肺血栓栓塞症诊断性试验的系统评价

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[摘要] 目的 对已发表的肺血栓栓塞症确诊性试验进行系统评价,为肺血栓栓塞症临床诊断提供决策证据。方法 检索相关文献,根据纳入标准筛选文献,利用 SPSS 和 RevMan 软件计算优势比、阳性似然比及阳性预测值,绘制汇总受试者工作特征曲线,比较曲线下面积,最后进行敏感性分析。结果 从 385 篇文献中选出符合纳入标准的 21 篇文献共 22 个研究,合并优势比、阳性似然比和阳性预测值表明,磁共振成像的诊断价值最高,其次分别为 CT 肺动脉造影、放射性核素肺通气/灌注显像及下肢多普勒血管超声检查;总受试者工作特征曲线综合分析显示,CT 肺动脉造影和磁共振成像的总受试者工作特征曲线几乎重叠在一起,以磁共振成像的诊断价值最大,部分试验的合并效应量比较差异无统计学意义。结论 本分析研究结果显示出一定的临床趋势,磁共振成像可能是诊断肺血栓栓塞症准确性最高的试验,但尚需更多高质量研究以增加证据的强度,并且随着检查技术的改进应不断更新荟萃分析的结论。

[关键词] 肺栓塞; 诊断性试验; Meta 分析; 系统评价
[中图分类号] R563.5 [文献标识码] A [文章编号] 1671- 5144(2008)03- 0147- 06

A Systematic Review of Diagnostic Tests for Pulmonary Embolism

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Abstract: Objective To assess diagnostic tests for pulmonary thromboembolism (PTE) systematically so as to provide decision-making evidence for clinical screening and diagnosis. Materials and methods The electronic databases were searched, including Chinese Biomedicine Database (CBM), CNKI, MEDLINE, Cochrane Library, and CEBM/CCD. We handsearched the data from the references of all included studies, Chinese journals related to diagnosis and the proceeding of correlated conferences. Criteria for inclusion and exclusion were established according to validity criteria for diagnostic research published by the Cochrane Methods Group on Screening and Diagnostic Tests. The studies meeting the inclusion criteria were selected, and their methodological quality was assessed. Data of these studies were extracted via the data extraction form. Heterogeneity of the included articles was tested, which was used to select appropriate effect model to calculate pooled odds ratio, likelihood ratio, predictive value, and the according 95% confidence intervals. Summary receiver operating characteristic curve was performed and the area under the curve was calculated. Finally, sensitivity analysis was performed. Statistical analysis was performed with SPSS and RevMan 4.2 software. Results Twenty-one articles of 385 retrieved articles were included, with a total of twenty-two studies, including positive computed tomography pulmonary angiography (CTPA), positive magnetic resonance imaging (MRI), high probability ventilation/perfusion scanning and positive leg vein doppler vascular ultrasound the pooled indexes of diagnostic performance of positive MRI was higher than the others. In patients with a high pretest probability, these

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findings were associated with a positive predictive value (PPV) greater than 85% of pulmonary embolism. The rest findings were associated with a PPV of pulmonary embolism below 85%. But some results had no statistical significance (P>0.05). The results of sensitivity analysis were consistent with the above. Conclusions Based on the systematic review of current eligible clinical trials, there aren't enough available evidences to support the selection of which test would be the best for diagnosis or screen the pulmonary embolism. MRI may be regarded as an effective and feasible diagnostic test for pulmonary embolism. Conclusions of meta-analysis will be displaced if the methodology of diagnostic test has been improved.

Key words: pulmonary embolism; diagnostic test; meta-analysis; systematic review

诊断肺血栓栓塞症(pulmonary thromboembolism, PTE)**的金标准——肺动脉造影**(pulmonary arteriography, PA)**是一种有创且费用较高的检查,临床应用受到一定限制;随着** CT **肺动脉造影**(computed tomography pulmonary angiography, CTPA)**和磁共振成像**(magnetic resonance imaging, MRI)**等无创技术的日趋成熟,其在** PTE **诊断中的作用越来越大。但是目前尚无证明** PTE **诊断性试验有效性的系统评价,也无对** PTE **诊断性试验的经济学效益和安全性进行评价的研究,本研究拟借助** Cochrane **系统,对** 2006 **年** 2 **月以前国内外所发表的** PTE **的诊断性试验进行评价,期望能依据现有的研究证据为临床医师选择适当的检查方法提供循证医学的证据。**

1 材料与方法

1.1 纳入与排除标准

按照 Cochrane **协作网关于诊断性试验研究的标准确定试验的纳入和排除标准**[1]**:纳入以** PA **为金标准且样本量至少在** 30 **例以上的前瞻性研究;排除失访率在** 5%**以上的研究。**

1.2 文献的检索和筛选

(1)**电子检索中国生物医学文献数据库、中国期刊全文数据库、**MEDLILE **光盘数据库、**Cochrane **图书馆以及中国循证医学/**Cochrane **中心数据库等数据库,并进行手工检索和其他的检索,如有关会议论文集、毕业论文、专著等。检索策略如下:①中文:肺栓塞[主题词] AND (肺* 造影 OR 随访);②英文:**(Sensitivity and Specificity/[Mesh terms] OR False Positive Reactions/[Mesh terms] OR False Negative Reactions/[Mesh terms]) AND Pulmonary Embolism/[Mesh terms] AND (pulmonary arteriography OR pulmonary angiography);③**语种仅限为中文或英文,研究对象限制在"人类",并将"综述"、"信件"、"病例报告"及"评论"类型的文章排除。**

(2)**在筛选文献和提取资料时由两名评价员根据既定的纳入和排除标准独立进行筛选,遇到不一致时协商讨论。**

1.3 评价文献的质量

根据 Cochrane **协作网推荐的诊断性试验的纳入标准筛选文献,对纳入的文献进行质量分级**[2]**:A 级:独立、盲法评价结果,有金标准与所研究的诊断方法进行比较,研究对象连续且研究对象不具有相同的特征(如性别、年龄、基础疾病及疾病的严重程度);B 级:独立、盲法评价结果,有金标准与所研究的诊断方法进行比较,研究对象非连续或研究对象具有相同的上述特征;C 级:非独立或非盲法评价结果。**

1.4 合并效应量的分析

首先进行异质性检验,根据异质性检验的结果选择相应的效应模型[3]**,计算合并优势比**(odds ratio, OR)**、阳性似然比**(positive likelihood ratio, PLR)**及其** 95%**可信区间**(confidence interval, CI)[4]**;采用"预测急性肺栓塞患病危险性的评分法**[5]**(加拿大评分法,表** 1**)"估计病例的验前概率,结合** PLR **计算病例患病的阳性预测值**(positive predictive value, PPV)**;绘制汇总受试者工作特征曲线**(summary receiver operation characteristic curve, SROC)[6]**,比较曲线下面积**(area under curve, AUC)**。所有统计分析用** RevMan4.2 **及** SPSS10.0 **完成。**

表 1 **预测急性肺栓塞患病危险性的评分法**

变 量	分值*
深静脉栓塞的临床症状和体征(如下肢肿胀或下肢深静脉触痛)	3.0
未发现有比急性肺栓塞更具有可能性的诊断	3.0
心动过速(心率 > 100 次/分)	1.5
近 4 周内手术或制动	1.5
深静脉血栓栓塞史或肺血栓栓塞史	1.5
咯血	1.0
近 6 个月内活动性的肿瘤	1.0

分值*:< 2 分:低度可能性,验前概率为 3.4%; 2~6 **分:中度可能性,验前概率为** 27.8%; > 6 **分:高度可能性,验前概率为** 78.4%**。**

2　结　果

2.1　文献描述

通过检索共获得385篇文献，阅读文献的题目、摘要以及可能合格的文献后，选出符合纳入标准的21篇文献共22个研究（表2），其中A级研究有3个，B级有12个，C级有7个；研究实施时间从1984年至2001年5月，样本量平均为75例（30～731例），所有文献均对研究对象的年龄和性别进行了详细描述，年龄13～93岁，男性占43%，女性占57%。诊断性试验的安全性和成本-效益指标进行评价的研究未纳入。

2.2　合并效应量的估计

所有试验的漏斗图法和秩相关检验法结果显示，样本量与OR值之间无显著相关性，样本量对发表性偏倚的影响可忽略，可以进一步做综合分析。由于所有试验的异质性均不明显，故选用固定效应模型进行效应量综合分析：合并优势比（odds ratio, OR）（表3）最高的是MRI，其次分别为CTPA、放射性核素肺通气/灌注显像（ventilation/perfusion scanning, V/P）及下肢多普勒血管超声检查（doppler vascular ultrasound, DVUS）；合并PLR为8.54～19.91（表4）；根据试验的PLR，结合患者的验前概率计算PPV，当PPV>85%时，认为试验结果阳性可确诊该病[7]，结果见表5，部分试验的合并效应量比较差异无统计学意义。

表3　确诊试验的合并优势比

确诊试验	OR（95%CI）	P
CTPA	81.68（43.18～154.49）	<0.000 01
V/P	23.33（14.44～37.69）	<0.000 01
MRI	103.38（33.18～322.13）	<0.000 01
DVUS	13.43（5.71～31.62）	<0.000 01

表4　确诊试验的合并阳性似然比

确诊试验	PLR（95%CI）	P
CTPA	14.13（7.47～26.72）	<0.000 01
V/P	9.52（5.89～15.38）	<0.000 01
MRI	19.91（6.39～62.04）	<0.000 01
DVUS	8.54（3.63～20.10）	<0.000 01

表5　确诊试验的阳性预测值　%

确诊试验	低度（3.4%）	中度（27.8%）	高度（78.4%）
CTPA	33.21（20.82～48.47）	84.47（74.20～91.14）	98.04（96.44～98.98）
V/P	25.10（17.17～35.12）	78.57（69.40～85.55）	97.12（95.53～98.24）
MRI	41.19（18.36～41.43）	88.46（71.10～88.56）	98.60（95.87～98.65）
DVUS	23.11（11.33～68.59）	77.68（58.29～95.98）	96.68（95.15～99.56）

2.3　SROC曲线分析

（1）首先计算各试验拟合的直线回归方程，然后根据回归参数绘制SROC曲线（图1）。

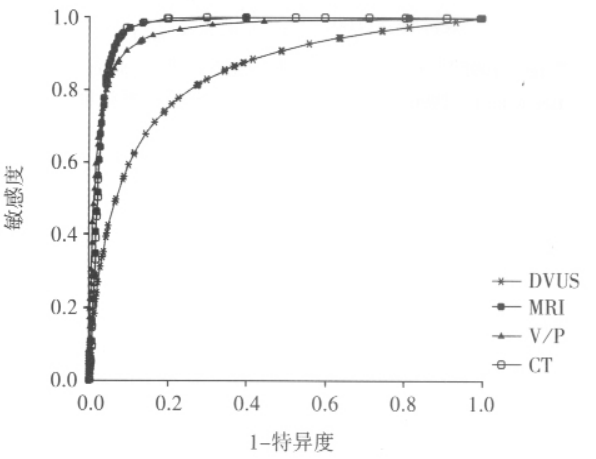

图1　各确诊试验的SROC曲线

（2）计算曲线下面积（AUC）

结果表明，CTPA、V/P及MRI的AUC均在0.90以上，诊断准确性较高，各确诊试验的AUC值比较差异无统计学意义。

（3）不同确诊试验比较的假设检验

由图1可见，CTPA与MRI试验的SROC曲线几乎重叠在一起，较其他曲线更靠近坐标轴左上角，即CTPA与MRI的确诊价值最高，V/P稍低，DVUS最低。

3　讨　论

当前用于确诊PTE的方法有很多，但哪一种方法敏感度和特异度最高仍存在争议，为了回答这个问题，目前最好的方法是采用Cochrane系统评价。本系统评价纳入的研究采用的技术和设备在较多医院是可行的，而且多数试验纳入的资料符合PTE的临床特征，因此，本系统评价纳入的文献具有一定的代表性和实用性。

3.1　合并效应量的评价

（1）诊断性试验的合并OR值和PLR值结果表明，MRI的诊断价值最高，DVUS最低；从各试验的PPV可以看出，临床评分为高度可能性的病例任一试验结果为阳性者可以确诊PTE，无需其它检查；临床评分为中低度可能性的病例即使试验结果为阳性仍需行进一步其它检查，但森林图显示其部分试验95%可信区间范围广，可能是样本量不足导致结果的精确性稍低。

表2 确诊试验的原始数据

作者	诊断间隔时间	诊断标准	金标准	质量	样本量	患病率%	分级样本 A	B	C	D
CTPA										
Remy-Jardin 1992[8]	<24 h	腔内充盈缺损、轨道征或亚段以上动脉内的附壁缺损(ts: 5 mm)	PA: 腔内充盈缺损或间接征豁,肺动脉截断征无明显充盈缺损或局部关注缺损	C	42	42.86	18	1	0	23
Teigen 1995[9]	<72 h	腔内充盈缺损(ts: 6 mm)	PA: NS	B	60	38.33	15	1	8	36
Remy-Jardin 1996[10]	<24 h	腔内充盈缺损、轨道征或亚段以上动脉内的附壁缺损(ts: 3~5 mm)	PA: 腔内充盈缺损或肺动脉截断征	C	75	57.33	39	0	4	32
van Rossum 1996[11]	<24 h	腔内充盈缺损(ts: 5 mm)	PA: 腔内充盈缺损或肺动脉截断征	C	42	14.29	5	1	1	35
Drucker 1998[12]	<24 h	腔内部分或完全充盈缺损(ts: 3 mm)	PA: NS	B	47	31.91	8	1	7	31
Qanadli 2000[13]	<12 h	腔内充盈缺损或栓子完全堵塞(ts: 2.7 mm)	PA: 腔内充盈缺损或直径≥2 mm血管出现截断征	A	137	39.49	56	3	6	92
Nisson 2002[14]	<12 h	腔内充盈缺损或管腔完全堵塞(ts: 3 mm)	PA: 腔内充盈缺损或可见栓子	A	90	36.67	30	2	3	55
Ruiz 2003[15]	<24 h	腔内充盈缺损(ts: 3 mm)	PA: 腔内充盈缺损	B	66	37.88	21	7	4	34
V/P										
PIOPED 1990[16]	<24 h	高度可能性	PA: 腔内充盈缺损或栓子完全堵塞	A	731	34.34	102	14	149	466
Teigen 1995[9]	<48 h	高度可能性(PIOPED标准)	PA: NS	B	38	39.47	3	1	12	22
Goldhaber 1993[17]	NS	高度可能性(NS)	PA: NS	B	135	23.70	9	8	23	95
Kutinsky 1999[18]	NS	高度可能性(PIOPED标准)	PA: 腔内完全堵塞或≥3 mm充盈缺损	B	98	30.61	1	5	29	63
MRI										
Meaney 1997[19]	NS	腔内充盈缺损	PA: 腔内充盈缺损	C	30	26.67	8	1	0	21
Gupta 1999[20]	<24 h	腔内充盈缺损或血管截断征	PA: 腔内充盈缺损或血管截断征	C	36	36.11	11	1	2	22
Oudkerk 2002[21]	<24 h	腔内充盈缺损	PA: 腔内充盈缺损	B	118	29.66	27	2	8	81
DVUS										
Quinn 1994[22]	<24 h	腔内可见栓子或静脉部分被压瘪或不能被压瘪	PA: 血管完全堵塞或≥2 mm充盈缺损	C	36	41.67	2	0	13	21
van Beek 1996[23]	<48 h	下肢近端静脉管腔不能被完全压瘪	PA: 至少2个体位的多体位平面影像方法显示充盈缺损或直径>2 mm血管截断征	C	145	27.59	4	0	36	105
Christiansen 1994[24]	<48 h	股静脉至胭静脉不能完全被压瘪	PA: 腔内充盈缺损和/或可见栓子堵塞	B	72	13.89	7	2	3	60
Turkstra 1997[25]	<48 h	下肢近端静脉管腔不能被完全压瘪	PA: NS	B	125	26.40	8	2	25	90
Velmahos 2004[26]	<48 h	NS	PA: 肺血管血流中断或腔内缺损	B	32	31.25	5	3	5	19
肺灌注显像										
Miniati 1996[27]	<24 h	单个或多个楔形灌注缺损合并/不合并X线胸片异常, 常合并楔形区过度灌注	PA: 可见栓子堵塞血管或腔内充盈缺损	B	390	60.51	217	20	19	134
超声心动图										
Miniati 2001[28]	<24 h	具备以下三项中其中两项:①右心室运动障碍;②右心室舒张末期直径≥27 mm(无右心室肥厚);③三尖瓣返流速度>2.7 m/s	PA: 可见栓子堵塞血管或腔内充盈缺损	B	110	39.09	24	7	19	60

注: ts: 层厚, NS: 未描述。

(2)诊断性试验的SROC曲线综合分析显示,CTPA和MRI试验的SROC曲线几乎重叠在一起,较其他试验的SROC曲线更靠近坐标轴左上角,以MRI试验的诊断价值最大,同样地,由于部分试验的95%可信区间较宽,需要更多的研究进一步分析。

诊断性试验中部分试验95%可信区间范围广,合并效应量的差异无统计学意义,可能与样本量较少,导致结果的精确性和检验效能稍低有关。因此,根据目前的资料尚不能对PTE确诊试验作出最后的结论,但可以观察到一定的临床趋势:MRI可能是诊断PTE价值最高的试验,与文献报道一致[19-21,29],尚需进一步开展更多大样本试验,并且随着临床技术的更新而不断更新检索文献,获得最新的循证医学证据。

3.2　纳入研究存在的问题

为了保证研究的质量和便于临床应用,所有的研究应按照国际有关组织公布的诊断性研究报告的质量核对清单(STARD)的要求进行[30],以提高诊断性试验研究和报告的质量,如描述研究对象的纳入和排除标准、可重复性研究的方法以及报告诊断试验与参照试验之间的间隔时间等,因为本系统评价纳入的部分研究的设计方案存在研究对象的选择等方面未能符合STARD的标准,因此,需谨慎看待评价结果。同时,由于目前缺乏有关成本-效益指标和安全性的文献,使本文未能对此方面内容进行系统评价。

4　结　论

本研究结果可显示出一定的临床趋势,MRI可能是诊断PTE准确性最高的试验,如能按照国际标准设计纳入文献,并不断完善和更新已有的系统评价,将得出对临床实践更有指导意义的结论。

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[收稿日期] 2008-12-06

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[收稿日期] 2007-12-12