

围手术期雾化吸入米力农与静脉注射米力农对行二尖瓣手术的肺动脉高压患者血流动力学的影响[△]

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摘要 目的:探讨术中雾化吸入米力农与静脉注射米力农对行二尖瓣手术的肺动脉高压患者血流动力学的影响。方法:纳入2020年9月至2022年12月与该院治疗的二尖瓣狭窄合并肺动脉高压患者152例,根据随机数字表法分为吸入组($n=76$)和静脉注射组($n=76$)。吸入组、静脉注射组患者在术中分别给予雾化吸入米力农、静脉注射米力农治疗。比较吸入组与静脉注射组患者胸骨切开后(T_0)、心脏手术体外循环(CPB)撤机后(T_1)和患者转移至重症监护室前(T_2)的肺毛细血管楔压(PCWP)、平均动脉压(MAP)、平均肺动脉压(MPAP)、心脏指数(CI)和肺血管阻力指数(PVRI)等血流动力学指标。比较两组患者 T_0 、 T_1 和 T_2 时的动脉血氧分压(PaO_2)/吸入气中的氧浓度(FiO_2)、混合静脉血氧饱和度(SvO_2)及肺内分流率(Qs/Qt)等动脉血气指标。比较两组患者 T_0 、 T_1 、 T_2 时的三尖瓣环收缩期位移(TAPSE)、右心室面积变化分数(RVFAC)等超声心动图指标。结果:与 T_0 时比较,吸入组和静脉注射组患者在 T_1 和 T_2 时的PCWP、MAP、MPAP及PVRI显著降低,CI显著升高,差异均有统计学意义($P<0.05$)。 T_1 和 T_2 时,吸入组患者的PCWP、MPAP和PVRI显著低于静脉注射组同期,CI显著高于静脉注射组同期;但静脉注射组患者的MAP较吸入组同期显著降低,差异均有统计学意义($P<0.05$)。与 T_0 时比较,吸入组与静脉注射组患者在 T_1 和 T_2 时的 $\text{PaO}_2/\text{FiO}_2$ 显著升高, Qs/Qt 显著降低,差异均有统计学意义($P<0.05$)。吸入组患者在 T_1 和 T_2 时 $\text{PaO}_2/\text{FiO}_2$ 较静脉注射组同期显著升高, Qs/Qt 显著降低,差异均有统计学意义($P<0.001$)。与 T_0 时比较,吸入组患者 T_1 和 T_2 时的TAPSE、RVFAC显著升高,差异均有统计学意义($P<0.05$)。在 T_1 和 T_2 时,吸入组患者TAPSE、RVFAC较静脉注射组同期显著升高,差异均有统计学意义($P<0.001$)。结论:二尖瓣狭窄合并肺动脉高压患者CPB前后雾化吸入米力农安全、方便,可显著改善右心室血流动力学、右心室功能和全身血流动力学指标。

关键词 米力农;雾化吸入;二尖瓣手术;肺动脉高压;血流动力学

Effects of Milrinone for Nebulized Inhalation and Intravenous Injection on Hemodynamics in Patients with Pulmonary Hypertension Undergoing Mitral Valve Surgery in Perioperative Period[△]

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ABSTRACT **OBJECTIVE:** To probe into the effect of milrinone for nebulized inhalation and intravenous injection on hemodynamics in patients with pulmonary hypertension undergoing mitral valve surgery in perioperative period. **METHODS:** Totally 152 patients with mitral stenosis complicated with pulmonary hypertension admitted into this hospital from Sept. 2020 to Dec. 2022 were enrolled and divided into inhalation group ($n=76$) and intravenous injection group ($n=76$) via the random number table method. The inhalation group and intravenous injection group were given milrinone for inhalation and intravenous injection during the surgery, respectively. The hemodynamics indicators including pulmonary capillary wedge pressure (PCWP), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), cardiac index (CI) and pulmonary vascular resistance index (PVRI) were compared between two groups before sternotomy (T_0), after cardiopulmonary bypass (CPB) withdrawn (T_1) and before the patient transferred to intensive care unit (T_2). The arterial blood gas indicators including arterial partial pressure of oxygen (PaO_2)/fraction of inhaled oxygen (FiO_2), mixed venous blood oxygen saturation (SvO_2) and intrapulmonary shunt (Qs/Qt) were compared between two groups at T_0 , T_1 and T_2 . The ultrasonic cardiogram including tricuspid

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annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RVFAC) were compared between two groups at T_0 , T_1 and T_2 . RESULTS: Compared with T_0 , the PCWP, MAP, MPAP and PVRI of the inhalation group and the intravenous injection group were significantly lower at T_1 and T_2 , while the CI was significantly increased, with statistically significant differences ($P<0.05$). At T_1 and T_2 , the PCWP, MPAP and PVRI values of the inhalation group were significantly lower than those of the intravenous injection group at the same period, and the CI was significantly higher than that of the intravenous injection group at the same period; while the MAP of the intravenous injection group were significantly lower than those of the inhalation group at the same period, with statistically significant differences ($P<0.05$). Compared with T_0 , the $\text{PaO}_2/\text{FiO}_2$ was significantly increased and the Qs/Qt was significantly lower in the inhalation group and the intravenous injection group at T_1 and T_2 , with statistically significant differences ($P<0.05$). The $\text{PaO}_2/\text{FiO}_2$ was significantly higher and the Qs/Qt was significantly lower in the inhalation group than those in the intravenous injection group at T_1 and T_2 , with statistically significant differences ($P<0.001$). Compared with T_0 , the TAPSE and RVFAC of the inhalation groups were significantly increased at T_1 and T_2 , with statistically significant differences ($P<0.05$). At T_1 and T_2 , the TAPSE and RVFAC in the inhalation group were significantly higher than those in the intravenous injection group at the same period, with statistically significant differences ($P<0.001$). CONCLUSIONS: The application of milrinone for inhalation in patients with mitral stenosis complicated with pulmonary hypertension before and after CPB is safe and convenient, which can improve the indicators of right ventricular hemodynamics, right ventricular function and systemic hemodynamics.

KEYWORDS Milrinone; Atomization inhalation; Mitral valve surgery; Pulmonary hypertension; Hemodynamics

二尖瓣狭窄是常见的瓣膜性心脏病,瓣膜性心脏病相关的肺动脉高压(pulmonary hypertension,PH)是指平均肺动脉压(MPAP) ≥ 25 mm Hg(1 mm Hg=0.133 kPa),肺毛细血管楔压(PCWP) >15 mm Hg^[1-2]。二尖瓣狭窄合并重度PH患者围手术期死亡率较高,患者在心脏手术体外循环(CPB)撤机期间发生的PH恶化可导致左心室前负荷和灌注压严重受损,造成CPB撤机延迟或失败,术后机械通气时间延长,死亡率升高^[3]。目前,预防二尖瓣狭窄合并PH患者术后PH恶化的主要方法为输注血管扩张剂,但输注后患者会伴随全身动脉血管扩张,右心室灌注不足,需要应用血管加压药,从而进一步加重PH,甚至发生右心衰竭^[4-5]。目前,雾化吸入肺血管扩张剂预防全身性低血压在临床得到了广泛应用,治疗时患者吸入一氧化氮、硝酸甘油、米力农或左西孟旦等药物^[6]。其中雾化吸入米力农价格较低,易于手术室操作,不需要复杂设备,不产生有毒代谢物。与静脉注射米力农相比,雾化吸入米力农在改善肺再灌注损伤、预防肺动脉内皮功能障碍、改善机体氧合方面更具优势^[7-8]。因此,本研究的目的是评价术中雾化吸入米力农对行二尖瓣手术的PH患者血流动力学的影响。

1 资料与方法

1.1 资料来源

纳入2020年9月至2022年12月于我院治疗的152例二尖瓣狭窄合并PH患者。诊断标准:根据2018年《中国肺高血压诊断和治疗指南》^[9]中规定的标准对PH进行诊断。纳入标准:符合上述PH诊断标准且计划行二尖瓣置换术;在手术期间吸入米力农或静脉注射米力农;年龄 ≥ 18 岁。排除标准:急诊手术患者;术前肌力支持、支气管哮喘和肺血栓患者;肾功能不全、凝血障碍患者。本研究经过我院医学伦理委员会批准同意,患者或家属均签署知情同意书。根据随机数字表法将患者分为吸入米力农组(吸入组, $n=76$)与静脉注射米

力农组(静脉注射组, $n=76$)。所有患者均患有严重二尖瓣狭窄,并进行二尖瓣置换术,患者右心室收缩压(RVSP)均 >50 mm Hg。两组患者年龄、性别、体重指数、美国纽约心脏病学会(NYHA)分级等基线资料相似,具有可比性,见表1。

表1 吸入组与静脉注射组患者基线资料比较
Tab 1 Comparison of baseline data between the inhalation group and the intravenous injection group

项目	吸入组($n=76$)	静脉注射组($n=76$)	t/χ^2	P
年龄/($\bar{x}\pm s$,岁)	34.95 $\pm$ 7.83	36.50 $\pm$ 8.62	1.160	0.248
男性/例(%)	43(56.6)	46(60.5)	0.244	0.621
体重指数/($\bar{x}\pm s$,kg/m ²)	20.93 $\pm$ 1.51	21.02 $\pm$ 1.38	0.384	0.702
NYHA 分级/例(%)			0.101	0.992
I 级	7(9.2)	6(7.9)		
II 级	20(26.3)	21(27.6)		
III 级	41(53.9)	41(53.9)		
IV 级	8(10.5)	8(10.5)		

1.2 方法

吸入组与静脉注射组患者分别给予吸入米力农和静脉注射米力农治疗。麻醉诱导期采用咪达唑仑0.1 mg/kg、芬太尼1 020 μ g/kg、维库溴铵0.15 mg/kg 诱导麻醉。插管后,开始容量控制通气,控制潮气量为8~10 mL/kg,呼吸频率为12~14 次/min,吸入空气和氧气,吸入气中的氧浓度(FiO_2)为0.5。吸入组患者给予0.9%氯化钠注射液5 mg 加入米力农注射液[规格:5 mL:5 mg(以米力农计)]5 mg,经A4002 型喷射式雾化器(江苏鱼跃医疗设备股份有限公司)给药;米力农吸入在2 段时间内进行:胸骨切开至CPB 开始、主动脉交叉钳释放至CPB 撤机,给药总剂量为120~180 μ g/kg。静脉注射组患者在主动脉交叉钳释放后10 min 内静脉注射50 μ g/kg 负荷剂量米力农。两组患者在手术完成并开始自发心律后进行肌力支持。

1.3 观察指标

比较吸入组与静脉注射组患者胸骨切开前(T_0)、CPB 撤

机后(T_1)、转移至重症监护室前(T_2)的PCWP、平均动脉压(MAP)、平均肺动脉压(MPAP)、心脏指数(CI)与肺血管阻力指数(PVRI)等血流动力学指标。比较吸入组与静脉注射组患者 T_0 、 T_1 及 T_2 时的动脉血氧分压(PaO_2)/ FiO_2 、混合静脉血氧饱和度(SvO_2)和肺内分流率(Qs/Qt)等动脉血气指标。比较吸入组与静脉注射组患者 T_0 、 T_1 及 T_2 时的三尖瓣环收缩期位移(TAPSE)、右心室面积变化分数(RVFAC)等超声心动图指标。

1.4 统计学方法

采用SPSS 22.0软件进行统计学分析,计数资料以率(%)表示,采用 χ^2 检验比较。计量资料以 $\bar{x}\pm s$ 表示,采用 t 检验比较。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 围手术期临床资料比较

吸入组所有患者均能耐受吸入米力农且无低血压发生,静脉注射组2例患者在CPB撤机后出现持续时间 $>10\text{ min}$ 的全身性低血压,并需要输注加压素,但两组CPB撤机困难患者所占比例的差异无统计学意义($\chi^2=0.507, P=0.155$);两组患者手术时间、主动脉钳夹时间和CPB时间比较,差异均无统计学意义($P>0.05$);术后,静脉注射组患者血管活性药-正性肌力药评分较吸入组显著升高,差异有统计学意义($t=3.020, P=0.003$);两组患者RVSP、TAPSE、RVFAC、左心室射血分数和手术类型等临床资料的差异均无统计学意义($P>0.05$),见

表3 吸入组与静脉注射组患者不同时间血流动力学指标比较($\bar{x}\pm s$)

Tab 3 Comparison of hemodynamic indicators between the inhalation group and the intravenous injection group at different times($\bar{x}\pm s$)									
组别	PCWP/mm Hg			MAP/mm Hg			MPAP/mm Hg		
	T_0	T_1	T_2	T_0	T_1	T_2	T_0	T_1	T_2
吸入组($n=76$)	281.22±65.75	125.08±45.63 *	135.37±63.16 *	751.33±25.90	677.26±27.82 *	661.67±29.42 *	441.73±80.49	261.73±88.33 *	311.05±87.63 *
静脉注射组($n=76$)	281.41±68.78	131.73±64.92 *	146.11±63.66 *	753.43±29.11	665.65±27.69 *	631.72±30.28 *	461.60±89.39	301.65±88.46 *	371.70±88.62 *
t/P	0.017/0.986	2.049/0.043	2.235/0.027	0.470/0.639	2.579/0.011	27.960/<0.001	1.440/0.152	2.784/<0.001	4.180/<0.001
组别	PVRI/[$\text{dyne}/(\text{cm}^5\cdot\text{m}^2)$]			CI/[$\text{L}/(\text{min}\cdot\text{m}^2)$]					
	T_0	T_1	T_2	T_0	T_1	T_2			
吸入组($n=76$)	6 561.77±110.15	4 491.37±105.72 *	5 251.16±666.70 *	21.52±0.46	31.98±0.62 *	31.93±0.24 *			
静脉注射组($n=76$)	6 581.97±111.86	5 931.40±95.63 *	6 011.32±660.79 *	21.65±0.43	30.03±0.51 *	30.27±0.28 *			
t/P	0.614/0.540	88.657/<0.001	7.066/<0.001	1.800/0.074	2.715/0.007	3.782/<0.001			

注:与 T_0 时比较,* $P<0.05$ 。

Note:vs. T_0 , * $P<0.05$.

2.3 动脉血气指标比较

吸入组与静脉注射组患者在 T_0 时的动脉血气指标比较,差异均无统计学意义($P>0.05$)。与 T_0 时比较,吸入组和静脉注射组患者在 T_1 和 T_2 时的 $\text{PaO}_2/\text{FiO}_2$ 显著升高, Qs/Qt 显著降低,差异均有统计学意义($P<0.05$);吸入组患者在 T_1 和 T_2 时的 $\text{PaO}_2/\text{FiO}_2$ 较静脉注射组同期显著升高, Qs/Qt 较静脉注射组同期显著降低,差异均有统计学意义($P<0.001$),见表4。

2.4 超声心动图指标比较

T_0 时,吸入组与静脉注射组患者TAPSE和RVFAC比较,差异均无统计学意义($P>0.05$)。与 T_0 时比较,吸入组患者 T_1 和 T_2 时的TAPSE、RVFAC显著升高,差异均有统计学意义($P<0.05$); T_1 和 T_2 时,吸入组患者的TAPSE、RVFAC较静脉注射组同期显著升高,差异均有统计学意义($P<0.001$),见表5。

表2。

表2 吸入组与静脉注射组患者围手术期临床资料比较

Tab 2 Comparison of perioperative clinical data between the inhalation group and the intravenous injection group				
项目	吸入组 ($n=76$)	静脉注射组 ($n=76$)	t/χ^2	P
RVSP/($\bar{x}\pm s$,mm Hg)	69.52±13.50	65.58±13.73	1.541	0.125
TAPSE/($\bar{x}\pm s$,mm)	18.52±2.15	18.47±2.29	0.139	0.890
RVFAC/($\bar{x}\pm s$,%)	38.50±3.11	39.26±2.99	1.536	0.127
左心室射血分数/($\bar{x}\pm s$,%)	55.46±3.82	54.60±3.39	1.468	0.144
手术时间/($\bar{x}\pm s$,min)	229.26±35.57	236.93±31.53	1.407	0.162
CPB时间/($\bar{x}\pm s$,min)	67.50±17.43	63.76±15.85	1.384	0.168
主动脉钳夹时间/($\bar{x}\pm s$,min)	49.58±15.90	48.82±14.37	0.309	0.758
CPB撤机困难/例(%)	0(0)	2(2.6)	0.507	0.155
血管活性药-正性肌力药评分/($\bar{x}\pm s$,分)	14.11±6.83	17.35±6.39	3.020	0.003

2.2 血流动力学指标比较

吸入组与静脉注射组患者在 T_0 时的PCWP、MAP、MPAP、PVRI和CI等血流动力学指标比较,差异均无统计学意义($P>0.05$)。与 T_0 时比较,吸入组与静脉注射组患者在 T_1 和 T_2 时的PCWP、MAP、MPAP和PVRI显著降低,CI显著升高,差异均有统计学意义($P<0.05$);吸入组患者在 T_1 和 T_2 时的PCWP、MPAP和PVRI显著低于静脉注射组同期,CI显著高于静脉注射组同期,差异均有统计学意义($P<0.05$);但静脉注射组患者在 T_1 和 T_2 时的MAP较吸入组同期显著降低,差异均有统计学意义($P<0.05$),见表3。

3 讨论

本研究评价了术中吸入米力农对接受手术的二尖瓣狭窄合并PH患者血流动力学的影响。结果表明,吸入组患者在 T_1 和 T_2 时的PCWP、MPAP和PVRI较静脉注射组同期显著降低,CI较静脉注射组同期显著升高($P<0.05$);在 T_1 和 T_2 时,吸入组患者的 $\text{PaO}_2/\text{FiO}_2$ 较静脉注射组同期显著升高, Qs/Qt 较静脉注射组同期显著降低($P<0.001$);在 T_1 和 T_2 时,吸入组患者的TAPSE、RVFAC均较静脉注射组同期显著升高($P<0.05$),上述差异均有统计学意义。以上结果提示,二尖瓣狭窄合并PH患者CPB前后吸入米力农安全、方便,右心室血流动力学、右心室功能和全身血流动力学指标显著改善。

对于伴有严重PH的二尖瓣狭窄患者,CPB撤机后PH严重程度是患者预后的重要影响因素。血管扩张剂常用于CPB撤机期间降低患者肺动脉压(PAP),但也会导致患者发生全身

表 4 吸入组与静脉注射组患者不同时间动脉血气指标比较($\bar{x}\pm s$)

Tab 4 Comparison of arterial blood gas indicators between the inhalation group and the intravenous injection group at different times($\bar{x}\pm s$)									
组别	PaO ₂ /FiO ₂			SvO ₂ /%			Qs/Qt		
	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂
吸入组(n=76)	2 371. 43±60. 85	3 671. 50±54. 69 *	3 871. 35±58. 50 *	651. 65±4. 67	647. 75±3. 78	649. 66±5. 77 *	271. 10±4. 18	191. 65±3. 22 *	191. 12±3. 85 *
静脉注射组(n=76)	2 361. 50±63. 36	3 031. 83±65. 17 *	3 371. 92±52. 19 *	656. 32±3. 93	649. 13±4. 12	651. 92±3. 89	251. 83±4. 67	231. 34±3. 76 *	221. 99±4. 16 *
t/P	1. 002/0. 318	66. 025/<0. 001	55. 957/<0. 001	1. 028/0. 305	1. 541/0. 125	1. 541/0. 123	0. 440/0. 660	17. 613/<0. 001	10. 356/<0. 001

注: 与 T₀ 时比较, * P<0. 05。
Note: vs. T₀, * P<0. 05.

表 5 吸入组与静脉注射组患者不同时间超声心动图指标比较($\bar{x}\pm s$)

Tab 5 Comparison of echocardiographic indicators between the inhalation group and the intravenous injection group at different times($\bar{x}\pm s$)						
组别	TAPSE/mm			RVFAC/%		
	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂
吸入组(n=76)	14. 32±2. 95	15. 57±1. 63 *	15. 82±1. 97 *	45. 52±3. 47	49. 43±2. 95 *	48. 72±3. 49 *
静脉注射组(n=76)	14. 75±3. 03	14. 11±2. 46	13. 49±1. 73 *	45. 71±3. 17	43. 55±3. 43 *	43. 60±2. 98
t/P	0. 886/0. 377	4. 313/<0. 001	7. 748/<0. 001	0. 352/0. 725	11. 331/<0. 001	9. 927/<0. 001

注: 与 T₀ 时比较, * P<0. 05。
Note: vs. T₀, * P<0. 05.

性低血压和右心室冠状动脉灌注不足^[10-11]。目前,吸入血管扩张剂疗法广泛用于选择性地向肺循环输送高浓度的血管扩张剂,而不会导致全身性低血压。但吸入一氧化氮和前列环素的成本较高,需要特殊设备。长期吸入一氧化二氮、硝普钠和硝酸甘油可导致患者发生高铁血红蛋白血症^[12]。而吸入米力农价格相对便宜,不需要特殊的输送设备,也不会产生有毒代谢物。吸入米力农起效迅速,能有效降低患者术后肺动脉收缩压。虽然有研究结果表明,吸入米力农的作用仅能持续 20~30 min,但本研究结果显示,吸入米力农能够使患者的 PCWP、MAP、MPAP 和 PVRI 显著降低,并最终导致 CI 升高,提示吸入米力农对肺血管系统有良好的舒张作用,可提高肺动脉平滑肌细胞中的环磷酸腺苷水平,促进肺血管扩张,与其他研究结果一致^[13]。

本研究结果发现,静脉注射组患者在 T₁ 和 T₂ 时的 MAP 较吸入组显著降低,差异均有统计学意义(P<0. 05);血管活性药-正性肌力药评分显示,静脉注射组患者血管收缩剂需求增加。其原因可能为静脉注射米力农导致患者全身血管舒张、MAP 降低,肺血管舒张不足导致静脉注射组患者 MPAP 升高。Wang 等^[14]的研究结果显示,静脉注射米力农患者的 MAP 更低,与本研究结果一致。研究结果表明,吸入米力农还可以减轻 CPB 相关炎症,保护肺动脉内皮细胞,同时使药物仅分布在通气区域以防止通气-灌注失配。由于吸入的米力农分布仅限于肺部,从而能够以较低剂量实现更好的肺血管舒张,而不会产生全身不良反应^[15-17]。但静脉注射的米力农分布在 CPB 后肺不张但灌注的肺段,导致先前存在的肺内分流加重。与静脉注射组相比,吸入组患者的 PaO₂/FiO₂ 显著升高,同样提示吸入米力农可减少通气-灌注失配^[18]。其他研究结果发现,静脉注射米力农患者的 Qs/Qt 降低,PaO₂/FiO₂ 升高^[19]。

除了改善血流动力学指标外,吸入米力农还通过降低 PAP 和右心室后负荷,显著改善患者的 TAPSE 和 RVFAC,并进一步改善右心室功能。本研究结果表明,静脉注射组患者的 TAPSE 和 RVFAC 均较吸入组显著降低,提示尽管 PAP 降

低,右心室功能障碍仍然急性加重,但只有 2 例术前低血压需要输注加压素的患者临床上表现为右心室功能障碍急性加重。Elbaser 等^[7]的研究报告了类似的发现,该研究评价了重度 PH 的二尖瓣置换术患者的血流动力学和右心室指标,结果发现尽管术后静脉注射米力农患者的血流动力学指标有显著改善,但右心室功能指标,尤其是 TAPSE 在术后显著降低;该研究中使用了多种静脉血管扩张剂。可见,与静脉注射米力农相比,吸入米力农在改善右心室功能方面具有优势。Denault 等^[20]在高危心脏手术患者中进行的研究也发现了类似的结果。

综上所述,二尖瓣狭窄合并 PH 患者行 CPB 术前后吸入米力农安全、方便,右心室血流动力学、右心室功能和全身血流动力学指标可显著改善。

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