Negative pressure artificial respiration: Use in treatment of respiratory distress syndrome of the newborn

L. S. LINSAO, M.D., A. AHARON, M.D.,
H. LEVISON, L.R.C.P.I. and
P. R. SWYER, M.B., M.R.C.P.(LOND.),
Toronto

Summary: Forty-five newborn infants in respiratory failure with respiratory distress syndrome were treated with intermittent negative pressure ventilation (INPV). There was a survival rate of 38% (17/45).

All infants were initially treated without nasotracheal intubation. However, 24 of these developed a $PaCO_2$ *greater than 70 mm.Hg and were subsequently intubated. Intubation was followed by a decrease in the degree of hypercarbia in each instance and simultaneous increase in* PaO_2.

Complications encountered during ventilation were: emphysema (one patient), aspiration pneumonia (two patients), septicemia (two patients), misplaced nasotracheal tube (one patient).

Follow-up of the 17 surviving patients for periods of four to 36 months disclosed two patients with post-intubation hoarseness. One infant initially had spastic quadriplegia with EEG abnormalities, both of which cleared by 5 months of age. In the remaining 14 infants, the results of physical, neurological and psychological examinations have remained within normal limits.

It has been shown that mechanically assisted ventilation is capable of arresting, sometimes permanently, the respiratory failure of the respiratory distress syndrome (RDS).[1-8] This suggests that death may occur not only from inadequate gas exchange, but also from inability to maintain respiratory effort.

During the first 60 hours of RDS there is a high respiratory work rate compared with a relatively low oxygen uptake,[9] and it is reasonable to suggest that the required increase in the work of breathing is hindered by the restricted oxygen uptake in the acute stages of the disease.[10]

The rationale of artificial ventilation is to reduce the mechanical work of the infant's respiratory muscles while improving alveolar ventilation and intrapulmonary gas exchange, with reduction in both respiratory and metabolic acidosis. Approximately four years ago a negative-pressure, temperature servo-controlled, incubator-respirator (Air-Shields Isolette Respirator No. 5, Hatboro, Pennsylvania, U.S.A.) was developed.[11] The infant servo-controlled heating system is important since cycling of pressure to subatmospheric levels is associated with cooling. This paper reports the results of a trial of this unit.

Clinical subjects

Over a 24-month period 312 infants referred to the Neonatal Unit of The Hospital for Sick Children were assigned the diagnosis of RDS on the basis of the usually accepted clinical and radiological criteria.[13] None of the patients had received specific treatment before admission other than supplemental oxygen. Forty-five of these infants were treated in the incubator-respirator after deteriorating on conventional treatment to a condition where they showed (1) central cyanosis and/or (2) arterial oxygen tensions (Pa_{O_2}) below 50 mm.Hg after breathing over 95% oxygen for more than 15 minutes (Table I).

TABLE I
Distribution of patients according to criterion used for entering trial

Criterion for Ventilation	*Survivors*	*Deaths*	*Total*
Central cyanosis after 100% O_2 breathing for >15 minutes	5	20	25
$PaO_2 < 50$ mm. Hg after breathing 100% $O_2 > 15$ minutes	12	8	20
	17	28	45

From the Research Institute of The Hospital For Sick Children and the Department of Paediatrics, University of Toronto, Toronto, Ontario.

L. S. LINSAO, M.D., Fellow in Paediatrics, University of Toronto, Toronto, Ontario.

A. AHARON, M.D., Coutts Research Fellow, Research Institute, The Hospital For Sick Children, Toronto, Ontario.

H. LEVISON, L.R.C.P.I., Medical Research Council of Canada Fellow, 1965-66.

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Reprint requests to: DR. P. R. SWYER, The Hospital for Sick Children, 555 University Avenue, Toronto 5, Ontario.

Methods

Ancillary treatment, before and during assisted ventilation included oxygen administration in concentrations required to keep arterial oxygen tensions between 60 and 100 mm.Hg, parenteral 10% glucose and electrolytes, maintenance of body temperature by servo-control and administration of sufficient sodium bicarbonate to maintain arterial blood pH above 7.30.

The incubator-respirator is divided into two compartments by an adjustable iris diaphragm. The head compartment is independently ventilated and heated at atmospheric pressure. Within this compartment the patient's head is enclosed in a plastic bag through which flows warmed humidified gas at a rate in excess of 5 l. per minute. The body compartment, isolated from the head compartment by the iris diaphragm closed around the neck, is cycled to subatmospheric pressures by venting intermittently to a vacuum reservoir maintained by a pump. The internal air temperature of the incubator-respirator is servo-controlled from the abdominal skin by a thermistor with a set point of 36.5°C.[12] Inspiration and expiration times are independently variable and the settings determine the cycling frequency. We operated the unit as a controller, but selected a rate approximating the infant's spontaneous breathing frequency. As the condition improved, a rate of about 60 per minute was imposed and not generally resisted. The inspiratory time was approximately half the expiratory time. Subatmospheric pressures down to −35 cm. H_2O were used. The pressure, cycling frequency and inspired O_2 concentration were determined by the efficiency of gas exchanging ventilation. This was monitored by blood gas and pH analyses at 4- to 6-hourly intervals of arterial blood obtained by way of a catheter passed through the umbilical artery to the descending aorta at the iliac bifurcation. The aim was to keep the arterial CO_2 tension between 35 and 50 mm.Hg and the Pao_2 between 60 and 100 mm.Hg by manipulating the incubator pressure and inspired oxygen concentration. A lead II electrocardiogram was monitored by oscilloscope and audible signal.

The earlier patients in the series were not intubated. However, failure of immediate response to artificial ventilation along with persistently high arterial carbon dioxide partial pressures suggested that there might be some glottic obstruction. Twenty-four of the 45 patients were therefore intubated with an appropriately sized (No. 3-4) nasotracheal tube for two to 72 hours.

TABLE II
Results in 45 patients ventilated

	Patients	*Survivors*	*Deaths*
Male	31	11	20
Female	14	6	8
	45	17	28

As the condition of the surviving infants improved, lowered inspired oxygen concentrations (50 to 60%) were sufficient to maintain arterial oxygen tensions between 60 and 100 mm.Hg. Increasingly frequent and prolonged periods of spontaneous breathing were then allowed until normal blood levels of oxygen and carbon dioxide could be maintained without ventilatory assistance.

During this weaning period, percussion postural drainage was given every four hours and the nasopharynx was carefully sucked clear of secretions.

If the airtight seal of the incubator-respirator was broken to permit access for nursing or other procedures, the infant was manually ventilated by positive pressure through a face mask or endotracheal tube.

Feedings were given by nasogastric tube from the third or fourth day of life.

Arterial blood pH, Pco_2, Po_2 and hematocrit were serially measured in duplicate at 37°C. by methods previously described.[14] (No corrections were necessary for body temperature variation since colonic temperature was maintained within 0.5°C. of 37°C. by the temperature servo-control.)

Results

Forty-five patients were ventilated and 17 lived (Table II). Details of age on admission to hospital, gestational age, birth weight, age at start of intermittent negative pressure ventilation and duration of INPV and of the hospital stay are shown in Table III.

The tendency to acidemia, as judged by the amount of neutralizing bicarbonate given prior to INPV, was less in those who survived (mean 0.41 mEq./kg./hr.) than in the fatal cases (mean 0.86 mEq./kg./hr.). Following initiation of INPV the survivors required even less (mean 0.17 mEq./kg./hr.) than those who died (mean 1.35 mEq./kg./hr.).

Before assisted ventilation, arterial oxygen tensions below 50 mm.Hg and severe acidemia, pH < 7.1 ([H+] > 80 nEq./l.), with both metabolic and respiratory components were present. Within one hour of starting ventilation more improvement was shown in the survivors than in those who eventually died. These and other biochemical details are shown in Table IV.

The arterial blood chemistry of one of the ventilated patients who survived is shown in Fig. 1. The Pco_2 at

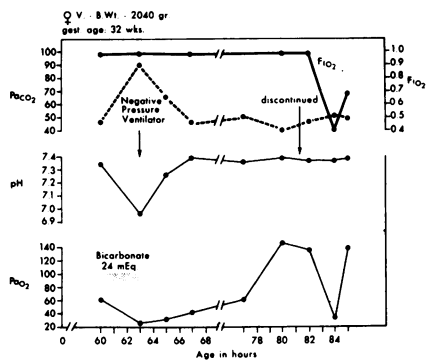

FIG. 1—Biochemical course of surviving patient.

TABLE III
Clinical characteristics of survivors and fatalities

	Mean	*Range*	*Standard Error*	*Significance of Difference (P value)*
1. *Age on admission* (hrs.)				
Survived	9.4	1-56	3.1	N.S.D.
Died	9.6	1-36	1.84	
2. *Gestation* (wks.)				
Survived	34.5	31-38	0.59	< .005
Died	32.0	24-40	0.61	
3. *Weight* (g.)				
Survived	2174	1440-2920	90	< .001
Died	1674	850-3200	105	
4. *Age at ventilation* (hrs.)				
Survived	37.32	3-87	5.57	< .001
Died	18.05	3.5-34	2.35	
5. *Duration of ventilation* (hrs.)				
Survived	39	14.5-82	4.31	N.S.D.
Died	33	1-169	7.76	
6. *Duration of hospital stay* (hrs.)				
Survived	1007	384-1560	88.8	< .001
Died	89	3-720	26.7	

TABLE IV
Biochemical characteristics before and within one hour after commencing INPV in the survivors contrasted with the fatalities

			n.	*Mean*	*Range*	*Standard Error*
[H+] (nano/eq./1)	before*	L	17	89	178-95	0.1
		D	28	102	178-52.5	0.015
	after*	L	17	58	100-40	0.01
		D	28	78	178-41	0.01
$Pa0_2$ (mm. Hg)	before	L	12	47	20-100	5.9
		D	13	37	18-70	4.5
	after	L	12	61	52-156	9.5
		D	15	57	30-142	9.2
$PaC0_2$ (mm. Hg)	before	L	17	76	36-120	6
		D	28	80	42-120	3.7
	after	L	17	59	36-86	3.5
		D	28	62	30-100	3.4
Buffer base p (mEq./l.)	before	L	17	35	26-48	1.7
		D	28	33	22-45	1.1
	after	L	17	40	32-52	1.3
		D	28	36	22-48	1.5
Bicarbonate infused (mEq./kg./hr.)	before	L	17	.41	.022-2.17	0.141
		D	28	.86	.036-4.90	0.227
	after	L	17	.166	.079-.442	0.239
		D	28	1.358	.039-7.812	0.345

*Values obtained immediately before and within one hour of starting INPV.

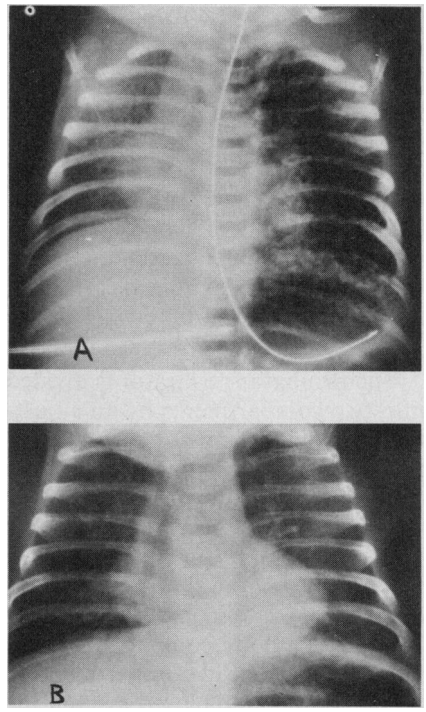

FIG. 2—Case 33, Birth weight 2040 g., gestational age 32 weeks. (a) Interstitial emphysema of the left lung during INPV. (b) Six weeks later, only slight accentuation of bronchovascular markings remains.

TABLE V
Complications or associated conditions

	No.	*Lived*	*Died*
Emphysema, interstitial (unilateral) left	1	1	
Pneumothorax (unilateral) left, prior to ventilation	2	2	
Aspiration pneumonia associated with RDS	2	1	1
Septicemia:			
Pseudomonas aeruginosa	1		1
Klebsiella pneumoniae and positive blood culture	1	1	
Hoarseness (post-intubation)	2	2	
Misplaced nasotracheal tube (esophagus)	1	1	
Hyperbilirubinemia, exchange transfusion	2	2	
26 endotracheal tube cultures:			
Pseudomonas aeruginosa	3	1	2
Aerobacter cloacae	1		1

the start of ventilation was over 90 and fell fairly rapidly to 45 mm.Hg. The pH was < 7.0 ($[H+] > 100$ nEq./l.) and was > 7.39 ($[H+] < 41$ nEq./l.) following ventilation. The initial Pa_{O_2} was 24 mm.Hg and the response to ventilation was somewhat slower than that of the other parameters, but nevertheless gradually improved to 65 over a 14-hour period.

Associated conditions (Table V)

Case 33 developed unilateral interstitial emphysema (Fig. 2a) at the 12th hour of ventilation using pressures of 30-35 cm. H_2O. In spite of this, ventilation was continued at these pressures and by the tenth day the left lung showed only an increase in bronchovascular markings (Fig. 2b) which have persisted for two-and-a-half years. This child has no symptoms. Three other patients had minor increases in bronchovascular markings which disappeared by 3 months of age.

No case of "broncho-pulmonary dysplasia"[18] was seen despite the administration of oxygen in the range of 80 to 90% for up to 96 hours.

Two cases of pneumothorax were detected before initiating INPV. Both infants had intercostal catheters inserted with suction drainage and both survived. No case of pneumothorax occurred during INPV.

Patient 12, who had been intubated for 97 hours, developed a Klebsiella pneumonia with septicemia on the fourth day and died at 193 hours despite treatment with cephalosporin. Patient 35 aspirated a feeding during the convalescent period after weaning from the incubator-respirator but recovered.

In one surviving patient, during reintubation following accidental extubation, the endotracheal tube entered the esophagus and had to be retrieved by esophagoscopy after the trachea had been correctly reintubated. Subsequently a new method of tube fixation modified by Tilak[19] from a method used by Thomas *et al.*,[6] requiring fixation by adhesive tape and sutures, was devised and has proved satisfactory.

Three patients were hyperbilirubinemic without blood group incompatibility; two of these had exchange transfusions; all survived.

Effects of nasotracheal intubation

Because of the possibility of laryngeal obstruction in seriously ill, comatose infants, 26 of the 45 patients received nasotracheal intubation. In only four (two lived, two died) was a marked fall in $Paco_2$ apparent, suggesting some relief of obstruction by the procedure. It is therefore suggested that if following initiation of INPV an immediate fall in $Paco_2$ does not occur, then a trial of nasotracheal intubation is justified, but that it should not be a routine procedure.

Eight of the 26 intubated patients survived. Four of these survivors were from the group of 15 intubated before INPV was started and four were among the 11 intubated after INPV had been started.

Condition of survivors

The survivors have been followed up by clinical, neurological, electroencephalographic, psychomotor and ophthalmological examination for periods varying from four to 36 months. All appear normal physically and mentally, though more prolonged follow-up is necessary in order to detect the less obvious manifestations of central nervous system damage, which may not be detectable for several years.

One patient at the conclusion of ventilation was obviously spastic and had definite EEG changes at 55 days of age. Further clinical and special examinations, including EEG, were normal at the age of 5, 11 and 30 months.

Two patients were transiently hoarse after extubation but there has been no evidence of persisting laryngeal or tracheal damage, either clinically apparent or on bronchoscopic examination (Dr. Blair Fearon).

Postmortem examination

Postmortem examination was performed in 21 of the 28 fatal cases. Hyaline membranes were found in the lungs of all (Table VI).

Light and electron microscopic examinations were performed on lung-tissue sections obtained by Menghini needle from 15 patients immediately after death. They were compared with sections from 12 infants who died from RDS and were not ventilated. No obvious differences were found. These findings have been reported separately.[15]

Central nervous system hemorrhages were present in 12 of 21 necropsies. The sites are indicated in Table VI. Four were intraventricular. The incidence of CNS hemorrhages is similar to that found in this centre in infants not treated by artificial ventilation.

TABLE VI
Postmortem findings in 21 of 28 fatal cases

Trachea:	
Superficial necrosis of lining mucosa	3
Heart	
Patent foramen ovale	18
Patent ductus arteriosus	21
Lungs	
Hyaline membranes	21
Atelectasis	19
Immaturity	20
Alveolar edema	5
Emphysema, patchy	2
Pulmonary hemorrhage – intra-alveolar, patchy	6
extensive	1
subpleural	1
Liver	
Hemorrhage (subcapsular) minimal	1
Brain	
subdural	1
Hemorrhage – intraventricular	4
subarachnoid	11
Cyst (septum pellucidum)	1

Discussion

Unpublished data of our own indicate that newborn infants with RDS and with a Pao_2 below 50 mm.Hg while breathing 100% O_2 have a greater than 90% chance of dying. These mortality figures are generally supported by those of Boston, Geller and Smith[16] and Stahlman *et al.*,[17] and can be compared with the mortality of 62% in our patients treated by INPV. Our patients are all outborn and are transferred to our unit. Thus many patients in this series were in poor condition when ventilation was started. It is possible that earlier intervention when the infant is in better condition would improve results. Silverman *et al.*[11] have demonstrated in a limited controlled study that such earlier intervention at least does not increase mortality.

Our experience suggests that a useful salvage of 20 to 30% can be obtained by the use of INPV in infants who are dying from respiratory failure due to RDS. More prolonged follow-up to school age is necessary to establish their neuropsychiatric integrity.

As noted previously in relation to patients treated by positive-pressure ventilation,[2,5] the infant most likely to survive weighs more than 1800 g. and has a gestational age of more than 33 weeks. The survival rate at levels above these was 60% while below them it was 10.5% ($P < .05$). It also appears that survival rate is significantly better (62% as opposed to 17.4%, $P < .05$) if the infant breathes spontaneously for longer than 24 hours (Fig. 3). However, examination of Fig. 3 shows that generally only infants weighing more than 1800 g. at birth have this capability, so there is no appreciable increase in prognostic precision to be gained from an analysis of the age of respiratory failure compared with the prognosis based on birth weight alone.

If, on the other hand, an infant weighed less than 1800 g. at birth and required assisted ventilation within 24 hours, the survival rate was only 12.5%. Our smallest surviving infant weighed 1450 g. We believe that the physical buffeting inevitable with INPV is deleterious to infants below 1500 g. in weight and of questionable benefit to those between 1500 and 1800 g.

Installation of a baby in the incubator-respirator had many practical problems in matters of nursing access, radiography and physical examination. Each procedure required breaking the seal in the body compartment, with resulting cessation in ventilatory assistance. Under these circumstances respiration was assisted temporarily by positive pressure applied through a mask or nasotracheal tube.

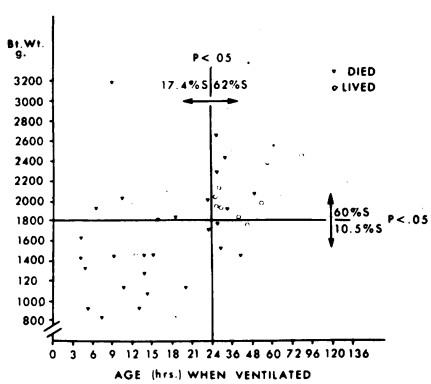

FIG. 3—Scattergram of birth weight plotted against age of starting ventilation, with mortalities of 45 patients with respiratory failure due to RDS. S=survival.

Abdominal distension, common during RDS, may be increased during INPV and may require orogastric tubal decompression. Feeding is also a problem, especially if ventilation is continued for longer than three days. Fifteen per cent glucose, protein hydrolysates and plasma infusions help to provide nutritional support, but adequate calorie intake is difficult to achieve. Nasogastric tube feeding is hazardous because of the danger of aspiration. Constant nursing alertness is the only defence. The risks may have to be accepted.

All types of artificial ventilation in infants impose a very heavy burden on medical, nursing and laboratory staff. Artificial ventilation should not be used unless adequate staff and equipment are available on a 24-hour basis.

The entire body below the neck, including the heart and the great vessels, is subjected to subatmospheric pressures during inspiration, and therefore the gradient between peripheral and central venous pressure should not be altered. Venous return from the head should be aided since the head remains at atmospheric pressure. During inspiration alveolar capillary transmural pressure, diameter and blood flow will depend on the difference between the driving pressure (pulmonary artery pressure–left atrial pressure) and the alveolar pressure, which approaches a maximum equal to atmospheric at the end of inspiration at varying velocities and times, depending on the lung regional time constants. In so far as subatmospheric pressures are communicated indirectly through the thoracic wall to the intrapulmonary capillaries, intracapillary pressure might be lowered to a greater extent than intra-alveolar pressure. The resulting transmural pulmonary capillary pressure would tend to constrict the vessels and lower or prevent blood flow. The degree to which this would occur in any region would depend on the temporal and absolute relationships in the changes in pressure in the pleural space, pulmonary blood vessels and alveoli.

Experimental work on isolated dog lungs under negative pressure ventilation suggests that lung volume is a more direct determinant of pulmonary vascular resistance than transpulmonary pressure.[21] At the extremes of deflation and inflation pulmonary vascular resistances were highest at a constant blood perfusion pressure. It is not clear how these findings obtained under static conditions in normal isolated dog lungs can be applied to the diseased lungs of infants under dynamic conditions of changing transpulmonary pressure and pulsatile blood flow. However, they do suggest that the geometry of the lung parenchyma is an important factor in determining blood flow. If INPV helps to prevent progressive lung deflation, then pulmonary blood flow might be aided in a condition in which pulmonary hypoperfusion has been implicated.[20]

On theoretical grounds, therefore, there is some reason for believing that INPV and IPPV are not analogous in their effects on hemodynamics. This reasoning requires to be tested by animal experimentation.

We wish to thank the physicians of The Hospital For Sick Children, Toronto, for permission to treat and investigate patients under their care. Miss W. A. Hannah and the nurses of the Neonatal Unit made possible the management of these patients. We thank Dr. Maria Arstikaitis for the ophthalmoscopic examinations and the physicians of the Department of Neurology for the electroencephalographic studies. Dr. J. U. Balis performed postmortem microscopic studies on the lungs. Mr. D. McIntosh helped technically. We thank Mrs. C. Robinson and Miss P. Taggett for secretarial assistance.

Addendum

Since this paper was completed, a report has been published by Stern *et al.*[22] detailing the results in a series of newborn infants with respiratory failure treated by the same type of incubator-respirator as the one we have used.

Résumé

Respiration artificielle à pression négative: mode de traitement du syndrome de la souffrance respiratoire chez le nouveau-né

Nous avons traité par ventilation à pression négative intermittente (VPNI) 45 nouveau-nés qui présentaient une insuffisance respiratoire dépendant du syndrome de la souffrance respiratoire. Cette méthode nous a donné une proportion de survie de 38% (17 sur 45).

Au début, nous avons appliqué ce traitement sans intubation endotrachéale. Mais comme 24 de ces enfants présentaient une $Paco_2$ supérieure à 70 mm de Hg, nous avons décidé de les intuber. Cette manœuvre s'est traduite dans chaque cas par une diminution de l'hypercapnie et par une augmentation concomitante de la Pao_2.

Parmi les complications que nous avons rencontrées figuraient: emphysème (un malade), pneumonie par aspiration (deux malades), septicémie (deux malades), mauvaise position du tube endotrachéal (un malade).

La catamnèse des 17 survivants durant une période variant de quatre à 36 mois a révélé une raucité vocale relevant de l'intubation chez deux malades. Un nourrisson présenta au début une quadriplégie spasmodique avec anomalies de l'EEG, qui disparurent à l'âge de 5 mois. Chez les 14 enfants restants, tous les examens somatiques, neurologiques et psychologiques sont demeurés dans leurs limites normales.

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