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瓣膜手术同期射频消融改良迷宫术治疗心脏瓣膜病并发房颤患者的疗效及对血清细胞因子的影响*

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摘要 目的：分析瓣膜手术同期射频消融改良迷宫术治疗心脏瓣膜病并发房颤患者的疗效及对血清细胞因子的影响。**方法：**将 80 例心脏瓣膜病并发房颤患者依据简单随机法分为对照组和观察组，每组 40 例。对照组采用心脏瓣膜置换术治疗，观察组采用心脏瓣膜置换术同期射频消融改良迷宫术治疗，比较两组窦性心律转复情况，手术情况，手术前后心功能、血清金属蛋白酶组织抑制因子 -1(TIMP-1)、基质金属蛋白酶 -1(MMP-1)和基质金属蛋白酶 -9(MMP-9)水平的变化以及术后并发症的发生情况。**结果：**观察组术后当天、术后 1 月、术后 3 月及术后 6 月的窦性心律转复率均显著高于对照组(P<0.05)，体外循环时间、主动脉阻断时间及术后 24 h 引流量均明显多于对照组(P<0.05)。两组呼吸机使用时间和监护室时间比较差异无统计学意义(P>0.05)。术后 6 个月，两组左室舒张末期内径、左室收缩末期内径、血清 MMP-1 和 MMP-9 水平均较术前显著下降，且观察组以上指标明显低于对照组；两组 LVEF 及血清 TIMP-1 水平较术前显著上升，且观察组以上指标均显著高于对照组(P<0.05)。两组术后均无严重并发症发生。**结论：**瓣膜手术同期射频消融改良迷宫术治疗心脏瓣膜病并发房颤安全有效，早期窦性心律的转复率高，且可改善患者血清 TIMP-1、MMP-1、MMP-9 水平。

关键词：心脏瓣膜病；房颤；瓣膜手术；射频消融改良迷宫术；细胞因子

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Efficacy of Radiofrequency Ablation Combined with Modified Maze In the Treatment of Patients with Atrial Fibrillation Caused by Valvular Disease and Its Effect on the Serum Cytokines*

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ABSTRACT Objective: To analyze the efficacy of radiofrequency ablation combined with modified maze in the treatment of patients with atrial fibrillation caused by valvular disease and its effect on the serum cytokines. **Methods:** 80 patients with valvular heart disease complicated with atrial fibrillation were divided into control group and observation group according to simple random method, 40 cases in each group, the control group was treated with cardiac valve replacement, while the observation group was treated with valve surgery concomitant radiofrequency ablation modified maze. The sinus rhythm reversion, operation conditions, changes of cardiac function, levels of metalloproteinase -1(TIMP-1), matrix metalloproteinase -1(MMP-1) and matrix metalloproteinase -9(MMP-9) before and after operation, and occurrence of postoperative complications were compared between the two groups. **Results:** The sinus rhythm conversion rates of observation group on the day after operation, at 1, 3, 6 month after operation were significant higher than those of the control group (P<0.05). The extracorporeal circulation time, aortic occlusion time and postoperative 24 h drainage volume were significantly higher than those in the control group (P<0.05). there was no significant difference between the two groups in the ventilator usage time and intensive care unit time (P>0.05). At six months after operation, the left ventricular end diastolic diameter, left ventricular end systolic diameter, serum levels of MMP-1 and MMP-9 in both groups were significantly lower than those before operation, and the above indexes in the observation group were significantly lower than those in the control group. The levels of LVEF and TIMP-1 in serum of the two groups were significantly higher than those before operation, which were higher in the observation group than that of the control group (P<0.05). No severe complication occurred in both groups. **Conclusion:** Valve surgery concomitant radiofrequency ablation modified maze is safe and effective in the treatment of atrial fibrillation complicated by valvular heart disease, has high conversion rate of early sinus rhythm, and can improve the serum levels of TIMP-1, MMP-1 and MMP-9.

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前言

心脏瓣膜病为心脏病的主要类型之一,慢性风湿性病变为其最常见诱因,其病情迁移,多呈慢性发展,早期无明显症状,随着病情加重,心功能不断恶化,容易并发房颤,影响心脏血流动力学稳定性,增加血栓形成风险[1,2]。人工心脏瓣膜置换或者瓣膜成形术为心脏瓣膜病的根治手段,其临床疗效肯定,但大部分患者术后房颤仍持续存在。相关研究报道[3,4]心脏瓣膜病合并房颤多为长期持续性房颤或永久性房颤,常规抗心律失常药物对此类房颤的效果有限,窦性心律转复的成功率极低。迷宫手术是心脏瓣膜病并发房颤的重要治疗手段,传统迷宫手术通过切割缝合法恢复传导系统,尽管其有效率较高,但操作复杂,且创伤明显[5,6]。

近年来,射频消融改良迷宫术用消融替代手术切口,明显简化手术操作和创伤,既可达到和传统迷宫术类似的治疗效果,又可减少手术并发症[7,8]。但目前临床有关心脏瓣膜病并发房颤的发病机制的认识较为局限,有研究认为基质金属蛋白酶(MMPs)在心脏瓣膜病并发房颤发生中有重要作用,可参与心房的结构性重塑,促进房颤发作[9,10]。金属蛋白酶组织抑制因子(TIMP) 和 MMP-1 及 MMP-9 结合后可形成可逆的复合物,抑制 MMPs 表达和对基质的降解。Mlodawska E 等[11]研究报道血清 TIMP-1、MMP-1 及 MMP-9 水平与瓣膜病合并房颤射频消融术的疗效有良好相关性,且有助于评价术后复发情况。因此,本研究主要探讨了瓣膜手术同期射频消融改良迷宫术对心脏瓣膜病并发房颤患者血清 TIMP-1、MMP-1 和 MMP-9 水平的影响。

1 资料与方法

1.1 一般资料

选择本院 2017 年 6 月 ~2018 年 6 月收治的 80 例心脏瓣膜病并发房颤患者,纳入标准[12]:经症状、体征、彩色血流、X 线片和超声心电图等检查确诊为风湿性瓣膜病并发房颤;瓣膜置换术指征明确,并均接受生物瓣置换术;左室射血分数(LVEF)大于 40%; 房颤持续时间超过 12 个月; 患者均知情同意本研究。排除标准:甲状腺功能异常;近期外伤或感染;恶性肿瘤;心源性恶液质;严重室性心律失常;心脏彩超左房内径超过 65 mm;严重心肝肾功能不全;凝血功能障碍;近期接受血管紧张素Ⅱ受体阻滞剂、血管紧张素转换酶抑制剂治疗。所有患者依据简单随机法分为对照组和观察组,每组 40 例,对照组男 16 例,女 24 例;年龄 37~68 岁,平均(54.19± 4.03)岁;主动脉瓣替换术 13 例,二尖瓣替换术 21 例,主动脉瓣 + 二尖瓣替换术 6 例;心功能:Ⅱ级 8 例、Ⅲ级 32 例;阵发性房颤 7 例、持续性房颤 33 例。观察组男 13 例,女 27 例;年龄 36~66 岁,平均(53.61± 4.78)岁;主动脉瓣替换术 10 例,二尖瓣替换术 24 例,主动脉瓣 + 二尖瓣替换术 6 例;心功能:Ⅱ级 5 例、Ⅲ级 35 例;阵发性房颤 9 例、持续性房颤 31 例。两组基线资料比较无统计学差异(P>0.05),具有可比性。

1.2 方法

对照组采用心脏瓣膜置换术治疗, 全身气管插管麻醉,于胸骨症中劈开切口,常规创建体外循环,于主动脉根部或者左、右冠状动脉开口处灌注中度低体温心肌保护液。充分显露并参照常规操作进行瓣膜置换手术,关闭左房,复温,排除左心气体,开放升主动脉。使右房关闭,待血流动力学恢复稳定后结束体外循环,并放置心外膜临时起搏导线。

观察组采用瓣膜手术同期射频消融改良迷宫术治疗,患者取气管插管全身麻醉,选择胸骨正中入路,在低体温体外循环下进行, 首选进行环绕左右静脉开口沿左右肺静脉的消融线路,再取左上肺静脉口沿左心耳消融,左下肺静脉口沿二尖瓣环消融, 部分患者同时予以右房内冠脉静脉窦沿下腔静脉消融。每条线路消融 3~5 次,以消融系统自控透壁提示完成。射频消融结束后进行瓣膜置换, 术后常规予以心外膜临时起搏线。两组术后均微泵输入 <30 mg/h 胺碘酮,持续 3 d,进食后改为口服 200 mg 胺碘酮,每天 3 次,持续 3 个月,若房颤未消除或复发,则持续服用胺碘酮至术后半年。术后均常规抗凝。

1.3 观察指标

记录患者术后当天、术后 1 月、术后 3 月及术后 6 月的窦性心律转复情况,体外循环时间、主动脉阻断时间、术后 24h 引流量,呼吸机使用时间和监护室时间,和并发症发生情况。于术前及术后 6 个月通过超声心动图测定患者左室舒张末期内径、左室收缩末期内径、LVEF。于术前及术后 6 个月采集患者空腹外周静脉血 4 mL,常规分离血清,用酶联免疫吸附法测定血清 TIMP-1、MMP-1、MMP-9 浓度。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包,计量资料用($\bar{x}\pm s$)表示,组间比较采用 t 检验,计数资料用[例(%)]表示,组间比较采用 χ^2 检验,以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组窦性心律转复情况的比较

观察组术后当天、术后 1 月、术后 3 月及术后 6 月的窦性心律转复率均高于对照组,差异有统计学意义(P<0.05),见表 1。

2.2 两组手术情况的比较

观察组体外循环时间、主动脉阻断时间及术后 24 h 引流量均明显多于对照组,差异有统计学意义(P<0.05),两组呼吸机使用时间和监护室时间比较差异无统计学意义(P>0.05),见表2。

2.3 两组手术前后心功能指标的比较

术前,两组左室舒张末期内径、左室收缩末期内径及 LVEF 比较差异无统计学意义(P>0.05);术后,两组左室舒张末期内径、左室收缩末期内径均较术前下降,且观察组以上指标均显著低于对照组,两组 LVEF 均较术前明显上升,且观察组以上指标均显著高于对照组,差异有统计学意义(P<0.05),见表 3。

表 1 两组窦性心律转复情况比较[例(%)]

Table 1 Comparison of the sinus rhythm conversion between two groups [Cases (%)]

Groups	n	On the day after surgery	One month after operation	Three months after operation	Six months after operation
Control group	40	7(17.50)	18(45.00)	16(40.00)	13(32.50)
Observation group	40	37(92.50)#	34(85.00)#	32(80.00)#	31(82.50)#

Note: Compared with the control group #P<0.05.

表 2 两组手术情况比较($\bar{x}\pm s$)

Table 2 Comparison of surgical conditions between two groups($\bar{x}\pm s$)

Groups	n	Extracorporeal circulation time(min)	Aortic occlusion time (min)	Postoperative 24 h drainage volume(mL)	Ventilator usage time(h)	Intensive care unit time(h)
Control group	40	87.42± 10.95	51.02± 7.03	459.22± 60.32	13.11± 1.39	2.86± 0.32
Observation group	40	126.55± 16.32#	67.53± 8.75#	490.01± 69.44#	12.68± 1.65	2.65± 0.44

Note: Compared with the control group #P<0.05.

表 3 两组手术前后心功能指标比较($\bar{x}\pm s$)

Table 3 Comparison of cardiac function indexes between two groups before and after operation($\bar{x}\pm s$)

Groups	n	Time	Left ventricular end diastolic diameter(mm)	Left ventricular end systolic diameter(mm)	LVEF(%)
Control group	40	Before operation	55.41± 7.13	59.42± 8.02	48.96± 7.42
		After operation	50.22± 6.94△	53.36± 8.11△	56.70± 8.26△
Observation group	40	Before operation	56.35± 8.42	57.09± 8.87	50.03± 6.88
		After operation	45.79± 6.05△#	47.88± 6.04△#	61.75± 9.03△#

Note: Compared with the control group #P<0.05; Compared with the same group before treatment, △ P<0.05.

2.4 两组手术前后血清 TIMP-1、MMP-1 和 MMP-9 水平的比较

术前,两组血清 TIMP-1、MMP-1 和 MMP-9 水平比较差异无统计学意义(P>0.05);术后,两组血清 TIMP-1 水平均较术前上升,且观察组显著高于对照组,两组血清 MMP-1 及 MMP-9 水平均较术前下降, 且观察组以上指标均显著低于对照组,差异有统计学意义(P<0.05),见表 4。

表 4 两组血清手术前后 TIMP-1、MMP-1 和 MMP-9 水平的比较($\bar{x}\pm s$)

Table 4 Comparison of the derum levels of TIMP-1, MMP-1 and MMP-9 between two groups before and after operation($\bar{x}\pm s$)

Groups	n	Time	TIMP-1(ng/mL)	MMP-1(ng/mL)	MMP-9(ng/mL)
Control group	40	Before operation	40.96± 6.41	3.75± 0. 41	198.77± 23.11
		After operation	50.33± 7.66△	2.01± 0.30△	142.15± 16.53△
Observation group	40	Before operation	42.02± 5.02	3.62± 0.49	193.26± 26.03
		After operation	59.05± 8.75△#	1.39± 0.22△#	102.64± 12.19△#

Note: Compared with the control group #P<0.05; Compared with the same group before treatment, △ P<0.05.

2.5 两组术后并发症发生情况的比较

两组术后均无出血、肝肾功能不全、迟发性心包填塞等并发症发生。

3 讨论

房颤是心脏瓣膜病的常见并发症之一,房颤发生时心房无法有效机械收缩,导致快而不规则的心室率,缩短心室舒张期时间,影响血液循环,降低心脏输出量,从而影响心功能。另外,房颤患者心房内容易产生附壁血栓, 导致体循环栓塞等并发症,增加患者致死、致残的风险[13,14]。目前人工心脏瓣膜置换术治疗心脏瓣膜病已取得了不错的效果,但有研究表明[15]此术式难以有效改善心脏瓣膜病患者的房颤症状。药物是房颤的主要治疗方式,可恢复并维持窦性心律,但药物难以终止房颤所致的心房重构及电重构,彻底恢复患者心功能,消除房颤的发生机制[16,17]。另外,长时间接受抗心律失常药物容易发生多种药物副反应。

临床研究报道[18]同期手术治疗房颤较单纯心脏瓣膜置换术可显著改善心脏瓣膜病合并房颤患者的生存情况。多子波假说认为心房结构和电生理的不均一性导致电冲动于心房内不均匀传导,形成折返性冲动,引起房颤发生,为迷宫手术治疗房颤提供了理论依据[19,20]。已有研究证实传统迷宫手术对于房颤的治愈率高达 95%以上,但其切口较多,心脏创伤大,和心脏瓣膜置换术同步进行可增加手术风险,临床应用有一定限制[21,22]。射频消融改良迷宫术通过电流产生局部高热,导致心肌细胞脱水、坏死,从而产生连续、透壁的消融线,阻断异常兴奋的传递通道,从而针对性治疗兴奋局灶及折返环路[23]。Abadir S 等[24]研

究发现射频消融改良迷宫术在简化操作流程和优化手术路径的同时,仍可具有和传统迷宫术令人相似的令人满意的转复效果。本研究结果也显示瓣膜手术同期射频消融改良迷宫术患者术后当天、术后 1 月、术后 3 月及术后 6 月窦性心律的转复率相对较高,证实二者联合的优良性,仅少数患者表现为窦房结功能不良,考虑为手术影响心脏自主神经的调节或者术中损伤右窦房结支,从而影响窦房结血供,且多为一过性,大部分患者能够自行恢复。但同期射频消融改良迷宫术患者体外循环时间、主动脉阻断时间及术后 24 h 引流量相对较多,但未延长患者呼吸机使用时间和监护室时间,未增加患者围手术风险。但单从手术情况比较二者的应用价值可能有一定局限性,临床可通过分析相关实验室指标以进一步反映此术式的效果。

国外研究显示[25]心房结构重构在房颤发生及维持中有重要作用,MMPs 可降解基质蛋白, 且可刺激细胞外基质细胞分泌活性因子,促进胶原蛋白及结缔组织的生成,从而参与心房肌间质纤维化和房颤发生。TIMP-1 为 MMPs 的抑制物,其表达失衡能够促进细胞外基质的降解,增加心房壁的硬度,影响心房壁的顺应性,导致心房的结构性重塑[26,27]。有关研究报道[28],心脏瓣膜病合并房颤患者 MMP-1、MMP-9 水平呈明显上升趋势,TIMP-1 水平相应下降。本研究结果显示, 术后患者 MMP-1、MMP-9 水平显著下降,TIMP-1 有所上升,但同期射频消融改良迷宫术组变化更明显,说明此术式更能有效调节以上指标表达, 考虑与瓣膜手术能够纠正心脏血液动力学紊乱,促进心脏压力负荷和容量负荷的恢复,而同期射频消融改良迷宫术又可恢复心脏窦性心律,恢复心房收缩功能,增加心脏输出量,从而减轻心室重构,维持 MMPs 和 TIMP 的平衡。相关研究显示[29]心脏瓣膜病并发房颤可导致心室或心房代偿性扩大,引起心室重构, 加上房颤持续存在又影响心室舒张末期血液回流,减少心输出量,降低 LVEF。Sugumar H 等研究报道[30]心功能的改善是评价瓣膜置换同期射频消融疗效的重要指标之一。本研究结果显示两组术后左室舒张末期内径、左室收缩末期内径均较术前减小,LVEF 相应增加, 且同期射频消融改良迷宫术组变化更明显,进一步证实其应用价值。此外,两组术后均无严重并发症发生,提示安全性较高。

综上所述,瓣膜手术同期射频消融改良迷宫术治疗心脏瓣膜病并发房颤安全有效,可消除房颤,早期窦性心律的转复率高,且可改善 TIMP-1、MMP-1、MMP-9 水平。

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