



## 食管胃腔外血管对内镜预防食管胃静脉曲张再出血的影响

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· 专题报道 ·

## 食管胃腔外血管对内镜预防食管胃静脉曲张再出血的影响

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**[摘要]** 目的 探讨食管和胃腔外血管对内镜预防食管胃静脉曲张再出血的影响。方法 回顾性分析2020年1月至2020年12月在复旦大学附属中山医院因肝硬化食管胃静脉曲张出血，接受肝静脉压力梯度（HVPG）检测并行内镜下套扎和（或）组织胶注射预防再出血的患者。根据门静脉CT显示的食管和胃腔外血管情况，将患者分为有腔外血管团组和无腔外血管团组，评价内镜治疗后2年内再出血情况。结果 共纳入69例患者，其中27例合并腔外血管团。两组患者一般基线资料、血液学指标（血红蛋白水平、凝血酶原时间、白蛋白水平）、HVPG、手术方式差异均无统计学意义。2年内共25例发生再出血，包括有腔外血管团组15例、无腔外血管团组10例。Kaplan-Meier生存分析显示，有腔外血管团组内镜治疗后的2年内累积再出血率高于无腔外血管团组（60.07% vs 32.79%， $P=0.022$ ）。多因素Cox回归分析显示，有腔外血管团是食管胃静脉曲张出血患者内镜治疗后再出血的独立预测因素（HR=2.33, 95% CI 1.01~5.39,  $P=0.047$ ）。结论 存在食管胃腔外血管团能独立预测内镜治疗后食管胃静脉曲张再出血，建议食管胃静脉曲张出血患者接受内镜预防再出血时，通过门静脉CT评估食管和胃腔外血管情况；对于合并巨大腔外血管团患者，建议充分评估后采用经颈静脉门体分流术等方法，或根据密切随访结果及时调整内镜治疗策略。

**[关键词]** 食管胃腔外血管；肝硬化；食管胃静脉曲张；内镜治疗；再出血

**[中图分类号]** R 575.2<sup>+</sup>

**[文献标志码]** A

## Para-esophageal and para-gastric vessels affect the secondary prophylactic efficacy of endoscopic treatment for varices

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**[Abstract]** **Objective** To evaluate the effect of para-esophageal and para-gastric vessels (PEPGV) on endoscopic secondary prophylaxis for varices. **Methods** The clinical data of patients with cirrhosis-related esophagogastric varices (EGV) who underwent endoscopic variceal ligation and/or obliteration, and had hepatic venous pressure gradient (HVPG) result between January 2020 and December 2020 in Zhongshan Hospital, Fudan University were retrospectively analyzed. Patients were divided into a group without PEPGV and a group with PEPGV based on CT imaging of the portal vein. The main outcome was 2-year re-bleeding. **Results** A total of 69 patients were included, and 27 of them had PEPGV. There was no statistical difference in baseline characteristics, blood indexes (included hemoglobin level, prothrombin time and albumin level), HVPG, and the secondary prophylactic endoscopic treatment ways between the two groups. A total of 25 patients experienced re-bleeding within 2 years after endoscopic treatment, including 15 in the group with PEPGV and 10 in the group without PEPGV. Kaplan-Meier analysis showed that the cumulative 2-year re-bleeding rate was significantly higher in the group with PEPGV than in the group without PEPGV (60.07% vs 32.79%,  $P=0.022$ ). Further multivariate Cox analysis showed that PEPGV was an independent predictor of re-bleeding after endoscopic treatment in EGV patients (HR=2.33, 95% CI 1.01-5.39,  $P=0.047$ ). **Conclusions** The PEPGV is an independent predictor of re-bleeding after endoscopic treatment in EGV patients. It is suggested that when patients with EGV receive endoscopic treatment to prevent re-bleeding, portal vascular CT is suggested to evaluate PEPGV. For patients with giant extraluminal vascular

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masses, fully evaluating other treatment options such as transjugular intrahepatic portosystemic shunt, or adjusting endoscopic treatment ways is recommended.

[Key Words] para-esophageal and para-gastric vessels; cirrhosis; esophagogastric varices; endoscopic treatment; re-bleeding

食管胃静脉曲张(esophagogastric varices, EGV)是门静脉高压常见的临床表现,发生于约50%的肝硬化患者中<sup>[1]</sup>。肝静脉压力梯度(hepatic venous pressure gradient, HVPG)是评估门静脉压力的金标准; HVPG≥10 mmHg是肝硬化患者静脉曲张形成的独立危险因素,≥12 mmHg时静脉曲张出血风险增加<sup>[2-3]</sup>。EGV出血患者即使接受标准方案(内镜下套扎+血管活性药物+抗生素)治疗,死亡率仍达16%<sup>[4]</sup>。目前,EGV二级预防的一线方案为联合非选择性β受体阻滞剂和内镜治疗<sup>[5-7]</sup>。未接受二级预防患者的再出血率高于60%,2年内再出血致死率高达50%;接受二级预防患者的再出血率仍达30%<sup>[8]</sup>。因此,识别EGV内镜治疗后再出血相关危险因素对改善患者预后具有重要意义。目前的临床研究结果<sup>[9-10]</sup>提示,EGV的内镜二级预防效果与HVPG、静脉曲张类型、药物种类、基础肝病类型及患者机体状况等相关。

内镜下套扎治疗及硬化剂、组织胶注射均为曲张静脉局部治疗方法。EGV的内镜治疗基于曲张静脉侧支的解剖基础,胃静脉曲张常发生于远端食管和近端胃之间,其中约3/4曲张静脉食管段经过贲门延伸至胃小弯,为GOV 1型,2型曲张静脉延伸至胃底,另外还有孤立型胃静脉曲张<sup>[11]</sup>。但内镜下可见及治疗的曲张血管局限于黏膜及黏膜下层,而食管及胃腔外可能存在曲张血管团,且这些腔外血管团须通过CT等影像学检查发现。CT、MRI等提供的信息,包括曲张血管直径及门静脉侧支循环等,对预测EGV治疗后预后有重要意义<sup>[12-13]</sup>。但是,目前食管胃腔外血管对EGV二级预防效果的影响不明确,因此本研究对此进行探讨。

## 1 资料与方法

1.1 研究对象 回顾性分析2020年1月至2020年12月在复旦大学附属中山医院因肝硬化EGV出血,行内镜下套扎和(或)组织胶治疗预防再出血的患者。患者均接受HVPG测定。排除标准:(1)合并肿瘤;(2)既往脾切除;(3)出院后

失访。根据门静脉CT影像,将患者分为有腔外血管团组和无腔外血管团组。

1.2 治疗方法及观察指标 患者首次内镜治疗后每8周入院复查,并再次内镜下治疗,至EGV消失,必要时补充内镜治疗,不需要内镜治疗后每半年复查。收集患者入院时的一般临床资料、HVPG、二级预防首次内镜治疗时间及方式、CT特点,随访患者再出血情况。主要终点指标为首次内镜治疗后2年内再出血。出血定义为呕血或黑便,伴血红蛋白下降大于10 g/L,或明显的呕血或血便。

1.3 统计学处理 采用Stata 13.0软件进行统计分析。符合正态分布的计量资料以 $\bar{x}\pm s$ 表示,否则以 $M(P_{25}, P_{75})$ 表示。符合正态分布且组间方差齐性的计量资料比较采用独立样本t检验,不符合正态分布时采用Wilcoxon秩和检验。分类资料以n(%)表示,组间比较采用 $\chi^2$ 检验或Fisher确切概率法。通过Kaplan-Meier生存曲线及log-rank检验比较两组及联用卡维地洛与否患者累积再出血率。通过Cox比例风险模型分析临床重要预后因素对再出血的影响。所有检验均为双侧,检验水准( $\alpha$ )为0.05。

## 2 结 果

2.1 两组患者的基线特征比较 共纳入69例患者,其中27例有食管胃腔外血管团、42例无腔外血管团(图1)。结果(表1)显示:两组患者年龄、性别、合并症,凝血指标、血红蛋白、白蛋白水平,Child-Pugh分级差异均无统计学意义。两组除酒精性脂肪肝外的门静脉高压病因差异无统计学意义。两组HVPG及内镜二级预防方式差异无统计学意义。

2.2 两组患者再出血事件比较 首次内镜治疗后2年内,共25例患者发生再出血,其中有腔外血管团15例、无腔外血管团10例。Kaplan-Meier生存分析(图2A)显示:有腔外血管团患者内镜治疗后2年累积再出血率高于无腔外血管团患者(60.07% vs 32.79%,  $P=0.022$ )。

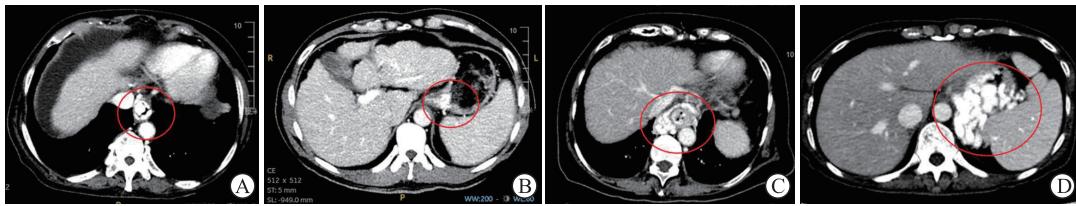


图1 肝硬化 EGV 患者门静脉 CT 影像

Figure 1 Portal CT imagings of patients with cirrhosis-related EGV

A, B: without para-esophageal and para-gastric vessels; C:para-esophageal vessels; D: para-gastric vessels.

表1 EGV 患者基线信息

Table 1 Baseline characteristics of patients with EGV

Index	Total (n=69)	Group with PEPGV (n=27)	Group without PEPGV (n=42)	t/Z/ $\chi^2$ value	P value
Age/year	55.3±11.8	54.7±11.8	55.8±11.9	0.374	0.709
Male n(%)	42(60.9)	17(63.0)	25(59.5)	0.082	0.775
Carvedilol n(%)	12(17.4)	4(14.8)	8(19.1)	0.205	0.651
HVPG/mmHg	14.4±6.7	14.6±7.0	14.3±6.6	- 0.216	0.829
Hemoglobin/(g•L <sup>-1</sup> )	88.7±20.9	91.1±22.7	87.2±19.8	- 0.754	0.454
Platelet/(×10 <sup>9</sup> •L <sup>-1</sup> )	60±35	58.9±24.2	62±38	0.947	0.344
Prothrombin time/s	14.7±1.6	15.0±1.5	14.5±1.6	- 1.389	0.169
INR	1.3±0.1	1.3±0.1	1.3±0.1	- 1.491	0.141
Albumin/(g•L <sup>-1</sup> )	37.0±5.3	37.1±5.7	36.9±5.1	- 0.172	0.863
C-reaction protein /(mg•L <sup>-1</sup> )	1.64(0.52, 3.05)	1.63(0.465, 2.725)	1.64(0.59, 3.05)	0.224	0.823
Total bilirubin/(μmol•L <sup>-1</sup> )	17.2(11.2, 24.9)	18.3 (12.1, 27)	16.7(11.2, 21.1)	- 0.998	0.318
White blood cell/(×10 <sup>9</sup> L <sup>-1</sup> )	2.49(1.68, 3.23)	2.53(1.65, 3.48)	2.28(1.68, 3.22)	- 0.621	0.535
Serum creatine/(μmol•L <sup>-1</sup> )	69(59, 80)	62(56, 75)	70(61, 85)	1.628	0.104
Re-bleeding time/d	417 (122, 730)	311(127, 730)	423(121, 730)	0.519	0.604
Child-Pugh grade n(%)				1.887	0.170
A	44(65.7)	19(76.0)	25(59.5)		
B	23(34.3)	6(24.0)	17(40.5)		
Sarin varices type n(%)					0.741
EV	10(14.5)	4(14.8)	6(14.3)		
GOV1	38(55.1)	15(55.6)	23(54.8)		
GOV2	20(29.0)	7(25.9)	13(31.0)		
IGV	1(1.5)	1(3.7)	0		
Endoscopic treatment method n(%)					0.337
EVL	17(24.6)	4(14.8)	13(31.0)		
EIC	6(8.7)	3(11.1)	3(7.1)		
EVL+EIC	46(66.7)	20(74.1)	26(61.9)		
Comorbidity n(%)					
Hypertension	7(10.1)	2(7.4)	5(11.9)		0.697
Diabetes	17(24.6)	5(18.5)	12(28.6)	0.894	0.344
Portal vein thrombosis	17(24.6)	6(22.2)	11(26.2)	0.139	0.709
Etiology of portal hypertension n(%)					
Hepatitis B	39(56.5)	14(51.9)	25(59.5)	0.394	0.530
Hepatitis C	3(4.3)	0	3(7.1)		0.275
Alcoholic	8(11.6)	0	8(19.0)		0.019
Autoimmune hepatitis	5(7.2)	2(7.4)	3(7.1)		1.000
Primary biliary cholangitis	6(8.7)	4(14.8)	2(4.8)		0.201
Schistosoma	5(7.2)	1(3.7)	4(9.5)		0.641
Idiopathic	10(14.5)	6(22.2)	4(9.5)		0.173

PEPGV: para-esophageal and para-gastric vessels; HVPG: hepatic venous pressure gradient; INR: international normalized ratio; EV: esophageal varices; GOV: gastroesophageal varices; IGV: isolated gastric varices; EVL: endoscopic variceal ligation; EIC: endoscopic injection of cyanoacrylate.

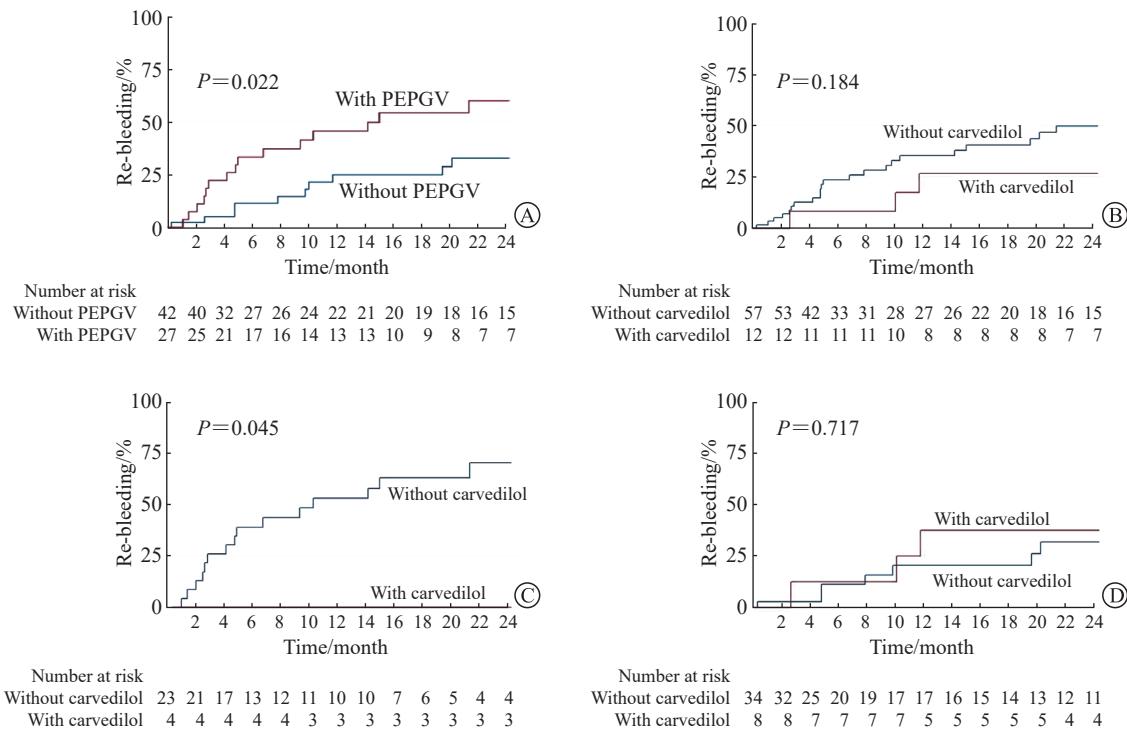


图 2 Kaplan-Meier 生存曲线分析 EGV 内镜治疗后 2 年累积再出血率

Figure 2 Kaplan-Meier curve analysis of 2-year cumulative re-bleeding rate in patients with EGV after endoscopic treatment

A, B: total patients; C: patients with PEPGV; D: patients without PEPGV.

2.3 卡维地洛对再出血的影响 按服用卡维地洛与否分层(图 2B~2D): 总体患者中, 联合治疗者与未联合治疗者治疗后 2 年累积再出血率差异无统计学意义 (26.7% vs 49.9%,  $P=0.184$ ) ; 有腔外血管团患者中, 联合治疗者累积再出血率低于未联合治疗者 (0 vs 70.5%,  $P=0.045$ ) ; 无腔外血管团患者中, 联合治疗者与未联合治疗者再出血率差异无统计学意义 (37.5% vs 31.9%,  $P=0.717$ )。

2.4 再出血危险因素分析 单因素 Cox 回归 (表 2) 显示, 有腔外血管团增加 EGV 患者内镜治疗后再出血风险 ( $HR=2.48$ , 95% CI 1.11~5.52,  $P=0.026$ ) ; 将有无腔外血管团、肝硬化预后重要影响因素 (HVPG、腹水、白蛋白) 纳入多因素 Cox 分析, 发现有腔外血管团是 EGV 患者内镜治疗后再出血的独立预测因素 ( $HR=2.33$ , 95% CI 1.01~5.39,  $P=0.047$ )。

表 2 Cox 回归分析 EGV 出血患者内镜治疗后 2 年内再出血相关临床因素

Table 2 Cox regression analysis of clinical factors related to 2-year re-bleeding after endoscopic treatment in EGV patients

Variable	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age (<60 years vs ≥60 years)	1.41	0.63-3.14	0.403			
Male	1.50	0.66-3.42	0.331			
HVPG (≤5 mmHg vs >5 mmHg)	0.73	0.22-2.43	0.605	0.49	0.13-1.84	0.293
Carvedilol	0.45	0.13-1.51	0.196			
Para-esophageal and para-gastric vessels	2.48	1.11-5.52	0.026	2.33	1.01-5.39	0.047
Ascites	0.70	0.32-1.54	0.371	0.52	0.21-1.31	0.165
Albumin (<35 g/L vs ≥35 g/L)	0.98	0.40-2.39	0.967	0.73	0.28-1.85	0.500
Portal vein thrombosis	1.20	0.48-3.03	0.693			
Hypertension	1.56	0.54-4.57	0.413			
Diabetes	0.72	0.27-1.93	0.517			
Endoscopic treatment method (EIC+EVL vs EIC/EVL)	0.78	0.35-1.76	0.549			

HVPG: hepatic venous pressure gradient; EIC: endoscopic injection of cyanoacrylate; EVL: endoscopic variceal ligation.

### 3 讨 论

侧支血管形成是门静脉血流动力学改变的特征之一。门静脉高压状态下，侧支血管主要来源于胃左静脉、胃后静脉、胃短静脉、肠系膜下静脉和脾肾分流，这些侧支血管可单独或同时存在；临幊上对这些侧支血管的评估依赖于B超、CT、MRI<sup>[14]</sup>。相关研究<sup>[15-16]</sup>认为，单一侧支循环对门静脉高压患者预后无明显影响。但另一项纳入1 729例患者的回顾性队列研究<sup>[17]</sup>表明，侧支循环增加门静脉高压患者并发症风险，与患者的不良预后有关，且其大小与患者肝功能状态相关，而这些影响与侧支循环种类无关。上述研究未纳入腔外血管团。

侧支循环中腔外血管团的存在提示门静脉高压持续时间长、压力高。目前基于CT影像评估食管胃腔外血管团与EGV患者内镜治疗疗效的研究较少。本课题前期研究<sup>[18]</sup>发现，存在胃腔外血管团与EGV患者内镜二级预防效果差相关（OR=5.374），治疗后再出血率高于无胃腔外血管团患者。本研究中，有食管胃腔外血管团的EGV出血患者内镜治疗后再出血风险更高，治疗后2年累积再出血率达60.07%，高于无腔外血管团组（32.79%）及一般EGV治疗后<sup>[19]</sup>，可能与本研究中GOV2型静脉曲张、合并门静脉血栓比例较高等因素有关。

本研究Cox回归分析显示，存在腔外血管团是EGV出血患者治疗后再出血的独立危险因素，而与肝硬化患者结局密切相关的HVPG、腹水和白蛋白水平对再出血无明显影响。内镜治疗后，局部侧支循环平衡被打破，侧支血管进一步发生结构改变以获得新的平衡，这可能同时增加了再出血风险。HVPG是评估静脉曲张破裂出血的重要参考指标，使HVPG低于12 mmHg或降低至少20%可减小出血风险<sup>[20]</sup>。而血管团存在可能影响HVPG检测的准确性，这可能是本研究中HVPG与再出血的相关性不明显的原因，此时通过直接测压或排除门体分流因素影响可能有助于获得更准确的结果。

内镜下套扎和组织胶注射能栓塞食管和胃腔内的曲张静脉，减少出血风险，而对腔外血管的影

响较小。CT影像中巨大的腔外血管可能表明腔内曲张静脉存在穿通支。EGV内镜治疗后再出血常与其相关。这部分患者通过多次内镜治疗后，可能仍然存在较为明显的静脉曲张或早期复发，此时很难再通过内镜治疗取得EGV根除和保证远期疗效，可能需要通过超声内镜引导穿刺壁外血管，置入弹簧圈联合组织胶栓塞腔外血管团，或通过经颈静脉肝内门体分流术降低门静脉压力，减小出血风险。此外，本研究分层分析显示，在有腔外血管团的患者中，联合卡维地洛治疗者2年累积再出血率低于未联合卡维地洛治疗者，表明有腔外血管团的患者可能从联合卡维地洛治疗中获益。

本研究存在一定的局限性：为单中心回顾性分析，纳入的样本量较小，同时排除出院失访、合并肿瘤和脾切除的患者，限制结论的推广应用，而且未分析内镜治疗次数，结论存在一定局限性。

综上所述，食管胃腔外血管的存在是EGV出血患者内镜治疗后再出血的独立预测因素，因此，对于内镜预防再出血的EGV出血患者，通过CT评估食管和胃腔外血管情况非常重要；当CT显示存在巨大腔外血管团时，建议充分评估后进行经颈静脉门体分流术等。

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