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肝硬化大鼠门静脉高压症不同手术方式对其肝脏的影响

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Effects of different operations on cirrhotic portal hypertensive liver in rats

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Abstract

AIM: To evaluate respectively the effects of portaazygous disconnection (PAD), mesocaval shunt (MCS) and distal splenocaval shunt (DSCS) on the portasytemic shunting (PSS), hepatic function (HF), hepatic mitochondrial respiratory function (HMRF) and its ultrastructure, anti-oxidation ability (HAOA) and lipoperoxide (LPO), so as to provide theoretical basis to select a suitable operation.

METHODS: Using the cirrhotic portal hypertensive model induced by CCl_4/ethanol in Wristar rats, we investigated PSS, HF, HMRF and its HAOA and LPO during three weeks after MCS, DSCS and PAD.

RESULTS: After MCS, the PSS were further increased, HF, HMRF and HAOA were significantly decreased, and LPO increased. Hepatic mitochondrial ultrastructure showed severely damaged. Only a little improvement was found on the third week. After DSCS and PAD, above mentioned indexes were less influenced, and they were restored a little more quickly in DSCS groups than that in PAD groups. During the first postoperative week, the PAD group showed the highest mortality.

CONCLUSION: DSCS may be a desirable operation among the three kinds of operation.

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摘要

目的: 评价门奇断流术(PAD)、肠腔分流术(MCS)、远端脾腔分流术(DSCS)对门体分流率(PSS)、肝脏功能、线粒体功能和抗氧化能力的影响,为合理选择手术方式提供理论依据.

方法: 用 CCl_4/乙醇诱导大鼠肝硬化门脉高压症模型, 观察了不同术式(MCS、DSCS、PAD)的死亡率及手术前后肝功能、门体分流率(PSS)、肝细胞线粒体功能和超微结构及肝组织 SOD 活性、巯基水平、LPO 含量的变化, 并探讨了线粒体功能与抗氧化能力的内在关系.

结果: 肝硬化门脉高压时, PSS 远高于正常, 肝细胞线粒体功能、抗氧化能力均下降; 肠腔分流(MCS)组术后肝细胞线粒体功能、抗氧化能力进一步下降且恢复慢; 选择性远端脾腔分流术(DSCS)组和门奇断流术(PAD)组的上述指标变化小且恢复较快, 其中 DSCS 组恢复更快且死亡率低.

结论: 选择性分流术(DSCS)可能是较理想的术式.

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0 引言

肝硬化时, 机体能量代谢发生异常[1], 主要表现为脂肪供能显著增加而糖供能相应减少. 能量代谢的微观机制表现为线粒体结构的异常和功能的显著下降[2-9]: 线粒体蛋白含量下降; Ⅳ态呼吸率升高[5], 呼吸控制比下降, 合成 ATP 能力降低, 导致肝细胞能荷下降; 电子传递链活性下降; 氧耗量下降可达 40% 以上; 葡萄糖合成(按每个线粒体的体积计算)可减少 60% 以上. 肝硬化门脉高压症也伴有肝脏抗氧化机制受损, 表现为肝组织谷光甘肽(GSH)含量、GSH-Px (谷光甘肽过氧化物酶)活性[10]和超氧化物歧化酶(SOD)活性[11]均下降. 同时, 自由基损伤加重, 肝组织脂质过氧化物(LPO)明显高于正常人[12-13]. 但也有报道 LPO 变化不明显者[14].

目前, 外科手术仍然是治疗肝硬化门脉高压症的重要手段[15-17]. 据认为, 线粒体损害会使机体产生对胰岛素的抵抗[18]. 肝脏线粒体结构和功能的正常有赖于门脉有效血流量及门脉血中的胰岛素等肝营养因子[19-21]. 因为胰岛素等营养因子能够部分纠正硬化肝脏异常的基因表达[22], 改善营养物质的吸收[23-24], 部分减轻肝硬化的程度[25]. 已知门体分流能引起和加重能量物质代谢障碍[26-30], 这可能与肝脏线粒体结构和功能遭到进一

步破坏有一定关系. 我们研究大鼠肝硬化门脉高压症及不同手术方式对其门体分流率、肝脏功能、线粒体功能和抗氧化能力的影响,并探讨了肝脏线粒体功能与抗氧化能力之间的内在联系,旨在从多方面综合评价各种手术方式的治疗价值,为临床上合理选择手术方式提供理论依据.

1 材料和方法

1.1 材料 采用 CCl_4/乙醇诱导 Wistar 大鼠形成肝硬化门脉高压模型[31]. 模型制成后正常饲养 3 wk,再分为 3 组,在腹腔麻醉下(10 g/L 戊巴比妥钠 30 mg/kg),分别行肠腔侧侧分流术(MCS)、选择性远端脾腔分流术(DSCS)[32]和门奇断流术(PAD). 手术完成前后各测门压力 1 次. 每组观察术前及术后 1、2、3 wk 共 3 个时相点,每组每个时相点保证 8-10 只鼠.

1.2 方法 测谷丙转氨酶(ALT)、总蛋白(TP)、白蛋白(ALB)、球蛋白(G)和白/球比值(A/G); 肝脏线粒体呼吸功能检测 II 态呼吸速率(S_3)和 IV 态呼吸速率(S_4),计算呼吸控制率(RCR= S_3/S_4)和磷氧比(P/O)[33]; 肝组织ATP含量采用荧光素酶法测定[34]; 门体分流率(PSS)测定采用放射微球法[35]; 肝组织总巯基(T-SH)、非蛋白巯基(NP-SH)和蛋白巯基(P-SH)采用光谱法测定[36]; 肝组织超氧化物歧化酶(SOD)采用光谱法测定[37]; 肝组织脂质过氧化物(LPO)含量采用荧光分光光度计法测定[38]; 肝组织学检查:光镜及透射电镜检查.

统计学处理 以mean±SD表示. 进行方差分析检验、直线相关与回归分析,以 $P<0.05$ 为显著性界限.

2 结果

模型制成后见肝脏缩小呈结节状. 光镜下见典型假小叶结构. 电镜下见狄氏间隙有大量成束排列的胶原纤维; 部分线粒体嵴紊乱,但结构基本完整; 未见或极少有糖原颗粒. 自由门脉压力(FPP): 硬化组(CL)显著高于正常组(NL)(1.45 ± 0.08 kPa *vs* 0.77 ± 0.04 kPa, $P<0.01$). MCS 组术后超微结构改变明显,可见肝脏部分线粒体肿胀、嵴排列紊乱、断裂或消失、空泡化甚至崩解、髓鞘样结构形成,个别核染色质边集、核膜溶解,DSCS 组、PAD 组术后肝组织超微结构与 CL 组相比较变化不明显.

2.1 肝代谢指标 肝硬化门脉高压时,PSS 远高于正常,肝细胞线粒体功能和抗氧化能力下降; 肠腔分流(MCS)术后肝细胞线粒体功能、抗氧化能力进一步下降且恢复慢; 选择性远端脾腔分流术(DSCS)组和门奇断流术(PAD)组的上述指标变化小且恢复较快,其中 DSCS 组恢复更快且死亡率低. 详见表 1-7.

表 1 SD 大鼠肝硬化手术后 FPP 的变化(n =10, mean±SD, kPa)

手术	MCS	DSCS	PAD
前	1.46 ± 0.07	1.45 ± 0.05	1.45 ± 0.06
后	1.10 ± 0.03[b]	1.41 ± 0.04	1.43 ± 0.05

[b]$P<0.01$, *vs* 术前.

表 2 SD 大鼠肝硬化手术死亡情况(n =10, %)

术式	n	术中	1 wk	2 wk	3 wk	1-3 wk	合计
MCS	58	5 8.6	2 3.4	1 1.7	2 3.4	5 8.6	10 17.2
DSCS	52	1 1.9[a]	1 1.9	1 1.9	0 0.0	2 3.8	3 5.8[a]
PAD	72	0 0.0[a]	17 23.6[bd]	4 5.6	2 2.8	23 31.9[bd]	23 31.9[bd]

[a]$P<0.05$, [b]$P<0.01$ *vs* MCS; [d]$P<0.01$ *vs* DSCS. n 代表手术例数.

表 3 SD 鼠肝硬化手术后 PSS 的变化(n =8, %)

术式	术前		术后(wk)		
	NL	CL	1	2	3
MCS			75.0 ± 7.6[b]	81.8 ± 7.0[b]	86.7 ± 5.9[bc]
DSCS	0.9 ± 0.3	16.3 ± 3.5	10.2 ± 2.9[ad]	11.6 ± 2.7[d]	15.1 ± 3.3[dc]
PAD			9.3 ± 2.7[ad]	10.0 ± 2.8[d]	13.9 ± 3.1[dc]

[a]$P<0.05$, [b]$P<0.01$ *vs* CL; [d]$P<0.01$ *vs* MCS; [c]$P<0.05$ *vs* 1 wk. n 代表大鼠数目.

表 4 SD 大鼠肝硬化手术后肝功能的变化(n =10)

分组	ALT(IU/L)	TP(g/L)	ALB(g/l)	G (g/L)	A/G
NL	12 ± 6[b]	72.6 ± 3.3[a]	35.6 ± 2.5[b]	37.0 ± 2.5	0.97 ± 0.13[b]
CL	30 ± 7	67.0 ± 2.4	26.7 ± 2.7	40.3 ± 2.7	0.67 ± 0.11
MCS_1	53 ± 9[b]	59.2 ± 4.2[b]	20.5 ± 3.3[b]	38.7 ± 3.3	0.53 ± 0.10
$DSCS_1$	31 ± 8[d]	63.3 ± 3.4	24.2 ± 2.7	39.2 ± 3.1	0.62 ± 0.10
PAD_1	66 ± 14[bf]	58.1 ± 3.6[be]	22.0 ± 2.3[a]	36.1 ± 2.8	0.61 ± 0.09
MCS_2	57 ± 10[b]	56.1 ± 5.0[b]	18.5 ± 2.6[b]	37.6 ± 4.7	0.50 ± 0.10[a]
$DSCS_2$	31 ± 7[d]	64.2 ± 3.6[d]	25.0 ± 2.2[d]	39.2 ± 3.2	0.64 ± 0.09
PAD_2	48 ± 7[bf]	60.4 ± 2.9[a]	23.3 ± 2.5[d]	37.1 ± 3.1	0.63 ± 0.10
MCS_3	61 ± 11[b]	53.7 ± 5.0[b]	16.9 ± 1.8[b]	36.8 ± 4.8	0.47 ± 0.09[a]
$DSCS_3$	31 ± 7[d]	64.8 ± 3.2[d]	25.5 ± 2.5[d]	39.3 ± 3.4	0.66 ± 0.10[d]
PAD_3	31 ± 7[d]	64.2 ± 3.5[d]	25.3 ± 2.7[d]	38.9 ± 3.1	0.66 ± 0.10[d]

[a]$P<0.05$, [b]$P<0.01$ *vs* CL; [d]$P<0.01$ *vs* MCS; [e]$P<0.05$, [f]$P<0.01$ *vs* DSCS. n 代表大鼠数目.

表 5 SD 大鼠肝硬化手术后肝脏线粒体功能的变化(n =8)

分组	S_3	S_4	RCR	P/O	ATP(μmol/g)
	$nmolO_2$/min/mg				
NL	125.03 ± 13.48	30.29 ± 2.36[b]	4.12 ± 0.23[b]	1.74 ± 0.08[b]	2.25 ± 0.15[b]
CL	115.05 ± 3.82	38.66 ± 2.78	2.99 ± 0.25	1.57 ± 0.06	1.45 ± 0.29
MCS_1	106.05 ± 13.77	55.00 ± 4.98[b]	1.93 ± 0.23[b]	1.25 ± 0.05[b]	0.38 ± 0.10[b]
$DSCS_1$	118.65 ± 0.39	41.34 ± 3.46[d]	2.88 ± 0.20[d]	1.53 ± 0.05[d]	0.95 ± 0.08[bd]
PAD_1	115.15 ± 4.70	46.66 ± 3.93[bd]	2.48 ± 0.19[bed]	1.34 ± 0.11[be]	0.93 ± 0.09[bd]
MCS_2	111.86 ± 4.76	49.26 ± 1.72[b]	2.23 ± 0.18[b]	1.33 ± 0.10[b]	0.68 ± 0.08[b]
$DSCS_2$	113.08 ± 6.27	38.56 ± 1.67[d]	2.94 ± 0.25[d]	1.56 ± 0.04[d]	1.38 ± 0.24[d]
PAD_2	113.94 ± 4.93	42.26 ± 3.37[d]	2.73 ± 0.23[d]	1.51 ± 0.08[d]	1.35 ± 0.23[d]
MCS_3	113.14 ± 6.09	44.58 ± 1.99[b]	2.54 ± 0.16[b]	1.36 ± 0.06[b]	0.92 ± 0.08[b]
$DSCS_3$	133.23 ± 7.53	38.48 ± 1.47[d]	2.95 ± 0.24[c]	1.56 ± 0.05[d]	1.43 ± 0.29[d]
PAD_3	111.53 ± 7.34	38.50 ± 2.10[d]	2.91 ± 0.26[c]	1.57 ± 0.15[d]	1.42 ± 0.28[d]

[b]$P<0.01$ *vs* CL; [c]$P<0.05$, [d]$P<0.01$ *vs* MCS; [e]$P<0.05$ *vs* DSCS. n 代表大鼠数目.

表 6 SD 大鼠肝硬化手术后肝组织巯基含量的变化(n =8, mean±SD, μmol/g)

组别	T-SH	NP-SH	P-SH
NL	28.20 ± 2.25[b]	8.29 ± 0.69[a]	19.92 ± 2.67[a]
CL	23.88 ± 3.71	6.43 ± 0.92	17.42 ± 2.45
MCS_1	13.24 ± 1.51[b]	4.84 ± 1.26[a]	8.40 ± 1.44[b]
$DSCS_1$	21.14 ± 2.14[bd]	6.56 ± 0.40[d]	14.58 ± 2.23[bd]
PAD_1	17.96 ± 1.84[bdf]	4.31 ± 0.85[bf]	13.65 ± 1.59[bd]
MCS_2	17.50 ± 1.80[b]	5.26 ± 1.65	12.24 ± 2.06[b]
$DSCS_2$	23.40 ± 2.69[d]	5.95 ± 1.69	17.46 ± 1.43[d]
PAD_2	20.82 ± 2.89[bde]	6.73 ± 0.74	14.08 ± 1.08[bf]
MCS_3	17.65 ± 2.98[b]	4.80 ± 1.23[a]	12.84 ± 1.75[b]
$DSCS_3$	23.63 ± 2.59[d]	6.34 ± 1.20	17.29 ± 1.11[d]
PAD_3	21.35 ± 2.07[ade]	6.45 ± 0.97[c]	14.90 ± 1.39[be]

[a]P <0.05, [b]P <0.01 *vs* CL; [c]P <0.05, [d]P <0.01 *vs* MCS; [e]P <0.05, [f]P <0.01 *vs* DSCS. n 代表大鼠数目.

2.2 手术组综合相关分析 将所有手术治疗的大鼠作为一个总体，对上述指标进行分析，结果发现: RCR 与 ATP、T-SH、SOD 均呈显著正相关，r 分别为 0.76、0.81、0.72，P 值均为 0.0 000; ATP 与 T-SH、SOD 呈显著正相关，r 分别为 0.77、0.77，P 值均为 0.0 000; T-SH 与 SOD 呈显著正相关(r =0.80，P =0.0 000); LPO 与 RCR、ATP、T-SH 及 SOD 均呈显著负相关，r 分别为 -0.53、-0.58、-0.67 及 -0.69，P 值均为 0.0 000.

3 讨论

据文献报道，CCl_4 诱导的肝硬化门脉高压症大鼠具备了人类肝硬化的绝大多数病理特征，其能量代谢特点和抗氧化能力变化也类似于人类肝硬化[4-6, 14, 18-21]. 因此，本实验采用该模型是合理的.

目前，晚期肝硬化门脉高压症的外科治疗主要有断流术、分流术、TIPS (transjugular intrahepatic portosystemic shunt)和肝移植术. 在我国，断流术和门体分流术依然是最主要的外科手术方式. 因此，我们对常用的三种手术方式进行了比较全面的实验研究. PAD组术后死亡率显著高于 MCS 组和 DSCS 组，MCS 组又显著高于 DSCS 组. PAD组术后1 wk内死亡较多主要与手术破坏了胃的神经支配和血供，导致急性胃缺血、胃潴留、胃扩张和胃坏死有关，当然与脾切除后免疫功能下降所致的感染也有关系[39]. MCS组死亡原因主要是门脉血流丧失过多所致的肝衰[26-30]. DSCS 组死亡率最低，这与他有效地保存了门脉血流量[32]和脾脏免疫功能有关. 各手术组术后 3 wk 时的 PSS 均显著高于 1wk 时的 PSS，这与新的侧枝循环形成及/吻合口扩大和断流(含 DSCS 时的脾胰断流)不彻底[40]有关.

肝硬化本身就可引起线粒体结构和功能的显著下降[1-2, 4-8]. 肝硬化门脉高压症时所伴发的自发性门体分流减少了肝脏有效血流量，使肝脏对能量物质吸收障碍，加重线粒体功能障碍[6, 9, 13, 21, 41-43]，因为门脉血中存在来自肠道和胰腺的激素及营养因子. 正常肝脏至少要接纳 20% 的从胰腺回流来的血液才能维持肝线粒体氧化磷酸化的最低需要[44]. 门静脉血流减少或外科性门体分流可导致正常肝糖原含量、cAMP 和细胞色素 P_{450} 含量降低，引起线粒体功能下降[21, 45-47]，引起或加重肝性脑病[48]. MCS 组术后肝脏线粒体功能、ATP 含量、巯基水平及 SOD 活性基本上均进一步显著下降，肝功能恶化，LPO 含量显著升高，到术后 3 wk 上述指标仍未恢复. 而 DSCS 组、PAD 组的上述指标变化较小，至术后 2 wk 或 3 wk 大多恢复; 其中 DSCS 组恢复更快些. 各组的线粒体功能变化与其超微结构改变基本一致. 各手术组肝脏线粒体功能与肝组织 ATP 含量、SOD 活性及巯基含量之间均呈显著正相关，与 LPO 含量呈显著负相关. MCS组术后发生的上述变化与其向肝门脉血流的大量丧失有关. MCS 组的 PSS 于术后陡然增加了近 5 倍，致使肝脏有效血流量锐减，硬变肝脏处于低灌流、甚至缺氧状态，能量基质吸收减少，进一步损害了其线粒体结构和功能; 同时激发肝脏氧自由基(OFR)生成增加，LPO 升高; 由于合成减少和消耗增加，SOD 活性和巯基水平下降. 由于上述变化，细胞膜性结构进一步受损，不能维持离子的正常运转，导致细胞外 Na^+、Ca^{2+} 等离子大量流入细胞内，线粒体内 Ca^{2+} 也随之增加. Ca^{2+} 的超负荷引起线粒体肿胀，以至于空化、崩解或形成髓鞘样结构. MCS 术后肠系膜静脉系

表 7 SD 大鼠肝硬化手术后肝组织 SOD 活性和 LPO 含量的变化(u/mg) (n =8, mean±SD)

指标	术式	术前		术后(wk)		
		NL	CL	1	2	3
SOD(u/mg)	MCS	238.16 ± 16.94[b]	193.59 ± 13.80	66.45 ± 26.74[b]	124.58 ± 16.54[b]	161.56 ± 8.77[b]
	DSCS			135.06 ± 11.48[bd]	163.89 ± 8.13[bd]	191.22 ± 11.54[d]
	PAD			135.71 ± 12.28[bd]	162.51 ± 8.45[bd]	191.70 ± 10.93[d]
LPO(μmol/g)	MCS	2.36 ± 0.29[b]	3.35 ± 0.46	0.39 ± 1.45[b]	5.78 ± 0.31[b]	4.44 ± 0.35[b]
	DSCS			4.46 ± 0.36[bd]	3.44 ± 0.42[d]	3.37 ± 0.43[d]
	PAD			4.54 ± 0.39[bd]	3.47 ± 0.39[d]	3.40 ± 0.42[d]

[b]P <0.01 *vs* CL; [d]P <0.01 *vs* MCS. n 代表大鼠数目.

统压力下降，可引起一些毒素吸收增加[49]，加上肝脏解毒功能下降，这些毒素也可不同程度地破坏线粒体功能. MCS术后的高胆酸血症也可损害线粒体功能.

DSCS组和PAD组术后维护了向肝门脉血流灌注[28]，因此，其线粒体功能和抗氧化能力受到了较小的影响. DSRS与其他非选择性分流相比，能够较好地保护肝脏功能[50]. PAD组由于切除了脾脏，硬变肝脏承担了更多的过滤、解毒及免疫等功能，因此，抗氧化能力恢复较SDCS组缓慢. MCS组术后向肝门脉血流灌注锐减，肝功能、肝脏线粒体功能及抗氧化能力进步一下降，术后3 wk各指标仍未恢复. DSCS组及PAD组的上述指标变化较小且恢复较快，其中DSCS组恢复更快些. PAD组术后近期死亡率高. 上述分析说明DSCS可能是较理想的术式，也说明选择性分流较好地维护了硬变肝脏的线粒体功能和抗氧化能力.

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