

## 急性期脑出血中组织因子途径抑制物、组织因子、纤维蛋白原、D-二聚体、超敏C反应蛋白的浓度及凝血因子VII所致的变化

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**【摘要】目的:**分析脑出血(ICH)患者组织因子途径抑制物(TFPI-1)、组织因子(TF)、纤维蛋白原(FIB)、D-二聚体、超敏C反应蛋白(hs-CRP)及凝血因子VII(FVII:C)的变化,为早期诊断ICH提供更多的实验依据。**方法:**随机抽取53例ICH患者及50例体检健康者,分别作为ICH组和正常对照组。采用双抗夹心酶联免疫吸附法测定两组血清中的TFPI-1、TF、FIB、D-二聚体、hs-CRP浓度;采用一期凝固法检测FVII:C(%);统计分析ICH组与正常对照组间的差异及三者(FIB、D-二聚体、hs-CRP)单检和联检对ICH的诊断效能。**结果:**ICH组的TFPI-1、TF、FIB、D-二聚体、hs-CRP浓度及FVII:C均高于对照组,差异有统计学意义( $P < 0.01$ )。血清FIB、D-二聚体及hs-CRP诊断ICH的受试者工作特征(ROC)曲线下面积分别为0.85(95%CI:0.720~0.980)、0.87(95%CI:0.731~0.970)及0.76(95%CI:0.590~0.930),三者联合检测诊断ICH的ROC曲线下面积为0.89(95%CI:0.760~0.980)。FIB、D-二聚体、hs-CRP三者联合检测的诊断灵敏度和特异度(89.5%、90.0%)较三者单检高(94.7%、75.0%)、(84.2%、90.0%)、(73.7%、89.1%)。**结论:**TFPI-1、TF、FIB、D-二聚体、hs-CRP水平及FVII:C与ICH的发生、发展有关;FIB、D-二聚体、hs-CRP三者联合检测可以提高诊断灵敏度和特异度。

**【关键词】**脑出血;组织因子;凝血因子VII;纤维蛋白原;D-二聚体;超敏C反应蛋白

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## Concentrations of tissue factor pathway inhibitor-1, tissue factor, fibrinogen, D-dimer, hypersensitive C-reactive protein, and differences caused by coagulation factor VII in acute stage of intracranial hemorrhage

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**Abstract: Objective** To provide more laboratory evidence for early diagnosis of intracranial hemorrhage (ICH) by analyzing the concentrations of tissue factor pathway inhibitor-1 (TFPI-1), tissue factor (TF), fibrinogen (FIB), D-dimer, hypersensitive C-reactive protein (hs-CRP), and differences caused by coagulation factor VII (FVII:C). **Methods** Totally, 53 ICH patients and 50 healthy persons were randomly selected and respectively taken as ICH group and normal control group. The concentrations of serum TFPI-1, TF, FIB, D-Dimer, hs-CRP in the two groups were detected by double-antibody sandwich enzyme-linked immuno sorbent assay; the activity of plasma F VII:C was detected by a one-stage clotting assay; the differences between the two groups, and the diagnosis efficiencies of single detection (FIB, D-Dimer, hs-CRP) and combined detection were statistically analyzed. **Results** The concentrations of TFPI-1, TF, FIB, D-Dimer, hs-CRP and FVII:C in ICH group were significantly higher than those in normal control group, with statistically significances ( $P < 0.01$ ). The area under the receiver operating characteristic (ROC) curve of serum FIB, D-Dimer and hs-CRP for the diagnosis of ICH were respectively 0.85 (95% CI: 0.720-0.980), 0.87 (95% CI: 0.731-0.970) and 0.76 (95% CI: 0.590-0.930). The area under the ROC curve of combined detections for the diagnosis of ICH was 0.89 (95% CI: 0.760-0.980). The sensitivity and specificity of detection combined FIB, D-Dimer and hs-CRP were respectively 89.5%, 90.0%, higher than those of three single detections which were respectively (94.7%, 75.0%), (84.2%, 84.2%),

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(73.7%, 89.1%). **Conclusion** The concentrations of TFPI-1, TF, FIB, D-Dimer, hs-CRP and FVII:C are associated with the development of ICH. And the detection combined FIB, D-Dimer and hs-CRP improves the sensitivity and specificity.

**Key words:** intracranial hemorrhage; tissue factor; coagulation factor VII; fibrinogen; D-dimer; hypersensitive C-reactive protein

## 前言

脑出血(ICH)是指脑中血管破裂引起的出血,出血对周围神经组织的压迫会导致患者瘫痪,甚至死亡<sup>[1-2]</sup>。在我国脑血管病患者中,急性患者占30%左右,急性期死亡率为30%~40%,ICH是导致中老年人死亡最主要的原因之一<sup>[3]</sup>。目前国内外学者对ICH实验诊断指标的研究逐渐增多,但根据凝血机制进行研究的报道较少,临床尚没有一种准确、有效方法来预测和诊断ICH。本文通过对比ICH患者与健康者中组织因子途径抑制物(TFPI-1)、组织因子(TF)、纤维蛋白原(FIB)、D-二聚体、超敏C反应蛋白(hs-CRP)浓度及凝血因子VII(FVII:C)的凝血系统变化,为ICH的早诊断早治疗提供更多依据<sup>[4]</sup>。

## 1 资料与方法

### 1.1 研究对象

本研究得到广州市第一人民医院伦理委员会批准,所有入组患者签署知情同意书,选取2015年1~6月ICH住院患者53例作为ICH组,诊断标准参照2015年美国ICH诊治指南<sup>[5]</sup>。另选50例本院体检健康者(包括本院退休职工)作为对照组。所有入选病例均排除肝肾功不全、急慢性感染、自身免疫性疾病、外科手术、创伤等。ICH组与对照组年龄、性别、高血压、高血脂及血肌酐水平差异均无统计学意义( $P>0.05$ ),具有可比性,基本资料如表1所示。

表1 ICH及对照组基本资料比较( $n, \%, \bar{x} \pm s$ )

Tab.1 Information of ICH group and normal control group ( $n, \%, Mean \pm SD$ )

Group	$n$	Age (Year)	Gender (male)	Hypertension	Hyperlipidemia	Serum creatinine (umol/L)
Normal control	50	56.30 $\pm$ 15.50	27 (54.00)	19 (38.00)	13 (26.00)	68.92 $\pm$ 26.22
ICH	53	57.80 $\pm$ 16.20	31 (58.49)	23 (43.40)	17 (32.07)	70.12 $\pm$ 25.45
$t/\chi^2$ value		2.25	5.73	6.91	3.19	1.67

ICH: Intracranial hemorrhage

### 1.2 实验原理

采集静脉血1.8 mL,并将其加入含有0.2 mL的枸橼酸钠溶液的一次性塑料针筒或真空采血管内,立即上下颠倒(10次)混匀,采血30 min内以2500~3000 r/min离心10~15 min,吸取上层血浆。采用双抗夹心酶联免疫吸附法,计算样本血清中TFPI-1、TF、FIB、D-二聚体、hs-CRP浓度。采用一期凝固法测定FVII:C,根据CA-1500全自动凝血分析仪器所得凝固时间,在标准曲线对应查出受检标本血浆VII:C数值(%)。

### 1.3 效能评价方法

采用受试者工作特征(Receiver Operating Characteristic, ROC)曲线分析,曲线下面积在0.50~0.70表示诊断价值较低;0.70~0.90表示诊断价值中等;0.9以上表示诊断价值较高。在ROC曲线分析中,采用灵敏度与特异度之和减去1,从而计算出约登指数,取约登指数最大的点作为最佳诊断截断值,并获得

其对应的灵敏度与特异度。

### 1.4 统计分析

采用SPSS 18.0统计软件,计量资料符合正态分布用均数 $\pm$ 标准差表示。若正态分布且方差齐则采用两个独立样本的 $t$ 检验进行比较分析;若非正态分布或方差不齐则采用K-S检验进行比较分析, $P<0.05$ 有统计学意义。

## 2 结果

### 2.1 TFPI-1浓度值结果

本研究收集ICH患者及健康体检人群共103例。与健康人群相比,急性期ICH患者的TFPI-1浓度、TF浓度、FVII:C、FIB、D-二聚体、hs-CRP都明显升高。TFPI、TF浓度、FVII:C活性值的结果如表2所示。

### 2.2 血清FIB、D-二聚体、hs-CRP对ICH诊断效能评价

血清FIB、D-二聚体及hs-CRP诊断ICH的ROC曲

表2 两组血浆TF、TFPI抗原浓度、FVII:C、FIB、D-二聚体、hs-CRP比较表( $\bar{x} \pm s$ )Tab.2 Comparison of TF, TFPI antigen concentration, FVII:C, FIB, D-dimer, hs-CRP between two groups ( $Mean \pm SD$ )

Group	n	TFPI (ng/mL)	TF (ng/L)	FVII:C (%)	FIB (g/L)	D-dimer ( $\mu$ g/L)	hs-CRP (mg/L)
ICH	53	32.66 $\pm$ 2.61*	4741.00 $\pm$ 1765.00*	202.75 $\pm$ 25.80*	4.32 $\pm$ 0.62*	1170.42 $\pm$ 879.17*	16.45 $\pm$ 6.32*
Normal control	50	16.76 $\pm$ 2.62	558.00 $\pm$ 279.00	194.20 $\pm$ 36.70	2.98 $\pm$ 1.00	131.05 $\pm$ 99.83	5.94 $\pm$ 3.91
t/ $\chi^2$ Value		490.00	510.00	2.25	566.00	511.00	6.28

Compared with normal control group, significant differences were found between two groups, \* $P < 0.001$ .

TF: Tissue factor; TFPI: Tissue factor pathway inhibitor; FVII:C: Coagulation factor VII; FIB: Fibrinogen; hs-CRP: Hypersensitive C-reactive protein

线下面积分别为0.85(95%CI:0.720~0.980)、0.87(95%CI:0.731~0.970)及0.76(95%CI:0.590~0.930),三者联合检测诊断ICH的ROC曲线下面积为0.89(95%CI:0.760~0.980),即FIB、D-二聚体、hs-CRP单检及三者联检对ICH诊断有中等价值。血清FIB诊断ICH的最佳截断值为3.33 g/L,对应的诊断灵敏度和特异度分别为94.7%、75.0%;血清D-二聚体诊断ICH的最佳截断值为275.00  $\mu$ g/L,对应的诊断灵敏度和特异度分别为84.2%、90.0%;血清hs-CRP诊断ICH的最佳截断值为12.70 mg/L,对应的诊断灵敏度和特异度分别为73.7%、89.1%;三者联检的诊断灵敏度和特异度分别为89.5%、90.0%,即三者联检的灵敏度、特异度均高于单检。

### 3 讨论

ICH是我国脑血管疾病死亡率最高的临床类型,与病理性血管壁受损密切相关。本次研究发现ICH组的TFPI-1、TF浓度较正常人群明显升高,同时FVII%亦较正常组增强,可能是脑血管破裂时释出大量TF进入血液循环中,在Ca<sup>2+</sup>存在条件下,TF通过细胞外区与FVII激活并结合,形成TF/FVIIa复合物<sup>[6-7]</sup>,进而激活内外源凝血系统<sup>[8]</sup>。TFPI-1有3个功能结构域(K1、K2、K3)对TF起抑制作用,对FVII也有负反馈调节<sup>[9-10]</sup>。其中,K1与TF/FVIIa复合物发生静电相互作用;K2抑制FXa的活性;K3使K2结构域结合到FXa上,通过分别与FXa和TF/FVa复合物结合而产生抗凝作用<sup>[11]</sup>。Monteiro等<sup>[12]</sup>研究发现弥散性血管内凝血(DIC)患者早期血液呈高凝状态,血液中TFPI及TF血浆浓度较正常明显增高。本研究证明急性ICH患者的凝血-纤溶系统发生病理性变化,存在高凝状态,这为早期诊断ICH提供方向。

FIB、D-二聚体、hs-CRP是临床反应心脑血管病的指标,较TF、TFPI、FVII%常用,可为ICH病情转归评估等提供有价值的信息。高浓度的FIB与冠状动脉病变程度明显相关,其作用途径在于高浓度的FIB

能够增强血小板膜上某些糖蛋白受体如CD62PE的表达,从而促进血小板活化,使不稳定心绞痛患者在心梗前的FIB水平常升高<sup>[13]</sup>。C反应蛋白是由肝脏合成的一种全身性炎症反应急性期的非特异性标志物,研究指出急性脑梗死患者的CRP升高者预后不佳,与梗死面积、神经功能缺损程度相关<sup>[14]</sup>。2003年欧洲高血压防治指南正式推荐高血压患者需检测hs-CRP水平<sup>[15]</sup>。D-二聚体交联碎片可反映血栓形成后的溶栓活性。

本文发现血清FIB、D-二聚体、hs-CRP对ICH诊断有中等价值,三者联检对ICH诊断有较高价值。在ROC曲线下D-二聚体面积最大,hs-CRP特异度高,因而D-二聚体面积与hs-CRP结合的诊断价值更高,但FIB诊断ICH的灵敏度高于D-二聚、C反应蛋白,三者联合检测可弥补二者的不足,既可提高灵敏度,也能提高特异度,推荐用三者联检辅助诊断ICH。

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