

# Precision and Safety of the Pulsed Electron Avalanche Knife in Vitreoretinal Surgery

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**Background:** We have developed a new surgical instrument, called the pulsed electron avalanche knife (PEAK; Carl Zeiss Meditec, Jena, Germany), for precise, “cold,” and tractionless dissection of tissue in liquid media.

**Objective:** To evaluate the 3-dimensional damage zone induced by the PEAK compared with 2 other standard intraocular surgical instruments, diathermy and retinal scissors.

**Methods:** Damage zone and minimum safe distance were measured in vitro on chick chorioallantoic membrane and in vivo on rabbit retina with the use of propidium iodide staining.

**Results:** The PEAK produced a paracentral zone of cellular structure disruption surrounding a crater and a peripheral zone of structurally intact but abnormally per-

meable cells. The instrument induced a damage radius that varied from 55 to 300  $\mu\text{m}$  for the range of voltages and pulses typically used during surgery. For comparison, damage radius for microsurgical scissors was 50  $\mu\text{m}$ , and for diathermy, 400 to 850  $\mu\text{m}$ . The PEAK also damaged tissue up to 1.4 mm away by the creation of water flow that formed at the tip of convex probes during collapse of a cavitation bubble. Concave probes, which prevent formation of the water jet, eliminated this effect.

**Conclusions:** The PEAK operated well within acceptable safety limits and may greatly facilitate both posterior segment surgeries (eg, membrane dissection and sheathotomy) and anterior segment procedures (eg, capsulotomy, nonpenetrating trabeculectomy, and iridectomy).

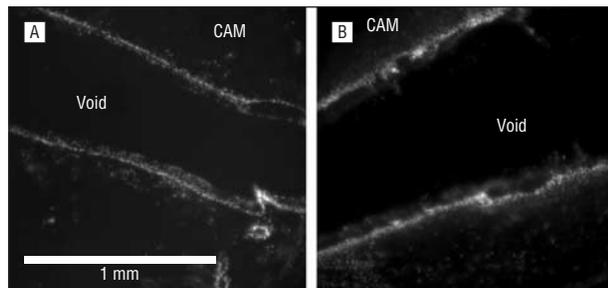
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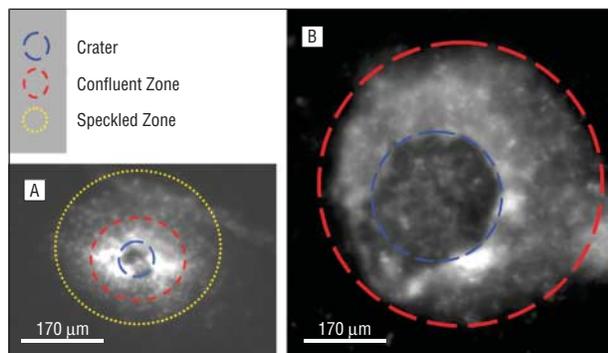
**C**URRENT MECHANICAL approaches toward vitreoretinal surgery carry distinct risks, including traction tears and imprecise depth or width of cuts (leading to excessive collateral damage, nicked vessels, etc). Plasma-mediated dissection of tissue with short-pulsed (0.1-picosecond to 10-nanosecond durations) lasers,<sup>1-3</sup> while helping to reduce traction-related damage and improving cutting precision, is limited in vitreoretinal applications because of potential damage to the photosensitive retina<sup>1,4</sup> by light propagating beyond the focal point. In addition, large optical aberrations, for example, while operating on peripheral retina, reduce the precision and safety of this procedure. Pulsed shallow-penetrating lasers (erbium-YAG [Er:YAG] and argon-fluorine [ArF] excimer) delivered into the eye via optical fibers<sup>5-7</sup> enable localized treatment of tissue with uniform accuracy at all points in the fundus. However, these instruments have failed to achieve widespread acceptance in vitreoretinal surgery because of their prohibitively high cost, large size, and relatively slow pace.<sup>7,8</sup>

To address the disadvantages of both mechanical and laser-based instrumentation for tissue dissection in intraocular surgery, we designed and previously described a device called the pulsed electron avalanche knife (PEAK; Carl Zeiss Meditec, Jena, Germany).<sup>9,10</sup> This instrument uses high electric field rather than laser photons to create plasma in front of an intraocular probe, and thus it is compact and inexpensive. Overheating of water by a plasma-mediated discharge causes explosive vaporization and rapid expansion of a vapor (cavitation) bubble (approximately 90 m/s) that fragments or ablates tissue. Previously, our group demonstrated<sup>9,10</sup> that PEAK is capable of precise dissection of retinal tissue as well as epiretinal membranes, lens capsule, and cortex.

In this study, we explored the extent of collateral damage introduced by the instrument on a model tissue (chick chorioallantoic membrane [CAM]) as well as on rabbit retina in vivo and compared PEAK damage with that created by 2 standard instruments used in intraocular surgery, retinal scissors and diathermy.



**Figure 1.** Propidium iodide staining of cuts on chick chorioallantoic membrane (CAM) produced with microsurgical scissors (A) and with the pulsed electron avalanche knife at 2.75 kV (B). While damage zones are similar, the pulsed electron avalanche knife offers tractionless dissection with increased maneuverability and precision.



**Figure 2.** Propidium iodide-stained damage zones induced by 1 pulsed electron avalanche knife pulse at 5 kV (A) and by 0.5 seconds of diathermy (B) at a standard retinal surgery setting (see Table).

## METHODS

The PEAK was operated with 100-nanosecond-long, negative, high-voltage pulses applied to a 25- $\mu\text{m}$  wire embedded in a tapered insulator with tip diameter varying between 100 and 200  $\mu\text{m}$ . The end of the wire was exposed to a conductive liquid medium (typically isotonic sodium chloride solution), while a concentric stainless-steel needle 0.9 mm in diameter (20 gauge) served as the return electrode. Two different insulating tip shapes were studied: convex and concave.

The zone of collateral damage was assessed by means of propidium iodide (PI), which has been shown to be a sensitive fluorescent indicator of cell permeability.<sup>11,12</sup> In cells with loss of membrane integrity, whether that loss is temporary or permanent, PI can enter and bind to its preferred target, nucleic acids.<sup>11,12</sup> The CAM from white leghorn chicken embryos 14 to 18 days into incubation served as our model soft tissue. A piece of CAM was pinned down to a 0.8% agarose layer in a Petri dish, covered with isotonic sodium chloride solution containing PI at a concentration of 4 $\mu\text{M}$ , and loaded onto a fluorescent inverted microscope (IMT-2; Olympus Corp, Lake Success, NY). The PEAK probe was positioned at 45° to the tissue surface with an XYZ micromanipulator. One pulse and 50 pulses at 5 Hz were applied at various distances from the tissue. The presence and size of a fluorescent zone could be observed a few tens of seconds after the application was made, and the zone was photographed 4 to 6 minutes later by means of a CCD camera (NL/CCD-512; Princeton Instruments [now Roper Scientific, Inc], Tucson, Ariz). The same procedure was applied for evaluation of the damage zone produced by retinal scissor cuts and diathermy. For diathermy, a Wet-Field Coagulator (Mentor Division of Codman and Shurtieff Inc, Randolph, Mass) at a setting typical for retinal applications (25/70 on its scale) was

used. Duration of diathermy application varied between 0.5 and 5.5 seconds. Reproducibility of all measurements was confirmed by repeating all experiments 3 times.

Dimensions of the cavitation bubbles accompanying the PEAK's electric discharges were measured by means of fast flash shadow photography with a light-emitting diode (LMR51WF; Sun-LED Corp, Walnut Creek, Calif). For these measurements, the probe was immersed into a Petri dish filled with isotonic sodium chloride solution and positioned on the same inverted microscope. With the same CCD camera and a flash duration of 0.5 microsecond, maximal size of the bubble was found by varying the delay between discharge and light-emitting diode flash.

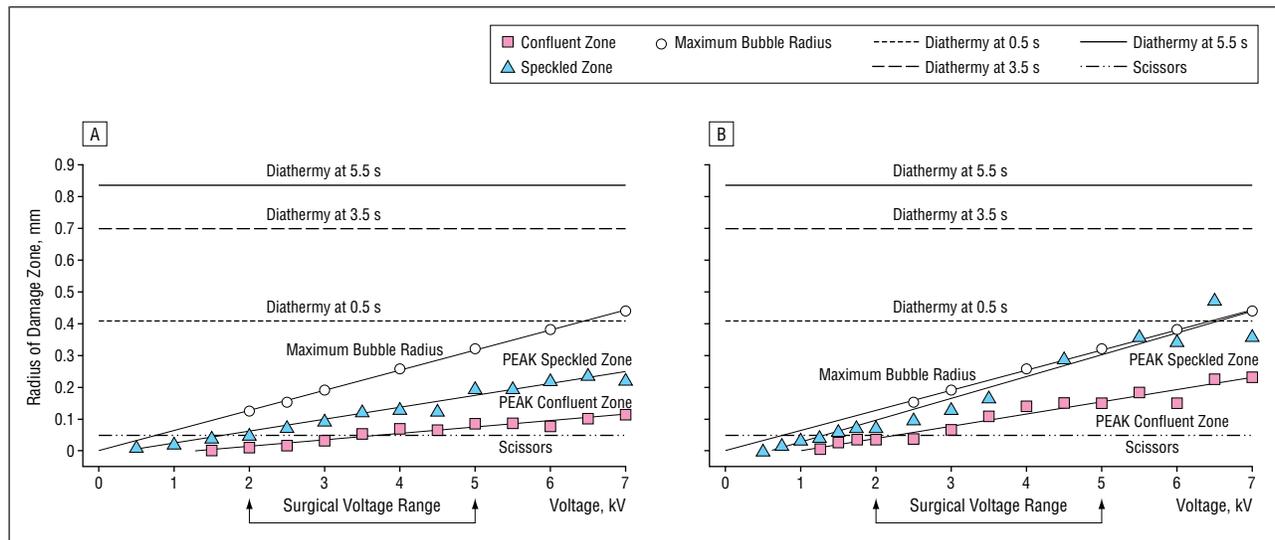
To measure damage-zone radius in rabbit retina *in vivo*, open-sky vitrectomies were performed on deeply anesthetized white albino rabbits. Institutional approval for animal experimentation was obtained, and protocol guidelines for care were followed at all times. The PEAK probe was scanned over detached retina at a repetition rate of 10 Hz and a voltage of 3.25 kV (optimal value for retinectomy in rabbits). Immediately after the cut, 2 to 3 mL of PI-isotonic sodium chloride solution (35 $\mu\text{M}$ ) was introduced into the globe. After 6 minutes, the globe was thoroughly flushed with pure isotonic sodium chloride solution. Retina was then excised from the eye and wet whole mounted onto a microscope slide. The width of the damage zone was measured on a fluorescent inverted microscope with Win-View software (Roper Scientific, Inc).

## RESULTS

### RADIUS OF THE DAMAGE ZONE

**Figure 1** demonstrates that there is PI fluorescent staining of CAM at the edges of a typical cut produced by scissors or PEAK. For quantitative evaluation of the size of the damage zone as a function of pulse settings, we applied PEAK to single spots on or above the tissue and measured radii of the resulting fluorescent patterns. In the first set of experiments, we measured the size of the damage zone produced by PEAK applied in contact with tissue. The damaged area can typically be divided into 3 distinct zones (**Figure 2**). The first, inner zone is dark, representing a crater or denatured material. The second zone stains with a dense, confluent fluorescence. Since PI stains primarily nucleic acids,<sup>11,12</sup> a zone of confluence suggests that nuclear material in this area has been scattered across the entire cell. Thus, the confluent zone most likely represents a set of cells that has been structurally disrupted by PEAK. The third peripheral zone stains in a speckled, much less dense pattern (Figure 2), suggesting that some cells in this region are uncompromised while others are structurally intact but permeable. Initial results from time-delayed PI staining experiments in progress suggest that a part of the permeabilized cells in the speckled zone recover from PEAK insult.

**Figure 3** demonstrates the relationship between PEAK voltage and damage zone. Application of a single pulse of the PEAK in contact with tissue at typical voltages for vitreoretinal surgery (2-5 kV) resulted in damage zones with radii ranging from 20 to 70  $\mu\text{m}$  for the confluent zone and from 55 to 155  $\mu\text{m}$  for the speckled zone (Figure 3A). Application of an increasing number of pulses to one point of tissue increased the damage zone size until a saturation level was reached after approximately 20 pulses. To create and measure the maximum possible dam-



**Figure 3.** Radius of the damage zone created by pulsed electron avalanche knife (PEAK) pulses applied in contact with chick chorioallantoic membrane. For comparison, we plot the maximum radius of the vapor bubble at each respective voltage, as well as the damage zone produced by microsurgical scissors and by diathermy at a standard (25/70) retinal surgery setting (see Table). The typical range of voltages used by PEAK during retinal surgery is 2 to 5 kV. A, Results from 1 pulse. B, Results from 50 pulses.

age zone size, we applied 50 pulses to one point of tissue (the instrument was fixed in a micromanipulator). Under this 50-pulse regimen, as voltage varied from 2 to 5 kV, the damage radius ranged from 40 to 150  $\mu\text{m}$  for the confluent zone and from 95 to 300  $\mu\text{m}$  for the speckled zone (Figure 3B). The size of the speckled zone after application of a single pulse is about half of the maximal radius of the cavitation bubble produced after discharge, while after 50 pulses, the speckled zone is practically identical to the maximum radius of the bubble (Figure 3A and B).

We also examined the effects of diathermy and scissors on viability of CAM to compare them with the effects of PEAK. To standardize the setting on our bipolar diathermy probe (at a setting of 25/70) with other posterior pole coagulators, we produced the chart of application time vs full coagulation of vessel size and type in the **Table**. A 0.5-second application of diathermy to CAM (the time necessary to coagulate a 100- $\mu\text{m}$ -diameter CAM vein) produced a damage zone radius of 410  $\mu\text{m}$ . When application time was increased to 3 seconds (the approximate duration necessary to coagulate a 400- $\mu\text{m}$ -diameter CAM vein or a 300- $\mu\text{m}$ -diameter CAM artery), the damage zone radius increased to 700  $\mu\text{m}$ . At an application time of 5.5 seconds (the time necessary to coagulate a 400- to 500- $\mu\text{m}$ -diameter CAM artery), the damage zone radius jumped to 840  $\mu\text{m}$ . The diathermy damage zone is more uniform in fluorescence than the speckled zone seen with PEAK application to CAM, but it is less uniform than PEAK's confluent zone (Figure 2). The width of the damage zone at the edges of the retinal scissors' cut was approximately 50  $\mu\text{m}$  and was similar in appearance to CAM's confluence zone (Figure 1).

To evaluate the accuracy of CAM as a model tissue for evaluation of PEAK's effects on retina, we carried out a limited set of similar PI studies in 3 live albino rabbits. Damage to rabbit retina induced by PEAK was very similar in appearance to damage on CAM. The width of the speckled damage zone at the edges of rabbit retinal cuts

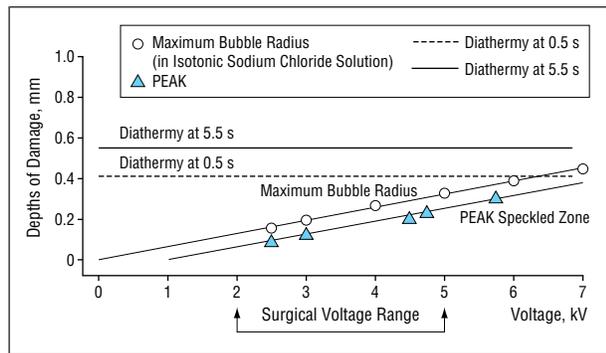
#### Application Time Necessary for Complete Coagulation in Chick Chorioallantoic Membrane

Vessel Type and Size	Application Time, s
100- $\mu\text{m}$ vein	0.5
100- $\mu\text{m}$ artery	1-2
250- $\mu\text{m}$ vein	1-2
200- $\mu\text{m}$ artery	2-3
400- $\mu\text{m}$ vein	3
400- $\mu\text{m}$ artery	4-6
600- $\mu\text{m}$ vein	3-4
1000- $\mu\text{m}$ artery	13

produced at a voltage of 3.25 kV and a pulse repetition rate of 10 Hz was about 120  $\mu\text{m}$ . This value is between the sizes of speckled zone PI staining for 1 and 50 shots of PEAK measured on CAM at the same pulse energy. Diathermy and scissors produced slightly larger damage zone radii (by about 15%) on rabbit retina in vivo than on CAM in vitro.

#### DEPTH OF DAMAGE

To determine depth of damage induced by PEAK and diathermy, we placed a 0.7% agarose layer of varying thicknesses between the PEAK (or diathermy) probe and CAM and determined the minimal voltage (duration for diathermy) necessary to induce fluorescence in the CAM underneath. Because the intervening agarose carries many of the properties of soft tissue, we interpreted gel thickness to be the maximum depth of damage for the corresponding voltage (duration for diathermy). As voltage was varied between 2.5 and 5.75 kV, a set of 50 pulses (applied at 5 Hz) created damage at a depth ranging from 100 to 300  $\mu\text{m}$ . In contrast, diathermy produced a damage zone depth that varied from 400 to 550  $\mu\text{m}$  as application time ranged from 0.5 to 5.5 seconds (**Figure 4**).



**Figure 4.** Depth of damage for different levels of diathermy and pulsed electron avalanche knife (PEAK) (50-pulse regimen) application. Diathermy was operated at a setting of 25/70 (see Table). Maximum radius of the PEAk vapor bubble produced in isotonic sodium chloride solution at each respective voltage is also shown. The typical range of voltages used by PEAk during retinal surgery is 2 to 5 kV.

### MINIMUM SAFE DISTANCE

Tissue damage may be produced not only by the expanding cavitation bubble but also by water flow created in front of the probe subsequent to bubble collapse. This jet may propagate and impinge on tissue at some distance from the probe.<sup>13,14</sup> To evaluate the influence of such flow, we measured the distance between probe and tissue at which minimum detectable fluorescence of the CAM appeared (using background subtraction techniques) for 50 pulses at a given pulse energy. We performed these “minimum safe distance” experiments on “naked” CAM and on CAM covered by the 20- $\mu$ m-thick, acellular, calcium-rich collagen layer that naturally covers the CAM, the inner shell membrane.<sup>15,16</sup> Such a layer may act as a protective “shield” against water jet damage to the underlying CAM, much like an epiretinal membrane would protect retina in humans undergoing vitrectomy and epiretinal tissue dissection or removal. Finally, since PEAk tip geometry affects velocity and direction of the water jet,<sup>17</sup> we performed these tests with 2 different types of probes: convex and concave (**Figure 5**).

**Figure 6** shows results obtained with 50 pulses applied by convex and concave probes with and without the shell membrane. The minimum safe distance for naked CAM with a convex probe varied from 0.4 to 1.4 mm when voltage spanned from 2 to 5 kV. These distances are substantially larger than the maximum radius of the cavitation bubble produced by PEAk at each respective voltage, indicating that tissue damage is created by water flow rather than by direct contact of tissue with the bubble. Further evidence supporting the water jet (rather than vapor bubble) as the source of damage at a distance for convex probes comes from the observation that PI staining was always found along the axis of the probe (positioned at 45° to the tissue), and not directly under the tip, where the spherically symmetric expansion of a vapor bubble would cause damage. The minimum safe distance measured on CAM covered by the inner shell membrane was substantially smaller than on simple naked CAM: 0.3 to 1 mm for the same voltage range and same number of pulses (**Figure 6**), suggesting a strong protective role for the shell membrane against a water jet.

With a concave tip, the PEAk’s vapor bubble collapses without generation of a forward-directed water jet.<sup>17</sup> Not surprisingly, minimum safe distance for these tips was much smaller and corresponded closely to the radius of the vapor bubble (**Figure 6**). In addition, PI staining for concave probes was always found under the PEAk’s tip and not in front of it (the probe was positioned at 45° to the tissue). Together, these data indicate that, with probes of concave geometry, damage is produced through expansion of vapor bubbles into tissue and not via a water jet.

Minimum safe distance for diathermy was measured at the same settings as experiments previously mentioned (**Table**). When diathermy was applied for 0.5 second, minimum safe distance was 400  $\mu$ m. With a 3-second application, it jumped to 800  $\mu$ m, while at 5.5 seconds, minimum safe distance was 1000  $\mu$ m (**Figure 6**). In these experiments, PI staining occurred directly under the tip (and not along the axis of the probe) since thermal damage is associated with spherically symmetric expansion of heat rather than axial water flow.

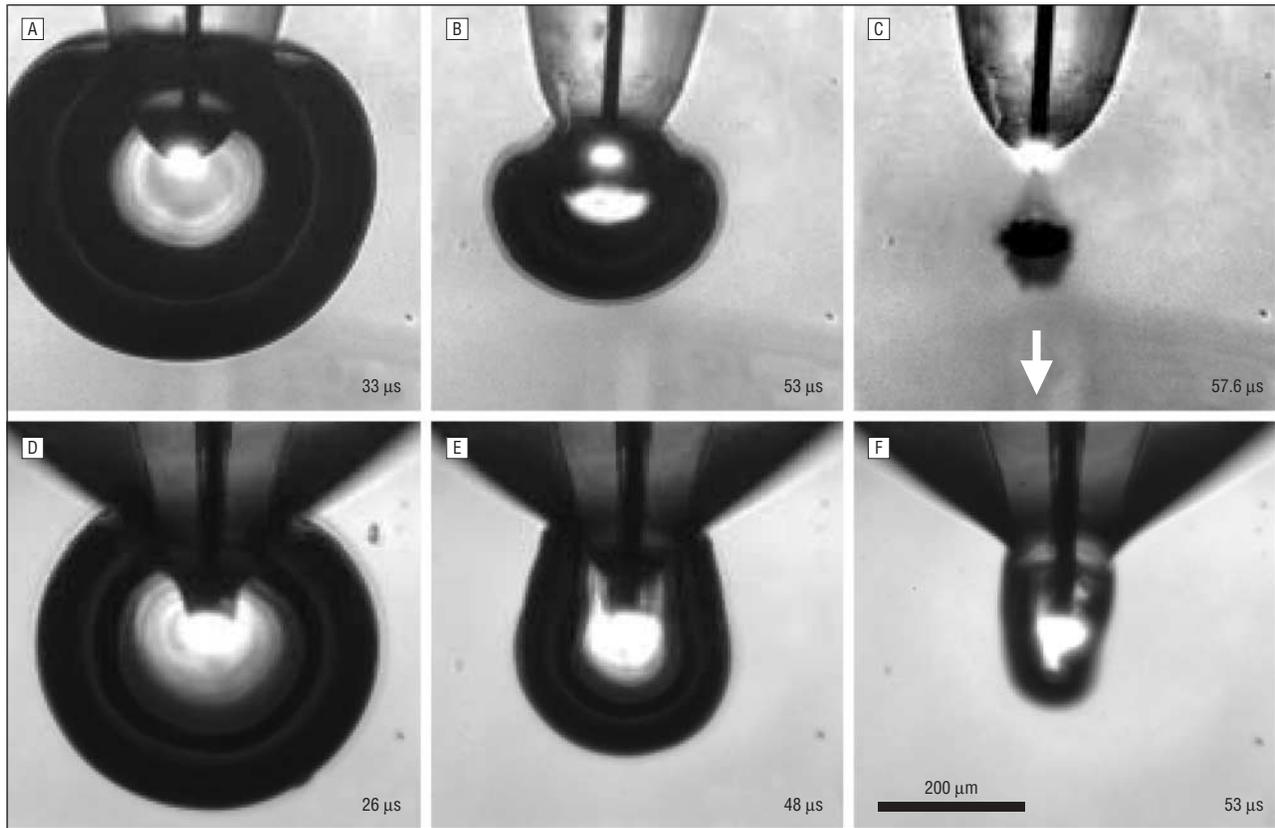
### COMMENT

#### RADIUS OF THE DAMAGE ZONE

Our group previously showed that application of the PEAk to retina produces cuts with sharp edges and no signs of coagulation, thus indicating the mechanical rather than thermal mechanism of PEAk ablation.<sup>9</sup> The present set of experiments, with PI staining of CAM, demonstrates that a zone of cellular structural damage and a zone of cellular permeability extend beyond the visibly ablated areas. The type of damage demonstrated by PI staining in this article cannot be attributed to chemical or UV light toxicity.<sup>10</sup> The tissue damage can, however, be attributed to the following potential sources: (1) stress or shock waves produced during explosive evaporation,<sup>18</sup> (2) electroporation by strong electric fields,<sup>19</sup> (3) water jet formed during collapse of the vapor (cavitation) bubble,<sup>17</sup> and (4) expansion of the vapor bubble into tissue.

Strong shock or acoustic waves can be generated by pulsed energy deposition under stress confinement conditions, ie, when the stress wave does not propagate out of the energy deposition zone during the pulse. Even under such conditions, the zone of biological damage induced by stress waves is usually smaller than the damage zone produced by concurrent cavitation.<sup>20</sup> In our case, the energy deposition zone is on the order of 25  $\mu$ m, giving a stress confinement time on the order of 17 nanoseconds (assuming the speed of sound in water is  $\approx$ 1.45 km/s). Since the PEAk discharge time (100 nanoseconds) far exceeds this limit, we can dismiss shock waves as a significant source of damage.

A typical value of threshold electric fields ( $E_{th}$ ) producing transient permeability of cells (with a resealing time of 6 minutes) is 1.8 kV/cm for 5 pulses of 100-microsecond duration.<sup>21</sup> The minimal electric field required for electroporation increases with decreasing pulse duration; for the PEAk’s pulse duration (100 nanoseconds), the electric field would need to be approximately 10 times higher to produce the same effect.<sup>22</sup> The distance  $r$  from an electrode with radius  $a$  and potential  $U$



**Figure 5.** Collapse of cavitation bubbles on convex (A-C) and concave (D-F) pulsed electron avalanche knife probes. Delay between the pulse and the flash is shown in the corner of each frame. The shapes of the tips are clearly seen in the right frames of each series (C and F), during the final stages of the collapse. Collapse on a convex tip produces a forward-propagating water jet (C; direction of the flow is shown by an arrow). On the concave tip, the bubble collapses toward the probe without generation of a water jet (F).

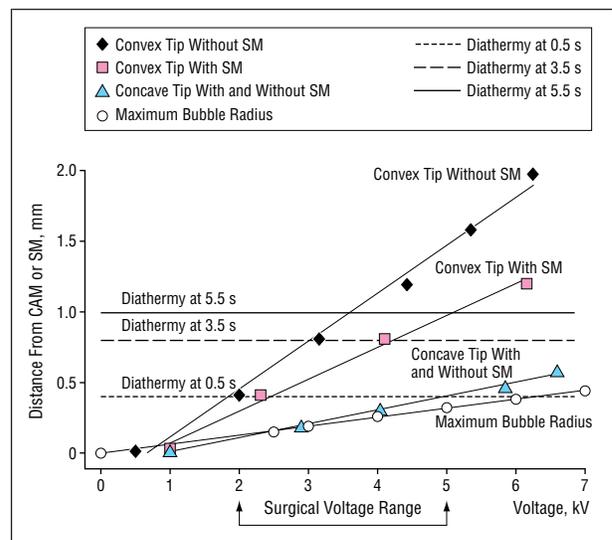
at which the electric field is no longer sufficient to induce permeability ( $E_{th}$ ) can be estimated as follows:

$$r = \sqrt{\frac{U \times a}{E_{th}}}$$

Thus, maximum distance at which cells may be affected by transient electroporation with the PEAK's pulse duration is 120 mm at a probe potential of 2 kV. Electroporation could, therefore, theoretically account for all speckled zone damage at this voltage. However, cavitation bubble size at 2 kV is slightly larger than 120 mm, making it an overriding factor in extent of CAM damage. In addition, the square root dependence of the electroporation zone ( $r$ ) on applied potential ( $U$ ) does not match the linear dependence of the damage zone in our experimental data (as shown in Figures 3 and 4).

Since a water jet forms only when the probe is not in contact with tissue,<sup>17,23</sup> only the expanding vapor bubble remains as the principal source of damage when the probe is touching tissue. This conclusion is further supported by the observation that the maximal bubble radius is essentially identical to the maximal damage zone under saturating conditions (50 shots), as plotted in Figure 3B.

The smallest damage zone (1 pulse) produced by PEAK in the range of voltages typically used during surgery (2-5 kV) ranges from 20 to 70 mm for the confluent radius (structural damage) and from 55 to 155 mm for the speckled radius (permeability). The maximum damage



**Figure 6.** Minimum safe distance for application of 50 pulses on chick chorioallantoic membrane (CAM) with the use of convex and concave tips with and without the inner shell membrane (SM) and for diathermy on "naked" chorioallantoic membrane. Maximum radius of the vapor bubble at respective voltages is plotted for comparison. The typical range of voltages used by the pulsed electron avalanche knife during retinal surgery is 2 to 5 kV.

zone (simulated by application of 50 pulses to the same spot) is approximately 2 times larger. Thus, under normal operating conditions the PEAK creates a zone of collateral damage of 2 to 3 times larger than that of micro-

surgical scissors and 2 to 10 times smaller than that of diathermy. However, compared with the PEAK, scissors provide less maneuverability and precision while creating unwanted traction. In addition, preliminary results from experiments still in progress suggest to us that the PEAK's speckled zone, which contains cells that are permeable but structurally intact, shows some potential for recovery.

The PEAK produces an almost identical damage zone in rabbit retina in vivo as in CAM in vitro, while diathermy and scissors both demonstrate slightly larger damage zones in rabbit retina (for selected settings). These results validate CAM as a useful model for evaluating the role of instrument-induced damage to live retina.

#### DEPTH OF DAMAGE ZONE

Depth of damage is another important characteristic of a surgical instrument, especially in applications where ablation of unwanted membranes must not compromise important underlying tissue. In the range of surgical voltages that can safely be used for membrane removal applications (2-3 kV), the PEAK's depth of damage for 50 pulses applied to a single point (a worst-case scenario) spans from 50 to 150  $\mu$ m. Because of viscoelastic resistance of tissue, depth of damage is slightly (25%) smaller than the size of the vapor bubble produced in isotonic sodium chloride solution at each respective voltage (Figure 4). Diathermy produced a significantly deeper damage zone than the PEAK, increasing from 400 to 550  $\mu$ m as application time increased from 0.5 to 5.5 seconds.

#### MINIMUM SAFE DISTANCE

Measurements of the minimum safe distance between probe tip and tissue at which PEAK no longer causes damage to the underlying tissue at a given voltage provide surgeons a scale of the safe working distances. Results from the experiments on CAM show that, with convex probes, tissue is damaged by water flow that forms during collapse of the PEAK cavitation bubble.<sup>14</sup> At surgical voltages (2-5 kV), PEAK has a minimum safe distance that ranges from 0.4 to 1.4 mm for 50 pulses. Covering CAM with the naturally occurring, acellular inner shell membrane significantly reduces minimum safe distance for the convex tips, most likely by dampening the impact of water jets. This protective effect suggests that the presence of epiretinal tissues may safeguard underlying retina during membrane dissection or removal surgeries in humans.

Concave PEAK probes are much safer because they do not create a forward-propagating water jet and thus do not produce damage beyond impingement of the bubble into tissue. This conclusion is supported by the close correlation between the minimum safe distance and maximum radius of the vapor bubble measured at various PEAK voltages (Figure 6). By eliminating the water jet with concave probes, the PEAK can be applied to tissue at all angles without changing the instrument's minimum safe distance (since vapor bubble damage is spherically symmetric). The concave probe's minimum safe distance is less than that of diathermy applied for 0.5 second.

Since our results demonstrate that formation and collapse of cavitation bubbles is responsible for most of the

collateral damage induced by the PEAK, we are working on a second version of the PEAK that cuts by a different mechanism. Instead of mechanically fragmenting tissue by microexplosions, this next generation of the PEAK cuts by vaporization and ionization of tissue, thus preventing cavitation-related damage while still limiting heat diffusion length to a few micrometers. This PEAK derivative will be described in a forthcoming publication.

#### CONCLUSIONS

We have determined that the PEAK operates within acceptable safety standards when compared with 2 other commonly used vitreoretinal surgical tools, microsurgical scissors and bipolar coagulation. Previously, we determined that PEAK presents no threat of chemical or UV toxicity and that it cuts without coagulating tissue.<sup>9,10</sup> In this study, we demonstrate that the collateral damage produced during dissection of tissue with the PEAK is dominated by expansion of the vapor (cavitation) bubble. When operating away from tissue with convex probes, a water jet formed during collapse of the cavitation bubble can produce collateral damage to the underlying tissue at distances 3 to 4 times larger than the size of the bubble. This damage can be greatly reduced by application of concave probes, which prevent flow formation.

The PEAK's ability for fast, efficient, tractionless dissection of tissue with minimal collateral damage may significantly facilitate many types of anterior- and posterior-segment ocular surgeries as well as nonocular procedures.

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