Supplementary Note

We consider the mechanism for vascular insult with ultrashort laser pulses. At energies above the threshold for optical breakdown, past studies show that the absorption of ultrashort laser pulses leads to the formation of a cavitation bubble and a shock wave[1-6]. At energies well above the threshold for breakdown, the size of cavitation bubbles can approach the size of the core of a hemorrhage (Fig. 2). The hemorrhage core could be formed by RBCs and blood plasma from the ruptured vessel that fill in a volume disrupted by the rapid expansion of the cavitation bubble. Thus, in vessel rupture, the spherical feature that is observed by TPLSM immediately after photodisruption may be representative of the maximum radius of a cavitation bubble (Fig. 2B, panel ii). We found that the volume of the hemorrhage core, denoted v, scales with the estimated laser pulse energy at the focus in the *in vivo* brain, according to the phenomenological relation (Fig. SA1):

$$v \simeq \left(280\ \text{pL}\right)\ e^{\frac{E_{focus}}{0.15\ \mu J}}$$

where E_{focus} is the energy at the focus and the fit is valid ($p < 0.01$) for $0.05\ \mu J < E_{focus} < 0.3\ \mu J$. The energy at the focus is decreased by absorption and scattering in comparison with the incident energy, denoted $E_{incident}$, and can be approximated by an exponential dependence on depth, z, with an attenuation length, Λ, *i.e.*,

$$E_{focus} \simeq e^{-z/\Lambda}\ E_{incident}\ .$$

We take an attenuation length of $\Lambda \approx 200$ μm as representative of values found in the literature[7-9] and neglect optical aberrations. In contrast, the volume of fluorescently-labeled plasma extravasation does not correlate with laser energy suggesting that the plasma extravasation may be dependant on local tissue properties rather than laser parameters.

The energies used to yield the extravasations (Fig. 3) and the intravascular clots (Fig. 4) are nearer the threshold for photodisruption and lower than those that yield vessel ruptures (Fig. 2). At low energies, several effects act to limit tissue damage so that the mechanical events that follow irradiation may only partially disrupt vessels and thus minimally affect the surrounding tissue. First, a smaller fraction of the laser pulse is

absorbed at laser pulse energies near threshold than at energies substantially above threshold[10]. Thus the fraction of energy available for cavitation bubble formation and damage by shock waves is likely to be less in the cases of extravasations and clots, which occur near threshold, compared to that for vessel ruptures. Second, the velocity and pressure of the shock wave decreases rapidly with radius from the center of the photodisruption[2,11,12]. Thirdly, the cavitation bubble and shock wave are likely to induce circumferential strain in the vessel wall. Thus, vascular cells that wrap around the target vessel, *e.g.,* endothelial cells, are likely preferentially damaged by photodisruption when compared to cells that abut the vessel.

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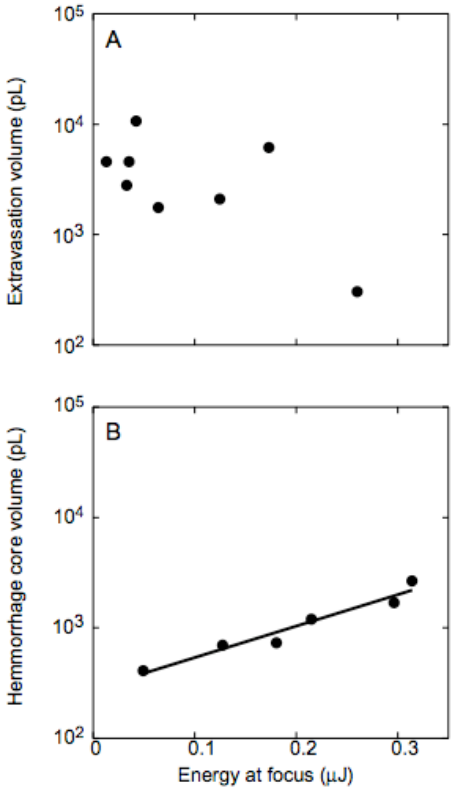

Figure SA1. Hemorrhage size versus laser pulse energy at focus. (A) Extravasation volume as measured in *in vivo* TPLSM image stacks. **(B)** Hemorrhage core radii were measured in TPLSM images of vessel rupture formation within 1 s after photodisruption.