Author’s response to reviews

Title: Predictive risk factors for postoperative pneumonia after heart transplantation

Authors:

Charles Vidal (charlesvidal@orange.fr)
Romain Pasqualotto (romain.pasquolotto@aphp.fr)
Arthur James (arthur.a.james@orange.fr)
Pauline Dureau (pauline.dureau@aphp.fr)
Julie Rasata (julie.rasata@aphp.fr)
Guillaume Coutance (guillaume.coutance@aphp.fr)
Shaida Varnous (shaida.varnous@aphp.fr)
Pascal Leprince (pascal.leprince@aphp.fr)
Julien Amour (profjulien.amour@gmail.fr)
Adrien Bouglé (adrien.bougle@aphp.fr)

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Author’s response to reviews:

Dear Reviewers,

Thank you for your letter concerning our manuscript entitled Predictive risk factor of postoperative pneumonia after heart transplantation. The comments were stimulating and challenging. We have therefore deeply modified the manuscript, taking all of the suggestions into account.

Response to Carmen Barbas (Reviewer 1).

Thank you for your comments and suggestions. About the general comment, there is no control group because patient admitted with decompensated heart disease are heterogenous group requiring different treatment depending on the severity. Some only needed medical treatment but the most severe patients required more aggressive therapeutic strategy such as VAD implantation or transplantation. In the discussion, we approach the fact that recipients have a higher incidence of POP than patients with conventional cardiac surgery (33.7 versus 5.7%)

About the specific comments:
1. Indeed, some recipients presented recurrent (2 or more) POP. Eleven recipients had 2 POP, 5 recipients had 3 and 3 recipient had 4. The were no significative difference between recipients with
only 1 POP (n=40) and recipients with recurrent POP (n=19) about the transplantation condition (pre operative ECMO, transplantation in emergency, allosensitization, or pre-operative mechanical ventilation). Recurrent POP was not associated with significant increased 30 days or one year mortality (5% vs 18% and 31% vs 25%, ns) but the median of mechanical ventilation and hospitalization duration were longer (19 vs 7 days, p<0.01 and 37 vs 37 days, p=0.05).

2. Given these risk factors, we extubate all patients under ECMO (whether there is a transplant project or not) to prevent the risk of pneumonia. Patients can thus re-nourish themselves and participate in physiotherapy in order to arrive at the transplantation in the best conditions. To limit the haemorrhagic risk, we anticipate perioperative haemostasis disorders and our surgeons are vigilant about surgical haemostasis.

Response to Anna Kedziora (Reviewer 2)
Thank you for your comments and suggestions. The new manuscript has been revised by the English language editing service recommended by the journal.
We studied the impact of plasmapheresis and IgIV, not the allosensitization, on the incidence of POP. There is no difference about the use of plasmapheresis and IgIV in the two group. So these parameter cannot appear as risk factor in the univariate and multivariate Cox regression models.
Sequent or recurrent pneumonia was defined by the recurrence of clinical and paraclinical criterias of POP after the improvement of the first POP symptoms with appropriate antibiotic therapy
The perioperative antimicrobial prophylaxis used in the center has been added in the new manuscript. Intraoperative antibioprophylaxis consisted of the administration of 2 gr of Cefazolin followed by 1 gr every 4 hours. Antibiotic prophylaxis was not continued postoperatively. Prophylaxis with valganciclovir and cotrimoxazole was introduced postoperatively from the 6th postoperative day.
The main causes of death at 30 days and one year were septic complications (respectively 64% and 59%) followed by neurological complications (21% and 18%). All deaths due to infectious complications were not attributable to pneumonia alone. In our cohort, 13 recipients died of septic complications, 6 due to pneumonias, 2 due to peritonitis, 2 fungal mediastinitis, 2 isolated bacteriemias, and 1 femoral cannulation site infection.
We modified the discussion for more clarity. We hypothesized that low cardiac output or intraoperative instability may lead to POPs due to bacterial translocation explaining the higher rate of post-operative ECMO for recipients with POP.

Response to Achim Koch, MD, PhD (Reviewer 3)
Thank you for your comments and suggestions. Indeed, we had a high rate of recipient with post operative ECMO. In our cohort, a large proportion of recipients presented risk factors of primary graft dysfunction such as allosensitization (54%), preoperative VA-ECMO support (32%) or mechanical ventilation at the time of transplantation (9%). The important part of sensitized and assisted by ECMO patients can be explain by the modality of graft attribution in France during 2004 – 2017. To improve the access to transplantation for critically ill patients, the French national transplant organization “Agence de biomédecine” established new rules for the prioritization of graft attribution in 2004, as it had been done in the USA (with United Network of Organ Sharing status) in 1989 and in Germany in 2000. By Super Urgence program, patients on high dose of inotropic drugs or with extracorporeal life support (equivalent to UNOS 1A status and Intermacs 1-2 classification) can access to super urgence 1 (SU1) to have priority for heart transplantation during a short time (48 hours, renewable once). Eligible patients must present hemodynamic stability under inotropic or mechanical support but with the impossibility of weaning from this support. This new modality of graft attribution allows critically ill patients to benefit quicker of transplantation. However, the efficiency of this new strategy of
prioritization is uncertain as heart transplantation performed under this urgent procedure has increased (28% in 2007 and 42% in 2014). Since 2018, new modalities of access to transplantation are being tested with a point system depending on patient characteristics and degree of urgency of transplantation.

I hope that the modifications of the manuscripts and the explanations will be appropriate for publication.

Best Wishes

Charles Vidal, MD