PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Extubation from high-frequency oscillatory ventilation in extremely low birth weight infants: a prospective observational study
AUTHORS	Vento, Giovanni; Tana, Milena; Lio, Alessandra; Tirone, Chiara; Aurilia, Claudia; Tiberi, Eloisa; Serrao, Francesca; Purcaro, Velia; Corsello, Mirta; Catenazzi, Piero; D'Andrea, Vito; Barone, Giovanni; Ricci, Cinzia; Pastorino, Roberta

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Jeremy Miles Institution and Country: Google, Inc, USA Competing interests: No competing interests.
REVIEW RETURNED	12-Aug-2018

GENERAL COMMENTS	(Statistical review). I have one minor comment only: P8: Rather than p< 0.02, give the exact p-value.

REVIEWER	Reviewer name: PO-NIEN TSAO Institution and Country: National Taiwan University Hospital, Taiwan Competing interests: none
REVIEW RETURNED	21-Aug-2018

GENERAL COMMENTS	Extubation from HFOV in ELBW infants was not a novel idea. In addition, why the authors used initial Hz with 10 instead of 15, which was more protective lung strategy in using HFOV for ELBW infants?

REVIEWER	Reviewer name: Anton van Kaam Institution and Country: Emma children's Hospital Amsterdam UMC Competing interests: None
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	In this study, Tana and colleagues assessed the rate of extubation failure in a group of extremely low birth weight (ELBW) infants treated with and extubated from high-frequency ventilation (HFV). They report that extubation failure was approximately 20% in the first 7 days after extubation. Variables associated with extubation failure were gestational age (GA) and mean airway pressure (MAP) prior to surfactant treatment. They conclude that direct extubation from HFV is feasible and results in less or equal failure than extubation from conventional ventilation. This is an interesting study from a well know research group in Rome, Italy. As noted by the authors, data on extubating directly from HFV are limited. This study adds more knowledge to this topic, although the novelty is somewhat limited compared with previous reports. I have some comments I would like the authors to address.

	Major comments 1. I think the authors should make a better case in the introduction section what is missing in the van Velzen paper and what their study adds. 2. The authors claim that a period of 48-72 hours to assess extubation failure is not sufficient as previous work shows that prolonging the observation period results in an increase of extubation failure. I am sure this observation is correct, but there is a downside to prolonging the observation period. I guess the authors are interested in the extubation failure rate after a ventilation period for a specific cause of respiratory failure. Looking at the inclusion criteria, in the current study this would be respiratory distress syndrome (RDS). By prolonging the observation period, the chances of reintubation for a different cause of respiratory failure increase. For example, an ELBW infant with RDS is extubated after surfactant treatment at day 3 and does perfectly well until he/she develops a sepsis 6 days later and needs to be reintubated. This will be counted as an extubation failure of the initial extubation failure, while this is probably not the case. This is why most previous studies have used 48-72 hours as the observation period. The authors need to address this downside in the discussion, because it limits comparison with previous reports. Ideally, the could run an additional analysis using 48 or 72 hours as their observation period and see how this effects the extubation failure rate. 3. A second variable that affects extubation failure is the criteria to reintubate the infant. Compared to previous reports, the criteria used in this study result in a very high threshold for reintubation. This should be discussed in the paper. Please compare your criteria to previous reports on extubation failure during conventional ventilation and HFV. 4. The treatment after extubation will also affect extubation failure. Please provide explicit information on the use of nasal ventilation or use of doxapram in this cohort. And again, relate this to previous reports and discuss. 5. Looking at the time of extubation (median 4 [1-53]) I wonder if this is truly a homogenous group of infants. Is [1-53] the interquartile range (IQR)? If so, 25% of the infants were > 53 days old at their first extubation attempt. These infants are different from infants extubated on day 1-3. What if you limited the time of extubation to the first 5 or 7 days, targeting only RDS infants? This will improve the homogeneity of the group. Please comment and discuss in the paper. 6. It is important to assess if the study cohort is a selection of the total population. Please provide a flow diagram showing the total number of ELBW infants in the study period and the reasons why infants were excluded. 7. The authors used a MAP <= 6 and an FiO2 <= 0.25 as criteria to attempt extubation. Using these lower setting may improve the success rate of extubation. However, it may also prolong the time on the ventilator. Indeed, the study by van Velzen showed that the median ventilation time before extubation was 2.5 days compared to 4 days in the present study. And the actual percentage of extubation failure was similar. This needs to be discussed.

	Maybe extubation at even higher settings would results in similar rates of extubation failure while reducing the ventilation time. Minor comments 1. Abstract: I would delete the part on MAP in the conclusion. This is highly speculative. 2. Results: please provide the postnatal age of extubation failure. 3. Results: were there also combinations of reasons to fail extubation? 4. Discussion, page 8, first line: as indicated by the authors this is not the first report. Please correct. 5. Discussion, page 9, line 50: 83% vs 81% is no difference in terms of clinical relevance. Please change slightly higher to similar. 6. Table 1: interquartile range? 7. Table 3: I would express total ventilation and oxygen need in days 8. The paper needs English editing

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

(Statistical review).

I have one minor comment only:

P8: Rather than p< 0.02, give the exact p-value

Response: Thank you for your comment. The exact p-value of MAP pre surfactant is 0.02, as reported in Table 2 . We have corrected this value in the text (Page 8; line 20).

Reviewer: 2

Comments to the Author

Extubation from HFOV in ELBW infants was not a novel idea. In addition, why the authors used initial Hz with 10 instead of 15, which was more protective lung strategy in using HFOV for ELBW infants?

Response: Thank you for your comment. 10 Hz was the initial set Frequency for our babies because the ventilator used in the study was the Dräger Babylog 8000 plus, as reported in the Methods Section. The working frequency for this ventilator is 7-10 Hz and if higher frequencies are used, the absolute value of inspiration time is too short and the corresponding delivered tidal volume is too low. By using more powerful ventilators (Sensor Medics, VN-500, Fabian etc.) higher frequency up to 15 Hz can be used.

Reviewer: 3

Comments to the Author

In this study, Tana and colleagues assessed the rate of extubation failure in a group of extremely low birth weight (ELBW) infants treated with and extubated from high-frequency ventilation (HFV). They report that extubation failure was approximately 20% in the first 7 days after extubation. Variables associated with extubation failure were gestational age (GA) and mean airway pressure (MAP) prior to surfactant treatment. They conclude that direct extubation from HFV is feasible and results in less or equal failure than extubation from conventional ventilation.

This is an interesting study from a well know research group in Rome, Italy. As noted by the authors, data on extubating directly from HFV are limited. This study adds more knowledge to this topic, although the novelty is somewhat limited compared with previous reports.

I have some comments I would like the authors to address.

Major comments

1. I think the authors should make a better case in the introduction section what is missing in the van Velzen paper and what their study adds.

Response : We added the following sentence in the Introduction Section, as suggested: “Compared to the experience of van Velzen et al. our study is aimed at the extubation process from HFOV in ELBW infants only (i.e. the population at greater risk of ventilator-induced lung injury), evaluating the success or failure of the extubation attempt over a longer period of time (7 days instead of 48 hours after extubation) and the safety of lower pre-extubation MAP values (≤ 6 cm H2O instead of 8 cm H2O) as the most appropriate ventilatory set for extremely low birth weight neonates.”.

2. The authors claim that a period of 48-72 hours to assess extubation failure is not sufficient as previous work shows that prolonging the observation period results in an increase of extubation failure. I am sure this observation is correct, but there is a downside to prolonging the observation period. I guess the authors are interested in the extubation failure rate after a ventilation period for a specific cause of respiratory failure. Looking at the inclusion criteria, in the current study this would be respiratory distress syndrome (RDS). By prolonging the observation period, the chances of reintubation for a different cause of respiratory failure increase. For example, an ELBW infant with RDS is extubated after surfactant treatment at day 3 and does perfectly well until he/she develops a sepsis 6 days later and needs to be reintubated. This will be counted as an extubation failure of the initial extubation failure, while this is probably not the case. This is why most previous studies have used 48-72 hours as the observation period.

The authors need to address this downside in the discussion, because it limits comparison with previous reports. Ideally, the could run an additional analysis using 48 or 72 hours as their observation period and see how this effects the extubation failure rate.

2. Response: Thank you for the interesting and shareable comment. We asked the same questions and analyzed the failure of extubation in our patients using a 72-hour observation period, also to compare our data with those of previous studies. This analysis was initially excluded in our paper to not exceed the consented number of words and considering the recent remarks by Giaccone et al. (Reference #13), who showed that in the studies enrolling predominately infants with BW <1000 g, rates of extubation success were negatively associated with the duration of observation (as specified in the Discussion: Pages 8-9). By relying on shorter windows of observation, studies enrolling a large proportion of small infants may therefore underestimate the true rate of reintubation. In fact, the reintubation rate did not appear to plateau even at a week of observation, indicating that longer periods may be necessary to adequately capture this outcome in ELBW infants (Reference #13).

Nevertheless, this analysis has been added to the text in the Results Section, as requested: “Thirteen infants failed extubation within 72 hours and were reintubated at a median [range] time of 24 [2-48] hours for hypoxia (n 3), hypercapnia (n 5) and apnea (n 5). Another five newborns who failed extubation after 72 hours and within 7 days were reintubated at a median [range] time of 120 [96-160] hours for hypoxia (n 3), and apnea (n 2). In general, of the 18 infants who met failure criteria within 7 days after extubation, 7 (39%) failed due to apnea, 6 (33%) due to hypoxia and 5 (28%) due to hypercapnia. No newborn who failed extubation had an episode of suspected or confirmed sepsis during the 7-day period after extubation”.

We partly modified the sentence already written in the Discussion section: “Compared to the only study reporting the feasibility of weaning and direct extubation from HFOV in ELBW infants (20), our data showed similar rates of successful extubation: 88% within 72 hours and 83% within 7 days after the extubation attempt, vs 81% within 48 hours only, respectively”. Moreover, a new sentence has been added in the Discussion Section, to underline the potential side-effect to prolong the post extubation observation period: “It is however necessary to keep in mind that by prolonging the observation period, the chances of reintubation for a different cause of respiratory failure (i.e. sepsis) increase. In our experience, no newborn who failed extubation had an episode of suspected or confirmed sepsis during the 7-day period after extubation”.

3. A second variable that affects extubation failure is the criteria to reintubate the infant. Compared to previous reports, the criteria used in this study result in a very high threshold for reintubation. This should be discussed in the paper. Please compare your criteria to previous reports on extubation failure during conventional ventilation and HFV.

Response 3 We agree with you: an important variable affecting extubation failure is the criteria to reintubate the infants. Nevertheless it does not seems to be the case. In fact, by comparing our criteria to re-intubate the infants with those adopted by van Velzen et al. (ref. #20), no clear differences exist: in our study the indications for reintubation were: a) repeated episodes of apnea defined as >4 episodes of apnea per hour or >2 episodes of apnea per hour when ventilation with bag and mask was required; b) hypoxia defined as FiO_2 > 0.50 to maintain SpO_2 90-95% for more than 2 hours despite 8 cm H_2O of CPAP, c) development of respiratory acidosis indicated by 2 consecutive blood gases with $PaCO_2$ ≥65 mm Hg and pH < 7.20. In van Venzel study the indications for reintubation were: a) if the FIO_2 exceeded 0.6 or b) if the arterial PH dropped below 7.20 and the $PaCO_2$ exceeded 8.0 kPa (60 mHg), or c) if infants had recurrent apnea requiring repeated stimulation, or bag-and-mask ventilation, or d) if infants showed clinical signs of severe respiratory distress. This is why we did not add any additional sentence in the Discussion section.

4. The treatment after extubation will also affect extubation failure. Please provide explicit information on the use of nasal ventilation or use of doxapram in this cohort. And again, relate this to previous reports and discuss.

Response 4: Nasal ventilation and doxapram have not been used in our study. We have added a specific sentence regarding the use of doxapram in the methods section: “Doxapram was not used during the study period as per our departmental protocols”. Regarding the use of nasal ventilation, this aspect had already been considered in the Discussion as a limit of the study: “ …Moreover, higher level of CPAP post extubation (7-9 cm H_2O) or other non-invasive respiratory support such as synchronized nasal IPPV (25) or nasal HFOV (26) could be used to improve the success rate of extubation in ELBW infants”. Moreover, we have partly modified a sentence already written in the original version of the manuscript (Methods section), as follows: “After extubation all the patients were supported by nasal CPAP at 6-8 cmH_2O using short binasal prongs of appropriate size; nasal ventilation was not administered.”.

5. Looking at the time of extubation (median 4 [1-53]) I wonder if this is truly a homogenous group of infants. Is [1-53] the interquartile range (IQR)? If so, 25% of the infants were > 53 days old at their first extubation attempt. These infants are different from infants extubated on day 1-3. What if you limited the time of extubation to the first 5 or 7 days, targeting only RDS infants? This will improve the homogeneity of the group. Please comment and discuss in the paper.

Response 5: [1-53] refers to the range with minimum and maximum value and not to IQR, as declared in the Results section: “Extubation was attempted at a median [range] age of 4 [1-53] days”. Only 4 patients in the Extubation Success Group were extubated > 30 days of life. If we limit the time of extubation to the first week of life, as suggested, we have 66 successfully extubated patients (instead of 90) vs 14 not successfully extubated patients (instead of 18):

the percentage of Extubation success was the same of our original patients: 83%. We added a new sentence in the Results Section: “If we limit the time of extubation to the first week of life, the same percentage of successful extubation was reached (66 out of 80 patients - 83% -, data not shown)”. Moreover we considered this aspect as a limit of the study, and a specific sentence has been added to the Discussion: “Finally, our study population includes newborns extubated early (≤ 7 days of life) and newborns who have been extubated after the first week of life. If this aspect is certainly a limit rendering the studied infants a not homogeneous group, at the same time the attempted extubation directly from HFOV at the proposed ventilatory setting (MAP ≤6 cm H2O) has been proved to be valid even in ELBW infants ventilated for several days, with “incoming” BPD.

6. It is important to assess if the study cohort is a selection of the total population. Please provide a flow diagram showing the total number of ELBW infants in the study period and the reasons why infants were excluded.

Response 6: A flow diagram (Figure 1) has been added to the text, as suggested.

7. The authors used a MAP <= 6 and an FiO2 <= 0.25 as criteria to attempt extubation. Using these lower setting may improve the success rate of extubation. However, it may also prolong the time on the ventilator. Indeed, the study by van Velzen showed that the median ventilation time before extubation was 2.5 days compared to 4 days in the present study. And the actual percentage of extubation failure was similar. This needs to be discussed. Maybe extubation at even higher settings would results in similar rates of extubation failure while reducing the ventilation time.

Response 7: Thank you for your comment. We added a new sentence in the Discussion: “Importantly, we used MAP ≤ 6 cmH2O and FiO2 ≤ 0.25 as criteria to attempt extubation. Using these lower setting respect to those adopted by van Velzen (20) may improve the success rate of extubation but it may also prolong the time on the ventilator. Future studies could evaluate if extubation at higher HFOV settings in ELBW infants could results in similar rates of extubation failure while reducing the ventilation time”.

Minor comments

1. Abstract: I would delete the part on MAP in the conclusion. This is highly speculative.

Response 1 : Thank you, we deleted the indicated part about MAP in the abstact’s conclusion. Accordingly we modified the sentence in the Section “What this study adds” , as follows: “A recruitment HFOV maneuver prior to surfactant administration may be helpful for successful extubation in ELBW infants”.

2. Results: please provide the postnatal age of extubation failure.

Response 2: The postnatal age at extubation has been added in Table 1, as requested.

3. Results: were there also combinations of reasons to fail extubation?.

Response 3: We do not have combination of reasons to fail extubation.

4. Discussion, page 8, first line: as indicated by the authors this is not the first report. Please correct.

Response 4: As suggested we corrected the indicated sentence in the Discussion, as follows: “In comparison to the only experience reported on the successful extubation rates directly from HFOV by van Velzen et al (20), referring to a heterogeneous population of 214 preterm infants and including only 68 neonates with a birth weight ≤1000 g, our report provides……”

5. Discussion, page 9, line 50: 83% vs 81% is no difference in terms of clinical relevance. Please change slightly higher to similar.

Response 5: We changed “slightly higher” with “similar”, as suggested.

6. Table 1: interquartile range?

Response 6: No, values between the square brackets represent minimum and maximum.

7. Table 3: I would express total ventilation and oxygen need in days

Response 7: Table 3 has been modified, as suggested

8. The paper needs English editing

Response 8: English editing has been provided by an English-speaking editor, as suggested.