Protein oxidation injury occurs during pediatric cardiopulmonary bypass

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Objective: Proteins are the major effectors of biological structure and function. Oxidation-induced changes to protein structure can critically impair protein function, with important pathologic consequences. This study was undertaken to examine whether oxidation-induced changes to protein structure occur during pediatric cardiopulmonary bypass and to examine the association with postoperative outcome.

Methods: Elevation of the 3,4-dihydroxyphenylalanine content of a protein relative to its native tyrosine content indicates structural damage due to oxidation. Protein 3,4-dihydroxyphenylalanine/native tyrosine ratios were measured before surgery and up to 6 hours after institution of cardiopulmonary bypass in 24 children undergoing repair of congenital heart disease, who were prospectively selected to form a cyanotic and comparable acyanotic control group. Results were correlated with perioperative variables and postoperative outcomes.

Results: Elevation of protein 3,4-dihydroxyphenylalanine/tyrosine ratios above baseline (0.48 mmol/mol [SD, 0.11 mmol/mol] vs 0.36 mmol/mol [SD, 0.13 mmol/mol]; $P = .001$) occurred within 30 minutes of initiating cardiopulmonary bypass in cyanotic but not in acyanotic children and correlated inversely with preoperative arterial oxygen saturation ($R = -0.52$; $P = .03$). Protein 3,4-dihydroxyphenylalanine/tyrosine ratios were also increased above baseline at 120 minutes (0.44 mmol/mol [SD, 0.12 mmol/mol]; $P = .007$) and 180 minutes (0.40 mmol/mol [SD, 0.14 mmol/mol]; $P = .01$) after the institution of cardiopulmonary bypass in children who underwent prolonged procedures. Elevation of 3,4-dihydroxyphenylalanine/tyrosine during prolonged procedures was associated with postoperative arrhythmias and the need for increased inotropic support ($P = .001$).

Conclusions: Oxidative injury to proteins occurs during pediatric cardiopulmonary bypass. Cyanotic children are most at risk, particularly those undergoing prolonged procedures, in whom elevation of the protein 3,4-dihydroxyphenylalanine/tyrosine ratio is associated with increased postoperative morbidity.

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Proteins are the major effectors of the body's biological structure and function. The diverse nature of protein function critically depends on their exact conformation and pattern of folding. The pathologic implications of genetic-induced anomalies in protein structure are well recognized. Genomic anomalies, however, are not the only way in which the amino acid sequence of proteins can be disturbed. Proteins are also major targets of oxidative damage. Reactive oxygen and nitrogen species are capable of chemically altering protein structure. The amino acid tyrosine, for example (a component of virtually all proteins), is readily oxidized to the dihydroxylated species 3,4-dihydroxyphenylalanine (DOPA).[1] The "replacement" of tyrosine by DOPA residues in the amino acid sequence can have a critical effect on protein function.[2] Increasingly it is being recognized that oxidative

TABLE 1. Demographic and perioperative variables

Patient no.	Operation	Age (mo)	BSA (m^2)	Sat (%)	CPB (min)	XCT (min)	DOPA/tyrosine (mmol/mol) 3 min	30 min	120 min	180 min	A	Inotropic support (d)
Acyanotic patients												
1	Close secundum ASD	13	0.5	98	35	8	0.23	0.34	0.27	0.34		0.5
2	Close secundum ASD	138	1.7	98	40	19	0.27	0.28	0.30	0.28		0.9
3	Close primum ASD, repair cleft mitral valve	18	0.5	98	54	44	0.18	0.27	0.23	0.18	NB	2.6
4	Close primum ASD, repair cleft mitral valve	82	0.8	97	56	33	0.36	0.27	0.33	0.31		0.7
5	Repair acyanotic tetralogy of Fallot	4	0.3	100	72	44	0.50	0.43	0.47	0.45		1.6
6	Replace RV to PA conduit, augment right PA	17	0.4	97	104	0	0.12	0.16	0.16	0.15		0.7
7	Repair PAPVD	3.5	0.2	95	107	58	0.32	0.34	0.34	0.29	JB	6.9
8	Replace RV to PA conduit	47	0.7	95	125	0	0.56	0.51	0.52	0.41	JB	2.7
9	Replace mitral valve	151	1	99	127	83	0.46	0.55	0.46	0.46		1.2
10	Augment bilateral PA stenosis	13	0.4	97	139	0	0.30	0.32	0.34	0.41		2.5
11	Repair cleft mitral valve with severe regurgitation	15	0.4	98	177	57	0.53	0.54	0.46	0.43	2nd HB	9.9
12	Neonatal Marfan syndrome—graft repair aortic root	37	0.6	97	200	174	0.51	0.60	0.83	0.75	JET	Died
Cyanotic patients												
13	Close ASD, ligate central shunt	33	0.5	82	62	22	0.30	0.30	0.32	0.28		1.9
14	Completion extracardiac Fontan	52	0.7	81	63	0	0.30	0.57	0.18	0.28		4.7
15	Completion extracardiac Fontan	142	1.2	78	85	0	0.50	0.51	0.49	0.39		1.8
16	Bidirectional Glenn shunt/ atrial septectomy	33	0.7	80	96	13	0.61	0.65	0.52	0.54	JB	7.6
17	Repair tetralogy of Fallot	11	0.3	75	114	89	0.46	0.60	0.51	0.37	JET	5.7
18	Repair truncus arteriosus type 2	1	0.2	92	131	83	0.25	0.36	0.36	0.29		5.8
19	Rastelli procedure	10	0.4	78	148	62	0.42	0.54	0.57	0.49	JET	4.0
20	Close multiple VSDs, deband PA	5	0.2	73	150	89	0.16	0.42	0.39	0.20		3.7
21	Total cavopulmonary connection	174	1.3	77	160	11	0.36	0.37	0.45	0.51		6.0
22	Arterial switch, deband PA, close VSD	23	0.4	81	180	138	0.26	0.37	0.24	0.26		4.8
23	Arterial switch	0.5	0.2	65	192	74	0.28	0.45	0.51	0.47	JET	10.1
24	Repair severe tetralogy of Fallot	20	0.4	80	268	63	0.42	0.53	0.57	0.57	JET	Died

BSA, Body surface area; *Sat,* preoperative arterial saturation in air; *CPB,* cardiopulmonary bypass time; *XCT,* aortic root crossclamp time; *DOPA,* 3,4-dihydroxyphenylalanine; *A,* postoperative atrial arrhythmia; *ASD,* atrial septal defect; *PA,* pulmonary artery; *PAPVD,* partial anomalous pulmonary venous drainage; *RV,* right ventricle; *VSD,* ventricular septal defect; *JB,* junctional bradyarrhythmia; *JET,* junctional ectopic tachycardia; *NB,* nodal bradyarrhythmia; *2nd HB,* second-degree heart block.