Respiratory and haemodynamic effects of 6h-pronation in neonates recovering from respiratory distress syndrome, or affected by acute respiratory distress syndrome or evolving bronchopulmonary dysplasia: a prospective, physiological, crossover, controlled cohort study

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Summary

Background Pronation ameliorates oxygenation in adults with acute respiratory distress syndrome (ARDS); the effect in neonates with ARDS or other types of respiratory failure is unknown. We aimed to verify if pronation has similar respiratory and haemodynamic effects in three common types of neonatal respiratory failure.

Methods Prospective, physiologic, crossover, quasi-randomised, controlled cohort study performed in a tertiary academic neonatal intensive care unit. We enrolled neonates with: 1) recovering respiratory distress syndrome (RDS, mild restrictive pattern); 2) neonatal ARDS (NARDS, severe restrictive pattern); or 3) evolving bronchopulmonary dysplasia (BPD), that is chronic pulmonary insufficiency of prematurity (mixed restrictive/obstructive pattern). Neonates with other lung disorders, malformations or haemodynamic impairment were excluded. Patients were started prone or supine and then shifted to the alternate position for 6h; measurements were performed after 30' of "wash out" from the positioning and at the end of 6h period. Primary outcomes were respiratory ($PtcCO_2$, modified ventilatory index, $PtcO_2/FiO_2$, SpO_2/FiO_2, oxygenation index, ultrasound-assessed lung aeration) and haemodynamic (perfusion index, heart rate, arterial pressure, cardiac output) parameters.

Findings Between May 1st, 2019, and May 31st, 2021, 161 participants were enrolled in this study, and included in the final analysis. Pronation improved gas exchange and lung aeration (p always <0.01) and these effects were overturned in the alternate position, except for lung aeration in NARDS where the improvement persisted. The effects were greater in patients recovering from RDS than in those with evolving BPD than in those with NARDS, in this order (p always <0.01). Pronation produced a net recruitment as lung ultrasound score decreased in patients shifted from supine (16.9 (standard deviation: 5.8)) to prone (14.1 (standard deviation: 3.3), $p < 0.01$) and this reduction correlated with oxygenation improvement. Haemodynamic parameters remained within normal ranges.

Interpretation 6h-pronation can be used to improve gas exchange and lung aeration in neonates with recovering RDS, evolving BPD or NARDS without relevant haemodynamic effects.

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Keywords: Prone; Supine; Newborn; Infant; Respiratory failure; Gas exchange; Lung ultrasound

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Research in context

Evidence before this study

Evidence searched on PubMed (on Oct 15, 2022), with the following string ("pronate" [All Fields] OR "pronated" [All Fields] OR "pronating" [All Fields] OR "pronation" [MeSH Terms] OR "pronation" [All Fields] OR "pronations" [All Fields] OR "pronator" [All Fields] OR "pronators" [All Fields]) AND ("infant, newborn" [MeSH Terms] OR ("infant" [All Fields] AND "newborn" [All Fields]) OR "newborn infant" [All Fields] OR "neonatal"[All Fields] OR "neonate" [All Fields] OR "neonates" [All Fields] OR "neonatality" [All Fields] OR "neonatals" [All Fields] OR "neonates" [All Fields]) without language or date limitations. We found 10 old studies, with very short pronation on small groups of neonates with mixed gestational ages, entry criteria, diagnoses, and clinical severities, thus without a clear classification of their respiratory pathophysiology. These studies showed that pronated neonates have better respiratory parameters, reduced work of breathing and less apnoea. A meta-analysis detected high inconsistency between the studies and low-quality evidence. The importance of time to obtain significant effects on lung aeration and oxygenation, as demonstrated in adults, had not been considered and haemodynamics during neonatal pronation had never been studied.

Added value of this study

Our findings increase the knowledge because, they represent the first neonatal data about pronation obtained: *1)* for a long time period (i.e.: 6h, actually the longest so far); *2)* using coupled ultrasound-assessed lung aeration, multiple gas exchange and haemodynamic measurements; *3)* in patients classified per their respiratory pathophysiology using modern critical care definitions (recovering RDS, neonatal ARDS, evolving BPD, that is chronic pulmonary insufficiency of prematurity in the first weeks of life).

Implications of all the available evidence

6h of pronation can be provided to improve gas exchange and lung aeration in neonates recovering from RDS after surfactant replacement, in those with evolving BPD and in those affected by neonatal ARDS.

Introduction

Prone positioning has been actively studied in recent years and is considered an effective therapy for severe acute respiratory distress syndrome (ARDS) in adults,[1] as it improves oxygenation through several mechanisms.[1,2] First, there is a more homogeneous inflation distribution resulting in a steadier gas/tissue ratio, which allows a more evenly distributed transpulmonary pressure. Therefore, the energy provided by mechanical ventilation will also be more uniformly distributed, thus reducing the risk of ventilation-induced lung injury. Second, there is a decrement in chest wall compliance compared to the supine position, which facilitates a more homogeneous ventilation, particularly in ventral and para-diaphragmatic zones. Third, because of the lung tissue shape and distribution, pronation can produce a net positive difference between the recruitment and the de-recruitment of the dorsal and ventral lung zones, respectively, which results in a lower shunt fraction, as the lung perfusion is unchanged; more in general this mechanism may improve ventilation/perfusion matching. Conversely, in adults, prone ventilation seems to lack any haemodynamic side effect,[3,4] despite it could theoretically reduce venous return or peripheral perfusion and neonates could be more susceptible because of their transitional circulation. Through these mechanisms, if pronation is applied for several hours per day, in adults, mortality can be significantly reduced, even in patients needing extracorporeal life support.[5–7]

The current pandemics has spread the use of pronation since it is a relatively simple and inexpensive therapy. Although prone positioning is obviously easier to perform in neonates than in adults, scanty data are available about its effects on critically ill neonates: ventilation distribution has been studied only for short periods, in small groups of babies and without the latest monitoring techniques, whereas haemodynamics had never been investigated.[8–11] Furthermore, these studies did not consider recently acquired important concepts of pathophysiology, such as the distinction between neonates with different types of respiratory failure and its severity. For instance, preterm neonates recovering from respiratory distress syndrome (RDS, due to primary surfactant deficiency) after surfactant replacement have a mild restrictive pattern; conversely, patients with neonatal ARDS (NARDS) have a more restrictive disorder and are more similar to adults with ARDS.[12] Preterm infants may experience chronic pulmonary insufficiency of prematurity (CPIP), which refers to respiratory morbidity starting after RDS resolution and lasting for the first 2 years of age.[13] CPIP patients have impaired alveolarization, present a mixed obstructive/restrictive pattern,[14] need ongoing respiratory support, and evolve towards bronchopulmonary dysplasia (BPD) which may eventually be diagnosed, usually at 36 weeks postmenstrual age.

We investigated the respiratory and haemodynamic effects of pronation applied for several hours in neonates with respiratory failure of different types. We

hypothesized that prone positioning has the same effects observed in adults.

Methods

Study design

This prospective, physiological, crossover, controlled cohort study was performed, from May 1st, 2019 to May 31st, 2021, at a tertiary academic neonatal intensive care unit (NICU) at the Paris Saclay University - "A. Béclère" Hospital (France). The study was pragmatic as it was performed during routine patient positioning without altering it (see below). Clinical management was provided according to routine NICU protocols, and essentially based on optimal perinatal care and international guidelines.[15] Respiratory support was provided as previously described.[16–18] The study protocol was granted ethical approval (French Critical Care Ethical Commission, n.SRLF19/36), and informed consent was obtained from parents upon NICU admission. The research was carried out in accordance with the standards set by the ethical committee and the Declaration of Helsinki. Relevant privacy regulations were respected. STROBE guidelines were followed for the manuscript preparation.[19]

Patients

Patients were considered eligible for the study if they were admitted to the NICU for respiratory failure and diagnosed with either: 1) RDS in the recovery phase, 2) NARDS, or 3) evolving BPD (i.e.: CPIP in the first weeks of life). To be considered in the recovery phase of RDS, neonates had to fulfil the following criteria: *a)* gestational age ≤32 weeks; *b)* diagnosis of RDS with prompt, sustained, and complete response to surfactant[12] administered via enhanced intubation-surfactant-extubation technique, as previously described;[18] *c)* surfactant replacement occurred at least 12h prior to study enrolment;[20] *d)* postnatal age at enrolment ≤5 days. These criteria were chosen to identify neonates with recently improved compliance due to surfactant replacement.[21] To be diagnosed with NARDS, infants needed to fulfil the Montreux definition.[12] To be considered as having evolving BPD (i.e.: CPIP in the first weeks of life), neonates had to satisfy the following criteria: *a)* gestational age <30 weeks; *b)* lung ultrasound score ≥5[22] and ongoing need for oxygen supplementation at 14 days of postnatal age; *c)* postnatal age at enrolment >14 days; similar criteria have been recently used to study pathophysiology of evolving BPD.[23] These infants usually have lower compliance and increased resistance,[24] causing respiratory morbidity persisting once they completely recovered from RDS.[13] Thus, improving RDS, NARDS, and evolving BPD represent disorders with a mild restrictive, severe restrictive, and mixed restrictive/obstructive pattern, respectively. Exclusion criteria were: *a)* complex malformations or chromosomal abnormalities; *b)* congenital lung anomalies; *c)* airleaks; *d)* any lung disorders other than RDS, NARDS or evolving BPD; *e)* acute worsening of clinical conditions due to other diseases during the study or in the week prior to enrolment; *e)* haemodynamic impairment defined as need for inotropes in the last 72h; *f)* any medical reasons dictating a mandatory patient position. Finally, if a patient position had to be changed for medical reasons during the study, the neonate was excluded.

Procedures

In our NICU, nurses routinely switch infants between the supine and prone positions every 6h, unless there is a clinical reason to do otherwise. Eligibility was screened daily by an investigator (BL), and infants were enrolled at the beginning of their supine or prone period, following their positioning routine. Thus, the position at study onset was the one that infants had according to the standard clinical care and was not decided by the investigators for study purposes. As such, the study can be considered a "quasi-randomized" and natural experiment.[25] There were two cohorts consisting of patients starting supine or prone (data illustrated in green and blue, respectively) with a classical AB/BA design. The initial position was maintained for 6h. Measurements were performed after 30′ of "wash out" from the original positioning (T1) and at the end (T2) of the first 6h period. Patients were then moved into the alternate position, another 30' "wash out" was allowed, and measurements were performed again (T3). The duration of wash-out period was similar to previously published studies on neonatal pronation.[8–11] The new position was kept for 6h, and measurements were finally repeated at the end (T4) of this second 6h period. The study workflow is described in Fig. 1. Infants were always positioned in a flexed neutral position, avoiding excessive neck flexion/extension, with soft nesting rolls placed around them. During prone positioning, infants had a flattened roll supporting the baby (as a 'surfboard'), and the head was turned to the right or left. All infants were in incubators with mattresses parallel to the floor; temperature and humidity were unchanged during the study. A small sterile gauze was placed on the cord stump in infants with umbilical lines during pronation. Nursing was performed without changing the position and concentrating interventions at the end of each 6h period.

Data and measurements

Clinical and demographic data were extracted from electronic patient files. Several respiratory and haemodynamic parameters were considered as primary outcomes to comprehensively describe lung and heart

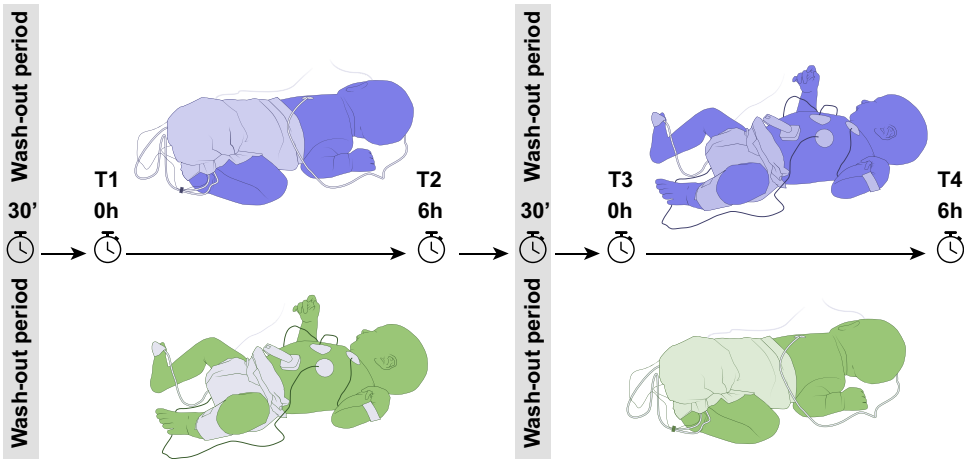

Fig. 1: **Study workflow.** Patients were started prone (blue) or supine (green) and a classical AB/BA design was applied. Each patient underwent two 6-h observation periods. Data were recorded after 30′ of "wash out" time from the original positioning (T1); position was kept for 6 h, and data were recorded again at the end of the 6-h period (T2). Subsequently, patients were switched to the alternate position, a new 30′ "wash out" time was allowed and then data were again recorded in the new position (T3); position was kept for 6 h, and data were recorded again at the end of the 6-h period (T4).

function and they were obtained as follows. Blood gases ($PtcO_2$ and $PtcCO_2$) were estimated with adequately calibrated transcutaneous devices (TCM4, Radiometer, Copenhagen, Denmark) as suggested by the Montreux definition.[12] These devices were applied and used according to the manufacturer's recommendations and American Association for Respiratory Care guidelines.[26] Values were recorded as soon as a stable measurement was achieved. Mean airway pressure (P_{aw}) and other ventilatory parameters were recorded from the ventilator at the same time. Pressure leaks were minimized for patients receiving non-invasive respiratory support by using appropriately sized interfaces and closing the mouth with gentle pressure on the chin.[27] Pre-ductal peripheral haemoglobin saturation (SpO_2) and perfusion index (PI) were recorded using an artifact filtering algorithm ([*NPi*], Nihon Kohden, Shinjuku, Japan) when the pulse wave was regular and smooth. SpO_2 and PI were averaged with 5″ intervals over 1'. These data were used to calculate a modified ventilatory index (MVI = P_{aw} × respiratory rate × $PtcCO_2$/1000), the $PtcO_2$/inspired oxygen fraction (FiO_2), SpO_2/FiO_2 ratios and the oxygenation index (OI = [P_{aw} × $FiO_2/PtcO_2$] ×100). Within 10′ of collecting these data, lung aeration was assessed calculating the extended lung ultrasound score (eLUS) specifically validated for neonates.[28] eLUS is based on classical lung ultrasound signs[29] evaluated on 10 chest areas (5 per side [upper and lower anterior, lateral, upper and lower posterior], ranging from 0 (best) to 30 (worst aeration). eLUS includes the scan of the dependent lung areas (the dorsal and ventral areas when the infant is lying supine and prone, respectively), obtained by slightly tilting the infant. Right after respiratory measurements, the following haemodynamic parameters were assessed. Cardiac output (CO) was measured using electrical cardiometry as previously described.[30] In detail, measurements were considered when an optimal signal was achieved (signal quality index >480, for at least 1′ without ECG artifacts). Mean arterial pressure (MAP) and heart rate (HR) were measured by oscillometry and ECG using the NICU monitoring system. Other oxygenation metrics (arterial/Alveolar ratio, Alveolar-arterial gradient, oxygen saturation and respiratory indexes) were calculated as previously described[31,32] and considered as secondary respiratory outcomes. During all measurements, ventilatory parameters were unchanged.

Statistics

We decided a convenience sample size of at least 50 infants for each type of respiratory failure. This was chosen as previous neonatal studies on patient positioning were performed on much smaller populations (10–20 infants),[8–11] and did not consider all the above mentioned outcomes; therefore, a formal sample size calculation was unfeasible. When needed, patient characteristics were compared using Student's t-, χ^2 and Fisher's test, as appropriate.

Respiratory and haemodynamic outcomes were studied with univariate repeated measures (RM)-ANOVA comparing patients starting supine and prone (between-subjects effects), as well as patients within each positioning (supine or prone) group over different timepoints (within-subjects effects). The initial position–time interaction was also considered, and sphericity (equality of variances of the differences between measurements) was estimated with the ε

coefficient and the Huynh-Feldt correction (ε always >0.75). The net recruitment produced by prone positioning was also studied using the eLUS difference calculated before and after 6h-pronation. This was subjected to paired Student t-test and correlated with the difference in OI, calculated at the same timepoints, using Pearson (*r*) and partial correlation (adj-*r*) adjusted for the type of respiratory failure.

We also performed the following additional analyses. Since the study followed an AB/BA design, we calculated the difference between the measurement at the end of the first (T2) and the second (T4) treatment. This difference was compared between neonates started prone and supine with Student t-test. We also performed multiple linear regressions having the respiratory and haemodynamic outcomes as dependent variables, while the initial position (prone as reference), the type of respiratory failure (RDS as reference) and their interaction term were inserted as covariates. The significant interaction would indicate that the effect sizes of pronation differ across the respiratory disorder as shown by the T2-T4 difference. We performed several multivariate ANOVA (MANOVA) procedures as sensitivity analysis for the repeated measures-ANOVA aiming to confirm the robustness of results obtained with repeated measures-ANOVA, despite the sphericity assumption was not always respected. MANOVA had each outcome as dependent variables, and, as independent variables, the patient position and the type of respiratory failure.

To confirm the relative influence of the underlying respiratory disorder (i.e.: RDS, NARDS and evolving BPD) on the effect of patient positioning, we performed several multi-level multivariable regressions having each of the aforementioned respiratory and haemodynamic parameters as outcome. Initial patient position, type of respiratory disorders and timepoints were inserted as covariates in each model. Since we could not exclude an influence of the initial position on the following measurements, we also added an interaction term between initial position and timepoints. In other words, we asked the technique to see if prone positioning was more effective in RDS, NARDS or evolving BPD and we did so adjusting for several covariates and their interaction term. Regressions were performed on the whole population fitting linear mixed models (estimated using REML and 'nloptwrap' optimizer) and considering timepoints and patient as random effects. To do a pairwise comparison between the three respiratory disorders, we estimate marginal contrasts at the initial patient position and type of respiratory disease. *p*-values were adjusted with the Holm method. The model details and analysis code are available in Supplementary material Table S1. To confirm the robustness of our analysis, model assumptions were checked by refitting the multilevel analysis with different covariance matrices (unstructured, autoregressive and heterogeneous compound symmetry), without intercept and random effect. Analyses were performed by, or under the supervision of, a senior biostatistician (LV) with SPSS 28 (IBM, Chicago,IL, USA) and R4.1.2 (https://www.r-project.org) and $p < 0.05$ were considered statistically significant.

Role of the funding source
There was no funding source for this study.

Results

General population characteristics

We enrolled 161 neonates: patients with RDS, NARDS or evolving BPD obviously have different characteristics as they were affected by different disorders (Table 1). All RDS patients were supported with nasal mask-delivered CPAP, and 32 were in room air. All neonates with NARDS were invasively ventilated and needed supplemental oxygen. According to Montreux criteria NARDS was mild, moderate and severe in 5, 13 and 37 patients, respectively; four of them died. NARDS was triggered by pulmonary haemorrhage (16), meconium aspiration (14), early-onset sepsis (10), late-onset sepsis (10), ventilator-associated pneumonia (4), or maternal blood aspiration (1). Twenty-two infants recruited in the RDS or NARDS groups eventually later qualified to have BPD at 36 weeks. Neonates in the evolving BPD group were supported in biphasic CPAP (8), non-invasive neurally adjusted ventilator assist (18), non-invasive positive pressure ventilation (17), or invasive ventilation (7); 47 of them also needed supplemental oxygen. RDS, NARDS, or evolving BPD patients were enrolled at 3 [interquartile range: 2–4], 2 [interquartile range: 0–6] and 24 [interquartile range: 20–29] days of life, respectively. The characteristics of patients affected by each condition are globally similar irrespective of the initial patient position (Supplementary material Table S2). No problem occurred, and there was no need to change the patient position during the study, which was completed for every infant. All respiratory and haemodynamic variables were similar at the initial point (T1) between patients starting supine or prone, while some variables were significantly different after the wash out period (T3). Thus, the wash out might have been insufficient but the carryover effect, when present, was clinically unmeaningful as the variables were always within the expected values (Figs. 2,3,4,5,6 and 7 and supplementary material Figs. S1–S3).

Effects of pronation in RDS patients

Gas exchange and lung aeration improve with prone positioning, and the effect is reversed by reverting to the supine position; conversely, supine positioning worsens

	Whole (161)	RDS (56)	NARDS (55)	Evolving BPD (50)
Gestational age (weeks)	26.5 (2)	27.6 (2.1)	31.6 (6.7)	25.4 (1.1)
Birth weight (g)	895 (301)	1026 (346)	1881 (1286)	746 (137)
Weight at enrolment (g)	1368 (857)	985 (337)	1914 (1257)	1217 (226)
Prenatal steroids	121 (75%)	48 (86%)	39 (71%)	34 (68%)
Caesarean section	102 (63%)	44 (79%)	31 (56%)	27 (54%)
Male sex	76 (47%)	25 (45%)	27 (49%)	24 (48%)
Female sex	85 (53%)	31 (55%)	28 (51%)	26 (52%)
SGA neonates	14 (9%)	4 (9%)	5 (9%)	5 (10%)
5′ Apgar score	6.8 (2.8)	7.3 (2.5)	6 (2.8)	7.1 (2.8)
CRIB-II score	10.1 (3.3)	8.4 (3.4)	10.5 (3.6)	11.8 (2)
OI at study onset	12.8 (10.1)	4.9 (2.7)	22.6 (10.3)	10.8 (5)

Data are expressed as mean (standard deviation) and number (%), as appropriate. % are rounded to the nearest integer. 5′ Apgar score, CRIB-II and OI are dimensionless variables. RDS: respiratory distress syndrome; ARDS: acute respiratory distress syndrome; BPD: bronchopulmonary dysplasia; CRIB-II: critical risk index for babies; OI: oxygenation index.

Table 1: **Basic population details.**

gas exchange and lung aeration, which are reversed with prone placement (Fig. 2). These effects are also associated with the initial position–time interaction (overall within-subjects effect $PtcCO_2$: $p = 0.01$, MVI: $p < 0.01$, $PtcO_2/FiO_2$: $p = 0.04$, SpO_2/FiO_2: $p = 0.03$, OI: $p < 0.01$, eLUS: $p = 0.02$; overall within-subjects effect for the interaction: $p < 0.01$ for all parameters).

MAP and CO are decreased in pronated neonates, the original values are recovered by supine positioning and further increased after 6h. A specular effect is observed in patients started in the supine position. Peripheral perfusion and heart rate change during the observation without a clear relationship with the patient position. These effects are shown in Fig. 3 and are also associated with the initial position–time interaction (within-subjects effect HR: $p < 0.01$, PI: $p = 0.01$, MAP: $p < 0.01$, CO: $p < 0.01$; overall within-subjects effect for the interaction: $p < 0.01$ for all parameters). All haemodynamic parameters remain within the normal ranges.

Effects of pronation in NARDS patients

Gas exchange is improved and worsened by prone and supine positioning, respectively, and this effect is reversed or at least partially recovered by turning the patient in the alternate position. Lung aeration improves in the prone position, and this is not significantly changed returning to the supine position; conversely, turning neonates prone after supine positioning results in a similar improvement in lung aeration. These effects are shown in Fig. 4 and also associated with the initial position–time interaction (overall within-subjects effect $PtcCO_2$: $p = 0.01$, MVI: $p = 0.03$, $PtcO_2/FiO_2$: $p < 0.01$, SpO_2/FiO_2: $p = 0.36$, OI: $p < 0.01$, eLUS: $p < 0.01$; overall within-subjects effect for the interaction: $p < 0.01$ for all parameters).

MAP and CO are lowered in prone-positioned neonates, and this is reversed by supine positioning, while a specular effect is observed in patients initially in the supine position; peripheral perfusion and heart rate change during the observation without a clear relationship with the patient position. These changes are shown in Fig. 5 and are also associated with the initial position–time interaction (within-subjects effect HR: $p < 0.01$, PI: $p < 0.01$, MAP: $p < 0.01$, CO: $p = 0.02$; overall within-subjects effect for the interaction: $p < 0.01$ for all parameters). All haemodynamic parameters remain within the normal ranges.

Effects of pronation in patients with evolving BPD

Gas exchange and lung aeration are improved and worsened by prone and supine positioning, respectively, and these effects are reversed or at least partially recovered by turning the patient in the alternate position (Fig. 6). These effects are also associated with the initial position–time interaction (overall within-subjects effect $PtcCO_2$: $p < 0.01$, MVI: $p < 0.01$, $PtcO_2/FiO_2$: $p < 0.01$, SpO_2/FiO_2: $p < 0.01$, OI: $p < 0.01$, eLUS: $p = 0.01$; overall within-subjects effect for the interaction: $p < 0.01$ for all parameters).

MAP and CO are lowered during pronation, and this is reversed by supine positioning, while a specular effect is observed in patients started in the supine position. Peripheral perfusion and heart rate change during the observation without a clear relationship with the patient position. These effects are shown in Fig. 7 and are also associated with the initial position–time interaction (within-subjects effect HR: $p < 0.01$, PI: $p < 0.01$, MAP: $p < 0.01$, CO: $p = 0.01$; overall within-subjects effect for the interaction: $p < 0.01$ for all parameters). All haemodynamic parameters remain within the normal ranges.

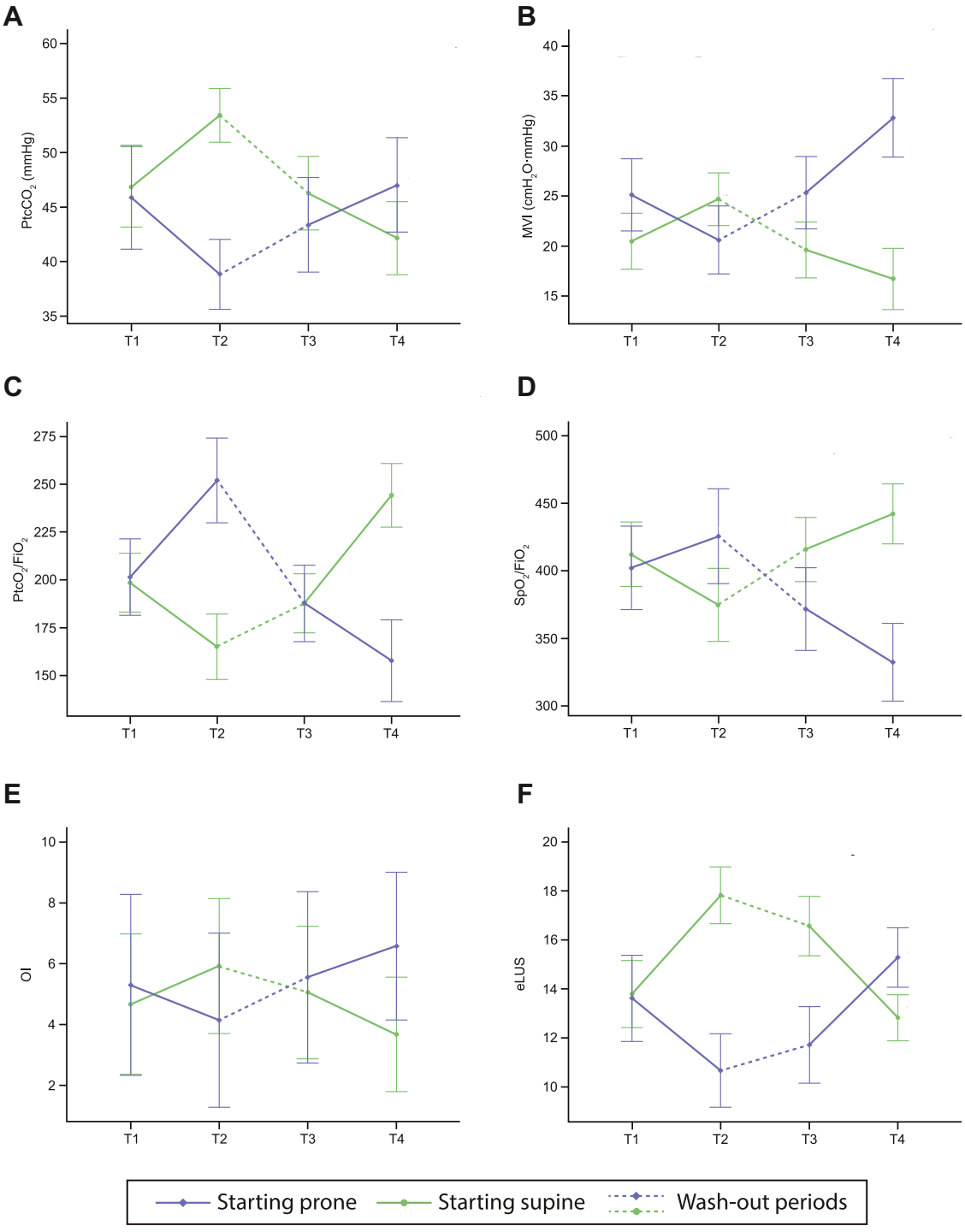

***Fig. 2:* RDS group: respiratory effects of patient positioning.** Transcutaneous partial pressure of CO_2 (panel A), modified ventilatory index (panel B), the ratio between transcutaneous partial pressure of CO_2 and inspired oxygen fraction (panel C), the ratio between peripheral arterial haemoglobin saturation and inspired oxygen fraction (panel D), the oxygenation index (panel E) and the lung aeration assessed by extended lung ultrasound score (panel F) are illustrated. Blue (squares) and green (circles) lines represent patients who were started prone or supine, respectively. Squares, circles and T-bars represent means and 95% confidence intervals, respectively. Lines were full and dotted to depict the observation and wash out periods, respectively. $PtcCO_2/FiO_2$, SpO_2/FiO_2, OI and eLUS are dimensionless variables. eLUS: extended lung ultrasound score; FiO_2: inspired oxygen fraction; MVI: modified ventilatory index; OI: oxygenation index; $PtcCO_2$: transcutaneous partial pressure of CO_2; $PtcO_2$: transcutaneous partial pressure of oxygen; SpO_2: peripheral haemoglobin oxygen saturation.

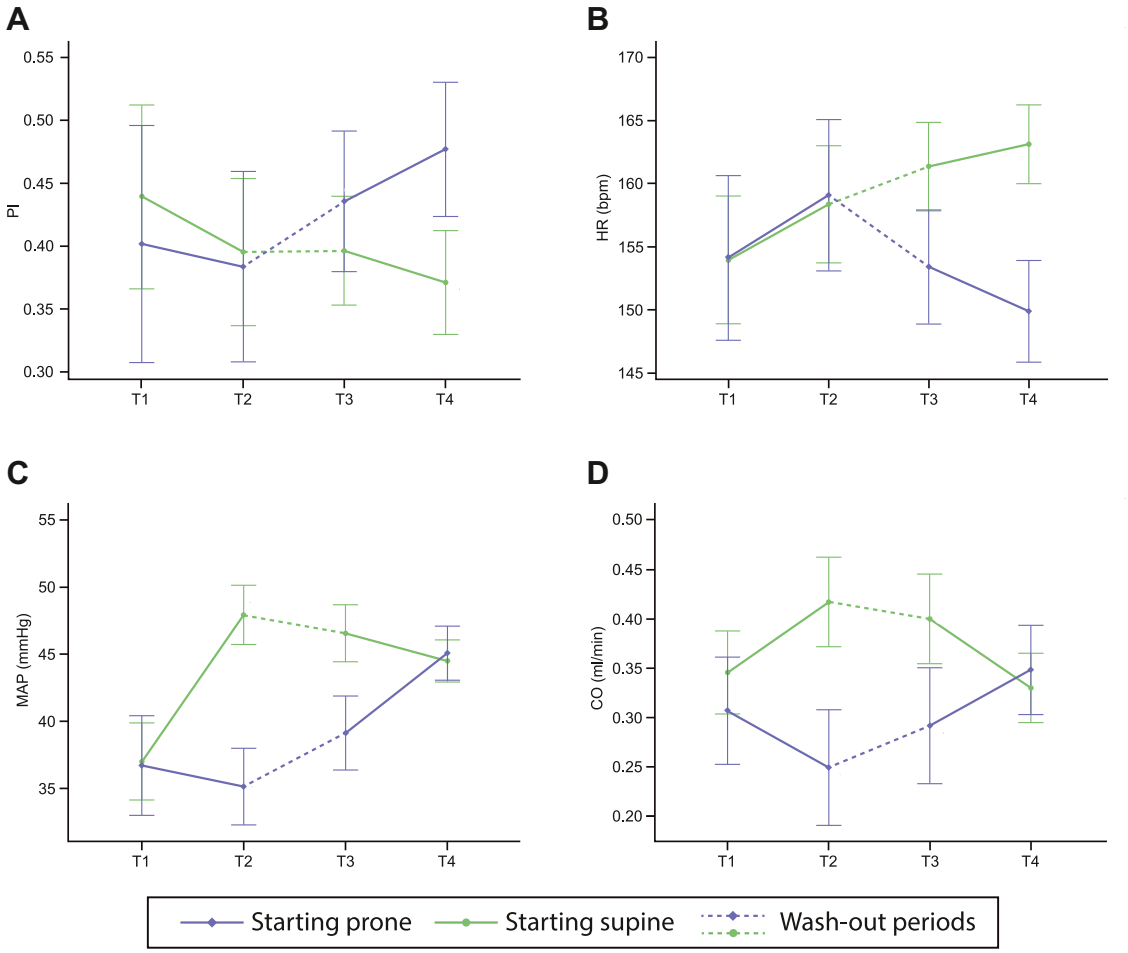

***Fig. 3:* RDS group: haemodynamic effects of patient positioning.** Perfusion index (panel A), heart rate (panel B), mean arterial pressure (panel C) and cardiac output (panel D) are illustrated. Blue (squares) and green (circles) lines represent patients who were started prone or supine, respectively. Squares, circles and T-bars represent means and 95% confidence intervals, respectively. Lines were full and dotted to depict the observation and wash out periods, respectively. PI is a dimensionless variable. CO: cardiac output; HR: heart rate; MAP: mean arterial pressure; PI: perfusion index.

Effects of pronation on ultrasound-assessed lung aeration

Changing patient position modified the distribution of ultrasound-assessed lung aeration in all patients, irrespective of their group, as illustrated in Fig. 8, and lung consolidations shifted from the dorsal to the ventral areas and vice versa in the prone and supine position, respectively. From a quantitative point of view, this produced: 1) a net lung recruitment as the mean eLUS significantly decreased in patients shifted from supine (16.9 (5.8)) to prone for 6h (14.1 (3.3), $p < 0.01$), and 2) an oxygenation improvement as the difference in eLUS is significantly correlated with the difference in OI ($r = 0.645$, $p < 0.01$; adj-r: 0.650, $p < 0.01$); similar correlations were found with other gas exchange parameters (data not shown).

Additional analyses

The effects of pronation on secondary oxygenation metrics (Supplementary material Figs. S1–S3) are identical to those described with metrics chosen as primary outcomes. The analysis of the mean T2–T4 difference for the three groups of patients confirmed the results: significant improvements in respiratory outcomes were noticed in pronated neonates (that is, the same direction as described above; supplementary material Tables S3–S5). In the linear regression models the interaction term was always significant for all respiratory outcomes (MVI: $p = 0.04$; eLUS: $p = 0.04$; all others $p < 0.01$) indicating that effect sizes of pronation is different for the three studied respiratory disorders (effect sizes are described in supplementary material Tables S3–S5). MANOVA confirmed results of the RM-ANOVA (supplementary material Table S6).

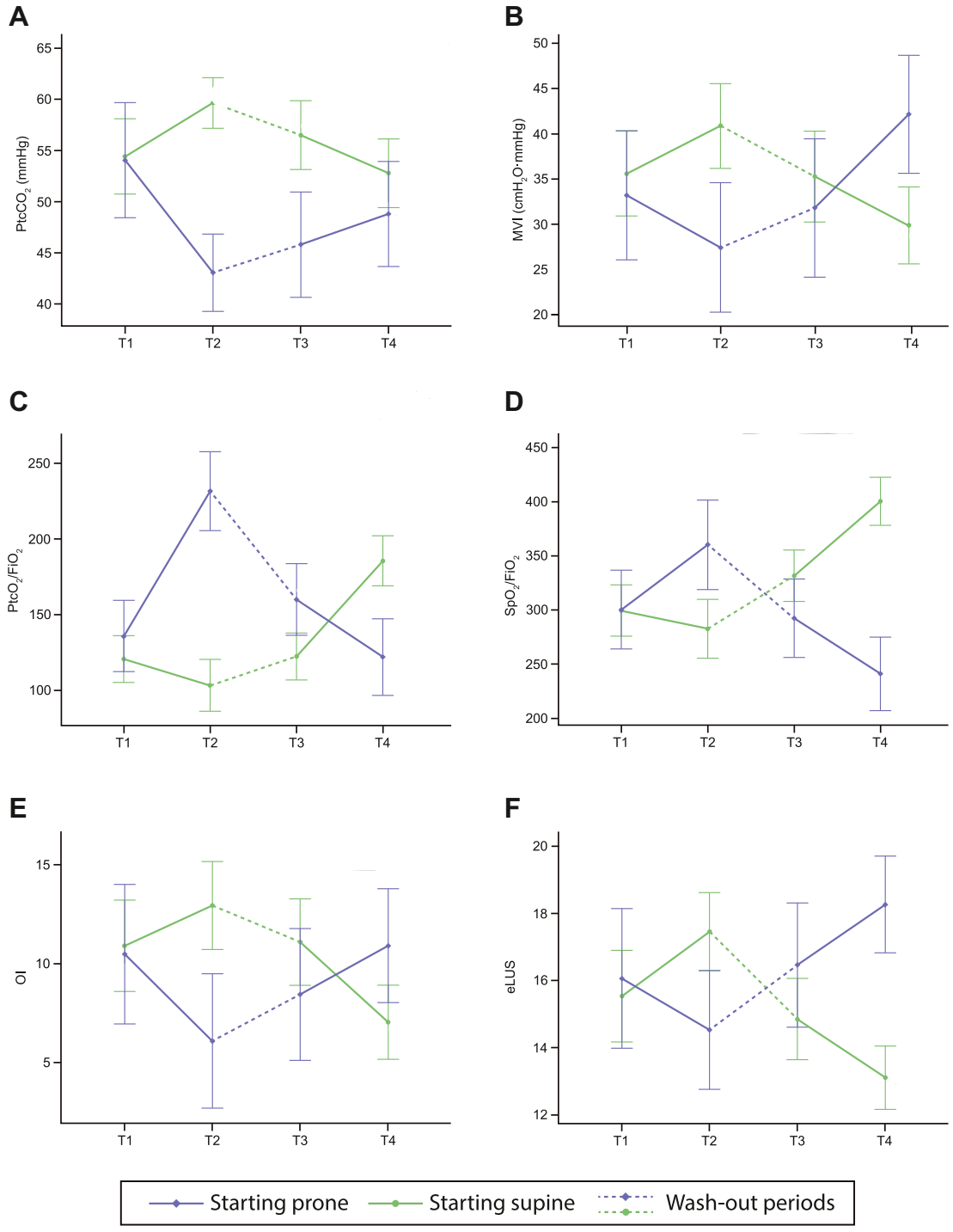

***Fig. 4*: NARDS group: respiratory effects of patient positioning.** Transcutaneous partial pressure of CO_2 (panel A), modified ventilatory index (panel B), the ratio between transcutaneous partial pressure of CO_2 and inspired oxygen fraction (panel C), the ratio between peripheral arterial haemoglobin saturation and inspired oxygen fraction (panel D), the oxygenation index (panel E) and the lung aeration assessed by extended lung ultrasound score (panel F) are illustrated. Blue (squares) and green (circles) lines represent patients who were started prone or supine, respectively. Squares, circles and T-bars represent means and 95% confidence intervals, respectively. Lines were full and dotted to depict the observation and wash out periods, respectively. $PtcCO_2/FiO_2$, SpO_2/FiO_2, OI and eLUS are dimensionless variables. eLUS: extended lung ultrasound score; FiO_2: inspired oxygen fraction; MVI: modified ventilatory index; OI: oxygenation index; $PtcCO_2$: transcutaneous partial pressure of CO_2; $PtcO_2$: transcutaneous partial pressure of oxygen; SpO_2: peripheral haemoglobin oxygen saturation.

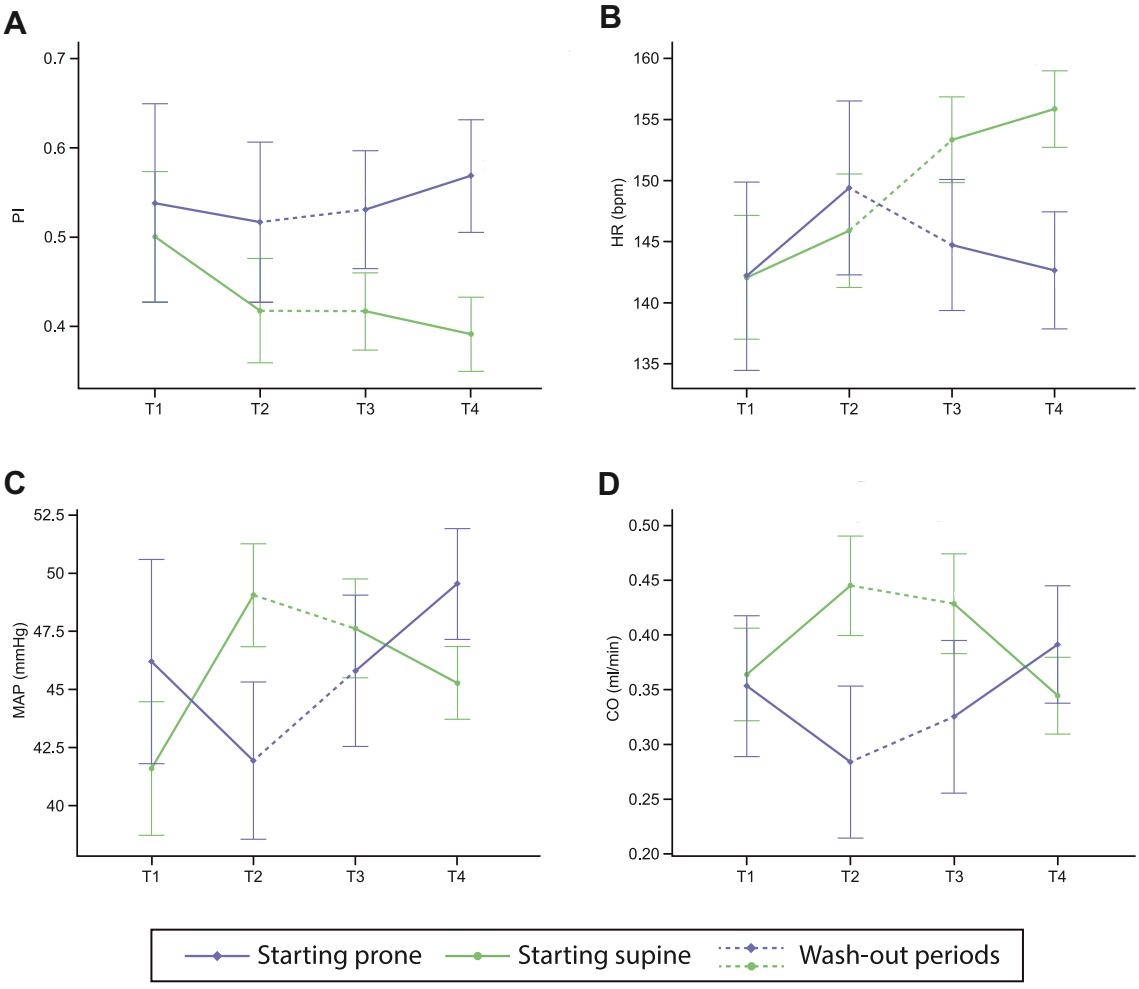

Fig. 5: **NARDS group: haemodynamic effects of patient positioning.** Perfusion index (panel A), heart rate (panel B), mean arterial pressure (panel C) and cardiac output (panel D) are illustrated. Blue (squares) and green (circles) lines represent patients who were started prone or supine, respectively. Squares, circles and T-bars represent means and 95% confidence intervals, respectively. Lines were full and dotted to depict the observation and wash out periods, respectively. PI is a dimensionless variable. CO: cardiac output; HR: heart rate; MAP: mean arterial pressure; PI: perfusion index.

Multivariable analyses confirm the different effect size (Tables 2 and 3); explanatory power (fixed effects marginal R^2) was 0.78. Validity of the model assumptions have been verified: results for a single outcome (eLUS) are shown supplementary material Table S7, but no differences were noted for all other outcomes (data not shown). All respiratory outcomes are ameliorated in the prone compared to supine position, and prone positioning is proportionally more effective in RDS, than in evolving BPD, than in NARDS, in this order. Almost all haemodynamic outcomes are changed by prone positioning with a variable effect size; nonetheless, the absolute differences are tiny and haemodynamic outcomes remain within the normal ranges.

Discussion

Our study shows that 6h-pronation improves gas exchange and lung aeration without haemodynamic side effects in neonates needing respiratory support for three common types of respiratory failure. In detail, pronation consistently improves oxygenation and CO_2 elimination, while these effects are at least partially reversed in the alternate position. Ultrasound-assessed lung aeration is ameliorated, and the improvement is reversed by supine positioning except for NARDS patients for whom the effect is unchanged on turning supine. The beneficial effects of prone positioning are significant for all patients, but they seem greater in patients recovering from RDS than in those with evolving BPD (i.e.: CPIP in the first weeks of life) than in those with NARDS, in this

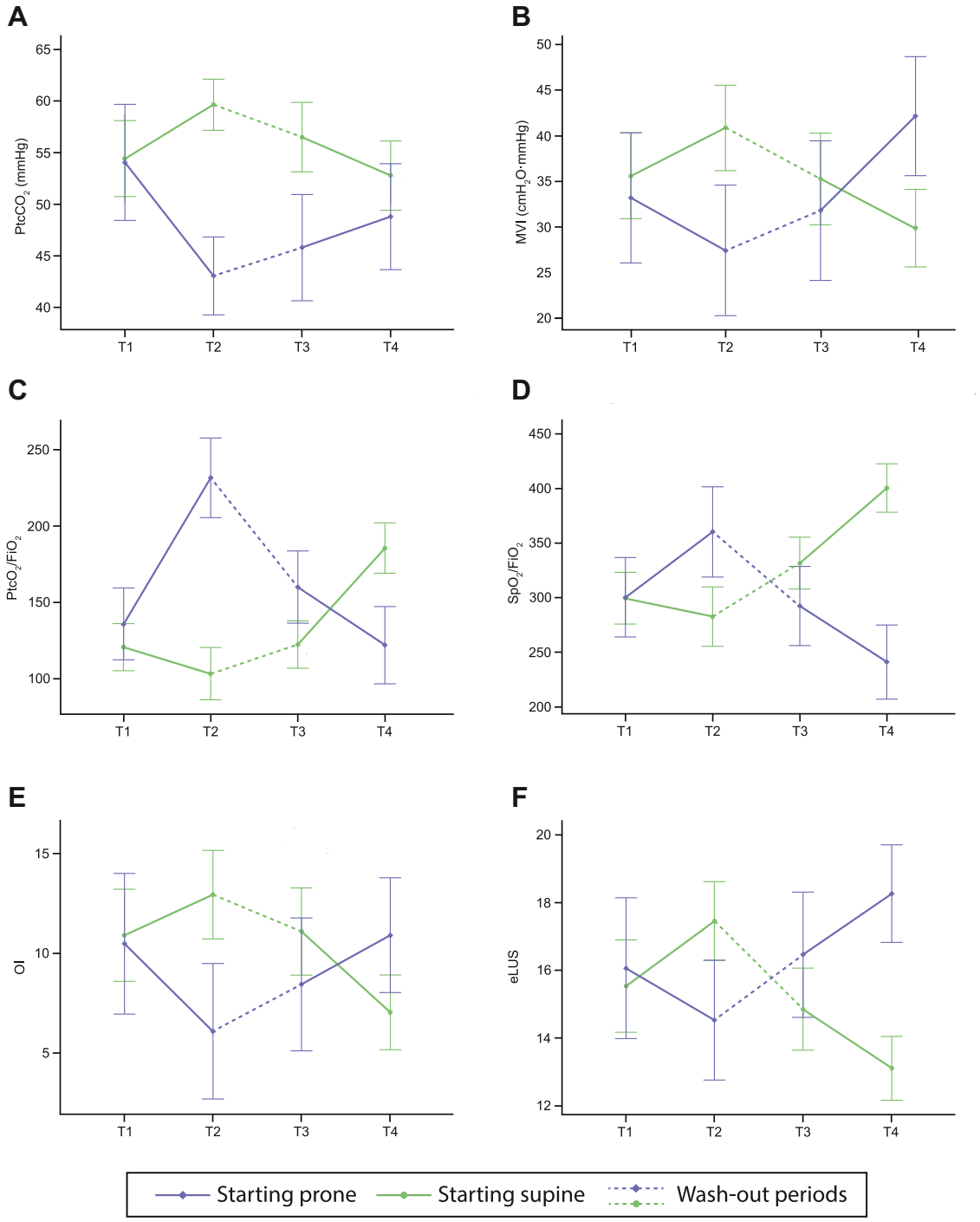

***Fig. 6:* Evolving BPD group: respiratory effects of patient positioning.** Transcutaneous partial pressure of CO_2 (panel A), modified ventilatory index (panel B), the ratio between transcutaneous partial pressure of CO_2 and inspired oxygen fraction (panel C), the ratio between peripheral arterial haemoglobin saturation and inspired oxygen fraction (panel D), the oxygenation index (panel E) and the lung aeration assessed by extended lung ultrasound score (panel F) are illustrated. Blue (squares) and green (circles) lines represent patients who were started prone or supine, respectively. Squares, circles and T-bars represent means and 95% confidence intervals, respectively. Lines were full and dotted to depict the observation and wash out periods, respectively. $PtcCO_2/FiO_2$, SpO_2/FiO_2, OI and eLUS are dimensionless variables. eLUS: extended lung ultrasound score; FiO_2: inspired oxygen fraction; MVI: modified ventilatory index; OI: oxygenation index; $PtcCO_2$: transcutaneous partial pressure of CO_2; $PtcO_2$: transcutaneous partial pressure of oxygen; SpO_2: peripheral haemoglobin oxygen saturation.

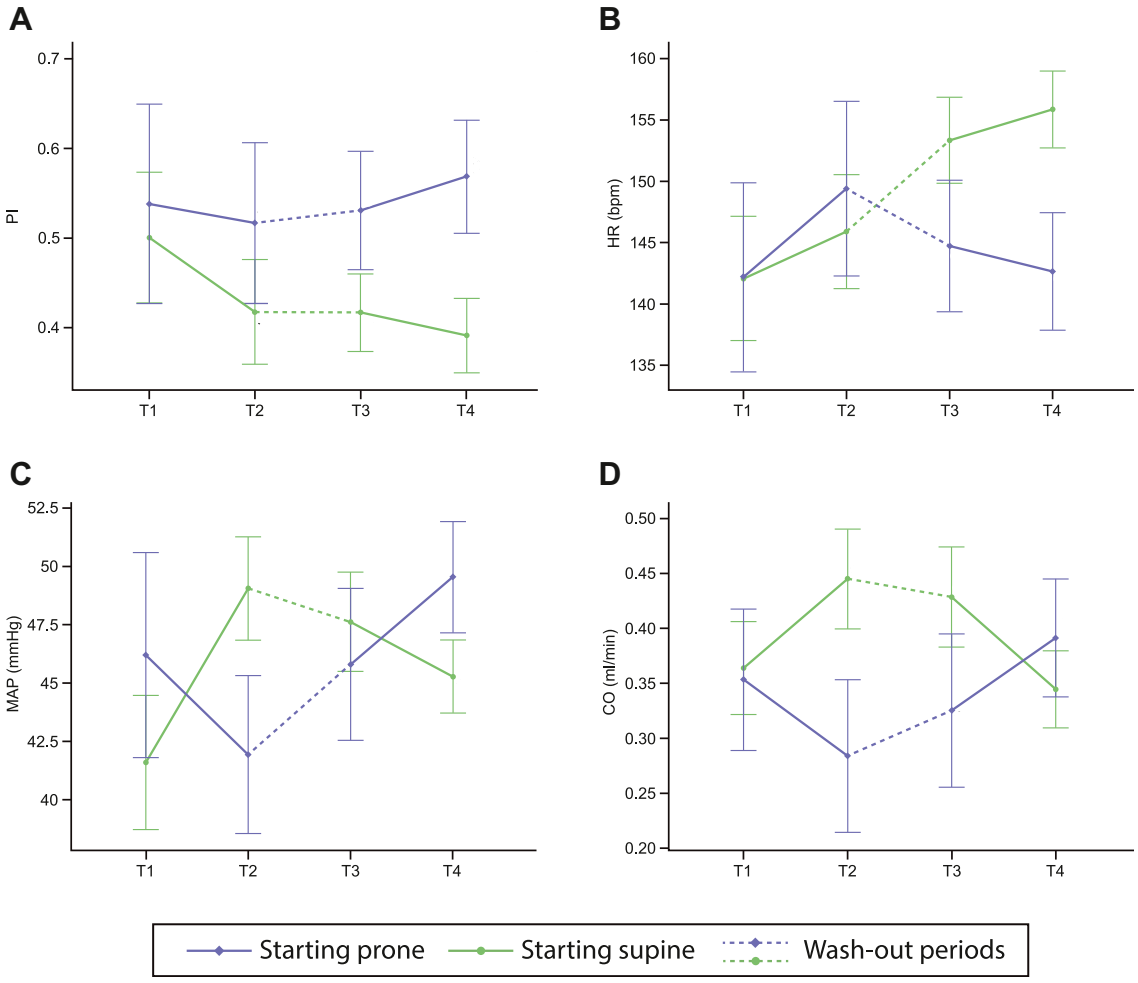

***Fig. 7*: Evolving BPD group: haemodynamic effects of patient positioning.** Perfusion index (panel A), heart rate (panel B), mean arterial pressure (panel C) and cardiac output are illustrated (panel D). Blue (squares) and green (circles) lines represent patients who were started prone or supine, respectively. Squares, circles and T-bars represent means and 95% confidence intervals, respectively. Lines were full and dotted to depict the observation and wash out periods, respectively. PI is a dimensionless variable. CO: cardiac output; HR: heart rate; MAP: mean arterial pressure; PI: perfusion index.

order. Pronation slightly reduces CO and MAP, but these remain within the normal ranges.

To the best of our knowledge, these are the first data on respiratory and haemodynamic effects after several hours of pronation in critically ill neonates classified according to their respiratory pathophysiology, which is different between the three studied disorders. Thus, our project consists of three independent studies whose results increase the knowledge in various contexts. They should be interpreted considering recent pathophysiology concepts[1,2] and they present important analogies with adult data. Oxygenation is improved in patients with mild (recovering RDS) or severe restrictive (NARDS) disorder, that is, in patients spontaneously breathing under CPAP or invasively ventilated, respectively. Recent experience regarding pronation in ARDS due to COVID-19 is consistent with our findings as the improvement has been observed in both types of patients.[5–7] CO_2 elimination is also increased by pronation, consistently with data obtained in adults subjected to 6h-positioning for whom this has also been associated with improved ARDS survival.[33] This is due to the recruitment of well-perfused but previously collapsed alveoli and the reduced overdistention of pulmonary units that can collapse alveolar capillaries and increase the dead space.[1,2] The consolidations seen at ultrasound (corresponding to unaerated lung zones) were seen to redistribute from the dorsal to the ventral position after pronation, as already suggested by magnetic resonance of a few neonates.[34] Moreover, the total amount of well-aerated (that is, recruited) lung tissue increased, as the eLUS decreased. This is coherent with data accumulated

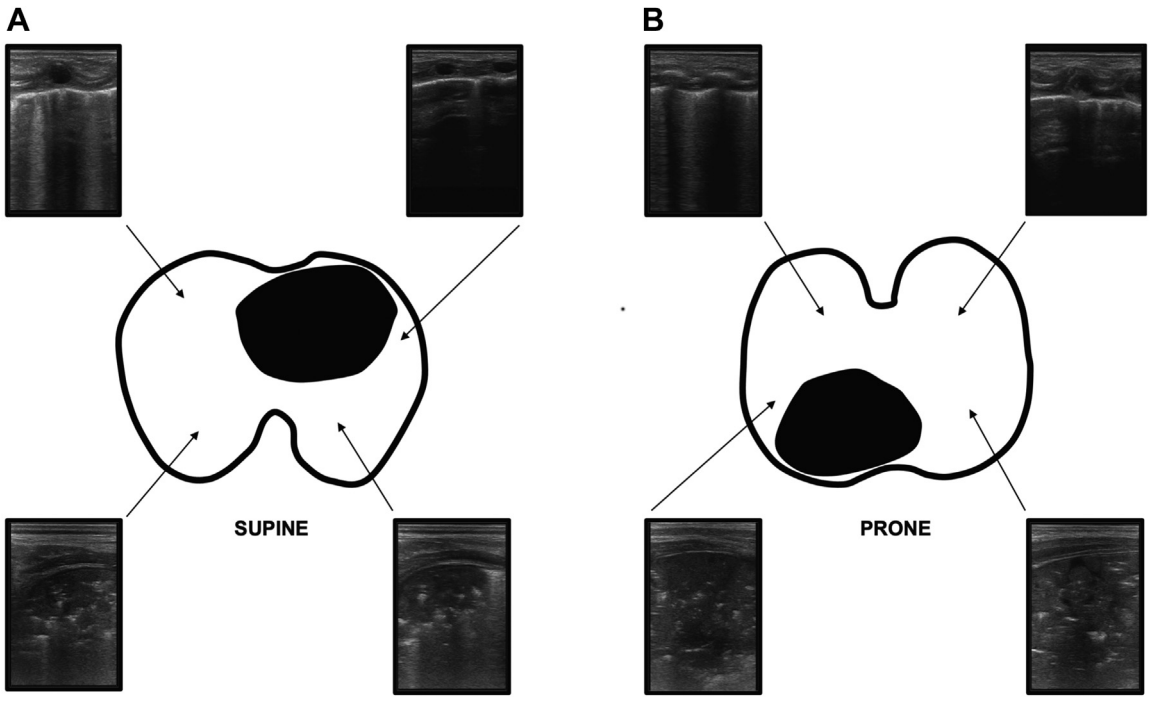

Fig. 8: **Illustrative pictures showing the typical changes in ultrasound-assessed lung aeration.** This produces a net recruitment as demonstrated by the extended lung ultrasound score. Pictures are taken from a NARDS patient, although these modifications were observed in every patient, irrespective of the type of respiratory failure (more details in the text). Panels A and B show the supine and prone position, respectively. The heart is depicted in black; the thorax is sketched in transversal section as done in CT-scans. Dependent (i.e.: dorsal and ventral areas, in supine and prone position, respectively) lung regions show marked loss of lung aeration appearing as consolidated, tissue-like areas (of >1 cm size) with irregular borders and mixed hypo- and hyperechogenic spots representing the bronchogram; they are sometimes surrounded by a severe alveolar-interstitial pattern represented by crowded and coalescent B-lines. Non-dependent (i.e.: ventral and dorsal areas, in supine and prone position, respectively) lung regions show a better lung aeration with normal lung tissue represented by only B-lines, or a mild alveolar-interstitial pattern represented by ≥3 well-spaced, not coalescent B-lines or a consolidation of smaller size (≤1 cm).

in adult critical care using CT-scan demonstrating that the amount of lung tissue in dorsal is greater than that in the ventral regions, so pronation results in positive net recruitment.[1,2] Consistently, the ventilation distribution measured in basal conditions with electrical impedance tomography is also identical in spontaneously breathing healthy infants and adults.[35] Finally, the changes observed in haemodynamics are small, and the absolute values remain within the normal ranges.[30,36] These changes could be due to a reduced venous return as the pronated heart is relatively compressed between the bed and the spine. However, the global haemodynamic stability of our patients was evident, similar to what has been previously observed in adults.[3,4] The results of a recent systematic review on the effect of infant position on peripheral perfusion and cerebral oxygenation also support these findings.[37]

Interestingly, we also observed these beneficial effects in infants with evolving BPD (i.e.: CPIP in the first weeks of life). These patients suffer from an impaired alveolarization. Consequently, they do not have a purely restrictive respiratory failure, but a mixed and evolutive lung mechanics pattern with variably reduced compliance and increased airway resistance making lung aeration inhomogeneous.[23] As the beneficial effects of pronation depend on the more uniform gas/tissue ratio, a patient with greater inhomogeneity can benefit more from this intervention and this might explain our findings.[1,2] These results are also interesting because pronation has never been studied in patients with a similar lung mechanics (such as for instance, chronic obstructive pulmonary disease) and might suggest some benefits in similar conditions. Conversely, we cannot provide definite data about the effect of pronation during the acute phase of RDS (i.e.: before surfactant replacement) as these patients have a homogeneous although stiffer lung[38]; the effect of pronation on haemodynamics could have been more evident as these patients have a transitional circulation. We did not study patients in the acute phase of RDS, because they should be quickly managed, undergoing umbilical lines placement to start parenteral nutrition and caffeine as soon as possible.[39] Moreover surfactant, if needed, should be administered within the first 3h of life to maximise its effect,[40]

	Comparison between respiratory disorders		Δ of β coefficient (95% CI)	p
	Disorder 1	Disorder 2		
MVI (mmHg x cmH_2O)	NARDS	Evolving BPD	21.6 (17.4; 25.7)	<0.01
	RDS	Evolving BPD	−10.7 (−14.4; −6.94)	<0.01
	RDS	NARDS	−32.2 (−36.6; −27.8)	<0.01
$PtcCO_2$ (mmHg)	NARDS	Evolving BPD	3.67 (1.08; 6.25)	<0.01
	RDS	Evolving BPD	−3.10 (−5.44; −0.77)	<0.01
	RDS	NARDS	−6.77 (−9.52; −4.02)	<0.01
OI	NARDS	Evolving BPD	12.8 (11.2; 14.5)	<0.01
	RDS	Evolving BPD	−3.08 (−4.53; −1.64)	<0.01
	RDS	NARDS	−15.9 (−17.7; −14.2)	<0.01
$PtcO_2/FiO_2$	NARDS	Evolving BPD	−56.2 (−68.2; −44.3)	<0.01
	RDS	Evolving BPD	45.7 (35; 56.3)	<0.01
	RDS	NARDS	102 (89; 115)	<0.01
SpO_2/FiO_2	NARDS	Evolving BPD	−123 (−141; −104)	<0.01
	RDS	Evolving BPD	69.6 (53.2; 85.9)	<0.01
	RDS	NARDS	192 (173; 212)	<0.01
eLUS	NARDS	Evolving BPD	5.25 (4.38; 6.12)	<0.01
	RDS	Evolving BPD	−1.87 (−2.66; −1.09)	<0.01
	RDS	NARDS	−7.12 (−8.06; −6.19)	<0.01

Marginal contrasts are shown for initial patient positions and each type of respiratory failure. Δ indicates the (disorder n.1 - disorder n.2) difference in β coefficients (and its 95% confidence interval) induced by pronation. β coefficients are those given by the regression and describe the effect of pronation on every respiratory outcome for each respiratory disorder. For instance, the Δ of β coefficient (for the regression model having MVI as outcome) is much negative for the difference RDS (disorder n.1) – NARDS (disorder n.2): this means that pronation reduced MVI more in RDS than in NARDS and the same applies for the difference RDS – evolving BPD. Conversely, the difference NARDS – evolving BPD is positive, and this means that pronation reduced MVI more in evolving BPD than in NARDS patients. OI, $PtcCO_2/FiO_2$, SpO_2/FiO_2, and eLUS are dimensionless variables. CI: confidence interval; eLUS: extended lung ultrasound score; FiO_2: inspired oxygen fraction; MVI: modified ventilatory index; OI: oxygenation index; $PtcCO_2$: transcutaneous partial pressure of CO_2; $PtcO_2$: transcutaneous partial pressure of oxygen; SpO_2: peripheral haemoglobin oxygen saturation.

Table 2: **Results of multivariable multi-level analyses for respiratory outcomes.**

thus a long pronation trial would have interfered with this.

Several earlier studies suggested that pronated neonates have better respiratory parameters, reduced work of breathing and less apnoeas.[8–11,41–45] Studies have also been meta-analysed showing low-to-moderate quality evidence in favour of pronation for slightly improved oxygenation in invasively ventilated neonates.[46] However, the meta-analysis detected a high inconsistency between the studies, was based on a small number of patients and did not analyse patients under non-invasive respiratory support (who represent the majority in most NICUs).[46] Moreover, these studies were performed for very short periods on small groups of neonates with mixed gestational ages, entry criteria, diagnoses, and clinical severities, thus patients also lacked a clear classification of their respiratory pathophysiology and one study only recruited stable infants ready to be discharged.[8–11,41–45] Finally, previous studies did not evaluate haemodynamics, thus the safety of neonatal pronation was unknown so far. Therefore, all these represent important flaws in light of the current state-of the-art knowledge and prevent the direct application of these old data to the current care. In particular, measurements were performed using electrical impedance tomography, inductance plethysmography or lung mechanics over 15′–3h time periods,[8–11,41–45,47] whereas recent adult data have demonstrated the importance of time to obtain significant effects on lung aeration and oxygenation.[5] Our findings have been produced using coupled ultrasound-assessed lung aeration, multiple gas exchange and haemodynamic measurements and represent the neonatal data obtained for the longest period. The lack of intermediate (between 0 and 6h) measurements prevents to clarify if a shorter period would provide any benefit, although this might be considered unlikely, as at least 12h were needed to observe any benefit in adults.[5] Clarifying how long the effect can be maintained or investigating the effect of pronation for more than 6h would require studies with different design and our findings may be helpful to design them.

We enrolled a homogeneous group of extremely preterm, CPAP-treated neonates recovering from RDS, 57% of which were supported in room air. Conversely, the NARDS group consisted of preterm or term, invasively ventilated neonates needing supplemental oxygen: 91% and 94.5% of them were classified as severe-to-moderate according to the Montreux or Berlin definition, respectively.[12,48] Their clinical features were similar

	Comparison between respiratory disorders		Δβ coefficient (95% CI)	p
	Disorder 1	Disorder 2		
PI	NARDS	Evolving BPD	0 (−0.03; 0.02)	0.70
	RDS	Evolving BPD	−0.09 (−0.11; −0.07)	<0.01
	RDS	NARDS	−0.09 (−0.12; −0.06)	<0.01
HR (bpm)	NARDS	Evolving BPD	−5.77 (−7.79; −3.76)	<0.01
	RDS	Evolving BPD	10.6 (8.86; 12.4)	<0.01
	RDS	NARDS	16.4 (14.2; 18.6)	<0.01
MAP (mmHg)	NARDS	Evolving BPD	−3.3 (−4.74; −1.85)	<0.01
	RDS	Evolving BPD	−3.2 (−4.49; −1.90)	<0.01
	RDS	NARDS	0.1 (−1.46; 1.66)	0.99
CO (L/min)	NARDS	Evolving BPD	−0.03 (−0.04; −0.01)	<0.01
	RDS	Evolving BPD	−0.07 (−0.08; −0.05)	<0.01
	RDS	NARDS	−0.04 (−0.06; −0.02)	<0.01

Marginal contrasts are shown for initial patient positions and each type of respiratory failure. Δ indicates the (disorder n.1 - disorder n.2) difference in β coefficients (and its 95% confidence interval) induced by pronation. β coefficients are those given by the regression and describe the effect of pronation on every haemodynamic outcome for each respiratory disorder. For instance, the Δ of β coefficient (for the regression model having PI as outcome) is negative for the difference RDS (disorder n.1) – NARDS (disorder n.2): this means that pronation reduced PI more in RDS than in NARDS and the same applies for the difference RDS – evolving BPD. Conversely, the opposite happens for HR. PI is a dimensionless variable. CI: confidence interval; CO: cardiac output; HR: heart rate; MAP: mean arterial pressure; PI: perfusion index.

Table 3: **Results of multivariable multi-level analyses for haemodynamic outcomes.**

to those reported by epidemiological studies on NARDS.[49] These two groups really represent basically different respiratory disorders with distinct severity. Infants with evolving BPD were at high risk of long-term chronic respiratory morbidity and received respiratory support with several techniques, so their clinical severity was variable. Overall, our results indicate that pronation is beneficial in neonates recovering from RDS, in those with evolving BPD (i.e.: CPIP in the first weeks of life) and in those affected by NARDS, proportionally to this order. This order is evident for most primary respiratory outcomes as indicated by the effect sizes shown in supplementary material Tables S3–S5, whereas the multivariable multi-level analysis confirmed this order for all primary outcomes. Patients that are recovering from a mild and restrictive disorder probably have the greatest benefit because their lungs are not significantly diseased anymore. Infants with evolving BPD within their chronic pulmonary insufficiency may benefit more than those affected by NARDS, likely because the former have a greater lung aeration inhomogeneity and because the latter have a stiffer and less recruitable lung.[1,2] Anyhow, pronation has a significant effect in all the three groups and the absolute changes in terms or gas exchange and lung aeration can be clinically relevant for all patients. Therefore, 6h-pronation may be considered to improve gas exchange and lung aeration in patients recovering from RDS or affected by NARDS or evolving BPD.

We acknowledge some limitations. First, the study was pragmatic and not randomized. This was decided to avoid changes in clinical practice: in fact, serial position change is our standard of care, and nursing is concentrated at the time of changes. This is common and easy in neonatology, and, given the beneficial effects on comfort, quality of nursing, work of breathing, and apnoeas, it would have been ethically difficult to change. However, all basic patient characteristics were similar between those starting in the supine or prone position; moreover, the initial position was assumed within the clinical routine and not decided by the investigators. These characteristics prevented, at least partially, the influence of possible confounders. The 30' wash-out period might have been insufficient to completely avoid the carryover effect in all investigated variables: however, when this effect occurred, it was clinically unmeaningful, as the differences between the variables at T3 were always within the expected values for those types of patients. The fact that all values were always similar at T1 also demonstrate the absence of a relevant carryover effect. Of note all the additional analyses confirmed the robustness of our results. Apart from NARDS patients, most neonates were spontaneously breathing and supported with several non-invasive techniques. This was due to our personalized approach to the respiratory assistance of very preterm infants[17] and gives a pragmatic picture of routine neonatal care, where less invasiveness is always preferred whenever possible. We did not analyse the effect of pronation according to the different respiratory support modality: however, the needed respiratory support depends on the lung pathophysiology and we comprehensively considered it by studying three different disorders. Moreover, in adults, pronation resulted beneficial both in spontaneously breathing and invasively ventilated patients.[5–7] We could not study lung inflation by CT-scan and we used lung ultrasound: the two techniques are different but their results are known

to be correlated.[50] Patient position was obviously unmasked during ultrasound and this could be considered a bias, however patient position is impossible to be masked during CT-scan too. Finally, we studied patients without haemodynamic instability and our results cannot be generalized to other populations.

In conclusion, 6h of pronation significantly improve gas exchange and lung aeration in neonates recovering from RDS after surfactant replacement, in those with evolving BPD (i.e.: CPIP in the first weeks of life) and in those affected by NARDS. The effect size is proportional to this order and the benefits are generally overturned by shifting to the alternate position. Pronation has no clinically meaningful haemodynamic effects and can be used to ameliorate gas exchange and lung aeration in critically ill neonates.

Contributors

BL: data acquisition, interpretation and analysis, study design and manuscript draft preparation.

GR, SF, RC: data acquisition and interpretation.

NY: study design and data interpretation.

LV: data interpretation and statistical analysis and manuscript preparation.

DDL: study conception and design, data analysis, manuscript preparation.

All authors reviewed the manuscript for important intellectual content, approved the final version to be published directly accessed and verified the underlying data reported in the manuscript. They all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement

The deidentified datasets used during the current study are available to clinical researchers from the corresponding author, on reasonable request, with publication, with a signed data access agreement.

Declaration of interests

DDL served in the advisory board for Chiesi farmaceutici, Airway Therapeutics, Masimo and Ophirex. He received research grants or assistance from Chiesi Farmaceutici, Vyaire and Getinge. He received speaker fees from Chiesi farmaceutici, Getinge, Vyaire, Philips, Radiometer, Medtronic, Masimo, AstraZeneca and BD. All these were unrelated to the present work. NY received research and travel grant from Chiesi Farmaceutici, unrelated to the present work. RC received research assistance and travel grant from Vyaire, unrelated to the present work. Other authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101791.

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