

散斑血流灌注成像在医学中的应用

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摘要 散斑血流灌注成像是一种利用红细胞对激光的散射特性监测血流灌注信息的医学成像技术。同传统血流灌注监测方法相比,其具有实时显像、分辨率高、成本低、无需造影剂等优点,尤其在体表血流监测方面独具优势。简述了散斑血流灌注成像的基本原理,总结了其技术进展及在眼底血流、脑血流、体表微循环监测及肿瘤血流灌注监测几个方面的应用,并介绍了其在监测鸡胚肿瘤血管新生方面的新应用。

关键词 散斑成像; 医学光学诊断; 血流成像; 实时监测

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Application of Speckle Perfusion Imaging in Medicine

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Abstract Speckle blood perfusion imaging is a medical imaging technique that monitors blood perfusion information based on the scattering characteristics of red blood cells to the laser. Its benefits over traditional blood perfusion monitoring technologies include real-time imaging, high resolution, cheap cost, and the absence of contrast chemicals, particularly in surface blood flow monitoring. This review focuses on the basic principle of speckle blood perfusion imaging, technical advancements, and its application in monitoring fundus blood flow, cerebral blood flow, body surface microcirculation, and tumor blood perfusion, as well as its new application in monitoring angiogenesis of chicken embryo tumors.

Key words speckle imaging; optical diagnostics for medicine; flow imaging; real-time monitoring

1 引言

传统的血流灌注监测方法主要有核磁共振成像^[1]、核素成像^[2]、X线成像^[3]、超声多普勒成像^[4]等,这些方法在应用中普遍存在成像成本高、对微血管分辨率低、需造影剂等缺陷,且X线成像和核素成像具有放射性、需考虑放射防护。散斑血流灌注成像(SFPI)是一种新型光学血流灌注监测技术,可克服传统成像方法的不足、适用于体表血流灌注监测,目前已在生物医学领域得到广泛应用。本文简述了SFPI的基本原理、最新技术进展,总结其主要应用领域及优势,并介绍其

在血管作用类药物药效评价方面的应用新进展。

2 散斑血流灌注成像设备及原理

SFPI设备主要由激光器、CCD相机及计算机系统构成,如图1所示。

血流灌注监测过程中,由激光器产生的激光照射至生物体表面产生散射光,体表血管中红细胞的运动使得散射光强度发生变化,而该变化与血流速度有关。CCD相机采集相应的散射光强,经计算机处理得到散斑血流灌注图可表征体表血管血流灌注的高、低。SFPI设备的具体成像原理及工作步骤如下:

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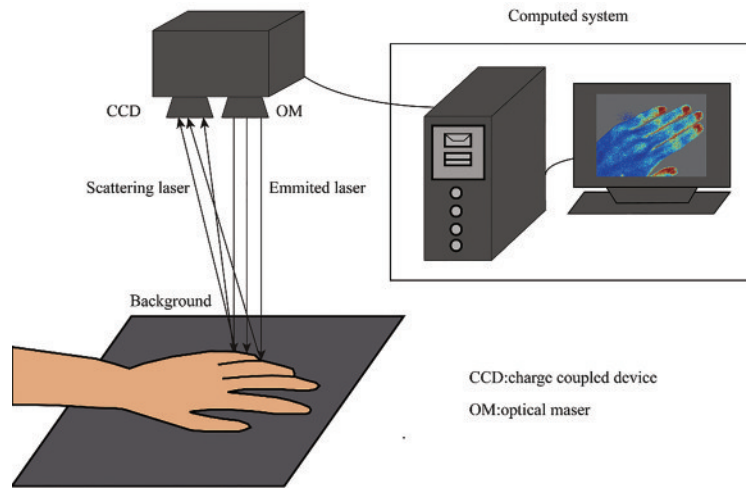


图 1 SFPI 设备

Fig. 1 SFPI equipment

1) 由激光器发射激光照射至生物体表面,生成散射光,CCD 相机将采集到的散射光作为一个“二维光强矩阵”(如 $N \times N$ 矩阵)记录下来,俗称“散斑图”。所谓“散斑”,是指由于散射体表面粗糙度不同导致的散射光光程改变形成的明暗相间的斑点状图案^[5]。由于被照生物体体表存在血液流动,红细胞运动会不断影响散射光强度及角度,由此形成的一系列动态散斑图可被 CCD 相机记录^[6]。

2) CCD 相机记录的单张散斑图可反映各空间位点血流速度的相对快慢。Briers 等^[7]将散射光强度标准差 δ 和散射光强度平均值 I 的比值定义为散斑衬比值 K ,

$$K = \frac{\delta}{I} \quad (1)$$

K 与血流速度有关。实际血流监测过程中,计算机使用二维空间滤波模板(如 $M \times M$ 的二维矩阵)计算单帧散斑图相邻位点的 δ 与 I ,然后将两者比值赋值予中心像素,如图 2(a)所示。当血流速度越快时,相邻位点的光强对比越小、 δ 值越小,而 I 值保持不变,故 K 值越小;反之,当血流速度越慢时,相邻位点的光强对比越大、 δ 值越大,故 K 值越大。理想状态下, K 为介于 0 到 1 之间的常数,可间接反映该散斑图中各位点的相对血流速度,上述即为经典的激光散斑空间衬比分析(LSSCA)^[7]。

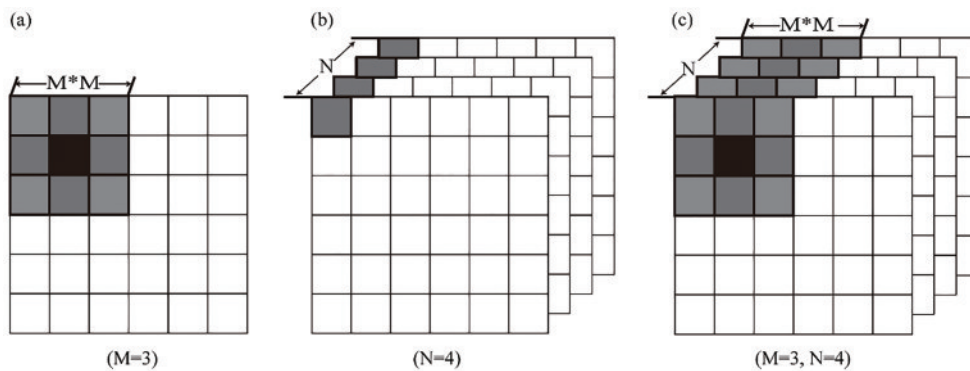


图 2 SFPI 算法。(a)空间衬比分析^[7];(b)时间衬比分析^[8];(c)时空联合衬比分析^[9]

Fig. 2 SFPI algorithms. (a) Spatial contrast analysis^[7]; (b) time contrast analysis^[8]; (c) spatial-temporal contrast analysis^[9]

尽管经典的 LSSCA 可获得血流速度信息,然而该方法中 K 值的计算降低了 SFPI 的空间分辨率。因此,Cheng 等^[8]进一步提出了激光散斑时间衬比分析(LSTCA),即计算机根据连续多帧散斑图(如 25 帧及以上)在同一位点上的散射光强值计算 δ 与 I ,得出该位点的 K 值,如图 2(b)所示。然而,该方法在提高 SFPI 空间分辨率的同时降低了时间分辨率,因此在实际应用中仍存在缺陷。

为使 SFPI 在血流监测中的时间分辨率与空间分辨率同时达到最优,孔平等^[9]提出了更为优越的激光散斑时空衬比分析(LSSTCA)。即计算机使用三维空间滤波模板(如 $N \times M \times M$ 的三维空间矩阵)根据连续 N 帧散斑图(如 25 帧及以上)对模板覆盖区域内的像素求取 δ 与 I ,计算 K 值,并赋予中心像素,最终得到一幅散斑衬比图,如图 2(c)所示。这样,通过选择合适的空间矩阵大小,可同时减少 K 值计算对图像空间

分辨率和时间分辨率的损失,使得血流灌注监测效果达到最优。

3) Duncan 等^[10]为改进对血流速度的表征方式,进一步定义了灌注指数(PI)这一概念,并将PI值以伪彩图的形式表示,从而反映血流速度快慢。

首先,假设红细胞的布朗运动和洛伦兹速度分布之间存在功率谱关系,以波动的去相关时间 τ 和相机曝光时间 T 表示散斑衬比值 K ,即

$$K = \frac{\delta}{I} = \left\{ \frac{\tau}{2T} \left[1 - \exp\left(\frac{-2T}{\tau}\right) \right] \right\}^{\frac{1}{2}}, \quad (2)$$

$$\tau = \frac{\lambda}{2\pi\nu}, \quad (3)$$

式中: λ 为激光波长; ν 为物体运动速度。

而 T 为有限长时间,因此 $1 - \exp\left(\frac{-2T}{\tau}\right)$ 非常接近于1,故式(2)可简化为

$$K = \frac{\delta}{I} = \left(\frac{\tau}{2T} \right)^{\frac{1}{2}}. \quad (4)$$

然后,定义PI值为

$$V_{PI} = \frac{T}{\tau}, \quad (5)$$

式中: V_{PI} 为PI值。由式(4)及式(5)可得,

$$V_{PI} = \frac{1}{2K^2}. \quad (6)$$

最后根据PI值的大小生成相应伪彩、填充入散斑图的各位点,生成散斑血流灌注图。散斑血流灌注图由红、黄、绿、蓝等4种颜色构成,其所表征的PI值依次降低。非血管区组织由于红细胞运动速度慢,因此PI值最小,伪彩图为蓝色;血管区因红细胞运动速度快,因此PI值较高,伪彩图为红色或黄色。伪彩图中血管的宽窄反映了血管管径的大小,颜色反映了血流速度的快慢,因此整体上表征了体表血管的管径、流速及灌注量等信息。

综上所述,SFPI通过激光照射体表血流中的红细胞、采集其背向反射光、计算各位点的 K 值反映血流相对速度,再推算出PI值、并生成相应的散斑血流灌注图,通过伪彩图反映血流速度、血管管径及灌注量等相关信息。

3 SFPI技术进展

3.1 SFPI图像质量提升

现有的SFPI算法主要通过降低静态组织散射、减少物体运动伪影、改善扫描光源均匀性、优化曝光时间等方法提升SFPI的图像质量。2006年,Choi等^[11]指出,选择合理的曝光时间(高流速长曝光、低流速短曝光)可以保证 K 与血流速度之间的线性关系,提高SFPI的准确性。2009年,Miao等^[12]通过“空间卷积”对原始散斑图像分块配准、空间插值,降低了动物实验

中呼吸、心跳对图像质量的影响。次年,他们通过“单调点变换技术”增强了SFPI的动态范围^[13]。之后,他们针对SFPI中存在光强分布不均、成像区存在曲面效应等问题,提出了一种基于模型不均匀性影响的校正方法,并获得了大鼠脑皮层的相对血流速度图像^[14]。2012年,He等^[15]将“横向激光照射”和“直线束扫描”结合使用,有效提升了SFPI的采样深度。同年,Rege等^[16]通过在空间上各向异性(沿血流方向采集像素)处理散斑血流灌注图,提高了SFPI的时间分辨率。2013年,Rice等^[17]利用“蒙特卡罗模型”消除了生物体表面静态散射对动态散斑测量的影响,提高了SFPI对深层血管的分辨率。同年,Zeng等^[18]通过“快速傅里叶变换”滤除了图像中的静态散斑信号,提高了图像的分辨率和信噪比。2014年,Ringuette等^[19]通过减小SFPI过程中错焦产生的运动伪影,使该技术对血管管径及血流速度的测量更为精确。同年,Li等^[20]通过散斑衬比的频域分析得到自协方差函数,后又将流体模型与自协方差函数拟合获取了绝对血流速度。2017年,Li等^[21]通过特征矩阵分解获取动态散斑信号,提高了散斑图像的分辨率和信噪比。2017年,Wang等^[22]对单次曝光散斑血流图中的静态散射光进行了校正,提高了SFPI对相对血流速度估计的准确性。2019年,Lü等^[23]通过基于轮廓波变换的多聚焦图像融合法改善了SFPI中的误聚焦现象,提高了其对非平面生物组织的观察效果。总体来看,对SFPI成像算法的优化进一步提高了散斑血流图的时空分辨率,使其对血流速度检测的准确性进一步提升。

3.2 其他方面

SFPI研究中有大量工程技术人员在成像速度提升和便携化设备开发方面做出了努力。2008年,Liu等^[24]通过引入图形化处理单元解决了SFPI中处理数据量大、耗时多的问题。2010年,Tang等^[25]利用数字信号处理技术开发了便携式SFPI系统,在提升图像处理速度的同时降低了设备体积。2013年,Richards等^[26]通过网络摄像机搭建SFPI系统,降低了SFPI系统的成本。2019年,Senarathna等^[27]发明了一种有荧光通道的SFPI迷你显微镜,该设备实现了对实验动物模型体表血流灌注的在体观察。2021年,Kong等^[28]开发了基于手机相机的散斑衬比系统,通过对原始散斑图像进行二维离散小波变换、图像插值和形态学运算,提高了图像的对比度和信噪比。总的来说,随着可穿戴装备的发展,制造便携、高效、智能化的SFPI设备已成为未来发展、应用的新趋势,工程上也将在该领域开拓创新,服务于医学研究。

4 SFPI在医学中的应用

4.1 眼底血流灌注监测

眼底血流灌注与青光眼^[29]、糖尿病^[30]等疾病的发生密切相关,对其进行监测有助于眼底疾病的早期诊

断和治疗。目前临床应用中,常使用眼底血管造影法监测眼底血流,需注射造影剂,且成像时间受造影剂在体内代谢速率的影响、无法实现实时评估^[31]。激光多普勒血流成像可无创检查眼底血流灌注,但其为单点测量、需机械扫描、重复性差,不利于长期监测^[32]。相比之下,SFPI具有无需扫描、实时成像、无需注射造影剂等优点,可对眼底血流进行无创、动态监测。

临床前研究中,SFPI已在家兔、大鼠和猴等动物模型的眼底血流灌注监测中得到应用。1994年,Tamaki^[33]通过CCD相机采集了家兔视网膜的激光散斑血流图。5年后,该课题组^[34]在局部给药多唑胺治疗青光眼的研究中通过SFPI发现:药物多唑胺可使青光

眼家兔眼压降低,但视神经乳头血流灌注未受影响,表明了该药在青光眼治疗中的有效性。2006年,Sasaoka等^[35]利用SFPI发现内皮素-1引起的家兔眼球血流灌注不足可导致眼底视网膜功能受损。2012年,Wang等^[36]利用SFPI发现青光眼恒河猴慢性眼压的上升可使其视神经乳头血流灌注下降。2010年,Srienc等^[37]将SFPI与激光共聚焦显微镜结合使用证实大鼠在经受光刺激后视网膜血流灌注的变化主要与小动脉管径的改变有关,而与毛细血管和小静脉无关。2013年,Ponticorvo等^[38]将内窥镜和SFPI结合使用证实高碳酸血症和视觉刺激可使大鼠视网膜血流量增加,高氧血症可使大鼠视网膜血流量减少,如图3所示。

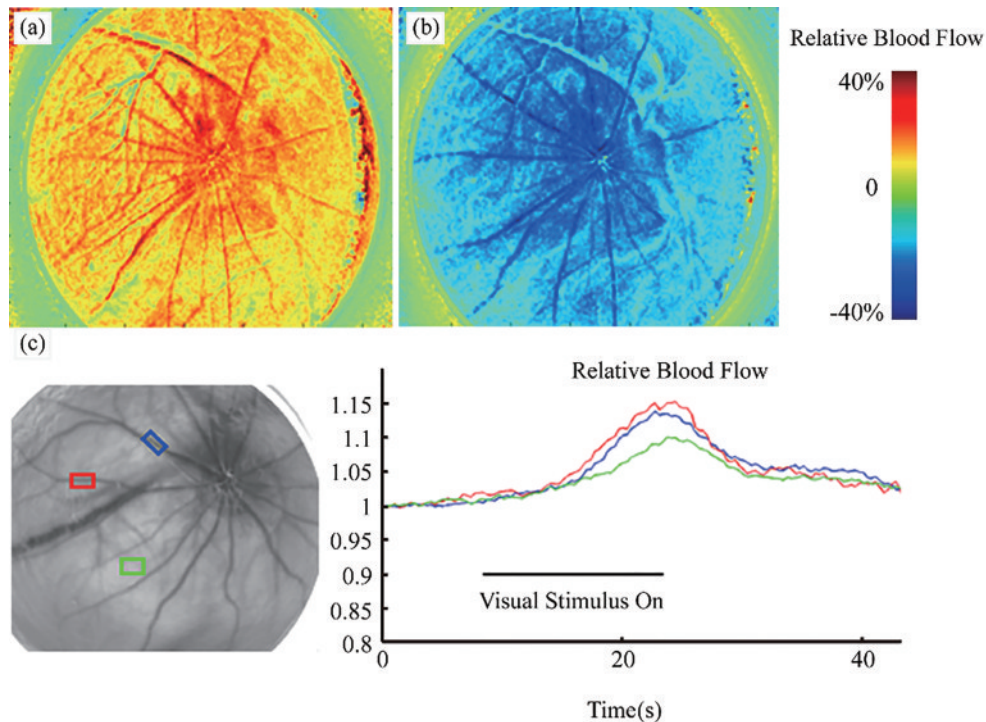


图3 SFPI监测的高碳酸血症、高氧血症和光刺激对大鼠视网膜血流灌注的影响^[38]。(a)高碳酸血症导致视网膜血流灌注增加;(b)高氧血症导致视网膜血流灌注减少;(c)光刺激导致视网膜相应位点血流灌注增加

Fig. 3 Effects of hypercapnia, hyperxemia, and light stimulation on retinal blood perfusion in rats monitored by SFPI^[38]. (a) Increased retinal blood perfusion due to hypercapnia; (b) decreased retinal blood perfusion due to hyperxemia; (c) increased blood perfusion at corresponding sites of retina caused by light stimulation

临床中,SFPI主要用于评价眼科药物疗效、诊断眼底疾病。1981年,Fercher等^[6]首次应用SFPI对人体视网膜血流灌注进行监测,实现了眼底血管区和非血管区的分辨,如图4所示。2008年,Hirose等^[39]使用SFPI证实系统性皮质类固醇治疗小柳原田综合征可降低由黄斑区炎症引起的脉络膜微循环损害。2012年,Saito等^[40]利用SFPI发现持续摄入虾青素可使人体视网膜黄斑区血流灌注增加,从而改善眼底微循环。2013年,Shiga等^[29]发现通过分析SFPI图像中视神经乳头血流灌注波形的变化能够对眼压正常但有青光眼的患者进行识别。2014年,Matsumoto等^[41]使用SFPI发现在玻璃体内注射贝伐珠单抗可使黄斑区水肿患者

眼部血流灌注明显改善。2017年,Iwase等^[42]使用SFPI发现,使用巩膜扣带术治疗孔源性视网膜脱落时,引起的磷下窝脉络膜厚度增加可导致引流静脉的阻塞。SFPI在眼底血流灌注监测中的应用极大提高了眼底疾病的诊断效率,减轻了病人注射荧光造影剂的痛苦,推动了眼科医学发展。

4.2 脑血流监测

脑缺血与脑卒中等疾病的发生密切相关,及时快速地脑血流监测有助于医生诊断^[43]。传统的脑血流监测方法在实际应用中存在缺陷:如激光多普勒血流成像可从大脑中有限的孤立点(约 1 mm^3)获取脑血流信息,但其成像速度和分辨率受机械扫描的限制^[44];动态

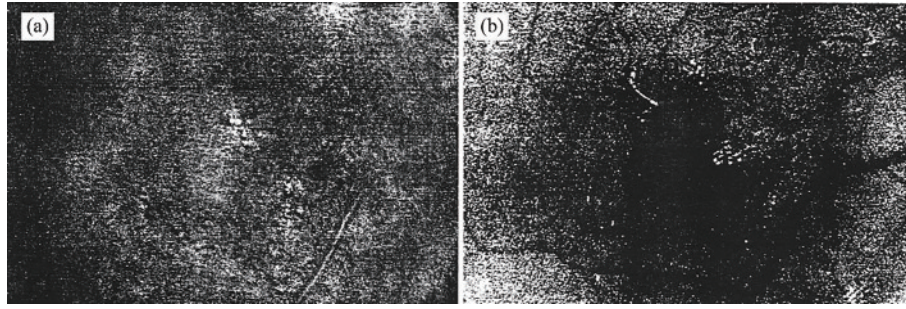


图4 SFPI首次用于监测人体视网膜血流灌注^[6]。(a)高通滤波前视网膜血管;(b)高通滤波后视网膜血管
Fig. 4 SFPI first used to monitor human retinal blood perfusion^[6]. (a) Retinal vessels before high-pass filtering; (b) retinal vessels after high-pass filtering

对比度增强核磁共振成像可提供动态脑血流的时空分布图,但成像成本高、时间长、需注射钆造影剂^[1];放射性自显影法因需对脑组织进行连续切片才可获取脑血流的三维空间信息,无法实时成像,仅用于临床前研究^[45];核素成像可获取脑血流的三维空间信息,但具有放射性,且设备、核药及人工成本高^[2];吲哚菁绿造影和数字血管剪影常在脑外科手术中用于脑血流监测,需注射造影剂,若脑血管堵塞、则会影响血流监测的时效性^[46-47]。相比于传统脑血流监测方法,SFPI可在无需注射造影剂、无辐射的条件下实现低成本快速脑血流监测,目前已应用于临床前研究及临床脑外科手术。

临床前研究中,SFPI广泛应用于动物脑血流监测和行为学研究。在脑血流监测方面:2001年,Dunn等^[43]率先将SFPI用于大鼠脑缺血模型的研究发现,脑中动脉阻塞引起的局灶性脑缺血和皮层扩散性抑制可

使大脑非缺血区血流灌注呈梯度分布,如图5所示;2004年,Ayata等^[48]首次证实了SFPI可在无创条件下穿透小鼠颅骨获得脑血流图像;2008年,Zhou等^[49]通过SFPI发现,局灶性脑缺血可影响大鼠的脑血流灌注基线、降低其对外界刺激的响应,从而证实了脑缺血对脑功能具有损害作用。在动物行为学研究中:2004年,Durduran等^[50]首次通过SFPI获得了小鼠脑皮层躯体感觉区在接受电刺激后的血流灌注变化;2009年,Li等^[51]通过SFPI发现,小鼠三叉神经在接受电刺激后脑皮层血管管径没有改变、而硬膜外血管出现扩张,但两者血流速度都有所加快,表明SFPI可能成为进一步了解神经血管偶联机制、偶联不平衡(如偏头痛)的有力工具;2009年,Sakadzic等^[52]将SFPI与磷光寿命成像结合使用,获取了小鼠前爪在接受电刺激时脑皮层的血流动力学参数和氧分压分数。

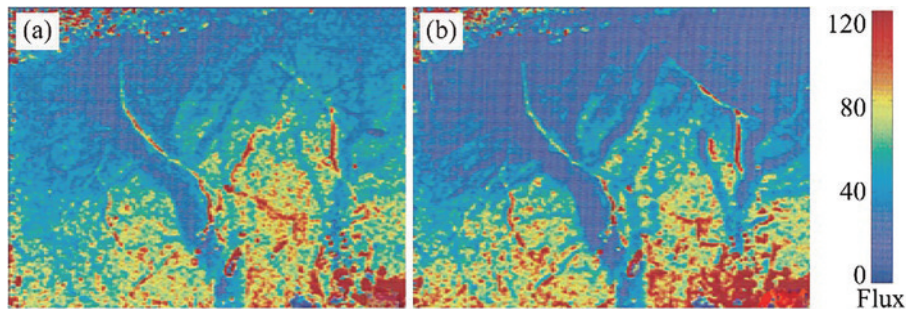


图5 SFPI用于监测大鼠脑中动脉阻塞开始和阻塞20 min后的血流灌注变化。(a)开始脑中动脉阻塞时脑血流的分布;(b)脑中动脉阻塞20 min后脑血流的分布^[43]
Fig. 5 SFPI used to monitor the changes of blood perfusion at the beginning of middle cerebral artery occlusion and 20 min after occlusion in rats. (a) Distribution of cerebral blood flow at onset of cerebral artery occlusion; (b) distribution of cerebral blood flow 20 min after cerebral artery occlusion^[43]

使大脑非缺血区血流灌注呈梯度分布,如图5所示;2004年,Ayata等^[48]首次证实了SFPI可在无创条件下穿透小鼠颅骨获得脑血流图像;2008年,Zhou等^[49]通过SFPI发现,局灶性脑缺血可影响大鼠的脑血流灌注基线、降低其对外界刺激的响应,从而证实了脑缺血对脑功能具有损害作用。在动物行为学研究中:2004年,Durduran等^[50]首次通过SFPI获得了小鼠脑皮层躯体感觉区在接受电刺激后的血流灌注变化;2009年,Li等^[51]通过SFPI发现,小鼠三叉神经在接受电刺激后脑皮层血管管径没有改变、而硬膜外血管出现扩张,但两者血流速度都有所加快,表明SFPI可能成为进一步了解神经血管偶联机制、偶联不平衡(如偏头痛)的有力工具;2009年,Sakadzic等^[52]将SFPI与磷光寿命成像结合使用,获取了小鼠前爪在接受电刺激时脑皮层的血流动力学参数和氧分压分数。

SFPI在临床脑血流监测上的应用多是配合脑外科手术。2009年—2015年,Hecht等^[53-55]多次使用SFPI在脑外科手术中监测动脉搭桥术后脑血流的畅通情况,提高了神经外科脑血流旁路术的安全性,如图6所示。2010年,Parthasarathy等^[56]使用神经外科手术显微镜结合SFPI,全程记录了脑肿瘤切除手术过程中患者的脑血流灌注图,并利用心电图在图像后处理中进行图像配准,降低了动脉脉动形成的运动伪影。

4.3 体表微循环监测

烧创伤后皮瓣的恢复、系统硬化病的病情分期、鲜红斑痣的治疗效果及医学美容、中医理疗效果等都与体表微循环状态密切相关。SFPI可快速获取体表微循环信息,为以上疾病的诊断和治疗提供依据。

由于皮瓣烧创伤后在恢复过程中血流灌注存在先上升后下降的趋势,判定皮瓣血流灌注高、低有助于判断移植皮瓣的成活率,为新临床治疗方案的提出提供

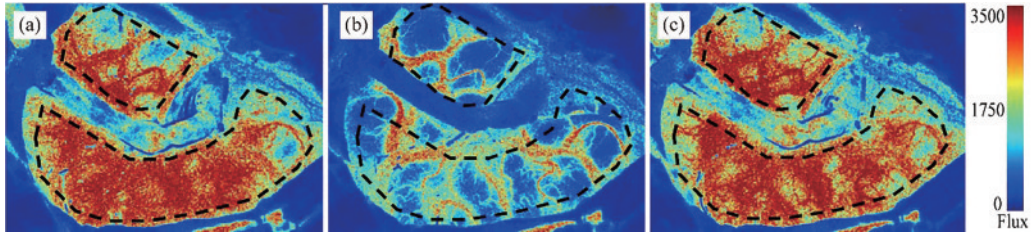


图 6 SFPI 监测术中大脑中动脉阻塞中的脑血流灌注变化^[54]。(a)阻塞前(基线);(b)阻塞中;(c)旁路开通后
Fig. 6 SFPI used to monitor changes of cerebral blood perfusion in intraoperative middle cerebral artery occlusion^[54]. (a) Pre-blocking (baseline); (b) blocked; (c) after bypass open

评价依据。目前常用的皮瓣血流灌注监测方法中高频超声对微血管灌注监测效果不佳^[57]、吲哚菁绿造影存在微毒性^[57],而 SFPI 可在无创条件下实现烧创伤后皮瓣血流灌注的动态观察,且具有非接触、高分辨率、成像视野广等优点。1990 年,Ono 等^[58]利用 SFPI 证实血栓烷合成酶抑制剂可有效延长家兔移植皮瓣的生存

期,减少术后血栓生成;2005 年,Stewart 等^[59]利用 SFPI 发现,烧伤恢复后皮瓣组织的血流灌注指数出现下降;2016 年,Mirdell 等^[60]在使用 SFPI 监测儿童烫伤恢复情况的研究中发现,烫伤皮肤与正常皮肤的血流灌注在烫伤 4 天时差异最大,从而推测此时可能是对烫伤深度进行定量评估的最佳时间,如图 7 所示。

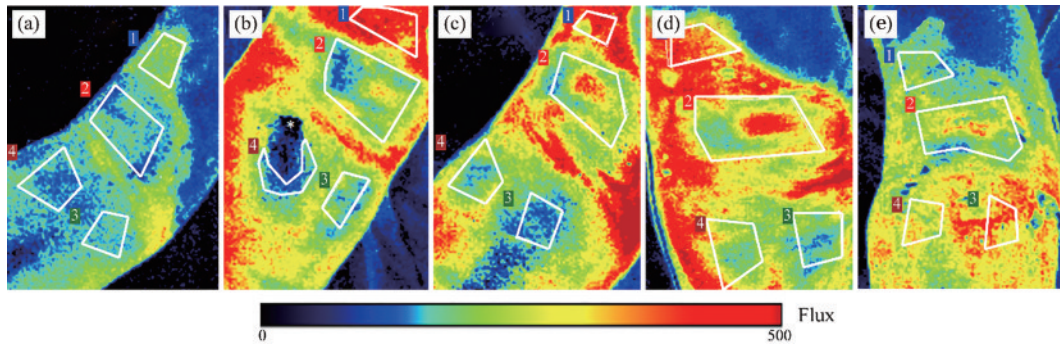


图 7 SFPI 用于监测儿童烫伤后 15 天内皮肤的血流灌注变化^[60]。(a)烫伤后 14 小时;(b)烫伤后 4 天;(c)烫伤后 6 天;
(d)烫伤后 8 天;(e)烫伤后 15 天
Fig. 7 SFPI used to monitor change of skin blood perfusion within 15 days after scald in children^[60]. (a) 14 hours after scald; (b) 4 days after scald; (c) 6 days after scald; (d) 8 days after scald; (e) 15 days after scald

系统硬化病是一种体表毛细血管形态异常的自身免疫性疾病。目前可通过观察甲襞毛细血管判定系统硬化病病程,但由于受观察视野限制(仅能观察甲襞),无法对体表毛细血管进行全面评估^[61]。SFPI 可评估

体表毛细血管形态及血流灌注水平,进而判定系统硬化病病程。2014 年,Ruaro 等^[62]通过 SFPI 证实系统硬化病的加重可导致外周皮肤血流灌注降低,如图 8 所示,其中右下角插图对应血流灌注下的甲襞毛细

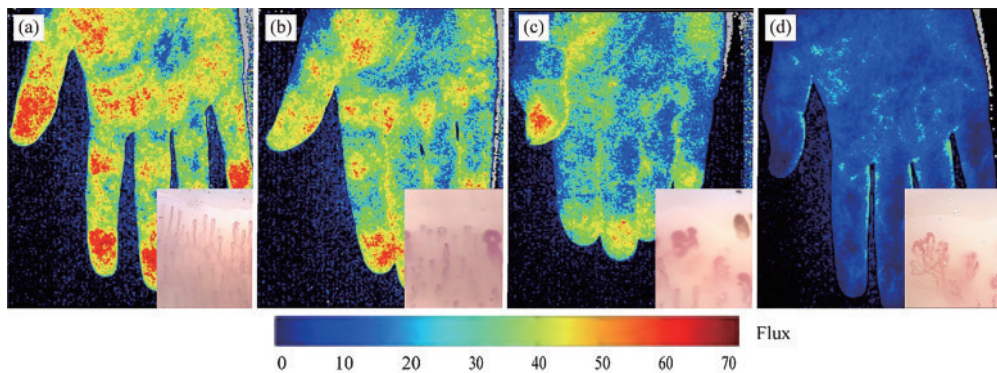


图 8 SFPI 用于监测系统硬化病不同病程对手掌血流灌注的影响^[62]。(a)正常手掌血流灌注;(b)早期系统硬化病血流灌注;(c)中期系统硬化病血流灌注;(d)晚期系统硬化病血流灌注
Fig. 8 SFPI used to monitor influence of different courses of systemic sclerosis on palm perfusion^[62]. (a) Normal palmar blood perfusion; (b) blood perfusion in early systemic sclerosis; (c) blood perfusion in metaphase systemic sclerosis; (d) blood perfusion in advanced systemic sclerosis

管形态;4年后,该课题组^[63]进一步通过高频超声和SFPI证实真皮厚度加厚、皮肤血流灌注降低是系统硬化病病情加重的重要表现。

鲜红斑痣是一种先天的毛细血管畸形,可通过光动力疗法治疗^[64]。2014年,Ren等^[65]通过SFPI监测了脸部鲜红斑痣患者在进行光动力治疗时,光敏剂注射剂量对治疗区和非治疗区血流灌注的影响,防止了光敏剂过量对非治疗区造成损害,保证了光敏剂注射的安全性、有效性。2016年,Choi等^[66]利用SFPI监测了脉冲治疗鲜红斑痣手术中治疗区的血流灌注变化,这有助于医生及时调整治疗中所需的光敏剂剂量。

长期以来,对医学美容和中医理疗的诊疗效果缺乏评估手段,SFPI的出现使其量化评估成为可能。

在医学美容方面:2018年,Nguyen等^[67]利用SFPI监测到透热疗法可降低眼睑血流灌注,因此建议在眼睑美容(移植眼睑皮瓣)中应谨慎使用透热疗法;次年,To等^[68]在女性乳房再造术中发现,SFPI提供的血流灌注信息有利于减少术后相关并发症的发生;2019年,Kelman等^[69]通过对SFPI进行技术改进、测量了人体皮肤水分含量,并提示该方法可能有利于化妆品行业质控标准的制定。在中医理疗方面:2017年,贾亚威等^[70]利用SFPI对中医艾灸后的功效进行量化评估证实艾灸对所对应经络区的血流灌注影响更为明显,如图9所示;2019年,李博等^[71]使用SFPI证实针刺放血疗法可改善小鼠创伤性脑损伤造成的微循环障碍。

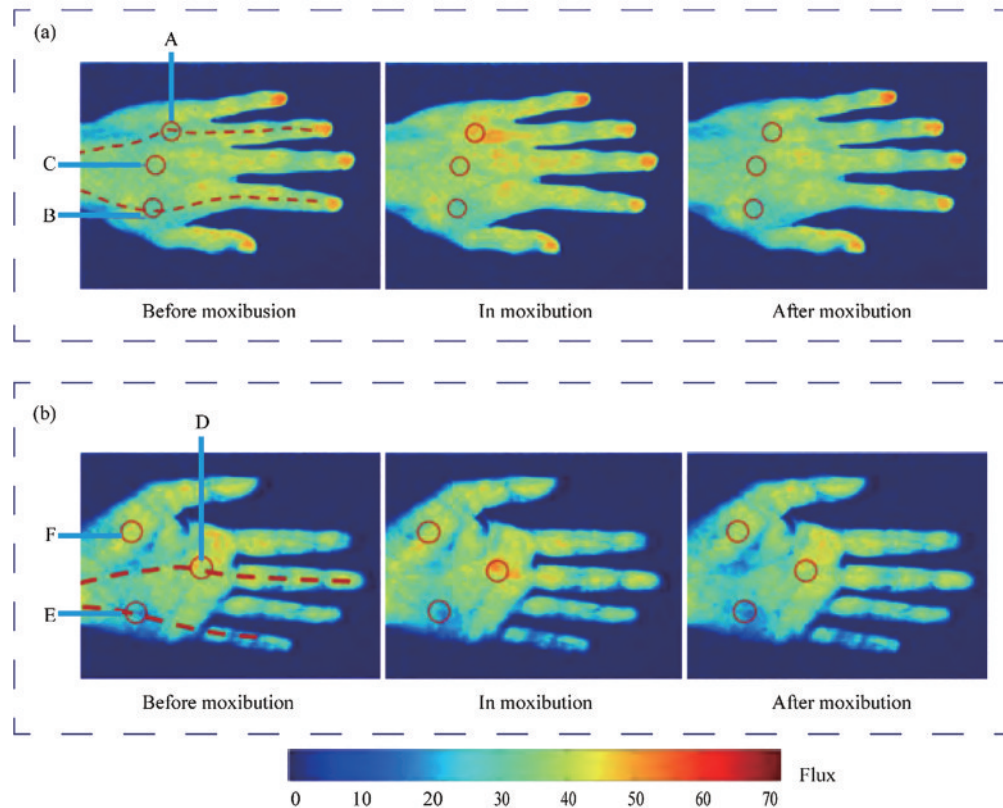


图9 SFPI用于监测艾灸对手背及手掌血流灌注的影响^[70]。(a)艾灸外关穴前、中、后手背对应经络散斑血流灌注图;(b)艾灸内关穴前、中、后手背对应经络散斑血流灌注图

Fig. 9 SFPI used to monitor effect of moxibustion on blood perfusion of hand back and palm^[70]. (a) Speckle flow perfusion image of back of hand corresponding to meridian before, during, and after moxibustion at Waiguan point; (b) speckle flow perfusion image of back of hand corresponding to meridian before, during, and after moxibustion at Neiguan point

4.4 肿瘤血流灌注监测

肿瘤血供与肿瘤发育密切相关,临床治疗中可通过减少肿瘤血供、剥夺肿瘤生长中的氧气、养料供给,达到促进肿瘤凋亡的目的^[72]。动态对比度增强核磁共振成像可动态监测肿瘤血流,但成像时间长、成本高、需注射造影剂^[73]。动物实验中常利用活体显微镜及荧光分子探针对体表皮窗模型中的肿瘤血流灌注进行监测,但该模型为有创模型,可能会影响实际的血流灌注监测效果^[74]。同以上传统方法相

比,SFPI在临床前研究中可无创监测动物皮下肿瘤的血流灌注,具有成像成本低、实时成像、无需注射造影剂等优点。2007年,Kalchenko等^[75]采用SFPI无创观测了小鼠结肠癌鼠耳模型的血流灌注水平。同年,Zhu等^[76]利用SFPI发现热疗可通过改变小鼠结肠癌的血管管径影响其血流灌注。2012年,Rege等^[77]利用SFPI在无创条件下观察到大鼠脑胶质瘤区血管密度比正常组织高,如图10所示。2016年,Robl等^[78]利用SFPI发现动脉内注射顺铂比静脉内

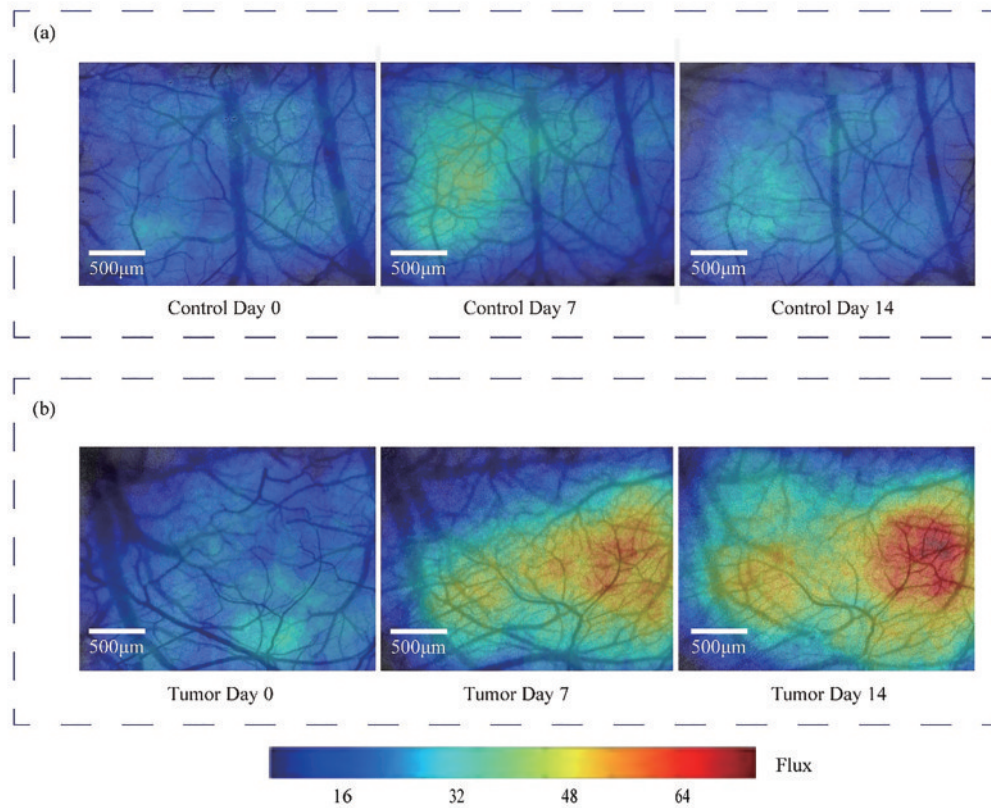


图 10 SFPI 用于监测大鼠脑胶质瘤发育过程中血管密度的变化^[77]。(a)0 天、7 天、14 天对照组正常大鼠脑血管密度；(b)0 天、7 天、14 天实验组脑胶质瘤大鼠脑血管密度

Fig. 10 SFPI used to monitor changes of vascular density during glioma development in rats^[77]. (a) Cerebral vascular density of normal rats at day 0, 7, and 14 in control group; (b) cerebral vascular density of glioma group at day 0, 7, and 14 in experiment group

注射顺铂更有助于减少小鼠骨肉瘤血流灌注,从而增加肿瘤坏死率。目前,SFPI在肿瘤血流灌注监测中的应用仅限于临床前研究;由于多数肿瘤位于体内,而 SFPI 所采用的激光光源为近红外光源、穿透力低(约 1 mm),因此在肿瘤血流灌注监测上未用于临床诊断^[79]。

4.5 应用新进展

SFPI 对体表血流灌注的监测具有快速、实时、低成本、高分辨率、无需造影剂等优点,因而在动物体表肿瘤血流灌注监测中广泛应用。2021 年,Pion 等^[80]利用 SFPI 观察了鸡胚绒毛尿囊膜(CAMs)胚胎/肺泡横纹肌瘤模型的血管新生状况,如图 11 所示,并提出或

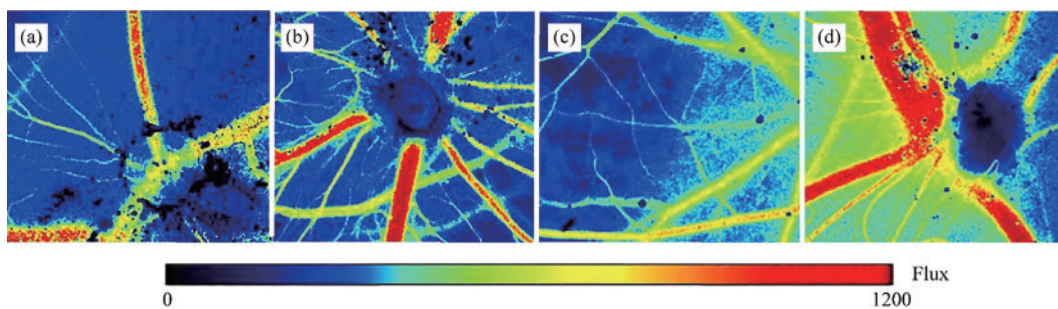


图 11 SFPI 用于测量鸡胚 CAMs 肿瘤发育过程中新生血管的血流灌注变化^[80]。(a)细胞植瘤的 CAM 血流灌注图像(鸡胚发育 8 天,开始植瘤);(b)细胞植瘤的 CAM 血流灌注图像(鸡胚发育第 16 天,观察肿瘤);(c)瘤块植瘤的 CAM 血流灌注图像(鸡胚发育第 8 天,开始植瘤);(d)瘤块植瘤的 CAM 血流灌注图像(鸡胚发育第 16 天,观察肿瘤)

Fig. 11 SFPI used to measure changes of neovascular perfusion during the development of CAMs tumor in chick embryo^[80]. (a) CAM blood perfusion image of cell transplanted tumor (8 days after embryo development, tumor transplanted); (b) CAM perfusion image of cell transplanted tumor (tumor observed on day 16 of chick embryo development); (c) CAM blood perfusion image of tumor mass implantation (tumor implantation began on day 8 of chick embryo development); (d) CAM perfusion image of tumor graft (observation of tumor on day 16 of chick embryo development)

许可利用其对抗肿瘤血管新生药物进行筛选。由于鸡胚这一动物模型不具有免疫源性,可将不同种属的肿瘤细胞移植到鸡胚绒毛尿囊膜上,通过 SFPI 监测抗肿瘤药物对肿瘤血流灌注的影响,这将大大降低医学实验的实验成本,提高动物福利。此外,该项技术的检测范围可扩展至所有对血管管径、血流灌注有影响的药物的检测。

5 总 结

SFPI 从最初的基础理论研究到如今的科研、临床应用至今已走过 40 多年的历程。从最初的第 1 张视网膜模拟照片,到第 1 张相机成像的时变散斑衬比图,再到如今 SFPI 实现与其他技术的联合使用,无一不显示出科学技术进步带给医学的飞跃发展。在此回顾了 SFPI 的主要应用领域,但这并非 SFPI 应用的全部范畴,越来越多的新技术将与 SFPI 相结合,它们会进一步改变我们的生活,期待 SFPI 在未来给我们带来更多的惊喜。

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