Endovascular Laser–Tissue Interactions Redefined: Shining Light on Novel Windows of Therapeutic Opportunity Beyond Selective Photothermolysis

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THE MOST WIDELY used treatment of port wine stains (PWSs) entails the flashlamp-pumped pulsed dye laser, which was developed in conformity with the theory of selective photothermolysis.¹ This noninvasive treatment modality relies on the conversion of radiant energy to heat by hemoglobin and the ensuing coagulation of blood and necrosis of (peri-)vascular tissue due to thermal diffusion. By irradiating skin at a well-absorbed wavelength and sufficient irradiance, supracritical temperatures ($>70^{\circ}\text{C}$) can be generated in the vessel lumen and confined spatially if the pulse duration is kept within the thermal relaxation time of blood and target vasculature, resulting in photocoagulation of the vascular lumen.

The underlying principles of selective photothermolysis and the procedure itself seem plain and effective in theory: PWSs persist because of a chronically hyperdilated dermal microcirculation; ergo, removing the aberrant microcirculation with a few zaps of laser light containing a healthy dose of rationale from the fields of physics and biology should take care of the problem. On the contrary, 28 years after the conception of selective photothermolysis,¹ we have come to fully appreciate the abysmal complexity of the underlying laser–tissue interactions. Bound by the finite combinations and permutations of clinically justifiable laser parameters and the prerequisite to completely photocoagulate the vascular lumen for optimal lesional blanching,^{2,3} it seems as if a therapeutic plateau has been reached. And as is often the case with plateaus, the only way they can be breached is by changing strategies. So an alternative to conventional selective photothermolysis must be sought to resolve its lurking dead ends with respect to poorly responding and refractory PWSs (Fig. 1): for the sake of $\sim 60\%$ of hopeful patients⁴ and for the sake of scientific challenge.

Several alternative treatment modalities for selective photothermolysis arise when one accepts the premise that endovascular laser–tissue interactions are governed by a photothermal response,^{5–7} the photocoagulation of blood as a result of supracritical heat generation, and a subsequent hemodynamic response,^{8,9} characterized by the activation of

primary and secondary hemostasis in consequence of endovascular damage (M. Heger et al., unpublished observations) (Fig. 2). The former constitutes a static component, in that a laser-induced semioclusive thermal coagulum is unable to expand and thus incapable of inducing emphraxis of the vascular lumen after the laser pulse.⁷ The hemodynamic response, in contrast, comprises a highly dynamic component of endovascular laser–tissue interactions and thus provides room for a certain degree of manipulation.

Consequently, site-specific pharmaco-laser therapy (SSPLT) was developed⁸ to tackle the therapeutic inefficacy associated with semiphotocoagulated vasculature at the root of the recalcitrance (*i.e.*, from within the vascular lumen) (Fig. 3). This modality takes advantage of the hemodynamic response by combining conventional selective photothermolysis with the prior systemic administration of a prothrombotic and/or antifibrinolytic drug-encapsulating liposomal drug-delivery system. In this configuration, laser irradiation is performed with a conventional pulsed-dye laser to induce endovascular damage through the photothermal response (Fig. 3, λ_1), which is ensued by a second pass (Fig. 3, λ_2) to trigger release of pharmaceutical agents from the drug carrier.

We have shown that the hemodynamic response, comprising a predominantly thrombotic phase followed by a predominantly fibrinolytic phase, exhibits a turning point after ~ 6 min (M. Heger et al., unpublished observations).⁹ Correspondingly, we developed a thermosensitive liposomal drug-delivery system encapsulating tranexamic acid, a potent FDA-approved antifibrinolytic agent, that is capable of releasing almost 100% of tranexamic acid within 2.5 min (M. Heger et al., unpublished observations).¹⁰ These highly favorable drug-release properties allow ample time for the liposomes to target the developing thrombus after laser irradiation and to release their contents at the site of laser-induced damage before or at the onset of the fibrinolytic phase, resulting in a locally amplified antifibrinolytic effect. The ultimate end point of SSPLT is that, when used in conjunction

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laser. E = epidermis; D = dermis; HF = hair follicle; CP = completely photocoagulated vascular lumen; IP = incompletely photocoagulated vascular lumen. Scale bar, 200 μ m. (Color image can be found at www.liebertonline.com).

with a prothrombotic drug carrier, the exacerbated hemodynamic response will result in complete and chronic thrombus-mediated occlusion of the otherwise incompletely photocoagulated ectatic vessel, thereby mimicking the ideal endovascular damage profile associated with lesional blanching (*i.e.*, complete photocoagulation).

In the final analysis, scientists from several continents have been working diligently on the improvement of sub-optimal PWS blanching rates, which has generated >950 publications since as far back as Thomson Scientific's Web of Science database stretches; quite a remarkable number for a condition that is not life threatening and has an incidence

FIG. 2. Dual-component model of endovascular laser-tissue interactions based on experimental data from references 9 and 10. Hamster dorsal skinfold venules were irradiated with a 532-nm frequency-doubled Nd:YAG laser (30 ms pulse duration) and visualized with intravital fluorescence microscopy. In the case of the photothermal response (*bottom curve*, progresses in the order of ms), thermal coagula (white arrowhead) were visualized by transillumination of the skinfold. Thermal coagula comprise the static component of endovascular laser-tissue interactions, as evidenced by the relatively flat lesional size (*y*-axis) kinetics as a function of time (*x*-axis). The hemodynamic response (*top curve*, progresses in the order of minutes) was visualized in fluorescence mode after *in vivo* staining of platelets with antibodies against P-selectin, a platelet epitope.

The laser-induced thrombus (black arrowhead) undergoes a growth phase in which prothrombotic conditions dominate. After ~6 min, the prothrombotic conditions recede, and fibrinolysis causes the thrombus to degrade. This phase may prevail up to 30 min and possibly beyond. (Color image can be found at www.liebertonline.com).

FIG. 3. Schematic representation of the principles of site-specific pharmaco-laser therapy. (1) A thermal coagulum is induced by irradiating (λ_1) a vessel with a pulsed dye laser (i.e., selective photothermolysis). The laser-induced damage activates primary and secondary hemostasis that culminates in thrombus formation (yellow aggregates). Prothrombotic and/or antifibrinolytic pharmaceutical-encapsulating thermosensitive liposomes (blue spheres) that had been infused before laser irradiation accumulate in the developing thrombus. (3) A heat stimulus, e.g., near-infrared laser irradiation (λ_2), is administered to induce drug release, causing a localized amplification of the hemodynamic response and complete occlusion of the vascular lumen (4). This damage profile is analogous to complete photocoagulation of the vascular lumen and is thus expected to result in optimal lesional blanching.⁸ (Color image can be found at www.liebertonline.com).

of 0.3–0.5%. However, a considerable patient population that does not respond optimally to laser therapy remains, despite the recent advances in laser technology and ancillary techniques, such as dynamic cooling (to reduce thermal damage at the dermo-epidermal junction),¹¹ application of vacuum pressure (to increase dermal blood volume and reduce the minimal threshold fluence required for optimal photocoagulation),^{12,13} and topical pharmaceutical agents (e.g., anti-angiogenesis agents to reduce vascular remodeling in the treated dermal volumes).^{8,14,15} This letter was therefore intended to open a novel window of therapeutic opportunity by combining current knowledge of endovascular laser-tissue interactions with suitable therapeutic approaches.

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