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Original Investigations

Consecutive Study of Early CPAP-Application in Hyaline Membrane Disease*

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Abstract. Continuous positive airways pressure (CPAP) has been applied with a face-chamber in 74 infants with hyaline membrane disease (HMD) before 10 h of age. The total survival rate was 91% and the complication rate of pneumothorax was low (5%). The incidence of long term developmental and neurological sequelae was also low (4%). Among the 19 surviving very low birth-weight (VLBW) infants below 1501 g, only one has shown neurological sequelae at follow-up examinations after 18 months to 3 years of age. The incidence of cerebellar hemorrhage was not higher in infants treated with the CPAP face chamber than in infants not receiving assisted ventilation. Bronchopulmonary dysplasia did not occur in any infant treated with CPAP face chamber only. The main advantages with the face chamber technique are: no disturbance of glottis function, no mucosal damage and tube obstruction, or sudden pressure drops, as seen with other modes of CPAP application. The face chamber technique is suitable for early application of CPAP in infants with HMD as it is efficient, without hazards, and easily applied.

Key words: Neonate – Hyaline membrane disease – Continuous positive airways pressure.

Continuous positive airways pressure applied via a face chamber (CPAP-f.c.) for treatment of infants with hyaline membrane disease (HMD) has been described previously [1, 3]. The results were comparable to those reported by other investigators [5, 7, 17, 26, 30]. However, our findings suggested that further improvement might be obtained if CPAP-f.c. was applied as soon as HMD was diagnosed. The present investigation was undertaken to evaluate the survival rate, the rate of pulmonary and cerebral complications—especially the incidence

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of cerebellar hemorrhage—and the effect of early CPAP in very low birth weight infants. The rate of pulmonary and neurodevelopmental long term sequelae after early CPAP has also been studied.

Material and Methods

The present study is comprised of 74 consecutive infants with HMD in whom CPAP-f.c. was started within 10 h of age. The diagnostic criteria for HMD (clinical, radiological and estimated right-left shunt) are shown in Table 1. The chest X-ray was graded as showing a reticulogranular pattern (HMD I) or opaque lung fields with bronchogram (HMD II), according to Prod'hom et al. [29].

Before CPAP application a postductal umbilical artery catheter had been inserted for arterial blood gas and pH analysis using an Instrumentation Laboratory Blood Gas Analyzer-413. Venous admixture (right-left shunt) was assessed according to Gupta et al. [18].

The face chamber with its supporting intensive care crib, gas mixer and humidifier (Fc 100, Siemens-Elema AB, Solna, Sweden) (Fig. 1) has been presented previously [3]. When HMD had been diagnosed according to the criteria shown in Table 1, CPAP-f.c. treatment was started with a pressure of 4—6 cm H_2O and an inspired O_2 concentration of 40%. If grunting continued the pressure was increased in steps of 2 cm H_2O up to 8 or 10 cm H_2O.

At an arterial pO_2 less than 7 kPa (53 mm Hg) the oxygen concentration of the inspired gas was increased in steps of 10%, aiming at arterial pO_2 between 7 and 10 kPa. When clinical, radiological and laboratory data (pH and blood gases) showed definite improvement CPAP treatment was tailed off, starting with 2- to 6-hourly stepwise 5% reductions of inspired O_2 concentration down to 40%. Thereafter the pressure was lowered stepwise by 2 cm H_2O every 6 to 24 h. Each step was followed by clinical re-evaluation and repeated blood gas analyses. The weaning from CPAP generally takes 1 to 2 days.

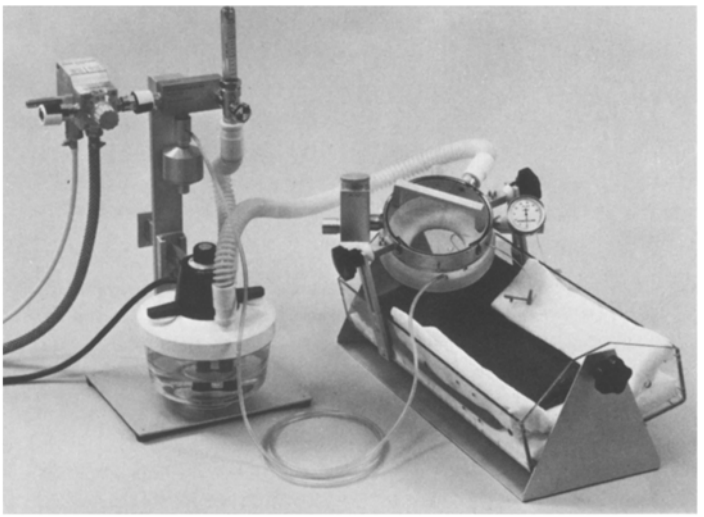
Intermittent positive pressure ventilation (IPPV) via nasoendotracheal tube (Portex size 2.5 to 3) was started if recurrent apnoeic spells or increasing pCO_2 occurred, or decreasing arterial pO_2 values indicated an increasing venous admixture in spite of CPAP treatment. The Servo Ventilator 900 B (Siemens-Elema AB) or Amsterdam Infant Ventilator (Loosco) were used for pressure-cycled ventilation. Positive end expiratory pressures (PEEP) of 2 to 5 cm H_2O were used during IPPV treatment. At weaning from IPPV, extubation was immediately followed by CPAP application with the face chamber with slow lowering of pressure from 4—6 to 2 cm H_2O over a period of 12 to 48 h as described earlier [11].

All surviving infants have been examined in the special follow-up outpatient clinic at 3 to 6 months interval for at least 18 months to 3 years. Follow-up included the following studies: ophthalmological and neurological examination, and chest X-ray before discharge; developmental and neurological examination at every visit; and audiometry at 10—14 months of age.

For statistical comparison of groups Chi-square and Student's *t*-test have been used.

Table 1. Diagnostic criteria for hyaline membrane disease (HMD)

Clinical (2 or more)	Grunting Tachypnoea (above 60/min) Intercostal/sternal retraction Cyanosis
Radiological	Reticulogranular pattern (HMD I) Opaque lung fields with bronchogram (HMD II)
Venous admixture (estimated right-to-left shunt)	More than 30% or rising above 30% (corresponding to arterial pO_2 less than 8.5 kPa in 40% inspired oxygen)



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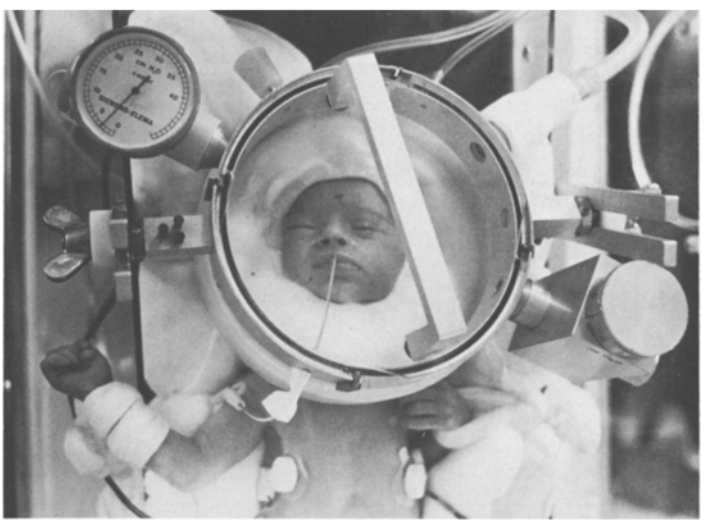

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Fig. 1. a) O_2 and air are mixed in a gas mixer (to the left). The gas flow is regulated with a flow meter and fed to a humidifier and then to the face chamber. The gas leaves the chamber via a pressure-regulating valve adjusted according to the reading on a manometer. A water seal can be connected to one of the port holes of the chamber. The face chamber is hinged on an intensive care crib facilitating the care and providing truly continuous positive airways pressure during nursing, feeding (via a gastric tube), X-ray and transportation. **b)** A close up of the infant and the face chamber

Results

Effects of Early CPAP-f.c. on HMD

In 56 of 74 cases (76%) early CPAP-f.c. was fully successful, i.e. adequate oxygenation (PaO_2 7—10 kPa and right-left shunt < 30%) was obtained and the HMD treatment could be accomplished with CPAP-f.c. only. In 18 cases CPAP-f.c. was replaced by IPPV. A compilation of the most relevant clinical data is shown in Table 2. The mean birth weight, gestational age and 5-min Apgar score were significantly lower in the group of infants requiring IPPV. As expected, these infants were more seriously affected as judged by chest X-ray and estimated venous admixture. These 18 cases are further described in Table 3.

In 6 of 7 fatal cases (No. 1—7, Table 3) IPPV had to be started within 22 h because of apnoea related to the complications shown in Table 3.

In case 8 with HMD only, and in case 9 with patent ductus arteriosus as well, CPAP-f.c. was replaced by IPPV during the first day because of progressive signs of HMD with rising $PaCO_2$ and increasing venous admixture. These were the only cases without severe complications in which CPAP-f.c. had an inadequate effect concerning oxygenation and shunting.

In cases 10—18 an adequate effect of CPAP-f.c. was observed during the first 24 h. Consequent apnoeic spells were associated with a patent ductus arteriosus (case No. 10) and sepsis (case 11—15). No reason other than immaturity appears to account for the apnoeic spells in cases 16—18 which were classified as apnoea repetens or the respiratory insufficiency syndrome of immaturity [11].

Mortality

Table 4 shows the number of survivors and the total survival rate. The total survival rate was 91% and 98% in infants above 1500 g. In the infants with birth weights less than 1501 g (range 800—1500 g) the survival rate was 19 out of 25

Table 2. Infants treated early with CPAP-face chamber. *Group A: CPAP-f.c. only. Group B: CPAP-f.c. + IPPV as well.* Data are given as mean and range

	A ($n = 56$)	B ($n = 18$)	P-value
Birth weight (g)	2045 (950—3800)	1360 (800—2340)	—
Gestational age (weeks)	33.3 (29—36)	30 (28—34)	—
Apgar score at 5 min	7.5 (4—9)	5.6 (1—9)	—
Chest X-ray: HMD I	33	6	$P < 0.05$
HMD II	23	12	$P < 0.05$
Venous admixture: 30%—50%	44	9	$P < 0.05$
>50%	12	9	$P < 0.05$
Age at start of CPAP (hours)	4.4 (2—10)	4.5 (1—10)	n.s.
Duration of CPAP-treatment (days)	4.5 (1.5—9)	1.9 (0.2—6)	—
Maximal pressure applied (cm H_2O)	6.0 (4—10)	6.5 (4—11)	n.s.

Table 3. Infants treated with early CPAP-f.c. and IPPV (group B)

No.	Birth weight (g)	Gest. age (weeks)	Apgar score (5 min)	Age at start CPAP (h)	Age at start IPPV	Duration of IPPV	Clinical course Autopsy finding ( )
1	800	26	5	7	11 h	24 h	Died (HMD, IVH)
2	2120	34	4	7	14 h	5 h	Died (HMD, IVH, CH) (Breech delivery)
3	1000	30	4	2	22 h	13 h	Died (HMD, IVH, CH, Septicemia-E. coli, DIC) (Transverse delivery)
4	1270	28	5	1	7 h	9 d	Died (HMD, IVH, Septicemia-β strept. B)
5	1000	28	5	1	15 h	10 d	Died (HMD, IVH, Septicemia-β strept. B)
6	1330	30	1	4	3 d	2 d	Died (HMD, IVH, Septicemia-candida)
7	1500	31	4	2	22 h	1 d	Died (HMD, IVH, CH, hypoplastic left heart)
8	2100	35	6	10	16 h	6 d	Sequelae: none
9	1300	32	4	3	6 h	14 d	Persist. duct. art. Sequelae: none
10	1030	28	9	7	1½ d	26 d	Persist. duct. art. Sequelae: none
11	1000	29	5	4	3 d	15 d	Septicemia. Sequelae: spastic diplegia
12	2340	34	3	8	1½ d	16 d	Septicemia. Sequelae: none
13	1400	29	9	4	4 d	6 d	Septicemia. Sequelae: none
14	970	28	9	2	6 d	46 d	Septicemia. Sequelae: none
15	1980	31	8	5	1 d	3 d	Septicemia. Sequelae: none
16	900	28	5	8	3 d	7 d	Apnoea repetens. Sequelae: none
17	1300	30	8	2	2 d	4 d	Apnoea repetens. Sequelae: none
18	1150	29	8	5	5 d	9 d	Apnoea repetens. Sequelae: none

HMD, hyaline membrane disease; IVH, intraventricular hemorrhage; CH, cerebellar hemorrhage; DIC, disseminated intravascular coagulation

Table 4. Results of early CPAP-f.c. treatment of HMD

Treatment	All infants		Infants > 1500 g		Infants < 1501 g	
	N	Survivors	*N*	Survivors	*N*	Survivors
CPAP-f.c. only	56	56	45	45	11	11
CPAP-f.c. + IPPV	18	11	4	3	14	8
Total	74	67	49	48	25	19
Survival rate		91%		98%		76%

(75%). There were 7 infants below 1001 g and 4 survived. CPAP-f.c. was the only treatment in 11 VLBW-infants and had an initially adequate effect on arterial oxygenation in 10 of the remaining 14 VLBW infants. However, IPPV was required because of apnoea related mainly to complicating septicemia and recurrent apnoea of immaturity, as shown in Table 3. Six of 7 non-survivors (case 1—7, Table 3) were VLBW-infants. At autopsy intraventricular hemorrhage (IVH) was found in all 7 and cerebellar hemorrhage in 3 (vide infra). All 7 babies who died had 5-min Apgar scores of less than 5, indicating severe perinatal asphyxia.

Pulmonary Complications

In 4 of 74 infants (5%) pneumothorax occurred during CPAP-f.c. application. However, the CPAP treatment was successfully concluded in all 4 cases. Four additional cases of pneumothorax developed during later IPPV. All cases of pneumothorax were treated with continuous pleural drainage.

Bronchopulmonary dysplasia was not seen in any of the 54 infants treated with CPAP-f.c. only but was diagnosed in 5 of 11 surviving infants also treated with IPPV. Clinical symptoms of obstructive bronchitis subsided and chest X-rays gradually normalized within the first year of life. All five infants had normal lung mechanics—as measured according to Ahlström and Jonson [2]—at 6 to 10 months of age.

Neurological Sequelae

Late neurological sequelae were found in 3 of 67 surviving infants, i.e. 4%. Hydrocephalus developed in one child after neonatal meningitis with group B streptococci. Cerebral palsy (diplegia) was present in two infants, one treated only with CPAP-f.c. the other with IPPV as well (case No. 11 in Table 3). This is the only child with late neurological sequelae among the 19 surviving VLBW-infants. Psychomotor retardation has not been observed so far in any child in the study.

Apart from two infants with slight-to-moderate strabismus, all infants were normal at ophthalmological and audiological follow-up. No case of retrolental fibroplasia has been found.

Other Complications. Small cutaneous scars, the longest one 0.5×1.5 cm, at the hair line or under the chin due to the face mask were seen in five surviving infants. In only two cases was the scar clearly visible at 18 months of age.

Discussion

In a previous study [3] we found that treatment with the CPAP-f.c. technique was efficient in most cases of HMD (see Table 5). In that study CPAP was started at 3 to 30 h of age when the arterial pO_2 fell below 100 mm Hg (12.5 kPa) while breathing 100% oxygen. The total mortality rate was 15%. However, 22% required IPPV—5 of 34 infants with births weights more than 1500 g and 4 of 5 VLBW infants (mean birth weight 1300 g, range 1020—1500 g). It was supposed that an earlier start of CPAP-f.c. might be advantageous. However, it was considered unethical to start yet another controlled trial as stated by Chernick 1973 [13] and Roberton 1976 [32].

Consequently, during the following two years CPAP-f.c. treatment was started as soon as HMD had been diagnosed according to the criteria presented in Table 1, i.e. at a mean age of 4.5 h (range 1 to 10 h).

In this study with *early* CPAP-f.c. the mortality rate was 9%. The difference in survival rate is not statistically significant (P-value > 0.05) but it should be noted that only 4 of 49 HMD infants above 1500 g needed IPPV and only 1 infant died, i.e. the survival rate was 98% as compared to 85% in such infants in the previous study.

Although early CPAP-f.c. application will reduce the number of infants who need IPPV and possibly the duration of IPPV, an adequate IPPV technique will be necessary in a few non-responders and infants with late complications [6].

The effect of CPAP in VLBW-infants has been considered unsatisfactory [8, 25]. In this study CPAP-f.c. was fully adequate in 11 out of 25 VLBW infants (mean birth weight 1100 g, range 800—1500 g). Only 14 (56%) needed IPPV compared to 4 out of 5 (80%) in our previous study. The VLBW-infants requiring later IPPV may possibly have benefited from CPAP-f.c.with delayed intubation and IPPV in several cases. Thus early CPAP with the face chamber also seems to be advantageous for VLBW infants.

Lately CPAP has been questioned as the therapy of choice for HMD and the *mode of application* has also been widely discussed. Several clinical studies of CPAP therapy for HMD have shown results that have been considered successful. CPAP has been applied by various means such as endotracheal tube, nasal prongs, face masks, face chambers and devices for continuous negative body pressure, as shown in Table 5. In two controlled studies using CPAP via face mask a significant increase in survival was reported with early application [6, 30]. However, in the only controlled study with nasal prongs for CPAP published so far [25], and in another study with face mask [8], no difference was found. Discrepancies in clinical results are related to several factors. Differences in routine neonatal care, variations in the indications and postnatal age for starting CPAP, and *technical problems* with the CPAP method must be taken into consideration. Such problems are, for instance, tube obstruction or displacement, unavoidable

Table 5. CPAP-treatment of HMD

Authors	Method	Number of cases	Survival rate	CPAP failure (%)	Survival rate among CPAP failures (%)	Incidence of pneumothorax
Gregory et al. (1972) [17]	CPAP via endotracheal tube	78	80%	24%	26%	10%
Kamper et al. (1972) [23]	CPAP via endotracheal tube	36	56%	67%	33%	9%
Chernick et al. (1972) [12]	Continuous negative body pressure	23	100%			13%
Fanaroff et al. (1973) [16]	Continuous negative body pressure	15	73%	33%	20%	15%
Kattwinkel et al. (1973) [24]	CPAP via nasal prongs	22	86%	18%	25%	0
Harris et al. (1974) [20]	CPAP via nasal prongs	30	83%	20%	17%	10%
Risemberg et al. (1974) [31]	CPAP via nasal prongs	76	67%	25%	19%	3%
Boros et al. (1975) [9]	CPAP via nasal prongs	69	83%	22%	20%	4%
Krouskop et al. (1975) [25]	CPAP via nasal prongs	21	71%	28%		4%
Rhodes et al. (1973) [30]	CPAP via face mask	22	72%	29%	15%	5%
Allen et al. (1977) [6]	CPAP via face mask	24	83%	41%	60%	8%
Ahlström et al. (1976) [3]	CPAP-f.c.	39	85%	22%	33%	7%
Present study	CPAP-f.c.	74	91%	24%	61%	5%

mucosal damage [7, 14, 23, 25, 29], or considerable sudden and uncontrollable pressure drops or rises occurring with nasal prongs or endotracheal tubes [4, 10, 25, 26]. These problems, which may be crucial for the eventual outcome of CPAP treatment, are avoided by the face-chamber technique.

The face-chamber can be easily applied by a trained nurse. Naso-oral suction is seldomly required as there are no tubes causing mucosal irritation. The glottis function and capacity to grunt is undisturbed, in contrast to cases treated with endotracheal intubation [3, 13]. Furthermore, the pressure can be kept constant without interruption during the crucial first 24—48 h [4]. Thereafter, the latex mask should be remolded to avoid undue pressure on sensitive skin areas.

Besides survival rate and technical problems, the incidence of *short term hazards and long term sequelae* must be taken into consideration when evaluating the total outcome. Hitherto the rate of long term sequelae has not been included in reports of CPAP treatment in HMD infants.

Bronchopulmonary dysplasia did not occur in this study, nor in our previous series [3], after CPAP-f.c. treatment alone. The bronchopulmonary dysplasia observed in 5 infants treated with IPPV in addition to initial CPAP was fully reversible. Infants in need of IPPV after initial CPAP-f.c. treatment could usually be ventilated with low airway pressures and oxygen concentrations. This may be of great importance in reducing the incidence and severity of bronchopulmonary dysplasia, as also observed by Allen et al. [6].

A link between CPAP treatment and *cerebellar hemorrhage* (*CH*) has been suggested [27]. The basis for this suggestion has been questioned by others [33]. For comparison we have reviewed all the postmortem examination charts of the 169 nonsurviving infants treated in our neonatal unit during the 6-year period 1971—1976. CH was found in 5 of 39 infants treated with CPAP—3 in the present study and 2 previous cases of whom one was treated with nasal CPAP. Thus the incidence among lethal cases treated with CPAP-f.c. was 4 out of 38 (10.5%). It should be noted that all infants treated with CPAP in the autopsy material had also been intubated and treated with IPPV via a nasotracheal tube before death. Among 81 dead infants treated only with IPPV via endotracheal tube, 10 (12%) had CH. Infants dying without having either IPPV or CPAP showed CH in 6 out of 50 cases (12%). Therefore CH was not seen more often after CPAP than after IPPV or in cases not given ventilatory support.

Among the 21 cases with CH at postmortem examination, 14 (67%) had been delivered in the breech (12 babies) or transverse positions. In the total autopsy material, breech or transverse position occurred in 33 out of 169 infants (20%). Furthermore, 13 of the 21 babies with CH at postmortem examination were VLBW-infants.

All 3 cases with CH in the present material had severe birth asphyxia and complications such as breech delivery, transverse delivery, septicemia with disseminated intravascular coagulation and hypoplastic left heart syndrome (Table 3).

Thus our present study and the autopsy review support the opinion [7, 15, 33] that intraventricular and cerebellar hemorrhage should be regarded as complications which are primarily related to the mode of delivery of vulnerable preterm infants [21].

The incidence of *neurological sequelae among survivors after early CPAP* was 4% in the present material. In our previous series [3] the incidence was 8% and this has remained unchanged at follow-up studies after 3 to 6 years. These figures of 4 and 8% are low in comparison to other published studies [27, 28].

The minor cutaneous scars seen in 5 children seem to be the only sequelae attributable to the face mask per se.

HMD is a disease characterised by rapid deterioration with sudden alveolar and airway collapse and hypoxia. It should be advantageous to break this vicious circle early by early application of truly continuous positive airways pressure.

Our conclusion is that CPAP-f.c. should be applied as soon as the diagnosis of HMD with a rising right-to-left shunt is established. An adequate initial response can be expected in almost every case, but IPPV will still be needed in exceptional nonresponders and if complications occur.

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