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Impact of carbon dioxide values after aortic impingement on postoperative morbimortality in pediatric patients undergoing cardiac surgery

Impacto de los valores de bióxido de carbono post-pinzamiento aórtico sobre la morbimortalidad postoperatoria en pacientes pediátricos sometidos a cirugía cardíaca

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ABSTRACT. Introduction: Inducing hypocapnia is a common practice during pediatric general anesthesia, even though it has not shown clear benefits. **Objective:** To compare the impact of carbon dioxide values after aortic impingement (< 32.7 vs ≥ 32.7 mmHg) on postoperative morbimortality among pediatric patients undergoing cardiac surgery. **Material and methods:** A case-control study included 90 pediatric patients undergoing cardiac surgery with cardiopulmonary bypass. The study cases consisted of 45 patients who died within 30 days of the postoperative period. Cases and controls were individually matched (1:1 ratio). Descriptive and inferential statistics (Mann-Whitney's U, Student's t and χ^2 tests) were used to analyze the results. A $p < 0.05$ was considered significant. A univariate analysis was also carried out. The strength of association between morbimortality and carbon dioxide values after aortic impingement was determined using the odds ratio. The data were processed using SPSS v-24.0. **Results:** The group with carbon dioxide values of < 32.7 mmHg after aortic impingement was associated with greater morbidity (OR 24.75; 95% CI 4.92-124.32) and mortality (OR 22.47; 95% CI 4.85-10.17) at 30 days. **Conclusion:** Pediatric patients undergoing cardiac surgery with carbon dioxide values of < 32.7 mmHg after aortic impingement showed higher postoperative morbimortality than those with carbon dioxide values of ≥ 32.7 mmHg.

***RESUMEN. Introducción:** La hipocapnia es una práctica común durante la anestesia general pediátrica; sin embargo, a lo largo del tiempo no ha mostrado beneficios bien definidos. **Objetivo:** Comparar el impacto del bióxido de carbono post-pinzamiento aórtico (< 32.7 vs ≥ 32.7 mmHg) sobre la morbimortalidad postoperatoria en los pacientes pediátricos sometidos a cirugía cardíaca. **Material y métodos:** Se realizó un estudio de casos y controles que incluyó 90 pacientes pediátricos sometidos a cirugía cardíaca con derivación cardiopulmonar. Se consideraron casos 45 pacientes que fallecieron dentro de los 30 días del postoperatorio. Los controles fueron pareados en relación 1:1. Para su análisis se realizó estadística descriptiva e inferencial con U de Mann-Whitney, t de Student y χ^2 según fue el caso. Una $p < 0.05$ fue significativa. Se realizó un análisis univariado. La fuerza de asociación entre la morbimortalidad y los valores de bióxido de carbono post-pinzamiento aórtico se obtuvo mediante el odds ratio. Los datos fueron procesados mediante SPSS v-24.0. **Resultados:** El grupo con valores de bióxido de carbono post-pinzamiento aórtico < 32.7 mmHg se asoció con una mayor morbilidad a los 30 días (OR 24.75; IC del 95% 4.92-124.32) y mortalidad (OR 22.47; IC del 95% 4.85-10.17). **Conclusión:** Los pacientes pediátricos sometidos a cirugía cardíaca con valores de bióxido de carbono post-pinzamiento aórtico < 32.7 mmHg tienen mayor morbimortalidad postoperatoria que los que tienen valores ≥ 32.7 mmHg.*

Keywords:
Carbon dioxide, hypocapnia, heart surgery, pediatrics, mortality.

Palabras clave:
Bióxido de carbono, hipocapnia, cirugía cardíaca, pediatría, mortalidad.

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INTRODUCTION

Until a few years ago, congenital heart diseases were considered «anatomical curiosities» and the therapeutic trend favored medical treatment and/or palliative surgery. It was not until 1953 that corrective surgery for cardiac abnormalities began to be performed successfully with the use of a cardiopulmonary bypass machine (CBP), a dramatic step forward in the surgical treatment of patients.

Cardiopulmonary bypass is a procedure that consists in maintaining the perfusion of oxygenated blood to organs and tissues by means of a pump and an external oxygenation system. The use of this procedure is required in 85-90% of congenital cardiac surgeries(1-3).

There is a growing trend towards the use of increasingly complex corrective treatments. These treatments require the coordination of a multidisciplinary team of professionals focused on maintaining an adequate balance in all organs and tissues, in order to improve the patient's postoperative prognosis(4).

It must be borne in mind that specific problems may arise during the CBP procedure that can significantly alter the surgical outcome of the patients, and that are not always related to cardiac disease or to surgery(5). In this sense, we consider hypocapnia, defined as arterial oxygen blood pressure (PaCO$_2$) < 35 mmHg at sea level, or < 32.7 mmHg at the level of Mexico City, as a risk factor(6).

Inducing mild hypocapnia is a common practice during pediatric general anesthesia, even though it has not shown clear benefits. Its use may have been introduced due to concerns over hypertension and tachycardia related to hypercapnia, which may increase the demand for oxygen in the myocardium. Other proposed benefits of intraoperative hypocapnia include a reduced need for muscle relaxants and reduced hypnotic requirements(7,8). However, there is no good evidence for such benefits. Despite the lack of evidence, the induction of mild hypocapnia is still accepted in pediatric clinical practice.

Hypocapnia has many harmful effects; it causes vasodilation and relative hypovolemia, it can cause a significant reduction in venous return, insufficiency of the right heart and increased demand for oxygen at the myocardial level. Furthermore, it can cause prolongation of the QT interval and cardiac arrhythmias. Other effects of hypocapnia include decreased cerebral blood flow and cognitive function, increased pulmonary microvascular permeability, decreased pulmonary compliance (due to bronchoconstriction), increased intrapulmonary bypass fraction caused by inhibition of hypoxic pulmonary vasoconstriction, left shift of the oxyhemoglobin dissociation curve, hypercoagulopathy, and worsening of the patient's condition during cardiopulmonary resuscitation(9,10).

Previous experimental studies have shown inconsistent results regarding the effects of the partial pressure of arterial carbon dioxide (PaCO$_2$) on the prognosis of patients undergoing surgery in other clinical settings. Although most studies have shown that hypercapnia increases myocardial blood flow above metabolic demands, the assessment of the effects of hypocapnia has yielded variable results(10-16).

Moreover, it seems questionable to rely on conclusions from experimental studies in animal models and other clinical settings to make prognostic predictions about pediatric cardiac patients undergoing surgery with CBP. Especially because the clinical effects of the different levels of PaCO$_2$ on myocardial blood flow, metabolism and global hemodynamics might be affected by the systemic inflammatory response produced by the use of CBP, increasing the risk of postoperative morbimortality in this type of patients. Based on this information, we compared the effect of carbon dioxide values after aortic impingement (< 32.7 vs ≥ 32.7 mmHg) on postoperative morbimortality in pediatric patients undergoing cardiac surgery.

MATERIAL AND METHODS

With the approval of the Local Research Committee, a case-control study was carried out on a group of 90 patients of the institution. The study population included pediatric patients undergoing cardiac surgery with cardiopulmonary bypass, of any age and gender. Patients with values of sodium bicarbonate (HCO$_3$), after aortic impingement, of $>$ 28 mEq•L^{-1} were excluded, as were those with important data missing from their clinical records.

The institutional record of anesthetic procedures was reviewed to elaborate the list of patients. The name and social security number of the pediatric patients who underwent elective or emergency cardiac surgery with cardiopulmonary bypass were recorded. Copies of the operative reports from the pediatric surgery, anesthesiology and extracorporeal medicine services were reviewed. The electronic clinical file system ECE® was reviewed too. This information was used to elaborate an initial list of patients.

Forty-five pediatric patients who underwent cardiac surgery with cardiopulmonary bypass during the study period and who died within 30 days of the postoperative period were included as cases. The controls were selected and matched, in a 1:1 ratio, by age (± 3 months), gender, type of surgery (elective or emergency), cardiac-surgical history (single-operated or re-operated) and by the pathology that motivated the surgery.

The information obtained was collected in an easy application form, with tests designed for this purpose. The patient identification process was carried out by the pediatric anesthesia resident. The data obtained were exported to an electronic database for further processing.

The variables were analyzed by means of descriptive statistics, using measures of central tendency and dispersion.

For quantitative variables with normal distribution, arithmetic means and standard deviations were obtained; for qualitative variables, ratios and proportions.

Regarding inferential statistics, the comparison of non-parametric data with Gaussian distribution was performed using the Mann-Whitney's U-test. To compare data with non-Gaussian distribution, Student's t-test was used, while categorical data were analyzed using the χ^2 test. A $p < 0.05$ was considered statistically significant. In addition, a univariate analysis was performed to detect the variables whose distributions showed significant differences between cases and controls. The strength of association between mortality and carbon dioxide values after aortic impingement, as well as other variables, was determined using the odds ratio (OR).

The data was processed using the statistical program SPSS for Windows, version 24.0. (SPSS Inc., Chicago, IL, USA).

RESULTS

No patient was excluded from the study. Data from a total of 90 patients were analyzed. The patients were distributed in 2 groups: group I (n = 25), with values of $PaCO_2$ after aortic impingement of < 32.7 mmHg; group II (n = 65), with values of $PaCO_2$ after aortic impingement of ≥ 32.7 mmHg. The average age of the patients was 16.63 ± 15.05 months. Sixty patients (66.7%) were male. The average value of $PaCO_2$ and of the baseline serum levels of HCO_3 were 39.98 ± 10.65 and 22.75 ± 3.64 respectively. No statistically significant differences were observed between both groups in terms of baseline characteristics *(Table 1)*.

Regarding transoperative variables, the cardiopulmonary bypass time and the aortic impingement time were practically the same in both groups of patients. Anesthetic-surgical times were within the customary standards of the institution. Twenty-four patients (26.66%) required cardiac arrest. No statistically significant differences were observed between both groups of patients *(Table 2)*.

Table 1: Baseline variables.

Variable	Group I (N = 25)	Group II (N = 65)	p
Age (months)	15.64 ± 12.48	17.02 ± 16.01	0.700
Gender (M/F)	18/7	42/23	0.506
Weight (kg)	8.38 ± 3.40	7.51 ± 4.26	0.175
Size (cm)	72.88 ± 12.21	70.18 ± 16.75	0.076
BSA (m^2)	0.41 ± 0.12	0.38 ± 0.15	0.168
RACHS-1 (I/II/III/IV)	0/22/0/3	0/52/8/5	0.166
Aristotle	8 (6-11)	7 (6-11)	0.090
$PaCO_2$-0 (mmHg)	36.76 ± 10.08	41.22 ± 10.68	0.076
HCO_3-0 (mmol/L)	22.22 ± 4.16	22.96 ± 3.44	0.392

M = male; F = female; BSA = body surface area; RACHS = risk adjustment in congenital heart surgery; $PaCO_2$-0 = baseline carbon dioxide blood pressure; HCO_3-0 = baseline serum sodium bicarbonate.

Table 2: Intraoperative variables.

Variable	Group I (N = 25)	Group II (N = 65)	p
Ax time (min)	262.08 ± 53.10	268.62 ± 58.18	0.626
Qx time (min)	207.40 ± 44.53	207.22 ± 59.08	0.989
CEC time (min)	78.08 ± 33.65	78.95 ± 40.94	0.925
PAo time (min)	45.52 ± 29.37	43.00 ± 33.38	0.741
Cardiac arrest (yes/no)	3/22	20/45	0.067
$PaCO_2$-1 (mmHg)	36.76 ± 10.08	41.22 ± 10.68	0.000*
HCO_3-1 (mmol/L)	22.22 ± 4.16	22.96 ± 3.44	0.009*

Ax = anesthetic; Qx = surgical; CEC = extracorporeal circulation; PAo = aortic impingement; $PaCO_2$-1 = carbon dioxide blood pressure after aortic impingement; HCO_3-1: = serum sodium bicarbonate after impingement. * Statistical significance.

The postoperative follow-up *(Table 3)* showed that morbimortality was significantly higher in group II than in group I (p = 0.000 and p = 0.000, respectively). However, the days of orotracheal intubation and the days of hospital stay were similar in both groups of patients, with no statistically significant differences (p = 0.156 and p = 0.406 for groups I and II respectively).

Table 3 shows the non-adjusted results of patients in the two groups. The univariate analysis indicated that group II was associated with an increased risk of morbidity, mortality, delayed extubation and prolonged hospital stay *(Table 4)*.

DISCUSSION

Over time, multiple risk factors for mortality, delayed extubation and prolonged hospital stay have been reported in pediatric patients undergoing cardiac surgery with cardiopulmonary bypass.

However, the values of $PaCO_2$ during surgery have been overlooked for a long time, especially when compared with other parameters. A study conducted by García-Hernández et al. identified risk factors for mortality, age, CBP time, inotropic score; lactate on admission, its maximum peak, its speed of variation and the time during which it peaked; venous saturation, base excess, dead space, oxygen extraction, and intrapulmonary shunt. The time of CBP, lactate at admission and its maximum peak were the variables that showed the highest predictive value for mortality. The authors also showed, through a multivariate analysis, that the independent risk factors for mortality are a lactate peak of 6.3 mmol/L and a hyperlactacidemia time of 24 hours(17). Carísimo et al. suggest that prolonged CBP time, prolonged aortic impingement time, young age, low body weight, use of deep hypothermia and circulatory arrest are precise predictors of mortality risk after pediatric cardiac surgery(18).

None of these authors considered the levels of $PaCO_2$, hence the relevance of our study, which shows evidence of an association between the status of $PaCO_2$ and the clinical outcome of pediatric patients who have undergone cardiac surgery with CBP.

For the present study, we considered that, since any alteration in the values of $PaCO_2$ is a trigger of multiple changes, it could potentially be harmful to patients. Hypercapnia can induce tachycardia, systemic and pulmonary hypertension, and an increase in cardiac output due to the release of endogenous catecholamines. Hypocapnia causes a left shift of the oxyhemoglobin dissociation curve and potent and systemic arterial and coronary vasoconstriction, in addition to decreasing the supply of cellular oxygen and increasing its demand. Consequently, hypocapnia aggravates tissue ischemia and can also worsen the outcome of patients(6,19).

Our study was designed to compare the effect of the levels of $PaCO_2$ after aortic impingement (< 32.7 vs ≥ 32.7 mmHg) on postoperative morbimortality in pediatric patients undergoing cardiac surgery. A cut-off point of 32.7 mmHg was chosen as a clear limit between «normal» and low levels, in accordance with what has been reported in the literature by Vázquez-García and Pérez-Padilla, who considered $PaCO_2$ values, in Mexico City, of 35.7 mmHg for patients with acute exposure and of 32.7 for acclimatized patients(7).

Because the values of $PaCO_2$ can be affected by various physiological imbalances, such as those caused by the intravenous administration of sodium bicarbonate, changes in cardiac output, gas exchange disorders and mechanical ventilation, it was necessary to exclude patients with values of HCO_3, measured after aortic impingement, of > 28 mEq•L^{-1}. Moreover, the determination of $PaCO_2$ values was done during cardiopulmonary bypass, immediately after aortic impingement, when the lung is still cut off from the general circulation (in the absence of mechanical ventilation), under constant temperature conditions and when cardiac output depends on the extracorporeal circulation pump.

Table 3: Postoperative variables.

Variable	Group I (N = 25)	Group II (N = 65)	p
Morbidity (yes/no)	14/11	63/2	0.000*
Mortality (yes/no)	2/23	43/22	0.000*
IOT (days)	4.22 ± 6.54	6.63 ± 7.36	0.156
EIH (days)	15.52 ± 8.00	13.37 ± 11.86	0.406
$PaCO_2$-2 (mmHg)	37.16 ± 6.86	39.83 ± 12.85	0.301
HCO_3-2 (mmol/L)	21.73 ± 2.80	20.47 ± 2.97	0.071

IOT = orotracheal intubation; EIH = inpatient stay; $PaCO_2$-2 = blood pressure of carbon dioxide at the end of surgery; HCO_3-2 = serum sodium bicarbonate at the end of surgery. * Statistical significance.

Table 4: Univariate analysis.

Variable	OR	95% CI Lower	95% CI Higher	p
Morbidity	24.75	4.92	124.32	0.000*
Mortality	22.47	4.85	104.17	0.000*
IOT	0.16	0.058	0.44	0.001*
EIH	1.59	1.32	1.91	0.001*

IOT = orotracheal intubation; EIH = inpatient stay; OR = odds ratio; CI = confidence interval. * Statistical significance.

In the present study, the total percentage of complications was 85.6%. Most complications appeared during the postoperative period but tended to resolve over time. Infections and acute renal dysfunction were the most common problems. The overall percentage of infections reported in the literature varies between 6 and 50%(20,21). In the present study, 57.77% of the total postoperative complications were of infectious type.

We found an acute renal failure rate of 10.38%, which is below the values that have been reported by other studies(22-24). This discrepancy could be explained by the difference in the definitions used by different studies. The definition of renal dysfunction as a 25% increase in creatinine levels and the reliance on creatinine clearance, leads to the detection of mild degrees of renal dysfunction, overlooking known error factors when the diagnosis is based only on serum creatinine levels(21-27).

All deaths occurred in the postoperative period, and the most frequent cause was septic shock (24.3%), followed by cardiogenic shock (11.2%), which coincides with what was reported by Castillo-Espínola et al., who in a retrospective cohort study that included 85 patients with surgical intervention for congenital heart disease, reported a mortality of 11.76% during the postoperative period, with the most frequent causes being septic shock, followed by atrioventricular block, low cardiac output syndrome, cardiogenic shock and pulmonary hemorrhage(21).

In the present study, values of $PaCO_2$ after aortic impingement of < 32.7 mmHg were associated with higher postoperative morbimortality.

In agreement with our results, Dony et al., in a prospective cohort study that included 5,317 surgical patients whose levels of tele-exhaled carbon dioxide ($ETCO_2$) were measured every 5 seconds and who were grouped into normocapnia and non-normocapnia groups, according to a cut-off point of 35 mmHg, found that a low level of $ETCO_2$ during anesthesia was associated with an increase in the postoperative mortality rate and an increase in the days of in-hospital stay (more than six days)(10). Brat et al., in a retrospective multicenter study that included 76 patients who underwent thoracotomy, found that low end-tidal carbon dioxide levels at rest (28.1 ± 4.3 vs 31.5 ± 4.2 mmHg; $p < 0.01$) were the best predictor of respiratory complications (OR: 1.21; 95% CI: 1.06-1.39; $p = 0.01$)(16).

In other clinical settings, and in contrast with the results of the present study, Choi et al., in a retrospective cohort study that included 1,011 patients who entered the intensive care unit after cardiac surgery found that only the combined exposure to hypocapnia and hypercapnia within 24 hours after cardiac surgery was independently associated with a higher risk of mortality at 30 days and late extubation. Exposure to hypocapnia or hypercapnia alone was not associated with the patient's outcome(13).

Although our initial results showed that the length of hospital stay was not significantly different between both groups, this could be explained by the higher mortality in the latter group, which included a relatively high proportion of patients who died within a short period. When the results were adjusted, in the univariate analysis, the group with $PaCO_2$ values after aortic impingement of < 32.7 mmHg was associated with an increase in late extubation and longer hospital stays.

Although we were unable to determine whether strict control of a normal $PaCO_2$ target affected the patient's outcome or if temporary exposure to abnormal $PaCO_2$ was detrimental to pediatric patients undergoing cardiac surgery with cardiopulmonary bypass, our study showed that a $PaCO_2$ imbalance was associated with a poor patient outcome. Specifically, we demonstrated that exposure to hypocapnia after aortic impingement was independently associated with a mortality almost 25 times higher compared with that of patients not exposed to abnormal $PaCO_2$ at the same time.

The present study had several limitations. First, we used a retrospective study design. Although a univariate analysis was applied to reduce bias, our results may have been influenced by unmeasured confounding factors, some of which, such as comorbidities, could have been expressed incorrectly. Second, we were unable to analyze the difference in the duration of exposure to abnormal $PaCO_2$ levels. While the duration or degree of exposure to abnormal $PaCO_2$ might have a differential effect on the results, it is difficult to continuously measure the duration of exposure to abnormal $PaCO_2$. Future studies should use continuous end-tidal carbon dioxide as a substitute for the continuous monitoring of $PaCO_2$. Finally, this was not a randomized clinical trial; thus, we can only report an association between $PaCO_2$ levels and the result, not infer causality.

CONCLUSION

In conclusion, pediatric patients undergoing cardiac surgery with cardiopulmonary bypass, with carbon dioxide values after aortic impingement of < 32.7 mmHg, are independently associated with an increased risk of postoperative morbimortality. These results suggest that preventing hypocapnia during cardiopulmonary bypass may decrease postoperative morbimortality.

However, further prospective studies are required to confirm this finding and to determine whether carbon dioxide values after aortic impingement have predictive value in these patients.

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