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右美托咪定在体外循环下心内直视手术患儿肺保护、心肌保护的作用及对应激反应的影响 *

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摘要 目的:探讨右美托咪定对体外循环(CPB)下心内直视手术患儿肺保护、心肌保护的作用及对应激反应的影响。**方法:**选取2017年3月~2019年9月期间我院收治的CPB下行室间隔缺损修补术患儿80例,上述患儿根据随机数字表法分为对照组(n=40)和研究组(n=40),麻醉诱导后研究组给予右美托咪定维持至术毕,对照组给予等容量生理盐水。比较两组患儿麻醉诱导前(T1)、停机后6h(T2)、停机后24h(T3)的肺功能[呼吸指数(RI)、氧合指数(OI)和肺顺应性(CL)],心肌功能[心肌肌钙蛋白I(cTnI)、铁调素(IMP)、炎症因子[白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)、白介素-1 β (IL-1 β)]及应激反应[皮质醇(Cor)、血糖(Glu)、去甲肾上腺素(NE)和肾上腺素(E)]情况。**结果:**两组T2~T3时间点RI呈下降趋势,且研究组低于对照组($P<0.05$),两组T2~T3时间点OI、CL呈上升趋势,且研究组高于对照组($P<0.05$)。两组T2~T3时间点cTnI、IMP呈下降趋势,且研究组低于对照组($P<0.05$)。两组T2~T3时间点Cor、Glu、NE、E呈下降趋势,且研究组低于对照组($P<0.05$)。两组T2~T3时间点IL-6、TNF- α 、IL-1 β 呈下降趋势,且研究组低于对照组($P<0.05$)。**结论:**CPB下心内直视手术患儿术中予以右美托咪定,可有效保护其肺功能、心肌功能,减轻机体应激反应及炎症刺激,有一定的临床应用价值。

关键词:右美托咪定;体外循环;心内直视手术;肺保护;心肌保护;应激反应

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Effects of Dexmedetomidine on Pulmonary Protection, Myocardial Protection and Stress Response in Children Undergoing Cardiopulmonary Bypass*

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ABSTRACT Objective: To investigate the effect of dexmedetomidine on pulmonary protection, myocardial protection and stress response in children undergoing open heart surgery under cardiopulmonary bypass (CPB). **Methods:** 80 children with ventricular septal defect repair by CPB who were admitted to our hospital from March 2017 to September 2019 were selected, children were divided into control group (n=40) and study group (n=40) according to the random number table method. After anesthesia induction, the study group was treated with dexmedetomidine until the end of operation, while the control group was treated with saline of equal volume. The pulmonary function [respiratory index (RI), oxygenation index (OI) and lung compliance (CL)], myocardial function [cardiac troponin I (cTnI), iron deficiency modifying protein (IMP)], inflammatory factors [interleukin-6 (IL-6), tumor necrosis factor - α (TNF- α), interleukin-1 β (IL-1 β)], and stress response [cortisol (Cor), blood glucose (Glu), noradrenaline (NE) and Adrenaline (E)] in the two groups before anesthesia induction (T1), 6h after shutdown (T2) and 24h after shutdown (T3) were compared. **Results:** RI showed a decreasing trend at T2~T3 time points in both groups, and the study group was lower than the control group ($P<0.05$). OI and CL showed an increasing trend at T2~T3 time points in both groups, and the study group was higher than the control group ($P<0.05$). cTnI and IMP showed a decreasing trend in the two groups at T2~T3 time points, and the study group was lower than the control group ($P<0.05$). Cor, Glu, NE and E showed a decreasing trend in the two groups at T2~T3 time points, and the study group was lower than the control group ($P<0.05$). IL-6, TNF- α and IL-1 β showed a decreasing trend in both groups at T2~T3 time points, and the study group was lower than the control group ($P<0.05$). **Conclusion:** Dexmedetomidine in children with CPB undergoing open heart surgery can effectively protect their pulmonary function and myocardial function, reduce stress response and inflammatory stimulation, and which has a certain clinical application value.

Key words: Dexmedetomidine; Cardiopulmonary bypass; Open heart surgery; Pulmonary protection; Myocardial protection; Stress response

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前言

先天性心脏病是指由于胎儿时期心血管发育异常引起的先天性疾病,临床主要表现为呼吸困难、活动耐力减低、紫绀等症状^[1]。据统计^[2],全世界每年约有 1.35 亿名婴儿出生,其中约有 130 万名婴儿伴有先天性心脏病。室间隔缺损作为先天性心脏病的一种,约占其中的 20%。心内直视手术是指打开心脏进行手术操作,以恢复心脏的生理功能、解剖外观的一种手术方式^[3,4]。体外循环(CPB)是用人工管道将患儿的血液从心脏和肺部转移,通过机器暂时替代肺和心脏的正常生理功能,再经血泵将血输回体内的一种技术^[5,6]。CPB 下心内直视手术现已成为室间隔缺损患儿的主要治疗方式,有效挽救患儿生命,降低病死率^[7]。但患儿术后仍存在不同程度的肺损伤、心肌损伤及应激反应,影响患儿预后。右美托咪定在临床应用中主要表现为镇静、交感阻滞和镇痛作用。本研究将右美托咪定应用于 CPB 下心内直视手术患儿的治疗中,疗效显著,整理如下。

1 资料与方法

1.1 一般资料

选取 2017 年 3 月~2019 年 9 月期间我院收治的 CPB 下行室间隔缺损修补术患儿 80 例,纳入标准:(1)均符合手术指征,择期行手术治疗的患儿;(2)年龄 6~11 月龄;(3)患儿监护人知情本研究且签署同意书;(4)美国麻醉医师协会(ASA)^[8]分级 II~III 级。排除标准:(1)非第一次心脏手术患儿;(2)合并凝血功能障碍性疾病;(3)合并肝肾功能异常的患儿;(4)术前合并肺部疾病患儿;(5)恶性肿瘤、自身免疫性疾病患儿;(6)慢性炎症性疾病、感染性疾病患儿;(7)心脏传导阻滞作为右美托咪定的禁忌证患儿;(8)3 周内服用激素、非甾体类抗炎镇痛药患儿。按照随机数字表法分为对照组(40 例)和研究组(40 例),其中对照组女 16 例,男 24 例,体质量指数 10~15 kg/m²,平均(12.84±0.82)kg/m²;年龄 6~10 月龄,平均(8.31±0.73)月龄;ASA 分级 II 级 26 例,III 级 14 例。研究组男 27 例,女 13 例,体质量指数 9~15 kg/m²,平均(12.57±0.73)kg/m²;年龄 6~11 月龄,平均(8.37±0.65)月龄;ASA 分级 II 级 28 例,III 级 12 例。两组一般资料对比无差异($P>0.05$),具有可比性。本次研究已通过我院医学伦理学委员会批准进行。

1.2 方法

术前 0.5 h 给予肌注东莨菪碱(成都天台山制药有限公司,国药准字 H20080375,规格:20 mg)0.01 mg/kg、氯胺酮(江苏恒瑞医药股份有限公司,国药准字 H32022820,规格:2 mL:0.1 g)

4~6 mg/kg。入室后开放静脉通道,监测患儿各项生命指征。麻醉诱导:咪唑安定(江苏恩华药业股份有限公司,国药准字 H10980025,规格:2 mL:21 mg)0.1 5mg/kg,舒芬太尼(IDT Biologika GmbH,注册证号:H20150125,规格:5 mL:375 μg)1 μg/kg,依托咪酯(江苏恩华药业股份有限公司,国药准字 H32022992,规格:10 mL:20 mg)0.3 mg/kg,罗库溴铵(福安药业集团庆余堂制药有限公司,规格:5 mL:50 mg,国药准字 H20183106)0.6 mg/kg,诱导成功后气管插管通气,维持二氧化碳分压 35~40 mmHg,潮气量 10~12 mL/kg,呼吸比 1:2。麻醉维持:间断静脉注射罗库溴铵 0.3~0.6 mg/kg、舒芬太尼 0.5~1 μg/kg,CPB 采用西安岱岱生物医学工程有限责任公司生产的 ODMO-100 膜式氧合器和天津汇康医用设备有限公司生产的 WEL-1000 人工心肺机。麻醉诱导后研究组给予初始剂量 0.5 μg/kg 的盐酸右美托咪定注射液(辰欣药业股份有限公司,规格:2 mL:0.2 mg,国药准字:H20130027),以 0.4 μg/(kg·h)的速率维持至术毕。对照组给予等容量生理盐水。

1.3 观察指标

(1)采集麻醉诱导前(T1)、停机后 6 h(T2)、停机后 24 h(T3)的静脉血 5 mL,经常规离心处理(3500 r/min 的离心转速,12 cm 的离心半径,离心 11 min),分离血清保存待测。采用酶联免疫吸附试验检测炎症因子:白介素-6(IL-6)、肿瘤坏死因子-α(TNF-α)、白介素-1β(IL-1β)。采用放射免疫法检测皮质醇(Cor),采用西门子 348 血气分析仪检测血糖(Glu),采用高效液相色谱法检测去甲肾上腺素(NE)和肾上腺素(E)。采用化学发光法经自动免疫分析系统测定心肌肌钙蛋白 I(cTnI),采用 ACB 实验比色法测定缺铁修饰白蛋白(IMA)。(2)于麻醉诱导前(T1)、停机后 6 h(T2)、停机后 24 h(T3)采用 MedikroSpiroStarUSB 便携式肺功能仪检测呼吸指数(RI)、氧合指数(OI)和肺顺应性(CL)。

1.4 统计学方法

采用 SPSS25.0 软件分析。计数资料以率的形式表示,采用卡方检验。计量资料以均值±标准差($\bar{x} \pm s$)的形式表示,采用 t 检验。检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组肺功能指标比较

两组 T1 时间点 RI、OI、CL 比较未见统计学差异($P>0.05$),两组 T2~T3 时间点 RI 呈下降趋势,且研究组低于对照组($P<0.05$),两组 T2~T3 时间点 OI、CL 呈升高趋势,且研究组高于对照组($P<0.05$),详见表 1。

表 1 两组肺功能指标比较($\bar{x} \pm s$)

Table 1 Comparison of pulmonary function indicators between the two groups($\bar{x} \pm s$)

Groups	Time point	RI	OI(mmHg)	CL(mL/cmH ₂ O)
Control group(n=40)	T1	0.29±0.08	527.87±25.02	529.33±23.12
	T2	0.56±0.12 ^a	424.03±34.82 ^a	418.90±36.21 ^a
	T3	0.43±0.15 ^{ab}	455.24±28.65 ^{ab}	468.98±32.19 ^{ab}
Study group(n=40)	T1	0.29±0.11	526.21±33.85	528.85±35.23
	T2	0.44±0.13 ^{ac}	458.61±30.13 ^{ac}	453.24±30.38 ^{ac}
	T3	0.37±0.09 ^{abc}	489.83±28.19 ^{abc}	497.21±36.27 ^{abc}

Note: Compared with T1 time point, ^a $P<0.05$; compared with T2 time point, ^b $P<0.05$; compared with control group, ^c $P<0.05$.

2.2 两组心肌功能指标比较 05), 两组 T2~T3 时间点 cTnI、IMA 呈下降趋势, 且研究组低于两组 T1 时间点 cTnI、IMA 比较未见统计学差异 ($P>0.05$), 对照组 ($P<0.05$), 详见表 2。

表 2 两组心肌功能指标比较($\bar{x} \pm s$)
Table 2 Comparison of myocardial function indicators between the two groups($\bar{x} \pm s$)

Groups	Time point	cTnI($\mu\text{g/mL}$)	IMA(U/mL)
Control group(n=40)	T1	0.07 $\pm$ 0.01	75.67 $\pm$ 6.86
	T2	4.79 $\pm$ 0.18 ^a	87.69 $\pm$ 4.72 ^a
	T3	3.31 $\pm$ 0.13 ^{ab}	83.89 $\pm$ 5.37 ^{ab}
Study group(n=40)	T1	0.07 $\pm$ 0.02	75.46 $\pm$ 6.33
	T2	3.69 $\pm$ 0.21 ^{ac}	83.07 $\pm$ 5.56 ^{ac}
	T3	1.97 $\pm$ 0.15 ^{abc}	79.41 $\pm$ 4.64 ^{abc}

Note: Compared with T1 time point, ^a $P<0.05$; compared with T2 time point, ^b $P<0.05$; compared with control group, ^c $P<0.05$.

2.3 两组应激反应指标比较 ($P>0.05$), 两组 T2~T3 时间点 Cor、Glu、NE、E 呈下降趋势, 且两组 T1 时间点 Cor、Glu、NE、E 比较未见统计学差异 研究组低于对照组 ($P<0.05$), 详见表 3。

表 3 两组应激反应指标比较($\bar{x} \pm s$)
Table 3 Comparison of stress response indicators between the two groups ($\bar{x} \pm s$)

Groups	Time point	Cor(ng/mL)	Glu(mmol/L)	NE(pg/mL)	E(pg/mL)
Control group(n=40)	T1	216.78 $\pm$ 35.21	4.91 $\pm$ 0.36	119.85 $\pm$ 16.56	23.37 $\pm$ 2.67
	T2	683.81 $\pm$ 40.19 ^a	8.02 $\pm$ 0.43 ^a	163.49 $\pm$ 15.62 ^a	88.05 $\pm$ 6.51 ^a
	T3	438.04 $\pm$ 39.36 ^{ab}	6.35 $\pm$ 0.38 ^{ab}	145.38 $\pm$ 20.26 ^{ab}	64.12 $\pm$ 5.27 ^{ab}
Study group(n=40)	T1	215.92 $\pm$ 36.43	4.98 $\pm$ 0.32	120.32 $\pm$ 19.34	23.75 $\pm$ 3.23
	T2	561.54 $\pm$ 31.21 ^{ac}	7.15 $\pm$ 0.25 ^{ac}	146.29 $\pm$ 17.59 ^{ac}	64.04 $\pm$ 5.48 ^{ac}
	T3	375.49 $\pm$ 29.03 ^{abc}	5.72 $\pm$ 0.27 ^{abc}	134.24 $\pm$ 18.43 ^{abc}	42.66 $\pm$ 5.32 ^{abc}

Note: Compared with T1 time point, ^a $P<0.05$; compared with T2 time point, ^b $P<0.05$; compared with control group, ^c $P<0.05$.

2.4 两组炎症因子指标比较 ($P>0.05$), 两组 T2、T3 时间点 IL-6、TNF- α 、IL-1 β 呈下降趋势, 两组 T1 时间点 IL-6、TNF- α 、IL-1 β 比较未见统计学差异 且研究组低于对照组 ($P<0.05$), 详见表 4。

表 4 两组炎症因子指标比较($\bar{x} \pm s$)
Table 4 Comparison of inflammatory factors between the two groups($\bar{x} \pm s$)

Groups	Time point	IL-6(ng/L)	TNF- α (ng/L)	IL-1 β (ng/L)
Control group(n=40)	T1	61.87 $\pm$ 7.22	8.71 $\pm$ 2.26	85.68 $\pm$ 9.71
	T2	118.26 $\pm$ 14.20 ^a	27.60 $\pm$ 3.17 ^a	134.62 $\pm$ 10.74 ^a
	T3	86.02 $\pm$ 10.57 ^{ab}	19.23 $\pm$ 2.97 ^{ab}	108.21 $\pm$ 12.89 ^{ab}
Study group(n=40)	T1	62.11 $\pm$ 8.47	9.08 $\pm$ 2.86	85.23 $\pm$ 8.75
	T2	97.34 $\pm$ 10.21 ^{ac}	21.23 $\pm$ 2.64 ^{ac}	112.25 $\pm$ 15.34 ^{ac}
	T3	76.29 $\pm$ 9.78 ^{abc}	15.10 $\pm$ 2.88 ^{abc}	92.14 $\pm$ 11.45 ^{abc}

Note: Compared with T1 time point, ^a $P<0.05$; compared with T2 time point, ^b $P<0.05$; compared with control group, ^c $P<0.05$.

3 讨论

CPB 下心内直视手术作为一种非生理过程, 可导致机体产生强烈而持久的应激, 从而引起各重要脏器不同程度的受损^[9,10]。应激反应可诱发中枢性儿茶酚胺释放, 导致血流动力学紊乱, 心肌细胞无氧代谢增加、乳酸聚集、心肌细胞内酸中毒, 进而诱

发心肌损伤^[11-13]。同时肺功能损伤也是影响 CPB 下心内直视手术后死亡率和术后恢复的主要因素^[14]。不少患儿术后可出现从轻度肺损伤到危及生命的急性肺损伤及呼吸窘迫综合征等。CPB 下心内直视手术导致的肺损伤的发病机制尚不十分明确, 多认为与术中强烈的应激反应、炎性反应、释放的活性氧、缺血-再灌注损伤产生的氧自由基等有关^[15,16]。手术时肺组织相对缺

血,加之肺部降温不足而处于相对的"高温"状态,增加肺部耗氧量,产生大量氧自由基,进而引起机体氧化和抗氧化系统失衡,产生强烈的应激反应^[17,18]。此外,CPB使血液暴露于氧合器,硅胶管道内表面与血液的接触,麻醉手术刺激等引起单核细胞及补体激活,引起细胞炎性介质的大量释放,引起全身炎性反应,加重组织损伤^[19,20]。

右美托咪定是一种作用于脊髓和大脑蓝斑的 α_2 -肾上腺素受体激动剂,其呼吸抑制作用较轻,临床常用于各类外科手术的辅助麻醉中,效果确切^[21]。但由于CPB后的低温、血液稀释以及循环管道存在吸附药物等因素可能会影响右美托咪定的药代动力学,同时患儿由于未发育完全的原因,其药物代谢与成人有明显的不同^[22]。因此关于其在CPB下心内直视手术中的应用仍需进行进一步研究以明确。本次研究结果显示,CPB下心内直视手术患儿术中予以右美托咪定,患儿的肺功能、心肌功能损伤明显减轻,应激反应及炎性反应均有所缓解。其中IMA可作为早期诊断心肌缺血损伤的生化标记物,在心肌缺血数分钟后即可升高;而cTnI是心肌收缩的调节蛋白,当心肌遭受缺血再灌注损伤时,心肌细胞膜结构破坏被释放入血^[23]。机体在应激原的作用下可出现一系列的神经内分泌反应,以下丘脑-垂体-肾上腺皮质分泌的Cor、Glu、NE、E等因子最为显著,可有效反映机体的应激状态^[24]。RI、OI、CL可反映患者肺弥散功能,准确的评估患者肺损伤情况^[25]。CPB时肺处于高代谢、相对高温、高氧耗状态,易导致肺泡细胞凋亡、坏死,产生炎性反应,引起IL-6、TNF- α 、IL-1 β 等炎性因子大量分泌^[26]。本研究结果显示,术中应用右美托咪定的患儿炎性因子水平更低,分析右美托咪定发挥作用的机制主要在于以下几点:右美托咪定可增强巨噬细胞作用,促进细胞凋亡,同时其对中性粒细胞的影响较轻,发挥良好的抗炎作用^[27]。右美托咪定可通过作用于中枢和外周神经系统发挥抗交感系统作用,同时还可对血管肌源性反应、局部代谢调节以及血流依赖性扩张产生间接的促进作用,对缺血心肌产生一定的保护作用^[28]。右美托咪定还可通过激活神经节突触前膜上 α_2 肾上腺素能受体发挥良好的抗焦虑作用,从而降低血浆中儿茶酚胺的浓度,抑制NE的释放,有效抑制机体应激反应,维持心率、血压的平稳^[29]。右美托咪定通过有效抑制炎症和机体应激反应,避免了大量炎性因子在肺组织的蓄积,减少其进一步的肺损伤^[30]。

综上所述,CPB下心内直视手术患儿术中予以右美托咪定,可有效保护其肺功能、心肌功能,减轻机体应激反应及炎性刺激,有一定的临床应用价值。

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