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Patient-ventilator synchrony in extremely premature neonates during non-invasive neurally adjusted ventilatory assist or synchronised intermittent positive airway pressure: a randomised crossover pilot trial

Short Title: EASYNNEO, Evaluation of ASYNchrony in NEOnates

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ABSTRACT

Introduction: Synchronisation of non-invasive ventilation is challenging in extremely premature infants. We compared patient-ventilator synchrony between non-invasive neurally adjusted ventilatory assist (NIV-NAVA) using transdiaphragmatic (Edi) catheter and synchronised intermittent positive airway pressure (SiPAP) using abdominal trigger.

Methods: Monocentric, randomised, crossover trial in premature infants born before 28 weeks of gestation, aged 3 days or more and below 32 weeks post-menstrual age. NIV-NAVA and SiPAP were applied in a random order for 2 hours with analysis of data from the second hour. The primary outcome was the asynchrony index.

Results: Fourteen patients were included (median (IQR) gestational age at birth 25.6 (25.3-26.4) weeks, median (IQR) birth weight 755 (680-824) g, median (IQR) postnatal age 26.5 (19.8-33.8) days). The median (IQR) asynchrony index was significantly lower in NIV-NAVA vs SiPAP (49.9% (44.1-52.6) vs 85.8% (74.2-90.9), $p < 0.001$). Ineffective efforts and auto-triggering were significantly less frequent in NIV-NAVA vs SiPAP (3.0% vs 32.0% $p < 0.001$ and 10.0% vs 26.6%, $p = 0.004$, respectively). Double triggering was significantly less frequent in SiPAP vs NIV-NAVA (0.0% vs. 9.0%, $p < 0.001$). No significant difference was observed for premature cycling and late cycling. Peak Edi and swing Edi were significantly lower in NIV-NAVA as compared to SiPAP (7.7 (6.1-9.9) vs 11.0 (6.7-14.5) μV , $p = 0.006$; 5.4 (4.2-7.6) vs 7.6 (4.3-10.8) μV , $p = 0.007$, respectively). No significant difference was observed between NIV-NAVA and SiPAP for heart rate, respiratory rate, COMFORTneo scores, apnoea, desaturations, or bradycardias.

Discussion/Conclusion: NIV-NAVA markedly improves patient-ventilator synchrony as compared to SiPAP in extremely premature infants.

INTRODUCTION

The use of non-invasive respiratory support has significantly reduced morbidity and mortality in premature infants by reducing ventilator-induced lung injury.[1] In a meta-analysis from 2021, synchronised non-invasive positive pressure ventilation (sNIPPV), as compared to continuous positive airway pressure (CPAP), reduced bronchopulmonary dysplasia, extubation failure rate and non-invasive ventilation failure.[2] In a network meta-analysis from 2020, sNIPPV was possibly the most effective strategy to prevent extubation failure.[3] However, these two meta-analysis acknowledged a limited level of evidence. The factors precluding the ability to firmly demonstrate the benefits of synchronisation during NIPPV in extremely premature infants include technical challenges [4] and an immature control of breathing. [5] Whereas breathing control is difficult to modulate in extremely premature infants, technical limitations can be overcome.

Synchronised intermittent positive airway pressure (SiPAP) and non-invasive neurally adjusted ventilatory assist (NIV-NAVA) are two options to synchronise non-invasive ventilation.[4] SiPAP uses a variable flow device and a Graseby abdominal capsule [6] and is very frequently used in many neonatal intensive care units.[7,8] NIV-NAVA delivers assistance to spontaneous breaths in proportion to the electrical activity of the diaphragm, using an electrode-equipped feeding tube.[9] It allows a breath-by-breath regulation of inspiratory pressure and time by the patient him/herself.[10] During invasive ventilation NAVA seems to stabilise oxygenation and decrease neural inspiratory efforts as compared to synchronized intermittent mandatory ventilation + pressure support.[11] During NIV-NAVA only one study to date compared NIV-NAVA to another synchronised NIV mode (NIV pressure support) using the Servo-i ventilator.[12] After analysing 5-minutes recordings, this crossover study found a significant decrease in asynchrony, peak inspiratory pressure, FiO_2 , frequency and length of desaturations in the NIV-NAVA group.

Considering that improved synchronisation might help in the future to demonstrate the clinical benefits of synchronised non-invasive ventilation in extremely premature neonates, we aimed at comparing NIV-NAVA with another synchronised non-invasive ventilatory mode.

Since variable flow CPAP is preferentially used in premature neonates [7] for its potential to decrease work of breathing as compared to other flow sources [13,14], we considered that SiPAP was the most appropriate comparator to NIV-NAVA. We hypothesized that synchronisation would be improved with NIV-NAVA as compared to SiPAP.

METHODS

This randomised crossover trial was conducted from December 2019 to March 2021 in the neonatal intensive care unit of the Centre Hospitalier Intercommunal de Créteil, France (full protocol as Supplement) and was registered on Clinicaltrial.gov as NCT04068558.

Subjects

Premature infants born before 28 weeks of gestation, aged 3 days or more and below 32 weeks post-menstrual age, receiving non-invasive ventilation using any intermittent positive pressure mode, equipped with an orally-inserted appropriately-sized Edi catheter, treated with caffeine to prevent apnoea were eligible. The presence of an Edi catheter as an inclusion criterion was requested by the ethics committee in order to avoid the discomfort of its insertion for the sole purpose of this study.

Exclusion criteria were: more than 1 apnoea per hour requiring bag-mask ventilation; pH < 7.2 and/or transcutaneous partial CO₂ pressure (TcPCO₂) > 70 mmHg, and/or FiO₂ > 0.6 in the 6 hours preceding randomisation; nasal trauma precluding the use of non-invasive ventilation; major congenital anomalies; grade III or higher intraventricular haemorrhage; haemodynamic compromise defined as a mean arterial blood pressure (in mmHg) less than post-menstrual age (in weeks) or a capillary refill time over 3 seconds; neuromuscular disorders; anaesthetics or sedative drugs within the 24 hours preceding randomisation, except opioids for iatrogenic withdrawal treatment.

Study protocol

Randomisation, allocation and blinding

After their inclusion in the trial, infants were randomised online following a computer-generated list using fixed block size of 2. Investigators were unaware of block size. Allocation of the first and second ventilatory mode was performed by the investigator who randomised the patient. Due to the nature of the study, blinding was not feasible.

Intervention

Each patient received the 2 ventilatory modes in a randomised order while in prone position. They received each type of ventilation for 2 hours. The first hour was considered a “wash-out” period and the second hour was used for recording and analysis (shown in supplementary Fig. 1). All patients were equipped with TcPCO₂ (TCM4, Radiometer, Ca. USA).

Devices, settings and interfaces

For NIV-NAVA, the Servo n ventilator (Getinge, Sweden) was used in the NIV-NAVA mode with automatic leak compensation. The positive end-expiratory pressure (PEEP) was set to 5 cm H₂O, with an initial NAVA level of 1.5 cm H₂O/μV. This value was consistent with two previous studies: in a study among extremely premature infants, the mean post-extubation breakpoint value – i.e. the NAVA level corresponding to the optimal support level - was 1.6 during NIV-NAVA [15] ; in a previous cross-over trial, the median NAVA level at baseline was 1.5.[12] Adjustments of the NAVA level are detailed in the supplement. Back up ventilation was set at a respiratory rate of 50/min, inspiratory time at 0.4 sec, and an inspiratory pressure of 17 cm H₂O (12 above PEEP). Apnoea time was set at 2 seconds, based on previous publication.[16] The interface was an appropriately sized Easy Flow nCPAP nasal mask (Stephan, Gackebach, Germany).

For SiPAP, the Infant Flow device (Care Fusion, USA) was set to ‘biphasic trigger’ mode. The PEEP was set to 5 cm H₂O, PIP to 10 cm H₂O and inspiratory time to 0.3 sec.[8,17] Although longer inspiratory times usually improve non-synchronised bi-level CPAP [18], this inspiratory time was chosen to best match previously published neural inspiratory times [12,19] and give more opportunities to synchronise all inspiratory efforts in the absence of an expiratory trigger. A SiPAP abdominal capsule (Graseby capsule, Care Fusion, USA) was

taped to the infant's abdomen below the ribs in order to avoid contact with the bed and to detect a proper signal, and was attached to the SiPAP transducer device. All efforts were made to optimize the abdominal capsule placement. Back up ventilation was set for an apnoea time of 10 seconds (lowest possible value) and the following settings were used: respiratory rate 50/min, inspiratory time 0.4 sec, PIP 10 cm H₂O. For back up ventilation PIP during SiPAP was set at a lower value than during NIV-NAVA. Indeed, maximal peak inspiratory pressure (PIP) of the Servo n is set by the manufacturer to 25 cm H₂O, but the machine will automatically stop pressurisation at 20 cm H₂O. This difference in PIPs between the two modes is justified by a more efficient pressure transmission during SiPAP as compared to nasal intermittent positive pressure ventilation.[20,21] The interface was an appropriately sized Infant Flow LP mask (SEBAC, France).

A heater-humidifier device MR835 (Fisher and Paykel, Auckland, New Zealand) was used for both machines. For both ventilatory modes, FiO₂ was adjusted to maintain SpO₂ between 85% and 92%, as recommended in our unit for infants below 32 weeks post-menstrual age in accordance with recommendations from the French Society of Neonatology.

The protocol was discontinued if any of the following problems occurred: an increase in FiO₂>0.2 to maintain SpO₂ within the target range; more than 2 apnoea requiring bag mask ventilation during the study period; increase in PCO₂> 15 mm Hg from baseline (either from TcPCO₂ or from blood gas); or newly observed nasal injury.

Data acquisition

At inclusion, all infants were equipped with an electrode-equipped feeding tube (Edi catheter, Getinge) to detect electric activity of the diaphragm (Edi). During NIV-NAVA, data were acquired from the Servo n ventilator using the SERVO tracker SCI software V 1.1 (Maquet Critical Care AB). During SiPAP, data were also acquired through the Servo n using the same software by connecting the circuit of the SiPAP device to the circuit of the Servo n as shown in supplementary Fig. 2.

Primary outcome

The primary outcome was the asynchrony index as previously defined in the literature [22-24] (definition and illustrations in the supplement).

Secondary outcomes

Each asynchrony, peak and minimal Edi, swing Edi, apnoea, desaturations, bradycardias, heart rate, respiratory rate, COMFORTneo score [25] and TcPCO₂ (detailed definitions in the supplement).

Statistical analysis

Based on previous publications and personal observations, the expected AIs were 20% and 70% for NIV-NAVA and SiPAP, respectively.[12,17,20,23] With 80% power and a type 1 error of 0.05 (two-sided), this would have required a total of 12 patients. To account for possible dropouts, 14 patients were planned.

Variables were described using percentages or median (IQR) values. Comparisons of primary and secondary outcomes between ventilatory modes were performed using the Wilcoxon signed-rank test. For all statistical analysis, $p < 0.05$ was considered statistically significant and R software (4.0.5) was used.

Ethics

A national ethics committee (CPP Sud-Ouest et Outre-Mer 4) approved the study on July 12th 2019. A written informed consent was obtained from parents of all participants.

RESULTS

Among 51 infants born before 28 weeks of gestation admitted to our NICU between December 2019 and March 2021 and aged 3 days or more, 14 were included with 7 patients randomised to NIV-NAVA then SiPAP and 7 patients randomised to SiPAP then NIV-NAVA (shown in Fig. 1). No patient required discontinuation of the protocol based on predefined criteria. Data were available and analysed for all patients.

Table 1 summarises the baseline characteristics of the patients. The median (IQR) gestational age at birth was 25.6 (25.3-26.4) weeks, and the median (IQR) birth weight was 755 (686-824) grams. All patients were receiving NIV-NAVA at inclusion.

Primary outcome

A median (IQR) of 4153 (3773-4236) and 3523 (3043-4151) respiratory cycles per infant were analysed during NIV-NAVA and SiPAP, respectively. The median (IQR) percentages of back up cycles were 2.4 % (1.7-2.7) and 0.0 % (0.0-0.03) during NIV-NAVA and SiPAP, respectively.

The median (IQR) asynchrony index was significantly lower in NIV-NAVA than in SiPAP (49.9% (44.1-52.6) vs 85.8% (74.2-90.9), $p < 0.001$) (Table 2, shown in Fig. 2).

Secondary outcomes

Regarding each asynchrony shown in Figure 2, median (IQR) frequencies of ineffective efforts and auto-triggering were significantly lower in NIV-NAVA than in SiPAP (3.0% (1.7-3.4) vs 32.0% (26.0-44.8), $p < 0.001$, and 10.0% (8.8-13.1) vs. 26.6% (17.2-34.4), $p = 0.004$, respectively). Median (IQR) frequencies of double triggering events were significantly lower in SiPAP than in NIV-NAVA (0.0% (0.0-0.0) vs 9.0% (4.4-12.2), $p < 0.001$). No statistically significant difference was observed between NIV-NAVA and SiPAP regarding median frequencies of premature cycling and late cycling.

Peak Edi, min Edi and swing Edi were significantly lower when infants were ventilated with NIV-NAVA as compared to SiPAP (Table 2). During NIV-NAVA, median (IQR) PIP was 11.7 (9.3-14.0) cm H₂O. Post-hoc analyses of correlation between peak Edi and delivered pressures are shown in supplementary Fig. 3.

No differences were noted between NIV-NAVA and SiPAP regarding the other secondary clinical outcomes (Table 2). Changes in TcPCO₂ over time were superimposable for the two ventilatory modes (shown in supplementary Fig. 4). No infant was reintubated within 7 days of randomisation.

DISCUSSION

In this study, NIV-NAVA dramatically improved patient-ventilator synchrony, as compared to SiPAP in extremely premature infants. The tolerance of both devices regarding physiological and comfort parameters was good during the study period.

This improvement in patient-ventilator synchrony was expected, due to the known performances of NIV-NAVA to detect respiratory efforts in extremely premature infants.[12] Lee *et al.* observed an AI of 19.7% in NIV-NAVA, which is lower than in our study.[12] However, these authors collected data for 5 minutes, whereas we performed 60 minutes recordings that might more appropriately reflect patient-ventilator synchrony in extremely premature infants who have a highly changing breathing pattern.[26] In addition, we observed a relatively high rate of premature cycling in NIV-NAVA, defined as a ventilator's inspiratory time shorter than the neural inspiratory time. Although this definition is common in the adult population [27] it might not be appropriate for extremely premature infants who frequently have very short neural inspiratory times.[28] Indeed in neonates, alternative definitions for late or premature cycling have been proposed.[29] Thus, in our study, the AI during NIV-NAVA might have been increased by this item, which might not be clinically relevant in the studied population.

Previous studies on SiPAP have shown that the Graseby abdominal capsule could detect 72% to 82% of infants' inspiratory efforts.[6,17] This item mirrors the rate of ineffective efforts, which was 32.0% during SiPAP in our study, suggesting that we had no major issues regarding the capsule's placement as compared to previous studies. Asynchrony has many components and our study also evaluated other items that are frequently used in the literature. Thus, in our study, the overall AI was very high in SiPAP, as compared to the sole item of ineffective efforts.

It is hard to know if the difference in apnoea time for back up ventilation between ventilatory modes influenced our results, although these periods were not frequent and removed from the analysis. For SiPAP we used the shortest available apnoea time (10 sec) and for NIV-NAVA the most appropriately documented apnoea time (2 sec). We aimed at using each

ventilatory mode with optimal settings, but also by taking into account the limits of each device in order to be representative of bedside daily care.

To date, it is unknown whether synchronising non-invasive ventilation offers clinical benefits, especially regarding the chances of successful extubation. Although our study could not address this outcome, it suggests that NIV-NAVA can deliver efficiently synchronised non-invasive ventilation. We consider that NIV-NAVA should be the preferred respiratory mode to conduct future prospective trials on the effectiveness and safety of synchronised non-invasive ventilation in this population, as prompted by a meta-analysis from 2017.[30] Mean peak and swing Edi were lower in NIV-NAVA than in SiPAP, which might reflect a decreased work of breathing.[26,31] This decrease in work of breathing could be attributed to the improved synchronisation during NIV-NAVA and to the ability of NIV-NAVA to deliver a variable PIP, whereas PIP was more constant when using SiPAP. Although this PIP could be adjusted to maintain TcPCO₂ within the target range during SiPAP, this adjustment was not performed on a breath-by-breath basis as allowed in NIV-NAVA.

Our study has several strengths. First, this is the first study to our knowledge to compare NIV-NAVA with SiPAP, following the current recommendations on randomised cross-over trials.[32] Second, we compared NIV-NAVA to a respiratory support that is broadly disseminated in NICUs and that uses variable flow, which is considered one of the most efficient positive pressure device in extremely premature infants. Third, we provided detailed procedures to adjust both ventilatory modes, permitting reproducibility of these practices in daily care.

There are some limitations to the present study. First, this study was a monocentric study with a small sample size. Second, patients included in this study had stable respiratory conditions, with very few cardiorespiratory episodes recorded, limiting the possibility to detect differences regarding desaturations, bradycardia and/or apnoea. Third, we used masks because it is probably the most efficient interface for non-invasive ventilation in premature infants.[33] Whether our results apply to other interfaces is unknown. Fourth, we did not

collect information on SpO₂ or change in FiO₂ and thus were not able to analyse oxygenation in details.

CONCLUSION

This study showed that NIV-NAVA markedly improves patient-ventilator synchrony as compared to SiPAP. Future studies should integrate NIV-NAVA as the preferred mode of synchronised non-invasive ventilation in premature infants.

STATEMENTS

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Statement of Ethics

Study approval statement This study protocol was reviewed and approved by CPP Sud-Ouest et Outre-Mer 4, a national ethics committee (approval number CPP2019-05'-041a).

Consent to participate statement: a written informed consent was obtained from both parents of all participants.

Conflict of Interest Statement

All authors have no conflicts of interest to declare. Dr Carteaux reports personal fees from Air Liquide Medical System, Dräger, Medtronic and Löwenstein, outside the submitted work.

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Author Contributions

Charles Treussart, Fabrice Decobert, Laura Bourgoïn, Claude Danan, Gilles Dassieu, Guillaume Carteaux, Armand Mekontso-Dessap, Bruno Louis and Xavier Durrmeyer initiated and designed the protocol. Charles Treussart and Bruno Louis participated in the data collection. Manon Tauzin and Bruno Louis performed all data analysis, and Xavier Durrmeyer validated them. Charles Treussart wrote the first draft. All authors participated in data interpretation and reviewing of the manuscript. All authors approved the final manuscript.

Data Availability Statement

The procedures carried out with the French data privacy authority (CNIL, Commission nationale de l'informatique et des libertés) do not provide for the transmission of the database. Consultation by the editorial board or interested researchers may nevertheless be considered, subject to prior determination of the terms and conditions of such consultation and in respect for compliance with the applicable regulations.

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FIGURE LEGENDS

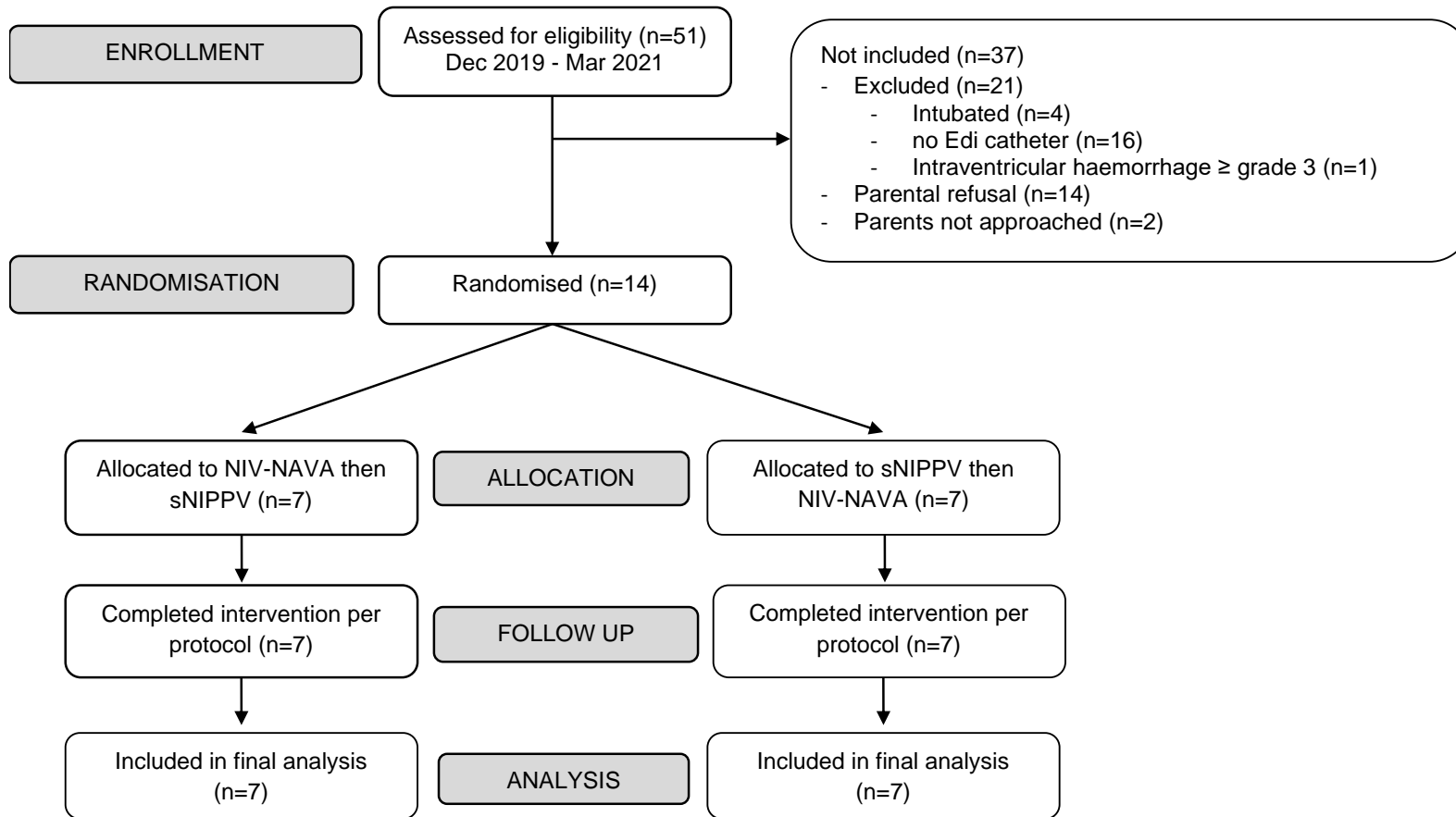
Fig. 1: Population flowchart

Fig. 2: Asynchrony index and incidence of each asynchrony during NIV-NAVA and SiPAP

Legend: Boxes represent the 1st and 3rd quartiles of collected values during NIV-NAVA (red) and SiPAP (blue). The bar within the box indicates the median value. Vertical bars indicate values' range within 1.5 times the interquartile range. Dots indicate values exceeding 1.5 times the interquartile range value.

Abbreviations: NIV-NAVA, non-invasive neurally adjusted ventilatory assist; SiPAP, synchronised intermittent positive airway pressure; sNIV, synchronised non-invasive ventilation.

Figure 1. Population flowchart



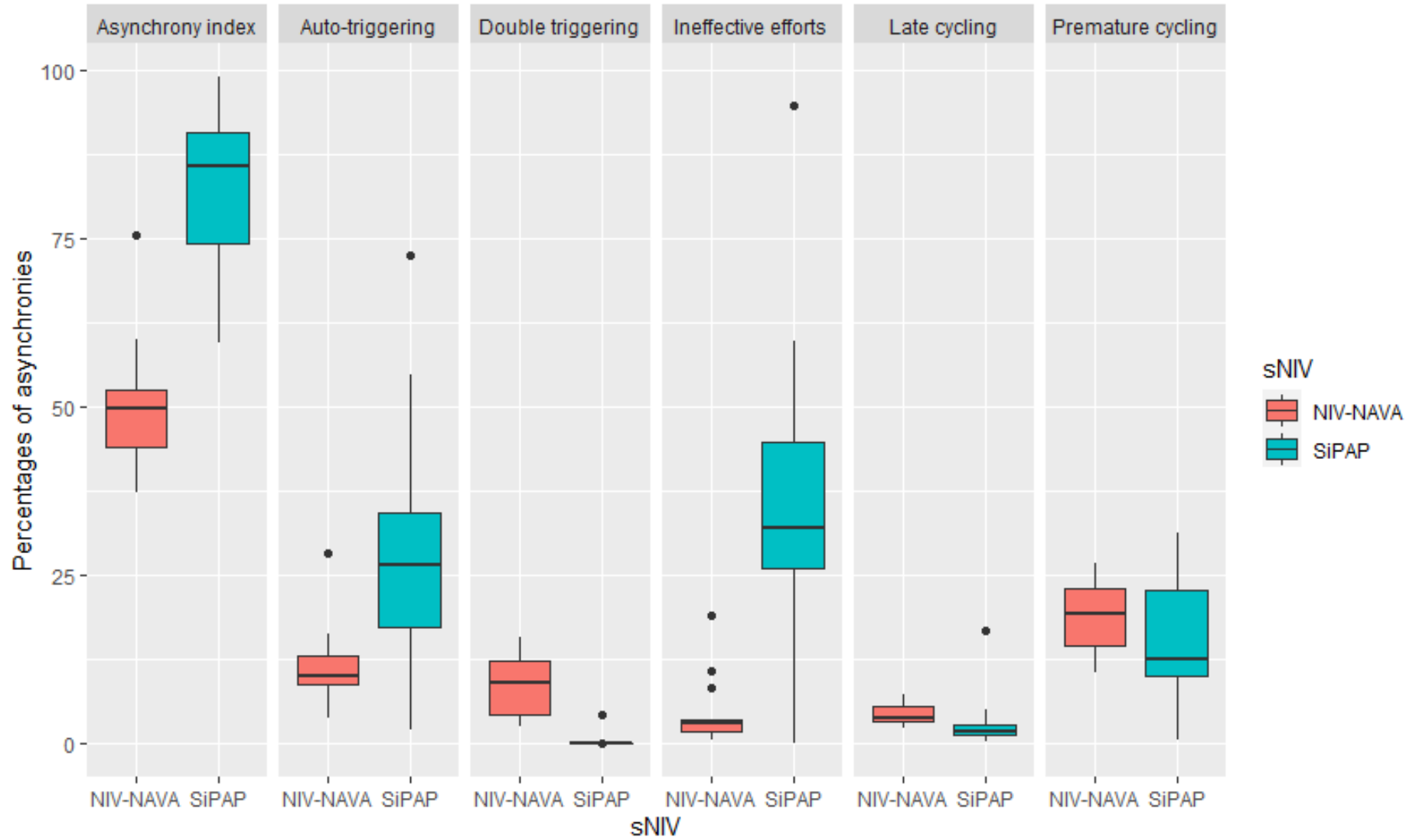


Table 1. Patients' baseline characteristics and characteristics at inclusion

Baseline characteristics	N (%) or median [IQR] (min-max)
Male sex	8 (57)
Gestational age at birth (weeks)	25.6 [25.3, 26.4] (24.1-27.4)
Birth weight (grams)	755 [686, 824] (490-955)
Antenatal steroids	
Complete (2 doses)	12 (86)
Incomplete (1 dose)	2 (14)
Delivery route	
Vaginal delivery	7 (50)
Caesarean section	7 (50)
5-min Apgar score	8 [5, 10] (3-10)
Exogenous surfactant administration	
1 dose	6 (43)
2 doses	7 (50)
None	1 (7)
Clinical characteristics at inclusion	
Postmenstrual age (weeks)	29.8 [29.0, 30.7] (28.4-31.9)
Postnatal age (days)	26.5 [19.8, 33.8] (15-47)
Weight (grams)	1105 [958, 1140] (885-1460)
Cumulated time of invasive ventilation (days)	3.5 [1.0, 11.5] (0-35)
Cumulated time of non-invasive ventilation (days)	18.0 [14.0, 22.8] (11-30)
Ventilatory mode	
NIV-NAVA	14 (100)
Nasal interface	
RAM cannulae	9 (64)
Easyflow mask	3 (22)
Easyflow prongs	2 (14)
Ventilation parameters	
NAVA level (cmH ₂ O/ μ V)	1.5 [0.6, 1.5] (0.5-2.5)
PEEP (cm H ₂ O)	7 [5.2, 7] (5-7)
FiO ₂ (%)	22 [21, 23] (21-28)

Abbreviations: NIV-NAVA, non-invasive neurally adjusted ventilatory assist; PEEP, positive end-expiratory pressure

Table 2. Primary and secondary outcomes

Outcomes	NIV-NAVA	SiPAP	p value*
Primary outcome			
Asynchrony index, median % (IQR)	49.9 (44.1- 52.6)	85.8 (74.2-90.9)	<0.001
Secondary outcomes			
Edi values (μV), median (IQR)			
Swing Edi	5.4 (4.2-7.6)	7.6 (4.3-10.8)	0.007
Peak Edi	7.7 (6.1-9.9)	11 (6.7-14.5)	0.006
Min Edi	2.0 (1.4-2.9)	3.2 (1.8-4.7)	0.013
Heart rate (bpm), median (IQR)			
Beginning of recording	164 (150.8-170)	160.5 (160-163.8)	0.9
End of recording	162 (155-165)	163.5 (155.2-170)	0.3
Respiratory rate (breaths per min), median (IQR)			
Beginning of recording	50 (40-60)	60 (44-70)	0.06
End of recording	55 (46-62)	52 (45-64)	0.9
COMFORTneo score, median (IQR)			
Beginning of recording	11 (11-12)	11 (11-11)	0.3
End of recording	11.5 (11-12)	11 (11-11)	0.3
Cardiorespiratory episodes, median n (min-max)			
Apnoeic episodes	0 (0-2)	0 (0-7)	0.09
Desaturation < 80%	0 (0-11)	1 (0-7)	0.9
Bradycardia < 100 bpm	0 (0-1)	0 (0-1)	0.1
Bag-mask ventilation	0	0	1.0

* Wilcoxon signed-rank test

Patient-ventilator synchrony in extremely premature neonates during non-invasive neurally adjusted ventilatory assist or synchronised intermittent positive airway pressure: a randomised crossover pilot trial - Supplemental data

- Adjustments of NAVA level during NIV-NAVA

- Supplementary Fig. 1: Crossover design

- Supplementary Fig. 2: Data acquisition set-up during SiPAP

- Primary outcome definition and assessment

- Illustrations of asynchrony events

- Definitions of secondary outcomes

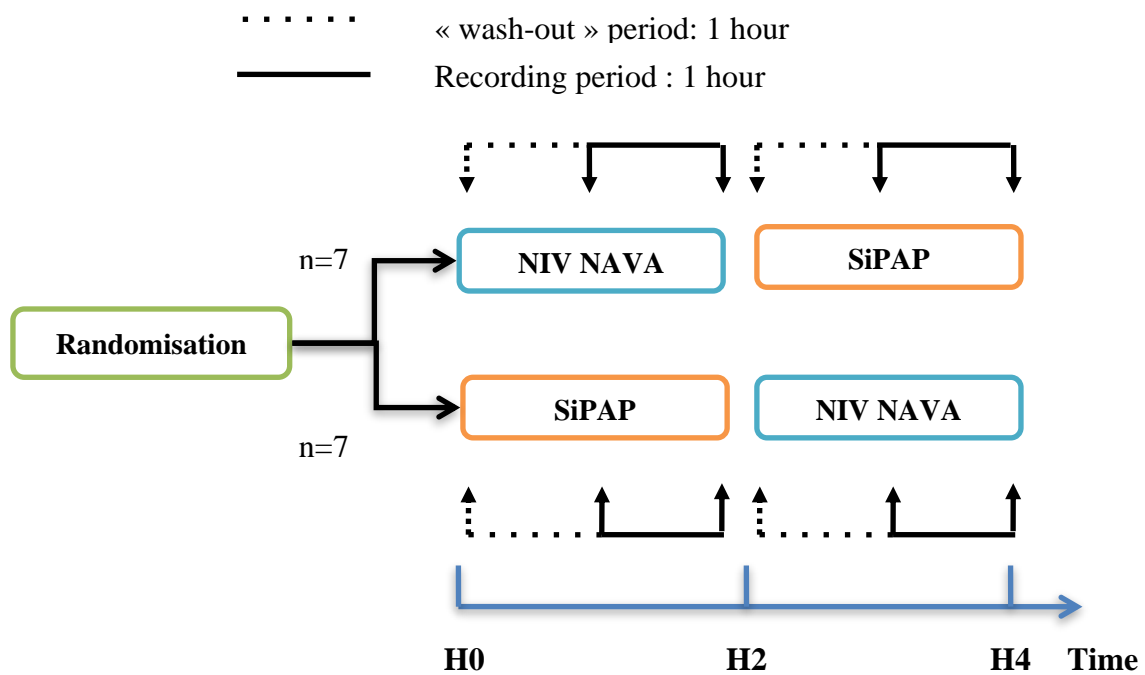
- Supplementary Fig. 3: Correlations between peak Edi and PIP or PIP-PEEP (pressure support)

- Supplementary Fig. 4: TcPCO₂ changes over time during NIV-NAVA and SiPAP

Adjustments of NAVA level during NIV-NAVA

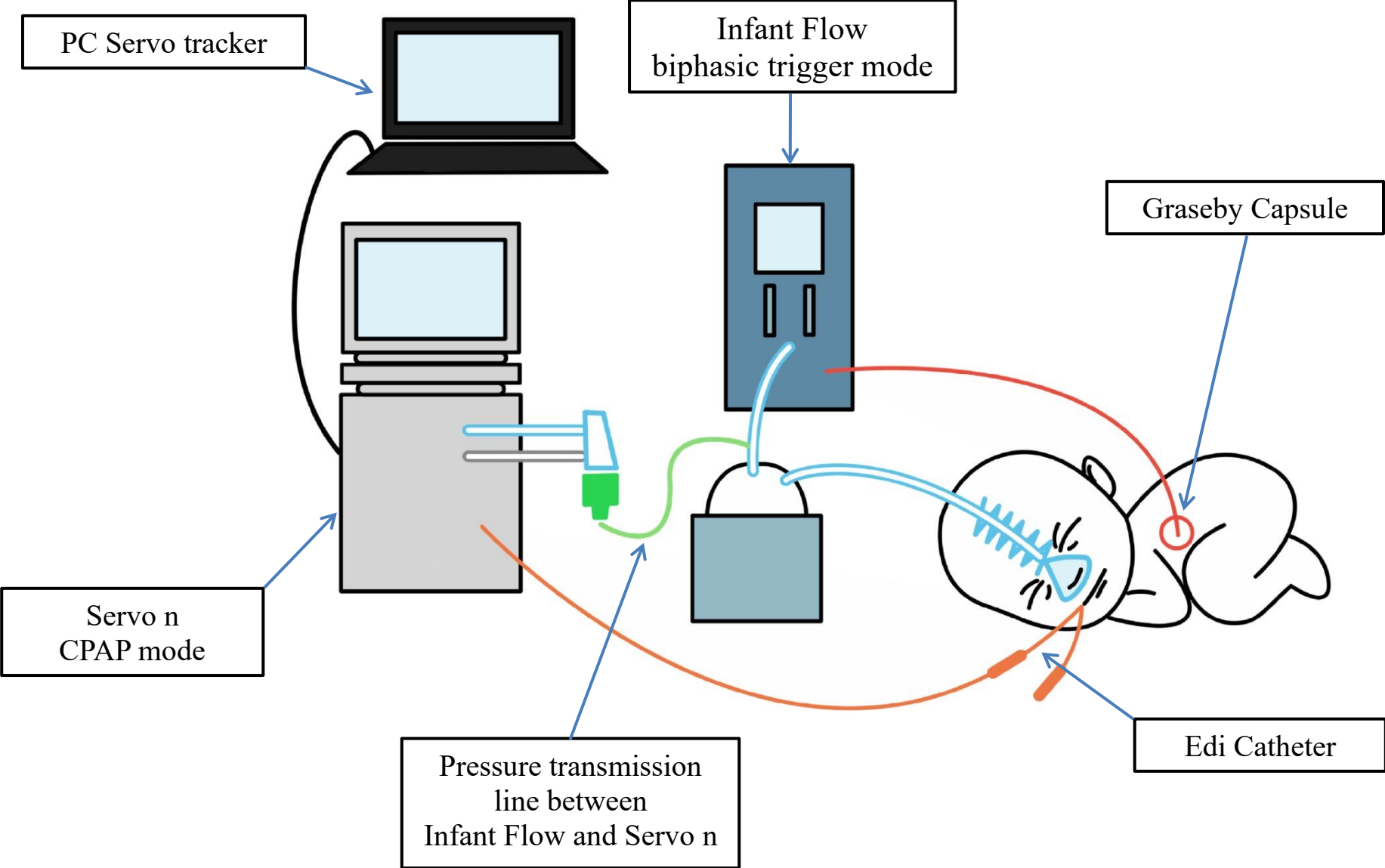
During NIV-NAVA, the NAVA level was adjusted by 0.2 increments or decrements by the attending physician in order to maintain TcPCO₂ values within a +/- 10 mm Hg range of the baseline value. The threshold for Edi detection was at 0.4 μV, the lowest possible value.

Supplementary Fig. 1: Crossover design



Legend: H0, inclusion; H2, inclusion +2 hours; H4, inclusion +4 hours. NIV NAVA, non-invasive neurally adjusted ventilatory assist; SiPAP, synchronised intermittent positive airway pressure.

Supplementary Fig. 2: Data acquisition set-up during SiPAP



Primary outcome definition and assessment

Asynchrony index was defined using the following definitions for asynchronies

- Ineffective effort (IE): presence of an inspiratory electromyographic signal not followed by pressurisation;
- Late cycling (LC): a cycle with a ventilator's inspiratory time longer than twice the patient's neural inspiratory time;
- Premature cycling (PC): a cycle with a ventilator's inspiratory time shorter than the neural inspiratory time;
- Double triggering (DT): two ventilator-delivered cycles triggered by one neural inspiration;
- Auto-triggering (AT): a cycle delivered by the ventilator in the absence of Edi signal occurring before the set apnoea time.

Asynchrony Index (AI) was expressed as a percentage using the following formula:

$$AI = [(IE + LC + PC + DT + AT) / (\text{neural RR} + AT)] \times 100.$$

These different parameters were automatically detected by an in-house software programmed in Matlab language (Matlab R2019b, MathWorks Inc., Ma. USA) that was being fed by the signals directly recorded by the ventilator.

The procedure of automatic detection consisted in:

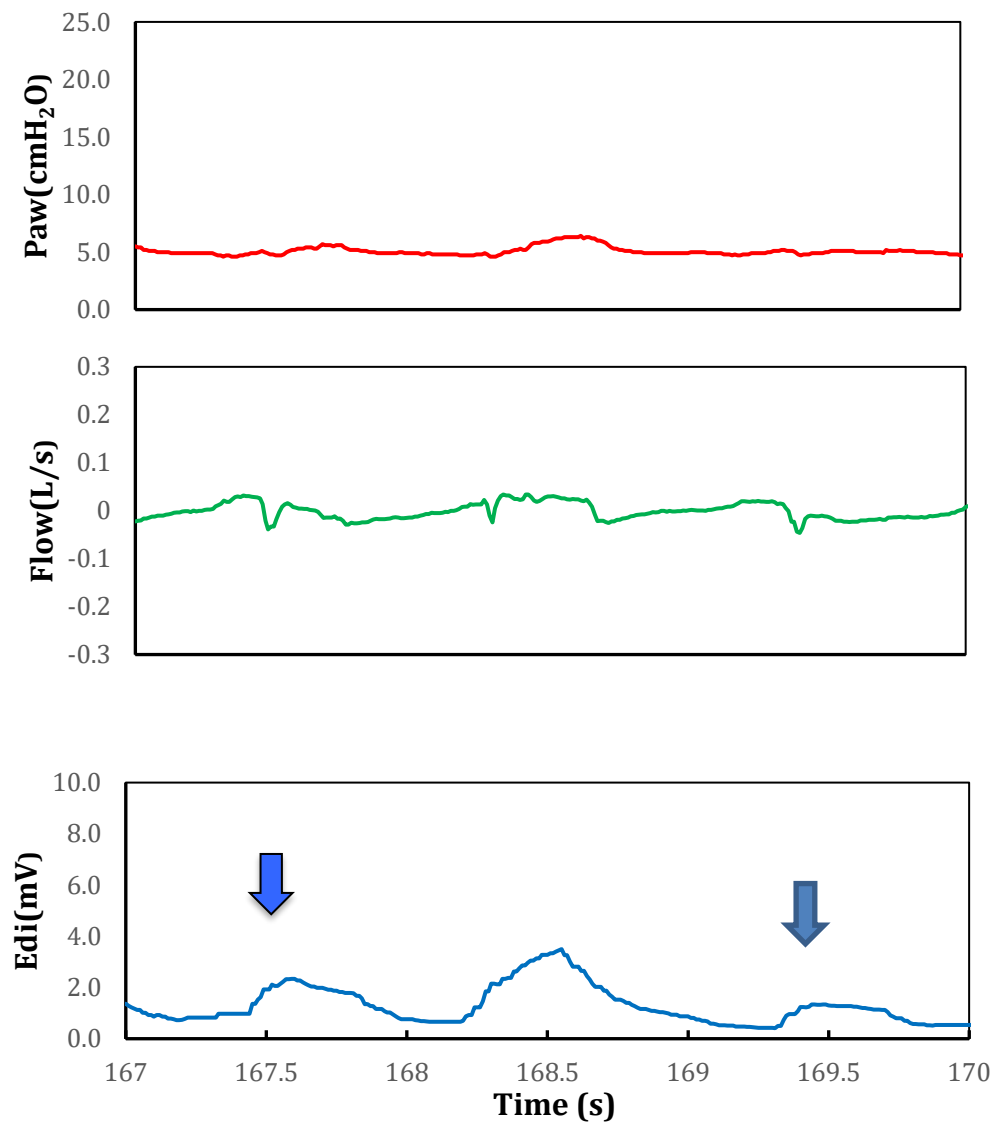
- 1) Defining the start of the respiratory cycle from the flow curve by detecting the moment when the flow passes from a negative (expiration) to a positive value (inspiration).
- 2) Detecting around this flow-based start point the point in Edi curve corresponding to a local minimum of Edi followed by a positive and significant slope after this local minimum of Edi. This increase in the Edi slope was considered the start of neural inspiration.

To limit aberrant results during data analyses we defined several thresholds within the algorithm for the following parameters: absolute minimum flow, minimum V_t , minimum slope for E_{di} , maximum temporal delay before the inspiration start to detect the pseudo local minimum E_{di} , maximum temporal delay after the inspiration start to detect the pseudo local minimum of E_{di} , minimum pressure variation, temporal delay for the detection of backup ventilation according to the set apnoea time. These different parameters were chosen to have a global agreement between the clinician interpretation and the automated results in various situations identified by clinicians.

For the analysis of the NIV-NAVA ventilatory mode, periods of rescue ventilation using intermittent positive pressure ventilation (NIV-PC mode) after a 2 seconds apnoea were removed from the analysis in order to avoid false auto-triggering events. The same was applied during SiPAP after 10 seconds apnoea.

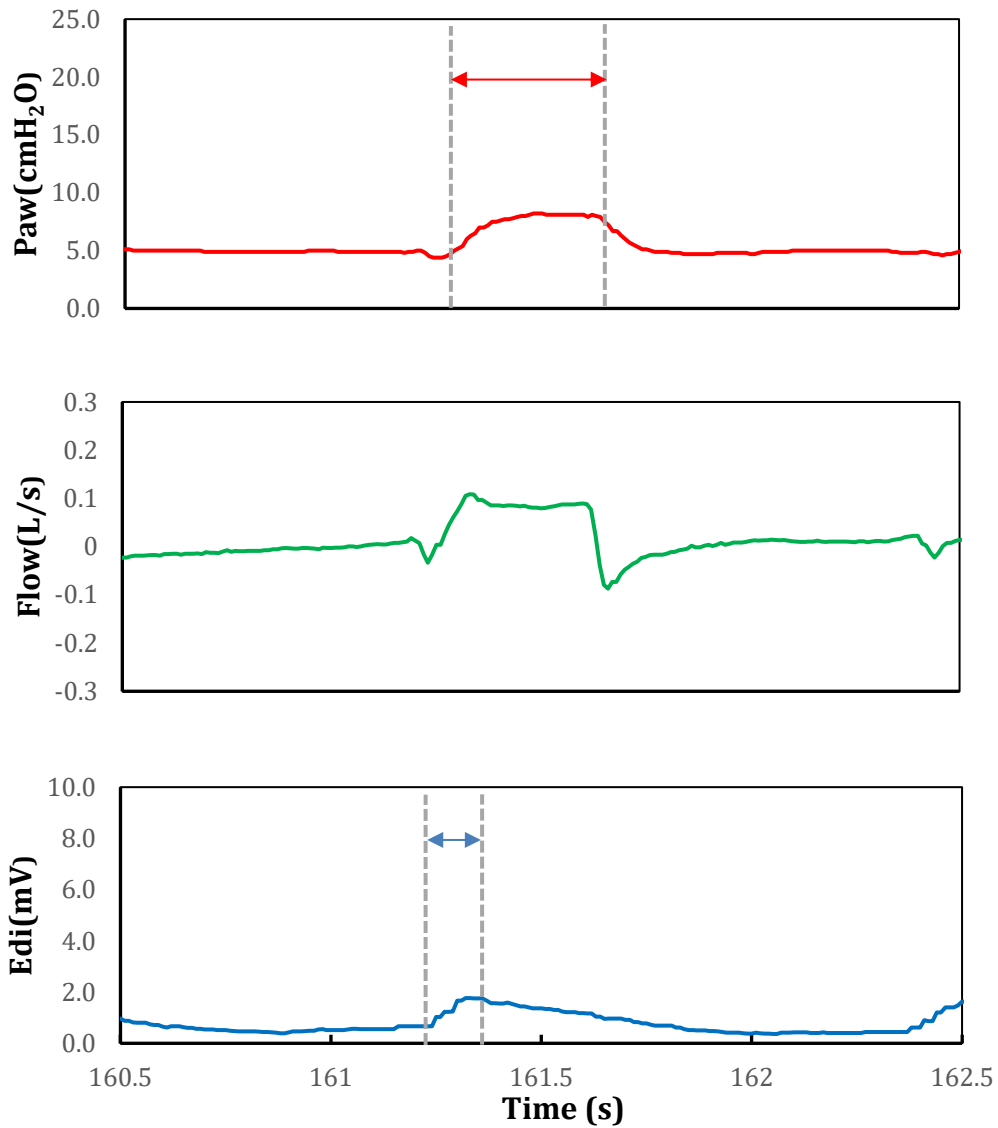
Illustrations of asynchrony events

Ineffective effort



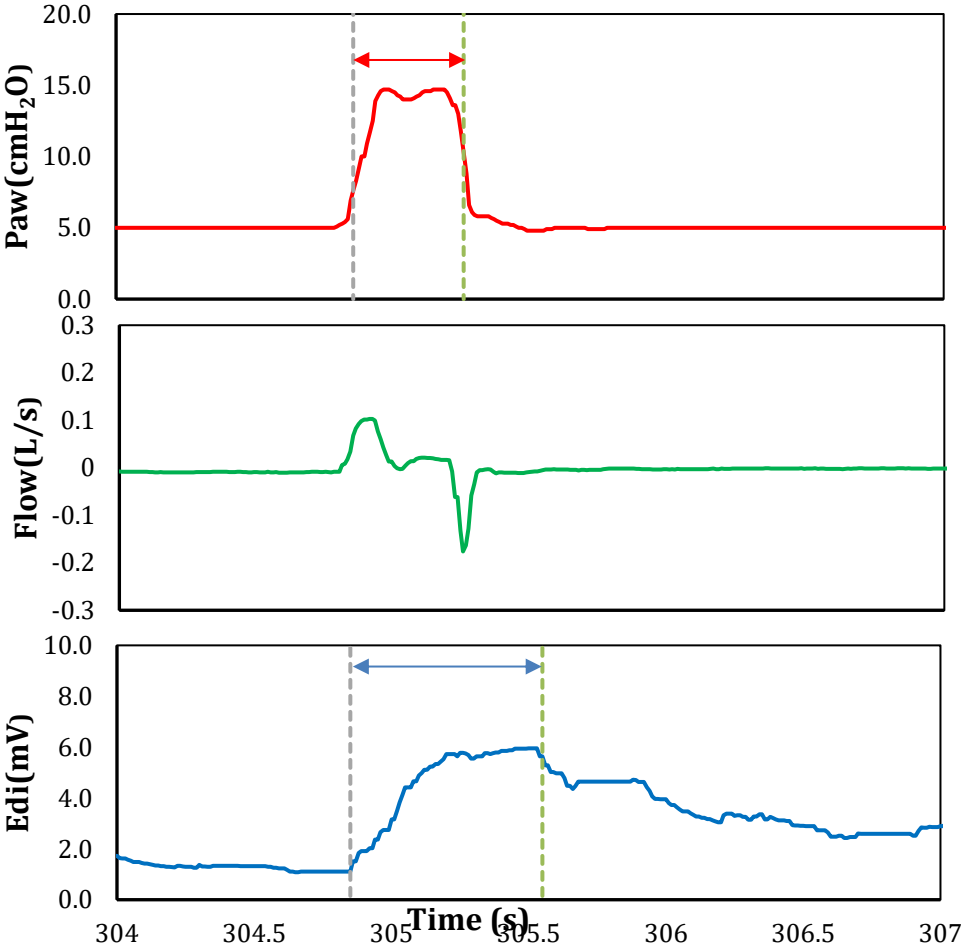
An Edi signal (blue curve and arrows) is not followed by pressurisation (flat red curve).

Late cycling



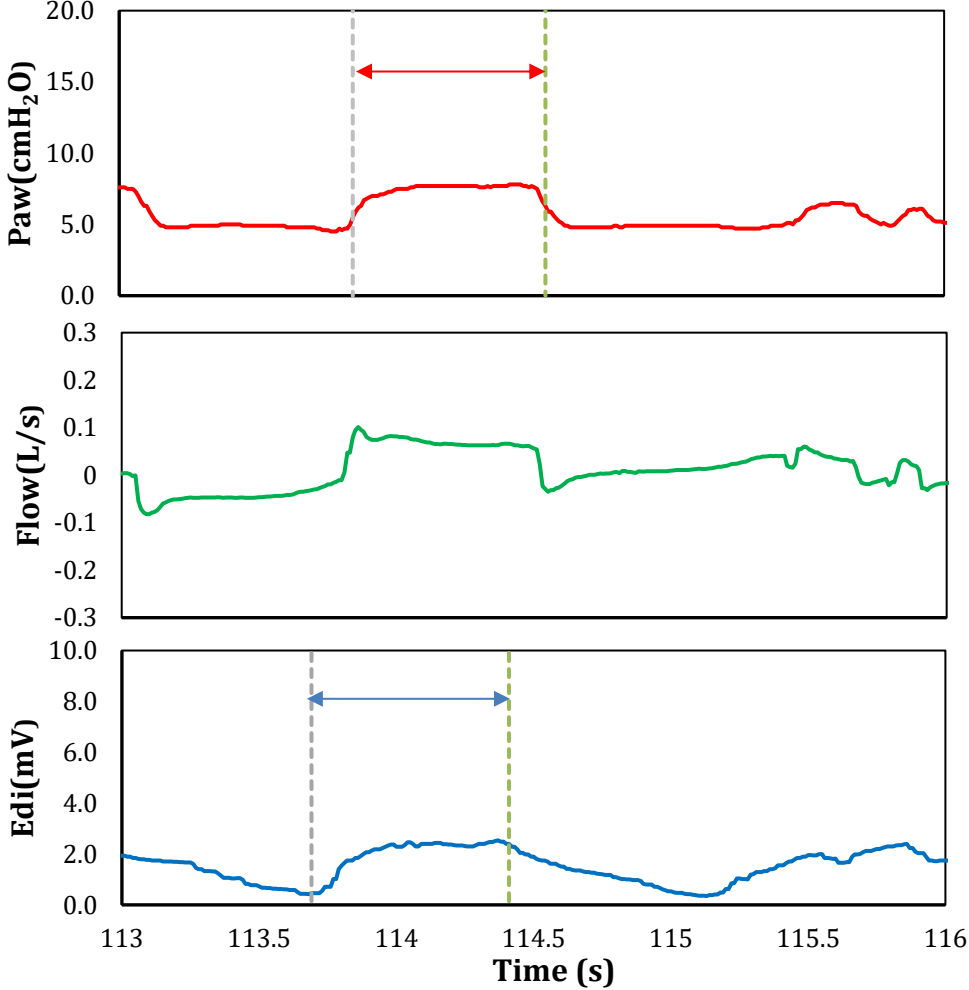
The ventilator's inspiratory time (red double arrow) is at least twice longer than the neural inspiratory time (blue double arrow).

Premature cycling (1)



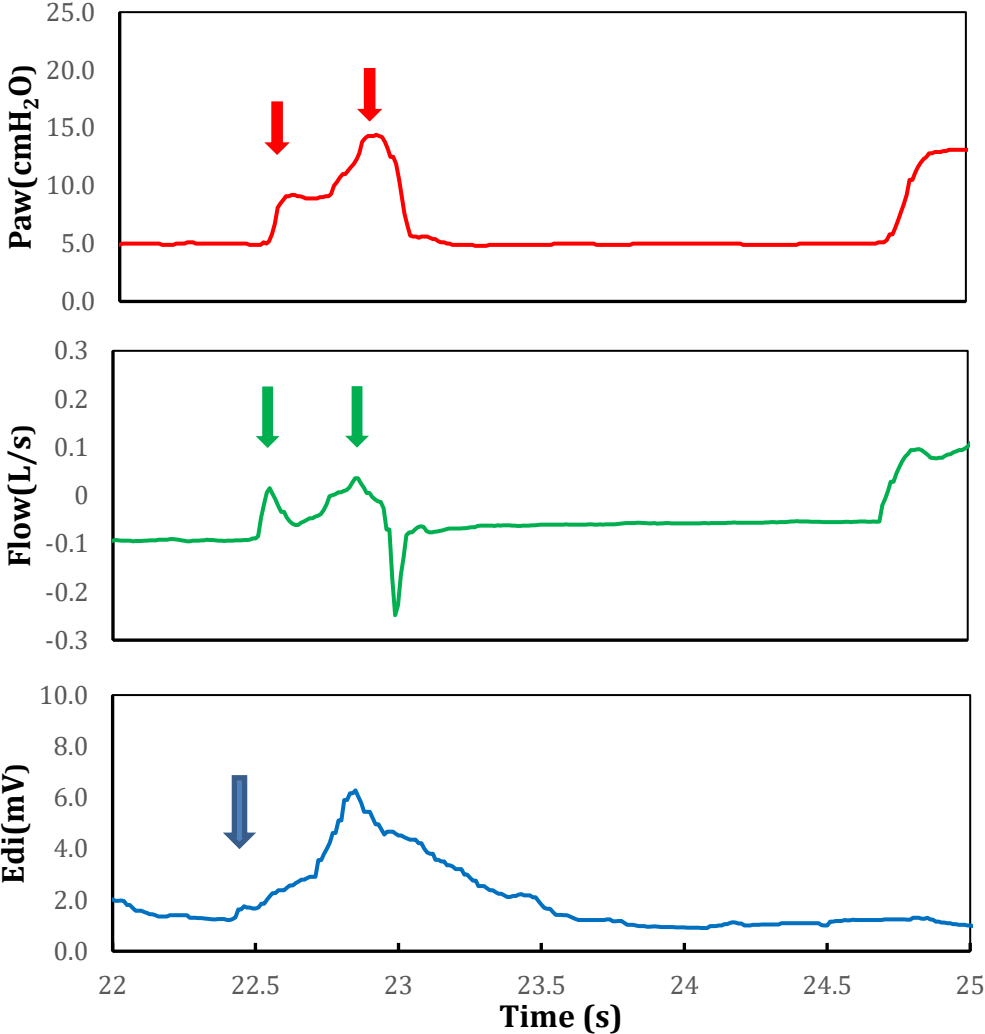
The ventilator's inspiratory time (red double arrow) is shorter than the neural inspiratory time (blue double arrow) due to premature interruption of pressurisation.

Premature cycling (2)



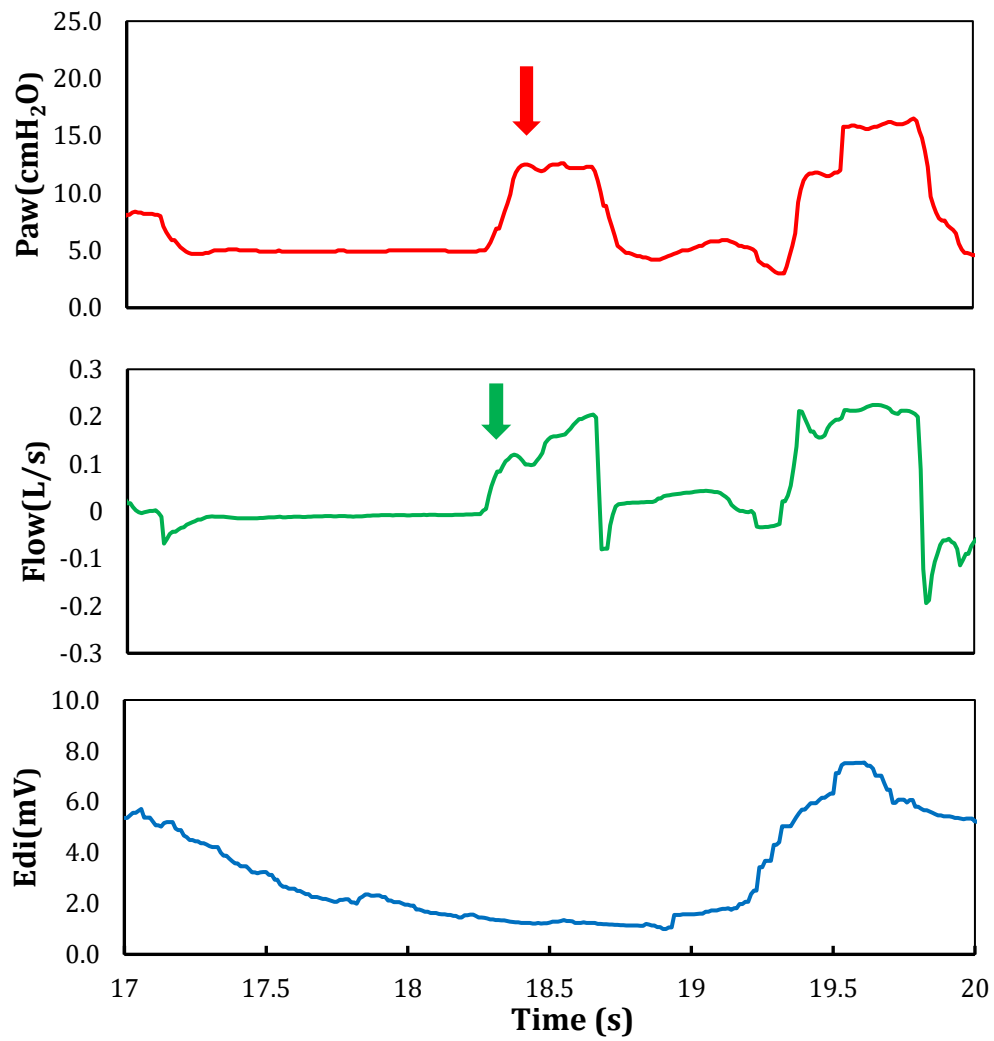
The ventilator's inspiratory time (red double arrow) is shorter than the neural inspiratory time (blue double arrow) due to an inspiratory trigger delay.

Double triggering



A single Edi signal (blue arrow) triggers 2 increases in inspiratory flow (green curve and arrows) and 2 increases in inspiratory pressure (red curve and arrows).

Auto-triggering

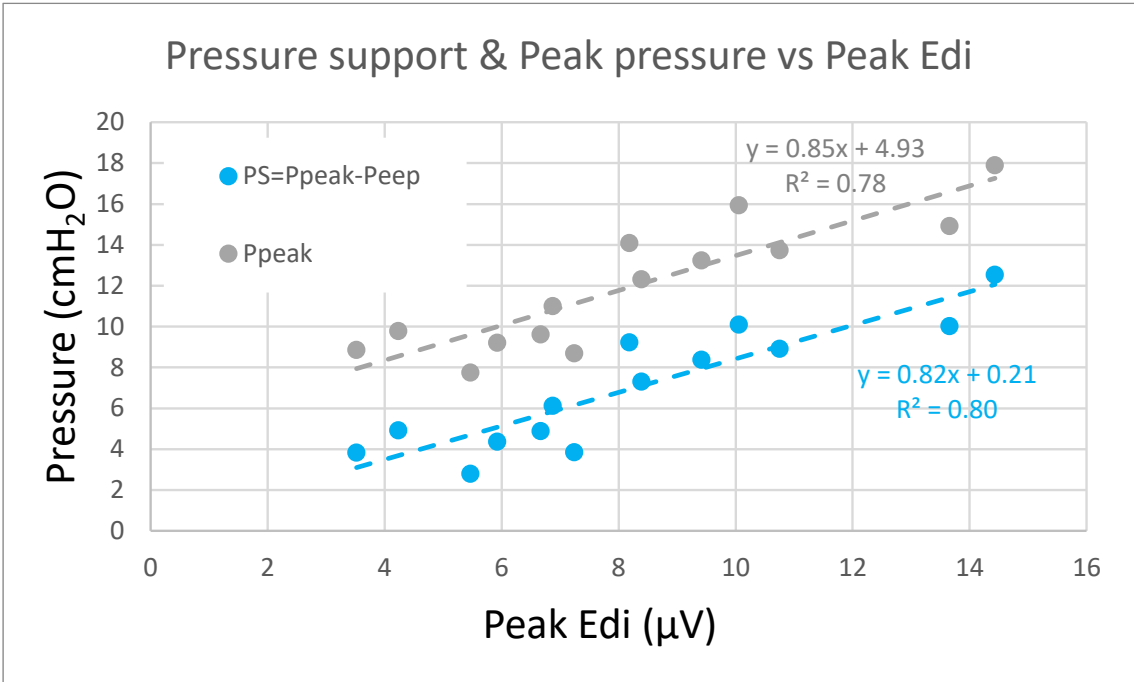


The ventilator delivers an inspiratory flow (green curve and arrow) and pressure (red curve and arrow) not triggered by an Edi signal (flat blue curve).

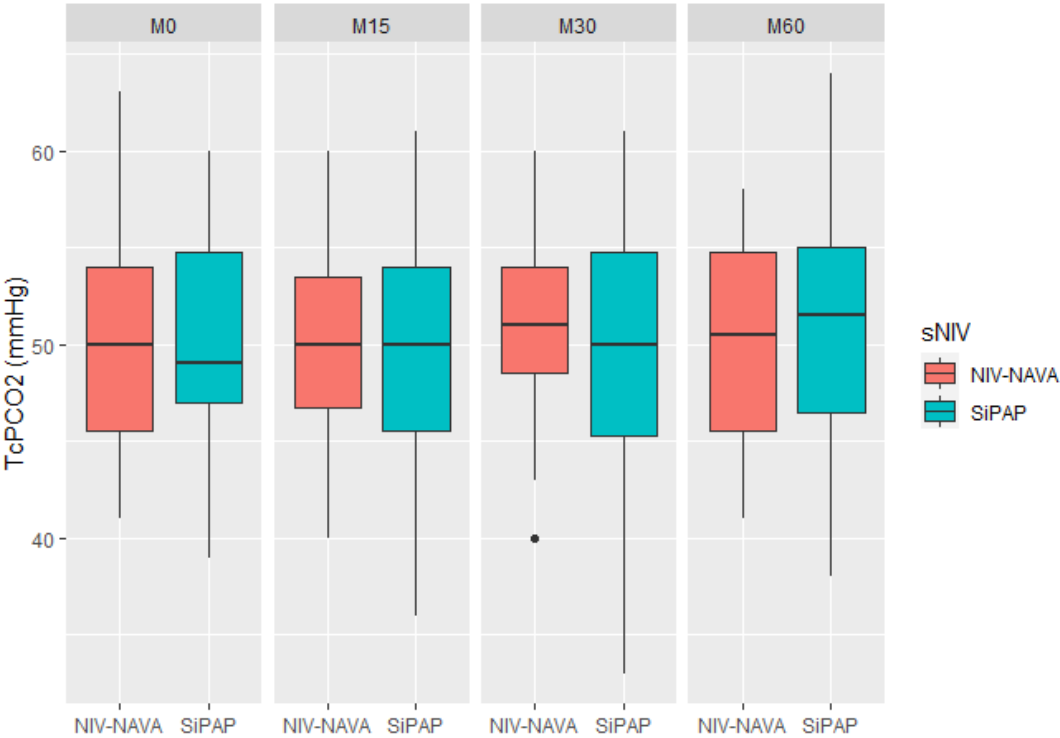
Definitions of secondary outcomes

During the whole recording periods for each ventilatory mode, the following parameters were collected and analysed: incidence of each asynchrony; median peak Edi; median minimal Edi; median swing Edi defined as the difference between peak and minimal Edi values for each cycle; number of apnoeic episodes lasting more than 20 seconds; number of desaturations below 80%; number of bradycardias < 100 bpm, and number of apnoea requiring bag-mask ventilation. The following parameters were collected and analysed at the beginning and end of each recording period: heart rate, respiratory rate, and COMFORTneo score assessed by the nurse. TcPCO₂ was collected at the beginning of the recording and every 15 minutes during the recording.

Supplementary Fig. 3: Correlations between peak Edi and PIP or PIP-PEEP (pressure support)



Supplementary Fig. 4: TcPCO2 changes over time during NIV-NAVA and SiPAP



Boxes represent the 1st and 3rd quartiles of collected values during NIV-NAVA (red) and SiPAP (blue). The bar within the box indicates the median value. Vertical bars indicate values' range within 1.5 times the interquartile range. Dots indicate values exceeding 1.5 times the interquartile range value.

M0 denotes the beginning of the recording, M15, M30 and M60 denote 15, 30 and 60 minutes time-points after the beginning of the recording, respectively.

Abbreviations: TcPCO₂, transcutaneous partial CO₂ pressure; NIV-NAVA, non-invasive neurally adjusted ventilatory assist; SiPAP, synchronised intermittent positive airway pressure; sNIV, synchronised non-invasive ventilation.