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医学生物物理

空化增效高强度聚焦超声治疗研究进展

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【摘要】高强度聚焦超声(HIFU)已被证实是一种安全、有效的无创实体肿瘤消融方法,但目前面临的主要问题是治疗时间相对较长、治疗效率低。在HIFU治疗中可以通过空化实现增效,通过何种方式产生空化效应,如何提高空化对热效应的增效作用一直是研究者关注的问题。本文分别从体外引入空化核、声学驱动产生空化核两个角度,综述在HIFU治疗中通过微泡造影剂、相变纳米液滴、双频HIFU、脉冲波增强热效应、调强峰值声压增强HIFU的治疗效果。

【关键词】高强度聚焦超声;空化效应;热效应;增效;综述
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Advances in research on cavitation-enhanced HIFU therapy

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Abstract: High intensity focused ultrasound (HIFU) has been proven to be a safe and effective non-invasive solid tumor ablation method, but the main problems currently faced are relatively long duration of treatment times and low treatment efficiency. In HIFU treatment, it is possible to achieve synergy through cavitation. How to generate cavitation effects, and how to improve the synergistic effect of cavitation on thermal effects have always been a concern of researchers. From the perspective of *in vitro* introduction of cavitation nucleus and acoustically driven cavitation nucleus, the effects of microbubble contrast agent, phase change nanodroplets, dual-frequency HIFU, pulse-enhanced thermaleffect and intensified peak sound pressure enhance in HIFU treatment are reviewed.

Keywords: high intensity focused ultrasound; cavitation effect; thermal effect; synergy; review

前 言

高强度聚焦超声(High Intensity Focused Ultrasound, HIFU)是近年来兴起的非侵入性体外肿瘤治疗技术,可在超声或者MRI监控下对局部肿瘤进行定点消融[1]。HIFU消融肿瘤的原理为:体外以一定的方式将低能量的超声聚焦到体内形成局部高能量靶点,利用超声波的热效应、空化效应、机械效应等生物学效应使靶区内组织产生凝固性坏死,而不对周围组织产生伤害[2]。目前HIFU疗法已应用于肝[3]、肾[4]、膀胱[5]、脑[6]和前列腺[7]等良恶性肿瘤治疗中,许多临床试验对HIFU治疗的可行性和安全性进行了研究。然而,目前临床上主要采用单点辐照方式治疗肿瘤,对于体积较大、血供丰富、位置较深的肿瘤,其治疗时间相对较长、治疗效率较低。为解决这些问题,本文对从体外引入空化核方法、通过声学驱动产生空化核方法增强HIFU治疗的热效应的研究进行综述。

1 体外引入空化核

1.1 微泡造影剂

微泡造影剂增效HIFU的机制为:首先,微泡造影剂与靶组织之间有显著的声阻抗差,有利于将声能转变成热能;其次,微气泡可作为空化核增强空化效应,而空化的发生可以增效HIFU治疗[8]。Kaneko等[9]比较了等量微泡造影剂(Levovist)与盐水对HIFU损伤离体兔肝的组织温升和凝固性坏死体积。使用频率为2.18 MHz超声分别辐照两组兔肝60 s,

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发现使用造影剂后,靶区温度升高更快且损伤面积更大。Umemura等[10]采用微泡结合3.2 MHz超声波消融小鼠肾组织,结果表明微泡剂(Definity)的使用使组织温度升高数倍且与模拟仿真[11]的预测一致。Tung等[12]研究超声造影剂(Optison)增强HIFU热效应时,用1.85 MHz HIFU脉冲作用于透明组织模型,结果提示病变大小强烈依赖于声功率和UCA的浓度并且所需的声功率降低约30%。国内外研究证实,微泡造影剂可以明显增强HIFU治疗[13-17],但通过B超成像[18]和数值仿真[15-17]针对离体牛肝、活体白兔腿部的研究发现,联合微泡造影剂的HIFU消融后,出现治疗区域焦点移位、焦斑不可控、病变形状由雪茄形向蝌蚪形的转变等现象,从而限制了其临床应用。

1.2 相变纳米液滴

在体内产生含有微溶气体的微泡增强HIFU治疗的热效应,可以通过短脉冲激励纳米乳剂(nm尺度)在体内相变为微气泡,微气泡可改变组织的声学特性增强声散射,使能量损耗在靶区,增强HIFU对靶区的损伤[19-20]。Kopechek等[21]利用1.5 MHz的HIFU脉冲辐照兔VX2肿瘤,在实验中发现注入纳米乳剂后,惯性空化强度和温度明显升高。Zhang等[19]将组织模拟材料中有无十二氟戊烷液滴分为实验组和空白组,采用2 MHz的HIFU短脉冲分别辐照后发现,实验组的材料粘度和声致液滴相变阈值升高。Kawabata等[22]研究2H,3H-全氟戊烷和全氟戊烷的乳剂性质与产生相变所需超声强度的关系时发现,强度阈值随该比例的增加而增加,结果表明可以通过超声能量控制纳米乳剂的相变。以上研究提示纳米乳剂可以实现组织被动靶向治疗的作用,增强HIFU的热效应,但是产生的微气泡留存时间过短。Kawabata等[23]进一步研究了低压连续超声对维持微泡的影响,提出同时采用1 MHz脉冲波叠加低幅度的连续波辐照含有纳米乳剂的凝胶体模,结果显示可以延长微泡的存活时间同时控制其活性。相变纳米液滴对于增强HIFU肿瘤治疗不仅在效率而且在靶向性方面都是非常理想的,但是相变纳米液滴和HIFU仪器组合仍然需要长时间的临床试验。

2 声学驱动产生空化核

2.1 双频HIFU

近年来研究发现双频HIFU可显著增强空化效应,不仅有助于提高温升,还有助于监测热沉积的位置,进而缩短治疗时间。按照频差大小可分为两种:频差较小,不超过0.1 MHz;频差较大,一般大于500 kHz。Gilles等[24]采用相同压力幅度,频差为34 kHz(531 kHz,565 kHz)激励信号线性叠加和仅单频(552 kHz)激励,经皮超声溶栓治疗中研究发现,双频HIFU的惯性空化阈值降低了38%。Saletes等[25]进一步比较了单频(550 kHz)和双频(535和565 kHz)激发的效率,当实现80%溶栓时,双频所需的功率较单频小50%。Dingjie等[26]也得出了类似结论,并在研究占空比与超声溶栓效率的关系时发现,双频率(1.45和1.50 MHz)叠加激励仅在单频激励占空比一半时即可达到相同的溶栓率且溶栓速度能提高2~4倍。以上研究均表明,相比单频HIFU辐照,频差较小的双频HIFU可以优先降低治疗所需的声功率和空化阈值,有效提高HIFU治疗效率。

Li等[27]研究了不同频差导致双频HIFU聚焦声场的变化,结果显示频差越大,声压分布越均匀,非线性现象越明显。Rybyanets等[28]提出了一种多频谐波技术,使用双函数发生器和功率放大器同时激励第一(205 kHz)和第三(690 kHz)奇次频率信号,在相同的超声能量下辐照脂肪细胞,与仅690 kHz频率激励相比,显著增强了组织消融体积。Lu等[29]在使用频差为1.2 MHz(1.2 MHz, 2.4 MHz)的双频HIFU消融离体肝脏和凝胶体模中发现,产生的病变大小比使用1.6 MHz的单频HIFU大约两倍。Feng等[30]还发现使用三频(28 kHz, 1 MHz和1.66 MHz组合)正交连续超声与单频HIFU相比,联合辐照可以显著提高空化产率。以上研究均证明通过改变双频HIFU的频差大小可以显著地提高组织的消融率,但消融率效果达到最佳与使用频差的范围尚有争议。

2.2 脉冲波增强热效应

在空化增强超声波热效应的研究中,由高强度短脉冲组成的HIFU序列产生气泡云,称为“触发脉冲”,并伴随中等强度长加热波以增强热效应,名为“加热波”,这个组合统称为“触发HIFU”。触发脉冲的总持续时间为10~100 μs,加热波的总持续时间为10~500 ms,强度类似于传统HIFU治疗中的强度[31-35]。Moriyama等[36]研究脉冲波产生的空化泡对组织温度升高的影响,通过使用1.12 MHz球形聚焦压电换能器先激励触发脉冲后加热波与单加热波作用于体模相比,实验和模拟均表明触发HIFU序列温升更高。Jimbo等[37]采用1 MHz扇形涡旋阵列换能器辐射出加热波产生环形聚焦区域覆盖6个扫描触发脉冲的焦点处消融鸡胸肉,实验结果表明组织温度升高是单独加热波的3倍。Sukovich等[35]还提出使用1 MHz的相控阵换能器通过改变输出声波的相位,在90、100、110 mm焦距上使用高能量触发脉冲产生空化云,用自身不能产生凝固性坏死的低强度

加热波进行辐照后，产生了坏死体积，证实采用该方法可显著缩短HIFU治疗时间。Taguchi等[38]进一步提出优化触发HIFU序列中的持续时间，研究中发现在触发脉冲产生空化泡的前提下，随着HIFU加热波单持续时间增加到10 ms左右时，空化气泡的振荡变得不再活跃。通过高强度短脉冲产生空化泡，后续加热波振荡空化泡产生热量增强HIFU治疗中的热效应，可以缩短治疗时间，增加消融率。

2.3 调强峰值声压增强热效应

负压对于产生空化气泡而正压使它们膨胀到空化气泡云是非常重要的。然而，由于非线性传播，在焦点处获得高负压是困难的，可以通过在基波叠加二次谐波形成调强负声压或正声压作为触发脉冲加速空化效应的产生[39-41]。Yoshizawa等[42]发现向水中的固体壁面采用特定超声序列先调强负声压峰值波（N波）之后立即调强正声压峰值波（P波）照射时，超声波可以高效地产生空化气泡。Sasaki等[43]将实验分为两组，组一使用0.8 MHz的基波和1.6 MHz的二次谐波的叠加激励后进行1 MHz的加热波辐照肌肉组织，组二仅单独触发脉冲后加热波辐照组织，结果发现组二产生的坏死体积明显大于组一。Takagi等[44]采用共焦球形压电换能器激发1.14 MHz的基波和2.28 MHz的二次谐波叠加的双频模式与单频激发基波1.14 MHz辐照鸡胸肉组织相比，结果表明双频模式产生空化所需的超声强度比单频模式减少约一半。采用这类方法可以有效地产生空化气泡，提高HIFU的治疗效率。

3 总结与展望

随着HIFU技术的不断发展和临床上取得的研究进展，人们对空化效应及其生物学效应的进一步研究已经成为热点。除上述报道外，各类研究层出不穷，如利用空化进行碎石术，组织摧毁术等，均显示出空化良好的应用前景。相信高强度聚焦超声技术也将随空化效应的应用而不断发展和完善，将从HIFU治疗机制、治疗方式及提高肿瘤治疗的效率上取得突破性进展，促进HIFU技术的发展和在临床的推广应用。

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