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The Breathing Effort of Very Preterm Infants at Birth

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Objective To compare the respiratory effort of very preterm infants receiving positive pressure ventilation (PPV) with infants breathing on continuous positive airway pressure (CPAP), directly after birth.

Study design Recorded resuscitations of very preterm infants receiving PPV or CPAP after birth were analyzed retrospectively. The respiratory effort (minute volume and recruitment breaths [>8 mL/kg], heart rate, oxygen saturation, and oxygen requirement were analyzed for the first 2 minutes and in the fifth minute after birth.

Results Respiratory effort was analyzed in 118 infants, 87 infants receiving PPV and 31 infants receiving CPAP (median gestational age, 28 weeks [IQR, 26-29] vs 29 weeks [IQR, 29-30; $P < .001$); birth weight, 1059 g [IQR, 795-1300] vs 1205 g [IQR, 956-1418; $P = .06$]). The minute volume of spontaneous breaths of infants receiving PPV was lower at 2 minutes (37 mL/kg/minute [IQR, 15-69] vs 188 mL/kg/minute [IQR, 128-297; $P < .001$]) and at 5 minutes (112 mL/kg/minute [IQR, 46-229] vs 205 mL/kg/minute [IQR, 174-327; $P < .001$]). Recruitment breaths occurred less in the PPV group at 2 minutes (0 breaths/minute [IQR, 0-1] vs 4 breaths/minute [IQR, 1-8; $P < .001$]) and 5 minutes (0 breaths/minute [IQR, 0-3] vs 2 breaths/minute [IQR, 0-11; $P = .01$). The heart rate was lower in the PPV group (94 beats/minute [IQR, 68-128] vs 124 beats/minute [IQR, 100-144; $P = .02$]) as was oxygen saturation (50% [IQR, 35%-66%] vs 67% [IQR, 34%-80%; $P = .04$]), but not different at 5 minutes (heart rate, 149 beats/minute [IQR, 131-162] vs 150 beats/minute [IQR, 132-160; P = NS]; oxygen saturation , 91% [IQR, 80%-95%] vs 92% [IQR, 89%-97%; P = NS]). The oxygen requirement was higher (at 2 minutes, 30% [IQR, 21%-53%] vs 21% [IQR, 21%-29%; $P = .05$]; at 5 minutes, 39% [IQR, 22%-91%] vs 22% [IQR, 21%-31%; $P = .003$]).

Conclusion Very preterm infants breathe at birth when receiving PPV, but the respiratory effort was significantly lower when compared with infants receiving CPAP only. The reduced breathing effort observed likely justified applying PPV in most infants. *(J Pediatr 2018;194:54-9).*

During transition at birth, very preterm infants need respiratory support for clearing their airways of lung liquid and replacing it with air to establish a functional residual capacity (FRC).[1] To minimize lung injury during this stabilization period, intubation and mechanical ventilation are avoided. This practice is reflected by a shift in the focus toward noninvasive ventilation using a facemask: continuous positive airway pressure (CPAP) is applied when spontaneous breathing is present or positive pressure ventilation (PPV) when breathing is absent or insufficient.[2,3] However, as PPV can deliver tidal volumes (V_T) that are variable[2,4] and inadvertently high, avoiding PPV whenever possible is likely to reduce the potential for lung injury.[5,6]

The question remains whether CPAP alone is capable of providing sufficient respiratory support for most preterm infants, thereby avoiding the use of PPV. O'Donnell et al showed that the majority of preterm infants breathe and cry at birth.[7] Schilleman et al also reported that most infants receiving PPV breathe during or between inflations, which is often missed by the caregiver.[2] Assessing spontaneous breathing and the adequacy of breathing can be difficult in preterm infants,[8,9] because breathing can be subtle and easily missed, particularly when infants are wrapped for the prevention of heat loss.

Several studies have described the respiratory effort of preterm infants breathing on CPAP[4,10,11]; however, less is known about the breathing effort while PPV is given. It is possible that the respiratory effort of infants receiving PPV is underestimated and that potentially harmful V_T are delivered by PPV when inflations coincide with breaths.

CPAP	Continuous positive airway pressure
FiO_2	Oxygen requirement
FRC	Functional residual capacity
HR	Heart rate
MV	Minute ventilation
PPV	Positive pressure ventilation
RFM	Respiratory function monitoring
RR	Respiratory rate
SpO_2	Oxygen saturation
V_T	Tidal volume
V_{Te}	Expiratory V_T
V_{Ti}	Inspiratory V_T

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The aim of this study was to determine the respiratory effort in the first minutes after birth of very preterm infants receiving PPV vs CPAP.

Methods

A retrospective, observational study was performed at the Neonatal Intensive Care Unit of the Leiden University Medical Center, The Netherlands. The local institutional review boards approved physiological and video recordings at birth in the delivery room when respiratory support was necessary. Written parental consent to use these recordings for research was obtained after birth. Recordings of all infants <32 weeks of gestation from April 2008 until June 2013 were reviewed. Infants were included for analysis when they received noninvasive respiratory support (PPV and/or CPAP).

Respiratory support was delivered with a T-piece infant resuscitator (Neopuff; Fisher & Paykel Healthcare, Auckland, New Zealand) combined with a Laerdal silicone round mask (Laerdal, Stavanger, Norway). Initial settings were a gas flow rate of 8 L/minute to give an inflation pressure of 20 and a positive end-expiratory pressure of 5 cm H_2O for PPV and a positive end-expiratory pressure of 5-8 cm H_2O for CPAP.[12] Respiratory function monitoring (RFM), heart rate (HR), oxygen saturation (SpO_2), and oxygen requirement (FiO_2) were recorded, starting as soon as the infants' shoulder was delivered. Respiratory measures were recorded with either a Florian RFM (Acutronic Medical Systems AG, Hirzel, Switzerland), or a New Life Box (Applied Biosignals, Weener, Germany) connected to an MRT-A RFM (Applied Biosignals). The Florian RFM used a hot wire anemometer and the MRT-A RFM a variable orifice pneumometer (Avea Varflex Flow transducer; Carefusion, Yorba Linda, California). The SpO_2 and HR were recorded using a Masimo SET pulse oximeter (Masimo Radical, Masimo Corporation, Irvine, California) with the pulse oximetry probe placed around the infant's right wrist. Gas flow, pressures given, V_T, SpO_2, HR, and breathing signals were digitized using Spectra physiological software (Grove Medical Limited, Hampton, United Kingdom) for the Florian RFM, and Polybench software for the New Life Box (Applied Biosignals).[12,13] We reported in 2013 that most caregivers did not use the parameters of the respiratory function monitor for evaluation of resuscitation.[2] We conducted training in 2013, but it is likely that RFM was not used to adjust the respiratory support in most infants recorded between 2008 and 2013.

For this study, the respiratory rate (RR) of spontaneous breathing, minute ventilation (MV), V_T, HR, SpO_2, and FiO_2 were analyzed in 2 time periods: the first 2 minutes after the infant was placed on the resuscitation table and the fifth minute of stabilization. For analysis, the infants were divided into 2 groups: a PPV group (infants receiving PPV at any time during the resuscitation) and a CPAP group (infants receiving only CPAP). Infants receiving PPV in the first 2 minutes remained in the PPV group even if breathing on CPAP at 5 minutes.

In the time period the recordings were obtained, the local resuscitation guidelines recommended to start with initial sustained inflation(s). Depending on the time period, the guidelines recommended an initial 5 sustained inflations each lasting 2-3 seconds or a single sustained inflation lasting 10 seconds. When sustained inflation(s) were followed by consecutive inflations, the infants were included in the PPV group. When no consecutive inflations were given and only CPAP followed, infants were included in the CPAP group.

Normal values of V_T and MV of preterm infants breathing on CPAP at birth have been published.[4,10,11] However, there is no clear definition of when breathing is adequate. For the purposes of this study, to compare the respiratory effort we calculated how often the MV in the PPV group was >25th percentile of the MV of the infants in the CPAP group, and how often recruitment breaths of >8 mL/kg per minute occurred.[14]

Because we were interested in the respiratory effort, inspiratory V_T (V_{Ti}) was used for the analysis of volume. Most of the mask leak arises from pressurization of the mask when inflations are given; leak rarely occurs during spontaneous breaths. Signals were only analyzed when there was no mask leak. V_{Ti} and expiratory V_T (V_{Te}) were determined, percent leak was calculated by the difference between the V_{Ti} and the V_{Te} using the formula $([V_{Ti} - V_{Te}]/V_{Ti}) \times 100\%$. However, a discrepancy between V_{Ti} and V_{Te} could also reflect a relative increase in FRC.[15] To differentiate between mask leak and increase in FRC, the following rules were maintained: when inspiratory flow did not return to zero before the end of inflation, this was considered to be leak. When inspiratory flow wave did return to zero, the difference between V_{Ti} and V_{Te} was most likely a change in FRC.

The characteristic flow patterns created by spontaneous breaths have been described in detail in a previous publication.[2] Spontaneous breaths were identified during CPAP (**Figure 1**, A), in between inflations (**Figure 1**, B), and coinciding with inflations (**Figure 1**, C and D). Because the inflation can contribute to the V_T, the V_T of breaths coinciding with an inflation were only included in the V_{Ti} and MV analyses when the flow signal of the spontaneous breath returned to baseline, resulting in 2 separate flow peaks (**Figure 1**, D). However, when the flow signal did not return to baseline before a second flow peak was formed (**Figure 1**, C), V_T could not be differentiated from the volume of the inflation. These breaths were excluded from the V_{Ti} analysis, but were still counted as a breath for the RR. MV was then calculated using the average V_{Ti}.

SPSS (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, New York) was used for the statistical analysis. Descriptive statistics are presented as median (IQR) for nonnormally distributed values and number (%) for categorical parameters. Homogeneity between groups was tested with Mann-Whitney *U* tests or with χ^2 tests when the data was categorized. Reported *P* values are 2-sided and considered as statistical significant when $P < .05$. The outcome parameters of the groups were compared using a Mann-Whitney *U* test when non-normally distributed, and a χ^2 test when the data was categorized.

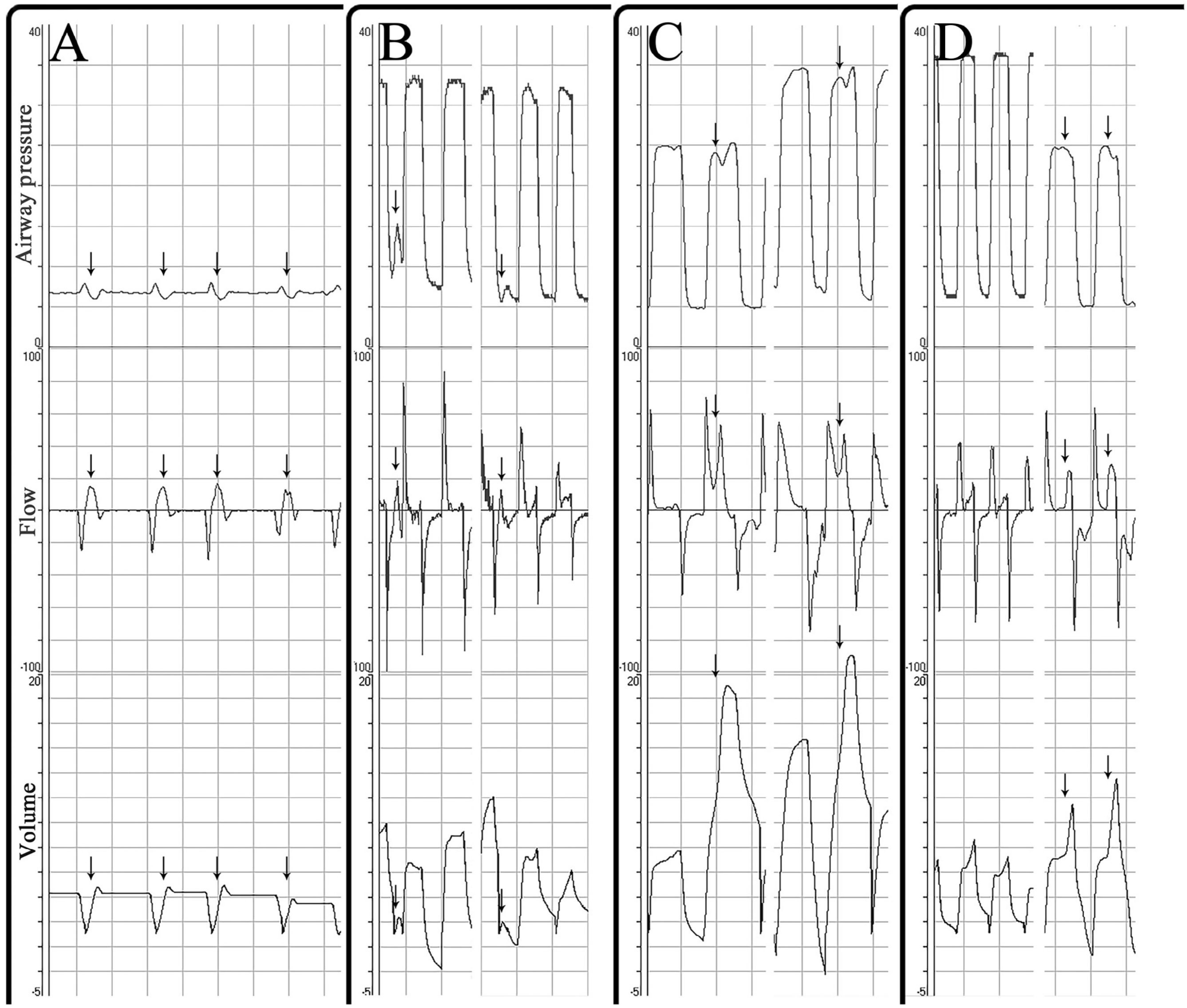

Figure 1. **A,** Spontaneous breathing during CPAP, **B,** Spontaneous breaths between manual inflations of PPV. **C,** Spontaneous breaths coinciding with manual inflations were the flow wave does not return to baseline. **D,** Spontaneous breaths coinciding with manual inflations were the flow-wave returned to baseline before forming a second flow peak. The depicted arrows show where a spontaneous breath is taken.

Results

In total, 154 recordings were reviewed, of which 36 recordings were excluded for congenital anomalies (n = 6), receiving mask-bag ventilation (n = 6), not receiving any respiratory support (n = 9), and persistent large mask leak during both periods (n = 15).

Recordings from 118 infants were suitable for analysis, of which 87 infants were allocated to the PPV group and 31 infants to the CPAP group. The infants receiving PPV were younger (28 weeks [IQR, 26-29] vs 29 weeks [IQR, 29-30; $P < .001$]) and the birth weight was lower (1059 g [IQR, 795-1300] vs 1205 g [IQR, 956-1418; $P = .06$]) compared with the CPAP group. Except for the Apgar score at 1 minute (5 [IQR, 3-6] vs 7 [IQR, 6-8; $P < .001$]), the characteristics of the 2 groups were not different (Table).

At 28 seconds after birth (IQR, 12-40), the infants were placed on the resuscitation table. During the first 2 minutes, a total of 1473 spontaneous breaths were recorded, of which 1055 breaths (71%) could be analyzed for V_{Ti}, MV, and number of recruitment breaths. At 5 minutes, 3175 spontaneous breaths were recorded, of which 2676 (84%) could be analyzed. In the PPV group 32 of 78 infants (41%) still received PPV at 5 minutes, and 46 of 78 infants (59%) were breathing on CPAP.

Table. Demographic and clinical characteristics of the studied infants

Characteristic	CPAP (n = 31)	PPV (n = 87)	P
Gestation (wk)	29 (29-30)	28 (26-29)	<.001
Birth weight (g)	1205 (956-1418)	1059 (795-1300)	.06
Male	19 (61)	51 (59)	.85
Celestone administration	11 (36)	26 (31)	.67
Cesarean delivery	22 (71)	43 (51)	.06
PROM	4 (13)	15 (18)	.53
IUGR	10 (32)	19 (23)	.31
Preeclampsia	11 (36)	20 (24)	.23
Apgar score at 1 minute	7 (6-8)	5 (3-6)	<.001
Apgar score at 5 minutes	8 (7-9)	7 (6-8)	.48

IUGR, Intrauterine growth restriction; *PROM*, premature rupture of the membranes.
Values are median (IQR) or n (%).

In the first 2 minutes, the V_{Ti} was significantly smaller in the PPV group compared with the CPAP group (3.1 mL/kg [IQR, 1.6-5.2] vs 4.1 mL/kg [IQR, 2.2-7.6; $P < .001$]). Similarly, the RR was significantly lower (10 breaths/minute [IQR, 5-16] vs 33 breaths/minute [IQR, 28-44; $P < .001$]) in the PPV group compared with the CPAP group, leading to a significantly lower MV for spontaneous breathing during PPV (37 mL/kg/minute [IQR, 15-69]) vs mL/kg/minute 188 [IQR, 128-297; $P < .001$]).

At the fifth minute, the V_{Ti} was significantly less in the PPV group compared with the CPAP group (3.7 mL/kg [IQR, 2.1-5.8] vs 5.0 mL/kg [IQR, 3.5-7.0; $P < .001$]). The RR was also significantly lower in the PPV group (33 breaths/minute [IQR, 21-45] vs 40 breaths/minute [IQR, 29-48; $P = .03$]), leading to a significantly smaller spontaneous breathing MV in the PPV group (112 mL/kg/minute [IQR, 46-229] vs 205 mL/kg/minute [IQR, 174-327; $P < .001$]).

The V_{Ti} of the infants that still received PPV at 5 minutes was smaller compared with the infants that switched to CPAP (2.5 mL/kg [IQR, 1.1-4] vs 4.2 mL/kg [IQR, 2.6-6.2; $P < .001$]). The RR was lower (19 breaths/minute [IQR, 7-27] vs 42 breaths/minute [IQR, 32-48; $P < .001$]), as was MV (42 mL/kg/minute [IQR, 15-77] vs 189 mL/kg/minute [IQR, 120-270; $P < .001$]).

The 25th percentile for MV in the CPAP group was 128 mL/kg/minute. Although 75% of infants in the CPAP group had an MV greater than this value in the first 2 minutes, only 18% of infants in the PPV group had an MV above this value ($P < .001$). At the fifth minute, more infants in the PPV group had MVs above the 25th percentile of MV in CPAP group (>205 mL/kg/minute), but was still significantly fewer than in the CPAP group (31% vs 75%; $P < .001$).

Significantly fewer recruitment breaths (>8 mL/kg) were observed in the PPV group when compared with the CPAP group (0 breaths/minute [IQR, 0-1] vs 4 breaths/minute [IQR, 1-8; $P < .001$]) at 2 minutes. Although fewer recruitment breaths were recorded during the fifth minute compared with the first 2 minutes in both groups, recruitment breaths continued to be less common in the PPV group (0 breaths/minute [IQR, 0-3] vs 2 breaths/minute [IQR, 0-11; $P = .01$]).

HR was significantly lower in the PPV group compared with the CPAP group (94 beats/minute [IQR, 68-128] vs 124 beats/minute [IQR, 100-144; $P = .02$]) in the first 2 minutes, as was SpO_2 (50% [IQR, 35%-66%] vs 67% [IQR, 34%-80%; $P = .04$]; **Figure 2**). There was a trend toward a higher FiO_2 given to the infants in the PPV group (30% [IQR, 21%-53%] vs 21% [IQR, 21%-29%; $P = .05$]; **Figure 2**).

At 5 minutes, HRs and SpO_2 levels were similar in the PPV and CPAP groups (149 breaths/minute [IQR, 131-162] vs 150 breaths/minute [IQR, 132-160; P = NS] and 91% [IQR, 80%-95%] vs 92% [IQR, 89%-97%; = NS]). However, this was achieved with a significantly higher FiO_2 requirement in the PPV group (39% [IQR, 22%-91%] vs 22% [IQR, 21%-31%; $P = .003$]).

Discussion

This observational study demonstrated that most very preterm infants receiving PPV breathe spontaneously at birth, but the respiratory effort was lower when compared with infants receiving CPAP only. The V_{Ti} was significantly lower in infants receiving PPV when compared with infants receiving CPAP, both in the first 2 minutes and at 5 minutes.

Predominantly owing to a large difference in RR, the MV was significantly lower in the infants receiving PPV. Moreover, infants receiving PPV rarely took recruitment breaths in the first 2 minutes, and SpO_2 and HRs were lower and more oxygen was required. Although it remains difficult to define adequate breathing at birth and the decision to apply PPV or only CPAP can be subjective, our findings indicate that the respiratory efforts made by preterm infants receiving PPV were probably not sufficient to sustain the infant's respiratory needs. It is questionable whether these respiratory efforts contributed significantly to the stabilization of the infant, but they likely assisted the PPV by contributing to the transpulmonary pressure gradient during the inflation and ensuring the glottis was open.

This study adds new information comparing the V_{Ti} and MV of only spontaneous breaths between infants receiving PPV and infants breathing on CPAP. Previous studies have compared the V_T of infants receiving PPV vs CPAP, but the reported V_{Te} was the result of breaths vs inflations given by PPV.[4,8,11] The volumes we observed do not contain volumes of inflations during PPV and are, therefore, lower than the V_{Te} reported in previous studies.[8,11] Although Kaufman et al and Schilleman et al do not report MV, the V_T we measured is comparable with the spontaneous breath volumes they measured between PPV inflations.[2,4] Kang et al measured much higher MVs compared with our results, but they included volumes from positive pressure inflations.[11]

More data are available for the V_T of preterm infants breathing on CPAP, and we observed comparable V_{Ti} of the infants breathing on CPAP to the volumes reported by those studies.[2,4,10,11,16-18] We found a median V_T of 4.4 mL/kg (IQR, 2.0-8.3) in the first 2 minutes and 5.3 mL/kg (IQR, 3.8-7.3) in the fifth minute, whereas most studies describe a V_T ranging between 4 and -8 mL/kg in the first 5 minutes.[10,11,16-18] Te Pas et al measured MV values that were comparable with our findings.[18] Similarly, Mian et al reported MV similar to ours in the

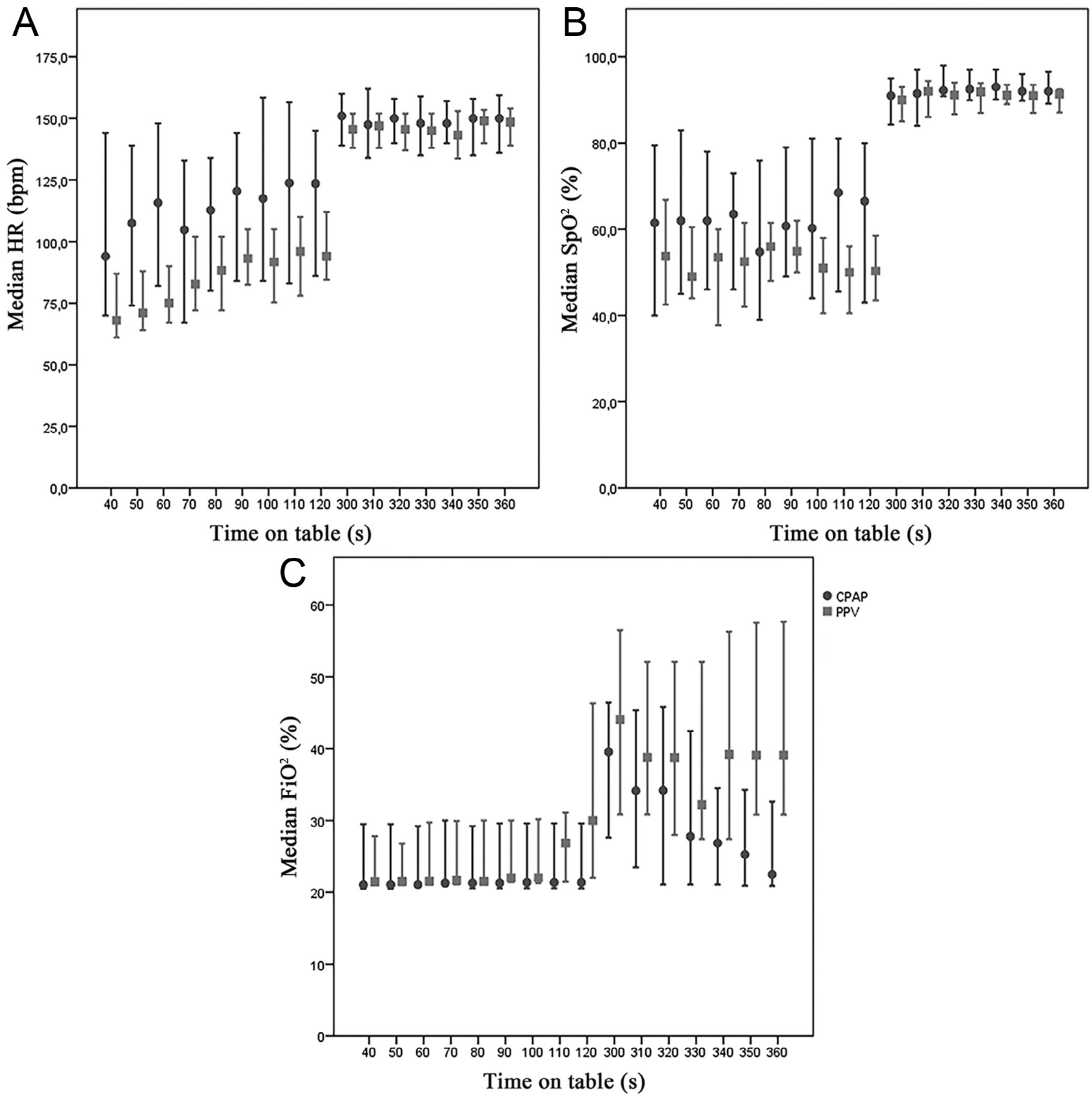

Figure 2. **A,** Median HR with 95% CI. **B,** Median SpO_2 with 95% CI. **C,** Median FiO_2.

first 2 minutes and at 5 minutes,[10] but they included more mature infants in their study. In a separate study, Mian et al also reported much lower MV in the first minute directly after birth.[16] Other studies reported a higher MV in infants breathing on CPAP, which was mostly due to a higher RR.[4,11,17]

Because the infants breathing on PPV had a lower gestational age, they were more likely to have weak inspiratory efforts that were insufficient to adequately aerate the lung at birth.[1] Rather than the degree of respiratory effort, it is possible that the lower V_T generated were due to the younger gestational age of infants receiving PPV, but no such correlation has been demonstrated so far. In contrast, te Pas et al previously reported that V_T relative to body weight are similar in preterm vs term infants breathing on CPAP.[17] It is also possible that the respiratory drive was more suppressed in infants receiving PPV as they were more hypoxic during the first 2 minutes after birth. Hypoxia is known to inhibit fetal breathing movements owing to a direct inhibitory input into the respiratory center,[19] and this inhibitory effect of hypoxia persists well into the newborn period,[19] particularly in preterm infants,[20] and likely causes closure of the larynx.[21] It is not surprising, therefore, that better oxygenation has been shown to improve respiratory drive in preterm infants.[22]

In this a retrospective observational study, the caregiver decided whether PPV or CPAP should be given. Despite using HR and SpO_2 in making this decision, it seems that this decisions remains a subjective choice and is not solely based on the available objective parameters. A second limitation is that not all breaths could be analyzed. Because we were interested in respiratory effort during inspiration, we only assessed breaths where leak was absent. However, we think that the average V_{Ti} of the breaths that could be analyzed, which we used to calculate MV, is a good reflection of all the spontaneous breaths. Another limiting factor was the use of pulse oximetry in the assessment of HR. Van Vonderen et al reported an underestimation of HR by pulse oximetry compared with electrocardiographs in the first minutes after birth.[23] However, in our study the HR of both groups would presumably have been underestimated to the same degree. Furthermore, currently all the available nomograms are based on the HR derived from pulse oximetry.

In conclusion, the respiratory effort of very preterm infants receiving PPV was significantly lower when compared with the infants receiving CPAP. Although most infants breathe spontaneously during PPV, it is unlikely that the observed low respiratory effort contributed sufficiently to stabilization. Although the decision to apply PPV or only CPAP remains subjective, we speculate that the reduced breathing effort we observed justified the application of PPV in most of the infants. An RFM with a visible display of the pressure, flow, and volume curves could help in a more objective assessment of the adequacy of breathing, because it makes the effort of spontaneous breaths visible for the clinician.[24] ■

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