·论著·

经颅多普勒超声与经胸超声心动图对卵圆孔未闭诊断价值比较的Meta分析

毛如雪，李维，刘雅芳，匡良洪，顾文菊

摘要　目的：使用Meta分析的方法，比较对比增强经颅多普勒超声（c-TCD）与对比增强经胸超声心动图（c-TTE）对卵圆孔未闭（PFO）右向左分流（RLS）的诊断价值。**方法：**检索PubMed、Web of Science、Embase、Cochrane Library CNKI、VIP、WanFang Data及CBM数据库等自建库至2021年7月3日的文献，采用统计学软件Stata15.1和RevMan5.0进行数据统计分析。**结果：**共检索出766篇文献，确定纳入38篇文献。Meta分析结果显示，c-TCD的合并敏感度（0.96，95%*CI* 0.93～0.98）高于c-TTE（0.91，95%*CI* 0.82～0.96），有显著性差异（*Z*=2.664，*P*=0.008）；c-TCD的合并特异度（0.93，95%*CI* 0.86～0.97）低于c-TTE（0.95，95%*CI* 0.90～0.97），差异无统计学意义（*Z*=0.481，*P*=0.630）；c-TCD的合并DOR（DOR=384，95%*CI* 156～943）和c-TTE（DOR=180，95%*CI* 78～415）之间差异无统计学意义（Z=0.674，*P*=0.441）。c-TCD的sROC AUC大于c-TTE，差异无统计学意义（c-TCD的AUC为0.99，95%*CI* 0.97～0.99；c-TTE的AUC为0.98，95%*CI* 0.96～0.99；*Z*=0.357，*P*=0.507）。**结论：**c-TCD与c-TTE对PFO-RLS均具有较高的诊断价值。

关键词　对比增强经颅多普勒超声；对比增强经胸超声心动图；卵圆孔未闭；Meta分析

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Transcranial Doppler versus Transthoracic Echocardiography in Diagnosis of Patent Foramen Ovale in Patients: A Meta-Analysis *MAO Ru-xue, LI Wei, LIU Ya-fang, KUANG Liang-hong, GU Wen-ju. Department of Neurology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Hubei 435000, China*

Abstract　Objective: Using Meta-analysis to compare diagnostic value of contrast transcranial Doppler (c-TCD) and contrast transthoracic echocardiography (c-TTE) in right-to-left shunt (RLS) of patients with patent foramen ovale (PFO). **Methods:** Relevant literature from PubMed, Web of Science, Embase, Cochrane Library, CNKI, VIP, WanFang Data, and CBM from databases built until July 3, 2021 were retrieved. Statistical software Stata 15.1 and RevMan5.0 were used for statistical analysis. **Results:** A total of 766 articles were retrieved and 38 were included. Meta-analysis results showed the overall sensitivity of c-TCD (0.96, 95%*CI* 0.93～0.98) was higher than that of c-TTE (0.91, 95%*CI* 0.82～0.96), and the difference was statistically significant (*Z*=2.664, *P*=0.008). The overall specificity of c-TCD (0.93, 95%*CI* 0.86～0.97) was lower than that of c-TTE (0.95, 95%*CI* 0.90～0.97), but the difference was not statistically significant (*Z*=0.481, *P*=0.630). The diagnostic odds ratio of c-TCD (DOR=384, 95%*CI* 156～943) and c-TTE (DOR=180, 95%*CI* 78～415) showed no significant statistical difference (*Z*=0.674, *P*=0.441). The area under the sROC curve (AUC) of c-TCD was higher than that of c-TTE but showed no statistical difference (AUC=0.99, 95%*CI* 0.97～0.99 for c-TCD *v.s.* AUC=0.98, 95%*CI* 0.96～0.99 for c-TTE; *Z*=0.357, *P*=0.507). **Conclusion:** For the diagnosis of PFO-RLS, both c-TCD and c-TTE have high diagnostic value.

Key words　contrast transcranial Doppler; contrast transthoracic echocardiography; patent foramen ovale; Meta-analysis

卵圆孔未闭（patent foramen ovale，PFO）是胚胎时期在心脏房间隔遗留的通道，在普通人群中检出率约20%～30%[1]。右向左分流（right-to-left shunt，RLS）是指血液通过不正常的通道直接从静脉循环系统流向动脉循环系统，而不经肺脏过滤[2]。PFO是目前RLS类型中最多见的，达到95%[3]。已有多种疾病如隐匿性脑卒中、短暂性脑缺血发作（transient ischemic attack，TIA）、不明原因晕厥、偏头痛等被证实与PFO-RLS存在关联。目前，PFO-RLS诊断的金标准是对比增强经食道超声心动图（contrast transesophageal echocardiography，c-TEE），但由于该检测耗费时间较长且存在侵入性，其使用受到限制[3]。对比增强经颅多普勒超声（contrast transcranial Doppler，c-TCD）与对比增强经胸超声心动图（contrast transthoracic echocardiography，c-TTE）在使用过程中无创

伤、操作简单、可重复性高的优势使其逐渐成为对PFO-RLS进行筛查的重要方法[4,5]。但c-TCD与c-TTE两种检测方法哪种对PFO-RLS的检出更具有优势，不同观点差别较大。因此，本研究通过全面的系统回顾和Meta分析，综合比较c-TCD和c-TTE对PFO-RLS的诊断价值，以提高对两种方法临床应用的认识。

1 资料与方法

1.1 检索策略

检索平台包括PubMed、Web of Science、Embase、Cochrane Library、CNKI、VIP、WanFang Data及CBM数据库等，中文检索词为“经颅多普勒超声”、“经胸超声心动图”、“经胸超声心动图二次谐波成像”、“超声心动图二次谐波成像”、“经食道超声心动图”、“卵圆孔未闭”、“右向左分流”，英文检索词为“transcranial Doppler”、“transthoracic echocardiography”、“transthoracic echocardiography second harmonic imaging”、“echocardiography second harmonic imaging”、“transesophageal echocardiography”、“patent foramen ovale”、“right to left shunt”。检索时限为各数据库建库至2021年7月3日。

1.2 纳入与排除标准

纳入标准：前瞻性研究；c-TCD、c-TTE为待评价试验，c-TEE为金标准，如不是以c-TEE为金标准，则以c-TEE作为参照计算出合适的参数；能通过文中的真阳性、假阳性、真阴性、假阴性数计算出诊断准确度。排除标准：研究类型不符合；文献中出现的相关数据资料完整性、全面性差；综述、仅有摘要、病例报告等类型的文献；重复发表。

1.3 资料提取及质量评价

由两名研究人员根据纳入和排除标准对相关文献进行初步筛查、提取数据及质量评价。质量评价采用诊断准确性研究的质量评价工具QUADAS-2[6]进行。

1.4 统计学处理

采用统计学软件Stata15.1和RevMan5.0进行数据统计分析。基于每个研究中真阳性、假阳性、真阴性和假阴性率，敏感度、特异度、诊断比值比（diagnostic odds ratio，DOR）及受试者工作特征曲线（summary receiver operator characteristics curve，sROC）下的面积（area under curve，AUC），分别估算c-TCD和c-TTE的95%置信区间（95% *CI*）。这个估计是基于广义线性混合模型方法对敏感度和特异度的双变量Meta分析[7]。然后，使用适当的z检验比较c-TCD和c-TTE的DOR和sROC AUC，统计学显著性水平设为0.05。最后使用Deek’s漏斗图来判断纳入文献是否存在发表偏倚。

2 结果

2.1 文献检索结果和纳入文献基本特征

本研究最终纳入38篇文献，见图1、表1，均为前瞻性研究。

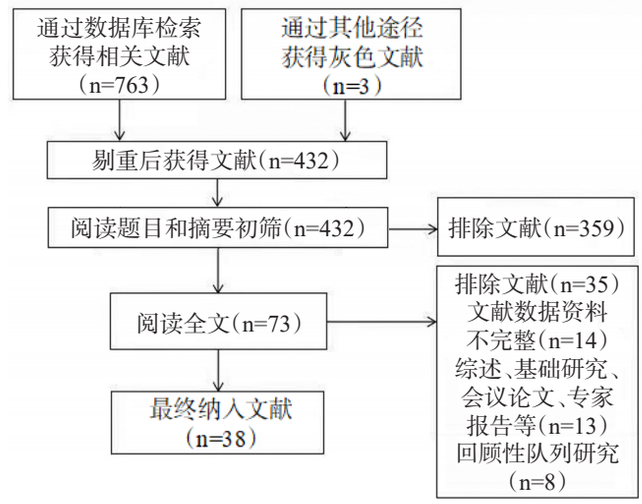


图1 文献筛选流程图

2.2 质量分析

29项（76%）研究纳入病程连续的患者，初始招募后未排除；在18项（47%）研究中，进行待评价试验（c-TCD或c-TTE）的研究人员不知道金标准（c-TEE）的结果；相反的，在27项（71%）研究中，进行金标准（c-TEE）的研究人员不清楚待评价试验（c-TCD或c-TTE）的结果；18项（47%）研究的试验是双盲进行的；在22项（58%）研究中，未提及研究人员进行待评价方法及金标准的时间间隔，见图2、图3。

2.3 定量分析

在纳入的研究中，有23个研究将c-TCD作为待评价试验，10个研究将c-TTE作为待评价试验，有3篇文献同时将c-TCD和c-TTE作为待评价试验，c-TEE作为参考金标准，见表1。对所有纳入研究计算其敏感度和特异度的95% *CI*。由森林图可知纳入研究的针对c-TCD敏感度和c-TTE特异度相关文献异质性较低；然而，针对c-TCD特异度和c-TTE灵敏度的研究异质性较大，见图4。

c-TCD和c-TTE相关的sROC曲线见图5。c-TCD的合并敏感度（0.96，95% *CI* 0.93～0.98）高于c-TTE（0.91，95% *CI* 0.82～0.96），有显著性差异（Z=2.664，P=0.008）；c-TCD的合并特异度（0.93，95% *CI* 0.86～0.97）低于c-TTE（0.95，95% *CI* 0.90～0.97），差异无统计学意

表1 纳入文献基本特征

作者	年份	检查方法	总患者数	平均年龄/岁	男性	真阳性数	假阳性数	假阴性数	真阴性数
Kuhl等[8]	1999	c-TTE	111	56	58%	46	6	5	54
Van Camp等[9]	2000	c-TTE	109	64.6	55%	19	2	3	85
Ha等[10]	2001	c-TTE	136	59	无	25	0	15	96
Clarke等[11]	2004	c-TTE	110	58.3	68%	13	5	6	88
Buttignoni等[12]	2004	c-TTE	34	65	62%	13	0	9	12
Daniels等[13]	2004	c-TTE	256	63	60%	48	7	5	196
Madala等[14]	2004	c-TTE	71	无	56%	9	10	0	45
Thanigaraj等[15]	2005	c-TTE	94	45	40%	19	22	2	51
Souteyrand等[16]	2006	c-TTE	107	56	63%	36	2	4	65
Souteyrand等[16]	2006	c-TCD	107	56	63%	42	6	0	59
Trevelyan等[17]	2006	c-TTE	87	55	45%	19	7	8	53
Lefèvre等[18]	2008	c-TTE	121	54.2	74%	19	4	3	95
Zuber等[19]	2008	c-TTE	438	无	无	190	10	0	238
Lam等[20]	2011	c-TTE	112	46	43%	47	3	3	59
Albert等[21]	1997	c-TCD	69	44	41%	25	0	0	33
Belvís等[22]	2006	c-TCD	110	56.7	61%	36	0	0	74
Blersch等[23]	2002	c-TCD	40	47.9	58%	21	2	2	15
Caputi等[24]	2009	c-TCD	100	46	41%	61	8	2	29
Devuyst等[25]	1997	c-TCD	37	46	62%	24	5	0	8
Droste等[26]	1999	c-TCD	54	44	70%	18	6	1	29
Droste等[27]	1999	c-TCD	46	47	43%	20	10	0	16
Droste等[28]	2002	c-TCD	81	48.7	62%	27	15	0	22
Droste等[29]	2002	c-TCD	64	47	72%	31	22	0	28
González-Alujas等[30]	2011	c-TCD	134	46.4	56%	80	10	2	42
González-Alujas等[30]	2011	c-TTE	134	46.4	56%	80	13	0	41
Hamann等[31]	1998	c-TCD	44	34.7	41%	6	0	2	36
Heckmann等[32]	1999	c-TCD	45	41.4	53%	22	0	4	19
Horner等[33]	1997	c-TCD	45	41	47%	34	3	1	7
Jauss等[34]	1994	c-TCD	50	54.3	74%	14	0	1	35
Job等[35]	1994	c-TCD	137	46	55%	58	6	7	66
Karnik等[36]	1992	c-TCD	36	61	55%	13	0	2	21
Komar等[37]	2014	c-TCD	420	34.8	38%	220	20	21	159
Maffe等[38]	2010	c-TCD	75	49	37%	53	1	9	12
Maffe等[38]	2010	c-TTE	75	49	37%	55	0	7	13
Nygren等[39]	1998	c-TCD	23	56	70%	10	2	0	9
Orzan等[40]	2010	c-TCD	68	49	56%	6	15	0	47
Palazzo等[41]	2018	c-TCD	47	44	39%	34	0	0	13
Sastry等[42]	2009	c-TCD	39	39	46%	16	0	0	23
Stendel等[43]	2000	c-TCD	92	51	51%	22	0	2	68
Zito等[44]	2009	c-TCD	72	49	46%	45	1	1	25
Zivanović等[45]	2010	c-TCD	13	31.4	54%	7	0	0	3

义（Z=0.481，P=0.630）；c-TCD的合并DOR（DOR=384，95% CI 156～943）和c-TTE（DOR=180，95% CI 78～415）之间差异无统计学意义（Z=0.674，P=0.441）。c-TCD的sROC AUC大于c-TTE，差异无统计学意义（c-TCD的AUC为0.99，95% CI 0.97～0.99；c-TTE的AUC为0.98，95% CI 0.96～0.99；Z=0.357，P=0.507）。

2.4 发表偏倚

根据Deeks漏斗图可以得出，c-TCD诊断PFO-RLS研究不存在发表偏倚（P=0.49），见图6A；c-TTE诊断PFO-RLS研究存在发表偏倚（P=0.00），见图6B。

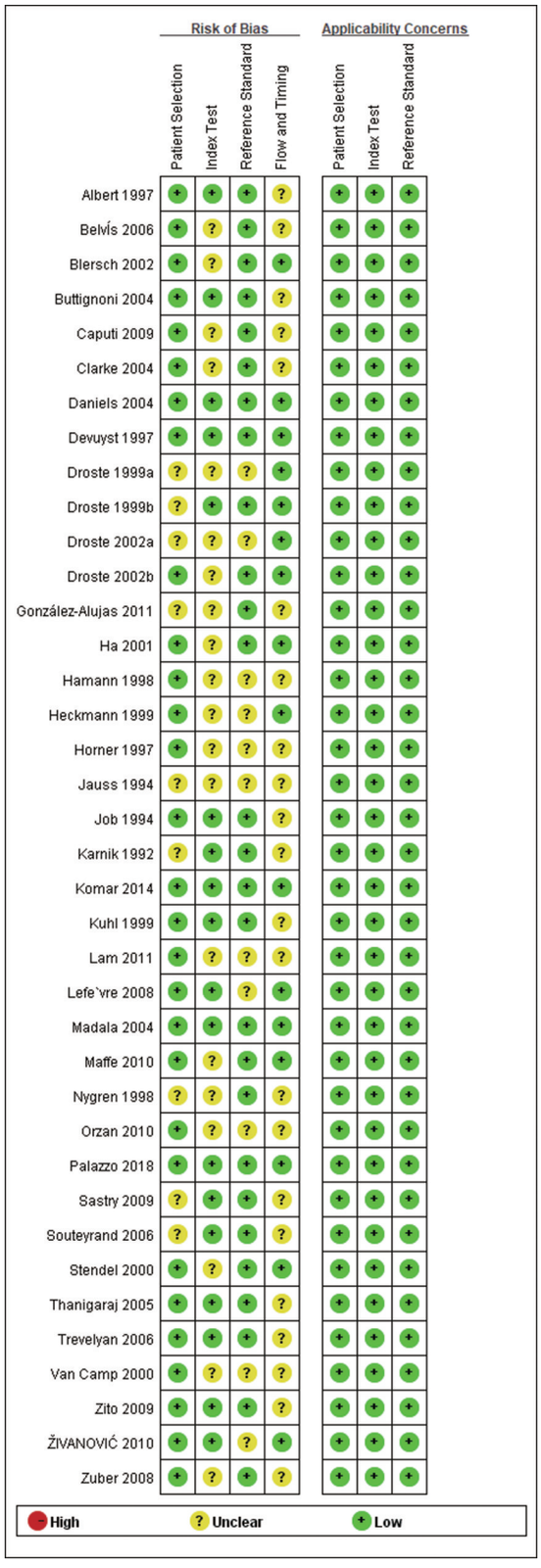


图2　风险偏倚评价

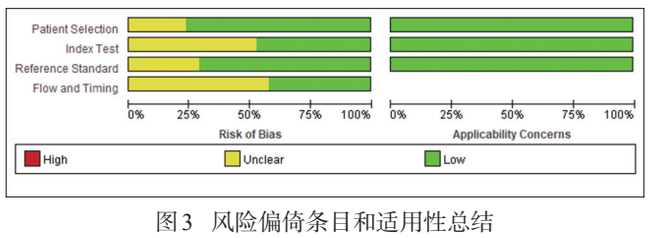
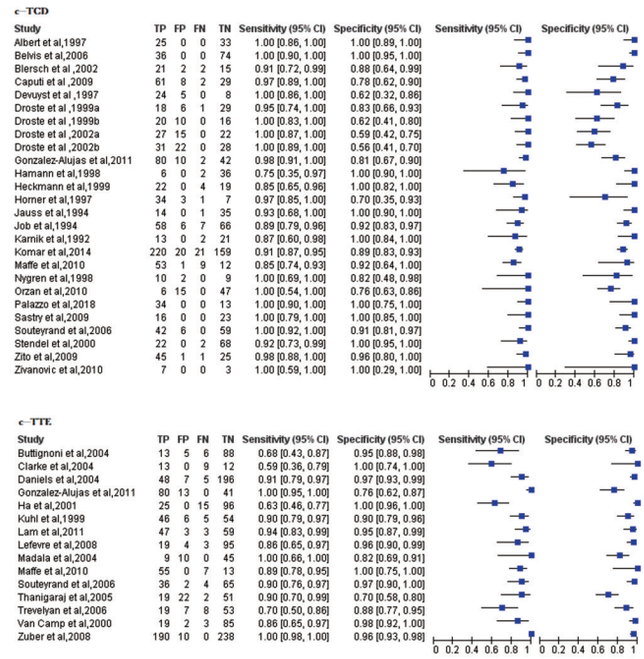


图3　风险偏倚条目和适用性总结



注：CI=置信区间；TP=真阳性；FP=假阳性；FN=假阴性；TN=真阴性

图4　单个研究的敏感度和特异度及95%置信区间的森林图

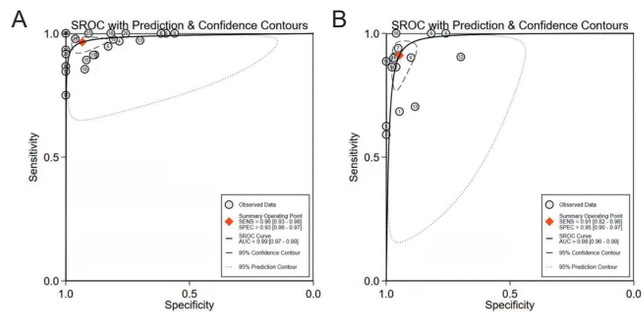


图5　c-TCD（A）和c-TTE（B）诊断PFO-RLS的sROC曲线

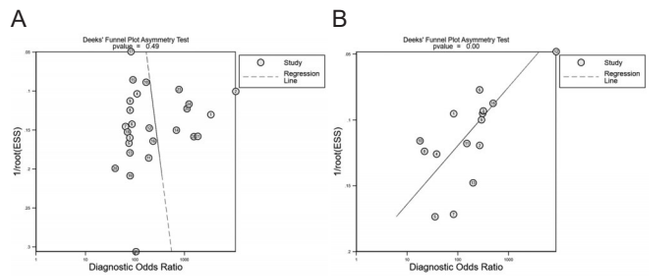


图6　c-TCD（A）、c-TTE（B）诊断PFO-RLS发表偏倚

3　讨论

卵圆孔是胚胎期房间隔的重要生理通道，若3岁后卵圆孔仍未闭合，即为PFO[1]。PFO是一个动态开放的通道结构，一般情况下，右房内压力低于左房，卵圆孔瓣贴合良好不发生分流，当左右房压力变化时，卵圆孔瓣无法紧密贴合导致血液在心房之间发生分流，分流的方向取决于左右心房之间的压差。当左心房压力比右心房压力低时，PFO通道打开，右心和静脉系统的

栓子反向进入左心和动脉系统[46]。研究显示，PFO-RLS在普通人群中发病率约20%～30%，在隐匿性卒中患者中发病率约40%，在先兆偏头痛患者中发病率高达60%[1]。因此，对PFO-RLS的诊断在临床工作中越来越受到重视。

目前，c-TEE作为PFO-RLS的诊断金标准，因其是半侵入性操作，会造成患者不适，局麻和食道插管的使用可导致Valsalva动作配合不佳，导致假阴性。c-TCD及c-TTE在使用过程中无创伤、操作简单等特点使其广泛在临床筛查中使用。c-TCD探查PFO-RLS的原理主要是通过肘静脉团注射微泡造影剂后通过TCD检测至少一侧大脑中动脉，确定是否有微栓子信号进入大脑中动脉。c-TTE的原理是首先进行经胸超声心动图检测，选择剑突下四腔心切面，经肘静脉团注微泡造影剂后，观察是否有微气泡进入左心房。

Souteyrand等[16]的研究表明，c-TCD的阴性预测值大于c-TTE，表示c-TCD排除PFO-RLS优于c-TTE。González-Alujas等[30]的研究表明，c-TCD诊断PFO-RLS的敏感度低于c-TTE，特异度高于c-TTE。本研究发现，c-TCD对于PFO-RLS检测的敏感度高于c-TTE，特异度低于c-TTE。分析原因可能为：①c-TCD的价格比c-TTE便宜，可在床边对残疾患者进行检查，可以不同体位进行重复实验，患者更有可能进行标准的Valsalva动作以提高检测敏感度[4,5]；②c-TCD是对心内型和心外型RLS进行检测，而PFO、室间隔缺损等属于心内型RLS，肺动静脉畸形、动脉导管未闭等则属于心外型RLS，故特异度较低[2]；③c-TTE敏感度低的原因可能由于检测图像质量不佳[11,13]，并且进行Valsalva动作时，由于患者胸壁活动幅度过大从而影响图像采集及结果判断；④c-TTE能直观检测心内结构以及房间隔等周围组织具体情况，鉴别RLS的来源，提高了特异度[47]；⑤操作时医生使用的手法、患者的身体条件及检测仪器特性的不同都会对结果产生影响。

2010年Maffe等[38]的研究发现，c-TCD的诊断准确度低于二次谐波成像c-TTE。而2016年Aristeidis等[48]的Meta分析表明，c-TCD的sROC AUC大于常规c-TTE，表明c-TCD对PFO-RLS的诊断准确度高于常规c-TTE。本次结果提示，c-TCD与c-TTE的sROC AUC差异无统计学意义，表明c-TCD和c-TTE诊断效力相当。分析原因可能是本研究纳入的c-TTE研究应用了二次谐波成像技术，相对于常规c-TTE，左心房内微泡回声更清晰，降低了微泡漏检的可能性。由此可见，随着二次谐波成像技术的发展，c-TTE与c-TCD之间诊断准确度差异已不断减小。最后，应该注意的是，即使使用c-TTE检测到PFO-RLS的存在，仍需使用TEE对分流处的解剖病变进一步确认，比如测量卵圆孔的大小，明确心腔内是否有血栓形成等[2]。

本研究存在以下局限性：①尽管在大多数研究中都报道了连续的患者入组，但在c-TCD作为待评价试验时不能完全排除选择偏倚，因为会有一些颞窗探测不佳的患者。c-TCD最大的局限性在于颞窗探测不佳，这会使得10%～15%的60岁以上患者无法进行检查[49]；②患者进行Valsalva动作后，PFO-RLS的阳性检出率增加，所以Valsalva动作规范与否对于检测的结果有很大影响，但该动作执行过程中的时间点、患者体位等方面没有统一标准，仍存在较大差异[50]；③纳入的c-TTE的文献存在发表偏倚，影响了研究结果。

综上所述，c-TCD在诊断PFO-RLS方面与c-TTE相比敏感度稍高，特异度稍低。c-TCD与c-TTE对PFO-RLS均具有较高的诊断价值，均可作为PFO-RLS的筛查方法。

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