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Research Article

Carbon Dioxide and Hemoglobin at Presentation with Hypertrophic Pyloric Stenosis—Are They Relevant? Cohort Study and Current Opinions

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Abstract: Background: Recurrent vomiting in infantile hypertrophic pyloric stenosis (IHPS) leads to metabolic alkalosis and a respiratory driven compensatory hypercapnia. Alkalosis has been identified as the main causal factor for respiratory depression on admission. The value of contribution of hemoglobin and carbon dioxide partial pressure to this phenomenon will be evaluated. **Materials and methods:** A retrospective cohort study was conducted on 105 infants with IHPS. The acid-base status, including levels of hemoglobin, sodium and lactate, were recorded. The U-test, correlation analysis, linear regression and multivariate regression analysis was applied. **Results:** Twelve (11.4%) infants had hypercapnia, and six (5.7%) low hemoglobin. Hypercapnia was associated with increased sodium ($p = 0.033$) and mean corpuscular hemoglobin concentration ($p = 0.029$). A positive correlation was found between pCO_2 and hemoglobin ($p = 0.042$). The multivariate linear regression analysis showed that pCO_2 is dependent on the pH ($p < 0.001$) and on hemoglobin ($p = 0.002$), among other factors. Increased pCO_2 was found in infants with low hemoglobin ($p = 0.056$). **Conclusion:** Increased carbon dioxide levels directly stimulate- respiratory drive, but in higher concentrations, elicid a depressant effect on respiratory drive. The extent to which low levels of hemoglobin and strongly increased pCO_2 contribute to respiratory depression needs to be further investigated.

Keywords: infantile hypertrophic pyloric stenosis; CARBON dioxide; hemoglobin; respiratory depression

1. Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is a common and enigmatic surgical disease of first trimester infants with a peak incidence in the 5th week of life. Traditionally, the incidence of IHPS is estimated at around 1 : 300. A decreasing incidence is described in the United States and Germany [1–3]. Nevertheless, this trend could not be substantiated in the Netherlands. The incidence rate there was 1.28 per 1,000 live births [4]. A particularly low incidence is also reported for Africa and Asia [5,6]. There is a clear male predominance with a gender ratio at 5 to 6 : 1. Clinically, affected babies with IHPS suffer from intractable propulsive and non-bilious, sometimes hematin-stained vomiting due to gastric outlet obstruction. This results in a loss of gastric fluids that mainly contain water, hydrochloric acid, and ~~salts~~ electrolytes. Repeated loss of hydrogen ions, chloride and sodium leads to an increased hypochloremic, hypokaliemic metabolic alkalosis (Figure 1) [7,8]. The standard

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treatment for IHPS is surgical intervention (Ramstedt's operation). It is imperative that any fluid, electrolyte and acid-base imbalance must be corrected prior to the procedure.

In essence, infants with IHPS typically exhibit a favorable prognosis, characterized by a low concomitant morbidity and a low incidence of respiratory events. A recent large-scale study published by van den Bunder et al. reported on preoperative apnea rates of about 5%. It is of particular interest note that infants with preoperative respiratory abnormalities not only display a marked alkalosis, but also a compensatory hypercapnia [9].

The present study examines the relationship between carbon dioxide and hemoglobin in children with hypertrophic pyloric stenosis. It demonstrates that these biomarkers are frequently underestimated at the time of diagnosis.

The authors are unaware of any published work that addresses the specific role of carbon dioxide in the pathophysiology of IHPS. Furthermore, the role of hemoglobin as a carbon dioxide transporter has yet to be subject of a comprehensive investigation.

In general, central nervous respiratory drive and respiratory rate are decreased in metabolic alkalosis [10,11]. Advanced dehydration and alkalosis may lead to serious pre- and postoperative oxygen desaturation and apnea [9,12,13]. However, the pathophysiology of desaturation has not yet been clarified in detail. Due to the particular physiological importance of carbon dioxide, it can be expected that this volatile component of the acid-base balance plays a critical role.

Carbon dioxide is not only the "waste product" of oxidative metabolism. Rather, changes in the partial pressure of carbon dioxide (pCO_2) affect a number of vital physiological functions, including the cerebral vascular tone and the blood flow. An increase in pCO_2 in the blood may be due to either metabolic production or as a result of compensatory hypoventilation caused by alkalosis. With this in mind, it seems reasonable to look at hemoglobin as a transporter and intracellular buffer, and lactate as a marker of hypoxia. In literature, hemoglobin has hardly been considered as a biochemical marker in the context of IHPS. The fundamental pathophysiology of IHPS is illustrated schematically in Figure 1. The hypercapnia that arises as a consequence of metabolic alkalosis exerts a range of effects on vital organs: the brain (inhibition of the respiratory drive, altered blood flow), the lungs (reduced alveolar gas exchange), and the kidneys (fluid, electrolyte, and acid balance) are considered as effector organs in the context of acid-base balance.

The presente~~d~~ study focuses on the pathophysiology and clinical significance of pCO_2 and hemoglobin in IHPS. In particular, the interconnection between alkalosis, hypercapnia, hemoglobin, and lactate will be eluciated.

2. Methods

2.1. Study Design and Ethics

Data of 117 consecutive infants with IHPS that were treated between 2007 and 2010, and between 2014 and 2017 at the Department of Pediatric Surgery at the Ruhr University of Bochum, St. Marie´s Hospital, Herne were retrospectively collected. Patient related data were extracted from personalized statutory German Yellow Book (particularly U1-Investigation at birth), the clinical records and the printouts of the acid-base analyzer. Diagnosis of IHPS was established by clinical appearance, ultrasound investigation and at laparoscopic pyloromyotomy. Twelve infants with incomplete core data sets were excluded from further analysis. Data of 105 infants were accepted for further data analysis.

Institutional review board approval was obtained from the Ethics Committee of the Ruhr-University of Bochum [Register No. 4271-12, and 16-5604).

2.2. Stratification of Patients and Definitions

Figure 2 provides an overview on patient selection and dichotomyzation of our patients into *normocapnia* ($pCO_2 \leq 50$mmHg or the equivalent of 6.6 kPa) and *hypercapnia* ($pCO_2 > 50$ kPa) group. Furthermore, a comparison was conducted between the pCO_2 and hemoglobin levels of premature

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babies up to 36 weeks of gestation and those of mature babies from 37 weeks of gestation. Mean corpuscular hemoglobin concentration (MCHC) was calculated as the ratio of hemoglobin concentration to hematocrit. Anemia was defined in accordance with the 10th percentile of age-related normal values, as proposed recently [15]. The lower limits of the normal range for infants aged less than 30 days are 10.6 g/dL; for those aged between 30 and 45 days, 9.4 g/dL; for those aged between 46 and 60 days, 9.4 g/dL; and for those aged 61 days and older, 9.6 g/dL, respectively

2.3. Technical Considerations

Point of care analysis of capillary blood was routinely performed immediately after initial presentation on admission. The laboratory values therefore represent the infant's condition before starting treatment.

Acid-base and blood gas analysis was performed with a commercially available blood gas analyzer (GEM Premier 4000-Device, Instrumentation laboratory, Lexington, MA). Blood samples were collected in heparinized capillary tubes and analyzed immediately.

2.5. Statistical Analysis

Data are presented as medians and interquartile ranges (IQR). Means and standard deviations as well as more statistical information is given in the supplemental material.

While the core datasets were fully available for analysis (n = 105), there were limitations in the dataset size for gestational age (n = 92), birth weight (n = 102), hematocrit (n = 98), MCHC (n = 98) and lactate (n = 80). The proportion of missing data is 3.5%.

The Mann and Whitney U-test was used to compare two independent samples. Linear regression was used to determine the relationship between the different parameters. The slope, intercept and Pearson's correlation coefficient (r) were then determined. In order to identify the parameters most predictive of pCO_2, multivariate linear regression analysis was applied. A p-value ≤ 0.05 was considered statistically significant.

To analyze the acid-base parameters of previous studies, we used the weighted mean, taking into account the respective sample sizes. For the comparison, we applied the arithmetic means. (see Table 5).

3. Results

3.1. Basic Data

There was a male predominance in a ratio of 5:1. Median postconceptional/gestational age was 39 weeks [IQR 37 – 40] and postnatal age was 36 days (5.1 weeks) [IQR 29 – 48]. A total of 22 out of 92 children (equivalent to 23.9%) were born prematurely.-At presentation, infants weighted 3850g [IQR 3440-4300]. Table 1 presents the biometric, biochemical and acid-base status data. Ninety-three infants (89%) presented with normocapnia and 12 infants (11%) had hypercapnia >50 mmHg pCO_2. Only 4 children (4%) were anemic. None of the children had received an initial erythrocyte transfusion. Further detailed statistical information on the overall population of the cohort can be found in the supporting material (additional file 1, Table S1).

Table 1. - Demographic data and laboratory results. Median values, (IQR).

Parameter	N	Median (IQR)
Gestational age [weeks]	92	39.0 (3.0)
Age at presentation [d]	105	36.0 (19)
Birth weight [g]	102	3215 (840)
Weight at presentation [g]	105	3850 (860)
pH	105	7.5 (0.1)
pCO_2 [mmHg]	105	42.0 (8.0)

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SBicarb, HCO_3^- [mmol/L]	105	28.0 (5.3)
BE [mmol/L]	105	4.6 (6.4)
Sodium [mmol/L]	105	137.0 (3.0)
Lactate [mmol/L]	80	1.8 (1.2)
Hemoglobin [g/dL]	105	12.9 (3.1)
Hematocrit	98	36.5 (10.0)
MCHC [g/dL]	98	35.1 (2.7)

3.2. Correlation Analysis and Linear Regression

A correlation analysis showed that pCO_2 and SBicarb ($r = 0.48$, CI 0.32 – 0.62, $p < 0.001$) and SBE ($r = 0.52$, CI 0.36 – 0.65), as well as hemoglobin ($r = 0.20$, CI 0.01 – 0.38) were positively correlated. The correlation between each of the parameters recorded is shown in a scatter plot in Figure 3. There was no significant link between pCO_2 and demographic or biometric data (gestational age, birthweight, and body weight) (additional file 2, Table S2).

Lactate was not correlated with either of the biometric or biochemical factors.

Linear regression analysis was used to determine the relationship between pCO_2 and pH:

$$pH = 7.459 + (-0.001 \times [pCO_2]),\ r = -0.11\ (CI\ -0.30\ ;\ 0.08),\ p = 0.262,\ n.s.$$

Furthermore, we estimated the dependence of pCO_2 on SBicarb, SBE, hemoglobin and MCHC.

$$pCO_2 = 28.2 + 0.5 \times [SBicarb],\ r = 0.48\ (CI\ 0.32\ ;\ 0.62),\ p < 0.001$$

The following regression equation relates pCO_2 to hemoglobin concentration:

$$pCO_2 = 35 + 0.6 \times [Hemoglobin],\ r = 0.20\ (0.01\ ;\ 0.38),\ p = 0.042.$$

3.3. Multivariate Regression Analysis

Multivariate linear regression analysis showed that pCO_2 was predominantly dependent on bicarbonate and base excess (both $p < 0.001$), pH ($p < 0.001$) and hemoglobin ($p = 0.002$).

Detailed statistical information regarding the multivariate linear regression analysis procedure can be found in the supplementary material (additional file 3, Table S3).

3.4. Comparison of Infants with Normo- vs. Hypercapnia

The mean pH values of the normocapnic and hypercapnic infants were 7.4 and 7.5, respectively, but with no significant difference ($p = 0.561$). However, there were significant differences in standard bicarbonate ($p = 0.015$), BE ($p = 0.007$), and sodium ($p = 0.033$). In addition, MCHC ($p = 0.029$) was significantly higher in the hypercapnia group (Table 2). There was no difference between the normocapnic and hypercapnic group in terms of gestational age, postnatal age, birth weight or body weight on presentation. The infants in the normocapnia groups had almost the same median gestational age (39.0 vs. 38.5weeks, p=0.919) and in the hypercapnia group there was formally a higher birth weight without significance (3200 vs.3435g, $p = 0.326$).

Table 2. Comparison of the normocapnia (≤ 50 mmHg) vs. hypercapnia group (> 50 mmHg).

Parameter	Normocapnia	N	Hypercapnia	N	p-value*
pH	7.5 (0.1)	12	7.4 (0.1)	93	0.486
pCO_2 [mmHg]	41.4 (2.0)	12	51.8 (5.0)	93	N.a.
HCO_3^-[mmol/L]	27.8 (4.7)	12	34.3 (1.3)	93	0.015
BE [mmol/L]	4.0 (5.7)	12	10.6 (12.3)	93	0.007
Sodium [mmol/L]	137.0 (3.0)	12	138.0 (6.5)	93	0.033
Lactate [mmol/L]	1.8 (1.2)	10	1.6 (0.8)	70	0.662
Hemoglobin [g/dL]	12.7 (3.3)	12	13.6 (1.6)	93	0.299
Hematocrit	36.0 (9.0)	10	40.2 (7.8)	88	0.110

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MCHC [g/dL]	35.3 (2.9)	10	33.8 (2.7)	88	0.029

* p-values, Mann-Whitney U-test, N.a., not applicable. Median value (IQR).

3.5. Comparison of Premature and Full-Term Infants

The comparison of the values for pCO_2 as well as for hemoglobin and for MCHC of the premature infants with those of the mature infants in the cohort revealed no statistically significant differences for any of the laboratory values (Table 3). There was a trend towards an increased postnatal age of premature babies at presentation (46 vs. 35 days, p = 0.057).

Table 3. Comparison of the values for pCO_2, hemoglobin and MCHC of twenty-two premature infants with those of full-term infants. Median value, (IQR).

	Preterm	N	Full term	N	p-value
Gestational age [weeks]	35.0 (2.8)	22	39 (2.0)	70	<0.001
pCO_2 [mmHg]	41.9 (8.4)	22	41.7 (8.4)	70	p = 0.728
Hemoglobin [g/dL]	12.3 (1.3)	22	13.4 (3.9)	70	p = 0.4654
MCHC [g/dL]	34.4 (3.4)	22	35.4 (2.8)	66	p = 0.952
Age at presentation [d]	46.0 (25.5)	22	35.0 (17)	70	P = 0.057

Median value (IQR).

3.6. Comparing Infants with Low Hemoglobin to Infants with Hemoglobin Above 10 g/dL

Children with a low hemoglobin level had a lower gestational age (p = 0.048) and a trend to higher pCO_2 levels (p = 0.056) (Table 4).

Table 4. Comparison of the values for pCO_2, hemoglobin and MCHC in infants with hemoglobin < 10 g/dl versus hemoglobin ≥ 10 g/dl.

	Low hemoglobin	N	Normal hemoglobin	N	p-value
Gestational age [weeks]	37 (3.0)	6	39 (3.0)	86	0.048
pCO_2 [mmHg]	47 (3.4)	6	42 (18.0)	99	0.056
Hemoglobin [g/dL]	9.3 (0.4)	6	13.0 (3.0)	99	0.020
MCHC [g/dL]	34.7 (3.2)	6	35.2 (2.60)	92	0.881
Age at presentation [d]	58 (9)	6	36 (18)	99	0.002

Median value (IQR).

4. Discussion

The clinical picture of IHPS, often described as enigmatic, is characterized by a particularly distinctive pathophysiology. The results of the treatment are generally favorable. It is very likely to expect a normal quality of life in the long term. The potential danger of pre- and perioperative apnea has been questioned, but recent literature data have provided compelling evidence to confirm its existence [9,12–14,21–23].

The risk of a decreased respiratory drive in the preoperative period represents a potential clinical threat to the welfare of the child. Clinical signs of preoperative apnea may include shallow breathing, cyclical breathing or wheezing. Apnea may occur as a result of a central or obstructive cause [9].

The regulation of the acid-base status in IHPS is a subject that has been the focus of much research in recent years. It is imperative to note that the lungs, kidneys and brain are of particular significance in this regard (Figure 4).

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4.1. Fundamental Configuration of the Acid-Base Status

The repeated loss of gastric juice in IHPS results in the onset of a "gastric type" of metabolic alkalosis [24]. The literature shows a largely consistent picture of acid-base disorders at the time of hospitalization, largely independent of the origin of the various studies. For the assessment of the values at the time of presentation from ten large case series from the literature, a broadly uniform pattern was found. It should be noted that only one of the ten references takes hemoglobin into account [14]. The differences between the mean values observed in our study and the weighted means of the meta-analysis ranged from -2% to +4% for the key data related to the acid-base status (Table 5). The minor deviations of our data from the metadata suggest that our population is representative. The only notable discrepancy was the age at presentation of our patients, being15% higher than the average age of the analyzed studies. This could be attributed to the high proportion of premature infants in our cohort.

Table 5. Mini-meta-analysis of cardinal median or mean values from 10 recently published series of infants with IHPS in comparison with mean values from the present study Weighted and arithmetic means [3,7,8,13,14,17–21].

Parameter	pH	SBicarb [mmol/L]	pCO_2 [mmHg]	Hb [g/dL]	Postnatal age [weeks]
Number of included series	8	7	7	3	2
Number of included data	1709	1607	998	634	122
Minimal; maximal mean value	7.42; 7.50	25.0; 30.0	33.7; 45.0	11.6; 12.8	4.4; 6.1
Metadata, weighted mean	7.45	28.4	43.8	12.8	34.0
Present study	7.50	29.4	42.9	13.1	40.0
Deviation	-1%	+4%	-2%	2%	15%

In accordance with the Henderson-Hasselbalch equation, our study showed a close correlation between pCO_2 and bicarbonate or base excess levels. However, in our analysis pCO_2 showed no significant effect on the pH value.

4.2. Carbone Dioxide

Carbon dioxide is the major stimulus of respiratory drive and hemoglobin is a relevant transporter of the respiratory gases. Nevertheless, less than 5% of carbon dioxide is bound to hemoglobin as carbamate. However, this 5% contributes to 15% of the carbon dioxide gas exchange in the lungs. The remaining 80% of carbon dioxide in the blood is transported in the form of bicarbonate. Furthermore, carbon dioxide is bound as a physically dissolved gas in the plasma [25].

The action of hydrogen ions as a respiratory stimulant in the respiratory center of the brain stem has been demonstrated [26]. These are formed during the dissociation of carbonic acid into bicarbonate ions and hydrogen ions. Conversely the absence of hydrogen ions in the context of metabolic alkalosis results in a reduction of respiratory drive, thereby causing hypoventilation and a secondary increase in carbon dioxide in the blood. This functions as a natural compensatory agent in the form of carbonic acid. The longer the history of pyloric stenosis, the more pronounced the alkalosis becomes. Furthermore, evidence indicates a positive correlation between the duration of the medical history and carbon dioxide levels [21]. As the disease progresses, an increase in pCO_2 can be found. Feng et al. observed a markedly elevated pCO_2 in the late onset group in comparison to the early onset group [27]. Nearly one-third of the children exhibited hypercapnia exceeding 45 mmHg (6kPa) after a symptom duration more than ten days [27]. However, the carbon dioxide associated compensation mechanism has natural limits. In the event of hypoxia due to hypoventilation, the lack of oxygen in the second instance takes over the trigger function for respiration [9]. It is unclear under what conditions this safety function, which is essential for survival, is also overridden.

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4.3. Hypercapnia

In our study, we deliberately set the threshold for moderate hypercapnia at 50 mmHg (equivalent to 6.66 kPa), that means 5 mmHg above the commonly accepted upper limit of normal for pCO_2 [28]. The aim of this consideration was to better visualize changes in the potentially pathological range (Table 2).

The effects of carbon dioxide on consciousness and central nervous function must be considered in the context of elevated pCO_2. In adults, an excess of bicarbonate above a threshold of 55 mmol/L may result in a notable elevation in pCO_2. The regression equation of our data indicates that an SBicarb of 26 mmol/L (1st quartile) is predictive of a pCO_2 of 41 mmHg, while an SBicarb of 31 mmol/L (3rd quartile) is predictive of a pCO_2 of 44 mmHg. Using the regression equation, we found that a bicarbonate of 55 mmol/L would give result in a pCO_2 of 56 mmHg.

This is likely due to the development of a coexisting respiratory muscle weakness resulting from severe hypokalemia, which is almost inevitable in this context [24]. Even moderate hypercapnia in the range of up to 70 mmHg leads to clouding of consciousness and respiratory inhibition. In particular, when pCO_2 exceeds 90 to 100 mmHg in adults, this is known as carbon dioxide poisoning or acute hypercapnic respiratory failure [29,30]. Five infants in the present series exhibited pCO_2 values between 55 and 62 mmHg. In these infants, an increased effect of hypercapnia on both alertness and respiratory drive would be expected. Furthermore, this range exceeds the upper limit of 52.5 mmHg (7 kPa), which has been proposed as a safe threshold for ventilated infants with permissive hypercapnia [28]. However, if IHPS is treated in time, the period of hypercapnia is short and long-term effects on the central nervous system are not of high concern.

4.4. Hemoglobin

New and, to the best of our knowledge and belief, probably for the first time in connection with an IHPS, is the proof of the interaction between hemoglobin and pCO_2. The relationship of pCO_2 with bicarbonate reflects the permanent chemical equilibrium between carbon dioxide and bicarbonate. According to the van Slyke equation, bicarbonate, hemoglobin and pH are the factors in the calculation of the artificial parameter base excess [31]. Despite the acidic effect of carbon dioxide, we found only a weak tendency to lower pH in the hypercapnia group (Table 2). The regression analysis between pH and pCO_2 showed a minimal slope of 0.001. This tiny absolute value of the slope is of course due to the logarithmic nature of pH. When assessing the hemoglobin, the physiological trimester anemia of the former newborn must be taken into account. The vast majority of our patients were within the normal age-physiological range. In infants at postnatal age of six to nine weeks, fetal hemoglobin makes up more than half of the total hemoglobin. Under hypoxic conditions, fetal hemoglobin allows an improved oxygen delivery to the tissue compared to adult hemoglobin [32]. The data show that the age of predilection for IHPS overlaps with the developmentally predicted lowest hemoglobin level.

In accordance with the consensus thresholds for operability, 41% (n=43) of infants surpassed the 'safety' threshold for pCO_2 of 43 mmHg (5.7 kPa) [33], yet no infant exhibited a hemoglobin level below 9 g/dl [33]. The occurrence of anemia appears to be rare, consistent with the limited existing literature on this subject [14,17,33,34]. It can be stated that anemia is an uncommon occurrence in the IHPS cohort. No child was below a threshold suggested by a recently published Delphi analysis [33]. In our cohort, there was a positive correlation between hemoglobin and pCO_2 and a clearly increasing regression line (slope 0.6). This finding reflects a general increase in hemoglobin levels during the observation interval. However, the age-related physiological decline in haemoglobin levels prior to the nadir is not reflected.

4.5. Sodium and Hemoconcentration

In general, increasing length of vomiting in IHPS is associated with a trend towards sodium depletion [21,27]. Normo- or hyponatremia is usually found. In contrast, hypercapnia > 50mmHg was

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associated with increased sodium in our cohort (Table 2). Furthermore, a formal increase in hematocrit was observed in the hypercapnia group, although this did not reach a statistically significant level (Table 2). This is a reflection of hemoconcentration due to dehydration and alkalosis- in the setting of hypercapnia. This observation is consistent with the rule that a contracted extracellular fluid volume can generally be assumed in gastric alkalosis [24]. Rehydration and administration of chloride and sodium ions as part of preoperative conditioning may reverse these changes and thus indirectly create the preconditions for normaliation of carbon dioxide partial pressure. Conversely, although expansion of the extracellular fluid volume with sodium chloride dilutes blood bicarbonate to a small extent, its corrective effect in these patients is mainly a result of renal bicarbonate excretion [24].

4.6. Anemia

Infants with low Hb had lower gestational age, higher pCO_2 and higher postnatal age compared with the normal Hb group (Table 4). Normally, the carbon dioxide balance is kept fairly constant under anaemic conditions. In IHPS, the conditions are different. Alkalosis leads to an increase in the substrate for the carbonic anhydrase reaction in the form of increased bicarbonate. In addition, alkalosis and hydrogen ion deficiency lead to a slowing of respiration with reduced gas exchange. Physiological hyperventilation as a compensatory mechanism in anaemia is therefore no longer possible. These mechanisms contribute to the establishment of an elevated equilibrium with increased pCO_2 [25]. Camporesi et al. found a causal relationship between reduced postoperative hemoglobin concentration and the occurrence of postoperative apnea after narcosis and after pyloromyotomy [14]. According to this study, postoperative apnea affects about 1 in 10 children with IHPS. Furthermore, these authors draw the conclusion that anemia is associated with reduced oxygen transport capacity and reduced oxygen supply to the brain [14]. This in turn would reduce the efferent output of the respiratory center. Significant evidence for an impaired cerebral and renal oxygenation under conditions of marked alkalosis has been reported in a previous study by our research group [35].

In contrast to the findings of the Camporesi et al., a large-scale epidemiological investigation demonstrated that preoperative anaemia has no impact on the postoperative outcome following pyloromyotomy. This study encompassed infants under one year of age, with anaemia defined as a haematocrit of less than 40% irrespective of age [34].

In infants with metabolic alkalosis, it is also necessary to consider the effects on the oxygen binding curve of hemoglobin. Alkalosis results in a stronger binding of oxygen to hemoglobin, which in turn leads to a reduction in the effective release of oxygen to the tissue (Bohr effect). This effect can be reversed by normalizing the pH value towards normal. Previously, we were able to demonstrate that cerebral oxygenation can be normalized in the context of preoperative fluid therapy and conditioning [35].

4.7. Lactate

It is commonly assumed that an elevation in lactate levels is indicative of a negative outcome. However, this assumption is not entirely accurate. In addition to its role in facilitating brain metabolism, lactate has been demonstrated to enhance cognitive function [36,37]. However, lactate plays a minor role in the routine diagnostik workup of IHPS.

When the lactate levels of babies with IHPS were compared with babies who vomited for other reasons, there were no differences [21]. Infants with IHPS did not differ in lactate concentration at hospital admission, pre- or postoperatively [14].

Surprisingly, infants with hypercapnia formally had a lower median lactate compared with normocapnoic infants (Table 2). While this difference is not statistically significant, it may nevertheless be indicative of a genuine trend. In this context, it is necessary to consider the potential influence of hypercapnia and alkalosis on glycolysis and gluconeogenesis, given the complex interaction between these factors. Conversely, it is possible that an erroneous conclusion regarding

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elevated lactate values may be derived from the analysis of individual venous blood samples. The results of our study show that lactate plays a more independent role in IHPS. The influence of hypercapnia in metabolic alkalosis on lactate requires further clarification.

4.8. Preterms

In alignment with the findings presented in Table 3, prior research has demonstrated that preterm infants with IHPS tend to manifest symptoms at a later stage. Their clinical course is more complex, and the length of hospitalisation is typically longer [38–40].

Given the high proportion of preterm infants in our study, an age-dependent decrease of hemoglobin and elevation of pCO_2 would be anticipated a priori. However, our results indicate that preterm infants did not have lower hemoglobin or higher pCO_2 compared with term infants (Table 3). It is probable that reduced respiratory drive or pulmonary dysfunction had played a subordinate role in this preterm cohort.

4.9. Clinical Considerations

For clinical practice, we recommend blood gas analysis and pulse oximetry monitoring of each child at presentation with IHPS and dehydration. Nevertheless, there is a need for further research to establish generally accepted guidelines for preoperative monitoring, which should also take prematurity and hemoglobin into account. The use of near-infrared spectroscopy (NIRS) in a clinical setting or scientific context has the potential to yield more comprehensive perioperative data regarding the oxygenation of the brain and other organs [35].

In the event of respiratory failure and hypoxia, respiratory supplementation may be required. It should be nated that oxygen administration is expected to displace hemoglobin-bound CO_2 (Haldane effect) [25]. Such an intervention could potentially exacerbate central respiratory depression, thereby inducing apnea as a consequence of iatrogenic factors.

4.10. Limitations

A significant limitation of our study is its retrospective and single-institution design. This has resulted in a relatively small number of patients being included in the study. Furthermore, the absence of clinical data on the preoperative course precludes a direct clinical correlation. As the study was retrospective in nature, only a reduced data set was available for statistical evaluation of certain facts. All data were obtained from routine blood samples. It can be reasonably assumed that the measured values of the specific soluble and volatile parameters are influenced by a number of factors, including the sampling conditions, such as the location from which the sample is taken, the length of time the sample has been stored, and the temperature. In routine practice, the sample used was typically capillary blood from the non-arterialised fingertip. However, in certain instances, venous blood may also have been used for the determination of the aforementioned parameters. It has been shown that the results of acid-base and blood gas analyses in newborns correlate with each other and are largely interchangeable. [41] Even storage times of 1 to 2 hours, as could possibly occur in cases of acceptance, appear to have only a minor effect on the results [42]**.** As blood sampling is associated with a painful stimulus, babies usually react by crying (hyperventilation) and sometimes also with brief respiratory arrest (hypoventilation). This leads to rapid changes in blood gases, which are detectable in arterial and therefore capillary blood samples, but less so in venous blood samples. Capillary blood samples may therefore reflect a short-term condition. Conversely, venous blood would be better suited to reflect the longer-term basic condition [43].The analyzer we used is subject to continuous quality control, which meets the legal requirements. It is important to note that the values obtained via a point-of-care analyzer cannot be directly equated with those of an automatic laboratory analyzer [44]. This is particularly relevant in the context of hemoglobin concentration and hematocrit. It is also notable that higher hemoglobin and hematocrit values are typically observed in capillary blood compared to venous blood [45].

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5. Conclusions

The pathophysiology of carbon dioxide in IHPS requires special consideration. Due to the direct effect of carbon dioxide on the central nervous system, it is likely to play a particularly important role in the development of preoperative apnea. The role of hemoglobin in this interaction needs to be further clarified. Lactate seems to play a minor role in this context. Future studies of the interaction between carbon dioxide partial pressure, hemoglobin and oxygenation may provide new insights. It would be beneficial for future studies to correlate pCO_2 and hemoglobin with respiratory gas estimation and cardiopulmonary physiology. In clinical practice, respiratory and baseline cardiopulmonary monitoring is useful for infants with IHPS and hypercapnia. However, it is logical to pursue the development of secure monitoring modes that also optimize use of the consumption of resources.

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