Intravascular Drug Delivery With a Pulsed Liquid Microjet

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Occlusions of the retinal veins and arteries, associated with diseases such as hypertension and arteriosclerosis, are a major cause of severe and irreversible loss of vision. Treatments for retinal vascular diseases have been unsatisfactory owing in part to the difficulty of delivering drugs to the site of disease within the eye. In this article, we demonstrate that a new device, the vapor bubble–driven pulsed liquid microjet, can deliver drugs into the lumen of small vessels such as those found in the retina. A 15-µm-diameter liquid jet traveling at more than 60 m/s was shown to penetrate and deliver fluid through the wall of a blood vessel that was 60 µm in diameter. Perforation of the wall of the blood vessel did not extend beyond the jet diameter. *Arch Ophthalmol. 2002;120:1206-1208*

The delivery of drugs into the bloodstream or to the site of a disease is critical to the treatment of most medical problems. Present techniques are not ideal for drugs that require precise drug localization, such as within a small organ like the eye.[1,2] The vascular occlusive diseases of the retina are particularly problematic, since eyedrops and drug injections outside the eye penetrate poorly, drugs injected within the eye may not be able to cross the blood-retinal barrier into the occluded vessel, and systemic drugs can cause adverse effects and may not reach the site of an occlusion because of reduced blood flow.[3,4] We describe herein a new device that can deliver drugs intravascularly or into other small spaces without needles. We believe it may prove useful for the localized treatment of small-vessel occlusions in the eye, among other applications. This device, called the *pulsed liquid microjet*,[5] produces high-velocity liquid pulses that can penetrate tissue and deposit picoliter volumes of liquid at controlled depths.

From the Hansen Experimental Physics Laboratory (Drs Fletcher, Palanker, and Huie) and the Department of Ophthalmology, School of Medicine (Drs Palanker, Huie, Marmor, and Blumenkranz and Mr Miller), Stanford University, Stanford, Calif. Dr Fletcher is now with the Department of Bioengineering, University of California, Berkeley. Stanford University has applied for a patent on the pulsed liquid microjet used in this study. The inventors are Drs Fletcher and Palanker.

The pulsed liquid microjet consists of a high-voltage metal electrode enclosed in a micronozzle filled with an electrolyte to which drugs can be added (**Figure 1**A). The electrode is a 25-µm-diameter wire surrounded by a glass insulator and steel sheath, and the micronozzle is a tapered glass capillary tube with a 15-µm-diameter hole at the tip. When a voltage pulse is applied to the electrode, current flows via ionic conduction in the electrolyte from the central electrode to the surrounding grounded metal sheath. At discharge voltages greater than 1 kV and pulse durations of 1 microsecond, high-temperature plasma streamers are formed[6,7] and the deposited heat causes explosive growth of a vapor bubble.[8-10] As the vapor bubble around the central electrode expands, it forces a liquid jet out the tip of the micronozzle at speeds close to 100 m/s.[5]

The energy of the electrical discharge and the diameter of the exit hole control the velocity, volume, penetration depth, and diameter of the liquid jet. We studied the dynamics of the pulsed liquid microjet by using an inverted microscope, a cooled CCD camera, and a light-emitting diode with a 100-nanosecond flash duration. We measured jet velocity by taking 2 successive photographs on a single frame and calculating the change in jet po-

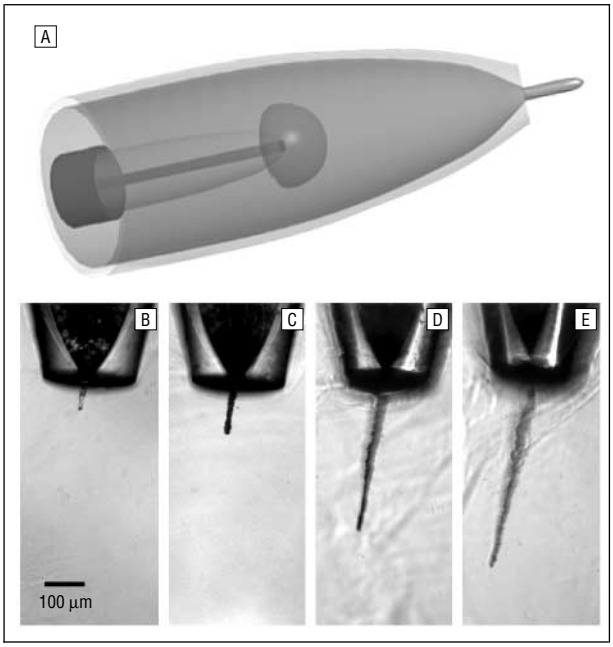

Figure 1. The pulsed liquid microjet. A, Schematic diagram of the electrode enclosed by the micronozzle. Liquid inside the micronozzle is ejected through the exit hole when a vapor bubble is formed at the electrode tip due to a high-voltage breakdown. B through E, Depth of the injection of isotonic sodium chloride solution mixed with 1.8-µm-diameter beads into 0.7% agarose gel is controlled by discharge energy at the electrode, eg, at discharge energies of 160 µJ (B), 310 µJ (C), 780 µJ (D), and 1560 µJ (E).

sition with time. We found that ejection velocities were typically 60 m/s for liquid jets that would effectively penetrate tissue. Jet velocities as high as 100 m/s could be obtained with high-energy discharges, but they were accompanied by hydrodynamic cavitation at the nozzle exit[5] and were therefore undesirable for drug injection.

Intravascular injection into small vessels requires careful control of the jet penetration depth and position. The energy of the jet must be sufficient to pierce the proximal, but not distal, wall of the vessel, and fast ejection is important for minimizing delivery time once the microjet is in position. We used 0.7% agarose gel to investigate the difference in penetration depth with varying discharge energy. The micronozzle was loaded with a mixture of isotonic sodium chloride solution and 1.8-µm-diameter polystyrene beads and positioned at the surface of an agarose gel immersed in isotonic sodium chloride solution. At a discharge energy of 160 µJ, a single pulse penetrated 80 µm, while at a discharge energy of 1560 µJ, the penetration depth was 500 µm (Figure 1B-E). Ejected volumes ranged from 50 to 200 picoliters per pulse. Similarly, we found that by varying the energy, we could control the jet penetration through the walls of blood vessels.

To demonstrate the ability of the pulsed liquid microjet to pierce the proximal wall of a small vessel and deliver liquid to the interior, we injected fluorescent dye (fluorescein sodium) into a 60-µm-diameter vessel of excised (in vitro) chorioallantoic membrane from a chicken embryo. A piece of membrane was pinned to an agarose gel and suspended in isotonic sodium chloride solution. The micronozzle was loaded with isotonic sodium chloride solution containing fluorescein sodium and positioned with a micromanipulator close to the wall of a 60-µm-diameter vessel. A single 780-µJ discharge of the 15-µm microjet pierced the vessel wall, and subsequent pulses injected dye. With the use of a fluorescent microscope, we observed the displacement of blood as pulses of fluorescein sodium entered the vessel (**Figure 2**). The dye was confined to the interior of the vessel and moved in the direction of blood leaking from the cut end of the vessel.

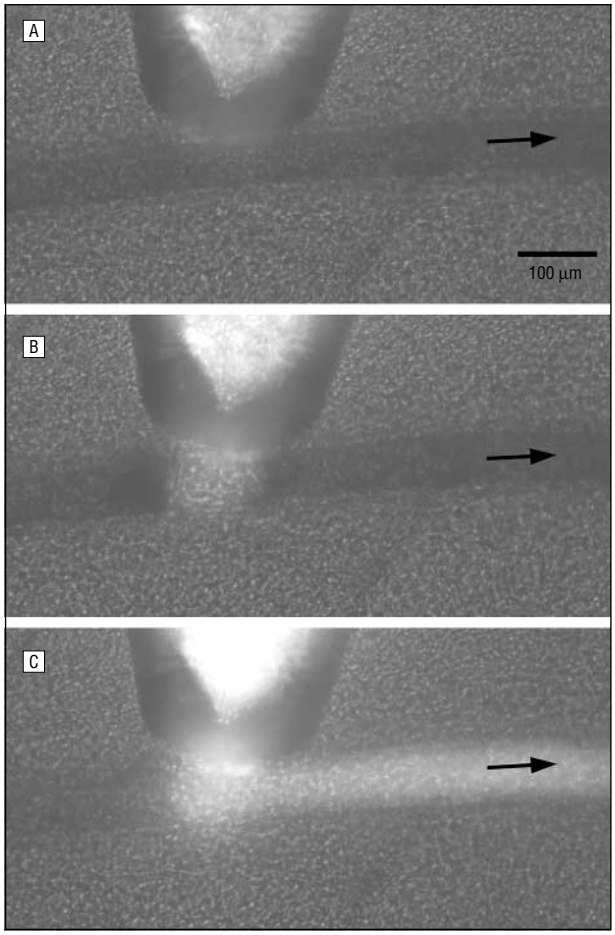

Figure 2. In vitro injection of fluorescein sodium into a 60-µm-diameter vessel. Arrows indicate the direction of blood leakage from the excised vessel. A, Before injection, the microjet is positioned against the wall of the vessel. B, After 5 injections, the blood in the vessel is displaced just below the microjet. C, After multiple injections, the blood is entirely replaced with fluorescein sodium in the direction of blood flow. No damage to the opposite wall of the vessel is evident.

To be useful clinically, the microjet must work when held by hand and in the presence of vascular pulsations. We found, through experiments on in vivo chorioallantoic membrane of the chicken embryo, that we could inject isotonic sodium chloride solution into a 100-µm-diameter artery under physiologic conditions with a handheld probe. Selected samples were excised, fixed, and embedded for histological study. Light microscopy of a histological section of the chorioallantoic artery pierced by a single 780-µJ discharge of the microjet showed that tissue damage was limited to a zone approximately 20 µm in diameter and that only the proximal wall of the vessel was penetrated (**Figure 3**). We observed no damage to the endothelium on the opposite side of the blood

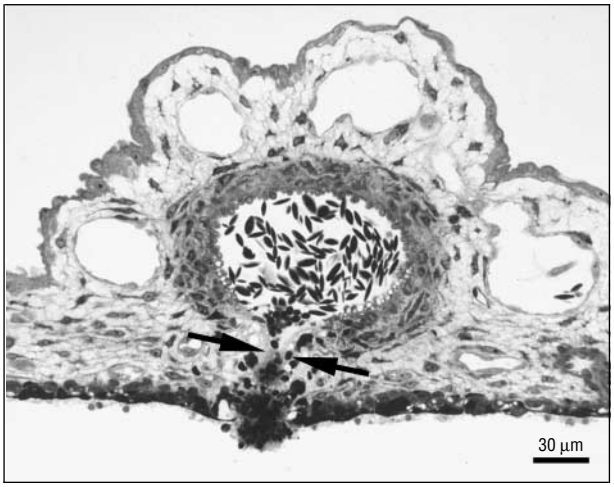

Figure 3. Light microscopy of a histological section of an artery from the chorioallantoic membrane of a chicken embryo after a single in vivo injection with a discharge energy of 780 µJ. The width of the damage zone (arrows) is limited to approximately 20 µm. The wall of the blood vessel opposite the injection site does not appear to be damaged, and the injection hole has been sealed by connective tissue or blood elements (toluidine blue).

vessel. Bleeding from the chorioallantoic artery after application of the microjet subsided within seconds, apparently due to the small diameter of the hole created in the vessel and normal hemostatic mechanisms.

Current maximum single-pulse ejection volumes are approximately 200 picoliters, so that single pulses of the microjet are unlikely to deliver sufficient quantities of a drug for treatment of some diseases. In theory, multiple pulses can be used to obtain the necessary volume, but in practice a surgeon's hand might shift during the time required for application of multiple pulses and create multiple perforations of the vessel wall with the risk of greater bleeding and vessel damage. To solve this problem, we are developing a large-volume microjet that can deliver microliter volumes with the same jet diameter in a single pulse.

To our knowledge, this is the first demonstration of the needle-free direct injection of drugs into small blood vessels. The pulsed liquid microjet offers a means of delivering drugs to small vessels such as those in the retina that may help in the management of blinding diseases for which there is no effective therapy at present.

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