The cardiovascular and intracranial effects of laryngoscopy and endotracheal intubation in hypercarbic neonatal piglets

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ostract **Laryngoscopy and endotracheal intubation is a potent sympathetic stimulus in adults. Neonates are frequently intubated, but few data exist on the cerebral effects of this intervention. The cardiovascular and intracranial effects of laryngoscopy and endotracheal intubation were studied in 17 hypercarbic neonatal piglets. The mean arterial pressure in the study group (11 piglets) increased significantly within 2 minutes of the stimulus, and remained elevated for almost 14 minutes. The intubated animals showed significantly more haemorrhage in the basal area of the brain than the 6 control animals. The distribution suggests bleeding in the choroid plexus of the 4th ventricle. The significance of such bleeds is not immediately apparent, since none of the animals was grossly neurologically affected by the intervention. However, subtle long-term neurological deficits cannot be excluded and this aspect requires further study. Laryngoscopy and endotracheal intubation may cause non-lethal haemorrhage in the choroid plexus and central canal of the hindbrain in hypercarbic, neonatal piglets.**

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Endotracheal intubation and tracheal suctioning are frequently performed in the delivery room in the management of neonates with respiratory distress and/or meconium-stained amniotic fluid. In addition, regular suctioning is required in ventilated neonates, some of whom are known to have raised intracranial pressure (e.g. caused by trauma, Reye's syndrome, near-drowning). A number of studies have described the cerebrovascular effects of endotracheal intubation and subglottic suctioning in neonates, with the uniform conclusion that laryngotracheal irritation

increases intracerebral pressure.[1-4] Laryngoscopy and endotracheal intubation clearly have a potent hypertensive effect in adult patients.[5-7] In many instances these responses have to be disregarded in neonates during emergency resuscitation, and 'awake' intubation is an accepted technique. The intense sympathetic stimulation of laryngoscopy and endotracheal intubation, combined with hypercarbia (which is known to interfere with cerebral autoregulation),[8] may cause intracerebral injury in distressed neonates.

This study was designed to test the hypothesis that laryngoscopy and endotracheal intubation induce changes in the cardiovascular and cerebrovascular systems capable of producing intracranial injury.

Materials and methods

The protocol was approved by the Ethics Committee of the Faculty of Medicine at the University of Cape Town. Seventeen hybrid Landrace/Large White piglets were used. All were less than 12 hours of age at the time of laryngoscopy and endotracheal intubation. The animals were randomised using a computer-generated table into a control group of 6 and a study group of 12. (1 animal from the study group died during preparation and was excluded). Since the study was designed to investigate the effects of laryngeal and tracheal irritation, it was decided to allow the animals to breathe the anaesthetic gas spontaneously during their preparation. This reduced any unintended and uncontrolled stimulation of the larynx and trachea that would necessarily accompany tracheostomy and ventilation. Hypercarbia was therefore an expected part of the design of this study and was considered to add to its value by closely approximating the clinical situation. The hypercarbia was expected to be maintained for the periods of time required for surgical preparation (usually 15 - 20 minutes) and stabilisation (10 - 15 minutes). Blood gases were measured to monitor acid-base status at the end of the stabilisation period. Hypercarbia was defined as a partial arterial carbon dioxide pressure ($PaCO_2$) of greater than 50 mmHg.

Anaesthesia was induced with 3% halothane in oxygen via a neonatal head box and a modified Ayre's T-piece delivery system. The animals were secured in the supine position and spontaneous inhalational anaesthesia was maintained with reduced halothane levels (1 - 1,5%). A Nellcor (Hayward, Calif.) pulse oximeter was placed on the right forelimb to monitor peripheral arterial oxygen saturation. A rectal probe (Mennen-Greatbatch) and a warmed air heat source were employed to maintain body temperature between 36 and 38°C.

A midline subumbilical incision was made to expose the umbilical arteries, and a neonatal umbilical artery catheter was advanced into an iliac vessel via an umbilical artery. Pressure and waveform were displayed (Mennen-Greatbatch monitor) and continuously recorded on a personal computer hard disk. The pulse rate was derived from the left ventricular arterial waveform. In 2 of the control group and 9 of the study group a Camino Laboratories (San Diego, Calif.) interstitial brain pressure transducer was inserted approximately 2 mm into the right parietal cerebral grey matter. This catheter was used to monitor interstitial brain tissue pressure continuously. Previous investigators have shown that the insertion of such interstitial brain pressure catheters in the manner described is associated with minimal microscopic haemorrhage confined to the immediate region of the catheter tip.[9] For this reason the cerebral tissue surrounding the pressure transducer tip was excluded from the analysis. After insertion of the monitoring catheters the animals' condition was allowed to stabilise for 10-15 minutes. Baseline measurements (blood pressure, heart rate, rectal temperature, brain tissue pressure and arterial blood gases) were then determined.

The control piglets were removed from the head box and allowed to breathe room air for 2 minutes. They were then held with their heads in the same position as the heads of the animals undergoing laryngoscopy and endotracheal intubation. This position ('sham intubation') was maintained for a period of 3 minutes during which time blood pressure, heart rate, temperature and oxygen saturation were continuously monitored. The monitoring equipment was then removed. The umbilical artery catheter was left *in situ*. The piglets were then placed in a warmed recovery area, and killed 4 hours later by intra-arterial injection of thiopentone sodium. They were then immediately decapitated, and the brains were removed and placed in a 10% formalin/saline solution.

The study group of 11 piglets was anaesthetised and monitored in the same way. After stabilisation and baseline recordings, the piglets were removed from the head box and allowed to breathe room air for 2 minutes. Direct laryngoscopy, with vigorous laryngopharyngeal stimulation, was then performed for a period of 1 minute. It should be stressed that the animals were still drowsy and did not show any evidence of discomfort during the procedure. Peripheral oxygen saturation was recorded continuously. After the laryngopharyngeal stimulation the trachea was intubated with a 3 mm Portex neonatal endotracheal tube. This procedure was carried out by the same investigator (M.B.) on all occasions. The endotracheal tube was allowed to remain *in situ* for a period of 2 minutes to prevent possible hypoxia from laryngospasm, and was then removed. The mean arterial pressure, heart rate, arterial blood gases and brain tissue pressure were recorded immediately after the intubation period. The animals were then managed as described above, being killed 4 hours after removal from the operating table to allow time for the development of any intracranial lesion.

After fixing, the brains were cut into 12-14 coronal slices and representative slides were prepared. Standard haemotoxylin and eosin stains, and in certain situations specialised neural staining techniques using silver stains, were used. The slides were then examined by an independent neuropathologist (R.B.) who was unaware of the randomisation.

Numerical data were analysed using a Wilcoxon nonparametric test with the level of significance set at $P = 0,05$. Fisher's exact test was used to analyse the histopathological data.

Results

Table I presents the mean arterial pressure and heart rate changes in the 17 animals evaluated as well as the time taken in minutes for these measurements to reach the highest recorded value and then to return to within 1 standard deviation of the baseline level. There was no significant change in mean arterial pressure in the 6 control animals. One animal in this group showed evidence of intracranial bleeding, possibly associated with an unexplained increase in mean arterial pressure and body temperature which occurred approximately 5 minutes after induction of anaesthesia. In the 11 intubated animals the mean arterial pressure (± SD) increased from 47 ± 8 mmHg to a peak of 68 ± 12 mmHg ($P < 0,01$) within 7 minutes of the laryngoscopy and intubation. The blood pressure remained elevated for nearly 14 minutes before returning to the baseline level. The heart rate changed minimally in the control group; in the study group there was an increase in heart rate over the

TABLE I.
Mean arterial blood pressure (MAP) and heart rate changes, and time intervals after laryngoscopy/intubation (mean ± SD) in the control and study groups

	Control group ($N = 6$)	Study group ($N = 11$)	Significance
Baseline Map (mmHg)	50 ± 5	47 ± 8	NS
Peak map (mmHg)	53 ± 11	68 ± 12	$P < 0,01$
Significance	NS	$P < 0,01$	
Time to peak (min)	—	4,1 ± 1,6	
Time to baseline (min)	—	13,8 ± 4,9	
Baseline heart rate (/min)	146 ± 12	146 ± 23	NS
Peak heart rate (/ min)	148 ± 14	163 ± 24	NS
Significance	NS	NS	
Time to peak (min)	—	2,2 ± 0,7	
Time to baseline (min)	—	6,0 ± 4,0	

NS = not significantly different.

laryngoscopy/intubation period. The stimulus had a more rapidly expressed effect on heart rate than on mean arterial pressure, but the hypertensive effect was significantly more protracted in duration.

Table II shows the brain interstitial tissue pressure changes following the stimulus. The brain tissue pressure tended to decrease in the control group (-2,5 ±0,5 mmHg) and to increase in the study group (7,5 ± 8,4 mmHg). This increase was maintained for a mean of 2,3 ± 1,1 minutes. These data are not sufficient to allow statistical evaluation, but are included for completeness.

TABLE II.
Brain interstitial tissue pressure changes (mean ± SD) after laryngoscopy/intubation

	Control group ($N = 2$)	Study group ($N = 9$)	Significance
Baseline (mmHg)	0	0	
Peak (mmHg)	-2,5 ± 0,5	7,5 ± 8,4	$P = 0,14$

Table III shows the arterial blood gas results. There were no significant changes in blood gas measurements during the study in either group, and no significant differences between the two groups at any time.

TABLE III.
Blood gas measurements (mean ± SD) at baseline, and after laryngoscopy/intubation, for the control and study groups.

	Control group ($N = 6$)	Study group ($N = 11$)	Significance
Baseline pH	7,33 ± 0,06	7,27 ± 0,06	NS
Post-event pH	7,31 ± 0,04	7,28 ± 0,09	NS
Baseline O_2	243 ± 80	285 ± 76	NS
Post-event O_2	252 ± 149	236 ± 114	NS
Baseline CO_2	57 ± 7	63 ± 9	NS
Post-event CO_2	58 ± 11	66 ± 21	NS

NS = no significant difference between the groups ($P = 0,05$).

Table IV shows the macroscopic and microscopic findings and includes an indication of the brain slice (in brackets) in which the lesion was found. The sections were numbered rostral to caudal, and each slice was approximately 1 cm in width. Bleeding in the area of catheter insertion was considered to be iatrogenic and was not included in the analysis. In none of the studied slides from the basal areas of the brain was there any evidence of iatrogenic haemorrhage. In addition, iatrogenic bleeds were always focal and subarachnoid in location. In none of the brain sections examined was there any histological indication of a communication between the catheter insertion zone and the ventricular system. No intraventricular haemorrhages were noted in either of the 2 control animals that had catheters placed. In addition, none of the 9 animals in the study group that had catheters placed had any evidence of lateral ventricle bleeds in relation to the catheter. There were no intraventricular haemorrhages higher than the 4th ventricle.

TABLE IV.
Histopathological findings in the control and study groups (section number in brackets)

No.	Sex	BTP	Histological findings (section)
Control group			
1	M	*	No abnormal findings
2	F	*	Focal subarachnoid bleed (3,4) Focal intraparenchymal bleed (4)
3	M		No abnormal findings
4	F		No abnormal findings
5	F		No abnormal findings
6	M		No abnormal findings
Study group			
7	M		Subependymal congestion (1)
8	F		Meningeal congestion (1) Subarachnoid bleed (3) Central canal bleed (6)
9	M	*	4th ventricle bleed (6) Central canal bleed (7)
10	F	*	Intraparenchymal bleed (4) Central canal bleed (6)
11	M	*	4th ventricle bleed (6) Central canal bleed (7)
12	M	*	Central canal bleed (7) Central canal protein (7)
13	M	*	Focal subarachnoid bleed (1) Central canal protein (6)
14	F	*	Focal subarachnoid bleed (3) Central canal bleed (5) Central canal protein (5) Choroid plexus bleed (6) Haemosiderin in choroid plexus (6)
15	F	*	Subarachnoid bleed (1, 2, 6) Central canal bleed (6)
16	M	*	Subarachnoid bleed (5,6) 4th ventricle bleed (7) Central canal bleed (5) Central canal protein (5,8)
17	F	*	Subarachnoid bleed (2, 3, 4, 6) Central canal bleed (6,8) Focal cellular oedema (4)

* BTP catheter inserted.
BTP = brain interstitial tissue pressure catheter.

Postoperatively all the animals recovered from the anaesthetic, and the intubated animals did not behave in any grossly different manner from those that had only been anaesthetised and monitored.

Fig. 1 shows a typical blood pressure response to laryngoscopy and endotracheal intubation in a hypercarbic neonatal piglet.

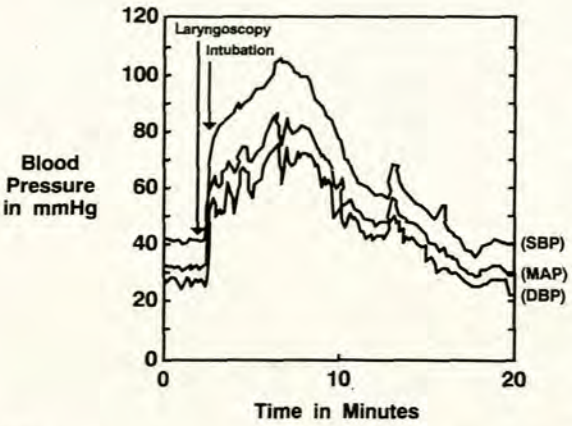

FIG. 1.
This figure graphically displays a typical blood pressure response to laryngoscopy and endotracheal intubation in a hypercarbic, neonatal piglet (SBP = systolic blood pressure; MAP = mean arterial pressure; DBP = diastolic blood pressure).

Fig. 2 shows an example of a central canal haemorrhage. There is no obvious interruption of the ependymal lining, and the blood in this specimen is presumed to have originated in the choroid plexus of the 4th ventricle. In no case in which central canal bleeds were noted was there evidence of intraventricular haemorrhage at any level higher than the 4th ventricle.

FIG. 2.
This photomicrograph shows a central canal haemorrhage in the region of the 4th ventricle noted in a piglet subjected to laryngoscopy and endotracheal intubation. Note the intact ependymal lining, and the intraluminal blood collection.

Analysis of the data using Fisher's exact test showed that when the control and study groups were compared, there were significantly more bleeds ($P = 0{,}005$) in the study animals. When only sections 6 and 7 were analysed the intubated animals showed significantly more haemorrhages ($P = 0{,}002$).

Discussion

The acute histopathological effects of laryngoscopy and endotracheal intubation in neonatal animals has not previously been reported. The results of this study suggest that vigorous laryngoscopy and endotracheal intubation in hypercarbic neonatal piglets may cause nonspecific bleeding and protein extravasation in the 4th ventricle of the hindbrain. The significance of this finding remains unclear, since all of the animals survived the insult without evidence of appreciable morbidity. The more subtle long-term effects of the intervention are unknown, however, and remain to be elucidated. The potential for aqueductal obstruction by thrombus is obviously present, and hydrocephalus is known to complicate such haemorrhages. Many reports on the response to hypertension in neonates implicate the periventricular cerebrum, or the choroid plexus of the lateral ventricles, as the areas at greatest risk for bleeding.[8,10-14] In most of these studies however, the beagle puppy and other preterm animal models were used. The brains of such animals still have a considerable amount of germinal matrix into which bleeding will readily occur.[13,15]

The piglet is a well-established model for the study of neonatal brain blood flow[16-19] and the neonatal piglet has been shown to have the equivalent neurodevelopmental stage of a 37-week human neonate.[20] The term piglet is significantly more mature at birth than the beagle puppy, and there is with very little germinal matrix still present. Moderate to severe hypertension may thus induce a different distribution of bleeding from that seen in the beagle pup. In our study, since there was no evidence of a breach in the ependymal lining, the choroid plexus in the 4th ventricle is the most likely area from which the bleeding originated. It is difficult to explain why the choroid plexus of the lateral ventricles was not similarly affected, but this may have resulted from differential intracerebral shunting of blood. Without long-term follow-up the prediction of any lasting effect of such haemorrhage is speculative, but it is possible that hydrocephalus and minimal brain dysfunction syndromes could be related to lesions of this nature.

Prolonged laryngoscopy and difficult intubation is not infrequently experienced in the emergency resuscitation of distressed neonates. These children are often delivered by caesarean section at which time they have been exposed to anaesthetic gases; in addition they are often suffering varying degrees of metabolic and respiratory acidosis. We consider that our animal model closely approximated such neonates; the laryngotracheal stimulation induced in our study was thus designed to represent the same level of stimulation to which a distressed neonate is exposed during an emergency intubation. There is, however, adequate data to suggest that even in optimal anaesthetic situations careful laryngoscopy and intubation will still induce significant increases in blood pressure and heart rate in neonates.[21,22]

Cerebral blood flow in distressed neonates is influenced by changes in blood pressure,[8] and an abrupt increase in systemic blood pressure is known to play a part in the genesis of intraventricular haemorrhage in neonatal animals.[13,14] Perlman and Volpe[3] showed a prominent, consistent increase in blood flow velocity in the anterior cerebral arteries during endotracheal suctioning in preterm neonates. This was associated with an increase in blood pressure and intracranial pressure. It is unlikely that a mean arterial pressure increase of only 45% would account for the pathological findings in this study. Fluctuations in systolic pressure of the order of 100% have been shown to be required to produce intraventricular haemorrhage.[14,23] A more acceptable explanation for our findings is that sudden increases in cerebral blood flow were transmitted into the hindbrain circulation, and that on a background of inefficient

autoregulation and increased vessel permeability[24,25] these pressure surges resulted in protein extravasation and haemorrhage in the choroid plexus. Prolonged hypercarbia interferes with cerebral autoregulation allowing pressure passive increases in brain blood flow.[26,27] In our study a $PaCO_2$ of 50 mmHg was used to define hypercarbia. This level was chosen arbitrarily, since little is known of the normal neonatal acid-base status in 12-hour-old piglets. The available data suggest that the normal $PaCO_2$ ranges from 62 mmHg at birth to 44 mmHg at 24 hours.[28]

The animals in this study were all hyperoxic and the possibility exists that some of the effects seen were related to oxidative tissue damage. Hyperoxia definitely has a pathological effect on brain tissue,[29] but this effect requires high pressures (greater than 3 atmospheres) and prolonged administration (longer than 24 hours). Neither of these conditions existed in this study, and it is unlikely that oxygen toxicity and free-radical oxidative, or lipid peroxidative, damage was responsible for the effects reported. In addition, there are data to suggest that the cerebral vasoconstriction produced by hyperoxia prevents much of the expected rise in brain tissue oxygen pressure (PO_2).[30]

The importance of cerebrovascular sympathetic regulation in neonates is still undefined, but in adults, sympathetic stimulation is known to limit cerebrovascular vasodilatation,and reduce increases in cerebral blood flow during hypercarbia, hypoxia and hypertensive episodes.[31] Piglets have poorly functional α-adrenergic sympathetic supply in most regional vascular beds at birth[16,32] and the sensitivity of this system only increases to mature levels after several weeks. Sympathetic innervation in these animals is less dense in the hindbrain regions than in the forebrain regions,[32,33] with a reduced concentration of α-adrenergic receptors in the carotid and basilar portions of the circle of Willis.[34] Thus, there is the possibility of intracerebral shunting to the hindbrain during periods of sympathetic stimulation. When this is compounded with a blood-brain barrier capillary basement membrane which has fourfold less ground matrix than that of the adult,[35] the propensity for these vessels to rupture is high.

Whether laryngoscopy and endotracheal intubation causes similar lesions in normoxic/normocarbic animals has not been addressed in this study. Hypercarbia may play a role in the development of the observed bleeds, with the laryngoscopy/intubation merely acting as the precipitating event. Nevertheless, there were significantly fewer abnormal findings in the control group, which was exposed to the same hypercarbic conditions as the study group. This evidence strongly supports the conclusion that the laryngoscopy and intubation was integrally related to the observed findings.

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