聚焦超声治疗脑部疾病的现状与应用

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摘要 超声治疗具有非侵入性、空间分辨率高、刺激靶点多等特点,其磁共振兼容效果良好,不良反应较少,逐渐应用于脑部疾病的治疗。综述了超声应用于治疗神经系统疾病的2种主要类型:高强度聚焦超声治疗和低强度聚焦超声刺激治疗。目前,高强度聚焦超声在治疗脑肿瘤、神经性疼痛、震颤、帕金森、强迫症和脑中风等疾病领域具有广泛的临床应用;低强度聚焦超声刺激在治疗抑郁症和癫痫等疾病方面具有临床应用。经颅精准聚焦的聚焦超声可非侵入性治疗神经系统疾病,有望成为治疗脑部疾病新的临床手段。

关键词 聚焦超声;经颅;脑部疾病

随着人口老龄化进程的加快以及各种精神压力的加大,脑部疾病的发病率呈逐年上升趋势,严重威胁着人类的健康与生命[1]。目前脑神经系统疾病主要疗法有开颅手术、脑深部电刺激(deep brain stimulation, DBS)、经颅神经调节(non-invasive brain stimulation,NIBS)和伽马刀放射外科(gamma knife radio surgery,GKRS)手术。开颅治疗有创,且预后差;DBS手术需植入式电极和需定期侵入性更换电池;NIBS主要有经颅磁刺激(transcranial magnetic stimulation,TMS)和经颅直流电刺激(direct cortical stimulation,DCS)2种方式,这些疗法虽具有非侵入性、作用机制较明确、适用范围广、安全性较高等特性[2],但尚存在穿透深度浅、空间分辨率低(大于1 cm)、可能诱发癫痫、软组织局部损伤等问题;GKRS手术虽然具有非侵入性的特点,但是也存在非靶区组织电离辐射的问题。

超声治疗具有非侵入性、空间分辨率高、刺激靶点多、磁共振兼容效果好等特性,可作为消融[3]、刺激[4]和可逆性抑制[5]神经元活动的新兴治疗手段。本文综述高强度聚焦超声治疗和低强度聚焦超声刺激治疗的研究现状及临床应用。

1 高强度聚焦超声治疗

高强度聚焦超声(high intensity focused ultrasound,HIFU)是利用超声波的组织穿透性和可聚

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焦性，将体外换能器发射的对组织无损伤的低强度超声波聚焦在体内待治疗区域上[6]，在超声波的热效应、机械效应和空化效应等作用下，使得体内待治疗区域瞬间能量集中，通过升温至54℃以上发生热凝固性坏死或者机械振动结合微泡进行血栓消融的治疗技术[7]。

1.1 高强度聚焦超声治疗现状

1927年Wood等[8]在聚焦超声的物理和生物效应实验时发现超声聚焦后会产生热效应。1944年Lynn等[9]提出将聚焦超声应用于医学治疗。1954年，Fry兄弟[10]通过动物实验发现聚焦超声可破坏大脑深处病变组织。1989年，Fink等[11]基于时间反转法使超声经不均匀介质后在目标靶点处聚焦。1996年Thomas等[12]利用时间反转法校正HIFU经颅聚焦的相位差。1998年Hynynen等[13]和2004年Pernot等[14]通过在离体人颅骨内植入水听器实现了时间反转聚焦及相位校正。1998年Sun等[15]利用MRI图像获得人颅骨结构参数并导入数值仿真模型。2002年Clement等[16]利用CT扫描数据获取人体颅骨结构及其声学参数并建立相对应的数值仿真模型。2003年Aubry等[17]利用头颅CT数据建立了含颅骨内部三层细微结构的超声经颅传播数值仿真三维模型，并基于时间反转法进行了经颅HIFU声压场的数值仿真和HIFU经颅自适应聚焦实验，验证了该模型的有效性。2006年Marquet等[18]提出了将时间反转法与幅值补偿法相结合经颅调控方法，并经活体猴脑的HIFU实验证明在颅内焦域处形成损伤。同年，McDannold等[19]利用1.5 MHz聚焦超声换能器对15只兔子的大脑中53个位置进行实验，结果发现在同样的条件下超声造影剂能够使诱发病变所需的声功率降为原来十分之一。2008年Tang等[20]利用移相键控法对驻波进行了消减研究，表明利用此方法可以抑制颅内驻波的形成。2009年Marquet等[21]基于头颅CT数据，结合时间反转和自适应校正技术对离体猴头骨和干燥人颅骨进行了数值仿真与离体实验研究，验证了通过数值仿真模拟活体颅内声束传播特性及HIFU经颅脑组织内聚焦治疗的可行性。2013年Marquet等[22]基于活体猴子颅骨的CT图像数据，通过数值仿真获取相控换能器阵元的相位信息并调控相控换能器，实验结果证明经颅聚焦时的散焦及焦点可以通过数值仿真获取的相位信息进行调控。2015年丁鑫等[23]基于人体头颅CT数据建模法和时间反转法提出了换能器相位和幅值调制相结合的颅骨热点消减法，可在降低颅骨处热点温度的同时提高目标焦点处的温升。2018年常诗卉等[24]基于多焦点融合经人体颅骨仿真形成了几乎温度均匀分布的平台温度的焦域。

由于具有非侵入性、无毒副作用和可重复治疗等特点，HIFU经颅治疗脑胶质瘤、神经性疼痛、震颤和帕金森等脑部神经系统疾病逐渐进入临床试验，并应用于临床治疗[25]。

1.2 HIFU的临床应用

1.2.1 脑肿瘤

胶质瘤是脑肿瘤中最常见的恶性肿瘤，目前主要疗法为外科手术切除、放疗和化疗，均存在对正常组织损伤的问题[26]。2006年Zvi等[27]利用ExAblate 2000系统对3例脑胶质瘤患者在开颅下进行了核磁共振引导高强度聚焦超声（magnetic resonance guided high intensity focused ultrasound，MRgHIFU）热消融临床试验，其中1名患者出现神经功能缺损。2010年McDannold等[28]利用开口直径30 cm的512阵元半球形相控换能器（以色列ExAblate 3000）对3例脑胶质瘤男性患者（23岁、34岁、47岁）进行I期临床试验，在连续超声波频率670 kHz、功率650~800 W的MRgHIFU经颅治疗条件下，临床试验结果表明由于设备功率限制未能形成有效焦域，此外在对第4名男性患者在频率0.22 MHz的条件下进行治疗时引起颅内出血并导致患者死亡。2014年Daniel等[3]利用曲率半径30 cm的1024阵元半球形相控换能器（以色列ExAblate Neuro）对1例63岁男性脑胶质瘤患者进行I期临床试验，在超声频率650 kHz、总功率150~950 W、持续时间10~25 s的经颅MRgHIFU治疗条件下辐照25次，术中17次辐照MRI检测到形成了温度峰值55~65°C的有效治疗焦域；术后通过弥散加权MRI发现在治疗目标肿瘤内有多个明亮致死组织，随访21 d后，MRI图像显示肿瘤消融，术后长期检查显

示神经功能缺损得到改善。HIFU治疗仅适用于手术位置不理想的界限分明的病变(如转移灶或良性肿瘤),但对于恶性胶质瘤等具有不理想病理学病变的治疗方案仍需要进一步探究[29]。

1.2.2 神经性疼痛

神经性疼痛(neuropathic pain,NP)是神经纤维受损或功能障碍疾病,常用化疗药物可能引发NP,常规疗法有药物和手术治疗,但存在抗药性和深部脑区手术位置不理想等问题[30]。2009年Martin等[31]首次报告利用开口直径30 cm的1024阵元半球形相控换能器(ExAblate 4000)经颅对9例药物顽固慢性NP患者(45~75岁)进行选择性中央外侧丘脑消融治疗,在超声频率650 kHz、辐照时间10~20 s、峰值温度53~60°C的经颅MRgHIFU治疗条件下,产生长度3~5 mm的治疗焦域,术后患者疼痛暂时缓解30%~100%,未产生神经功能损伤;术中患者出现前庭感觉和感觉异常等不良症状。2012年Jeanmonod等[32]利用ExAblate 4000对12例药物顽固的NP患者进行中枢外侧丘脑消融治疗,在超声频率650 kHz、靶区温度达到51~64°C的经颅MRgHIFU治疗条件下,术后48 h的平均疼痛缓解率68%;术后3个月随访平均疼痛缓解率49%(9例),术后1年随访平均疼痛缓解率57%(8例);有1名患者出现目标丘脑出血,并伴有运动性丘脑缺血。在经颅精准聚焦条件下,HIFU可通过消融中央外侧丘脑非侵入性治疗NP。

1.2.3 震颤

震颤(essential tremor,ET)是一种常见的运动障碍疾病,通常表现为上肢的动作性震颤,65岁以上人群患病率约4.6%[33],一般症状轻微者无需治疗,只有影响日常生活和工作时才需要药物治疗,而对于药物难治性的重症患者可考虑手术治疗,但药物治疗可能伴有剂量相关的不良反应,手术存在并发症的风险[34]。2013年Lipsman等[35]利用ExAblate Neuro系统对4例患有慢性和药物耐受性的男性ET患者,在超声频率650 kHz、功率300~1250 W、持续辐照时间10~25 s的治疗条件下,进行经颅MRgHIFU丘脑消融治疗,治疗后3个月震颤临床评估量和影像学检查结果表明患者手部震颤改善,同时出现了感觉异常和深静脉血栓等不良反应。2016年Elias等[36]利用与Lipsman等相同治疗方式,对15例药物难治性ET患者的丘脑单侧腹侧中间核进行辐照治疗,疗效表明丘脑靶区消融后手部及全身震颤均有明显改善,部分患者在治疗中也出现运动和言语障碍、永久性感觉异常。2017年Schreglmann等[37]对符合介入治疗标准的6例58~75岁ET患者进行了经颅MRgHIFU震颤手对侧小脑丘脑通道消融手术,术后患者手动敏捷性提升,注意力、协调性和整体认知能力无变化,同时也出现了约3个月的同侧手笨拙和轻度步态不稳的临床问题。同年,Zaaroor等[38]利用Exablate 2000系统,在超声频率650 kHz、靶区分阶段加温(41~46°C、46~50°C、60°C)的治疗条件下,对46~87岁(平均年龄68.9±8.3岁)、平均疾病持续时间12.1±8.9年的18例ET患者进行经颅MRgHIFU治疗,术中存在暂时性头痛(11例)、持续性眩晕(14例)和头晕(4例)、恶心(3例)、头皮灼热(3例)、呕吐(2例)和嘴唇感觉异常(2例),术后手部震颤停止,1个月随访震颤再次出现并逐渐恶化,同时出现持续性步态共济失调(5例)、不稳定感(4例)、味觉障碍(4例)、乏力(4例)和手部共济失调(3例)。2018年Tian等[39]利用Exablate 4000系统对8例药物难治性ET患者进行经颅MRgHIFU治疗,消融其优势手对侧丘脑的腹侧中间核,治疗后利用超声检查,治疗前后利用震颤评分等级(clinical rating scale for tremor,CRST)进行评估,患者术后CRST评分立即下降了45.90%±14.40%(P=0.0078),在术后3、6个月随访发现患者CRST评分上升了28.67%±40.48%(P=0.0312),即术后随时间的延伸患者震颤程度逐渐加重。HIFU可无创经颅进行丘脑腹侧中间核消融治疗,减轻手部及全身震颤,但聚焦位置不精确会影响周围组织,导致短期或长期异常反应。

1.2.4 帕金森

帕金森(Parkinson′s disease,PD)是神经退行性疾病,终生发病率约2%[40],传统的治疗方法有药物、手术和经颅电刺激治疗等,但长时间服药会导致剂量相关副作用如异动症等[41]、手术有创[42]、经颅电刺激需要侵入性放置电极和更换电池[43]。

2014年Magara等[44]首次利用ExAblate Neuro系统通过MRgHIFU对13例PD患者进行了经颅睑缘丘脑消融治疗,在超声频率710 kHz、最大功率1200 W、靶区达到52~59℃温度的治疗条件下,重复5次治疗,在T2加权图像上可见消融灶;术后随访中帕金森病综合评分(unified parkinson's disease rating scale,UPDRS)和整体症状缓解程度(global symptom relief, GSR)评估,发现术后患者的UPDRS(60.9%)和GSR(56.7%)均降低,临床症状得到改善。2015年Bauer等[45]利用ExAblate 4000系统通过经颅MRgHIFU方式对1名患有双相情感障碍和抗药性PD的45岁男性患者进行了下丘脑消融术,在超声最大能量1200 J、重复辐照3次、每次持续辐照15~25 s、最大温度达到60℃的治疗条件下,在丘脑上形成3 mm×3 mm×4 mm损伤区域;术后9个月后随访发现患者UPDRS评分下降、震颤得到抑制,双相情感障碍程度有所加深。2017年Raul等[46]利用MRgHIFU对10名明显不对称PD患者(16~39岁)单侧丘脑在超声声能1200~36680 J、辐照时间154~379 s治疗条件下进行经颅消融治疗,但术后6个月的随访中发现36例暂时性步态共济失调等不良反应。2018年Young等[47]使用Exablate 4000系统通过经颅MRgHIFU方式对10例药物顽固性且运动障碍为主的PD患者(52~73岁)在超声能量1500~33840 J、持续时间10~31 s和焦域平均温度54.9℃的治疗条件下进行了单侧苍白球消融治疗,治疗后8例1年后随访UPDRS和统一运动障碍评分可知震颤改善,其中1例66岁男性患者出现发声异常,另外2例未完成全部计划评估。2020年,Rafael等[48]采用MR成像技术评估了MRgFUS丘脑消融手术对患者大脑代谢的影响,结果表明,治疗后小脑、丘脑下区域、苍白球内膜、运动和运动前皮质区域以及扣带回均代谢降低($P<0.001$);顶叶后部和枕叶区域发现弥漫性代谢增加,PD相关的代谢性大脑模式表达显着下降($P<0.05$),从而为MRgHIFU治疗PD提供理论依据。HIFU通过经颅消融下丘脑或单侧丘脑、苍白球等位置,可改善PD临床症状,但聚焦位置不准会导致暂时性步态共济失调等不良反应,且可能会加深患者的双相情感障碍。

1.2.5 强迫症

强迫症(obsessive-compulsive disorder, OCD)是一种以强迫思维和强迫行为为主要临床表现的神经精神疾病,终身患病率约2%~3%[49],临床上常用治疗方式有药物治疗、心理治疗及其心药综合治疗,但心理治疗残余症状较多且治疗效果不持久[50],药物治疗仅对部分患者有效且存在副作用[51]。2014年Jung等[52]利用ExAblate 4000对4例难治性强迫症患者(22~44岁)进行了经颅MRgFUS内囊前肢消融,在超声频率650 kHz、靶区温度阶段性升温(40~42°C持续10 s、51~56°C持续3 s)的治疗条件下,超声处理次数23~36次、辐照时间10~31 s、整个过程持续5~7 h,术后6个月随访发现患者Yale Brown强迫症状量表评分逐渐改善(平均改善33%),抑郁(平均减少69.4%)和焦虑(平均减少61.1%)持续的改善。2015年,该团队[53]利用经颅MgFUS对6例OCD患者进行了双侧前肢囊消融治疗,经6个月随访并进行患者头部MRI检测,发现病变区域大小呈先增大后减小趋势,其中1例靶区温度不足(<52℃)治疗失败,可能与患者颅骨结构有关。2018年Kim等[54]利用ExAblate 4000系统通过经颅MgFUS方式对4名OCD患者(22~44岁)进行双侧前肢囊消融治疗,在超声频率650 kHz、辐照时间10~31 s、靶区温度达51~56℃的治疗条件下进行治疗,术后进行6个月随访,4名患者汉密尔顿焦虑量表(Hamilton rating scale for anxiety, HAMA)评分提升,MRI图像发现术后1周出现水肿。同年Kim等[55]利用ExAblate 4000系统通过经颅MgFUS方式对11例难治性OCD患者内囊前肢进行辐照,超声能量逐渐提升直至靶区温度达到51~56℃并持续辐照3 s,经2年随访,术后患者汉密尔顿抑郁量表(Hamilton rating scale for depression, HAMD)和HAMA评分均下降,但出现暂时性头痛和前庭症状。HIFU经颅消融内囊前肢消融可非侵入性治疗OCD,术后患者症状减轻,但聚焦位置不准会出现暂时性头痛等不良反应,靶区温度不足可导致治疗失败。

1.2.6 脑中风

脑中风又称为脑卒中,是由于脑栓塞(80%~

87%的病例为缺血性)或颅内出血(出血性)等原因使脑缺血而导致的突发性神经性症状,可致瘫痪、意识障碍、语言障碍甚至死亡[56]。机械取栓疗法是近端大血管闭塞中风患者的常规疗法,该疗法不适用于出血性和急性缺血性中风患者[57]。可利用超声波的机械效应[58]和空化效应[59]溶栓,成为一种潜在的脑中风治疗手段。缺血性中风治疗需恢复或增强患处血液再灌注,组织纤溶酶原激活剂(tissue plasminogen activator,tPA)是急性缺血性中风治疗主要药物[60],目前tPA仅对2%~6%的中风患者有效,且有增加脑出血的风险[61]。超声结合微泡能够有效溶栓[62-64],当HIFU脉冲长度、压力或激光注量增加时,溶栓效率增加[65-67],在相同声功率和激励条件下,双频溶栓效率在统计学上优于单频溶栓[68],随梗阻出现时间的增长超声对相对表观扩散系数影响越小,溶栓效果越差[69]。

2005年Daffertshofer等[70]将26名急性中风患者分为2组,对照组(n=2)仅接受tPA治疗,目标组(n=14)接受tPA注射后30 min在超声频率300±1.5 kHz(避免产生驻波)、时空平均声强700 mW/cm^{2}的治疗条件下接受4阵元菱形分布相控换能器超声治疗,术后随访表明,2组的发病率、死亡率和再通率均无明显差异,目标组14名患者中有13名在MRI中显示出血迹象,这项研究证明了低频超声会导致脑出血的发生率增大。2011年Hlscher等[71]利用ExAblate 4000系统,在超声输出功率为270 W、占空比20%、脉宽200 ms、辐照时间30 s的经颅治疗条件下在人体遗体上进行了420次溶栓治疗,结果表明超声可即时溶栓。2015年Schellinger等[72]发起了一项预计样本量为824例的III期临床试验,试验将年龄为18~80岁的中风患者分为2组,对照组仅接受tPA治疗,目标组接受tPA注射后30 min在超声频率为2 MHz的治疗条件下辐照2 h,治疗结束60 min后进行超声检查,90 d后随访,该临床试验尚未公布研究结果。此外,有研究表明缺血性中风小鼠小脑外侧核减轻栓塞。目前对于由颅内血管自发破裂引起的出血性脑中风,目前仅利用超声在猪及人体遗体上进行了少数实验,证明经颅MRgFUS可将脑血栓液化[73]。

2 低强度聚焦超声刺激

低强度聚焦超声(low intensity focused ultrasound,LIFU)脑刺激疗法是将超声波聚焦到体内治疗位置,主要利用超声波的机械效应刺激神经元使其兴奋或抑制的疗法,是一种新型、无创的神经调控技术,其在脑科学研究及脑疾病治疗方面具有巨大发展前景[74]。不同参数超声可通过兴奋或抑制神经元的活动[75]、刺激离子通道开放[76]、刺激神经传导环路[77]、调节蛋白表达水平等调节神经[78]。

2.1 低强度聚焦超声刺激的研究现状

1929年Harvey等[79]利用连续超声波照射青蛙和乌龟的静态心室肌实验时发现超声可诱发周围神经兴奋。1958年Fry等[5]利用连续超声波辐照猫的外侧膝状核,结果发现超声可诱发中枢神经系统发生可逆性功能变化。2005年Tsui等[80]利用连续超声波辐照青蛙离体坐骨神经束5 min,结果发现超声时间平均强度1 W/cm^{2}时可增加复合动作电位(CAP)的幅度,强度2、3 W/cm^{2}时可降低CAP幅度。2008年Tyler等[76]发现超声可通过电压门控的钠离子和钙离子通道进而调控离体海马片神经元活动。2010年Tufail等[81]首次在活体小鼠上证实超声波可对目标脑区进行可逆性兴奋与抑制双向刺激。2011年Yoo等[75]证实了超声波可以兴奋或抑制活体兔的躯体运动区域和视觉区。2014年Panczykowski等[82]指出低频超声可透过颅骨直接刺激人脑的初级躯体感觉皮层,进而影响人脑对触觉的分辨能力。上述研究表明,超声是一种潜在的NIBS手段[83]。

2.2 LIFU的临床应用

2.2.1 抑郁症

重度抑郁症(major depressive disorder,MDD)是一种精神障碍疾病,终生患病率约16%[49]。目前MDD主要用药物治疗,该病的耐药性和复发率高[84],与神经炎症导致的海马体体积减小和脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)水平有关。利用超声刺激海马体可导致BDNF蛋白水平升高[85]、增加海马齿状回新生神经元的增殖[86]从而达到治疗的目的。2018年Kim

等[87]利用ExAblate 4000系统通过MgFUS方式对一名患有药物顽固性MDD的56岁女性进行了双侧前囊消融治疗,焦域最高温度53~54℃,术后患者HAMD评分由26变成8,贝克抑郁量表(Beck depression inventory,BDI)评分由26变为12,均有显著下降。LIFU经颅刺激海马体或HIFU消融双侧前囊均可减轻MDD临床症状。

2.2.2 癫痫

癫痫是脑细胞群异常的超同步放电所引起突然的脑功能障碍,约有1/3的癫痫疾病具有抗药性,顽固性癫痫目前主要治疗方法为侵入性神经外科法[88-89],其中,超声可有效降低EEG功率[90]、抑制癫痫尖峰[91],利用LIFU辐照脑皮质、海马[92]可减少癫痫发作。2016年Monti等[93]利用开口直径和曲率半径71.5 mm的单阵元凹球面换能器对脑外伤后19 d处于昏迷状态的男性患者的丘脑部分进行刺激,在超声载波频率650 kHz、脉冲重复频率100 Hz、脉冲宽度0.5 ms、时空平均声强720 mW/cm^{2}的临床试验条件下,每次持续30 s、间隔30 s,重复辐照10次,治疗后3 d观察到临床意义的改善。LIFU经颅刺激脑皮质、海马或丘脑可非侵入性减少癫痫发作和改善临床症状。

3 结论

对聚焦超声治疗发展现状、在神经外科及中风溶栓方面的应用进行了综述,聚焦超声治疗具有无创/微创、分辨率高等特性。由于颅骨与周围组织声学差异较大会导致超声经颅聚焦位置偏移和靶区能量不足等问题,可基于头颅CT建立数值仿真模型筛选超声经颅聚焦临床治疗的有效参数,为临床治疗提供更加安全有效的治疗方案,可在一定程度上解决该问题,在不久的将来经颅聚焦超声有望成为脑部疾病新的临床治疗手段。

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Development status quo and applications of focused ultrasound in the treatment of brain diseases

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Abstract The incidence of neurological diseases is increasing year by year, which seriously threatens human health and life. Ultrasound has been gradually applied to the treatment of brain diseases due to its non-invasiveness, high spatial resolution, mutiple stimulation targets, good MR compatibility effect and less adverse reactions. At present, the treatment of ultrasound neurological diseases mainly includes high-intensity focused ultrasound thermally lethal disease tissue, mechanical vibration to dissolve thrombus and low-intensity focused ultrasound stimulation therapy. This article briefly describes the development status of high-intensity focused ultrasound and its clinical applications in brain tumors, neuropathic pain, tremor, Parkinson, obsessive-compulsive disorder and stroke, as well as the development status of low-intensity focused ultrasound and its clinical applications in depression and epilepsy. Transcranial focused ultrasound can be used to treat neurological diseases non-invasively, but the impact of the skull needs to be fully considered.

Keywords focused ultrasound; transcranial; brain diseased

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