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
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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. 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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Point by point response to referees' comments

Response to the Comments of Referee 1

We would like to appreciate your instructive review given to our manuscript. In the present manuscript, two patients with carotid artery stenosis (CAS) who have received complete stenting preoperatively were excluded from the analyses according to the comment of referee 2. According to your comment, we examined whether there were significant differences in changes in rSO$_2$ values between patients with bilateral CAS and those with unilateral CAS in the previous manuscript. However, since the number of patients with unilateral CAS became only 2, we could not analyze it statistically in the present manuscript. Thus, we revised Table 4. However, changes in rSO$_2$ values in the remaining two patients with unilateral CAS were similar with those in patients with bilateral CAS. We think that there were no significant differences in changes in rSO$_2$ values between patients with bilateral CAS and those with unilateral CAS. In addition, our main results were not affected by excluding the two patients in the present manuscript.
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:
Abstract: the degree of stenosis is a key factor for the interpretation of the results. The threshold of 50% must be indicated in the abstract.
Response:
The presence of carotid artery stenosis (CAS) ≥ 50% has been shown to be a risk factor of strokes in both cardiac and non-cardiac surgeries. In the present study, the severity of CAS was assessed using area stenosis as stenosis (stenosis ≥ 50%) or none (stenosis < 50%). Thus, as the referee pointed out, we have added the threshold of 50% in abstract.

Comment:
"In multiple logistic regression analysis, CAS was not associated with an increased risk of cerebral desaturation (OR 0.226, 95% CI 0.088–0.580, p < 0.001) . . . “With an OR of 0.226 we could speculate that CAS is protective vs cerebral desaturation. It sounds quite strange. A comment is mandatory (perhaps the operator may have paid more attention to hemodynamics and oxygen delivery in patients with CAS. This could be a bias related to the retrospective nature of the study).
Response:
As the referee pointed out, surgeons and anesthesiologists might have paid more attention to hemodynamics and oxygen delivery in patients with CAS. This was added to the Discussion section (Page 16, Line 10–17). However, under the same anesthetic management, hemodynamic status was similar among all of the patients, and the duration of cerebral desaturation during anastomosis did not differ between patients with and without CAS. Thus, we think that the bias related to the retrospective nature of the study is minor.

Cerebral blood flow is usually preserved within a wide range of mean arterial pressure (MAP) because of cerebral autoregulation. On the contrary, in patients with cerebrovascular disease, the cerebral autoregulation sets itself to guarantee an adequate cerebral blood perfusion in patients with reduced carotid flow due to stenosis (Powers WJ. Ann Neurol 1991; 29: 231–40 and Giustiniano E, et al. J Cardiovasc Med 2010; 11: 522–8). Giustiniano E, et al. have shown that an excessive increase in arterial pressure is not necessary to guarantee safe regional cerebral tissue oxygen saturation (rSO2) during carotid cross-clamping in patients receiving carotid endarterectomy and proposed intraoperative
strategy avoiding controlled hypertension for normotensive management during carotid clamping. In the present study, preoperative hemodynamic status (MAP, left ventricular ejection fraction (LVEF), and heart rate) and rSO$_2$ did not differ between patients with and without CAS, and anesthesia-induced hypotension did not impair cerebral oxygenation in both patients with and without CAS. Rather, a significant increase in rSO$_2$ from preoperative value was observed at heparin administration in patients with CAS ($p = 0.049$, paired-$t$-test). Thus, patients with CAS did not necessarily need excessive increases in MAP and cardiac output for preventing cerebral desaturation. Furthermore, in the present study, in patients with CAS, preoperative rSO$_2$ correlated with both preoperative LVEF and MAP, whereas in patients without CAS, preoperative rSO$_2$ correlated with neither preoperative LVEF nor MAP. These results are likely to be consistent with the concept of cerebral hemodynamic mechanism as mentioned above. Our results also suggest that cerebral oxygenation in patients with CAS depended on hemodynamic status more strongly compared with patients without CAS. In fact, in patients with CAS, MAP and cardiac index differed significantly between patients with and without cerebral desaturation (MAP: 59 ± 9 vs. 65 ± 11, $p < 0.002$; cardiac index: 1.9 ± 0.4 vs. 2.5 ± 0.5, $p < 0.001$), whereas in patients without CAS, cardiac index differed significantly between patients with and without cerebral desaturation (2.2 ± 0.6 vs. 2.5 ± 0.6, $p < 0.001$), but MAP did not differ between patients with and without cerebral desaturation (67 ± 9 vs. 69 ± 11, $p = 0.884$) (these data are not shown in the manuscript). Thus, cerebral oxygenation in patients with CAS is likely to be preserved easily if hemodynamic parameters are maintaining at normal level, whereas cerebral oxygenation in patients without CAS is not always to be preserved even if hemodynamic parameters are maintaining at normal level (other factors may affect cerebral oxygenation more strongly in patients without CAS than patients with CAS). Further prospective studies are warranted to confirm our findings.

In addition, our odds ratio (OR) of CAS for cerebral desaturation means that the risk of cerebral desaturation was lower in patients with CAS than those without CAS under the same anesthetic management, but does not mean that the presence of CAS could prevent cerebral desaturation.

Comment:
“In our hospital, pulmonary artery catheter is used routinely in cardiac surgery because pulmonary catheter is educational devise to understand hemodynamic status for residents.” It is opinion of the reviewer that in this sentence there one grammatical error “devise” vs “device” and a conceptual error: in the respect of any local habit, current recommendations from the literature discourage the use of PAC except in selected clinical conditions
characterized by complex packages of disease, co-morbidities and surgery. Your patients had a mean LVEF of 58 [41–61]%. Routine use is now not indicated also in cardiac surgery patients (Schwann NM, Hillel Z, Hoeft A, Barash P, Mohnle P, Miao Y, Mangano DT. Lack of effectiveness of the pulmonary artery catheter in cardiac surgery. Anesth Analg. 2011 Nov;113(5):994-1002). A so extensive use (ROUTINE in CABG) of PAC in patients without clear indications (e.g. pulmonary hypertension, right ventricular dysfunction) needs a comment.

Response:
In our hospital, pulmonary artery catheter (PAC) is used routinely in cardiac surgery because PAC is educational “device” to understand hemodynamic status for residents and used for postoperative management in the intensive care unit. However, most of the PACs are removed within 1 to 2 days of surgery, and no adverse events related to the use of PAC are identified. In addition, since many medical staffs, including nurses and clinical engineering technologists, can share about patient’s hemodynamic condition easily by using PAC, the insertion of PAC is usually performed in patients without clear indications, such as low cardiac output syndrome, pulmonary hypertension, and right ventricular dysfunction, in most Japanese university hospitals and cardiac centers. Of course, most of Japanese anesthesiologists and cardiac surgeons know a recent opinion on the use of PAC in cardiac surgery well. In a recent Annual Meeting of Japanese Society of Cardiovascular Anesthesiologists (9–11 October 2015, Fukuoka, Japan), the routine use of PAC in cardiac surgery was debated. Even after the debate, most of Japanese anesthesiologists agreed with the use of PAC in cardiac surgery. However, since routine use of PAC in cardiac surgery for patients without clear indications is not indicated worldwide, we have omitted the sentence including the reason of the insertion of PAC in the methods section.

Comment:
Thermodilution technique for CO estimation becomes unreliable with in presence of tricuspid regurgitation (as stated in the comment). The reviewer has great concerns about the accuracy of ThD during heart malposition for coronary revascularization (marginal, right …).

Response:
As the referee pointed out, cardiac index estimation by PAC may be inaccurate in the presence of tricuspid regurgitation. So, we had to assess the presence of tricuspid regurgitation during heart malposition for coronary revascularization. However, since transesophageal echocardiography is not useful in such situations, the presence of tricuspid regurgitation during anastomosis is not assessed routinely in our practice (In all of the study
patients, tricuspid regurgitation more than mild was not identified preoperatively). On the contrary, mixed venous oxygen saturation (SvO₂), which is known to be independent of tricuspid regurgitation, is a useful hemodynamic parameter for estimating cardiac output, but missing SvO₂ values were too much to confirm our results in the present study. However, consistent with a previously reported study, in which SvO₂ was considered, decreases in cardiac index was identified to be associated with decreases in rSO₂ during off-pump CABG in adult patients. These were added to the discussion section (Page 17, Line 6–11).

In addition, pulse pressure-derived cardiac output measurement may be also useful in such situations. However, this system is usually used for goal-directed fluid therapy rather than cardiac output monitoring. In patients with high systemic vascular resistance, such as patients receiving vasoactive drug administration, this system may be inaccurate measure for fluid management (Toyama S, et al. Br J Anaesth 2012; 108: 877-8), and thus it is unknown whether this system is useful in cardiac surgery or not.

Comment:
Table 1 and table 2 are contradictory about LVEF:
(Table 1) Patients with CAS: LVEF Range 41-61 %
(Table 2) Patients #6 has 20% LVEF and # has 22
Response:
In a previous manuscript, the result in Table 1 was presented as median (interquartile). In addition, other results on preoperative cardiac evaluation were also presented as median (interquartile). Thus, we have revised it (revised Table 2, in which two patients were excluded from patients with CAS).

Comment:
Two patients (#1 and 6), both with 80% stenosis, received complete stenting. They should be excluded from the CAS group.
Response:
In patients with CAS, preoperative rSO₂ correlated with both preoperative LVEF ($r = 0.534, p = 0.0107$) and MAP ($r = 0.603, p = 0.003$). Even if 2 patients, who received successful carotid artery stenting preoperatively, were excluded, preoperative rSO₂ correlated with both preoperative LVEF ($r = 0.509, p = 0.0306$) and MAP ($r = 0.572, p = 0.0129$). The correlation coefficients between preoperative rSO₂ and preoperative LVEF or MAP in patients with CAS were not affected by including the 2 patients who received successful carotid artery stenting preoperatively ($p = 0.9442$ and $p = 0.6892$, respectively). Meanwhile, in patients without CAS, preoperative rSO₂ correlated with neither preoperative LVEF ($r = 0.144, p = 0.437$) nor
MAP ($r = 0.288, p = 0.115$). Hemodynamic data and $rSO_2$ values did not differ between patients with and without these 2 patients (data are not shown). In addition, since preoperative carotid artery stenting was performed in patients with poor cerebral functional reserve on single photon emission computed tomography with acetazolamide stress, cerebral hemodynamics in patients with poor cerebral functional reserve might be impaired even if cerebral blood flow was increased by receiving carotid artery stenting preoperatively. Thus, perioperative data in 2 patients with CAS, who received complete carotid artery stenting preoperatively, were included in a previous manuscript. However, as the referee pointed out, 2 patients with CAS who received complete carotid artery stenting preoperatively were excluded from the analyses in the present manuscript. This was added to the result section (Page 10, Line 17–18). In addition, since the number of patients with unilateral CAS became only 2, we could not examine whether there were significant differences in changes in $rSO_2$ values between patients with bilateral CAS and those with unilateral CAS. Thus, we have reanalyzed the data (Page 10, Line 19–Page 12, Line 14, revised Table 2–6, and revised Figure 2–3).

**Comment:**
Conclusions: “In patients with CAS as well as those without CAS, increasing cardiac output in addition to maintaining MAP within normal ranges appears to be a better strategy for preventing a decrease in cerebral oxygenation during off-pump CABG”. The prevention of cerebral desaturation by increasing CO should be demonstrated but this is over the aim of the study. The sentences should be rephrased in a more blunted way.

**Response:**
As the referee pointed out, this conclusion is over the aim of the study. We have rewritten it (Page 18, Line 7–9).

**Comment:**
Abstract: “In both patients with and without CAS, decreases in $rSO_2$, decreased cardiac index, and increased CVP were observed during anastomosis.” Check of grammatical errors.

**Response:**
As the referee pointed out, we have rewritten it (Page 2, Line 18–19).

**Comment:**
“In our hospital, simultaneous carotid endarterectomy and CABG are not performed routinely in patients with CAS, irrespectively of symptomatic or asymptomatic.” This is more
a comment than a method.

**Response:**
As the referee pointed out, this is a comment more than a method. We have omitted the sentence including it. However, simultaneous carotid endarterectomy and CABG are rare in Japanese hospitals, including our hospital.

**Comment:**
List of abbreviations

**Response:**
As the referee pointed out, we have rewritten it (Page 19, Line 1).