Optimisation of Neonatal Ventilation: Neurally Adjusted Ventilator Assist (NAVA) versus Proportional Assist ventilation (PAV)

A randomised cross over study assessing the oxygenation index, thoracoabdominal asynchrony, work of breathing, and trigger delay on neurally adjusted ventilatory assist (NAVA) and proportional assist ventilation (PAV)

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Study Synopsis

Title	**Randomised crossover study of Neurally Adjusted Ventilator Assist (NAVA) versus Proportional Assist Ventilation (PAV)** (NAVA Vs PAV 1.0 15/08/2015)
Protocol Short Title/Acronym	Assessment of triggered ventilation – NAVA versus PAV
Protocol Version number and Date	NAVA Vs PAV 1.0 15/8/2015
Study Phase if not mentioned in title	
Is the study a Pilot?	Yes
Study Duration	24 months
Methodology	Open randomised crossover study
Sponsor name	Mr Keith Brennan
Chief Investigator	Professor Anne Greenough
REC number	
Medical condition or disease under investigation	Evolving Bronchopulmonary Dysplasia
Purpose of clinical trial	Evaluation of two newer ventilator modes - NAVA and PAV - to determine which is more advantageous
Primary objective	In prematurely born infants (less than 32 weeks gestation) with evolving bronchopulmonary dysplasia, that is ventilated since birth and still ventilated at one week of age, NAVA compared to PAV will be associated with decreased oxygenation index.
Secondary objective (s)	NAVA compared to PAV will be associated with decreased work of breathing, lower thoracoabdominal asynchrony, and shorter trigger delay
Number of Subjects/Patients	18
Trial Design	Randomised cross over
Endpoints	Oxygenation Index, length of trigger delay, work of breathing, and thoraco-abdominal asynchrony
Main Inclusion Criteria	All prematurely born (<32/40) infants with evolving bronchopulmonary dysplasia ventilated since birth and still ventilated at one week of age.
Statistical Methodology and Analysis	Non-parametric statistics

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

Despite improvements in survival rates of extremely preterm born infants, the incidence of bronchopulmonary dysplasia (BPD) remains unchanged over the last two decades. [1] As invasive ventilation is frequently necessary and indeed life saving, numerous ventilator strategies have been developed to reduce damage to the developing lung. Synchronisation of mechanical breaths with the patient's respiratory effort offers the theoretical benefit of improving oxygenation and ventilation, requiring lower ventilator pressures, fewer air leaks and increased patient comfort.

Conventional ventilation allows the clinician to set the inspiratory pressure or tidal volume delivered by the ventilator. The appropriateness of this target is then assessed via blood gas analysis and adjusted as necessary with changes in respiratory system mechanics and patient condition.

Compared to continuous mandatory ventilation, triggered ventilation (assist control (ACV) and synchronized intermittent mandatory ventilation (SIMV) have been shown to reduce duration of mechanical ventilation, but not rates of BPD.[2]

During ACV and SIMV, triggering is via either pressure or flow sensors which determine the initiation of inflation. In the neonatal population, with small tidal volumes, high respiratory rates and often significant leak from uncuffed endotracheal tubes, sensitive triggering can be challenging and hence, some of the benefits of triggered ventilation may not materialise.

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Recently, novel modes of ventilation have been introduced that aim to improve upon conventional ventilation. During both proportional assist ventilation (PAV) and neurally-adjusted ventilatory assist (NAVA), respiratory support is servo-controlled based on continuous input from the baby's respiratory effort. Both aim to improve synchronization of the timing of the respiratory cycle and also to vary the level of support offered breath-to-breath in proportion to the respiratory effort of the patient.

During proportional assist ventilation (PAV), the ventilator can vary inflation pressure in phase with both volume change and flow change in order to offload both elastic and resistive components of the work of breathing. We have previously shown that PAV, compared to ACV, reduces the oxygenation index and improves respiratory muscle strength in infants born prematurely who remain ventilated at or beyond one week of life [4,5].

Neurally adjusted ventilatory assist (NAVA) utilises the electrical activity of the diaphragm to trigger the ventilator. A modified nasogastric feeding tube with a series of electrodes allows monitoring of the diaphragmatic electromyogram (Edi). The waveform of the Edi is used to trigger and control ventilator support. We have recently shown that NAVA compared to ACV results in a lower oxygenation index in infants born prematurely who remain ventilated at or beyond one week of life.

Both PAV and NAVA have been shown to have advantages above conventional triggered ventilation in neonates, but they have not been compared to each other. Our aim is to determine whether NAVA or PAV is more effective in reducing oxygenation index, work of breathing, and thoracoabdominal asynchrony, and preserving respiratory muscle strength in prematurely born neonates with evolving or established BPD.

References

1. Costeloe K L, Hennessy E M, Haider S, Stacey F, Marlow N, Draper E S. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 2012;345:e7976.
2. Greenough A, Dimitriou G, Prendergast M, Milner A D. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database of Systematic Reviews 2008:CD000456.
3. Beck J, Reilly M, Grasselli G, Mirabella L, Slutsky A S, Dunn M S, et al. Patientventilator interaction during neutrally adjusted ventilatory assist in low birth weight infants. Pediatr Res 2009;65:6638.
4. Proportional assist versus assist control ventilation. S Shetty, P Bhat, A Hickey, JL Peacock, AD Milner A Greenough. Accepted for publication in European Journal of Pediatrics – June 2015.
5. Bhat P, Patel DS, Hannam S, et al. Crossover study of proportional assist versus assist control ventilation. Arch Dis Child Fetal Neonatal Ed 2015;100:F353F38

2 Trial Objectives, Design and Statistics

2.1. Trial Objectives

To compare NAVA and PAV in prematurely born infants (less than 32 weeks gestation) with evolving bronchopulmonary dysplasia, that is ventilated since birth and still ventilated at one week of age, measuring oxygenation index, work of breathing, respiratory muscle strength, and thoracoabdominal asynchrony.

2.2 Trial Design & Flowchart

Randomised crossover design - two hour epochs of NAVA versus PAV

Protocol:
1. Order of modes randomized for each baby using random number generator and sealed opaque envelopes
2. Infant examined before commencement of study
3. A dual pressure transducer catheter and catheter with Edi electrode array (similar in diameter to that of the infant's feeding tube) inserted via the infant's nose or mouth and secured in place
4. Baseline settings noted
5. Infant changed to ventilator for mode A (Stephanie or Maquet) with baseline settings
6. Allow period of stabilisation on baseline settings on the new ventilator – 1 hour
7. A blood gas performed and the compliance and resistance measurements noted (from ventilator screen) in the baseline mode
8. Enter into mode A for 2 hours
9. During last five minutes – measure
    a. PTPdi (Measure of the work of breathing)
    b. TAA (measure of asynchrony)

c. Blood gas measurement (CO_2 levels and calculating the oxygenation index)
10. Change to ventilator for mode B (Maquet or Stephanie)
11. Allow period of stabilisation on original settings on the new ventilator - 1 hour
12. Enter into mode B for 2 hours
13. During last five minutes measure
    a. PTPdi
    b. TAA
    c. Blood gas measurement (CO_2 levels and calculating the oxygenation index)
14. During each epoch: The number and length of desaturations, respiratory rate, heart rate, mean airway pressure, the tidal volumes and the FiO_2 utilised are noted every 10 min.
FiO_2 to maintain saturations 92-96%.

Ventilator settings:
NAVA level will be set so that the NAVA curve and pressure curves are matching. We will titrate NAVA level to aim for Edi between 5 and 15.
PAV – previous studies have shown waveform abnormalities and oscillations with resistive unloading, therefore elastic unloading only will be used. Elastic unloading will initially be set at 75% of full unloading, and then if the infant remains stable, increased after 10 minutes to 100% unloading. If pressure waveform abnormalities develop then the unloading will be reduced back to 75%.

Assessments:

Oxygenation Index will be calculated by blood gas analysis from an indwelling catheter or by heelprick at the end of the 2 hour period of each ventilator mode ie NAVA/PAV.

The WOB will be assessed by the measurement of the transdiaphragmatic pressure time product (PTPdi). Transdiaphragmatic pressure (Pdi) will be obtained from measurements of oesophageal (Poes) and gastric (Pgas) pressures, measured using a dual-pressure transducer tipped catheter and associated amplifier (Gaeltec, Dunvegan, UK). Correct positioning of the gastric transducer will be confirmed by a positive pressure deflection during inspiration while the position of the oesophageal transducer determined by comparing Poes and airway pressure during an occluded inspiratory effort. Airflow will be measured using a pneumotachograph (Mercury F10L; GM Instruments, Kilwinning, UK) connected to a differential pressure transducer (MP45; Validyne Corporation, Northridge, California, USA). Airway pressure will be measured from a side port on the pneumotachograph using a second differential pressure transducer (MP45; Validyne Corporation). The PTPdi will be obtained by integration of Pdi with time for each breath and expressed per minute. The mean PTPdi will be calculated from the first set of 20 consecutive breaths without artefact during the last five minutes of each period on NAVA and PAV modes.

Thoracoabdominal asynchrony will be assessed using uncalibrated respiratory inductance plethysmography (Respitrace model 10.9230, Ambulatory Monitoring, New York, USA) in ACcoupled mode. Inductance coils embedded in two elastic bandages will be placed around the ribcage (RC) and midabdomen. TAA will then be determined from five consecutive, artefact-free breaths during the 5 min measurement period. For each breath, the RC and abdominal wall (AB) movements will be derived from the recording software. A Lissajous figure is plotted and asynchrony between RC and abdominal motion quantified. The phase angle will be determined by comparing the difference between inspiratory and expiratory abdominal positions

at midRC excursion (ABdiff) with the maximum abdominal excursion (ABmax). The phase angle φ is calculated as sin φ=ABdiff/ABmax.

References
6. Beardsmore CS, Helms P, Stocks J, et al. Improved esophageal balloon technique for use in infants. J Appl Physiol 1980;49: 735–42.
7. Baydur A, Behrakis PK, Zin WA, et al. A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 1982;126: 788–91.

2.3 Trial Flowchart

Patient information and informed consent				
Physical examination				
	Baseline 1 hour	Mode A 2 hours	Baseline 1 hour	Mode B 2 hours
Oxygenation Index			x	
PTPdi	x		x	
TAA	x		x	
Adverse events				

2.4 Trial Statistics

Recruitment of 18 infants will allow detection of a difference in the results of OI and the physiological assessments between the two groups equivalent to one standard deviation in the results with 80% power and 5% significance.

3. Sample Size, Selection and Withdrawal of Subjects

Power calculation as stated in 2.4 requires the recruitment of 18 infants to participate in the study.

Inclusion Criteria

- Infants born at less than 32 weeks completed gestation who remain ventilator dependent one week after birth.

Exclusion Criteria

- Complex congenital cardiac abnormalities

- Infants on neuro-muscular blockade
- Contraindication to nasogastric/orogastric tube insertion.

Criteria for Premature Withdrawal
- Parental Request

4. Study procedures

Informed Consent Procedures

Participants will be identified from the daily admission list and the clinical research fellow will approach parents. Parents will be provided with both verbal and written information, allowing at least 24 hours for consideration prior to entry into study.

The clinical fellow will provide a full explanation of the study to the parents. They will highlight that the parents may choose not to allow their infant to be entered into the study and withdraw their child from the study at any time without compromising the child's care.

As the study involves hospital in-patients, consent will also be obtained from the consultant of the patient.

4.1 Screening Procedures

There are no study specific screening procedures prior to entry into the study. Eligible infants will be examined by the clinical fellow prior to undertaking physiological measurements in order to ensure they are in a stable condition.

4.2 Randomisation Procedures

Patients will be randomised using a sequential opaque-sealed envelope system, the contents having been determined by random number table generation.

4.3 Schedule of Treatment for each visit

The initial visit with the parents/carers of eligible infants will be primarily to provide information regarding the study, with a follow up meeting at least 24 hours later to ensure they have sufficient time to process the information and provide informed consent.

The physiological measurements of each study participant will be performed on a single occasion, lasting approximately 6 hours. It is unlikely that repeat study measurements will need to be taken and if required, the reasons will be explained to parents prior to taking place.

4.4 Follow up Procedures

There are no specific study procedures for follow up of the participating infants.

4.5 Radiology Assessments *(not applicable)*

4.6 End of Study Definition

Following completion of the physiological measurements and analysis of the results of the required number of infants, the REC will be informed that the study has been completed.

5. Laboratories (not applicable)

6. Assessment of Safety

All measurements are carried out whilst the patient is ventilated and closely monitored as part of routine clinical care. There have been no adverse effects or additional discomfort associated with previous studies which have used the same physiological assessments and similar study design. Infants will be fully examined to ensure clinical stability prior to undertaking measurements.

6.1 Ethics Reporting

Reports of related and unexpected serious adverse events will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The parents will be informed of any events as soon as possible and be provided with an opportunity to meet with clinical and research team. The results of any reports or investigations relating to the events will also be communicated to the parents in writing.

7. Trial Steering Committee (not applicable)

8. Ethics & Regulatory Approvals

We will submit via IRAS for HRA and NHS REC approval.

9. Data Handling

Confidentiality

Analysis of the data will take place at King's College Hospital and is to be undertaken by a clinical research fellow and by Professor Greenough, the principal investigator.

Each patient will be assigned a unique patient identifier, under which patient data will be anonymously stored on a password protected computer. All paper copies containing patient identifiable data will be kept in a locked filing cabinet until the patients are 16 years of age. Only the principal investigator and research fellow involved in the study will have access to the data, the principal investigator will act as custodian

Case Report Form

Elements included in each case report form (CRF):
-Unique patient identifier
-Date of parental consent
-Eligibility criteria checklist
-Date of measurements
-Record of clinical examination
-Study template documenting the order of volume targets as per randomisation and PTPdi results
-Any adverse events noted during measurements

Completion of the CRF will be the responsibility of the clinical research fellow.

Record Retention and Archiving

Records will be held in a locked filing cabinet located within the research office based at the neonatal unit of Kings College Hospital. Access is limited to the clinical research fellow and Chief Investigator.

Compliance
The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Clinical Governance Issues

-Audit and Inspection
Accurate records of all research activity including copies of the consent forms and completed case report forms will be safely stored and audited for compliance if requested.

-Non-Compliance

The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

10. Finance and Publication Policy

Consumables for this study have been funded by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The clinical research fellow salary is funded by Professor Greenough’s NIHR Senior Investigator grant.

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor