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心源性卒中诊断技术的研究进展

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摘 要

心源性栓塞性卒中(cardioembolic stroke, CES)约占据缺血性卒中20%，与其他类型的缺血性卒中相比，CES的病情更重、预后更差、复发率更高，同时治疗方案也存在差异，因此准确识别CES具有重要意义。然而，既往检查手段的限制和对该疾病的认识不足导致CES的诊断率偏低。近年来，随着心率监测技术、超声检查，影像技术等CES相关诊断技术的发展，临床对CES的识别能力显著提升。本文将从心脏以及颅脑相关影像学检查、辅助诊断人工智能技术、生物标记物、及临床量表评估心源性卒中相关评分等方面综述CES诊断技术最新的研究进展。

关键词

心源性卒中，诊断，影像技术，生物标记物

Advances in Diagnostic Techniques for Cardioembolic Stroke

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Abstract

Cardioembolic stroke (CES), accounting for approximately 20% of ischemic strokes, is characterized by more severe clinical manifestations, poorer prognosis, higher recurrence rates, and distinct therapeutic strategies compared to other ischemic stroke subtypes. Therefore, the accurate identification of CES is of great significance. However, historical limitations in diagnostic tools and insufficient understanding of the disease have contributed to suboptimal CES detection rates. In recent years, with the development of diagnostic technologies related to cardioembolic stroke (CES), such

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as heart rate monitoring, ultrasound examinations, and imaging techniques, the clinical ability to identify CES has significantly improved. This paper will review the latest research progress in CES diagnostic technologies from several aspects, including cardiac and cerebral imaging examinations, auxiliary diagnostic artificial intelligence technologies, biomarkers, and clinical scale assessments related to cardioembolic stroke scores.

Keywords

Cardioembolic Stroke, Diagnosis, Imaging Techniques, Biomarkers

1. 引言

心源性栓塞性卒中(cardioembolic stroke, CES)，简称心源性卒中，是指来自心脏和主动脉弓的栓子通过循环导致脑动脉栓塞引起相应脑功能障碍的临床综合征[1]。与其他类型的缺血性卒中相比，CES 患者的神经功能缺损症状更严重、预后更差、卒中再发风险也更高[2] [3]。CES 患者多存在心脏疾病或相关危险因素，如心房颤动、收缩性心力衰竭、急性冠状动脉综合征、卵圆孔未闭、主动脉弓粥样硬化、风湿性心脏病、人工心脏瓣膜、感染性心内膜炎、扩张性心肌病和心脏黏液瘤等[4]。

CES 的诊断需要综合患者临床表现和神经影像学特点，结合血管评估和心脏结构和功能等相关检查进行判断。由于与 CES 相关的危险因素较多，临床表现缺乏特异性，CES 的诊断率偏低。根据 TOAST 分型标准，大约 25%的缺血性卒中(Ischemic stroke, IS)被归类为不明原因性卒中(Embolic stroke of undetermined source, ESUS) [5]。不同的研究表明，ESUS 患者中隐匿性心房颤动(Atrial fibrillation, AF)的患病率为 11%至 30% [6]。随着诊断技术的进步，缺血性卒中归类为 CES 的比例逐步上升[7]。识别患者的心源性栓塞风险及明确 CES 的诊断可以指导临床制定恰当的治疗方案。本文将从心脏以及颅脑相关影像学检查、CES 相关生物标记物、辅助诊断人工智能技术及 CES 相关评分等方面综述 CES 诊断技术的研究进展。

2. 心脏相关诊断技术

2.1. 心脏节律方面

AF 是心源性卒中最常见的原因[8]，隐匿性阵发性心房颤动是不明原因性卒中的潜在病因之一[9]。检测心房颤动的传统监测技术包括常规心电图、24h 动态心电图、床旁心电监护以及可植入心脏监护仪(Insertable cardiac monitor, ICM)。研究表明，长程心电检测技术较短程心电检测技术能更有效地检测出 AF。与 30 天外部心电监测技术相比，12 个月植入式心电监测技术显著提高 AF 检测率[10]。一项不明原因性卒中和潜在房颤(CRYSTAL-AF)研究表明，与常规心电监测技术相比，使用 ICM 进行心电监测时长达 6 月的患者 AF 检出率为 8.9%，长达 12 月的 AF 检出率为 12.4%，远高于使用常规心电监测技术的 AF 检出率(1.2%~2%) [11]。常规的心电监测技术通过使用凝胶贴片将导线固定在患者胸部，对患者日常生活造成不便，因此传统心电监护设备使用率及患者满意度均较低，在家庭使用场景中难以推广。

随着科技的发展，美国食品药品监督管理局批准包括智能手表，可穿戴腰带、背心等在内的可穿戴设备用于心电监测。与常规心电监测技术相比，可穿戴设备心电监测技术使用更加便利，其可利用机器

学习算法自动分析监测数据以提高 AF 诊断率。一项对不明原因性卒中患者进行心电检测的荟萃分析结果表明，在不明原因性卒中患者中，与常规心电图等短程心电监测相比，可穿戴设备的新发 AF 检出率较高，然而与动态心电图及 ICM 等长程监测技术相比，使用可穿戴设备不能提高 AF 的检出率[12]。Ding 等人的研究表明，与常规贴片心电检测技术相比，老年人会更愿意使用智能手表和智能手机进行心电监测，它具有舒适性、简易性以及美观性优势，但其局限性在于穿戴设备需要定期充电，同时，其实时显示的监测结果会让使部分使用者产生焦虑情绪[13]。综上所述，长时程心电监护有助于提高 AF 检出率，而可穿戴设备的发展为患者居家监测心律变化情况提供可能，尤其适用于低中危患者的初步筛查和长期健康管理。

2.2. 心脏结构方面

经胸超声心动图(Transthoracic echocardiography, TTE)和经食管超声心动图(Transesophageal echocardiography, TEE)是发现心内血栓，心脏瓣膜疾病，心内赘生物，心内肿瘤以及卵圆孔未闭等心脏结构异常的重要检查。与 TTE 相比，TEE 在识别心源性栓子具有更高的敏感性和特异性[14]。CONTEST 研究表明，经过 TOE 检查后，11.5%患者的卒中分类发生改变，分类为心源性卒中的患者数量增加，而分类为不明原因性卒中的患者数量减少[15]。但 TEE 的局限性在于其是一项半侵入性的检查，不能用于接受轻中度镇静、神志不清以及全身状况较差的患者。因此 TTE 作为一项无创检查，在临床应用中更为常见。对于 50~55 岁以下患者或者怀疑 CES 栓塞来源但是 TTE 不足以确诊的患者，建议使用 TEE [16]。

经胸超声心动图声学造影(Contrast Transthoracic echocardiography, cTTE)和经食管超声心动图声学造影(Contrast Transesophageal echocardiography, cTEE)在发现心脏右向左分流血流动力学异常方面存在优势，有助于提高心脏卵圆孔未闭(Patent foramen ovale, PFO)的检出率。PFO 是心源性卒中的常见原因，在年轻患者中占比较大[15]。与 cTTE 相比，cTEE 对 PFO 的检出率较高且能提供更准确的分流形态[17]。CONTEST 研究表明，在符合 PFO 封堵术标准的患者中，cTEE 对 PFO 的检出率(11.5%)高于 TTE 识别 PFO 的检出率(6.2%) [15]。因此对存在 PFO 封堵术手术机会的患者来说，即使其 cTTE 结果为阴性，也有必要进一步完善 cTEE 检查。经颅多普勒声学造影在发现心脏右向左分流血流动力学异常方面同样存在优势，其作为一项非侵入性检查，价格低廉且检出率高。对分类为病因不确定性卒中的患者来说，与金标准 cTEE 相比，经颅多普勒声学造影在检测卵圆孔未闭方面具有较高的灵敏性和特异性[18]。与 cTTE 相比，经颅多普勒声学造影检测 PFO 的敏感性和特异性分别为 97%和 93% [19]。经颅多普勒声学造影的局限性在于其无法识别异常分流来自心内还是心外，同时也无法提供 PF0 形态的相关信息[20]。

与超声心动图相比，心脏计算机断层扫描(Cardiac computed tomography, CCT)和心脏磁共振成像(Cardiac magnetic resonance imaging, CMRI)在描述软组织特征方面存在优势，其能提供详细的解剖信息，通过多平面图像重建实现信息、空间以及时间的可视化。对于有 TEE 禁忌症的患者来说，CCT 是可视化左心耳血栓的最佳选择，其检测左心耳血栓的灵敏性和特异性接近 100% [21]。与 TTE 和 TOE 相比，CMRI 在诊断左心房血栓方面精确度更高，灵敏度为 82%~88%，特异度几乎为 100%，且能识别血栓的结构特征[22]-[24]。但是 CMR 的成本较高且普及率低，可能会限制其广泛应用。CCT 以及 CMRI 在检测左心耳血栓，发现心脏瓣膜疾病等方面的水平无明显差异，但是 CMRI 在显示左心房特征，左心室血栓，心脏肿瘤，左心室动脉瘤，心肌病，心室壁运动减弱等方面优于 CCT [25]。尽管如此，对于有 CMRI 检测禁忌症，如体内有金属植入物的患者来说，CCT 仍然是一种很好的替代检查。

正电子发射断层扫描(Positron emission tomography, PET)和单光电子发射计算机断层扫描(Single Photon Emission Computed Tomography, SPECT)通过提供代谢和功能信息，有助于提高心肌病，浸润性、炎症性心脏病、心脏肿瘤等疾病的诊断率[26]。然而该检查价格昂贵，其在心源性卒中的初步评估应用较少。

全身的 PET 对癌症诊断的敏感性和特异性为 90%以上[27]。由于癌症以及某些癌症治疗与血栓风险增加相关，因此怀疑潜在恶性肿瘤患者，可以考虑行 PET 检查。

2.3. 心脏血管方面

主动脉弓粥样硬化斑块 ≥ 4 mm 是心源性卒中的危险因素之一[28]。TEE 在检测主动脉弓粥样硬化斑块的灵敏度为 75%、特异度为 84%，可以检测斑块有无溃疡、钙化、血栓以及斑块厚度等各种测量值[29]。与 TEE 相比，TTE 可探及主动脉根部和近端升主动脉，但较难准确识别主动脉弓附着的粥样硬化斑块[30]，然而对于经皮胸骨上窗探查视野良好的患者而言，TTE 可探及突出的主动脉粥样硬化斑块，有助于补充 TEE 未能探及的血管结构[31]。传统二维 TEE 在单个平面或者双平面成像评估主动脉根部和主动脉弓的斑块，但二维 TEE 通常无法检测升主动脉和主动脉弓移动或者复杂成分的斑块。与此相比，三维 TEE 在检测伴有溃疡和活动性成分的复杂的主动脉斑块方面有显著优势，其应用为改善对主动脉斑块的评估提供帮助[32]。

CT 血管造影(Computed tomography angiography, CTA)是一项非侵入性检查，可以检测主动脉弓及其主要分支附壁斑块的位置、大小及密度，它可以检测 TEE 难以探及的区域(如远端升主动脉)，但无法评估斑块的活动性[33]。一项比较 TEE 与 CTA 评估主动脉弓疾病的研究表明，与 TEE 相比，CTA 的敏感性较低(53%)，但是特异性较高(89%)；然而其检测高风险主动脉弓粥样硬化的特异性上升至 99%，但敏感性下降至 23% [34]。因此 CTA 可以作为高风险动脉斑块的筛查工具。通过宽范围扫描成像方式，320 排 CTA 可通过图像重建观察主动脉的整体图像并且检测大而复杂的主动脉粥样硬化斑块[35]。而 CMRI 在发现脂质核心，纤维帽的厚度以及纤维帽内的炎症等决定动脉粥样硬化斑块稳定性的信息方面存在优势[36]，但与 TEE 相比，CMRI 低估了主动脉弓的斑块厚度[37]，在评估斑块风险时可能造成误判。正电子发射断层扫描(Positron emission tomography, PET)可以通过检测主动脉弓粥样硬化斑块中的氟脱氧葡萄糖摄取情况识别不稳定斑块[38]，并评估其破裂风险[39]。然而 CTA、CMRI 及 PET 等影像学检查的使用成本较高，图像处理等技术较复杂，在临床中应用较少。

3. 颅脑相关诊断技术

3.1. 颅脑结构方面

计算机断层扫描(Computed tomography, CT)和磁共振成像(Magnetic resonance imaging, MRI)是评估心源性卒中主要影像学检查方式。与 CT 相比，MRI 扩散加权成像(Diffusion-weighted imaging, DWI)对急性缺血性卒中的早期变化高度敏感，在疾病超早期提供脑梗死灶面积及分布情况的准确信息。由于心脏来源的栓子体积常大于颈动脉或者颅内动脉的原位血栓，其栓塞血管引起的脑梗死病灶也较非心源性脑卒中所致脑梗死病灶面积更大[40]。在心源性卒中的患者中，血栓常累及颈内动脉，大脑中动脉等大血管较常见。与其他类型的卒中相比，心源性卒中更容易累及皮层或者灰白质交接区、双侧前、后循环以及双侧前循环供血区[41] [42]。此外，心源性脑卒中患者的风险也更高，与其他类型的缺血性卒中相比，心源性卒中出现病灶内出血转化的概率较高[43]。

3.2. 颅内外血管方面

对于心源性卒中患者而言，CTA、MRA 以及数字减影血管造影数字减影血管造影(Digital Subtraction Angiography, DSA)通常显示颅内大血管主干或分支多发狭窄或闭塞，而其近心端血管无明显的动脉粥样化性狭窄。颈动脉血管超声(Carotid artery ultrasound, CAU)可评估颈动脉颅外段有无狭窄以及斑块形成。在心源性卒中患者中，CAU 通常显示无颈动脉或椎动脉粥样硬化性狭窄。经颅多普勒检查(Transcranial Doppler, TCD)聚焦于颅内动脉微栓子检测，是评估颅内闭塞血管是否再通的重要检查。

4. CES 相关生物标记物

CES 患者常合并心房或心室扩张及心肌损伤，BNP 与 NT-proBNP 是检测心房压力升高的敏感指标，其水平波动与心脏容量或者压力超负荷有关，提示患者可能存在房颤、心功能衰竭等异常。BNP 以及 NT-proBNP 在心源性卒中患者症状出现后 72 小时内显著提高，是心源性卒中的独立预测因素[44]。Kawase 等研究者发现 CES 患者的 BNP 水平较非 CES 患者的高(366.6 pg/ml vs.105.6 pg/ml, $p < 0.01$) [45]。一项荟萃分析结果提示 BNP 在预测 CES 的灵敏度为 65%、特异度为 85%，NT-proBNP 在预测 CES 的灵敏度为 55%、特异度为 93% [46]。CES 多存在心脏及主动脉来源的栓子，而 D-二聚体是纤维蛋白的降解产物，与凝血系统的激活有关及血栓形成密切相关。心源性卒中患者的 D-二聚体高于其他缺血性卒中，是心源性卒中的独立危险因素[47]。Takano 等研究者发现用于区分 CES 与非 CES 的 D-二聚体的最佳截点为 300 ng/ml，灵敏度为 80%、特异度为 70% [48]。此外，研究指出，炎症标记物与房颤的病理生理学机制以及房颤相关的血栓形成存在相关关系[49]。Licata 等人发现炎症标记物(白细胞介素-1、白细胞介素-6、肿瘤坏死因子-α、C 反应蛋白)在心源性卒中患者中显著提高[50]，可能作为 CES 的潜在生物标记物。Licata 等研究者评估了 CES 患者中血浆炎症标记物的水平，结果发现与非 CES 相比较，CES 患者中肿瘤坏死因子-α (38.5 (22.2~46) pg/mL; $p < 0.0001$)、白细胞介素-6 (11 (5.5~19) pg/mL; $p = 0.0029$)、白细胞介素-1 (11.5 (8~13) pg/mL; $p < 0.0001$)的水平中位数显著较高[50]。

Sporns 等人的研究表明，与非心源性卒中相比，心脏栓子主要为富含红细胞以及纤维蛋白等成分组成的红色血栓[51]。研究表明，CT 扫描发现的大脑中动脉高密度征(Hyperdense Middle Cerebral Artery Sign, HMCAS)更常见于红细胞为主的红色血栓和混合血栓[52]，提示 HMCAS 是预测大脑中动脉血栓栓塞的敏感指标[53]。MRI-T2WI 梯度回波(Gradient echo, GRE)扫描闭塞血管内的红色血栓时表现为管腔低信号，被称作 GRE 敏感性血管征[54]。研究表明，红色血栓 GRE 敏感性血管征占心源性卒中的 77.5%，与继发的血管再通密切相关[55]。这提示 HMCAS 及 GRE 敏感性血管征均可作为 CES 的潜在影像生物学标记物。大脑中动脉供血区脑梗死患者中，岛叶受累的患者确诊为心源性卒中的比例(30.1%)高于无岛叶受累的患者(3.3%) [56]，这提示岛叶受累可作为心源性卒中的影像学标志。

此外，随着新技术的发展，与房颤、心源性卒中相关的 miRNA、代谢组学产物等标记物也相继被发现。研究表明，miRNA 与心房颤动的发生机制有关，可以作为心源性卒中的生物标记物[57]。Lee 等人发现多种代谢组学产物可以区分心源性卒中和大动脉粥样硬化性卒中[58]。但该检查费用昂贵，当前多用于科研方面，在临床应用中存在局限性。

5. 辅助诊断人工智能技术

目前，机器学习、深度学习、卷积神经网络等多种人工智能模型在心源性栓塞源的分析方面应用广泛。基于人工智能的房颤预测模型可以根据心电图的特征预测房颤，预测模型结果表明，患者年龄分布越广，预测模型效果越好[59]。一项基于电子健康数据库的人工智能模型可以识别与 CES 相关的危险因素，对于 CES 的诊断率为 92.2% [60]。综上所述，以深度学习为代表的人工智能技术通过综合评估心电图特征和危险因素，显著提升了房颤预测与心源性栓塞源的识别效能，其泛化能力在跨年龄层数据中展现出临床价值。然而，当前模型性能仍受限于医疗数据的完整性与标注质量。未来通过构建多中心标准化数据库、融合多模态生物信号，有望突破现有技术瓶颈，实现从辅助诊断向精准预防的跨越发展。

6. CES 相关评估量表

在临床中，CHA_2DS_2-VASc 评分被用来评估非瓣膜性心房颤动发生卒中的风险。2024 欧洲心脏病学会(European society of cardiology, ESC)心房颤动管理指南将卒中风险评估更新为 CHA_2DS_2-VA，去除了

“性别”这一风险因素[61]。此外，随着基因检测技术的发展，多个与房颤和心源性卒中相关的基因被发现，房颤多基因风险评分(Atrial fibrillation- polygenic risk score, AF-PRS)可以帮助诊断心源性卒中[62]。

7. 展望与挑战

近年来，随着心电监测技术的迭代升级、影像学技术以及分子生物学检测技术的快速发展，结合人工智能辅助诊断系统的多维度数据分析能力，心源性卒中的早期识别准确率逐步提升，为个体化诊疗方案的制定提供了客观依据。然而，新型影像技术以及基因检测技术成本较高，基层医疗机构普及率不足，其在临床应用中存在局限性。未来可通过多学科协作推动技术迭代与成本控制，建立分层诊疗体系以实现精准医学与卫生经济学的平衡发展。

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