Histamine release during cardiopulmonary bypass in neonates and infants

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Purpose: Histamine release has been previously documented in adults and children during cardiopulmonary bypass (CPB). It has not been studied in neonates nor during deep hypothermic circulatory arrest (DHCA). Histamine effects could explain many perioperative complications of congenital cardiac surgery such as dysrhythmias and massive oedema. Therefore, documentation of histamine release in the perioperative period is of clinical importance. The source of histamine can be determined by measurement of tryptase which is released with histamine from mast cells but not basophils.

Methods: Blood samples for histamine and tryptase were taken before and after specific events eg. cross-clamp removal, during anaesthesia and CPB in 14 infants and seven neonates undergoing complex congenital heart repairs and were analysed by commercial radioimmunoassays. Haemodynamic variables and pre and post-op weights were recorded to look for correlation between pathophysiological events and histamine release.

Results: Histamine concentration decreased at the start of bypass (0.69 to 0.38 $ng \cdot ml^{-1}$ at five minutes, ($P < .005$). There were no changes associated with DHCA and a small rise with reventilation ($P < 0.02$). Histamine concentration was lower in neonates than in infants ($P < 0.05$) during CPB. Plasma histamine and tryptase concentrations did not correlate, suggesting histamine release was from basophils and not from mast cells. Haemodynamic variables did not correlate with histamine concentrations.

Conclusion: There was no major histamine release during CPB in infants and neonates. There was no relationship between histamine concentrations and clinical variables. Histamine released during CPB appears to come from basophils and may be a function of age.

Objectif : La libération d'histamine a déjà été documentée chez des enfants et des adultes pendant la circulation extracorporelle (CEC). Elle n'a pas été recherchée chez les nouveau-nés ou pendant l'arrêt circulatoire en hypothermie profonde (ACHP). Les effets de l'histamine pourraient expliquer plusieurs des complications postopératoires de la chirurgie des cardiopathies congénitales comme les dysrythmies et l'oedème pulmonaire massif. Il est donc important du point de vue clinique de corroborer la libération d'histamine à la période périopératoire. La source de l'histamine peut être déterminée par le dosage de la tryptase libérée avec l'histamine par les mastocytes mais non les basophiles.

Méthodes : Des échantillons sanguins ont été prélevés pour le dosage de l'histamine et de la tryptase avant et après des événements spécifiques, per ex. le retrait du clamp aortique, pendant l'anesthésie et la CEC, chez 14 enfants et sept nouveau-nés soumis à des corrections chirurgicales de malformations congénitales compliquées. Les échantillons ont été analysés par dosage radioimmunologique. Les variables hémodynamiques et les pesées pré- et postopératoires ont été enregistrées pour rechercher une corrélation entre les événements physiopathologiques et la libération d'histamine.

Résultats : La concentration d'histamine a diminué au début de la CEC de 0,69 à 0,38 $ng \cdot ml^{-1}$ à la cinquième minute ($P < 0,005$). Aucun changement n'a été associé à l'ACHP. Une légère augmentation est survenue avec la reprise de la ventilation ($P < 0,02$). Pendant la CEC, les concentrations d'histamine des enfants étaient inférieures à celles des nouveau-nés ($P < 0,05$). Il n'y avait pas de corrélation entre les concentrations de tryptase et d'histamine, suggérant ainsi que l'histamine était libérée à partir des basophiles plutôt que des mastocytes. Les variables hémodynamique ne corrélaient pas avec les concentrations d'histamine.

Conclusion : On n'a pas noté de libération importante d'histamine pendant la CEC chez les enfants et les nouveau-nés. L'histamine libérée semble provenir des basophiles et pourrait être en fonction de l'âge.

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HISTAMINE release has been demonstrated at initiation of cardiopulmonary bypass (CPB) in adults[1] and also on aortic cross-clamp removal and on reventilation of the lungs in children aged over nine months.[2] Neonates have not been studied in this context and are particularly at risk from any destabilizing event since they show a more rapid and profound response to physiological stress.[3]

The effect of deep hypothermic circulatory arrest (DHCA) on plasma histamine concentrations has not been documented. This technique is frequently used to facilitate delicate procedures by providing bloodless conditions[4] in neonates and small infants. Reperfusion after DHCA may be anticipated to cause mediator release since myocardial reperfusion after coronary occlusion in animals has been demonstrated to provoke histamine release.[5]

Histamine is the major mediator in systemic anaphylaxis,[6] producing effects ranging from urticaria to bronchospasm, capillary leak, cardiac dysrhythmias and haemodynamic collapse.[7,8] Similar events are seen during and after congenital heart surgery: dysrhythmias are common and capillary leak producing postoperative fluid overload with severe oedema is a major problem. Thus, histamine may play a rôle in the pathophysiology of CPB.

To be able to modulate histamine release, the source of histamine must be known since mast cells can be stabilised by disodium cromoglycate whereas basophil degranulation is managed with receptor blockade. The cellular origin of histamine can be determined by the simultaneous measurement of plasma tryptase,[9] which is released along with histamine from mast cells but not from basophils.

The objectives of the present study were: 1) to measure plasma histamine concentrations during CPB in neonates and infants; 2) to examine the effect of DHCA; 3) to determine the source of histamine and 4) to describe any relationship between histamine release and pathophysiological changes during and after CPB.

Methods

In our establishment DHCA may be used during the repair of complex congenital heart disease in children of less than one year of age or <10 kg body weight. Any child aged <15 mo undergoing open heart surgery was included in the study in order to include children of comparable ages and weights with and without DHCA. Children with a history of allergy and those taking anti-histamine medication or chronic corticosteroid therapy were excluded in order to eliminate any effect of longer acting anti-histamines or of diminished mast cell responsiveness. No children undergoing repeat surgery were studied. Ethics Committee and Institutional Review Board approval were given and written informed consent was obtained from parents.

Induction of anaesthesia was performed with 1–2 $mg \cdot kg^{-1}$ ketamine, 5–10 $\mu g \cdot kg^{-1}$ fentanyl and muscle relaxation was achieved with 0.08 $mg \cdot kg^{-1}$ pancuronium after nitrous oxide in oxygen had been given to facilitate venous access. Maintenance of anaesthesia was with fentanyl. Following anaesthetic induction direct arterial and central venous pressure (CVP) monitoring was instituted. Antibiotic prophylaxis with cefoxitin was given shortly after induction.

The pump circuit was primed with leucocyte filtered packed red blood cells and plasma mixed with sodium bicarbonate and Normosol™ or Ringer's Lactate to produce a physiological pH. Cardiopulmonary bypass was performed at an haematocrit of 20–22%. A membrane oxygenator (Terumo™) was used for all cases and an arterial filter was in circuit.

At the initiation of DHCA patients were routinely given 30 $mg \cdot kg^{-1}$ methylprednisolone, 0.1 $mg \cdot kg^{-1}$ phentolamine and 0.1 $mg \cdot kg^{-1}$ furosemide. All patients received 0.3–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ sodium nitroprusside during the rewarming period.

Blood samples for histamine assay, 1 ml in heparinized tubes kept on ice, were taken after arterial cannula placement before the start of surgery. Serum for tryptase assay was obtained from a clotted 0.5 ml sample. Plasma and serum were extracted by centrifuging the samples in a cold centrifuge (4°C, 150 g) for 20 min and were stored at −20°C until analyzed.

Pre-CPB samples were taken immediately before CPB to separate any effect of surgery from that of CPB and to provide a sample distant from induction of anaesthesia. A sample of prime solution was taken to compare with samples taken immediately after the start of CPB. Sampling times were chosen based on previous results[2] and are indicated in Figure 1.

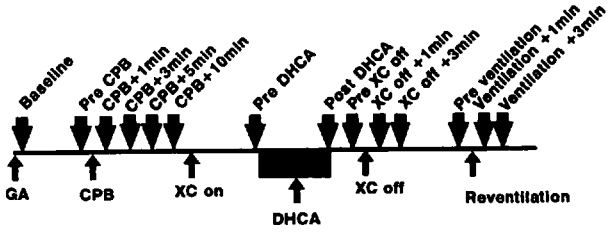

FIGURE 1 Plasma histamine sampling schedule. Events are shown below the line and sampling times above the line.

Key: GA = induction of anaesthesia; CPB = start of cardiopulmonary bypass; XC on = application of aortic cross clamp; DHCA = deep hypothermic circulatory arrest; XC off = aortic cross clamp removal.

All samples after the pre-CPB sample were taken from the arterial manifold of the pump until pulmonary artery and left atrial monitoring lines were placed by the surgeon following removal of the aortic cross-clamp. Samples at reventilation were taken simultaneously from right atrial (RA), pulmonary artery (PA) and left atrial (LA) cannulae to describe any concentration gradients across the heart and lungs.

Histamine was assayed in duplicate by radioimmunoassay (Immunotech™). The sensitivity of this assay is 0.05 $ng \cdot ml^{-1}$, range 0–15 $ng \cdot ml^{-1}$. The coefficient of variation (CV) was 11.5% at low and 8.2% at high concentration. Normal histamine concentrations[10] are < 0.3 $ng \cdot ml^{-1}$.

Plasma tryptase was assayed in duplicate by the Kabi Pharmacia™ Tryptase Immunoradiometric assay kit. The sensitivity of the assay is 0.5 $ng \cdot ml^{-1}$, range 2–50 $ng \cdot ml^{-1}$. CV is 2%. Normal values[9] are < 2.5 $ng \cdot ml^{-1}$.

Heart rate, systolic, diastolic and mean arterial pressures were recorded at each sampling point. Patients were weighed on the same scales before and after surgery as an assessment of fluid overload secondary to capillary leak. Maximum post-operative weight and fluid balance were noted.

Sample size was based on an anticipated change in histamine of 0.8 $ng \cdot ml^{-1}$ (SD 0.5 $ng \cdot ml^{-1}$) to give a power of > 0.9 at a significance level of $P < 0.05$. After logarithmic transformation a profile plot of histamine against time was performed. The BMDP statistical package was used to perform analysis of variance with repeated measures for unbalanced design.[11] All *post-hoc* comparisons were made using a paired t test analysis. A P value of < 0.05 was regarded as statistically significant.

Results

Twenty-one patients were studied, seven neonates and 14 infants of 2.5–13 mo. The demographic data and congenital heart lesions are shown in Table I. The duration of CPB was 150 ± 7.7 min (mean ± SD), XC time 76 ± 3.9 min and DHCA 36 ± 5.0 min. Neonates had longer XC times ($P < 0.05$) than infants, but comparable CPB and DHCA times. Four infants ≥ six months did not undergo DHCA. Of these, all received phentolamine and two also received methylprednisolone.

The histamine concentration was > 1 $ng \cdot ml^{-1}$ in pump prime in six cases (1.05–5.93 $ng \cdot ml^{-1}$, mean 2.89, median 1.5 $ng \cdot ml^{-1}$). Baseline histamine concentration was high in seven patients (1.18–8.33 $ng \cdot ml^{-1}$) and remained high pre-CPB in three, two of these (1.92 and 2.64 $ng \cdot ml^{-1}$) being those with the highest baseline levels. One further patient had an elevated pre-CPB histamine concentration (1.15 $ng \cdot ml^{-1}$). There was no statistical difference between the histamine concentration in the circulated prime and the patients' pre-CPB samples.

TABLE I Demographic data

#	*age*	*sex*	*lesion*	*CPBt*	*XCt*	*DHCAt*	*Tmin*
1.	5D	F	DORV	173	100	55	16
2.	6D	F	DORV	167	83	62	19.6
3.	3M	F	VSD,PDA	125	64	50	19.1
4.	7.5M	M	TOF	121	66	47	19.0
5.	7M	F	TOF	121	55	47	17.3
6.	9M	M	AVSD	116	57	52	17.3
7.	8M	F	MVR	257	117	25	17.4
8.	8.5M	F	CAVC	132	69	62	16.9
9.	6D	M	IAA	116	66	45	19.8
10.	10D	M	TGA	176	75	27	18.4
11.	6M	F	CAVC	120	77	–	19.7
12.	13M	M	PAG	168	74	–	26.2
13.	6M	F	AVSD	130	59	36	15.8
14.	23D	M	TA	163	96	18	15.4
15.	4M	F	TOF	121	55	51	18.5
16.	6M	F	CAVC	154	100	–	19.1
17.	9M	M	CAVC/TOF	151	88	–	18.5
18.	14D	M	DORV	185	85	67	18.1
19.	23D	F	TGA	169	91	14	17.3
20.	2.5M	M	DORV	134	61	54	16.3
21.	7M	F	TOF	115	52	49	19.3

D = Days; M = Months; t = time (mins); Tmin = lowest nasopharyngeal temperature °C; DORV = double outlet right ventricle; VSD = ventriclar septal defect; PDA = patent ductus arteriosus; TOF = tetralogy of Fallot; AVSD = atrio-ventricular septal defect; MVR = mitral regurgitation; CAVC = comlete atrioventricular canal; IAA = interupted aortic arch; TGA = transposition of great arteries; PAG = pulmonary artery graft; TA = truncus arteriosus

On initiation of CPB there was a decrease in histamine concentration at three ($P < 0.005$) and 10 min of CPB ($P < 0.005$). Neonates demonstrated a decrease in histamine concentration at 3, 5 and 10 min post-CPB ($P < 0.03$) whereas in infants the changes were not statistically significant (Figure 2).

Neonates had lower mean histamine concentrations than infants at initiation of CPB ($P < 0.05$), pre and post DHCA ($P < 0.01$), at cross-clamp removal ($P < 0.02$) and reventilation of the lungs ($P < 0.02$) (Figures 2, 4).

There was no difference between histamine concentrations before and after DHCA (mean 0.30 *vs* 0.18 ng·ml^{-1}, $P = 0.056$) or before, one and three minutes after cross-clamp removal (mean 0.19 *vs* 0.28 *vs* 0.25 ng·ml^{-1}, $P = 0.54$) (Figure 3).

Right atrial sampling demonstrated an increase at one ($P < 0.01$) and three minutes ($P < 0.02$) reventilation of the lungs (Figure 4). There was no difference before *vs* after reventilation in the PA samples. When analyzed separately the neonates had no changes in histamine around the reventilation period but the number with adequate sampling was small.

Left atrial sampling revealed an increase from pre-reventilation to three minutes for the whole group ($P < 0.02$). Three minute reventilation concentrations were also elevated in comparison with pre-reventilation RA samples (mean 0.39 *vs* 0.22 ng·ml^{-1}; $P < 0.01$). In infants LA histamine concentrations were higher comparing pre-reventilation values with those after reventilation plus three minutes (mean 0.39 *vs* 0.44 ng·ml^{-1}; $P < 0.02$) and LA histamine concentrations were numerically but not statistically higher than RA at three minutes reventilation (mean 0.44 *vs* 0.38 ng·ml^{-1}).

Tryptase assay was performed in 13 cases (seven neonates, six infants). Baseline tryptase was low (<0.6 ng·ml^{-1}) in all but one case (1.82 ng·ml^{-1}). There was no difference between the tryptase content of pump prime and baseline samples. Tryptase was higher in pump *vs* pre-CPB samples (1.16 *vs* 0.06 ng·ml^{-1}, $P < 0.05$) but there was no change from pre-CPB to CPB +10 min. There was a decrease in tryptase levels post-DHCA ($P < 0.05$). Neither cross-clamp removal nor reventilation affected tryptase concentrations. Histamine and tryptase concentrations did not correlate.

All changes in heart rate and mean arterial pressure were predictable by clinical events eg., reduction at start of bypass. Heart rate did not correlate with histamine concentrations at any stage of the study. Mean arterial pressure correlated with plasma histamine concentrations in seven patients ($0.3724 < r^2 < 0.9632$), all infants aged > 2.5 mo, but not for the entire group.

There was a 19.6% ± 2.8% weight gain post-operatively with weight gain continuing in the first 48 hr post-surgery (Table II). In neonates, there was no weight

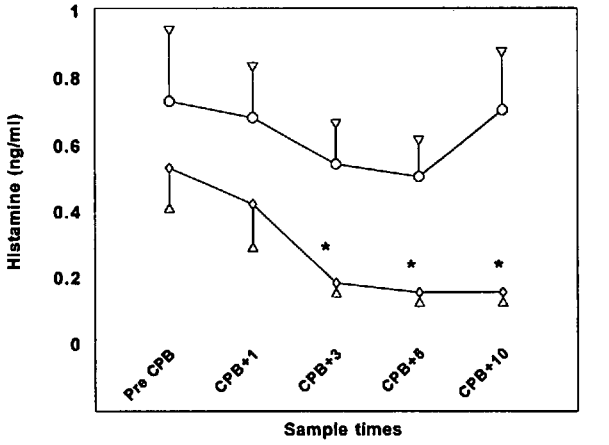

FIGURE 2 Plasma histamine concentrations during first 10 min of cardiopulmonary bypass: mean and SEM; neonates (♦) and infants (○), *$P < 0.03$ *vs* pre-CPB.

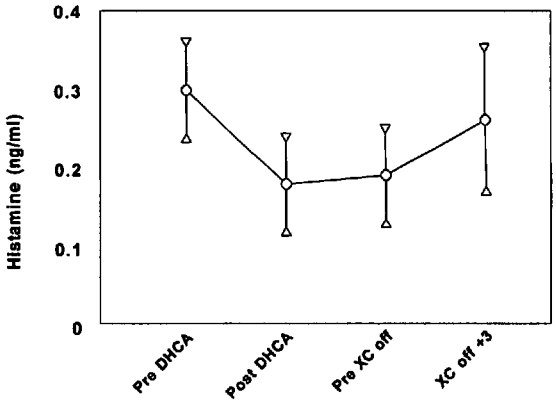

FIGURE 3 Plasma histamine concentrations related to DHCA and cross clamp removal: mean and SEM; *$P < 0.05$ *vs* pre cross-clamp removal.

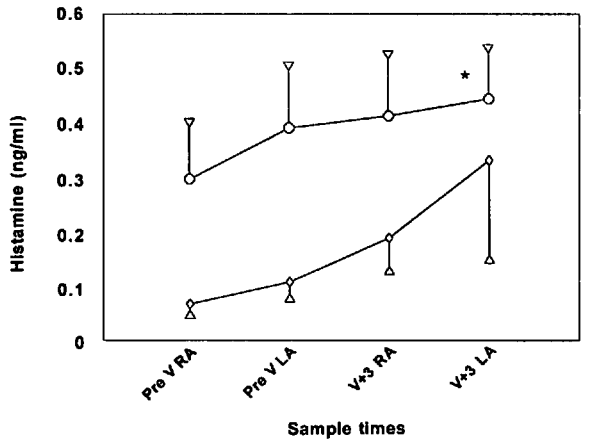

FIGURE 4 Plasma histamine concentrations related to reventilation: mean and SEM; neonates (♦) and infants (○), *$P < 0.05$ *vs* pre-reventilation.

TABLE II Weight gain post CPB

	mean (kg)	*SEM*
Pre-op weight	5.22	0.44
24 hr post-op weight	5.86	0.46
Max. post-op weight	6.12	0.46
Pre *vs* post-op: $P<0.001$		
Pre *vs* max post-op: $P<0.001$		
Post-op *vs* max post-op: $P<0.05$		

gain after the first post-op weight (≈24 hr) whereas weight gain continued in the infants. Percentage weight gain was not correlated with duration of bypass, but was related to cross-clamp time ($r^2 = 0.3183$, $P < 0.01$) (Figure 5). When neonates and infants were analyzed separately there was no relationship between weight gain and bypass times.

A variety of dysrhythmias occurred peroperatively in seven patients (supraventricular tachycardia, complete heart block, atrial flutter). Two patients developed bronchospasm during surgery and two patients with tetralogy of Fallot had cyanotic "spells" in the pre-bypass period. None of these episodes were associated with elevated plasma histamine concentrations although one case experienced a rise after reventilation (0.09 to 0.28 ng·ml^{-1}).

One patient died during surgery and two patients required ECMO several days after surgery, one of whom died. Two patients returned to the PICU with the chest open. Pulmonary hypertension occurred in two cases (one mitral valve repair, one truncus arteriosus repair). Neither baby had dramatically elevated histamine levels in the operating room, however in the mitral valve repair case plasma histamine rose on cross-clamp removal from 0.06 to 0.87 ng·ml^{-1} and the truncus patient had a ten-fold elevation of tryptase (0.09 to 0.96 ng·ml^{-1}) on reventilation.

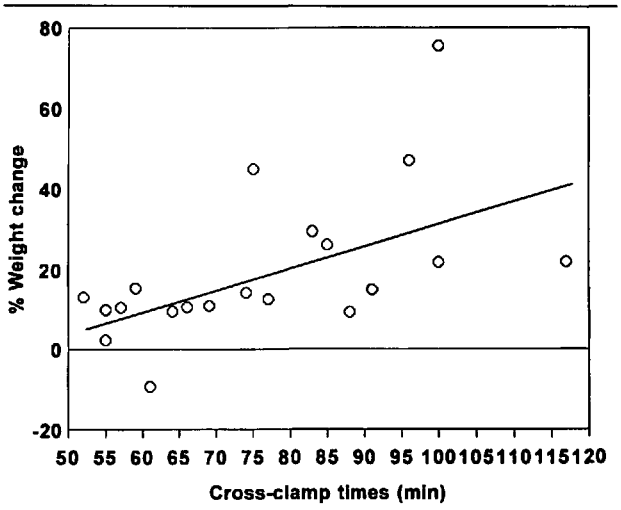

FIGURE 5 Correlation between weight gain following surgery and cross clamp time, line of regression $r^2 = 0.318$, $P < 0.01$.

Discussion

Histamine concentrations were lower in this study than in previous studies of older patients and were consistently higher in infants than neonates at all stages of surgery and CPB. The previous paediatric series[2] included children aged from nine months to 18 yr, whereas this study only included three infants of ≥ nine months. Adult (30–64 yr) series have reported higher concentrations[1] than either paediatric series. Thus, histamine concentrations during CPB appear to be greater with increasing age. The reasons for this are unclear.

Factors which may have affected histamine concentrations during this study include the method of preparation of pump prime. The mean histamine concentration in pump prime was 1.14 ng·ml^{-1} (range 0.19–5.93 ng·ml^{-1}) whereas some authors[12] have demonstrated concentrations >100 ng·ml^{-1}. In our institution, pump blood is reconstituted from packed red cells in citrate-phosphate-dextrose plus fresh frozen plasma and diluted to the required haematocrit with crystalloid. Thus, the solution should be effectively basophil free. In the previous paediatric study[1] whole blood was used along with albumin and mannitol. Albumin and mannitol may promote basophil histamine release due to their hyperosmolarity.[13,14] This may explain the higher prime histamine concentrations previously reported.

A second factor is the administration of methylprednisolone to all but two children in the study. However, since the mast-cell stabilising effects of steroids are not immediate this is unlikely to have influenced the results.[15]

In animal models of ischaemia and reperfusion[5] histamine release is triggered by free-radical generation during reperfusion and is decreased by drugs interfering with free radical production. Reperfusion of the entire body occurring at the end of DHCA was anticipated to be a stimulus to histamine release. However, this was not observed. If histamine is released from cardiac mast cells the small hearts undergoing DHCA (the largest infant was 6.57 kg) may limit the amount of histamine released, as may immaturity of the immune system.

In children,[2] histamine concentrations increased after cross-clamp removal, that is, once forward flow recommenced through the cardiopulmonary circuit. Some patients had further histamine release on reven-

tilation of the lungs, that is when the the lungs are reinflated and pulmonary vasodilatation and thus pulmonary reperfusion occurs. This was postulated to be due to release from pulmonary mast cells. In the current series there was no change on cross-clamp removal. There were increases in right and left atrial histamine concentrations at three minutes reventilation. Left atrial concentrations were either within or only slightly above the normal range. Difficulty in sampling blood through the long narrow catheters used for intra-cardiac lines may have been a factor in the failure to demonstrate a difference between pre and post-pulmonary sampling sites. The hypothesis of histamine release from pulmonary mast cells was not confirmed by a simultaneous rise in tryptase and the actual tryptase concentrations, although abnormal, were relatively low.

There were no instances of major histamine release in this series. High baseline levels may have been due to the administration of cefoxitin before arterial line insertion and sampling for baseline levels.[16] The most notable difference from previous studies is the lack of histamine release on cross-clamp removal. The majority of patients received sodium nitroprusside infusion during the rewarming phase of CPB, after cross-clamp removal. Sodium nitroprusside is a nitric oxide donor and nitric oxide is a mast cell stabilizer.[17] However, SNP was also used in the paediatric series,[2] and has been associated with high histamine levels during adult CPB.[1]

Histamine is known to increase vascular permeability both systemically and in the lung,[18] but this would not appear to be an important mechanism in weight gain post-CPB. Although there was a correlation between weight gain and cross-clamp time no relationship between weight gain and peak histamine release was found.

Histamine is a known dysrhythmogenic agent,[7] lowering the fibrillation threshold in animal preparations and man.[19] There were seven instances of dysrhythmias, four of which required pacing. None was associated with increased histamine concentrations, but one episode of SVT was associated with a high tryptase level.

A recent study in children seven months–13 years (mean 5.5 yr) demonstrated an association between histamine release and perioperative dysrhythmias.[20] In eight cases with post-operative dysrhythmias (seven, of whom were aged > nine months) histamine release was greater than in those without dysrhythmias, and was >200% greater than baseline. Actual histamine concentrations were 0.2–3.2 $ng \cdot ml^{-1}$ four hours after CPB but were normal in infants aged less than one year. Again, an age effect is apparent but the mechanism is unclear. Since haemodynamic responses to histamine have been shown to be more pronounced in older animals[21] it would be interesting to examine release of other vasoactive mediators in different age groups.

In summary, this investigation failed to demonstrate an association between histamine release and clinical events. There were no instances of massive histamine release and adverse events were infrequent. The differences between neonates and infants are of interest, particularly when added to observations from older children and adults, suggesting a continuum of increasing ability to release histamine, and perhaps to respond to it, with increasing age.

Acknowledgements

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