SURGERY FOR CONGENITAL HEART DISEASE

HISTAMINE LIBERATION RELATED TO CARDIOPULMONARY BYPASS IN CHILDREN: POSSIBLE RELATION TO TRANSIENT POSTOPERATIVE ARRHYTHMIAS

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Tumor necrosis factor- α production and products of mast cell, basophil, and eosinophil degranulation (prostaglandin D₂, histamine, and eosinophil cationic protein) were prospectively studied in 26 children undergoing cardiac operations. The relationship between inflammatory response to cardiopulmonary bypass and transient postoperative arrhythmias was analyzed. Cardiopulmonary bypass was conducted with circulatory arrest and deep hypothermia in 10 patients and with continuous low-flow and moderate hypothermia in 16 patients. Transient postoperative arrhythmias diagnosed on standard or atrial electrocardiograms (or both) were seen in eight of the 26 examined children: accelerated junctional rhythm ($n = 3$), junctional ectopic tachycardia ($n = 3$), second-degree atrioventricular block ($n = 1$), and third-degree atrioventricular block ($n = 1$). Children with transient postoperative arrhythmias were younger than those without ($p < 0.05$). Compared with baseline values, there was in all patients a significant release of histamine and eosinophil cationic protein ($p < 0.05$) related to cardiopulmonary bypass, reaching peak values 4 hours after the operation. In contrast, tumor necrosis factor- α production and prostaglandin D₂ release were not significant. This suggests that activated basophils but not mast cells are the major sources of histamine liberated during and after cardiopulmonary bypass. Histamine release but not eosinophil cationic protein release correlated with circulatory arrest and deep hypothermia ($p < 0.05$), suggesting the participation of physicochemical alterations of circulating basophils leading to histamine liberation. Four hours after the operation, patients with transient postoperative arrhythmias had significantly higher blood concentrations of histamine ($p < 0.02$) and eosinophil cationic protein ($p < 0.05$) than did those without transient postoperative arrhythmias. On the first postoperative day, four of the eight patients with transient postoperative arrhythmias had persisting elevated histamine levels, whereas in patients without transient postoperative arrhythmias histamine reached baseline values. The multivariate analysis retained histamine release and eosinophil cationic protein variations related to cardiopulmonary bypass for the emerging model to predict transient postoperative arrhythmias. The results of this study show significant histamine

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release related to cardiopulmonary bypass. Furthermore, they document a possible relationship between circulating histamine and transient postoperative arrhythmias. The latter may therefore be suspected among the consequences of the inflammatory response to cardiopulmonary bypass. (J Thorac Cardiovasc Surg 1996;111:971-81)

Cardiopulmonary bypass (CPB) operations induce a whole-body inflammatory reaction in which complement activation, neutrophil degranulation, and cytokine generation are mainly involved.¹⁻⁶ Tissue mast cells and circulating basophils are both target cells for a number of mediators generated during CPB, such as complement anaphylatoxins and cytokines,^{7,8} and thus are both possible sources of histamine liberation. Several cytokines are known to have an activity resembling histamine-releasing factor, such as interleukin-1 and interleukin-8, which are generated in response to CPB,⁹⁻¹¹ their actions on basophils being receptor-mediated.⁷ In contrast, tumor necrosis factor- α (TNF- α), whose generation during CPB remains controversial,^{10,12,13} does not seem to directly stimulate basophils but tissue mast cells.^{7,14}

Besides its immunomodulating effects,¹⁵ liberated histamine also has arrhythmogenic properties that could influence the postoperative course of patients undergoing cardiac operations. Histamine increases spontaneous sinus rate, produces various degrees of atrioventricular block, enhances the automaticity of ectopic pacemakers, shifts the pacemaker site, and decreases the ventricular fibrillation threshold.¹⁶ These properties have long been demonstrated in experimental models, but the potential relation of histamine to transient postoperative arrhythmias has not yet been studied. This prospective study was conducted to analyze the mechanisms of histamine liberation during CPB and its possible relation with transient postoperative arrhythmias in children having undergone cardiac operations.

Patients and methods

Twenty-six consecutive children (15 boys and 11 girls), aged 7 months to 13 years (mean 66 months), undergoing cardiac operations for congenital cardiac defects were entered into the study. Diagnosis and type of surgical procedure are shown in Table I. Besides routine preoperative laboratory investigations, standard and Holter electrocardiograms were performed in all patients, excluding preoperative arrhythmias. No patient had known immunologic disease before the operation.

Anesthesia and CPB protocol. Patients were premedicated with midazolam. General anesthesia induced with inhaled nitrous oxide and halothane was maintained with

diazepam and fentanyl sulfate. Pancuronium bromide was used for muscle relaxation. Cefotiam hydrochloride (25 mg/kg) and dexamethasone (3 mg/m²) were administered before sternotomy. The CPB equipment was standardized. This included a roller pump generating a nonpulsatile flow, a disposable membrane oxygenator, and an arterial filter. The priming solution consisted of a crystalloid solution and mannitol (0.75 mg/kg). When appropriate, compatible stored blood was added to obtain a hematocrit value of the circulating volume of about 25%. Heparinization was achieved with heparin sulfate (3 mg/kg). CPB was started after aortic and atrial or bicaval cannulation with a perfusion index of 2.7 L/m². Hypothermia was obtained by cooling the priming solution in the extracorporeal circuit and the circulating volume with a heat exchanger. For vasodilation during cooling, all patients were given sodium nitroprusside (0.5 to 2 μ g/kg per minute). In 10 patients, deep hypothermia (minimal nasopharyngeal temperature averaging 16° C) was obtained, and after aortic crossclamp and cardioplegia induced with a single injection of a 4° C cold Bretschneider solution (30 ml/kg), total circulatory arrest was established. When necessary, the surgical procedure was continued after circulatory arrest under low-flow perfusion (corresponding to 25% of the initial flow rate). In 16 patients, nasopharyngeal temperature was brought down to an average of 26° C, and after aortic crossclamping and cardioplegia surgical repair was performed under low-flow perfusion. In all children, lungs were reventilated when nasopharyngeal temperature reached 30° C, and neutralization of heparin was achieved by protamine sulfate (6 mg/kg). All children received sodium nitroprusside for vasodilation during rewarming (0.5 to 2 μ g/kg per minute). If necessary, catecholamines were given before weaning from CPB and were continued after the operation.

Postoperative care. In the intensive care unit, diazepam and morphine sulfate were given for sedation and analgesia. Continuous electrocardiographic monitoring was used in all children for at least 3 days after the operation. Electrocardiographic rhythm strips were recorded whenever cardiac arrhythmias were suspected. Standard electrocardiography was done at least once a day. When P waves could not be clearly identified, atrial electrocardiograms were performed with the use of the atrial electrode. Before discharge standard and Holter electrocardiograms were performed in all children.

Definition of transient postoperative arrhythmias. Transient postoperative arrhythmias were arbitrarily defined as arrhythmias occurring during the first 24 postoperative hours and resolving within 5 days after the operation.

Disregarding single supraventricular and ventricular extrasystoles, the following transient postoperative arrhythmias were observed: accelerated junctional rhythm, junctional

Table I. Clinical data

Patient	Age (mo)	Diagnosis	Type of operation	TPDR
1	69	Ebstein	TV reconst.	No
2	54	DORV operated, residual VSD	VSD closure	No
3	147	VSD	VSD closure	No
4	108	TOF operated, PI	Homograft implantation	No
5	94	DORV, MS	TCPC	JET
6	17	VSD	VSD closure	No
7	27	VSD	VSD closure	No
8	13	VSD, PS	VSD closure, PV commiss.	AJR
9	12	VSD	VSD closure	No
10	16	PS	PV commiss.	AVB II
11	88	ASD, SV	ASD closure	No
12	46	ASD II	ASD closure	AJR
13	12	Down; AVSD	Correction	JET
14	155	AoS	AoV commiss.	No
15	9	Down; VSD	VSD closure	AJR
16	48	TOF	Correction	No
17	7	TOF	Correction	JET
18	137	VSD, AI	VSD closure	No
19	135	Down; ASD I, MI	ASD closure, MV reconst.	AVB III
20	42	VSD, PS	VSD closure, PV commiss.	No
21	98	VSD	VSD closure	No
22	150	ASD I, MI	ASD closure, MV reconst.	No
23	164	ASD I, MI	ASD closure, MV reconst.	No
24	51	ASD II	ASD closure	No
25	8	VSD	VSD closure	No
26	18	ASD II	ASD closure	No

Ebstein, Ebstein's malformation; *DORV*, double-outlet right ventricle; *VSD*, ventricular septal defect; *TOF*, tetralogy of Fallot; *PI*, pulmonary valve insufficiency; *MS*, mitral stenosis; *PS*, pulmonary stenosis; *ASD*, atrial septal defect; *SV*, single ventricle; *Down*, Down's syndrome; *AI*, aortic insufficiency; *AVSD*, atrioventricular septal defect; *AoS*, aortic stenosis; *MI*, mitral insufficiency; *TV*, tricuspid valve; *reconst.*, reconstruction; *TCPC*, total cavopulmonary connection; *PV*, pulmonary valve; *commiss.*, commissurotomy; *AoV*, aortic valve; *MV*, mitral valve; *JET*, junctional ectopic tachycardia; *AJR*, accelerated junctional rhythm; *AVB II*, second-degree atrioventricular block; *AVB III*, third-degree atrioventricular block.

ectopic tachycardia, second-degree atrioventricular block (AVB II) type I, and third-degree atrioventricular block (AVB III). These arrhythmias were defined as follows¹⁷:

Accelerated junctional rhythm. Accelerated junctional rhythm is a supraventricular rhythm with normal QRS and no visible P wave, retrograde P wave after each QRS complex, or atrioventricular dissociation with a QRS rate faster than the normal junctional escape rate (50 to 80 beats/min up to 3 years and 40 to 60 beats/min over 3 years) but not exceeding the maximum normal sinus rate for age at rest. Normal sinus rate for age at rest is described elsewhere.¹⁸ Because no data have been reported, the influence of catecholamines on sinus and junctional rate could not be considered.

Table II. Sample time schedule

Sample time 1	Preoperative
Sample time 2	After heparin administration
Sample time 3	Ten minutes after initiation of CPB
Sample time 4	At the end of rewarming (core temperature = 30° C)
Sample time 5	After protamine administration
Sample time 6	Four hours after the operation
Sample time 7	First postoperative day

Junctional ectopic tachycardia. Junctional ectopic tachycardia is accelerated junctional rhythm with a QRS rate exceeding the maximum normal sinus rate for age.

AVB II type I. AVB II is failure of conduction of some, but not all, of the impulses from the atria to the ventricles, with progressive prolongation of the PR interval before a nonconducted P wave.

AVB III. AVB III is complete lack of transmission of atrial impulses to the ventricles with the atrial rate faster than the ventricular rate.

In cases of time-related variations of the heart rate in patients with transient postoperative arrhythmias, the fastest rhythm was retained for the diagnosis.

Collection of samples. Samples of venous blood were collected before the operation from a peripheral vein, during and after the operation from a central venous catheter, and during CPB from the arterial line of the oxygenator. Sample times are shown in Table II. For each sample, 2 ml of blood taken in plastic tubes containing ethylenediaminetetraacetic acid were necessary for the study of TNF- α , prostaglandin D₂ (PGD₂), eosinophil cationic protein (ECP), and histamine; 0.5 ml of whole blood was needed for leukocyte count and differentiation.

Determination of histamine, ECP, PGD₂, and TNF- α . Histamine (a marker of both basophil and mast cell degranulation) was determined by means of immunoenzymatic dosage based on competition between histamine to be determined and histamine-acetylcholine esterase from Immunotech International, Immunotech, Marseille, France. The specificity has been increased through acylation of sample and tracer histamine and by using monoclonal antibodies against acylated histamine. Normal plasmatic histamine values in healthy adults are less than 1000 pg/ml. ECP (a marker of eosinophil degranulation) was determined by means of double antibody radioimmunoassay (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden). Normal values for healthy adults range between 2.3 and 16 μ g/L.

PGD₂ (a marker of mast cell degranulation) was determined by means of a radioimmunoassay technique with PGD₂-[3H] as tracer (Amersham Belgium, Gent, Belgium).

TNF- α was determined with an immunoenzymetric assay (enzyme amplified sensitivity immunoassay; Medgenix, Medgenix Diagnostics SA, Fleurus, Belgium). Normal values for healthy adults are lower than 20 pg/ml.

Measured histamine, ECP, PGD₂, and TNF- α values were not corrected for hemodilution during CPB.

Leukocyte count and differentiation were performed with a Coulter counter (Coulter Electronics, Inc., Hialeah, Fla.). Leukocyte values were corrected for hemodilution

Table III. Variables entered for the multivariate analysis

Age
CPB duration
Circulatory arrest
Aortic crossclamp time
Epinephrine dose at the end of the operation
Circulating histamine after protamine administration
Circulating histamine 4 hours postop.
Circulating histamine on first postop. day
Histamine release during CPB
Histamine release between institution of CPB and 4 hours postop.
Histamine release between institution of CPB and first postop. day
ECP after protamine administration
ECP 4 hours postop.
ECP on first postop. day
ECP release during CPB
ECP release between institution of CPB and first postop. day
Ventricular septal defect closure

by multiplying the measured value by the quotient $H_t \text{ pre}/H_t \text{ sample}$, where $H_t \text{ pre}$ is preoperative hematocrit value and $H_t \text{ sample}$ is hematocrit value of the sample.

Polyspecific radioallergosorbent test (RAST) screening against common aeroallergens was performed with RAST Phadiatop (Kabi).

Statistical analysis. For statistical analysis, nonparametric tests (Wilcoxon test, Mann-Whitney U test) were used when appropriate. Fisher's exact test was performed for analysis of contingency tables. To investigate the influence of several clinical and biologic variables (Table III) on the probability of development of transient postoperative arrhythmias, we used a multivariate logistic regression model.¹⁹ Data were computerized and analyzed with the SAS program (SAS Institute, Inc., Cary, N.C.). Results are expressed as mean value $\pm$ 1 standard deviation ($m \pm SD$) in the text or as mean $\pm$ standard error of the mean ($m \pm SEM$) in the figures. All p values < 0.05 were considered significant.

Results

Clinical results. Transient postoperative arrhythmias developed in eight of the 26 children studied. Children with transient postoperative arrhythmias (mean age 41.5 ± 47.9 months) were younger than children without arrhythmias (mean age 77.4 ± 54.7 months) ($p < 0.05$). There was no difference between patients with and without transient postoperative arrhythmias with regard to CPB duration, aortic crossclamping time, and epinephrine, dopamine, and sodium nitroprusside dosage immediately after the operation. Circulatory arrest was more often used in patients with arrhythmias (6/8 patients) than in those without (4/18 patients) ($p <$

Table IV. Comparative clinical data in patients with and without transient postoperative arrhythmias

	Without arrhythmias ($n = 18$)	With arrhythmias ($n = 8$)	p Value
Age (mo)	77.4 ± 54.7	41.5 ± 47.9	<0.05
CPB (min)	77 ± 30	71 ± 30	NS
AXT (min)	52 ± 19	54 ± 19	NS
CA (n)	4	6	<0.05
CA (min)	45 ± 5	54 ± 12	NS
Epinephrine ($\mu\text{g/kg/min}$)	0.04 ± 0.09	0.17 ± 0.21	NS
Dopamine ($\mu\text{g/kg/min}$)	3.05 ± 2.48	3.28 ± 2.63	NS
SNP ($\mu\text{g/kg/min}$)	0.67 ± 0.35	0.74 ± 0.47	NS

CPB, Cardiopulmonary bypass; AXT, aortic crossclamping time; CA, circulatory arrest; SNP, sodium nitroprusside; NS, not significant. Drug doses are those at the end of the operation. Values are expressed by the mean $\pm$ SD.

0.05), but duration of circulatory arrest was identical in the two groups. Comparative data of the 26 patients with respect to transient postoperative arrhythmias are summarized in Table IV.

In the eight children with transient postoperative arrhythmias, the following arrhythmias were diagnosed: accelerated junctional rhythm, $n = 3$; junctional ectopic tachycardia, $n = 3$; AVB II type I, $n = 1$; and AVB III, $n = 1$. Three patients with arrhythmias (accelerated junctional rhythm, $n = 2$; AVB II, $n = 1$) were in normal sinus rhythm immediately after the operation and showed abnormal rhythm 4 to 5 hours (median 4 hours) later. The patient with AVB II had initial episodes of sinus tachycardia alternating with episodes of AVB II, persisting 12 hours after the operation. The other five patients had abnormal cardiac rhythm at the end of the operation (accelerated junctional rhythm, $n = 3$; AVB III, $n = 1$; junctional ectopic tachycardia, $n = 1$). Two of these three patients with accelerated junctional rhythm in the immediate postoperative period (patients 5 and 13) had junctional ectopic tachycardia 4 hours after the operation. Five children were treated for arrhythmias: atrial or ventricular stimulation (or both) in three (accelerated junctional rhythm, $n = 1$; AVB II, $n = 1$; AVB III, $n = 1$) and digoxin for 24 hours in two (both with junctional ectopic tachycardia). Transient postoperative arrhythmias ceased in six children after 12 to 96 hours (median 33 hours). In two patients, junctional ectopic tachycardia masked definitive arrhythmias (sick sinus syndrome and AVB III), which appeared 48 and 54 hours after the operation,

Table V. Clinical data of patients with transient postoperative arrhythmias

Patient no.	Arrhythmia	Maximal HR (beats/min)	Onset (hours postop.)	Termination (hours postop.)	Treatment	Arrhythmia at discharge
5	JET	150	Immediate	48	Digoxin	SSS
8	AJR	100	Immediate	36	Pacing	No
10	AVB II	150	5	36	Pacing	No
12	AJR	100	4	30	No	No
13	JET	180	Immediate	54	Digoxin	AVBIII
15	AJR	110	4	30	No	No
17	JET	200	6	36	No	No
19	AVB III	40	Immediate	96	Pacing	No

JET, junctional ectopic tachycardia; AJR, accelerated junctional rhythm; AVB, atrioventricular block; HR, heart rate; SS, sick sinus syndrome.

respectively, when the rate of the junctional rhythm decreased. Holter electrocardiograms in these two patients showed pathologic abnormalities on their discharge. On the contrary, the other six patients with transient postoperative arrhythmias and the 18 without arrhythmias had normal Holter electrocardiographic findings on discharge. Table V summarizes the clinical data and course of arrhythmia in the eight patients with transient postoperative arrhythmias.

Laboratory tests

Histamine. In the 26 patients studied, circulating histamine values averaged 176.6 ± 76.1 pg/ml (mean $\pm$ SD) 10 minutes after institution of CPB. Histamine concentration rose during CPB, reaching 217.6 ± 300.4 pg/ml after protamine administration ($p =$ not significant). Compared with the value measured at the start of CPB, circulating histamine levels were significantly higher 4 hours after the operation (464.9 ± 689.7 pg/ml) and on the first postoperative day (472.7 ± 584.7 pg/ml) ($p < 0.05$). Patients in whom circulatory arrest was used ($n = 10$) had higher levels of circulating histamine 4 hours after the operation (877.6 ± 747.0 pg/ml) than those in whom circulatory arrest was not used ($n = 16$) (171.6 ± 46.6 pg/ml) ($p < 0.05$).

Histamine values at institution of CPB were similar in patients with and without postoperative arrhythmias (179.7 ± 75.6 and 175.2 ± 78.5 pg/ml, respectively). The eight patients with postoperative arrhythmias had significantly higher levels of circulating histamine 4 hours after the operation (1029.2 ± 1068.9 pg/ml) than the 18 patients without postoperative arrhythmias (214.0 ± 112.3 pg/ml) ($p < 0.02$).

Considering the individual course of histamine release with respect to transient postoperative arrhythmias and the use of circulatory arrest, the following results emerged: An increase in circulating histamine

(as expressed in percent of the initial value measured on initiation of CPB) greater than 200% was measured 4 hours after the operation in eight patients (three of 18 patients without transient postoperative arrhythmias and five of eight patients with transient postoperative arrhythmias, $p = 0.06$). One of the 16 patients operated on without circulatory arrest and seven of the 10 patients operated on with circulatory arrest had an increase in circulating histamine of more than 200% 4 hours after the operation ($p < 0.005$).

Fig. 1 shows the course of circulating histamine during and after CPB in patients with and without transient postoperative arrhythmias, and Fig. 2 depicts the individual course of histamine in the eight patients with transient postoperative arrhythmias.

ECP. In the 26 patients investigated, ECP values averaged 3.9 ± 2.8 μ g/L (mean $\pm$ SD) before the operation. During CPB, the ECP value rose from 5.4 ± 4.8 μ g/L 10 minutes after institution of CPB to 8.0 ± 5.6 μ g/L at the end of rewarming ($p < 0.05$). ECP levels rose further after protamine administration to 10.3 ± 4.6 μ g/L ($p < 0.005$). ECP reached its peak value 4 hours after the operation (10.8 ± 7.7 μ g/L) and this value differed significantly from that measured at the onset of CPB ($p < 0.01$). ECP concentration remained slightly elevated on the first postoperative day (7.3 ± 9.5 μ g/L). Patients with transient postoperative arrhythmias had higher ECP values 4 hours after the operation than did patients without postoperative arrhythmias (16.8 ± 8.9 μ g/L and 8.2 ± 5.7 μ g/L, respectively) ($p < 0.05$). On postoperative day 1, the ECP level fell abruptly in patients with transient postoperative arrhythmias (3.7 ± 2.1 μ g/L), whereas the ECP concentration remained elevated in patients without transient postoperative arrhythmias (8.87 ± 11.1 μ g/L). This difference was not significant. No correlation was found between ECP release during CPB and circulatory

Fig. 1. Course of circulating histamine during and after CPB in eight patients with transient postoperative arrhythmias (*interrupted line*) and in 18 patients without arrhythmias (*solid line*). Results are expressed as mean $\pm$ SEM. Asterisk indicates a significant difference ($p < 0.02$) between the two groups. Sample times as in Table II.

arrest. Fig. 3 shows the course of ECP in patients with and without transient postoperative arrhythmias.

PGD₂. PGD₂ release was studied in 11 patients, nine without transient postoperative arrhythmias and two with transient postoperative arrhythmias. In four of these 11 patients, 4 hours after the operation, there was an increase in circulating histamine to more than 200% of the baseline value measured on institution of CPB. In these 11 patients, PGD₂ averaged 17.3 ± 7.1 pg/ml (mean $\pm$ SD) 10 minutes after initiation of CPB, 30.0 ± 22.3 pg/ml at the end of rewarming, and 25.7 ± 16.5 pg/ml 4 hours after the operation. PGD₂ levels during or after CPB were not significantly higher than the baseline value on institution of CPB. PGD₂ levels did not correlate with histamine levels at any time in the study period. The four patients with increased circulating histamine (200% of their baseline value at institution of CPB) did not have significantly different PGD₂ levels at the end of rewarming and 4 hours after the operation compared with the other seven patients.

TNF- α . In the 26 patients studied, TNF- α levels rose from 24.3 ± 30.9 pg/ml (mean $\pm$ SD) 10 minutes after the beginning of CPB to 39.1 ± 52.7 pg/ml at the end of rewarming and to 44.6 ± 46.2 pg/ml after protamine administration. TNF- α concentration averaged 41.2 ± 48.0 pg/ml 4 hours after the operation. The difference in TNF- α production during and immediately after CPB compared with the baseline value on institution of CPB was not significant. There was no difference in TNF- α values between patients with or without transient postoperative arrhythmias. There was no difference in TNF- α values between patients with or without an increased circulating histamine greater than 200% of the baseline value. In particular, TNF- α levels were not significantly different at the end of rewarming when those two patient groups were compared.

Leukocyte count and differentiation. Results of leukocyte count and differentiation are summarized in Table VI. With the exception of basophils (which did not change significantly during or after CPB),

Fig. 2. Individual course of circulating histamine during and after CPB in eight patients with transient postoperative arrhythmias. Numbers in parenthesis correspond to patient number in Table V. Sample times as in Table II. *JET*, Junctional ectopic tachycardia; *AJR*, accelerated junctional rhythm; *AVB II*, second-degree atrioventricular block type I; *AVB III*, third-degree atrioventricular block.

there was a significant decrease in all forms of leukocytes at institution of CPB followed by a rebound (except for lymphocytes) after protamine administration. There was no correlation between leukocyte count and differentiation and ECP or histamine release. There was no difference in leukocyte and differential count between patients with or without postoperative arrhythmias.

Polyspecific RAST screening. Positive RAST screening was found in seven of 26 examined children, in accordance with the prevalence of atopy in the normal population. There was no correlation between positive RAST screening and histamine release during and after CPB or postoperative arrhythmias.

Logistic regression. Of the 17 variables selected for the multivariate regression model, the release of circulating histamine between the time of institution of CPB and the fourth postoperative hour (parameter estimate $\pm$ standard error: 0.0059 ± 0.0032)

and the release of ECP between institution of CPB and the first postoperative day (parameter estimate $\pm$ standard error: 0.130 ± 0.098) and the intercept (1.85 ± 0.70), which were the most relevant, were used in the final model. The emerging model permitted the prediction of postoperative arrhythmias with a sensitivity of 94.4% and a specificity of 62.5%.

Discussion

Histamine liberation related to CPB has previously been reported,^{20, 21} but its mechanism and clinical implications have not been investigated so far. Our data demonstrate significant histamine release related to CPB in children undergoing cardiac operations. In our series, the absence of significant TNF- α production before histamine liberation and the absence of significant simultaneous release of PGD₂ from mast cells in the patients having elevated histamine values suggest that mast cells do not play a predominant role in histamine liberation.

Fig. 3. Course of ECP during and after CPB in eight patients with transient postoperative arrhythmias (*interrupted line*) and in 18 patients without arrhythmias (*solid line*). Results are expressed by the mean $\pm$ SEM. Asterisk indicates a significant difference ($p < 0.05$) between the two groups. For sample times, see Table II.

Nevertheless, inasmuch as PGD_2 levels were slightly elevated at the end of rewarming and 4 hours after CPB compared with the values measured on institution of CPB, the participation of mast cells in the inflammatory process caused by CPB is not excluded. The potential incidence of atopy as a predisposing condition for increased reactivity and histamine liberation was excluded both clinically and biologically because no patient had any atopic manifestation and the prevalence of immunoglobulin E antibodies against common aeroallergens was not discriminant. Thus, in our series, histamine liberation related to CPB was probably due to activated basophil degranulation. The parallel evolution of histamine and ECP levels during and after CPB suggests that both basophils and eosinophils are subjected to a stimulation process shared by neutrophils as well. This extends the known list of blood cells that are activated during CPB.^{4, 9, 22}

Our results showing a significant decrease of all

forms of leukocytes at institution of CPB followed by global count rebound after protamine administration confirm previous reports^{3, 22} and support the contention of global granulocyte and monocyte peripheral adhesion and mobilization in response to CPB and protamine administration. Nevertheless, in our series, the magnitude of the cellular traffic was not discriminant for cellular activation because the basophil and eosinophil cell count did not correlate with the amount of liberated histamine and ECP, respectively. The lack of evidence of significant basophil mobilization could be due to the technical impossibility to recognize and count degranulated basophils and to the overall difficulty in analyzing variations of small amounts of circulating cells.

Considering our patients individually, despite histamine liberation observed in all, eight of the 26 children emerged from the whole group. They showed an increase in circulating histamine of more than 200% of their individual value measured on

Table VI. *Leukocyte count and differentiation before, during, and after CPB*

	Sample times				
	1	2	3	4	5
Leukocytes	7,670 ± 2,388	8,592 ± 3,142	5,496 ± 2,834	5,886 ± 3,589	15,458 ± 8,874
Neutrophils	3,665 ± 2,000	4,278 ± 2,025	2,464 ± 1,643	3,383 ± 2,303	11,322 ± 7,030
Lymphocytes	3,546 ± 1,243	3,130 ± 1,230	2,480 ± 980	22,670 ± 1,380	3,010 ± 1,660
Monocytes	410 ± 230	510 ± 280	330 ± 280	240 ± 210	400 ± 460
Eosinophils	225 ± 258	190 ± 205	112 ± 129	56 ± 89	140 ± 164
Basophils	39 ± 47	21 ± 51	4 ± 21	13 ± 43	6 ± 23

Values for Leukocytes are expressed in cells per cubic millimeter by the mean ± standard deviation. For sample times, see Table II.

institution of CPB. In seven of these eight patients the operation was done with circulatory arrest. This observation suggests that, in addition to the effects of CPB, circulatory arrest and profound hypothermia also play a determinant role on histamine liberation. We³ showed in a previous study that circulatory arrest and deep hypothermia do not have any influence on the magnitude of C3 conversion and C5a liberation observed during and after CPB. Profound hypothermia, in contrast, is widely known to modify the rigidity of the cellular membrane and to allow increased accumulation of ligands on the cell wall, enhancing the pharmacologic response of activated cells to biologic mediators.²³ We suggest therefore that circulatory arrest and profound hypothermia influence histamine liberation by those physicochemical alterations of membrane function.

Five of eight patients with arrhythmias but only three of 18 patients without transient postoperative arrhythmias had an increase in circulating histamine greater than 200% of their own baseline value. Correspondingly, the eight patients with transient postoperative arrhythmias had significantly higher circulating histamine levels 4 hours after the operation than the 18 patients without transient postoperative arrhythmias. Histamine has a large number of arrhythmogenic properties well documented in the animal model and in isolated human heart preparations.^{16, 24-30} Our clinical data document a possible association between increased circulating histamine and transient postoperative arrhythmias in children having undergone CPB operations. In our series, patients having transient postoperative arrhythmias had significantly higher histamine blood concentrations at the time of onset of arrhythmias than did those without arrhythmias. However, five of the eight patients with transient postoperative arrhythmias had obviously undergone surgical repair possibly affecting the atrioventricular junction, such as closure of a ventricular septal defect or mitral

valve reconstruction. Although in our study ventricular septal defect closure was not a discriminant variable for the prediction of the occurrence of transient postoperative arrhythmias, the influence of surgical trauma on the development of transient postoperative arrhythmias cannot be excluded, as discussed elsewhere.³¹

Besides higher histamine release related to CPB, patients with transient postoperative arrhythmias also had higher ECP release than patients without transient postoperative arrhythmias; this difference reflects in the former a more pronounced eosinophil degranulation related to CPB, whereas the abrupt decrease of ECP concentration observed on the first postoperative day might suggest a consecutive exhaustion of ECP liberation. Thus, in patients with transient postoperative arrhythmias, a higher histamine and ECP release indicates a more important granulocyte stimulation related to CPB than occurs in patients without transient postoperative arrhythmias. In contrast to histamine, ECP has cardiotoxic properties but no known arrhythmogenic properties.³² It remains unclear which influence on cardiac function ECP has in patients undergoing cardiac operations.

In our series, transient postoperative arrhythmias correlated with the use of circulatory arrest for the surgical procedure. Inasmuch as aortic crossclamp time was similar in patients with and without arrhythmias, this observation supports the influence of profound hypothermia as discussed earlier, but not of myocardial ischemia in the development of transient postoperative arrhythmias in our patients. Because in our experience circulatory arrest is mainly used in small infants and young children, this probably explains the relationship between younger age and transient postoperative arrhythmias that we observed.

In our group of children with transient postoperative arrhythmias, all but two patients (with AVB II

and AVB III, respectively) had junctional rhythm, which was accelerated in three and defined as junctional ectopic tachycardia in four. Although junctional ectopic tachycardia can be assumed to be an active tachycardia, it is not clear in our series whether accelerated junctional rhythm was the result of sinus dysfunction allowing junctional escape rhythm to become manifest or whether accelerated junctional rhythm was the consequence of increased automaticity of the atrioventricular junction.

Accelerated junctional rhythm in children after cardiac operations is usually hemodynamically well tolerated and, if necessary, easy to treat symptomatically by atrial pacing. By contrast, junctional ectopic tachycardia, if prolonged and fast, is a serious complication, the treatment of which remains unsatisfactory. Junctional ectopic tachycardia is described as a self-limiting arrhythmia resolving spontaneously within about 72 hours after the operation if the patient survives.^{33,34} According to the literature,³⁴ the pathophysiology of postoperative junctional ectopic tachycardia is not clearly understood. Junctional ectopic tachycardia is thought to be related to several factors such as the underlying cardiac defect, the increased vagolytic activity, and the administration of sedatives or pancuronium bromide. The latter are widely known to induce histamine release from basophils or mast cells.^{35,36}

We suggest that histamine, as it has previously been demonstrated in the animal and in isolated human heart preparations,¹⁶ may induce junctional ectopic tachycardia and possibly accelerated junctional rhythm by a mechanism involving the enhancement of pacemaker automaticity and a shift in the pacemaker site.²⁷ This mechanism can be encouraged by transitory sinus node dysfunction resulting from surgical trauma.³¹ These actions of histamine are exclusively mediated by histamine receptors of the H₂ type, which activate cardiac adenylate cyclase and increase intracellular circulating adenosine monophosphate.¹⁶ Two of the three patients with junctional ectopic tachycardia had accelerated junctional rhythm immediately after the operation, which accelerated and developed after a few hours into junctional ectopic tachycardia. Because in our series in general and in these two patients in particular histamine continued to increase within the first 4 hours after the operation, this observation could reflect the dose-response relationship between histamine and heart rate, as previously demonstrated.²⁷

Because histamine has been shown in the animal

model to produce various degrees of atrioventricular block by a mechanism involving histamine H₁ receptors,¹⁶ it might theoretically have induced impaired atrioventricular conduction in our two patients with atrioventricular block. Although this is improbable in patient 19 with AVB III, who had undergone closure of an atrial septal defect type I with mitral valve reconstruction and who had low histamine concentrations during and after the operation, it is not excluded in patient 10 with AVB II, who had elevated histamine blood concentrations after pulmonary valve commissurotomy.

In conclusion, this study demonstrates significant histamine release related to CPB, the major source of which seems to be activated basophils. The possible relationship we found between histamine liberation and the development of transient postoperative arrhythmias after cardiac operations in children needs further study on a much larger series to be confirmed.

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REFERENCES

1. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. *N Engl J Med* 1981;304:497-503.
2. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1983;86:845-57.
3. Seghaye MC, Duchateau J, Grabitz RG, et al. Complement activation during cardiopulmonary bypass in infants and children: relation to postoperative multiple system organ failure. *J Thorac Cardiovasc Surg* 1993;106:978-87.
4. Faymonville ME, Pincemail J, Duchateau J, et al. Myeloperoxidase and elastase as markers of leukocyte activation during cardiopulmonary bypass in humans. *J Thorac Cardiovasc Surg* 1991;102:309-17.
5. Cavarocchi NC, England MD, Schaff HV, et al. Oxygen free radical generation during cardiopulmonary bypass: correlation with complement activation. *Circulation* 1986;74(Suppl): III130-3.
6. Steinberg JB, Kapelanski DP, Olson JD, Weiler JM. Cytokine and complement levels in patients undergoing cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1993;106:1008-16.
7. Kaplan AP, Reddigari S, Baeza M, Kuna P. Histamine releasing factors and cytokine-dependent activation of basophils and mast cells. *Adv Immunol* 1991;50:237-60.
8. Juergensen H, Braam U, Pult P, Kownatzki E, Schmutzler W. Human C5a induces a substantial histamine release in human basophils but not in tissue mast cells. *Int Arch Allergy Immunol* 1988;85:487-8.
9. Haeffner-Cavaillon N, Rousselier N, Ponzio O, et al. Induction of interleukin-1 production in patients undergoing car-

- diopulmonary bypass. *J Thorac Cardiovasc Surg* 1989;98:1100-6.
10. Finn A, Naik S, Klein N, Levinski RJ, Strobel S, Elliott M. Interleukin-8 release and neutrophil degranulation after pediatric cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1993;105:234-41.
11. Kalfin RE, Engelman RM, Rousou JA, et al. Induction of interleukin-8 expression during cardiopulmonary bypass. *Circulation* 1993;88:401-6.
12. Casey WF, Hauser GJ, Hannallah RS, Midgley FM, Khan WN. Circulating endotoxin and tumor necrosis factor during pediatric cardiac surgery. *Crit Care Med* 1992;20:1090-6.
13. Butler J, Pillai R, Rocker GM, Westaby S, Parker D, Shale DJ. Effect of cardiopulmonary bypass on systemic release of neutrophil elastase and tumor necrosis factor. *J Thorac Cardiovasc Surg* 1993;105:25-30.
14. Haak-Frendscho M, Dinarello C, Kaplan AP. Recombinant human interleukin-1 beta causes histamine release from human basophils. *J Allergy Clin Immunol* 1988;82:218-23.
15. Falus A, Merétey K. Histamine: an early messenger in inflammatory and immune reactions. *Immunol Today* 1992;13:154-6.
16. Levi R, Owen DAA, Trzeciakowski J. Actions of histamine on the heart and vasculature. In: Ganelli CR, Parsons ME, eds. *Pharmacology of histamine receptors*. Bristol: John Wright and Sons, 1982:236-97.
17. Garson A. Arrhythmias. In: Garson A, Gillette P. *The electrocardiogram in infants and children: a systematic approach*. Philadelphia: Lea & Febiger, 1983:195-375.
18. Garson A. The normal electrocardiogram. In: Garson A, Gillette P. *The electrocardiogram in infants and children: a systematic approach*. Philadelphia: Lea & Febiger, 1983:61-82.
19. Matthews DE, Farewell VT. Binary logistic regression. In: Matthews DE, Farewell VT. *Using and understanding medical statistics*. Basel: S. Karger, 1985:139-47.
20. Meyer-Burgdorff, Seidel G, Schlueter FJ. Freisetzung von Histamin und Serotonin bei extracorporaler Zirkulation. *Anaesthesist* 1973;22:212-6.
21. Withington DE, Elliot M, Man WK. Histamine release during paediatric cardiopulmonary bypass. *Agents Actions* 1991;33:200-2
22. Hammerschmidt DE, Stroncek DF, Bowers TK, et al. Complement activation and neutropenia occurring during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1981;81:370-7.
23. Sajani AN, Ranadive NS, Movat HZ. Redistribution of immunoglobulin receptors on human neutrophils and its relationship to the release of lysosomal enzymes. *Lab Invest* 1976;35:143-51.
24. Wolff AA, Levi R. Histamine and cardiac arrhythmias. *Circ Res* 1986;58:1-16.
25. Bristow MR, Ginsburg R, Harrison DC. Histamine and the human heart: the other receptor system. *Am J Cardiol* 1982;49:249-51.
26. Levi R, Malm JR, Bowman FO, Rosen MR. The arrhythmogenic actions of histamine on human atrial fibers. *Circ Res* 1981;49:545-50.
27. Levi R, Zavec JH. Acceleration of idioventricular rhythms by histamine in guinea pig heart. *Circ Res* 1979;44:847-55.
28. Levi R, Pappano AJ. Modifications of the effects of histamine and norepinephrine on the sinoatrial node pacemaker by potassium and calcium. *J Pharmacol Exp Ther* 1978;204:625-33.
29. Trzeciakowski JP, Levi R. Reduction of ventricular fibrillation threshold by histamine: resolution into separate H1- and H2-mediated components. *J Pharmacol Exp Ther* 1982;223:774-83.
30. Levi R, Capurro N, Lee C-H. Pharmacological characterization of cardiac histamine receptors: sensitivity to H1- and H2-receptor agonists and antagonists. *Eur J Pharmacol* 1975;30:328-35.
31. Waldo AL, MacLean WAH. Anatomy of the specialized conduction system of the heart. In: *Diagnosis and treatment of cardiac arrhythmias following open-heart surgery*. Mount Kisco, New York: Futura, 1980:237-44.
32. Spry CJF, Tai P-C, Davies J. The cardiotoxicity of eosinophils. *Postgrad Med J* 1983;59:147-51.
33. Grant JW, Serwer GA, Armstrong BE, Oldham HN, Anderson PAW. Junctional tachycardia in infants and children after open-heart surgery for congenital heart disease. *Am J Cardiol* 1987;59:1216-8.
34. Gillette PC. Diagnosis and management of postoperative junctional ectopic tachycardia. *Am Heart J* 1989;118:192-4.
35. Marone G, Stellato C, Mastronardi P, Mazzarella B. Mechanisms of activation of human mast cells and basophils by general anaesthetic drugs. *Ann Fr Anesth Reanim* 1993;12:116-25.
36. Moss J, Rosow CE. Histamine release by narcotics and muscle relaxants in humans. *Anesthesiology* 1983;59:330-9.

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