Predictive value of umbilical artery pH in preterm infants

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Abstract

Compared with term infants, little information is available about the usefulness of the umbilical artery pH in relation to outcome in extremely preterm infants. This prospective study evaluates the relation between umbilical artery pH (UapH), Apgar scores, perinatal events, and outcome in infants born at less than 32 weeks' gestation. Six hundred and twenty three infants of <32 weeks' gestation were studied. The median UapH was 7.25, with a range of 6.78-7.49. A low UapH was significantly associated with male sex, hyaline membrane disease, grade 3 or 4 intraventricular haemorrhage, and neonatal death. It was also associated with lower birth weight and lower birth-weight centile. The relations between the UapH and outcomes of neonatal death, cerebral palsy, and developmental quotient at 1 year, and other perinatal risk factors were then examined using multiple logistic regression. After adjusting for other risk factors, UapH was not significantly associated with any outcome. In contrast, a low one minute Apgar (<4) remained a significant risk factor, with odds ratios of 2.7 (95% confidence interval (CI) 1.5 to 5.2) for neonatal death and 3.8 (95% CI 1.4 to 10.4) for cerebral palsy.

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Debate persists about the definition of birth asphyxia, the best available methods for its assessment in the newborn period, and its implications for neurological outcome. With increasing medical litigation it is imperative that clinicians can precisely define and substantiate the occurrence of neonatal asphyxia. If 'asphyxia' is defined as 'insufficient oxygen (hypoxia) resulting in the accumulation of waste products'¹ it should be best assessed by the measurement of oxygen, carbon dioxide, pH, or other wastes such as lactate in newborn infants. 'Low Apgar scores' are still widely used for the clinical diagnosis of intrapartum asphyxia in newborn infants, however.

The Apgar score was originally introduced for the rapid assessment of vigour and cardiopulmonary status at birth and as a guide to the need for resuscitation.² This scoring system has limitations.³ It may be subjective, retrospective, or not scored at the appropriate times of one and five minutes.⁴ Depression or impairment of vital functions at birth will result in low Apgar scores, but has a variety of causes in addition to asphyxia. In particular, premature infants have been shown to have

Figure 1 Histogram of UapH values in preterm infants.

low one and five minute Apgar scores as a consequence of their physiological immaturity.^{5,6} With the increased use of umbilical artery pH (UapH) measurements at birth, it has become evident that this pH correlates poorly with Apgar scores. Although there are many workers⁷⁻¹³ who have published UapH data for term infants, data for extremely preterm infants are limited.^{6,14} Even less has been reported about the relation between UapH and short¹⁴ and long¹⁵ term outcomes in extremely premature infants. In this prospective study we evaluated the relation between UapH Apgar scores, perinatal events, neonatal outcome, and neurological status at 1 year in preterm infants.

Patients and methods

A total of 787 infants of less than 32 weeks' gestation were managed at King George V Memorial Hospital for Women during the years 1985 to 1990. Of these, 32 were excluded from further analysis because of major congenital anomalies. Of the remaining 755 infants, UapH values were determined for 630 (83%). There were a further seven infants without Apgar score data, giving a population of 623 (83%) who had both Apgar scores and UapH values; these were the subjects of this study. Of these, 285 (46%) were booked, 331 (53%) were transferred in utero from a peripheral hospital, and seven

Figure 2 Percentage of infants with low Apgar scores or UapH for different gestational ages.

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Figure 3 Relationship between one minute Apgar score and UapH.

(1%) were transferred ex utero. Wide ranging data for these infants were prospectively entered into a computerised database during the study period.

Except in exceptional circumstances (<1%), Apgar scores were given at one and five minutes for all infants. The score at one minute was considered low if <4, whereas at five minutes it was considered low if <7. Umbilical artery blood gas was measured routinely, but for practical reasons was only obtained in 630 (83%) infants. The UapH was coded as low if <7.10. Intraventricular haemorrhage was graded according to Papile *et al.*¹⁶ and was coded severe (grades 3 or 4) or not severe (normal, grades 1 or 2). Ultrasound of the head was performed during the first two weeks of life on 528 (85%) infants. The overall mortality was 111 (18%), of whom 88 (14%) were neonatal deaths. Necropsies were performed on 59 (53%) of the infants who died. Of 25 infants who died before having a head ultrasound, necropsies were performed in 10. Cases where the necropsy clearly indicated the presence of grade 3 or 4 intraventricular haemorrhage were combined to give a total population of 538 (86%) infants who had either a head ultrasound or necropsy result, or both. To confirm the diagnoses of hyaline membrane disease and intraventricular haemorrhage, the head ultrasound scans and chest radiographs were reviewed by a paediatric radiologist who was blind to the clinical course. The mother's drug treatment sheets and referral letters were double checked to confirm whether or not they received antenatal steroids, and were coded to have received them if at least one dose was given within two weeks before delivery.

Our newborn follow up programme only routinely enrolled infants born at less than

Figure 4 Relationship between five minute Apgar score and UapH.

30 weeks' gestation, so follow up at 1 year is reported for this subset of surviving infants. We included survivors born during the seven year period 1985 to 1991 to increase the power of the study. Of the 533 infants born in this period without major congenital anomalies, 371 (70%) were known to be survivors.

Neurodevelopmental outcome at a corrected age of 1 year was assessed by a team consisting of a paediatrician, psychologist, and physiotherapist who were blind to the neonatal course. Follow up data for the neurological assessment were available for 325 (88%) of these infants. For the developmental assessment, the Bayley scale was used during the early part of the study period, but after January 1988 the Griffith mental development scales were used, making comparison of total developmental quotient scores impossible for all infants. The analysis of developmental outcome was thus confined to the subset of infants with results for the Griffith scales (211 (65%)).

The relations between Apgar scores, UapH, and other perinatal factors were then examined; χ^2 analysis was used for dichotomous-dichotomous comparisons, and *t* tests or Mann-Whitney U tests for dichotomous-continuous comparisons. Epi-Info¹⁷ and SPSS¹⁸ statistics programs were used. In an attempt to estimate the predictive usefulness of Apgar scores and UapH, their relations with neonatal death and cerebral palsy at 1 year were then explored using logistic regression.

Results

Figure 1 shows the distribution of UapH values in the 623 study infants. The distribution is skewed, with a median value of 7.25, mode of 7.25, and mean (SD) of 7.23 (0.10). The relation between UapH <7.1 and gestational age is seen in figure 2, where there is a trend to more infants with low UapH at lower gestation, but this was not significant. Figure 2 also shows the relation between Apgar scores and gestational age. In these instances, more immature infants had a significantly higher frequency of low Apgar scores at both one and five minutes. Figures 3 and 4 show the relations between UapH and one and five minute Apgar scores. In both instances there was a statistically significant relation (one minute Apgar score $r=0.365$, $p<0.001$; five minute Apgar score $r=0.317$, $p<0.001$). Most infants with a one minute Apgar score ≥ 4 had a normal UapH. Similarly, most infants with a low UapH had a low one minute Apgar score. About 75% of infants with a low one minute Apgar score had a normal UapH, however.

Table 1 gives the relation between low UapH and a range of perinatal factors. A significantly higher proportion of infants with a low UapH had low Apgar scores at one or five minutes, were male, went on to develop hyaline membrane disease, grade 3 or 4 intraventricular haemorrhage, or died in the neonatal period. They also had a significantly lower mean birth weight and birthweight centile, but not gestational age. Low UapH was

Table 1 Number (%) or mean (SE) values for cord arterial pH <7.1 v other factors

Perinatal factor	pH <7.1 (n=58)	pH ≥7.1 (n=565)	p Value*
Pre-eclampsia	20 (34%)	158 (28%)	0.29
Prolonged rupture of membranes	17 (29%)	181 (32%)	0.67
Preterm labour	24 (41%)	291 (52%)	0.14
Antepartum haemorrhage	11 (19%)	111 (20%)	0.90
Male sex	42 (72%)	330 (58%)	0.04
Caesarean section	31 (53%)	331 (59%)	0.45
One minute Apgar score <4	43 (74%)	141 (25%)	<0.001
Five minute Apgar score <7	27 (47%)	89 (16%)	<0.001
Antenatal steroids	36 (62%)	412 (73%)	0.08
Hyaline membrane disease	35 (60%)	250 (44%)	0.02
Pneumothorax	13 (22%)	83 (15%)	0.12
Chronic lung disease	11 (19%)	123 (22%)	0.62
Neonatal death	17 (29%)	71 (13%)	<0.001
Grade 3/4 intraventricular haemorrhage†	13 (23%)	35 (7%)	<0.001
Cerebral palsy at 1 year‡	1 (6%)	19 (8%)	0.76
Gestational age (weeks)	28.3 (0.29)	28.7 (0.08)	0.09
Birth weight (g)	1082 (43.5)	1238 (14.6)	0.001
Birthweight centile (%)	35 (0.36)	50 (0.12)	<0.001
Developmental quotient at 1 year§	95.8 (7.3)	104.0 (1.0)	0.30

* χ^2 test for dichotomous factors, unpaired *t* test for continuous factors.

†Subset of 538 infants who had a head ultrasound. Number with UapH <7.10=56.

‡Subset of 255 survivors at 1 year <30 weeks' gestation. Number with UapH <7.1=17.

§Subset of 163 survivors at 1 year <30 weeks' gestation. Number with UapH <7.1=11.

not significantly associated with the method of delivery or antenatal factors such as pre-eclampsia, prolonged rupture of membranes, preterm labour, or antepartum haemorrhage.

For comparison, table 2 gives the corresponding results for the Apgar score at one minute. A significantly higher proportion of infants with a low one minute Apgar score had prolonged rupture of membranes, caesarean section, hyaline membrane disease, pneumothorax, grade 3/4 intraventricular haemorrhage, and neonatal death. The mothers of infants who had a low one minute Apgar score were less likely to have received antenatal steroids. Also, infants with a low one minute Apgar score had significantly lower gestational age, birth weight, and birthweight centile. A low one minute Apgar score was associated with cerebral palsy, but not with the developmental quotient at 1 year. The results for the five minute Apgar scores were overall very similar.

The usefulness of low UapH, low one minute Apgar scores, and low five minute Apgar scores in predicting neonatal death was then examined. For neonatal death, the value of 7.10 for UapH had a sensitivity of 0.19 (0.11–0.28) and specificity of 0.92 (0.90–0.95), reflecting the large number of deaths occurring with normal UapH values. Using a value of 7.20 instead increased the sensitivity to 0.33, but the

specificity decreased to 0.76. Another way of examining this question used logistic regression (table 3). For the outcome of neonatal death, the univariate odds ratio (OR) and 95% confidence interval (CI) for low UapH was 2.9 (1.6 to 5.4). Stepwise logistic regression identified an optimum model for neonatal death which included grade 3/4 intraventricular haemorrhage, birth weight, hyaline membrane disease, and absence of antenatal steroids as the best set of predictors. When low UapH was adjusted for these factors, the relation with neonatal death was no longer significant, with OR of 1.4 (0.6 to 3.6).

Using the cut off of 4 for the one minute Apgar score gave a sensitivity of 0.56 (0.45 to 0.66) and specificity of 0.75 (0.71 to 0.78). The corresponding values for the five minute Apgar score <7 were a sensitivity of 0.47 (0.36 to 0.57) and a specificity of 0.86 (0.83 to 0.89). As with UapH, increasing the cut off point gave better sensitivity but worse specificity. Table 3 also gives the OR for low one and five minute Apgar scores. With univariate statistics, the low five minute Apgar score was the better predictor of neonatal death (OR 5.4 v 3.7). Low one minute Apgar and low five minute Apgar scores were then separately entered into the logistic regression model for neonatal death, adjusting as above for grade 3/4 intraventricular haemorrhage, birth weight, hyaline membrane disease, and absence of antenatal steroids. They both remained significant predictors of neonatal death, each with an odds ratio of 2.7 and the low one minute Apgar score having a slightly better confidence interval of 1.5 to 5.2.

We also examined the predictive value of low UapH and low Apgar scores in relation to cerebral palsy and developmental quotient at 1 year for the subset of surviving infants with a gestational age of less than 30 weeks' at birth. Table 4 gives the results for cerebral palsy. The UapH was not significantly related to cerebral palsy either with univariate statistics or in logistic regression models. A low one minute Apgar score is seen to be a better predictor than a low five minute Apgar score (OR 4.9 v 3.5). Stepwise logistic regression identified a model containing abnormal neonatal head ultrasound results (grade 3/4 intraventricular haemorrhage, periventricular leukomalacia, or hydrocephalus), low birth weight, and a low one minute Apgar score as the best predictor of cerebral palsy. With adjustment for these factors, the one minute Apgar score remained significant with an OR (CI) of 3.8 (1.4 to 10.4), whereas the five minute Apgar score was no longer significant (OR 2.5, CI 0.9 to 6.9).

The relation between the developmental quotient and perinatal risk factors was tested using stepwise multiple linear regression. The optimum model arrived at for the developmental quotient contained abnormal head ultrasound and the time ventilated. Neither low UapH nor low Apgar scores was significantly associated with the developmental quotient, either using univariate statistics (tables 1 and 2), or using multiple linear regression adjusting for abnormal head

Table 2 Number (%) or mean (SE) for one minute Apgar score <4 v other factors

Perinatal factor	Apgar score <4 (n=184)	Apgar score ≥4 (n=439)	p Value*
Pre-eclampsia	45 (24%)	133 (30%)	0.14
Prolonged rupture of membranes	73 (40%)	125 (28%)	0.006
Preterm labour	93 (51%)	222 (51%)	0.99
Antepartum haemorrhage	41 (22%)	81 (18%)	0.27
Male sex	114 (61%)	260 (59%)	0.70
Caesarean section	128 (70%)	234 (53%)	<0.001
Antenatal steroids	123 (67%)	325 (74%)	0.05
Hyaline membrane disease	100 (54%)	185 (42%)	0.005
Pneumothorax	46 (25%)	50 (11%)	<0.001
Chronic lung disease	43 (23%)	91 (21%)	0.46
Neonatal death	49 (27%)	39 (9%)	<0.001
Grade 3/4 intraventricular haemorrhage†	21 (13%)	27 (7%)	0.04
Cerebral palsy at 1 year‡	16 (16%)	8 (4%)	<0.001
Gestational age (weeks)	28.2 (0.16)	28.9 (0.09)	<0.001
Birth weight (g)	1116 (26)	1269 (16)	<0.001
Birthweight centile (%)	42.8 (2.2)	51.1 (1.4)	0.001
Developmental quotient at 1 year§	101.5 (2.1)	104.8 (1.0)	0.17

* χ^2 test for dichotomous factors, unpaired *t* test for continuous factors.

†Subset of 538 infants who had head ultrasound. Number with one minute Apgar score <4=156. ‡Subset of 311 survivors at 1 year <30 weeks' gestation. Number with one minute Apgar score <4=99. §Subset of 203 survivors at 1 year <30 weeks' gestation. Number with one minute Apgar score <4=66.

Table 3 Odds ratio (OR) and 95% confidence interval (CI) for neonatal death

Risk factor	Unadjusted OR	Adjusted OR*
UapH <7.1	2.9 (1.6 to 5.4)	1.4 (0.6 to 3.6)
One minute Apgar score <4	3.7 (2.3 to 5.9)	2.7 (1.5 to 5.2)
Five minute Apgar score <7	5.4 (3.3 to 8.7)	2.7 (1.4 to 5.2)

*Logistic regression model for outcome of neonatal death, with each of the above risk factors separately adjusted for grade 3/4 intraventricular haemorrhage, birth weight, hyaline membrane disease, and antenatal steroids.

ultrasound and time ventilated (UapH $p=0.52$; one minute Apgar score $p=0.11$; five minute Apgar score $p=0.61$).

Discussion

This work aimed to evaluate the role of the UapH in the management of infants less than 32 weeks' gestation. We also wished to contrast the UapH with the Apgar score in relation to their relative usefulness in predicting neonatal death or cerebral palsy at 1 year. This study includes one of the largest published cohorts of preterm infants with data for important covariates such as intraventricular haemorrhage and antenatal steroids.

Although these two methods of evaluating the newborn infants' status are significantly correlated, as seen in the scatter plots (figs 3 and 4), they appear to be measuring different things. In agreement with previous reports,^{6,14} many infants with low Apgar scores had normal UapH values. The reasons for low Apgar scores not involving acidosis might include maternal drugs (general anaesthesia, pethidine, diazepam), difficult delivery with head trauma, or immature or abnormal lungs – that is, factors that would make it difficult for the infant to breath normally. With this group of infants, there could have been normal placental function up to the point of delivery, and hence a normal UapH. On the other hand, it was far less common for infants with low UapH values to have good Apgar scores.

Another way the UapH differed from the Apgar score was the relation with gestational age. In agreement with the results of Catlin *et al.*,⁵ infants with low gestational age had significantly lower Apgar scores. In contrast, UapH was not significantly associated with gestational age. This reflected the fact that UapH measures the intactness of placental function at the time of birth, whereas the Apgar score measures how quickly the infant can adapt to extrauterine life, something which is presumably much more difficult for the extremely premature infant.

Given the fact that a low Apgar score is significantly associated with many other factors (table 2), it is clearly important that multivariate analysis is undertaken. It is also important that the analysis includes other important predictors

of the outcome in question. Our results support the conclusion that a low Apgar score remains a significant risk factor for neonatal death after adjustment for other factors. It should be viewed as just one of several independent risk factors, however, relatively less important than birth weight or grade 3/4 intraventricular haemorrhage, and not regarded as a useful predictor of neonatal death by itself.

Our finding that a low UapH in preterm infants had no predictive value for neonatal death, cerebral palsy, or low developmental quotient was in full agreement with the findings of Fee *et al.*¹⁵ Dennis *et al* came to the same conclusion for term infants and even reported that acidosis was more common in unimpaired infants.¹¹

These results show that asphyxia is a difficult concept in extremely preterm infants and probably best avoided altogether. The clinical syndrome of hypoxic-ischaemic encephalopathy equates better to asphyxia, but is difficult to define in infants born at <30 weeks' gestation, as many such infants need to be intubated and ventilated with sedation, or even paralysis, during the first week, thus masking signs of encephalopathy. It clearly makes no sense to conclude that asphyxia has occurred on the basis of low Apgar scores or low UapH. Low Apgar scores are seen in this study to be useful predictors of neonatal death or cerebral palsy, but a low UapH was not a useful predictor in either case.

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Table 4 Odds ratio (OR) and 95% confidence interval (CI) for cerebral palsy at 1 year in infants born at <30 weeks' gestation

Risk factor	Unadjusted OR	Adjusted OR*
UapH <7.1	0.72 (0.1 to 5.7)	0.86 (0.1 to 8.4)
One minute Apgar score <4	4.9 (2.0 to 11.9)	3.8 (1.4 to 10.4)
Five minute Apgar score <7	3.5 (1.5 to 8.2)	2.5 (0.9 to 6.9)

*Logistic regression model for outcome of cerebral palsy, with above risk factors adjusted for abnormal head ultrasound and birth weight.