Author’s response to reviews

Title: Interprofessional two-man team approach for interhospital transport of ARDS-patients under extracorporeal membrane oxygenation: A 10 years retrospective observational cohort study

Authors:

Stefan Ehrentraut (stefan.ehrentraut@uni-bonn.de)
Barbara Schroll (barbara.c.schroll@gmail.com)
Stefan Lenkeit (stefan.lenkeit@ukbonn.de)
Heidi Ehrentraut (heidi.ehrentraut@ukbonn.de)
Christian Bode (christian.bode@ukbonn.de)
Stefan Kreyer (stefan.kreyer@ukbonn.de)
Florian Kögl (florian.koegl@ukbonn.de)
Felix Lehmann (felix.lehmann@ukbonn.de)
Thomas Muders (thomas.muders@ukbonn.de)
Martin Scholz (martin.scholz@ukbonn.de)
Claudia Strater (claudia.strater@ukbonn.de)
Folkert Steinhagen (folkert.stehagen@ukbonn.de)
Nils Theuerkauf (nils.theuerkauf@ukbonn.de)
Carsten Weißbrich (carsten.weissbrich@ukbonn.de)
Christian Putensen (christian.putensen@ukbonn.de)
Jens-Christian Schewe (jens-christian.schewe@ukbonn.de)

Version: 1 Date: 10 Dec 2018

Author’s response to reviews:
Dear Dr. Hinske,

First of all, we thank the editor and the reviewers for their valuable comments and contributions to our manuscript. Furthermore, we appreciate that all reviewers agree on the medical importance of our findings.

We addressed the reviewers’ comments to our best ability. All changes to the manuscript are highlighted, using the “track changes” option, as required. Comments not mandating changes to the manuscript are answered directly in a point-to-point fashion.

Again, we thank the reviewers and the editor and hope, that our revised manuscript is now suitable for publication in BMC Anesthesia.

Best regards,

Stefan Ehrentraut, Jens-Christian Schewe

Reviewer comments:

Reviewer#1

Please provide a STROBE checklist (may be included as supplementary material) and verify that all required items are reported within the manuscript

In our understanding, the STROBE checklist is a tool to better report observational studies. The STROBE commission states “We aimed to establish a checklist of items that should be included in articles reporting such research - the STROBE Statement“. We carefully checked our study against the checklist to make sure that recommended items are included. The relevant passages are now included in the table. We refrained from adding it as supplementary material. However,
we provided the checklist and leave it to the editor’s discretion to include it as supplementary material or not.

- I suggest to report also in the abstract the number of complications occurred

The number of observed complications has been included in the abstract

- The Authors report the use of standardised checklists and query protocol. These may be of interest for the reader, should someone be interested in applying the Authors protocol. Accordingly they could be reported in a Supplementary Appendix.

We translated said documents and included them as supplementary material.

- Did the Authors collect data on time from ECMO team alert to start ECMO? These may also be of interest

The authors agree with the reviewer, that this might be interesting. This parameter was unfortunately not routinely assessed and can thus not be evaluated for the reported cohort. As a result of this query, we added this to our protocol.

- I understand that no cardiovascular perfusion technician is involved neither in cannulation nor in transport, and that Authors use a full percutaneous cannulation technique, am I correct?

This is correct. As stated in lines 144-148, all cannulations were percutaneously performed by the anesthesiologist using ultrasound guidance. This was regardless of vv- or va-ECMO.

- The references to type and timing of ICU scores should be moved from Results to Methods section.

We moved said items to the Methods section

- The Authors calculated RESP and SAVE score assuming the best possible option in case of missing data. It might be useful to calculate the same scores also assuming the worst possible option. I expect the observed survival rate be higher than predicted. Of note, the sentence "Observed survival is [...] lower than predicted mortality" is unclear: it should probably be "mortality is higher than predicted..." OR "survival is lower than predicted..."
Thank you very much for your advice. In our opinion, using worst possible option does not provide any additional value in regard to outcome. Comparing our observed survival versus “worst predicted” survival would, as you stated yourself, probably show increased survival in our cohort. However, using worst possible RESP-Score would falsely make patients sicker than they actually were. For example, assuming worst possible option means, that every patient is immunocompromised, received bicarbonate infusion before ECMO, received inhalative NO and was ventilated with peak pressures >42cm H2O. This combination would most likely be evaluated as fatal from the start and thus not lead to positive evaluation for ECMO by itself. Providing both values, i.e. worst/best possible RESP/SAVE, would most likely only increase confusion, and is of little informative value in regard to patients survival estimation. Therefore, we chose not to provide this information.

We thank the reviewer for pointing out the misleading statement in regards to survival and mortality. The sentence has been changed to “Observed survival is minimally, […], lower than predicted survival[…].”

- If data are available, it would be interesting to provide in the Discussion a comparison with complications observed in studies reporting transport of patients with ECMO team of more than two people (e.g. studies by Bryner, Lucchini and Strauch

- Did the Authors collect also data on incidence of bleeding, ischemic, neurological complications related to ECMO and need for surgical revision of vascular access?

These data were not collected and were not focus of this study. We aimed solely on transport of this specific cohort of critically ill patients with the highlight on the two-man approach. If the reviewer would like to read more on bleeding under ECMO, we recommend “Hemorrhage under veno-venous extracorporeal membrane oxygenation in acute respiratory distress syndrome patients: a retrospective data analysis.”


- In my opinion, Table 3 might be improved dividing the complications in those occurred before, during, and after transport
We altered Table 3 indicating occurrence of complication (prior/during) transport and adjusted the discussion accordingly. The number of ECMO related complications after transport was not recorded/assessed for this study, since we solely focused on two-men ECMO initiation and interfacility transport, not subsequent complications.

- Please provide details on informed consent procedure/Ethics committee approval within the Methods (I assume both were waived due to the retrospective nature of the study)

The ethics committee waiver number was already included in the manuscript available for the reviewers. All necessary statements are included in the “Declarations” section at the end of the manuscript, as required by the journals “Instructions for authors”. Hence, this was not stated in the Methods section. If the Editor agrees with the reviewer, we will gladly incorporate this section into the Methods section.

Minor comments:

- Title: I think that the word "study" is missing a the end of the title
- Title: two-man or two-men?

According to the Merriam-Webster Dictionary, “two-man” is correct and refers to “to two individuals:” such as ”a : consisting of two individuals, e.g. a two-man committee”. We changed this accordingly throughout the manuscript.

- Abstract/Background: I think that the term anaesthesia nurse is better than nurse anaesthetist

We now use the term “critical care nurse”.

- Please provide link/reference for ELSO General Guidelines

The link https://www.elso.org/Portals/0/Files/ELSO%20GUIDELINES%20FOR%20ECMO%20TRANSPORT_May2015.pdf is now provided within the references.

- Page 3, lines 81-85: this sentence is not very clear. Please edit

Sentence was edited accordingly.
Reviewer 2: The work describes the safety of a two team approach for transportation of ECMO patients to a referral center and it is undoubtedly interesting, as the current ELSO recommendations are not based on evidence.

Yet a major revision is deemed necessary to make the manuscript ready for publication.

1. The authors themselves seem uncertain on the type of article they are submitting: first they indicate the will to "demonstrate" (line 92) the safety and efficacy of the intervention but then only describe their population without conducting any comparative statistical analysis with the referred numbers. To add to the confusion, they indicate in the methods the adoption of "Student paired t-test" (line 108) but then fail to actually use it or at least report the results of such comparison.

In this regard, the authors have two options: they can either adopt the concept of narrative article or retrospective study. With the former they can hardly say they have demonstrated, but it would require less rearrangement of the manuscript. If instead they opt for the latter, they should specify in the methods the origin of the percentages they intend to compare with their numbers, then perform an appropriate comparative testing (t-student, anova, mann-whitney, etc.), and finally report the results of their analysis. This part cannot be reserved to the discussion only.

We thank the reviewer and agree with his observation in regard to statistical analysis. This makes the whole study/statistic descriptive in nature. Thus we adopt the concept of narrative article. We changed the method section accordingly, pointing out data that were analysed using Student’s t-Test and indicated which data are presented as mean+-IQR due to their non-normal distribution. The title was also changed to incorporate the study design “observational study”.

2. Methods and Results sections need a bit of rearrangement, or a better justification on why they are structured this way. For example, lines 285-287 should fall in the methods rather than in the results.

Additionally, I would like to signal how paragraph on lines 135-141 feels very little informative: useless for the trained intensivist, redundant, and not descriptive of the population.

Redundant information was deleted.
3. The description of the analyzed population (lines 224-234) is hard to follow. The denominator of the fraction used to calculate the percentages may help in understanding how the subgroups are established, but a certain rephrasing is also recommended. 169 total patients are considered, of whom 126 were cannulated on site and 30 only transported (correct?). Out of these 30, 21 underwent subsequent cannulation while 9 did not. The four patients that died before arrival to which group belong? Out of all cannulated patients (to my understanding $126 + 30 = 156$), 137 received VV while 10 received VA: what about the other 9? There is some confusion to be addressed.

We agree with the reviewer and apologise for the confusion. This resulted from some patients being transported with the “intent to treat with ECMO” and some patients being transported without ECMO and no intent to treat with ECMO. Therefore it seemed, that some patients were counted twice, which was not the case. 10 patients were transported without intention for ECMO but in regard to upgrade of therapy. We clarify this by the following sentence, now included in the manuscript **“*In those patients, decision against ECMO support therapy was either due to preexisting contraindications for ECMO support previously not reported by the referring hospital. Other reasons included non-consent for extended life support therapy by patient’s living will or next of kin. Hence, transport to a tertiary university hospital environment was performed in terms of “step-up” of care.***

To summarise: 170 deployments of the ECMO TEAM, 3 Patients died prior to implantation, 166 patients underwent evaluation, 126 were cannulated on site, 1 died during implantation, 30 were transported with“ intent to treat for ECMO“; of those, 21 received ECMO subsequently, 9 did not. 10 patients were transported without „intention to treat with ECMO“.

We rewrote the whole paragraph and also inserted a flow chart as Figure 1 to make this clearer. Figure numbers and legends were changed accordingly. Our sincere apologies for the previously confounding presentation.

4. Language revision is also suggested. In most cases the text can still be understood but in a few this is an impediment to reading, e.g. lines 192-193.

The whole manuscript has been proof read by a native speaker, Dr. Mihiri Amarasekara. Changes are indicated in the manuscript by the “track changes” option.

Reviewer 3: The paper is at best descriptive. The authors detail their single institution experience with ARDS-patient transport under extracorporeal membrane oxygenation.
The conclusion of the paper is that an interprofessional two-man team for interhospital ARDS-patient transport under extracorporeal membrane oxygenation is safely and efficient tool with good outcome.

This is an interesting paper, with a good message for the ECMO community. The experience is substantial, however there are some major deficiencies and the key message is not clearly set out. The data presented in the Abstract and the section Results are at some points confusing. Using an English native speaker, rewriting the manuscript (shorter sentences, making the message of the study more crisp) and correcting grammatical errors (such as verbs or articles missing) should help to point out the message more clearly.

Moreover, using their own statistical significances with more care, should help the authors to present their findings better. My comments follow:

1. The study was not sufficiently described. Please concretize the statistical methods being used. E.g. the authors specify using the student's t-test (in fact, no other test is mentioned). However, parametric statistics require the data to follow a normal distribution. This contradicts the results being described in median values.

We changed the method section accordingly, pointing out data that were analysed using Student’s t-Test and indicated which data are presented as median with IQR due to their non-normal distribution. The title was also changed to incorporate the study design “observational study”.

Please report percentages of discrete data and continuous data as full numbers without decimals.

We changed discrete data to full integers. Continuous data was rounded to the next full integer, or left with one decimal number where appropriate.

2. Some sentences are very long and in a number of places it is hard to follow what the authors intended as the key message (e.g. line 193-195: there seems to be a verb missing..."after the final decision to perform an ECMO support therapy." -- better: "..therapy was made".

Sentence has been changed accordingly. Now reads: “The ECMO circuit is primed on site by the ECMO team in the referring hospital, after the final on-site decision for ECMO support is made.”
3. Typographic errors should be corrected (E.g. line 87;121;181(article missing)).

Typos have hopefully been eliminated. As mentioned above, additional language editing has been done by a native speaker.

4. Please use units homogeneous throughout the manuscript (E.g. 173 cm 10 cm vs. 93.9 kg ± 34.1)

This has been changed throughout the manuscript.

5. There are several confusing numerical values throughout the manuscript:

If 169 patients were evaluated for ECMO therapy, 4 died, how can the primary indication for ECMO treatment be 159 out of 166 patients (169-4)?

Continuing: Out of 166 patients?! 126 were cannulated at the the referring site, 30 were transported to the ECMO centre and 21 subsequently cannulated.

9 patients did not receive ECMO. 166-156=10. What happened to the 10 in the calculation missing patients?

We agree with the reviewer and apologize for the confusion. Please refer to Reviewer #2 Point 3 and our commentary there.


Survival refers to in-hospital survival. This is now mentioned in the manuscript. Thank you for pointing this out.

7. Line 373: "-- comparable to total mission time in our and other studies." Citation missing.

Sentence has been edited and citation is now included.

8. Conclusion, line 417-419. The authors postulate that ECMO transport by a two-men team comprising only anaesthesiological staff does not increase mortality." however, there is no evidence in the manuscript underlying this thesis as there was no direct comparison made.
It was not our primary intention to compare teams with only anaesthesiological members against other team compositions, but rather demonstrate feasibility and efficiency of smaller ECMO team composition. No direct comparison was done due to the observational nature of this study. Our observed survival rates are similar to predicted survival rates indicated by RESP/SAVE scores. We now include a comparison of predicted mortality vs. observed mortality by calculating Standard Mortality Ratios. Thereby, we can now show, that there is no statistical significance between our cohort mortality and mortality predicted by validated scores. We believe, that this sufficiently indicates non-inferiority of our two-man approach.

Furthermore, as indicated in our response to Reviewer 1, comment 7, predicted survival using best possible option probably overestimated calculated survival. In this context, the conclusion might have been to provocative. We changed the sentence to be more in line with our observations.

9. Line 227: "... 30 (17%) patients were transported by the ECMO team.."-Of all patients being transported, were only 30 patients transported by the ECMO team? If so, the title and key message of the manuscript does not appear to be appropriate, focusing on the described ECMO team when only a small proportion of patients were actually transported by this team.

Of the total population (n=167), 30 patients did not receive immediate ECMO therapy at the referring hospital. They were transported to our centre by the ECMO team, regardless. 21 one of these patients were subsequently cannulated at our hospital. Thus the majority (n=126) of all cases were cannulated at the referring site and then transported by the ECMO team under ECMO support. We agree with the reviewer, that this was not made sufficiently clear in the previous version. We rephrased the paragraph and hope that this is now made clear in the manuscript. We now also provide a flow chart.