

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of cardiopulmonary resuscitation on a cannot intubate, cannot oxygenate condition – A randomised crossover simulation research study of the interaction between two algorithms
AUTHORS	Ott, Thomas; Stracke, Jascha; Sellin, Susanna; Kriege, Marc; Toenges, Gerrit; Lott, Carsten; Kuhn, Sebastian; Engelhard, Kristin

VERSION 1 - REVIEW

REVIEWER	Hyuk Joong CHOI Emergency Department, Hanyang Univ. College of Medicine, Republic of Korea.
REVIEW RETURNED	27-Mar-2019

GENERAL COMMENTS	<p>The authors show that experienced physicians who manage emergent airway do not show the best action in CPR situations. I agree with the authors' opinion that the design and conclusions of the study do not show any problems, and that training in consideration of behavioral aspects is required to effectively implement the DAM.</p> <p>I have some questions and comments in this paper.</p> <ol style="list-style-type: none"> 1. If the CICO-arrest situation is due to complete airway obstruction, cricothyrotomy should be performed prior to any procedure. However, in situations where lack of ventilation and oxygenation is possible, the team reader thinks that even if they decide to do cricothyrotomy in their minds, they can first give an indication of the early stages of ALS. 2. During compression, can there be a delay in the time it takes for the movement to interfere with understanding the airway status? 3. In this study, what criteria did you judge the beginning and end of Cricothyrotomy?
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REVIEWER	Conrad Arnfinn Bjørshol RAKOS, Stavanger University Hospital, Stavanger, Norway.
REVIEW RETURNED	17-Apr-2019

GENERAL COMMENTS	Thank you for an interesting review of the impact of cardiac arrest and CPR on the performance of a cricotomy in a cannot intubate cannot ventilate situation. There are issues that should be addressed:
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	<p>-Abstract/Conclusion: You speculate that a determined decision making would make decision quicker, and that this could be improved by frequent training. None of this has been shown in your study, so please rephrase the conclusion according to the findings.</p> <p>-Background: You write that cricothyrotomy is "the crucial treatment for survival of asphyxia". It is only crucial for CICO events, not for all causes of asphyxia.</p> <p>-Conclusion: Again, the conclusion should state what you have found, while discussions should be listed in the discussion section.</p> <p>-Reference 13: This reference is incomplete.</p> <p>-Although the majority is well written, the manuscript should undergo language editing.</p>
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REVIEWER	Ottavia E. Ferraro University of Pavia, Italy
REVIEW RETURNED	29-Jul-2019

GENERAL COMMENTS	<p>The study of Ott et al. reported results from a simulation-based randomised cross over study performed by experienced staff anaesthesiologists of their tertiary university hospital centre concerning 2 subsets on CICO situation. Their primary endpoint was the difference in time ventilation between the two subsets. The main result was a higher time during the cardiopulmonary resuscitation.</p> <p>Abstract</p> <p>1) In the results, it could be better also to mention no carry over effect because it could be helpful for readers.</p> <p>2) The paragraph "conclusion" needs more details (clinical) on possible impact on this difference/delay on time ventilation.</p> <p>Methods</p> <p>3) Could the authors explain better how the randomisation was performed?</p> <p>4) In the Supplementary file 1 is it possible to add the sample size for each blocks?</p> <p>5) Could the participants have an idea, maybe talking with the colleagues, during the days of the simulations, on which sequences they could be? How did the authors manage this issue?</p> <p>Statistics</p> <p>6) I suggest to modify this paragraph in order to have a clearer sequence: Starting with sample size, index to describe data, how to control carry-over effect, main analysis and, at last, the software that were used.</p> <p>7) More details concerning the results on the evaluation of the time-difference among the two sequence groups using a Mann-Whitney U test, as reported in the second paragraph. Could be the pvalue reported near the estimation of Hodges-Lehmann in table 2 or table 2 in Suppl 4, the result of this test?</p> <p>8) In line 41-42 of page 7 was declared that the estimation using Hodges-Lehmann estimator was reported for the median time difference between the 2 subset. Is there any account for the different sequences or only the median for CPR and for NO-CPR?</p> <p>9) In the sample size paragraph is it possible to have a more detailed information on the reason on the parameters chosen</p>
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	<p>(effect-size and standard deviation)? Are there any pilot studies or explorative analysis or clinical explanation for this choice?</p> <p>10) All the analysis and the estimation of sample size were thinking for one or two tail as alpha or pvalue?</p> <p>11) Could the authors give more information on the choice of McNemar-test? Where did they report results?</p> <p>12) For a better comprehension for readers, it will be more useful report the table 2 as reported in the supplementary. This table gives more information on the simulation and the outcomes used.</p> <p>13) In supplementary 4 in Table 2 Is it possible to report, in the last column also for the first two secondary outcome, the overall median in the 2 subsets?</p> <p>14) Please check the value for the IQR in line 19 of pag 31 on 95% CI</p> <p>Results</p> <p>15) Concerning the "demography" could there be an association between the demography information and the primary outcome? Around 40% of people assisted at least at one cricothyrotomies and around 30% of the sample performed at least one. Is it possible for these people (with an experience on it) had a different time to manage the situation?</p> <p>16) In the figure (B) reported at page 21 of the Manuscript, there were some outliers, especially in the CPR subset. Did the author explain if they could affect the results? Instead concerning the figure (a) is it possible that there was a difference in the two performance of the no-CPR? If yes, the authors could explain if this difference could be clinical relevant?</p> <p>Discussion</p> <p>17) A large part on the devices was reported. Maybe could be useful also to report these findings in the abstract, and, if it is possible, it will be nice also to add information on it also in the background paragraph.</p> <p>Minor</p> <p>I) In "Background" pag 4 line 27 in order to pinpoint which is the principle aim, should be better, instead of primary endpoint, report "The aim of the study was to evaluate the influence of CPR on the 'time to ventilation', during a CICO situation, through cricothyrotomy"</p> <p>II) It could be better to report at least sec or seconds for clearer reading.</p> <p>III) The terms "by lot", in line 40 at pag 6, sounds strange. Is it possible to modify this sentence?</p> <p>IV) In line 35 pag 6 of the manuscript it should be better change "allocated" with "enrolled"</p> <p>V) Is it possible to avoid an exceed on 100%, as referred in the note, and report at least one decimal in the percentages as done in the table with the results of the study?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Hyuk Joong CHOI

Institution and Country: Emergency Department, Hanyang Univ. College of Medicine, Republic of Korea.

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below The authors show that experienced physicians who manage emergent airway do not show the best action in CPR situations. I agree with the authors' opinion that the design and conclusions of the study do not show any problems, and that training in consideration of behavioral aspects is required to effectively implement the DAM.

I have some questions and comments in this paper.

1. If the CICO-arrest situation is due to complete airway obstruction, cricothyrotomy should be performed prior to any procedure. However, in situations where lack of ventilation and oxygenation is possible, the team reader thinks that even if they decide to do cricothyrotomy in their minds, they can first give an indication of the early stages of ALS.

We completely agree with the reviewer, that cricothyrotomy should be performed as soon as possible. To emphasis this aspect of prioritisation on cricothyrotomy in a CICO situation, we rephrased the section "conclusion" entirely.

Concerning the decision of the team leader to perform a cricothyrotomy, we protocolled the time point at that the team leader finally articulated the decision to the team. We rephrased the definition in the section "data collection" to emphasis on this important aspect.

2. During compression, can there be a delay in the time it takes for the movement to interfere with understanding the airway status?

We added that aspect in the section "discussion", second paragraph.

3. In this study, what criteria did you judge the beginning and end of Cricothyrotomy?

We added the definition of time of performance by the definition of the calculation: time to ventilation minus time to start in the section "data collection"

Reviewer 2

Reviewer Name: Conrad Arnfinn Bjørshol

Institution and Country: RAKOS, Stavanger University Hospital, Stavanger, Norway.

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below Thank you for an interesting review of the impact of cardiac arrest and CPR on the performance of a cricotomy in a cannot intubate cannot ventilate situation. There are issues that should be addressed:

-Abstract/Conclusion: You speculate that a determined decision making would make decision quicker, and that this could be improved by frequent training. None of this has been shown in your study, so please rephrase the conclusion according to the findings.

We agree with the reviewer for this comment and rephrased the conclusion entirely.

-Background: You write that cricotomy is "the crucial treatment for survival of asphyxia". It is only crucial for CICO events, not for all causes of asphyxia.

We totally agree with the reviewer and rephrased the particular expression.

-Conclusion: Again, the conclusion should state what you have found, while discussions should be listed in the discussion section.

We rephrased the conclusion by deleting speculations and formulated conclusions that are strictly deducible from our results.

-Reference 13: This reference is incomplete.

We completed this reference.

-Although the majority is well written, the manuscript should undergo language editing.

We underwent a language editing as recommended by American Journal Experts.

Reviewer 3

Reviewer Name: Ottavia E. Ferraro

Institution and Country: University of Pavia, Italy Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below The study of Ott et al. reported results from a simulation-based randomised cross over study performed by experienced staff anaesthesiologists of their tertiary university hospital centre concerning 2 subsets on CICO situation. Their primary endpoint was the difference in time ventilation between the two subsets. The main result was a higher time during the cardiopulmonary resuscitation.

Abstract

1) In the results, it could be better also to mention no carry over effect because it could be helpful for readers.

We added a sentence to cite that there was no carry over effect in the results.

2) The paragraph "conclusion" needs more details (clinical) on possible impact on this difference/delay on time ventilation.

We rephrased the entire paragraph according to the reviewers advise.

Methods

3) Could the authors explain better how the randomisation was performed?

We rephrased the description of the randomisation in the manuscript and gave a more detailed information about the particular process.

4) In the Supplementary file 1 is it possible to add the sample size for each blocks?

Yes, we added the sample size for each block in the supplementary file 1.

5) Could the participants have an idea, maybe talking with the colleagues, during the days of the simulations, on which sequences they could be? How did the authors manage this issue?

Statistics

We agree with the reviewer. This might be a general problem in simulation-based research. We have a codex that commit participants to secrecy concerning talking about any scenario with colleagues. We described that in the manuscript in the particular section.

6) I suggest to modify this paragraph in order to have a clearer sequence:

Starting with sample size, index to describe data, how to control carry-over effect, main analysis and, at last, the software that were used.

We changed the structure of that section according to the reviewer's suggestion.

7) More details concerning the results on the evaluation of the time-difference among the two sequence groups using a Mann-Whitney U test, as reported in the second paragraph. Could be the pvalue reported near the estimation of Hodges-Lehmann in table 2 or table 2 in Suppl 4, the result of this test?

The reviewer is right: The p-value below the Hodges-Lehmann estimate in table 2 and supplement table 4 is the result of the Mann-Whitney U test, that evaluates the intervention-effect (i.e. CPR) on time to the respective outcome. To make that clearer in the manuscript, we added some additional explaining words in these tables.

8) In line 41-42 of page 7 was declared that the estimation using Hodges-Lehmann estimator was reported for the median time difference between the 2 subset. Is there any account for the different sequences or only the median for CPR and for NO-CPR?

In a classical 2 x 2 crossover trial (2 sequences, 2 periods = exposures), the Hodges Lehmann estimate is a robust and consistent estimate for the time-difference between exposure A (i.e. CPR) and exposure B (no CPR), see Putt and Chinchilli (2004) for a reference. Thus, the method of course accounts for the study design (especially for the sequences).

Reference:

Putt, M.E. and Chinchilli, V.M. (2004). Nonparametric Approaches to the Analysis of Crossover Studies. *Statistical Science*, Vol. 19, No. 4, 712–719.

9) In the sample size paragraph is it possible to have a more detailed information on the reason on the parameters chosen (effect-size and standard deviation)? Are there any pilot studies or explorative analysis or clinical explanation for this choice?

We agree with the reviewer that our sample size considerations are a bit sparse. However, there were no pilot data available for a proper sample size planning. For that reason we decided to power the study for the detection of an effect corresponding to one standard deviation. This was the rationale behind our planned sample size.

10) All the analysis and the estimation of sample size were thinking for one or two tail as alpha or pvalue?

We thank the reviewer for that important point: All the tests were two-sided at a 0.05-level. We added that information in the statistics section.

11) Could the authors give more information on the choice of McNemar-test? Where did they report results?

The McNemar test was used to compare the distribution of the binary variable cricothyrotomy-method (surgical vs puncture-based) between the two exposures (CPR vs no-CPR). The McNemar-test was chosen for that purpose, because we are basically comparing the distribution of two dependent binary variables ("method under CPR", "method under no-CPR"). We cited these aspects in the manuscript in the section statistics

12) For a better comprehension for readers, it will be more useful report the table 2 as reported in the supplementary. This table gives more information on the simulation and the outcomes used.

We agree with the reviewer that table 2 in the extended version (as displayed in the supplement) is better and more detailed. However, we think that the table 2 in the manuscript gives a short overview of the results that are essential to understand the duct of the study. Further, we are afraid, that editing the extended table 2 as displayed in the supplement in the format required for the manuscript (portrait format) will be difficult in a clearly manner. So, we suggest to leave the table 2 as cited in the original submission.

13) In supplementary 4 in Table 2 Is it possible to report, in the last column also for the first two secondary outcome, the overall median in the 2 subsets?

After re-evaluation of the table as required above, we decided to delete the "overall median" in the last column in supplementary file 4, because these values are misleading and irrelevant for the statistical analyses of the cross over design.

14) Please check the value for the IQR in line 19 of pag 31 on 95% CI Results

We thank the reviewer for the detailed correction: that was a transcription error. We corrected the particular value.

15) Concerning the "demography" could there be an association between the demography information and the primary outcome? Around 40% of people assisted at least at one cricothyrotomies and around 30% of the sample performed at least one. Is it possible for these people (with an experience on it) had a different time to manage the situation?

We aimed to conduct a cross section analysis, so we performed randomisation to achieve an appropriate distribution within our sample. Performing further subgroup analyses was out of the scope of our study.

16) In the figure (B) reported at page 21 of the Manuscript, there were some outliers, especially in the CPR subset. Did the author explain if they could affect the results? Instead concerning the figure (a) is it possible that there was a difference in the two performance of the no-CPR? If yes, the authors could explain if this difference could be clinical relevant?

The Wilcoxon-tests for comparison CPR vs. no-CPR and for the evaluation of carry-over effects are nonparametric and rank-based. Thus, the analysis is robust, i.e. insensitive with regard to outliers.

Discussion

17) A large part on the devices was reported. Maybe could be useful also to report these findings in the abstract, and, if it is possible, it will be nice also to add information on it also in the background paragraph.

We cited the documentation of the used airway instruments in the background and added a paragraph to specify this part of our study. However, the instruments are an aspect, that was not a mayor concern of the present study, so we apologise for not mentioning the specific aspect of the used instruments in the abstract and would leave the abstract as cited in the original submission. If it is judged as essential for the duct of the manuscript, we will add this aspect to the abstract.

Minor

l) In "Background" pag 4 line 27 in order to pinpoint which is the principle aim, should be better, instead of primary endpoint, report "The aim of the study was to evaluate the influence of CPR on the 'time to ventilation', during a CICO situation, through cricothyrotomy"

We rephrased the expression according to the reviewer's advice.

II) It could be better to report at least sec or seconds for clearer reading.

We think that we should use the official abbreviation of the SI-Unit which is "s" for seconds. However, we will change the abbreviation, if this is essential.

III) The terms "by lot", in line 40 at pag 6, sounds strange. Is it possible to modify this sentence?

We rephrased the entire section according to the reviewer's advice.

IV) In line 35 pag 6 of the manuscript it should be better change "allocated" with "enrolled"

We agree and rephrased the expression according to the reviewer's advice.

V) Is it possible to avoid an exceed on 100%, as referred in the note, and report at least one decimal in the percentages as done in the table with the results of the study?

We principally agree with the reviewer concerning the formal aspect of percents. However, we describe the percent of 40 participants, thus "one participant" is equal to 2.5 %. So, we decided not to cite the first decimal of the percentages in the original submission, but quoted an appropriate note concerning the mathematical rounding. However, we will change all percent values if this is essential.

VERSION 2 – REVIEW

REVIEWER	Hyuk Joong CHOI Hanyang Univ. Guri Hospital
REVIEW RETURNED	26-Aug-2019

GENERAL COMMENTS	I think it's a good paper. The authors express what they want to say in an appropriate way and respond to reviewers' comments. I think the "conclusion" paragraph is a bit long. I think the latter paragraphs of the authors' arguments should be moved to the discussion section.
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REVIEWER	Conrad A. Bjørshol RAKOS, Stavanger University Hospital, Norway
REVIEW RETURNED	31-Aug-2019

GENERAL COMMENTS	<p>Thank you for a rewritten submission. I have only one question: In table 1, you report that among 40 anaesthesiologists (median experience 7.5 years), 11 out of 40 have performed cricothyrotomies (two more than once). This is a surprisingly high number, as most anaesthesiologists will never have to perform an emergency cricotomy. How was the question asked, does it include elective tracheostomies as well?</p> <p>Otherwise I have no further comments to the manuscript.</p>
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REVIEWER	Ottavia E. Ferraro University of Pavia, Italy
REVIEW RETURNED	26-Aug-2019

GENERAL COMMENTS	<p>The authors improved their manuscripts with the suggestion made by reviewer. Minor clarifications still remained.</p> <p>1) Concerning the sample size as reported in the manuscript "This analysis resulted in a power of over 85 % if the median time-difference between the CPR and no-CPR situations comprised at least one standard deviation, e.g., an effect size of at least 1 was present." Which is the clinical meaning of at least 1 in the effect size? Why exactly one standard deviation? This information could be good for others clinicians and/or researchers.</p> <p>2) Concerning the differences on the years of the experience, among participants, could be interesting report, in order to avoid misleading due to this issue, some comments or underline this potential bias as limitation. Maybe the differences, found in timing, could be due to previous experience gained: in the sample 60% of subjects enrolled, never assisted to a cricothyrotomy vs 40% and 35 % had an anaesthesiology experience of up to 6 years and 65% more than 6 years.</p> <p>3) There are still few details in the background concerning cricothyrotomy methods that are then reported extensively in the discussions.</p> <p>4) It's better to report all the p-values in the same way with 3 decimals for the entire manuscript and it would be also preferable to uniform the percentages by adding the decimals in order to be more precise.</p> <p>5) The excel table supplementary file 4 needs a correction: "vive versa" should be "vice versa".</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Hyuk Joong CHOI

Institution and Country: Hanyang Univ. Guri Hospital Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below I think it's a good paper. The authors express what they want to say in an appropriate way and respond to reviewers' comments.

I think the "conclusion" paragraph is a bit long. I think the latter paragraphs of the authors' arguments should be moved to the discussion section.

We shortened the conclusion paragraph, deleted redundant issues und moved the essentials of the cited aspects into the discussion section: limitations.

Reviewer: 3

Reviewer Name: Ottavia E. Ferraro

Institution and Country¹¹: University of Pavia, Italy Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below The authors improved their manuscripts with the suggestion made by reviewer.

Minor clarifications still remained.

1) Concerning the sample size as reported in the manuscript "This analysis resulted in a power of over 85 % if the median time-difference between the CPR and no-CPR situations comprised at least one standard deviation, e.g., an effect size of at least 1 was present."

Which is the clinical meaning of at least 1 in the effect size? Why exactly one standard deviation? This information could be good for others clinicians and/or researchers.

We cited this reply under the Editor Comments to Author:

Before we started our trial, the following considerations led to our sample size decision: We initially expected a value of 20 sec, both for the mean and the standard deviation of the time difference between CPR and noCPR (e.g. effect size 1). However, it is important to note that these values were assumed solely based on clinical experience. To the best of our knowledge, there were no appropriate pilot data or literature regarding our research question available. Hence the study was

conducted with 20 participants in each sequence, as this sample size resulted in a power over 85% for the Mann Whitney U test, if the assumptions described above held true. We added this information to the statistic's section.

2) Concerning the differences on the years of the experience, among participants, could be interesting report, in order to avoid misleading due to this issue, some comments or underline this potential bias as limitation.

Maybe the differences, found in timing, could be due to previous experience gained: in the sample 60% of subjects enrolled, never assisted to a cricothyrotomy vs 40% and 35 % had an anaesthesiology experience of up to 6 years and 65% more than 6 years.

We agree and added these aspects of experience in the section: limitations. We have chosen the crossover design to minimise intraindividual differences. So, the measured times should be inert to the confounder: experience. However, we agree, that our sample provide an over-average experience number of cricothyrotomy. We cited this aspect in the revision in the section: limitations.

Of course, our results do at first only apply to similar populations, e.g. with similar distributions of age and experience.

3) There are still few details in the background concerning cricothyrotomy methods that are then reported extensively in the discussions.

We agree and added a section in the Background about the methods applied concerning the cricothyrotomy to launch this aspect, that is cited in the discussion.

4) It's better to report all the p-values in the same way with 3 decimals for the entire manuscript and it would be also preferable to uniform the percentages by adding the decimals in order to be more precise.

We corrected all p-values throughout the manuscript. Still, we have a different perspective on the aspect of preciseness of the decimals of percent. We respect the reviewer's appraisal and corrected the percent to one decimal as required.

5) The excel table supplementary file 4 needs a correction: "vive versa" should be "vice versa".

Thank you for this point, we corrected the expression.

Reviewer: 2

Reviewer Name: Conrad A. Bjørshol

Institution and Country: RAKOS, Stavanger University Hospital, Norway Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below Thank you for a rewritten submission. I have only one question: In table 1, you report that among 40 anaesthesiologists (median experience 7.5 years), 11 out of 40 have performed cricothyrotomies (two more than once). This is a surprisingly high number, as most anaesthesiologists will never have to perform an emergency cricotomy. How was the question asked, does it include elective tracheostomies as well?

Otherwise I have no further comments to the manuscript.

We agree, that our sample had a surprisingly high incidence of already performed or assisted cricothyrotomies compared to literature. Thus, we added this issue in the section: limitations. We asked our participants about their experience concerning cricothyrotomy by a demographic questionnaire before the session. One content of the questionnaire were the categories, that are cited in table 1: n=0 / < 3 / 3-6 / > 6; Elective tracheotomies were explicitly not included in the questionnaire and participants were informed, not to protocol tracheotomies.

VERSION 3 - REVIEW

REVIEWER	Ottavia E. Ferraro University of Pavia, Italy
REVIEW RETURNED	08-Oct-2019

GENERAL COMMENTS	Thanks to the authors that had answered at all of the revisions requested. I have no further comments concerning this manuscript.
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