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Ärztlicher Direktor: Professor Dr. C.F. Poets

Effect of four different nasal ventilation and CPAP systems on bradycardia and desaturation events in preterm infants

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Dekan:	Professor Dr. I. B. Autenrieth
1. Berichterstatter:	Professor Dr. C. F. Poets
2. Berichterstatter:	Professor Dr. M. Hofbeck

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List of abbreviations

CPAP	continuous positive airway pressure
nCPAP	nasal CPAP
IPPV	intermittent positive pressure ventilation
nIPPV	nasal IPPV
AOP	apnea of prematurity
NICU	neonatal intensive care unit
CER	cumulative event rate
AFRT	artefact-free recording time
RR	respiratory rate
HR	heart rate
SpO_2	arterial oxygen saturation
IFD	Infant Flow Driver
PEEP	positive end-expiratory pressure
PIP	inspiratory pressure

1 Introduction

Continuous positive airway pressure (CPAP) has been used as respiratory support in neonatal care since first described by Gregory in 1971(1). Nasal CPAP (nCPAP) is widely established as an effective treatment, both for the successful weaning from endotracheal intermittent positive pressure ventilation (IPPV) (2) and in the management of apnea of prematurity (AOP) (3). AOP is a common problem in preterm infants (4) and mostly treated with methylxanthines and/or nCPAP. Physiological effects of nCPAP potentially related to AOP include improved oxygenation (5, 6) and lung function (7, 8), reduced upper airway resistance (9, 10), stenting of the upper airway (3), and preservation of lung volume (11). Different nCPAP/nIPPV generators and modes are currently available, but have not yet been compared with regard to their treatment efficiency for the cumulative event rate of bradycardia and desaturation as a primary endpoint.

1.1 Study aims

The purpose of this study was to evaluate three nCPAP/nIPPV systems compared to the standard ventilator on our neonatal intensive care unit (in nIPPV mode) for their effect on bradycardia and desaturation events in preterm infants.

2 Patients and Methods

2.1 Patients

Between June 2004 and January 2006, inborn infants admitted to the neonatal intensive care unit (NICU) at Tuebingen University Hospital were screened for eligibility. Inclusion criteria were i) gestational age at birth < 34 weeks, ii) postconceptional age and body weight at study ≤38 week and >1000 g, respectively, and iii) requirement for nCPAP to treat AOP as judged by the attending neonatologist. Infants with congenital or chromosomal abnormalities, acute infections, intraventricular hemorrhage, additional inspired oxygen to maintain pulse oximeter saturation SpO2 >92%, or patent ductus arteriosus were excluded. Written informed parental consent was obtained for each infant. Twenty-two infants met inclusion criteria, but in 6, parents did not give consent. Therefore, a total of 16 infants were enrolled.

2.2 Study design and protocol

A randomized trial with a cross-over design and 4 treatment phases was conducted. Following recruitment, infants were allocated to a random sequence of four different nasal CPAP/nIPPV devices. The random sequence, corresponding to a 4x4 Latin square, was created by Byers´ random selection algorithm (12). Each device was applied for 6 h, yielding 24 h per patient total study duration. Infants were fed in 2 h intervals and received their routine nursing care while placed in an isolette at thermoneutrality and in a prone, 15° head-up tilt position. The study protocol was approved by the Ethics Committee of Tuebingen University Hospital.

2.3 Study variables

The primary outcome measure was the cumulative event rate (CER) of all bradycardias and desaturations per hour of artefact-free recording time (AFRT). Secondary study variables were the baseline respiratory rate (RR), heart rate (HR) and arterial oxygen saturation measured by pulse oximetry (SpO_2), apneas, desaturations, and bradycardias per hour and the proportion of time spent with bradycardia and/or desaturation.

2.4 Recordings

The following signals were monitored throughout and recorded by a computerized polysomnographic system (Embla N7000 and Somnologica Studio 3.0, Embla Inc.; Broomfield, USA): Chest and abdominal wall movements (respiratory inductance plethysmography, Embla) (Figure 1), pulse waveform and oximeter saturation (Radical with 2 s averaging mode, Masimo Inc.; Irvine, USA), electrocardiography and beat-to-beat heart rate (Embla), esophageal pressure (Microtip catheter, Mammendorfer Institute; Hattenhofen, Germany) and digital black-and-white video frame (Panasonic; Japan). Airway pressure was measured in line, close to the nostrils, via a built-in pressure transducer (Embla). The recording is shown in Figure 2.

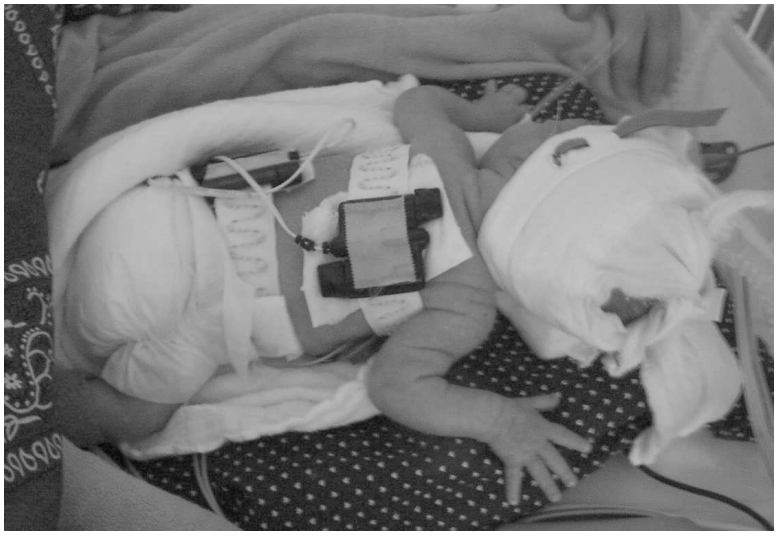

Figure 1: Measurement of chest and abdominal wall movements.

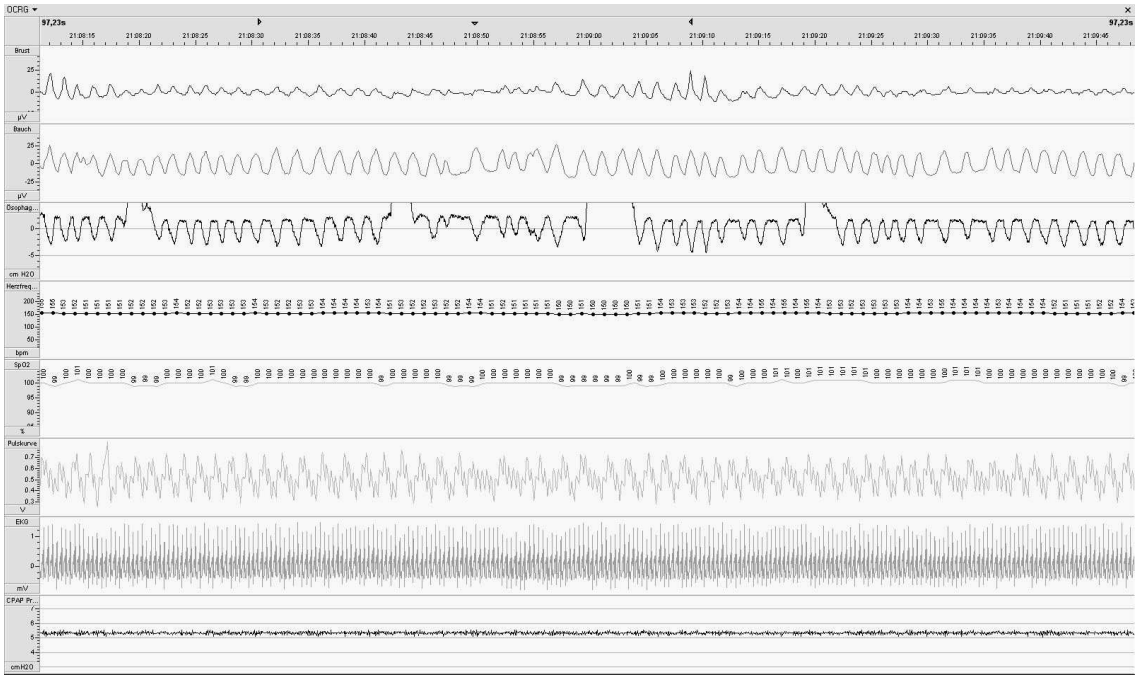

Figure 2: Section of a recording displaying the monitored signals (from top to bottom: chest wall movements, abdominal wall movements, esophageal pressure, heart rate, oximeter saturation, pulse waveform, electrocardiography, airway pressure)

Recordings were anonymized prior to analysis. The author (J.S.) who analyzed the recordings was not involved in clinical management, and analysis of cardiorespiratory events was done without access to the video frame to ensure blinding to the CPAP generator used. Total and artefact-free recording time (AFRT) was determined. AFRT was defined as all quiet resting periods minus nursing and feeding times. Recordings were then analyzed manually for the presence of central apneas, desaturation events, and bradycardias. A central apnea was scored if (i) the amplitude of the chest and abdominal wall movement channel fell to <20% of the average amplitude of the preceding breaths, (ii) no breathing movements were detected on the esophageal pressure channel, and (iii) the event comprised at least 10 s (13). Mixed/obstructive apnea could not be analyzed because the CPAP systems did not allow airflow recordings. A desaturation event was defined as a fall in SpO_2 to ≤80%. A bradycardia was defined as a fall in HR to ≤80 beats/min for more than one beat (Figure 3). Desaturation events with a distorted pulse waveform

signal within 7 seconds prior to their onset were considered artifactual and excluded (these 7 s being the signal processing time of the pulse oximeter). Bradycardias with a distorted electrocardiography signal immediately prior to their onset were also excluded. This was to exclude spurious events caused by body movements. A typical apnea followed by bradycardia and desaturation is shown in Figure 3.

Baseline HR and SpO_2 were defined as the mean of the respective parameter within AFRT and calculated using Somnologica Studio 3.0 (Embla). Respiratory rate (RR) was measured over one minute during each period of regular breathing; the mean of these values was calculated to determine an infant's baseline RR (14).

Finally, event rates for central apneas, desaturations and bradycardias were calculated as the number of respective events per hour of AFRT. The relative cumulative event time was calculated as the summed duration of all bradycardias and desaturations divided by AFRT and multiplied by 100.

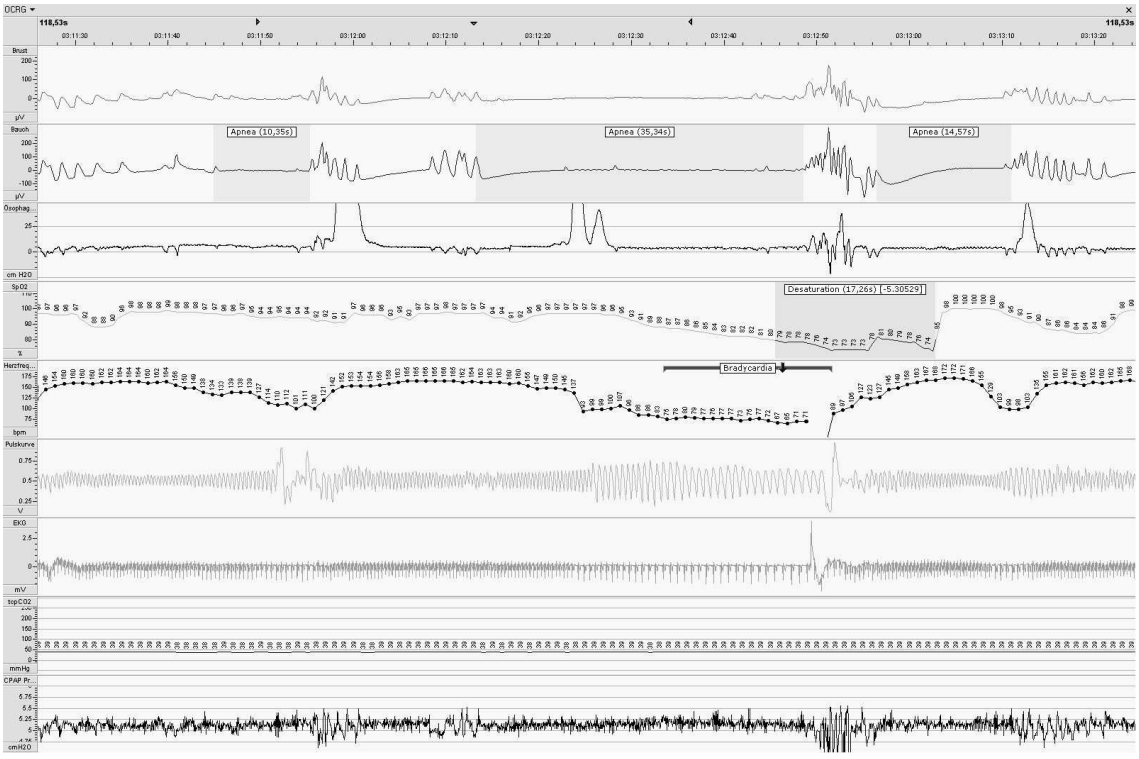

Figure 3: An apnoe followed by bradycardia and desaturation

2.5 Respiratory devices and drivers

CPAP was delivered via binasal prongs using the following systems:

(1) a conventional ventilator, which is the standard device on our NICU (Stephanie^{TM}, Stephan GmbH; Gackenbach, Germany) (Figure 4) delivering nIPPV via Hudson prongs (Hudson RCI; Temecula, USA) (Figure 5);

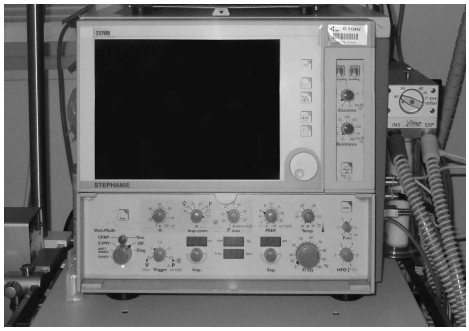

Figure 4: Stephanie^{TM}

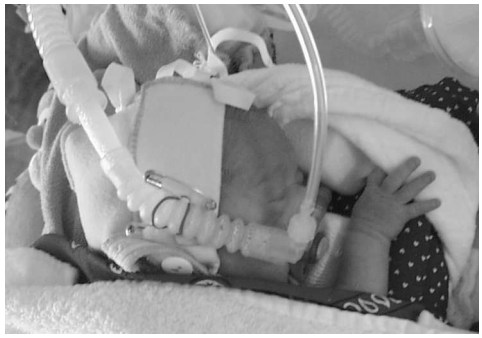

Figure 5: nIPPV delivered via Hudson prongs

(2) the Infant Flow Driver (IFD); Electro Medical Equipment; Brighton, UK) (Figure 6), delivering CPAP via specially designed binasal adapter devices of the Infant Flow system (Figure 7);

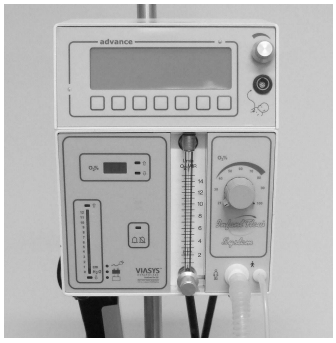

Figure 6: Infant Flow Advance^{TM} System

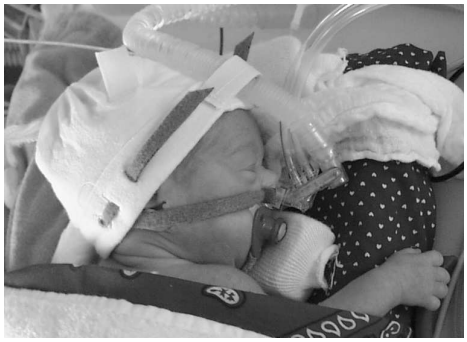

Figure 7: CPAP/nIPPV delivered via prongs of the Infant Flow System

(3) the Infant Flow Advance^{TM} System (Figure 6) in un-synchronized pressure assist (IPPV) mode (Electro Medical Equipment), delivering nIPPV via the same short binasal prongs (Figure 7);

(4) an underwater bubble CPAP (Figure 8) with Hudson prongs (Figure 9).

Figure 8: The expiratory limb of the Hudson prong is placed underwater

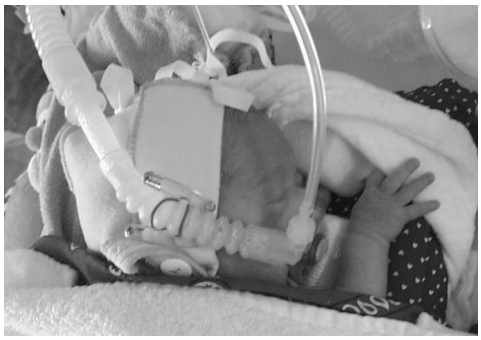

Figure 9: Bubble CPAP delivered via Hudson prongs

All systems were adjusted to achieve an approximate positive end-expiratory pressure (PEEP) of 5-6 cm H_2O. The systems were regularly monitored and flow adjusted to keep PEEP constant. Prong size was chosen to comfortably fit the infants' nostrils. IPPV was delivered with a peak inspiratory pressure (PIP) of 15 cm H_2O at a rate of 10 per min and an inspiratory time of 0.4 s; flow was usually 6 L/min, but could be increased up to 15 L/min by the Stephanie^{TM} ventilator to compensate for air leaks. The IFD delivered PEEP via a flow of 7-10 L/min. Inspiratory pressure with the Infant-Flow-Advance^{TM} system was achieved by adding a peak flow of 5 L/min above baseline, thereby achieving a PIP of 10 cm H_2O at a rate of 10 per min. Flow for the bubble CPAP (6 L/min) was delivered using the flow generator of the IFD with the end of the expiratory limb being placed 6 cm underwater (15).

2.6 Statistical analysis

The primary study variable was the cumulative event rate (CER) of all bradycardias and desaturations per hour of AFRT. Sample size calculations were based on a pilot study comprising 5 patients. This study revealed an expected overall mean of 7.5 events/h and a variance across treatments of 6.25. Hence, 30 study participants were considered sufficient to detect a treatment effect of +/- 2.5 events/h with a 0.05 type-I and 0.2 type-II-error. An interim analysis was planned to be performed after 16 patients. Using the O´Brien-Fleming criteria (16), the study would have been terminated if the actual p-value was <0.0052.

However, recruiting took longer than expected due to a lack of eligible patients. Most infants on the NICU either needed additional oxygen while on CPAP or did no longer need CPAP once in room air. Hence, the study was terminated after 16 patients and the analysis protocol changed. Initially, we had intended to compare each CPAP device with all others. Now, the protocol was changed to compare 3 test devices to the Stephanie^{TM} device, because this was the standard device used in our NICU.

Descriptive statistics as numbers and percentages as well as median, minimum, and maximum were used to summarize demographic and clinical characteristics. Comparisons between treatment modalities (i.e. CPAP devices) adjusted for study phase, interaction (study phase x treatment), and random effects (i.e. individuals) were done using univariate analysis of variance (ANOVA). Pair-wise post-hoc comparisons with the standard device as reference were performed using Dunnett’s t-test, if the global test (i.e. ANOVA) revealed significant differences between treatment modalities. All statistical hypothesis tests on the primary study variable were done after performing a Box-Cox transformation to obtain an approximately normally distributed test variable.

Non-parametric tests for paired data (i.e. Friedman's and Wilcoxon's test on ranks) were used for secondary study variables. Pair-wise comparisons using Wilcoxon's test were performed if the global test (i.e. Friedman's test) revealed significant differences between treatment modalities.

A statistical test result was considered significant if the corresponding p-value was less than 0.05. No adjustment for multiple testing was performed for secondary study variables. All analyses were done with statistical software packages: sample size calculations were done using nQuery Advisor 4.0 (Statistical Solutions; Saugus, USA), the remaining analyses were done using SPSS 12.0 (SPSS Inc.; Chicago, USA).

3 Results

Demographic and clinical characteristics of enrolled infants (N=16; 10 boys, 6 girls) are presented in Table 1. All infants were receiving caffeine as a respiratory stimulant.

Table 1.
Demographic and clinical characteristics of enrolled infants (N=16).

Characteristic	Median	Minimum	Maximum
Birth weight (g)	1013	480	1360
Gestational age at birth (wk)	28	24	29
Body weight at study (g)	1275	1030	1740
Age at study (d)	18	3	70
Corrected gestational age at study (wk)	31	28	34

The mean artifact-free recording time (4.7-5.0h) did not differ significantly between treatment modalities (Table 3).

When treated with the Stephanie^{TM} device, median CER was more than twice as high as with the IFD (2.8 vs. 6.7 events/h), and 50% higher than with the Infant Flow Advance^{TM} system (4.4 events/h). There was no significant difference to the underwater bubble CPAP (5.4 events/h). There was no significant study phase and interaction (treatment x phase) effect. (Table 2 and Figure 10)

Table 2.
The primary study variable: the cumulative event rate of all bradycardias and desaturations per hour of AFRT
p-Value delivered by Dunnett's t-test with the standard device (Stephanie™) as reference.

Device	Median	Min	1st Quartile	3rd Quartile	Max	p-Value
Infant Flow ™	2.8	0.0	1.5	7.7	36.6	0.023
Infant Flow Advance™	4.4	0.4	0.9	7.5	22.9	0.029
Bubble CPAP	5.4	0.5	3.0	9.8	24.7	0.756
Stephanie™	6.7	0.5	2.1	16.8	45.2	

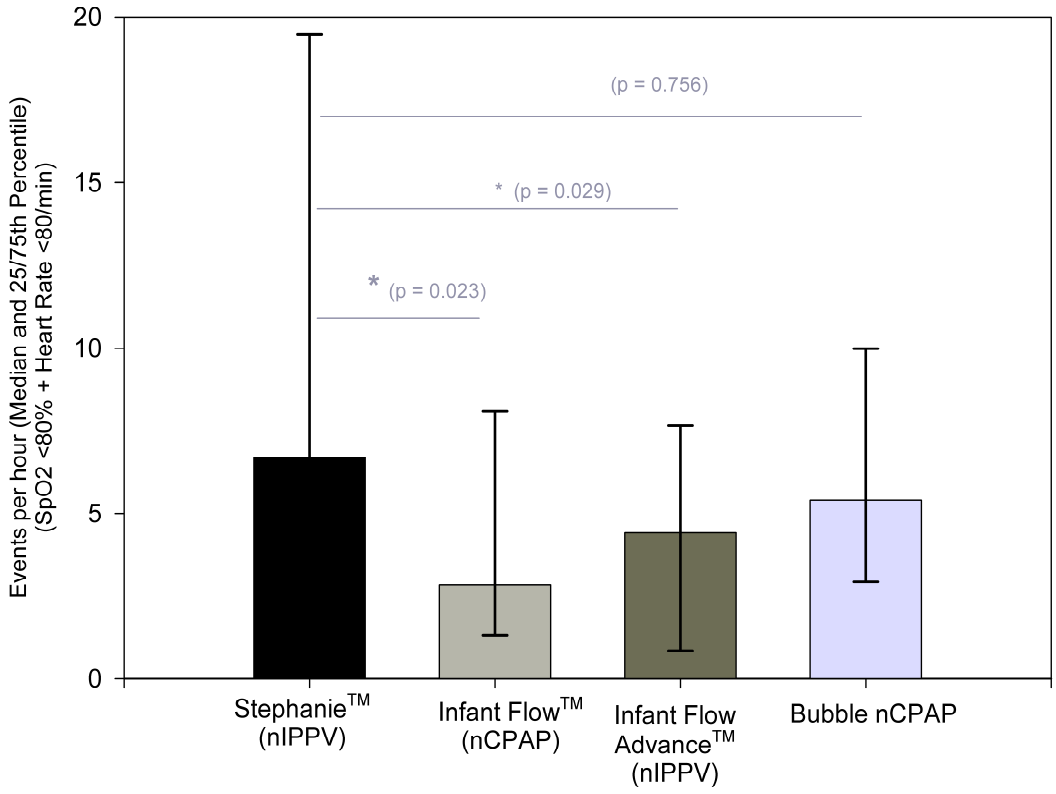

Figure 10: The primary study variable: the cumulative event rate of all bradycardias and desaturations per hour of artefact-free recording time (column median of the cumulative event rate; error bars = 1st and 3rd Quartile)

Concerning secondary study variables, baseline HR was significantly higher with the standard device (Stephanie^{TM}) than with either the Infant Flow Advance^{TM} or the bubble CPAP system, and baseline SpO_2 was significantly lower than with any other nCPAP/nIPPV device.

Total duration of bradycardia and desaturation was approximately halved with either Infant Flow device compared to the Stephanie^{TM} device, but this difference did not reach statistical significance (Table 3). All other secondary study variables (relative cumulative event time, apnea, desaturation, or bradycardia rate, baseline heart or respiratory rate, baseline SpO_2) were not significantly different between devices (Table 3). There was no severe adverse event (e.g. pneumothorax) observed with any system.

Table 3. Secondary study variables
(expressed as median (minimum-maximum))
p-Value delivered by Dunnett's t-test with the standard device (Stephanie™) as reference.

	Infant Flow™	Infant Flow Advance™	Bubble CPAP	Stephanie™
Relative cumulative event time (%)	0.4 (0.0-5.4)	0.4 (0.0-2.6)	1.1 (0.1-3.4)	0.8 (0.0-7.4)
Artefact free recording time (h)	4.8 (3.2-5.7)	5.0 (1.9-5.7)	4.7 (2.7-6.0)	4.9 (1.6-4.9)
Apneas (event/h)	3.7 (1.1-26.4)	4.5 (0.7-26.7)	6.4 (0.9-24.1)	3.4 (1.1-19.5)
Desaturations (event/h)	1.6 (0.0-36.2)	2.8 (0.0-21.9)	3.6 (0.0-24.3)	5.0 (0.0-44.8)
Bradycardias (event/h)	0.4 (0.0-3.1)	0.4 (0.0-4.4)	0.8 (0.0-6.3)	0.7 (0.0-3.0)
Baseline heart rate (Beats/min)	165 (144-178)	163 (145-180) p=0.047	163 (150-177) p=0.005	167 (150-181)
Baseline respiratory rate (Breaths/min)	53 (35-89)	56 (28-93)	54 (33-93)	56 (34-84)
Baseline SpO2 %	97 (95-99) p=0.002	96 (95-99) p=0.004	96 (95-99) p=0.01	96 (93-98)

4 Discussion

This study compared the effect of different devices for positive pressure support via binasal prongs on bradycardia and desaturation in infants with AOP. We found that a device that reportedly reduces work of breathing in infants (17) was significantly more effective in reducing the frequency of desaturation and bradycardia than a conventional ventilator used in nIPPV mode.

Various aspects of nCPAP delivery via conventional nCPAP devices have been compared to the IFD (18-22), showing a reduced oxygen requirement (20, 22, 23), work of breathing (24), and extubation failure with the IFD (21). Other investigators, however, could not show such differences (18, 21), and no study differentiated between effects related to the mode of application (double vs. single prongs) vs. the mode of flow generation (conventional vs. IFD). This is why we only included binasal CPAP devices in this trial.

One study compared a conventional nCPAP system in intubated infants with the underwater bubble CPAP and found a 39% reduction in minute volume and a 7% reduction in respiratory rate with the latter, but no change in blood pCO_2 or SpO_2 (25). Another study measured work of breathing with a bubble CPAP system compared to the IFD (26). It found a significantly lower resistive work of breathing and less thoraco-abdominal asynchrony with the latter, although the difference between the IFD and the bubble CPAP device was not as large as between the IFD and a conventional CPAP system.

The optimal PEEP for nCPAP treatment of AOP is unknown. Evidence suggests, however, that a PEEP of 5-6 cm H_2O in infants with no or only mild residual lung disease provides the best trade-off for both, keeping the upper airway open and avoiding lung overdistension (15).
The reason(s) why nCPAP is effective for AOP are incompletely understood. An early study found an effect only on obstructive, not on central apneas, pointing to an effect via mechanical stenting of the airway (3). Our study design did not

allow for a differentiation between obstructive and central apneas. The degree of airway stenting, however, depends on PEEP, and this was the same with all devices tested. Also, a growing body of evidence suggests that the distinction between obstructive and central apnea is somewhat arbitrary, i.e. that both represent two extremes of the interplay of forces regulating upper airway patency and diaphragmatic activity (27).

Baseline SpO_2 was significantly lower with the conventional nIPPV than with any of the other devices. While the median difference in SpO_2 may seem small, an increase in SpO_2 from 95.6 to 97.0%, as seen here with the change from the Stephanie^{TM}-device to the IFD, corresponds to an increase in arterial pO_2 by 13 mm Hg (28), suggesting that the IFD, the Infant Flow Advance^{TM} system and the bubble CPAP were more effective in improving ventilation-perfusion matching than the Stephanie^{TM}-device. Whether this difference, via its effect on the control of breathing (29), contributed to the decreased rate of bradycardia and desaturation with the IFD, or whether this was primarily due to a reduced work of breathing (17) is yet unclear.

While the mode of flow generation clearly had an effect on bradycardia and desaturation, adding intermittent positive pressure support had very little effect. This is surprising given that synchronized nIPPV is more effective than nCPAP in preventing extubation failure (30). This difference may be related to the fact that we used the Stephanie^{TM} ventilator in un-synchronized mode. This is because synchronized IPPV is not in use in the NICU where the study was conducted for concerns related to hyperventilation.
The reason we used our standard device in nIPPV-mode is that all modes applied in this study were treatment regimes randomly (i.e., depending on the neonatologist in charge) used in our NICU for infants in whom conventional CPAP fails.

Further limitations include the fact that only infants on room air were studied, which made recruitment more difficult and ultimately changed the protocol. This was considered necessary to separate out the effects of O_2 from the effects of the devices used to treat AOP. The change in study design, however, may have disguised a potential difference between bubble CPAP and the IFD, or between the IFD in CPAP vs. IPPV mode with regard to their effect on the cumulative event rate. It is unlikely, however, that a clinically relevant difference was missed given the small differences in bradycardia and desaturation rates observed between these systems and modes. Also, our decision to exclude infants on additional inspired oxygen led to the exclusion of infants with more severe residual lung disease.

Obstructive apneas could not be detected. This was because the nasal prongs used with the IFD and Infant Flow Advance^{TM} System prevented the use of a sensor to measure nasal airflow. Furthermore it was found impossible to maintain the esophageal catheter in a position that permitted reliable pressure measurements throughout the 24-h study period for detecting phase shift in the pressure curve during obstructive apneas.

Exclusion of distorted pulse waveforms and electrocardiography signals preceding an event may have concealed desaturation or bradycardia events during obstructive apneas, but was considered inevitable to ensure exclusion of spurious events. The focus of our study was on the effect of different nasal support systems on bradycardia and desaturation rather than on apnea type, which is why we considered this flaw in study design acceptable.

In conclusion, this study has shown marked differences in the effect different nasal respiratory support systems have on bradycardia and desaturation in a select group of infants with AOP who were already off oxygen. A nCPAP system that reduces work of breathing was found to be more effective in reducing bradycardia and desaturation than one delivering nasal ventilation via a conventional ventilator. Further data are needed to see whether synchronized nasal ventilation via the IFD reduces AOP even further.

5 Abstract

Apnea of prematurity (AOP) is a common problem in preterm infants, which is often treated with nasal Continuous Positive Airway Pressure (nCPAP) or nasal intermittent Positive Pressure Ventilation (nIPPV). It is unknown which type of nCPAP/nIPPV device is most effective.

Objective: To analyze the effect of three nCPAP/nIPPV systems, compared to a standard ventilator in nIPPV mode, on bradycardia and desaturation.

Study design: 16 infants (mean gestational age at study 30.6 wk) were enrolled in a crossover trial. They were randomly allocated to receive nCPAP/nIPPV for 6 hours each, using either our standard ventilator in nIPPV mode (Stephanie^{TM}), the Infant Flow^{TM} device in nCPAP-mode, the Infant Flow Advance^{TM} system in nIPPV mode or an underwater bubble-CPAP system. Chest and abdominal wall movements, pulse oximeter saturation and electrocardiogram were recorded. Primary outcome was the cumulative rate of bradycardia and desaturation events per hour.

Results: The median event rate was 6.7/h with the Stephanie^{TM}, compared to 2.8/h and 4.4/h with the Infant Flow^{TM} or Infant Flow Advance^{TM} system ($p<0.03$). There was no significant difference to bubble-CPAP (5.4/h).

Conclusion: The Infant Flow^{TM} Driver was found to be more effective in reducing bradycardia and desaturation in preterm infants than a system delivering nIPPV via a conventional ventilator.

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Curriculum vitae

Date of birth	April 14th, 1981
Place of birth	Heidelberg
Marital status	Unmarried
Nationality	German

Professional experience

since March 2008	Assistent doctor at children hospital Worms

Professional education

April 2001 – Nov 2007	Medical studies at University of Tübingen
November 22th, 2007	„2. Staatsexamen“; Grade 2
July 2004 – April 2008	Dissertation (intensive care unit at Tübingen University Hospital)
August 2006 – August 2007	Clinical elective (Klinikum Esslingen / Gesundheitszentrum Fricktal, Switzerland)
June/July 2006	Medical elective (Perth, Australia)
2003 - 2006	Several medical electives (internal medicine, surgery, pediatrics)
March 21th, 2003	„Physikum“; Grade 2,66

School education

June 21th, 2000	„Abitur“ at Gymnasium Neuenbürg; Grade1,5