

· 老年人肺血管疾病专栏 ·

血浆D-二聚体水平与肺动脉血栓负荷相关性研究

方春晓¹, 安俊¹, 季颖群^{1*}, 孙博², 李智勇², 张中和¹

(大连医科大学附属第一医院: ¹呼吸科, ²放射科, 大连 116011)

【摘要】目的 分析血浆D-二聚体(DD)水平与肺动脉血栓负荷的相关性。**方法** 顺次选取2009年1月至2011年8月间大连医科大学附属第一医院采用CT肺动脉造影(CTPA)首次确诊急性肺血栓栓塞症(PTE)患者69例。采用Mastora评分系统获得肺动脉阻塞指数(PAOI; PAOI>21.3%提示预后不良风险增加); CT影像测得右(RV)及左(LV)心室短轴直径, 计算两者比值(RV/LV>0.9提示右心功能不全)。采用免疫比浊法测定血浆DD。结果 血浆DD浓度中位数为765μg/L(95%CI: 750~1205μg/L), PAOI中位数为16.77%(95%CI: 16.49%~23.26%)。血浆DD水平与整体肺动脉PAOI呈正相关($r=0.417$, $P=0.000$)。PAOI>21.3%患者的血浆DD浓度(993μg/L)高于PAOI≤21.3%的患者(663μg/L), 差异有统计学意义($Z=-2.991$, $P=0.003$)。血浆DD水平与RV/LV之间呈正相关性($r=0.272$, $P=0.024$)。RV/LV>0.9患者的血浆DD浓度(880μg/L)高于RV/LV≤0.9的患者(634μg/L), 两者之间差异有统计学意义($Z=-2.070$, $P=0.038$)。整体肺动脉PAOI与RV/LV之间呈正相关($r=0.390$, $P=0.001$)。血浆DD水平与PTE发病时间呈负相关($r=-0.407$, $P=0.000$); PAOI与发病时间无相关性($r=-0.140$, $P=0.245$)。老年组(年龄>60岁)患者, 其DD水平(727μg/L)和PAOI(14.84%)与非老年组(年龄≤60岁; 792.5μg/L, 20.97%)比较, 差异均无统计学意义($Z=-0.180$, $P=0.857$; $Z=-1.382$, $P=0.167$)。规范抗凝3个月后, DD和PAOI水平均显著下降($Z=-6.976$, $P=0.000$; $Z=-7.009$, $P=0.000$), 二者具有相关性($r=0.609$, $P=0.000$)。结论 (1) DD水平与CTPA肺动脉新鲜血栓负荷和RV/LV呈正相关, 有助于急性PTE患者临床评估病情、指导治疗和判断预后。(2) 老年组与非老年组急性PTE患者的DD和PAOI水平差异无统计学意义。

【关键词】D-二聚体; 肺栓塞; 肺动脉阻塞指数; CT肺动脉造影

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Correlation of D-dimer level with clot burden of pulmonary embolism: report of 69 cases

FANG Chun-Xiao¹, AN Jun¹, JI Ying-Qun^{1*}, SUN Bo², LI Zhi-Yong², ZHANG Zhong-He¹

(¹Department of Respiratory Diseases, ²Department of Radiology, the First Affiliated Hospital of Dalian Medical University, Dalian 116011, China)

【Abstract】 Objective To determine the correlation of plasma level of D-dimer (DD) with clot burden of pulmonary embolism. **Methods** A prospective study was performed on 69 consecutive patients with acute pulmonary thromboembolism (PTE) confirmed by computed tomographic pulmonary angiography (CTPA) in our hospital from January 2009 to August 2011. A pulmonary artery obstruction index (PAOI, Mastora score) > 21.3% indicated severe obstruction of PTE. A right ventricle/left ventricle (RV/LV) > 0.9 indicated RV dysfunction. The plasma level of DD was determined by immunoturbidimetric assay. **Results** The median DD level was 765μg/L (95%CI: 750~1205μg/L) and that of PAOI was 16.77% (95%CI: 16.32%~23.06%). Plasma DD level was positively correlated with PAOI ($r=0.417$, $P=0.000$). The patients with PAOI > 21.3% had significantly higher DD levels than those with PAOI ≤ 21.3% (993 vs 663μg/L, $Z=-2.991$, $P=0.003$). DD level was positively correlated with RV/LV ($r=0.272$, $P=0.024$). The patients with RV/LV > 0.9 had obviously higher DD levels than those with RV/LV ≤ 0.9 (880 vs 634μg/L, $Z=-2.070$, $P=0.038$). There was a positive correlation between PAOI and RV/LV ($r=0.390$, $P=0.001$). Negative correlation was found in the PTE onset time with DD level ($r=-0.407$, $P=0.000$), but not with PAOI ($r=-0.140$, $P=0.245$). There was no significant difference in the DD level and PAOI between the elderly patients (> 60 years old) and those younger (≤ 60 years old) (727.0 vs 792.5μg/L, $Z=-0.180$, $P=0.857$; 14.84% vs 20.97%, $Z=-1.382$, $P=0.167$). After 3 months' standard anticoagulant therapy, both DD level and

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通信作者: 季颖群, E-mail: jiyingqun@163.com

PAOI were decreased in the cohort ($Z = -6.976, P = 0.000$; $Z = -7.009, P = 0.000$), and their decreases were correlated ($r = 0.609, P = 0.000$). **Conclusion** DD level is positively correlated with CTPA clot burden and RV/LV respectively, and is helpful in illness assessment, management guidance and prognostic evaluation for the acute PTE patients. There is no significant difference in DD level and PAOI between the patients older and less than 60 years.

【Key words】 D-dimer; pulmonary embolism; pulmonary artery obstruction index; computed tomographic pulmonary angiography
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Corresponding author: JI Ying-Qun, E-mail: jiyingqun@163.com

肺血栓栓塞症 (pulmonary thromboembolism, PTE) 是一种常见并具有潜在致死性的疾病, 占心血管系统死亡原因第3位, 仅次于心肌缺血及脑血管疾病^[1]。由于血浆D-二聚体 (D-dimer, DD) 水平检测具有快速、定量、价格低、重复性好等优点, 其对PTE的阴性预测价值现已得到公认。近年有研究表明血浆DD水平与PTE严重程度呈正相关, 也可作为PTE短期及中期死亡率的预测指标^[2,3]。另外, CT肺动脉造影 (computed tomographic pulmonary angiography, CTPA) 已成为确定PTE诊断的一线检查方法, 不仅可直接观察是否存在血栓及血栓位置、形态, 还可量化血栓负荷 [肺动脉阻塞指数 (pulmonary artery obstruction index, PAOI)], 并测量心血管参数, 从而评估PTE严重程度^[4,5]。本文研究血浆DD水平与CTPA肺动脉血栓负荷相关性。

Galle等^[6]首次提出急性PTE患者DD水平 (Asserachrom D-dimer) 与通气/灌注 (V/Q) 扫描的肺灌注缺损程度相关。随后, Kucher等^[7]研究表明PTE患者采用校正的Mille指数方法, 血栓负荷与DD水平 (法国生物梅里埃公司全自动免疫分析系统测定) 呈正比。另外, Ghanima等^[8]报道了采用Qanadli评分法, DD水平与CTPA的血栓负荷相关。Jeebun等^[9]也通过Qanadli评分法证实DD水平与CTPA的血栓负荷和右室功能不全相关。

然而, Qanadli评分法仅仅将肺动脉阻塞程度分为完全阻塞或部分阻塞予以评分^[8~10]。Mastora评分系统则对Qanadli评分法进行补充, 其优势在于通过五分制法对每支肺动脉进行阻塞程度评估, 进一步提供了肺动脉远端血栓的肺灌注状态。Mastora评分是最佳的肺动脉阻塞严重程度的评估方法, 因为不是通过近端血管阻塞程度来推测远端血管情况。上述二者的不同之处非常重要, 因为近端血管阻塞并不是影响远端血管血流的必要条件, 所以, 每一支中心肺动脉进行各自评分。而且, Mastora评分系统采用血流动力学“敏感”的五分制方法对每一支动脉分支进行阻塞等级评估^[11~13]。

目前尚无采用Mastora评分法探讨PTE严重程度与血浆DD水平相关性的报道。本研究目的是应用Mastora评分法探索CTPA影像严重程度与血浆DD

水平是否相关。

1 对象与方法

1.1 研究对象

顺次选取2009年1月至2011年8月大连医科大学附属第一医院采用CTPA首次确诊为急性PTE, 并在确诊前后24h内测定血浆DD水平的患者。排除标准: 明确诊断慢性血栓栓塞性肺动脉高压、既往明确静脉血栓栓塞性病史、血液系统疾病和妊娠。入选患者共69例, 男性34例 (49.3%), 女性35例 (50.7%), 年龄22~85 (58 ± 15) 岁。并将入选病例分为老年组 (>60岁) 和非老年组 (≤ 60 岁), 老年组31例, 男性16例, 女性15例; 非老年组38例, 男性18例, 女性20例。记录性别、年龄、基础疾病、诱发因素、发病时间 (从出现PTE症状至CTPA确诊时间)、临床表现等。

1.2 血浆DD检测

应用高敏免疫比浊法测定血浆DD水平, 正常人血浆DD < 300 μ g/L。

1.3 CTPA成像

所有患者行CT胸部平扫和肺动脉增强扫描, 应用GE light-speed 16排螺旋CT。扫描参数: 管电压120kV, 管电流260mA, 准直器宽度 16×0.625 mm, 层厚1.25mm, 螺距0.938:1, 扫描范围为肺部, 转数: 0.6s/r。增强扫描: 肘静脉以4ml/s注入碘普罗胺 (优维显, 碘浓度为370g/L) 进行增强扫描, 注射造影剂与显像的延迟时间为14s。CTPA影像阅读由至少>2名肺血管专业影像学医师进行双盲阅片。

1.4 PAOI

采用Mastora^[11]评分系统量化血栓负荷 (PAOI), PAOI > 21.3% 提示早期预后不良风险增加^[12]。

1.5 右心室及左心室短轴直径比值

CTPA影像四腔心层面测定右心室 (right ventricle, RV) 及左心室 (left ventricle, LV) 短轴直径, 计算两者比值 (right/left ventricular short axis diameter ratio, RV/LV), RV/LV > 0.9 提示右心室功能不全 (right ventricular dysfunction, RVD)^[13,14]。

1.6 随访

3个月后随访，复查血浆DD水平和CTPA。

1.7 统计学处理

应用SPSS19.0统计软件进行统计分析。应用Spearman相关系数及t检验、 χ^2 检验、Mann-Whitney检验或Wilcoxon符号秩检验。以 $P < 0.05$ 为差异有统计学意义。

2 结 果

2.1 两组患者临床资料比较

两组患者在性别以及有无诱发因素、基础疾病、晕厥、下肢深静脉血栓形成的临床资料方面比较，差异均无统计学意义 ($P > 0.05$ ；表1)。

表1 两组患者临床资料比较

Table 1 Comparison of clinical data between two groups
[n(%)]

Item	Elderly group (n = 31)	Non-elderly group (n = 38)	χ^2	P value
Gender			0.123	0.726
Male	16 (51.6)	18 (47.4)		
Female	15 (48.4)	20 (52.6)		
Precipitating factors			0.084	0.771
Yes	8 (25.8)	11 (28.9)		
No	23 (74.2)	27 (71.1)		
Underlying diseases			3.522	0.061
Yes	12 (38.7)	7 (18.4)		
No	19 (61.3)	31 (81.6)		
Syncope			0.000	1.000
Yes	4 (12.9)	5 (13.2)		
No	27 (87.1)	33 (86.8)		
Deep vein thrombosis			0.002	0.962
Yes	23 (74.2)	28 (73.7)		
No	8 (25.8)	10 (26.3)		

Precipitating factors include trauma, surgery, immobility, and oestrogen use. Underlying diseases include chronic heart disease, chronic lung disease, cancer, cerebrovascular disease, varicosity, diabetes mellitus, and connective tissue disease. The diagnosis of deep vein thrombosis is confirmed by computed tomographic venography or compression ultrasound

2.2 血浆DD水平与PAOI、RV/LV的相关性

69例患者血浆DD浓度中位值为765 $\mu\text{g}/\text{L}$ (95%CI: 752~1207 $\mu\text{g}/\text{L}$)，PAOI中位值为16.77% (95%CI: 16.49%~23.26%)。血浆DD水平与整体肺动脉PAOI呈正相关 ($r = 0.417$, $P = 0.000$; 图1)。血浆DD水平与RV/LV呈正相关 ($r = 0.268$, $P = 0.027$; 图2A)。PAOI与RV/LV呈正相关 ($r = 0.390$, $P = 0.001$; 图2B)。

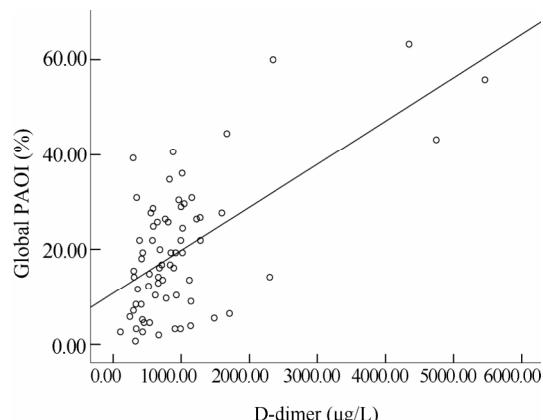


图1 D-二聚体与肺动脉阻塞指数的关系
Figure 1 Correlation between D-dimer and pulmonary artery obstruction index

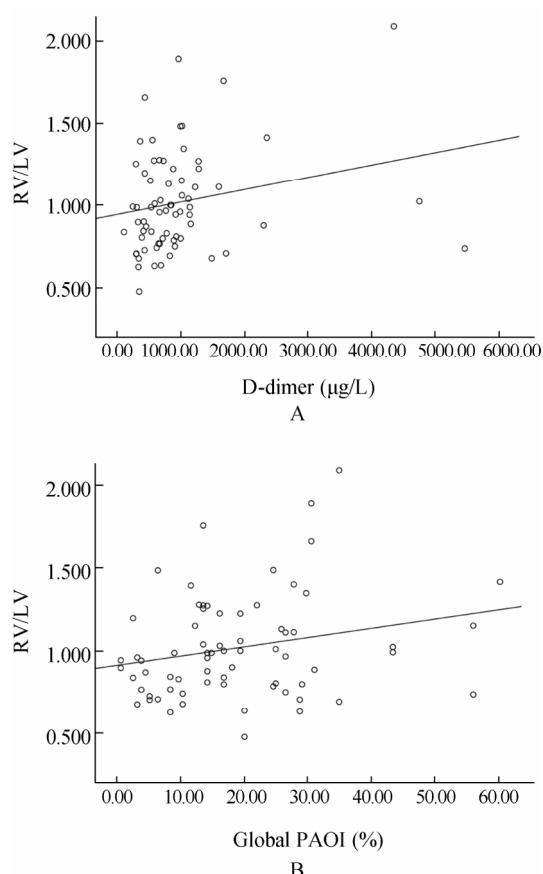


图2 右心室与左心室短轴直径比值与D-二聚体、肺动脉阻塞指数的关系
Figure 2 Correlations among RV/LV, D-dimer and PAOI
RV/LV: right/left ventricular short axis diameter ratio; PAOI: pulmonary artery obstruction index. A: correlation between RV/LV and D-dimer; B: correlation between RV/LV and PAOI

PAOI > 21.3%的患者29例 (42.03%)，其血浆DD中位值为993 $\mu\text{g}/\text{L}$ (95%CI: 856~1841 $\mu\text{g}/\text{L}$)，PAOI ≤ 21.3%患者40例 (57.97%)，其血浆DD中位值663 $\mu\text{g}/\text{L}$ (95%CI: 572~846 $\mu\text{g}/\text{L}$)，两者差异有统计学意义 ($Z = -2.991$, $P = 0.003$; 图3A)。根据受试者工作特征 (receiver operating characteristic, ROC) 曲线可得血浆DD浓度为

746 $\mu\text{g/L}$ 时，预测PAOI>21.3%的敏感度为36.6%，特异度为28.6%（曲线下面积为0.287；图4）；其中血浆DD>746 $\mu\text{g/L}$ 的患者35例，PAOI均值为 $24.99\% \pm 15.65\%$ ；而DD≤746 $\mu\text{g/L}$ 的患者34例，PAOI均值为 $14.29\% \pm 9.49\%$ ，两者差异有统计学意义（ $t = 3.447$, $P = 0.031$ ）。

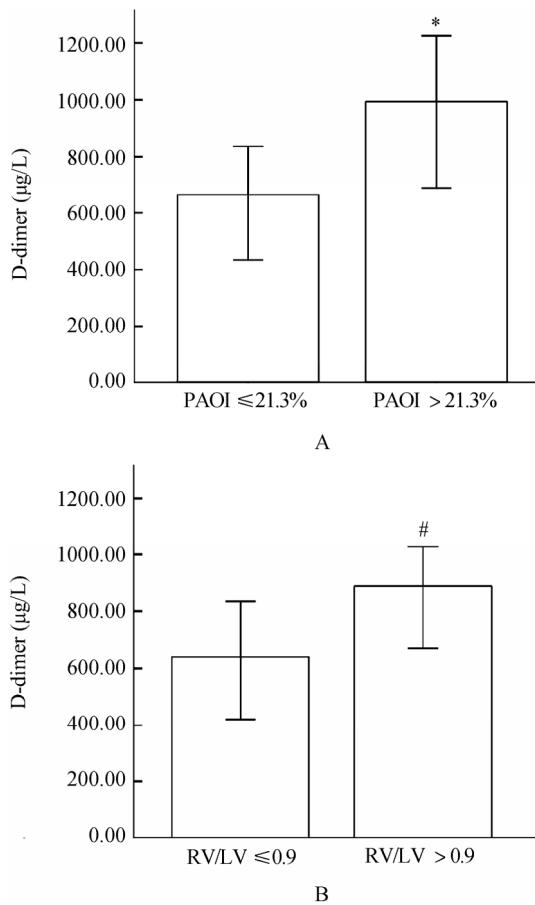


图3 不同组别患者D-二聚体浓度比较

Figure 3 Comparison of D-dimer level in different groups
RV/LV: the ratio of end-diastolic right ventricular diameter to left ventricular diameter; PAOI: pulmonary artery obstruction index. A: comparison of D-dimer level between the groups with PAOI $> 21.3\%$ and PAOI $\leq 21.3\%$; compared with PAOI $\leq 21.3\%$, $*P = 0.003$. B: comparison of D-dimer level between the groups with $\text{RV/LV} > 0.9$ and $\text{RV/LV} \leq 0.9$; compared with $\text{RV/LV} \leq 0.9$, $#P = 0.038$

$\text{RV/LV} > 0.9$ 的患者37例（53.6%），其血浆DD中位值为880 $\mu\text{g/L}$ （95%CI：767~1392 $\mu\text{g/L}$ ）， $\text{RV/LV} \leq 0.9$ 的患者32例（46.4%），其血浆DD中位值为634 $\mu\text{g/L}$ （95%CI：519~1211 $\mu\text{g/L}$ ），两者差异有统计学意义（ $Z = -2.070$, $P = 0.038$ ；图3B）。根据ROC曲线可得血浆DD浓度为721 $\mu\text{g/L}$ 时，预测RVD的敏感度为64.9%，特异度为62.5%（曲线下面积为0.645；图5）；其中血浆DD>721 $\mu\text{g/L}$ 的患者36例，RV/LV均值为 1.095 ± 0.334 ，而DD≤721 $\mu\text{g/L}$ 的患者33例，RV/LV均值为 0.934 ± 2.267 ，两者差异有统计学意义（ $t = 2.206$, $P = 0.001$ ）。

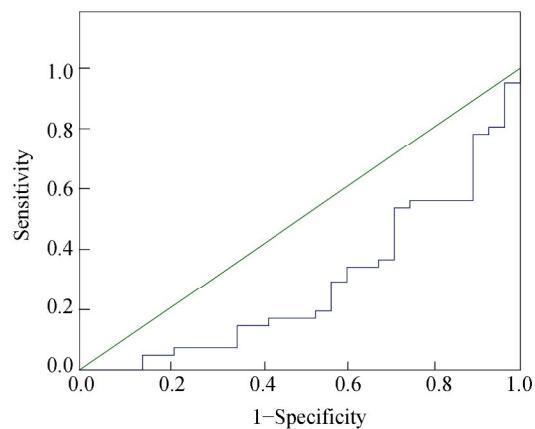


图4 D-二聚体用于预测PAOI $> 21.3\%$ 的ROC曲线
Figure 4 ROC curve for prediction of PAOI $> 21.3\%$ by D-dimer
PAOI: pulmonary artery obstruction index

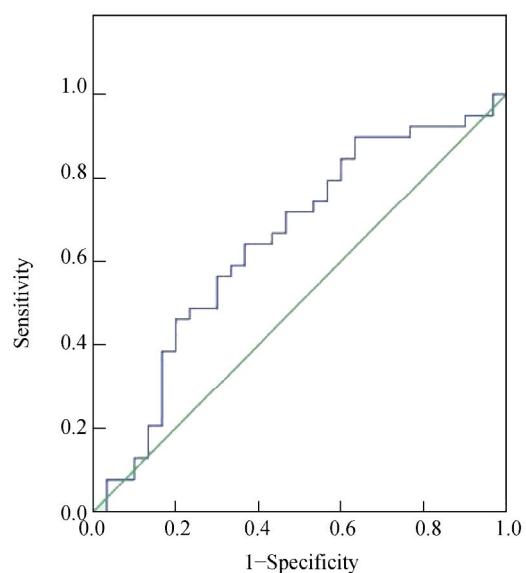


图5 D-二聚体用于预测RVD的ROC曲线
Figure 5 ROC curve for prediction of RVD by D-dimer
RVD: right ventricular dysfunction

2.3 血浆DD水平、PAOI与发病时间的相关性

69例患者发病时间中位数为2d（1h~15d）。血浆DD水平与发病时间之间呈负相关（ $r = -0.407$, $P = 0.001$ ；图6）。整体肺动脉PAOI与发病时间不存在相关性（ $r = -0.140$, $P = 0.252$ ；图7）。

2.4 血浆DD水平与PTE和（或）深静脉血栓（deep vein thrombosis, DVT）的关系

单纯PTE(无DVT)者18例, DD中位值611.5 $\mu\text{g/L}$ （95%CI: 458.93~1426.62 $\mu\text{g/L}$ ）；PTE伴DVT者51例, 血浆DD水平807 $\mu\text{g/L}$ （95%CI: 726.66~1259.40 $\mu\text{g/L}$ ），两者差异无统计学意义（ $Z = -0.806$, $P = 0.420$ ）。

2.5 年龄与血浆DD水平、PAOI的关系

老年组和非老年组血浆DD水平中位值分别为727 $\mu\text{g/L}$ （95%CI: 638.43~1203.23 $\mu\text{g/L}$ ）、792.5 $\mu\text{g/L}$

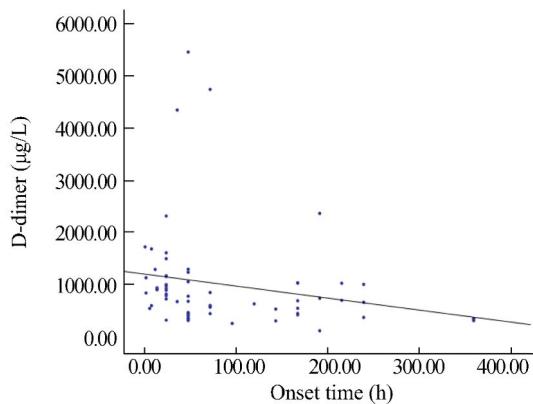


图6 D-二聚体水平与发病时间的关系

Figure 6 Correlations between D-dimer level and pulmonary thromboembolism onset time

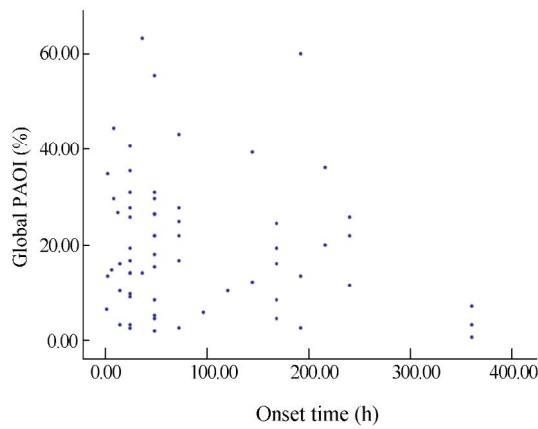


图7 PAOI与发病时间的关系

Figure 7 Correlations between PAOI and PTE onset time
PAOI: pulmonary artery obstruction index; PTE: pulmonary thromboembolism

(95%CI: 670.31~1397.86 $\mu\text{g}/\text{L}$),两者差异无统计学意义($Z = -0.180$, $P = 0.857$)。两组PAOI中位数分别为14.84% (95%CI: 12.79%~21.11%)、20.97% (95%CI: 17.02%~27.50%),两者差异无统计学意义($Z = -0.1382$, $P = 0.167$)。

2.6 治疗和随访

69例PTE患者中,2例溶栓治疗,67例抗凝治疗。3个月后随访,其中65例(失访4例)患者规范抗凝并复查血浆DD水平和CTPA,DD水平和PAOI均显著下降($Z = -6.976$, $P = 0.000$; $Z = -7.009$, $P = 0.000$;图8),两者具有相关性($r = 0.609$, $P = 0.000$),其中44例患者(67.69%)复查CTPA提示血栓完全吸收,余21例患者PAOI值波动于0.65%~5.16%;血浆DD水平中位数下降至190 $\mu\text{g}/\text{L}$ (95%CI: 179.69~238.61 $\mu\text{g}/\text{L}$),恢复到正常值范围内。

3 讨论

本研究结果证实,血浆DD水平与整体肺动脉PAOI呈正相关,表明DD水平(765 $\mu\text{g}/\text{L}$)与CTPA

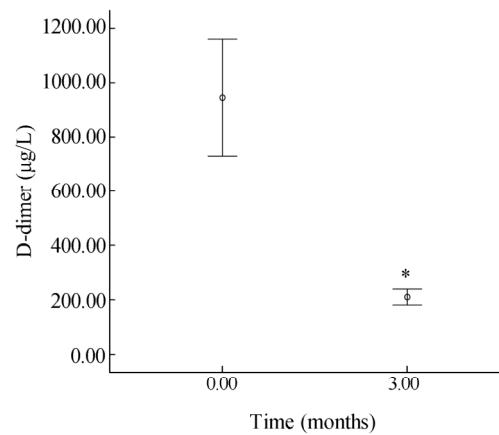


图8 治疗前后D-二聚体浓度和PAOI变化

Figure 8 Comparison of D-dimer level and PAOI before and after treatment

PAOI: pulmonary artery obstruction index. A: comparison of D-dimer level before and after treatment; compared with before treatment,

* $P = 0.000$. B: comparison of PAOI before and after treatment;

compared with before treatment, # $P = 0.000$

影像所示血栓负荷(16.77%)程度呈正比,即血栓或栓子负荷越多,血浆DD水平越高,与较低血栓负荷相比,较高栓子负荷能产生较多的纤维蛋白降解产物,上述结果与Galle等^[6]、Kucher等^[7]、Ghanima等^[8]及Jeebun等^[9]研究结果相似。并且,我们创新性地同时随访CTPA和DD,结果表明,规范抗凝3个月后大部分患者(67.69%)血栓完全吸收,部分(32.31%)残留血栓患者PAOI水平也明显下降(0.65%~5.16%);而血浆DD水平中位数(190 $\mu\text{g}/\text{L}$)则恢复到正常值范围内,两者仍具有相关性。因此,我们可通过定期监测DD水平评估急性PTE患者的血栓负荷,进一步指导治疗和判断预后。

Engelke等^[12]研究证实,PAOI>21.3%是PTE患者早期死亡的重要预测因子,其风险可增加约6.7倍($P = 0.017$);而PAOI≤21.3%的患者经规范抗凝后可获得较长期生存率。多项研究^[13~15]证实CTPA影像提示右室功能不全($RV/LV > 0.9$)的PTE患者预后不良。本研究结果证实,血浆DD水平和PAOI

均与RV/LV呈正相关；PAOI > 21.3%的患者血浆DD中位值高于PAOI ≤ 21.3%的患者；RV/LV > 0.9的患者血浆DD中位值高于RV/LV比值 ≤ 0.9的患者。因此，我们可通过定期监测DD水平评估急性PTE患者病情严重程度和危险分层。

另外，本研究创新性地探索了DD和PAOI水平与发病时间的相关性。结果证实，血浆DD水平与发病时间之间呈负相关；而整体肺动脉床的PAOI与发病时间不存在相关性。从而进一步表明，血浆DD水平是与“新鲜”血栓负荷呈正相关的。

近年来，多项回顾性研究^[16-19]证实DD的阈值与年龄相关，建议使用年龄校正的DD阈值，即年龄 > 50岁患者，DD阈值为年龄 × 10 μg/L（包括Vidas®、Tinaquant®、HemosIL-DD®、Liatest®和MDA®等检测方法），然而，对于明确诊断PTE的患者，年龄与DD和PAOI的关系尚未得到关注，本研究创新性地对比研究老年组（> 60岁）和非老年组（≤ 60岁）DD和PAOI水平，结果表明二者在两组患者中差异均无统计学意义。

4 结 论

DD水平与CTPA肺动脉新鲜血栓负荷和RV/LV呈正相关，因其检测方法的简便性、可重复性和应用普遍性，有助于急性PTE患者的临床评估病情、指导治疗和判断预后。老年与非老年急性PTE患者的DD和PAOI水平差异无统计学意义。

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· 消息 ·

《中华老年多器官疾病杂志》“临床病理讨论”栏目征稿

临床病理讨论 (Clinicopathological Conference, CPC) 是临床实践中的一个重要环节, 是多个学科合作对患者进行个体化诊治的一种形式, 尤其对于一些疑难和罕见病例更为重要。综合患者的临床表现、实验室检查、影像学检查和病理检查等各项结果, 一方面可以明确疾病的诊断并制定治疗方案, 使患者受益, 另一方面亦有利于为临床医师提供更好的经验和更开阔的思路, 提高医师的诊疗能力。一篇好的临床病理讨论, 往往是教科书上找不到的活教材, 也是其他文体难以取代的好形式。

“临床病理讨论”一直以来都是本刊的一个特色栏目, 深受广大读者喜爱。所刊登的一般多为回顾性的病例讨论与总结, 旨在总结经验、吸纳教训和传播知识。在工作实践中, 我们根据广大读者和作者的建议, 对临床病理讨论文章的格式进行了调整。(1) 作者在文题下署名(而非仅在文末注明由何人整理), 作者拥有本文的著作权。(2) 文章正文为中文(而非以前的中英文对照), 正文前有言简意赅的中英文摘要。论文性质等同于本刊“论著”。(3) 所选病例可以是疑难、罕见病例, 也可以是诊断明确、但病情危重或有诸多并发症、治疗上甚为棘手的病例, 亦可为其他对临床实践有指导或提示意义的病例。

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具体格式请参考本刊近期发表的“临床病理讨论”文章。

地址: 100853 北京市复兴路28号, 《中华老年多器官疾病杂志》编辑部

电话: 010-66936756

网址: <http://www.mode301.cn>

E-mail: zhlnldqg@mode301.cn