Author’s response to reviews

Title: Protocol of supra-visceral aortic ischemic preconditioning for open surgical repair of thoracoabdominal aortic aneurysm.

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Author’s response to reviews:

Responses to reviewer 1

Abstract

-Primary objectives: endpoints are now defined as suggested by the reviewer as “AKI according to KDIGO and pneumonia/prolonged ventilation-time/tracheotomy”. However, tracheotomy does not appear as an acute pulmonary complication, but more often consecutively to a long period of prolonged artificial ventilation.
-Secondary objectives: endpoints are now defined as cardiac complications within 48 hours, renal and pulmonary complications within 21 days
-The chapter starts now with the statistic description
“inflammation”: we agree with the reviewer. Our hypothesis is that ischemic preconditioning could reduce the inflammatory response associated with supra-visceral aortic clamping and unclamping. However, our study focused only on clinical endpoints without any inflammatory biomarker. We propose to amend the last sentence of the abstract.

Introduction
4. It seems to us that pulmonary and renal complications frequencies are well referenced in the text (line 9, for example). However, we have added a recent reference for global complication (Coselli JS Journal of Thoracic and Cardiovascular Surgery 2016, 151: 1323).
24. I am sorry but we didn’t find any reference on the potential role of Damage-Associated Molecular Patterns for lung injury / trauma patients or Damage-Associated Molecular Patterns for lung injury / aortic surgery

Methods
-Secondary objectives: 21 days
The primary objective of the study is to evaluate the efficacy of preconditioning to reduce pulmonary and renal damage occurring during the 8-day postoperative period.
In order to focused the study around the time of the operative procedure, we decided a 21-day post-operative period as an end-point for the secondary objectives, i.e. the occurrence of pulmonary and renal morbidity. Indeed, the reported postoperative intensive care stay period is about 4 days (Rocha RV J Vasc Surg 2018, 68: 1938) and nearly 11 days for hospital stay period (Locham S J Vasc Surg 2018, 68: 948). In order to note prospectively, and not retrospectively, the events occurring during the postoperative period with respect to the usual stay period, we proposed this 21-days period of prospective observation. Anyway, the follow-up period of a patient will correspond to the length of hospital stay postoperatively or will end at the 61st post-operative day, in case of hospitalization beyond 60 days.
-Cardiac morbidity: 48 hours
We decided a time interval of 48 h for cardiac complication as a secondary end point related to troponin sera elevation. Peak of postoperative troponin during the first 3 days after non-cardiac surgery has been demonstrated to be associated with 30-day mortality (JAMA 2017, 317: 1642). Otherwise, the third universal definition of myocardial infarction consensus statement recommends monitoring perioperative troponin in high-risk patients undergoing non cardic surgery (Circulation 2012, 126: 2020). In case of kidney function decrease, we agree with the reviewer: troponin will not be reliable. It’s the reason why we’ll propose amendment to the protocol in order to identify ischemic electrocardiographic findings during the hospital stay.

“Which kind of TAAA surgery?” : TAAA types are now expressed in the text
“Hybrid repair”: this procedure is not included
“Infectious aneurysm”: because of its inflammatory potential this kind of aortic pathology is not eligible for the study
“Marfan or other CTD patients” are eligible

Trial intervention
Fortunately, for the instance, we never experienced embolization since we started the study. However, in the study protocol approved by the French national ethic committee we have anticipated embolization as a severe adverse event, needed to be reported to the study sponsor, i.e. the Rouen University Hospital.

We thank the reviewer for this remark: for preconditioning, we decided to perform the experience of sequential aortic clamping up to visceral arteries, at the level required for clamping the aorta during the surgical open aortic repair. The process of preconditioning will be appliable only if the aorta is safe at this level without the presence intraluminal thrombus or shaggy aorta.

Table 1 and 2 are now amended taking into account the reviewer’s remarks:
- Intervention times in minutes
- Aortic clamping in minutes
- Peroperative perfusion: item deleted
- How will you assess bleeding? : item deleted

Surgical strategy is now added to the manuscript

Uniformity of the protocol

Indeed, patients’ heterogeneity is an important point to consider when the aim is to compare two strategies. One way of doing so is to stratify patients and then either prevent patients in some strata from entering the study via appropriate exclusion criteria or to use randomization of a sufficiently large number of patients. As a consequence, the first approach would allow to estimate the difference between both arms for those patients in the selected strata, e.g. patients with programmed CPB only. Whereas with randomization of more than 100 patients with or w/o CPB, we would expect that the proportion of CPB patients is the same in both arms and hence this approach allows first to estimate the difference between both strategies for patients – with or w/o CPB – and also to carry out an analysis stratified by CPB use, i.e. to estimate w/o bias the difference between both strategies once for those with CPB and another time for those w/o CPB, provided that neither stratum is covering almost all randomized patients. In sum, we’d like to thank you for your comment and will add a statement that stratified analyses will be carried out, for CPB and the other time-fixed covariates you mentioned.

Responses to reviewer 2

“Some of the endpoint are a 21-days. Why not 30-days?”

The primary objective of the study is to evaluate the efficacy of preconditioning to reduce pulmonary and renal damage occurring during the 8-day postoperative period. In order to focused the study around the time of the operative procedure, we decided a 21-day post-operative period as an end-point for the secondary objectives, i.e. the occurrence of pulmonary and renal morbidity. Indeed, the postoperative intensive care stay period is about 4 days (Rocha RV J Vasc Surg 2018, 68: 1938) and hospital stay period nearly 11 days (Locham S J Vasc Surg 2018, 68: 948). In order to note prospectively, and not retrospectively, the events occurring during the postoperative period with respect to the usual stay period, we proposed this 21-days period of prospective observation. Anyway, the follow-up period of a patient will
correspond to the length of hospital stay postoperatively or will end at the 61st post-operative day, in case of hospitalization beyond 60 days.

“The randomization even after the femoral assistance, the cannula is in so the ischemic preconditioning is not performed in the left leg, why?”

As mentioned in our paper, series reporting preconditioning applied to open or endovascular approach for AAA repair failed to show any beneficial effect on mortality, myocardial ischemia and renal impairment (27). These series were carried out during surgery of infrarenal AAA where the visceral arteries were not concerned by aortic cross clamping and mesenteric ischemia reperfusion (24,25). In a preliminary experience, we observed similar results in a prospective, randomized study conducted in our single surgical center (“Claris Study”, work actually in press) during open approach for infra renal AAA. In this later study preconditioning was applied on the left leg by iliac sequential cross clamping.

In order to focused on the rationale of this study, testing the direct efficacy of preconditioning for mesenteric and renal protection, we decided to perform the experience of sequential aortic clamping up to visceral arteries, at the level required for the surgical open aortic repair.

“Since you are clamp three times do you have safety / feasibility endpoint?”

Fortunately, for the instance, we never experienced aortic rupture during a three times aortic cross clamping. However, in the study protocol approved by the French national ethic committee we have anticipated aortic rupture as a severe adverse event, needed to be reported to the study sponsor, i.e. the Rouen University Hospital.

More frequently, we expect transient hemodynamic changes (hypotension and tachycardia) associated with clamping and un-clamping of the supra-visceral thoracic aorta during preconditioning.

Surgical strategy is now added to the manuscript

Uniformity of the protocol

Indeed, patients’ heterogeneity is an important point to consider when the aim is to compare two strategies. One way of doing so is to stratify patients and then either prevent patients in some strata from entering the study via appropriate exclusion criteria or to use randomization of a sufficiently large number of patients. As a consequence, the first approach would allow to estimate the difference between both arms for those patients in the selected strata, e.g. patients with programmed CPB only. Whereas with randomization of more than 100 patients with or w/o CPB, we would expect that the proportion of CPB patients is the same in both arms and hence this approach allows first to estimate the difference between both strategies for patients – with or w/o CPB – and also to carry out an analysis stratified by CPB use, i.e. to estimate w/o bias the difference between both strategies once for those with CPB and another time for those w/o CPB, provided that neither stratum is covering almost all randomized patients. In sum, we’d like to thank you for your comment and will add a statement that stratified analyses will be carried out, for CPB and the other time-fixed covariates you mentioned.