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血流灌注对高强度聚焦超声消融子宫肌瘤的影响

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【摘要】高强度聚焦超声(HIFU)治疗时,血流灌注会带走部分组织热量。为了保证治疗的安全性和有效性并提高治疗效率,需要在HIFU治疗过程中考虑血流灌注的影响。目前临床治疗已观察到血流灌注会降低HIFU疗效,但针对血流灌注的量化及如何控制血流灌注以提高HIFU疗效仍不明确。本研究以HIFU消融子宫肌瘤为例,分别从血流灌注对HIFU疗效的影响、子宫肌瘤血流灌注的检测、如何控制血流灌注以提高HIFU疗效这几个方面进行综述,旨在明晰血流灌注对HIFU疗效的影响,为临床控制并利用血流灌注提高HIFU疗效提供参考。

【关键词】子宫肌瘤;高强度聚焦超声;血流灌注;综述
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Effects of blood perfusion on high-intensity focused ultrasound ablation for uterine fibroids

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Abstract: Blood perfusion will take away part of the tissue heat during high-intensity focused ultrasound (HIFU) treatment. In order to ensure the safety and effectiveness of treatment and improve its efficiency, it is necessary to consider the effects caused by blood perfusion during HIFU treatment. At present, it is observed that blood perfusion will reduce the therapeutic effect of HIFU in clinic. However, the quantification of blood perfusion and its contribution mechanism on the therapeutic effect of HIFU are still unclear. Taking HIFU ablation for uterine fibroids as an example, the effect of blood perfusion on the therapeutic effect of HIFU, the detection of blood perfusion in uterine fibroids, and how to control blood perfusion to improve the therapeutic effect of HIFU are summarized in the study, aiming to clarify the effect of blood perfusion on the therapeutic effect of HIFU, and provide a reference for the clinical control and use of blood perfusion to improve the therapeutic effect of HIFU.

Keywords: uterine fibroids; high-intensity focused ultrasound; blood perfusion; review

前 言

高强度聚焦超声(High-Intensity Focused Ultrasound, HIFU)作为一种无创治疗技术能完整地保留患者子宫,具有良好的安全性和有效性,已被广泛应用于子宫肌瘤的临床治疗[1]。但由于受到不同患者肌瘤位置、深度、种类以及脂肪层厚度等组织特异性的影响[2-5],使得部分患者仍难以达到预期疗效[6]。影响HIFU疗效的另一个重要因素是血流灌注,活体组织中的血流温度通常为恒温,在HIFU消融过程中会带走部分热量,从而阻碍子宫肌瘤内的热沉积,导致消融靶区温度降低、单次消融体积减小、治疗时间延长和不规则的凝固性坏死区域[7-9]。临床研究表明,血流丰富的肌瘤由于声能量不容易沉积,在进行HIFU消融时往往难以达到理想的治疗效果[10]。因此,肌瘤的灌注特性与HIFU疗效有很大关系;然而,目前的研究对于血流灌注如何降低焦点处热沉积、如何量化血流灌注对HIFU消融靶区温升的影响仍缺乏清晰的认识。为此,本研究分别从血流灌注对HIFU疗效的影响、子宫肌瘤血流灌注的检测、如何控制血流灌注以提高HIFU疗效这几个方面

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进行综述，旨在为临床控制并利用血流灌注提高HIFU疗效提供参考。

1 血流灌注对HIFU疗效的影响

目前，国内外关于血流灌注对组织温升的影响已有大量的研究；针对超声消融中血流灌注对组织温升的影响也开展了相应的基础研究[11-12]。

先前的研究发现，聚焦超声治疗时的热扩散随着血流灌注率的增加而增大。在治疗过程中，血管直径大于200 μm会影响加热组织中的温度分布[13-15]。Yuan等[16]研究了不同血流灌注率对组织温升的影响，较高的灌注率可迅速带走组织中的热量，从而增加温度的振荡范围。Billard等[12]模拟了在灌注参数0~95 kg·m^{-3}·s^{-1}下，血流对组织温升的影响，结果显示随着灌注率的增加，峰值温度显著降低；当灌注率为95 kg·m^{-3}·s^{-1}时，峰值温度为无灌注时的一半，温度降低速率也随着灌注量的增加而增加；该研究还认为，在短脉冲超声辐照的情况下，灌注率对温升的影响较小。Zhao等[17]基于离体肝脏灌注系统研究灌注流量对HIFU消融体积的影响，结果表明，在连续波HIFU作用下，随着灌注流量的增加，坏死体积明显减小。在临床治疗中，陈锦云等[18]将靶区肌瘤的血液供应从大到小分为0~4级，研究了不同血供与HIFU消融剂量之间的关系，结果揭示血流灌注越丰富，实现相同损伤面积所需的超声剂量越高。综上可见，血流灌注对HIFU的临床影响是不可忽视的。

HIFU在治疗子宫肌瘤时会造成肿瘤血管的损伤，对肌瘤的血流灌注产生一定的影响。伍烽等[19]发现HIFU能从体外破坏肿瘤的小血管和毛细血管，从而增强HIFU治疗靶区的肿瘤细胞损伤。由于HIFU引起的血管损伤机制可能是对肿瘤血管壁的机械和高温作用，导致内皮和被膜介质破裂，随后是破坏性血管内血栓的形成[20]。因此，在HIFU治疗过程中同样也需要避免对正常组织，特别是重要器官的血管造成损伤。

以上研究表明，血流灌注会影响HIFU疗效，同时HIFU消融也会影响靶组织区域的血流灌注，为保证HIFU的安全性，需要在剂量预测研究中充分考虑血流灌注的作用。在早期的研究中，Pennes[21]提出一个带有灌注源项的简单传热模型，使得对活体组织温度预测的研究得到发展，模型反映了组织的温升还与血液灌注率和热传导有关。由于热容量和热导率在同一种组织中相对固定，血液灌注可能是HIFU治疗中影响温升的主要因素。Shih等[15, 22]利用Pennes模型探讨了热疗中热显著性血管对热剂量分布的影响；Patterson等[23]使用数学模型计算组织均匀加热时血流对温度分布的影响。两者的研究结果均表明，血液流动增加了实现相同温升所需的时间。Shih等[24]探讨了热显著性血管在热处理过程中对热损伤程度的冷却作用，结果表明，短时间高强度加热更能有效地实现整个靶区组织的消融；针对含有直径大于2 mm血管肿瘤组织的消融，研究观察到加热时间越长或加热功率密度越高，肿瘤完全坏死的可能性就越大。由此可见，剂量预测模型中考虑血流灌注率对HIFU疗效的影响是必要的。

2 子宫肌瘤血流灌注的检测

先前的研究表明，大多数肌瘤的外周都具有血管分布[25]，即假包膜，血管从该边缘渗入肌瘤中心[26]。肌瘤显示出高水平的促血管生成因子，导致肌瘤周围正常子宫肌层的血管生成以及血管密度增加[27]。与正常组织和良性病变相比，恶性病变（如肉瘤）可能具有更明显的血管形态和更大的血管直径[28-30]。因此，清楚地描述血管系统对于准确区分肌瘤和肉瘤非常重要，判别肌瘤是高度血管化还是接近无血管化对于选择合适的治疗方法也是至关重要的。目前用于评估量化血流灌注的方法大概有以下几种：激光或功率多普勒测量、动脉自旋标记（Arterial Spin Labeling, ASL）、超声造影（Contrast-Enhanced Ultrasound, CEUS）、4D血流成像、动态增强磁共振成像等。

激光多普勒流量测量和功率多普勒可以对血液供应进行评估[31-32]。Gannon等[31]利用激光多普勒技术研究子宫内膜在月经周期的变化，提供正常人月经周期子宫内膜单位体积红细胞通量变化的基准数据，但尚未建立标准化的方法。Takahashi等[33]利用ASL磁共振成像技术来评估子宫肌层灌注，由于临床限制，未能将造影剂用于肌瘤患者，因此无法将ASL信号数据与使用造影剂获得的灌注数据进行比较。但在脑磁共振成像中，使用ASL技术可以正确估计脑灰质的血流[34]。尚且需要进一步的研究以确定ASL信号与子宫血流的相关性。另外，CEUS也可用于组织中的血流评估。Stoelinga等[35]使用CEUS对子宫肌瘤微血管进行观测，对CEUS图像的分析揭示了外周边缘的初始灌注，随后通过从肌瘤外部到内部的血管增强整个病变。假包膜表现出轻微的高度增强，故使用这种方法可以将肌瘤的外周轮廓清晰地描绘出来。已有一些研究报道，CEUS还可以用于评估子宫动脉栓塞或消融治疗前后的消融率，以评估治疗的有效性。虽然CEUS是一项发展前景较

好的技术但也有其局限性，单次注射造影剂只能连续监测一个肌瘤，且扫描场比较小，所以较大的肌瘤（>8 cm）不能一次显示。因此，这种技术不适合描述具有多个纤维瘤的子宫肌瘤。

除了上述方法，磁共振成像技术也可用于血流灌注的检测。带有时间分辨率的3D相位对比磁共振血管成像（4D血流成像）已成为评估心血管系统血流的一种强有力的工具，可通过采集3D相位对比速度数据来评估心血管系统的血流[36-38]。4D血流成像允许在采集后对任何平面的血流进行量化，与常规2D相位对比是一个显著的进步。4D血流成像要求在每次采集前指定精确的平面，要求操作者必须具有丰富的专业知识和目标区域血管的先验知识[39]。大量的前期工作表明，4D血流成像与导管血管造影术、超声和2D相位对比磁共振成像等成熟的血流测量方法有很好的一致性[40-42]。然而，4D血流磁共振成像仅在少数特定的学术机构可用，尚未广泛应用于临床。除增强特征外，也可通过灌注参数来量化肌瘤的血液供应和血管化，而灌注参数可根据时间-强度曲线来计算获得。目前临床常用的技术为动态增强磁共振成像（DCE-MRI），可以定量评估肿瘤血液灌注，为临床子宫肌瘤供血的分级和量化提供重要手段，并进一步预测子宫肌瘤的HIFU疗效[43]。Suomi等[44]基于DCE-MRI数据，采用T1灌注反褶积算法，通过动脉输入函数曲线来量化血流（即灌注率），获得肌瘤和子宫肌层的灌注率分别为（301.0±25.6）和（233.8±16.2）mL/100 g/min，而臀大肌的灌注率为（30.1±3.7）mL/100 g/min。与周围肌层相比，肌瘤区域的血流增强，而高灌注率有很强的降温作用，从而揭示高灌注肌瘤较难消融的原因[45]。根据先前的报道，子宫肌瘤的灌注率一般为50~334 mL/100 g/min[46]，表1显示了部分组织的血流灌注参数W_b[47]。

表1 不同组织的血流灌注参数W_b

Tab.1 Blood perfusion parameter W_b of different tissues

组织	血流灌注参数W_b/kg·m^{-3}·s^{-1}
肾脏	63.0
心肌	17.0
肝脏	14.0
脑	9.0
子宫	8.0
脂肪	0.6
肌肉	0.6
肌瘤	5.5
无灌注组织	0.0

3 控制血流灌注以提高HIFU疗效

降低血流灌注对于提高HIFU疗效具有十分重要的临床意义。最小化灌注引起的冷却效应是增强子宫肌瘤HIFU疗效较为有效的策略。先前的一项研究表明，对子宫肌瘤的营养血管进行靶向HIFU消融可产生更有效的肿瘤坏死，且所需的超声剂量显著降低[48]。然而，目标血管消融在技术上是困难的，因为它需要血管造影术中图像的精确3D定位。因此，需要探究新的方法降低HIFU消融期间子宫肌瘤的血液灌注。有研究发现促性腺激素释放激素治疗会导致子宫肌瘤组织中微血管密度降低[49]，血管生成相关因子如血管内皮生长因子、碱性成纤维细胞生长因子和血小板衍生因子减少[50]。催产素也被认为是一种潜在的降低子宫肌瘤血流灌注的药物[51-53]。Wang等[54]使用增强对比超声观察了注射催产素前后子宫肌瘤血液灌注的变化，发现注射催产素后，所有患者肌瘤的血管体积显著降低，肌瘤内的血管体积减小，子宫肌瘤内的血流减慢。催产素的使用可显著降低肌瘤内的血液灌注，有助于提高HIFU治疗过程中的热沉积。此外，秦艳等[55]还开展了HIFU联合SonoVue损伤肝组织的实验研究，结果发现靶区含有较大血管时，HIFU联合SonoVue可形成有效损伤。因此，在HIFU治疗中加入促性腺激素释放激素、催产素以及SonoVue等也可以降低血流灌注的影响，从而提高HIFU疗效。

4 总结与展望

围绕血流灌注对HIFU治疗的影响，本研究以子宫肌瘤的治疗为例，首先综述血流灌注对HIFU疗效影响的相关研究，进一步介绍子宫肌瘤血流灌注的检测及量化方式，最后列举了控制血流灌注以提高HIFU疗效的临床及实验方法。通过综述可见，不同生物组织中存在不同大小的血流灌注，以子宫肌瘤为例可见消融靶区不同的血流灌注会带来较大的HIFU疗效差异。为实现安全有效的HIFU治疗并提高疗效，需要控制消融靶区的血流灌注，目前在临床上已有部分方法取得了较好的效果。但血流灌注对HIFU疗效的作用机制尚不明确，如何实现准确的血流灌注检测及量化研究仍不足。为了实现在HIFU治疗中控制并利用血流灌注，仍需要开展进一步的研究。

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