ during anastomosis (Page 13, Line 3–5), and multiple logistic regression analysis showed that stenosis side of the forehead was not always associated with a decrease in rSO₂ ≥ 10% from preoperative value (revised Table 6). Moreover, CAS > 50% has been shown to be an independent risk factor of postoperative stroke or TIA following off-pump CABG (Miyazaki S, et al. Interact Cardiovasc Thorac Surg 2011; 12: 379–83), while the degree of CAS was not shown to be associated with a risk of perioperative stroke after noncardiac surgery (Sonny A, et al. Anesthesiology 2014; 121: 922–9). We think that it is important for anaesthesiologists to know whether cerebral functional reserve in patients with CAS is good or poor, irrespectively of the degree of the stenosis, preoperatively (Page 16, Line 6–21).

Comment:
Page 12 – line 8: “and ETCO₂ was maintained between 35 and 40”. ETCO₂ depends on several factors including: minute ventilation, CO₂ production and flow to the pulmonary
system (cardiac output). Right ventricular stroke volume usually drop during OPCAB due to the hart dislocation and handling. In light of this observation, the sentence is not correct since CO2, as indicated in the text, is considered as regulator od cerebral blood flow but, in this case, a profound difference between PCO2 and ETCO2 may exist.

**Response:**
As the referee pointed out, ETCO2 depends on several factors including cardiac output. In fact, in our study, ETCO2 correlated with cardiac index ($r = 0.122, p = 0.0025$, data are not shown). Thus, we have omitted the results and discussion on ETCO2 from our manuscript.

**Comment:**
Page 12 – line 1-2: “In the present study, cerebral oxygenation significantly decreased during anastomosis in both the stenosis and normal groups.” I strongly disagree with this statement. rSO2 significantly decreased but not necessarily “cerebral oxygenation” decreased. In fact, as considered before, a reduction in rSO2 may result from an INCREASE in venous congestion rather than a decrease in arterial blood flow. The data has to be correlated with CVP. Probably, this is the reason that may explain that “However, the decrease in cerebral oxygenation during anastomosis was not statistically significant between the two groups”.

**Response:**
In our study, increased CVP was observed during anastomosis but was not associated with an increased risk of cerebral desaturation (Page 13, Line 14–Page 14, Line 4, revised Figure 4, and revised Table 6). As mentioned above, increased CVP might not be an independent risk factor of a decrease in rSO2 $\geq 10\%$ from baseline in patients with Trendelenburg position because of an increase in oxygen delivery (Page 17, Line 11–Page 18, Line 5).

**Comment:**
Page 4 –line 5: “CPB , such” – space

**Response:**
As the referee pointed out, we have rewritten it (Page 4, Line 6).

**Comment:**
Page 4 –line 7: replace “chronic kidney injury” with “chronic kidney disease”. Injury is mostly referred to an acute syndrome.

**Response:**
As the referee pointed out, we have rewritten it (Page 4, Line 7).
Comment:
Page 4 – line 7: “caused” – check
Response:
We have checked it.

Comment:
Page 4 – lines 13-16: “Since decreased cerebral perfusion pressure (CPP) due to CAS caused a decrease in cerebral blood flow (CBF) depending on the degree of the stenosis [19], CAS can provoke cerebral hypoperfusion to cause cerebral ischemia when hemodynamic impairment occurs during surgery.” – The sentence is difficult to read. Please re-phrase.
Response:
Cerebral circulation is impaired depending on the degree of stenosis (Powers WJ. Ann Neurol 1991; 29: 231–240). We have revised the manuscript (Page 4, Line 13–14).

Comment:
Page 6 – line 4: “Teikyo University Chiba Medical Center” … add the Country
Response:
We have added it (Page 6, Line 5).

Comment:
Page 6 – line 4: replace “to” with “into”
Response:
We have omitted the sentence including it.

Comment:
Page 12 – lines 11-2: “It is unclear whether CAS is associated with an increased risk of cerebral ischemia during off-pump CABG.” A ref is needed.
Response:
We have revised the sentence to “it is unknown whether the presence of CAS can affect cerebral oxygenation in patients undergoing off-pump CABG” (Page 15, Line 11–12). Although there are several studies showing the incidence of strokes in patients with CAS after off-pump CABG (Miyazaki S, et al. Interact Cardiovasc Thorac Surg 2011; 12: 379–83 and Wang B, et al. Heart, Lung and Circulation 2014; 23: 560–5), little information is available for cerebral oxygenation in patients with CAS during off-pump CABG. Thus, a ref
was not added in the revised sentence.

Comment:
Page 14 – line 25: “However, studies showing the incidence of strokes in patients with CAS after…” A ref is needed.

Response:
We have added a reference in the sentence (Page 15. Line 23–24).