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Abstract: OBJECTIVES: Fifty percent of implanted cerebrospinal fluid (CSF) shunts fail within two years, caused primarily by obstruction of the proximal ventricle. Percutaneous techniques to reduce the morbidity of shunt revision are being developed. We describe the development of a device that uses ultrasonic cavitation to unblock ventricular catheters.

METHODS: In collaboration with Cybersonics Inc., Erie PA, we designed, built, and tested a system that produces low-frequency ultrasound (20-28 kHz). Extensional ultrasonic waves are transmitted along a tapered wire (final diameter ~0.8 mm) to the tip where cavitation is produced in a highly localized region. An in vitro model of sheep choroid plexus occluding typical ventricular catheters was developed. The device was safety tested in vivo in rat and pig brains by introducing the device into shunt catheters inserted during simulated shunt surgery. A clinical safety trial using the device to attempt to remove blocked and adherent ventricular catheters has commenced.

RESULTS: In the sheep choroid plexus model, at least 90% of the occluded holes were unblocked in a few minutes, restoring normal flow. There was no adverse effect of the device within shunt catheters inserted into live animal brains. Four patients have undergone treatment with the device at open CSF shunt surgery without adverse effect and the device appears effective at unblocking and freeing the occluded catheters.

CONCLUSION: Ultrasonic cavitation produced at the end of a fine wire which is percutaneously introduced into a CSF shunt promises to be a useful technique for minimally invasive proximal ventricular CSF shunt catheter revision.



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To Whom It May Concern:

Re: Statement of authorship on manuscript "Recanalization of Obstructed
Cerebrospinal Fluid Ventricular Catheters using Ultrasonic Cavitation"

As per the manuscript submission requirements, the statement of authorship and notifications of conflicts of interest follow below:

"Dr. Howard Ginsberg performed the essence of the development work. Many ideas presented were developed by him alone. He also performed all the in vitro testing and with the help of Dr. Drake, the animal testing.

Dr. Jim Drake was the nominal PhD supervisor for Dr. Ginsberg and completed the clinical testing. He also participated and contributed to the discussions leading to the development of the concepts. He also prepared the initial draft of this manuscript based on Dr. Ginsberg's PhD thesis.

Prof. Richard Cobbold contributed to the development of the ultrasonic system and the initial work in developing the concept was done in his laboratory. He contributed in a significant way to the preparation of the manuscript.

The above work was done under the grants listed in the Acknowledgement section of the manuscript.

Tom Peterson (Cyberonics, Inc., Erie, PA) collaborated from an early stage in the development of the ultrasonic generator and was largely responsible for the features of the device contained in the final version shown in Figure 1b. Evidently, he has a financial interest through the work performed for his company. Virtually all the development work for the final version was funded by Cyberonics."

Further details of the notifications of conflicts of interest and ethical adherence are noted within the manuscript.

Sincerely,

Howard J. Ginsberg

ARTICLE SUMMARY

The authors have designed and tested a new device to unblock cerebrospinal fluid (CSF) shunts. Hydrocephalus is a common condition in which CSF builds up inside the brain leading to neurological problems. It is often treated with a CSF shunt, a valved tube which drains CSF inside the brain beneath the skin to the abdomen. While very effective, shunts often become blocked, usually at the end within the brain. Trying to remove a blocked shunt can be difficult or cause bleeding within the brain. This new device offers the promise of unblocking the catheter inside the brain without removing it, and perhaps one day, simply through the skin under local anaesthetic. The device uses ultrasonic waves passed down a wire inside the shunt to break up the tissues blocking it, converting it to a fine mist. The device was tested in the laboratory, in laboratory animals, and in a clinical trial in a small group of patients. The device appeared to work well and no adverse effects from use of the device were found. Following further testing, the device may be compared to standard surgical technique to see if it improves patient outcomes in those presenting with a blocked CSF shunt.

Recanalization of Obstructed Cerebrospinal Fluid Ventricular Catheters using Ultrasonic Cavitation

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ABSTRACT

OBJECTIVES: Fifty percent of implanted cerebrospinal fluid (CSF) shunts fail within two years, caused primarily by obstruction of the proximal catheter. Percutaneous techniques to reduce the morbidity of shunt revision are being developed. We describe the development of a device that uses ultrasonic cavitation to unblock ventricular catheters.

METHODS: In collaboration with Cybersonics Inc., Erie PA, we designed, built, and tested a system that produces low-frequency ultrasound (20-28 kHz). Extensional ultrasonic waves are transmitted along a tapered wire (final diameter ~0.8 mm) to the tip where cavitation is produced in a highly localized region. An in vitro model of sheep choroid plexus occluding typical ventricular catheters was developed. The device was safety tested in vivo in rat and pig brains by introducing the device into shunt catheters inserted during simulated shunt surgery. A clinical safety trial using the device to attempt to remove blocked and adherent ventricular catheters has commenced.

RESULTS: In the sheep choroid plexus model, at least 90% of the occluded holes were unblocked in a few minutes, restoring normal flow. There was no adverse effect of the device within shunt catheters inserted into live animal brains. Four patients have undergone treatment with the device at open CSF shunt surgery without adverse effect and the device appears effective at unblocking and freeing the occluded catheters.

CONCLUSION: Ultrasonic cavitation produced at the end of a fine wire which is percutaneously introduced into a CSF shunt promises to be a useful technique for minimally invasive proximal ventricular CSF shunt catheter revision.

RUNNING TITLE: Recanalization of Ventricular Catheters using Ultrasonic Cavitation

KEY WORDS: Cerebrospinal fluid shunts, Hydrocephalus, Recanalization, Shunt revision, Ultrasonic cavitation

INTRODUCTION

In the period 1988-1991 an estimated 33,000 shunts were placed annually in the United States (2) with an approximate annual cost (excluding hospitalization cost) of US\$94 million dollars in 1991. Recently, the cost of hydrocephalus treatment was estimated to exceed one billion dollars annually (24). Following the development of shunt systems, management of patients with hydrocephalus has focused almost entirely on the treatment of shunt related complications (3). The causes of shunt failure include mechanical obstruction, infection, fracture of components, and growth of the patient. Mechanical obstruction is the most common cause of shunt failure (26, 28), which results in a re-accumulation of cerebrospinal fluid within the brain with abnormally high pressure. The proximal ventricular catheter is the most likely site of obstruction and, in the pediatric population, it is obstructed in up to 90 percent of mechanical shunt failures (28). In fact, 40% of shunts will fail in the first year (11). The median survival of a shunt has been reported as 73 months (25), indicating that the failure rate slows down after the first year.

Over the past fifty years the standard treatment for mechanical shunt obstruction has been to surgically remove and replace the blocked shunt components. A shunt revision typically takes 1 to 2 hours, requires a general anesthetic, one or two surgical scars and a hospital stay of one or more days. A 31% risk of visible hemorrhage has been reported for shunt revision surgery, visualized during surgery or diagnosed by post-operative CT scan. Although most of these hemorrhages are not clinically significant, they can reduce the time to subsequent shunt revision by 70% (3). Severe hemorrhage from shunt revision can result in significant morbidity or mortality. It may therefore be advantageous to leave the shunt within the brain and attempt to clean out the obstruction and restore flow in the shunt as has been reported (17). There is currently no accepted minimally invasive technique for recanalizing obstructed ventricular shunt catheters. The major advantages of such a treatment include: reduced procedure time, no need for general anesthetic, avoiding the difficulty of inserting a new shunt into small ventricles, reduced risk of intracranial hemorrhage, shorter hospital stay, reduced incidence of infection, and a profound impact on patient comfort, family life and hospital costs.

Electrocautery and Laser Methods

Electrocautery has been used routinely for many years to remove shunts that are attached to the choroid plexus (5). Typically, a stainless steel wire is inserted into the ventricular catheter while it is in the brain and an electrosurgical unit is touched to the wire to pass current through it in an attempt to release the catheter. Since the majority of the current must pass through the holes of the catheter within the brain, a high current density will pass through the tissue obstructing the shunt. This suggests the

possibility of using electrocautery for recanalizing obstructed ventricular shunt catheters. In a clinical study, Pattisapu et al. (21, 22, 23) reported successful use of this method in unblocking shunts in twenty patients with a one-year follow up. However, our in vitro testing using this technique (13) was not as successful at unblocking shunts as the ultrasonic method described below, although it may be quite useful and necessary as an adjunctive treatment.

The benefits of combining electrocautery with the ultrasonic shunt cleaning system are threefold: (1) when used initially, electrocautery could provide coagulation, and thus prevent hemorrhage potentially caused by therapeutic ultrasound, (2) electrocautery may be useful in destroying the bond that causes some tissue specimens to tightly adhere to shunt catheters, (3) electrocautery itself will remove some debris from the shunt. It should be noted that in order to effectively remove tissue from an obstructed shunt with electrocautery alone, we observed that the current must flow continuously for several minutes, which generated spark discharges and boiled CSF during in vitro testing. These spark discharges are likely generated when the current is forced to conduct across a gaseous gap created by the boiling of CSF within the shunt catheter (16). Pattisapu (21) has suggested that intermittently pulsing the electrosurgical unit can effectively recanalize the shunt without generating significant heat, although experimental studies have not been published to confirm this.

Using fibreoptics, it is possible to send laser light directly into a ventricular catheter to the site of obstruction. The use of laser energy to remove occlusions in ventricular catheters has been experimentally investigated by Christens-Barry et al. (6), but does not appear to have been tested clinically. Their study also demonstrated that the laser pulse could damage the shunt material. Specifically, using 200–400 mJ pulses, at a distance of 600 μm , a distance approximately equal to the internal radius of the shunt tube, there was microscopically detectable damage. Thus, it would seem that inappropriately directed laser energy could seriously damage shunt tubing.

Ultrasound Based Methods

Ultrasound has been used for many years in neurosurgery as a means of desiccating tissue in order to safely facilitate tumour removal. The idea of using an ultrasonic wire for therapeutic purposes originated as a technique for the minimally invasive removal of atherosclerotic plaque (8) or the dissolution of thrombi (27, 12, 29). In this method, an electronic generator drives an ultrasonic transducer coupled to a wire. If the intensity is sufficient the wave that travels down the wire produces cavitation in the immediate vicinity of the tip,

The concept for the ultrasonic shunt cleaner described below, evolved from the Ph.D. work of Kwok Wei Lam (19). He had developed a system for producing cavitation inside a shunt catheter non-

invasively for the purpose of facilitating Doppler ultrasound measurement of flow velocity. We believed that if ultrasound can break up clots without harming arteries, then it may be possible to destroy shunt-obstructing tissues without harming shunt material – the elasticity of the shunt material (silicone rubber) would make it unlikely to be damaged by ultrasonic vibrations. Based on these thoughts and experimental work by Lam, we began the development of this concept. Several prototype systems were built and these were experimentally evaluated in the manner to be described.

Cavitation

Young (30) defines cavitation as the creation of bubbles or cavities in a liquid or, the activity of preexisting bubbles or cavities. He identifies four types of cavitation according to the technique of bubble initiation. One of these is acoustic cavitation, which arises from the time-varying pressure produced by a wave as it propagates in a fluid.

Of particular importance in relation to ultrasound shunt cleaning is transient cavitation. Transient acoustic cavitation occurs when the intensity is above a certain threshold: it is usually associated with the application of a high intensity short duration ultrasound burst. In this process, bubbles typically expand to more than double their size and collapse violently in one cycle, disintegrating into a mass of smaller bubbles. These new smaller bubbles can be used again as seed bubbles for further transient cavitation. The collapse of transient cavitation bubbles produces very high pressures and temperatures in a very localized region. Spherical shock waves are produced, which tend to be rapidly attenuated within a few bubble diameters by the bubble filled lossy medium (30). This process can cause erosion, molecular degradation, emulsification, sonoluminescence, and biological effects such as tissue disruption. The newly formed smaller bubbles act like a shield blocking the transmission of the ultrasonic waves, thus keeping the tissue destruction process in a very localized area around the shunt catheter in a toroidal distribution. A bubble at a solid liquid interface or in a crevice will have these forces directed asymmetrically and can act to rid surfaces of debris. The shunt cleaner utilizes transient cavitation to remove debris from occluded shunts. The bubbles oscillate non-linearly in an acoustic field thereby acting as acoustic radiators. This oscillation produces both higher and lower harmonics: the latter being a good means for indicating the presence of transient cavitation.

For therapeutic devices employing transient cavitation, the optimal frequency is particularly significant. In general, lower frequencies have a lower intensity threshold for inducing cavitation (1). The lower limit of usable frequencies is set by the normal frequency hearing range to avoid discomfort or hearing injury. Thus, frequencies in the range 25-100 kHz are generally considered to be optimal for ultrasound angioplasty (20).

PROTOTYPE SYSTEMS

As noted earlier, we developed (14) several prototype systems that used various wire probe designs. These included those with solid and hollow cores (cylinders) and those with small ball or mushroom shaped tips on the end. All these systems focused on the use of continuous-wave ultrasound in the 20-30 kHz range and the use of a transducer matched to the wire via a stepped acoustic matching transformer. Extensional waves are propagated down the wire causing cavitation in the tip region. However, these earlier versions suffered from a large amount of heat being dissipated at the junction between the proximal end of the wire and the matching transformer, often causing wire breakage. As a result a water-cooling jacket was needed. The most recent version, shown in *Fig. 1A*, consisted of an exponentially tapered titanium aluminum vanadium alloy solid wire. It had a length of 15.7 cm, a diameter of 1.2 mm, 10 cm from the end and a diameter of 0.8 mm at the tip. Ultrasound extensional waves propagated down the wire get amplified in intensity by the exponential taper producing an intense field at the tip. It was coupled by a crimp screw thread to an acoustic matching horn, which in turn was driven by a series of piezoelectric transducers. Because the new design was highly efficient, no water-cooling jacket was needed and wire breakage was less problematic. The device was designed and constructed in collaboration with Cybersonics Inc. (Erie, PA). Because the probe/horn has a very narrow resonant frequency range it was necessary to provide a means of automatic tuning so that the ultrasonic generator frequency exactly matched the resonant frequency. When the tuning button is depressed, the generator sends a frequency sweep to the transducer and the resultant signal detected by the small PZT element is fed back to the generator and it is locked onto the frequency, thereby producing the maximum efficiency. In the event that the resonant frequency drifts, simply depressing the tuning button quickly restores optimal performance. The unit has an adjustable digitally displayed power output and an upper power limit of 5 watts.

EXPERIMENTAL EVALUATION

The testing and evaluation of the shunt cleaning system was accomplished in a variety of ways, as described in this section. Some tests were also performed during the initial phase of the testing program using an early prototype version of the system and this is described next.

Unlike ultrasound angioplasty wires which generally have a ball at the tip, our probe tip had a flat surface. The radiation pattern in water was measured in order to verify that the wire tip produced a highly localized field. Measurements were made at low power to avoid damage to our calibrated hydrophone (Model 8103, Bruel & Kjaer). In addition, measurements of the emission spectrum were made at high power, but well away from the tip.

Extirpated Shunt Catheters

Eighteen ventricular catheter specimens were collected from patients. There was a startling diversity in the specimens. Notably, several different types of catheters were collected including those with 8, 20, and 40 flow holes, as well as flanged catheters. The flanged catheters were the most difficult to unclog since the tissue was collected on the flanges at a distance of 3-4 mm from the flow holes, which is most likely out of range for the shunt cleaner. Some catheters contained large clumps of tissue overlapping the holes, while others contained almost none, and some contained evidence of hemorrhage. The majority of these obstructed catheters (12 of 18) were not completely obstructed after removal and hence tissue was likely left behind when they were removed, which is often done forcefully. In some specimens there were anastomotic rings joining tissue from one hole to another, demonstrating that this tissue must be cut rather than simply pushed out.

Extirpated shunts are in fact just a model of the clinical specimens. Although these specimens were removed from patients due to mechanical obstruction, they are not identical to the actual in vivo blocked shunts, since the tissue is avulsed and devascularized. The shunt cleaner was successful in recanalizing clinical specimens, but the diversity in the specimens made it difficult to quantify the results of prototype testing in a meaningful way. We concluded that a more consistent blocked shunt model was needed.

Blocked Shunt Model

The choroid plexus from removed lamb brains was carefully injected into 10 transparent ventricular catheters (Medtronic PS Medical, Goleta, California) with a 5 ml syringe as a single piece until it blocked all the holes in an approximately equal manner. Shaking the catheter or inserting a wire into the shunt would not remove the obstruction. The obstructed catheters were tested with manometry to ensure that no flow was permitted and were inspected by microscopy to ensure that all 40 holes were occluded. The ultrasonic probe was then inserted into each catheter while in a saline bath, for a period of 4 minutes and the results were recorded with video microscopy. The probe was moved in a gentle up and down motion inside the catheter to ensure that the cavitation effects would reach all of the flow holes. The catheters were then inspected with microscopy for damage and the number of patent and obstructed holes were counted. The flow rate through each catheter was also measured and compared to that of a new ventricular catheter.

Although choroid plexus tissue was used for obstructing catheters, there are some important differences between this model and actual specimens. Firstly, the model uses post mortem tissue and does not necessarily have the same properties of living vascularized tissue in clinically obstructed

catheters. Secondly, close inspection of the clinical specimens revealed that the tissue is gradually pulled into the holes of the catheter and often forms closed rings from one hole to the adjacent one. This could not be achieved using this model. Although lamb brain obstructed catheters are not identical to the real scenario, we considered them to be a suitable model for in vitro prototype testing.

Safety Testing - Gelatin

Fixed gelatin has the property of memory - the precise region of cavitation activity can be observed and captured in the gelatin, whereas in water, the bubbles rapidly disappear leaving no trace. To assess potential thermal effects and to determine the region over which cavitation occurs, transparent ventricular catheters were set into a clear gelatin mould overnight in glass beakers and the ultrasonic probe was then inserted into the catheters. The generator was set to deliver ultrasound to the wire for 4 minutes. Because of the relative transparency of the system we could use video microscopy to record and study the physical effects on the gelatin and to determine the region of cavitation around the ultrasonic probe. The video microscopy studies of cavitation within a shunt fixed in a gelatin mould were very revealing. It was clearly demonstrated that the cavity produced is highly focal around the tip of the wire probe, and there is no significant disturbance to the gelatin at a distance of greater than one millimeter from the tip. It is highly effective at destroying the tissue within the holes of the catheter, but does not pose a significant threat to surrounding brain tissue. These studies also clearly demonstrated the dangers of heat to the integrity of the junction between the wire and horn, and the ability to eliminate them with a simple passive room temperature saline cooling system.

Animal Safety Testing

With approval from the Animal Care Committee at the Hospital for Sick Children, six 430-450 g Fisher white rats were induced with 2% Isoflurane® and nitrous oxide, then anesthetized with sodium thiopental (dose of 0.1 ml/100g of sodium thiopental solution containing 65 mg of sodium thiopental in 100 ml was given intraperitoneally). The rats were placed in a stereotactic frame where they were held in position with ear bars and a mandible clamp. The posterior aspect of the head was shaved and prepared for incision and insertion of ventricular catheter. A small incision was placed on the scalp in the occipital region, just lateral to midline and a small burr hole was created with a dental drill. A ventricular catheter was placed in one hemisphere of each animal. Three of the rats received a 4-minute treatment with the ultrasonic probe within their catheter, while the other three were used as controls and had the catheter placed without ultrasonic treatment. The rats were euthanized by pentobarbital overdose. They were *phlebotomized* and perfused with a 10% formaldehyde solution for brain fixation with the shunt catheters

left in situ. The brains were then removed with the ventricular catheter in situ. Sections were stained with hemotoxylin and eosin and examined by a neuropathologist blinded as to whether cavitation had been used.

Five Yorkshire pigs weighing 21-26 kg received were induced with 1.0 ml/6 kg IM of the following solution [Ketamine (100 mg/ml, 58.8%), Atropine (0.5 mg/ml, 18.8%), Acepromazine (25 mg/ml, 4.7%), Normal Saline (17.6%)]. Followed by 2.0 l/min oxygen, 2.0 l/min nitrous oxide, 5% Halothane by mask, endotracheal intubation and intravenous line insertion in an ear vein. The maintenance anesthesia consisted of: 2.0 l/min nitrous oxide, 1.0 l/min oxygen, 1-1.5% Halothane. Antibiotic prophylaxis was: Cefazoline 250 mg IV at start of procedure, followed by Pen-Di-Strep post operatively (250 mg Dihydrostreptomycin, 100,000 U Benzathine Penicillin G, and 100,000 U Procaine Penicillin G in 1.0 ml normal saline), given at 1 cc/22.5 kg IM. The pigs were taken to the operating room, placed in the *prone position*, prepped with iodine solution and draped in a sterile fashion. The pigs were mechanically ventilated and monitored for oxygen saturation, heart rate and airway pressure. Bilateral paramedian scalp incisions were made 1 cm from the midline and a small twist drill burr hole fashioned. One ventricular catheter was placed in the frontal lobe of each hemisphere. Catheters were inserted 1 cm lateral to the midline at an angle of approximately 45° in the lateral and 45° in the anterior directions to a depth of 3 cm.

The sterile prototype was tested and tuned in a saline filled bowl prior to insertion into the catheter. The shunt cleaner probe was inserted into the left ventricular catheter and gently moved up and down its entire length during the cavitation process while holding the ventricular catheter in place. A simple wire stylet was inserted into the right ventricular catheter as a control. The catheters were then tied shut and cut at the level of the skull. The scalp was then closed in two layers, the anesthesia was reversed and the pig was extubated. After a short recovery period, the pigs were taken back to their pens and observed for 72 hours. Pain relief was provided with Bupomorphine 1 ml of 0.5 mg/ml prn.

After 72 hours of observation, the animals were anesthetized with a titrated dose of intravenous Sodium Thiopental and taken to the autopsy room. Each pig was placed supine on the table, with the head elevated and a 10 cm midline incision was made in the neck. The internal jugular veins were identified and incised bilaterally. The carotid arteries were identified bilaterally, ligated and opened proximally for exsanguinations and formaldehyde perfusion. Following exsanguination, the pig was turned into the prone position with the head elevated. A total craniectomy was performed to remove the brain. The brains were stored in formaldehyde for a minimum of 24 hours and then sectioned through the tracts left by the ventricular catheters. The slices were then stained with hemotoxylin-eosin and luxol fast

blue (used to identify myelin). Five to seven slides were prepared for each hemisphere of each pig. An experienced neuropathologist examined the specimens blinded to the side of the cavitation.

Clinical Testing

A research protocol was approved by the Hospital for Sick Children, Toronto. Approval for investigational testing was also granted by the Medical Devices Bureau of Health Canada. The protocol specified that patients undergoing open shunt revision where the ventricular catheter was blocked and adherent and could not be removed with electrocautery were eligible. Patients with any infection, bleeding disorder, or unfavorable position or trajectory of the ventricular catheter tip were excluded. Consent was obtained from families and/or patients prior to surgery by a nurse practitioner or neurosurgery resident. In the operating room, the sterile system was connected and tested in a water bath and tuned to the optimal frequency. Following a variable period of electrocautery, the wire stylet of the device was passed down the catheter in some cases monitored under ultrasound imaging control, until contact was made with the catheter tip. Starting at the lowest power output or 3 Watts, the stylet was passed in and out over the length of the catheter holes, 1 to 2 cm, with the power on. The device was then removed and the catheter checked for spontaneous flow and any sign of hemorrhage. If there was no flow, the power output was increased and the procedure repeated. Typically the total duration of cavitation was 60 to 90 seconds with a power setting of up to 4.5 Watts. If the catheter was freed and unblocked it was gently removed. If it remained adherent, then either electrocautery was used again, or the catheter was left in situ.

RESULTS

Initial Testing

The results of *Fig. 2* show that the pressure reduces rapidly with distance suggesting that at high power the cavitation region should be in a highly localized volume surrounding the tip. The pressure field measurements taken along the probe axis (*Fig. 2A*) reveal that the transducer/horn/probe assembly functions essentially as a point source acoustic radiator causing the pressure to fall off approximately inversely as the radial distance from the source. The measurements of *Fig. 2B* show the radial variation at various depths from the tip. While both of these measurements were made in the absence of any shunt, it seems possible that the acoustic mismatch caused by the presence of the shunt wall would cause the pressure field exterior to the shunt to be appreciably reduced beyond that expected for a point source.

Measurements of the emission spectrum at high power showed the existence of subharmonics, which is good evidence that the primary mechanism of tissue destruction is transient cavitation.

Blocked Shunt Model

We observed that tissue was removed from the catheters in microscopic fragments that were much smaller than the size of a single hole in the ventricular catheter. Thus, the debris produced is unlikely to cause re-obstruction. All 10 catheters tested had 40 holes occluded by lamb brain choroid plexus before ultrasonic treatment. Activation of the ultrasonic device caused immediate fragmentation, and ejection of occluding choroid plexus from the catheter lumen (*Fig. 3A*). Microscopic inspection did not reveal any damage to the shunt tubing from ultrasonic cavitation. For all 10 catheters, 36-40 (90-100%) of the holes were reopened and normal flow rates were restored (*Fig. 3B*).

Safety Tests

It was clearly demonstrated that the cavitation produced is highly focal around the tip of the wire probe, and there was no significant disturbance to the gelatin at a distance of greater than one millimeter from the tip. Cavitation was also noted just proximal to the tip of the probe in a toroidal region with a radius of less than 1 mm. These tests suggested that the method is highly effective at destroying the tissue within the holes of the catheter, but does not pose a significant threat to surrounding brain tissue. In addition, these studies clearly demonstrated the dangers of heat to the integrity of the junction between the wire and horn. Subsequently this problem was eliminated through the use of an exponentially tapered wire and improvements in the acoustical matching of the wire to the transducer.

The histological study of the six rat brains did not reveal any significant differences in those animals that were treated with ultrasonic cavitation plus a ventricular catheter and those that simply had a catheter insertion alone. There was no difference in the size or the shape of lesion, or degree of trauma produced in either group. A sample histological whole mount section from both groups is shown in *Fig. 4*.

Similarly, in the 5 pig brains two specimens in the control group appeared slightly more damaged than their cavitation treatment counterparts, and the other three pairs were equivocal. Both groups demonstrated tissue injury beyond the tract of the ventricular catheter. There was evidence of *necrosis*, *axonal swelling*, *demyelination* and minor hemorrhage to a variable degree in the treatment and control specimens as shown in *Fig. 5*.

Clinical Testing

Our results are summarized in *Table 1*. The device has been used in four patients. In three cases it was able to unblock the ventricular catheter when cautery was unable to do so, and in two cases it was able to free the catheter when cautery was unable to do so. In two cases the catheter remained unblocked

but adherent, possibly from adhesions external to the shunt. For one patient (see case example below) the unblocked catheter was left in situ – the ultimate treatment envisioned for this device. There was blood tinged CSF in one patient. Two patients had small amounts of hemorrhage on CT scan, one along the shunt tract when the adherent shunt was removed manually after being unblocked by the cavitation device. In the other there was some subdural bleeding likely related to collapse of the ventricles. In neither case did the hemorrhage appear related to the use of the cavitation device.

Case Example: This 17-year old boy with hydrocephalus from prematurity and intraventricular hemorrhage, and who had had multiple previous shunt revisions, was presented with headache. A CT scan revealed enlargement of the ventricles beyond his baseline studies. At surgery a proximal obstruction of the ventricular catheter was identified. Use of electrocautery applied to the wire stylet of the ventricular catheter caused minimal flow of CSF fluid and catheter remained blocked. Ultrasound cavitation unblocked the catheter to the point that there was good flow. The catheter remained adherent and the decision was made to leave it in situ. Pre- and immediate postoperative scans are shown on *Fig. 6*. The patient has remained well almost one year following surgery

DISCUSSION

The mechanical obstruction of shunts is a complex biological process. The insertion of the ventricular portion of a shunt incites a similar response to a stab injury to the brain. Cell necrosis, and blood vessels are disrupted with resulting focal hemorrhage and local *edema* on a very small scale. Brain tissue and blood inevitably enter the ventricular catheter during insertion and serum proteins then adhere to the silicone rubber. Neutrophils and macrophages accumulate within hours, followed by capillary and *astrocyte proliferation* within days. Any of these cells can contribute to the blocking of the ventricular portion of a shunt (9). The catheters are most commonly obstructed by in-growth of choroid plexus, due to flow of CSF drawing the plexus in, and *glial tissue* from astrocyte proliferation (7). Less commonly, ventricular catheters are obstructed with connective tissue, clotted blood, ependymal cells, necrotic brain tissue, lymphocytes, multinucleated giant cells, neutrophils, and foreign materials (hair, fibre, etc). Despite modifications in ventricular catheter position and design, including changes in shape and material, no significant improvement has been shown.

Ultrasonic cavitation unblocks the catheters in microscopic fragments that are much smaller than the size of a single hole in the ventricular catheter during controlled in vitro experiments. Thus, the debris produced maybe unlikely to cause re-obstruction. Similar success has also been achieved in recanalizing

obstructed ventricular catheters that have been removed from patients. While this is much more difficult to control and quantify, it does provide added strength to the results from the lamb brain choroid plexus model of a blocked shunt. In a previous study, we demonstrated that only a single hole needs to be patent to provide normal shunt hydrodynamics (15)

The prototype was tested in order to characterize its behaviour and mechanism of action. It was shown to behave like a point source acoustic radiator and produce transient cavitation. A number of tests were also conducted to determine the safety and efficacy of shunt recanalization with ultrasonic cavitation. Efficacy of shunt cleaning was demonstrated using obstructed ventricular catheters extirpated from patients as well as a model of blocked catheters using sheep brain choroid plexus. The device performed exceptionally well in these tests. Computer and experimental models were developed to determine the number of holes that need to be opened in a blocked shunt in order to restore appropriate hydrodynamics. The opening of a single hole was shown to be sufficient to restore hydrodynamics. Reopening a single hole may not prove to be practical since it would likely reobstruct soon after treatment, however, the shunt cleaner was able to open at least 90% of the holes in every case.

Safety tests were divided into in vitro and in vivo studies. The device was compared to the CUSA and was shown to produce a much lower pressure. Since the CUSA has never been shown to induce hearing loss, and the shunt cleaner operates at a similar frequency, it is not likely to produce hearing loss either. The other in vitro studies consisted of video microscopic observations of cavitation in a clear gelatin mould. Studies revealed the focality of the region where cavitation takes place, which is confined to a 1 mm region surrounding the tip of the wire probe.

Animal studies showed the acute changes of passage of a ventricular catheter into the brain, but nothing further with the use of cavitation. The rat experiments were acute studies, since the size of the catheter and extent of injury precluded keeping the animals alive. The pig experiments evaluated the effects of cavitation at 72 hours when any remote effects, or delayed injury would be present. There was no additional injury from the cavitation device. It should be added that these experiments tested the worst-case scenario with the shunt placed within the brain substance, since typically the device will be used within a dilated ventricle, surrounded predominantly with CSF.

The clinical study is part of an ongoing safety study. The device is being used after cautery deliberately so that any bleeding from disruption of the blocking tissue can be minimized. The device is being used at open shunt surgery, when cautery has failed, as being the most controlled situation in case of any complications. To date there have been none, and moreover it appears that the device has some efficacy when cautery has failed. Our ultimate goal is to use this device percutaneously when the patient

has an apparent proximal catheter obstruction, and with hardware suitable for direct percutaneous cannulation such as a Rickham reservoir.

Limitations and Risks

The cavitation device may likely not be able to dislodge tissue external to the shunt, and may be ineffective with some particularly firm tissue. If the wire probe were to pass beyond the catheter lumen, through a side hole, then brain injury or hemorrhage could occur. Fluoroscopic guidance may be necessary. The wire needs to follow a straight trajectory, so going around sharp bends, i.e. from the flat of the skull into the burr hole are virtually impossible with ultrasound acoustic devices. The debris released by the device may occlude the shunt farther down stream, as raised intracranial pressure will likely flow the CSF and cavitated material down the ventricular catheter lumen. In the envisioned percutaneous technique, this might occlude the downstream valve or catheter.

CONCLUSIONS

Ultrasonic cavitation appears to be a promising technique to be added to the tools for proximal shunt revision. Other potential catheter unblocking techniques include externally applied focused ultrasound, (4, 18) or the injection of biological agents such as enzymes for which no prototypes have so far been developed to the best of our knowledge. Prevention, through the development of new biomaterials to resist tissue ingress, is another possible strategy.

The ultrasonic shunt recanalization technique is highly focal and there is no issue with dangerous levels of heat production. The main drawback is that the ultrasonic probe requires a pathway into the ventricular catheter that is relatively free from any abrupt changes in direction, and hence, a Rickham type reservoir would be required. This drawback may seem insignificant compared to the potential benefits of a shorter procedure time (actual cavitation time less than one minute), no need for general anesthetic, minimally invasive, reduced shunt infection rate, avoiding the difficulty of inserting a new shunt into small ventricles, reduced risk of intracranial hemorrhage, significantly reduced treatment costs, and improved quality of life.

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FIGURE LEGENDS

FIGURE 1. *A*, details of the 15 cm long, exponentially tapered wire probe. It tapers to a diameter of 0.8 mm at the tip. A precision-machined thread allows the probe to be changed. *B*, ultrasonic generator (~20 kHz), cavitation probe and foot switch. The adjustable energy output delivered to the probe is shown on the display panel.

FIGURE 2. Measured pressure distribution in water for small-signal excitation at 20 kHz using a calibrated hydrophone. *A*, along the probe axis with reference to the probe tip. The two symbols correspond to two measurement sequences. *B*, radial variation from 1 mm to 5 mm below the tip (see insert).

FIGURE 3. In vitro testing of blocked shunt model using sheep choroids plexus. *A*, single frame from a video microscopy recording. Cavitation is taking place and choroid plexus material can be seen being finely fragmented and ejected into surrounding water bath. The wire probe has a diameter of 1 mm. *B*, results showing the number of holes blocked after four minutes of treatment with the ultrasonic probe. All 10 catheters initially had all 40 holes blocked by lamb brain choroid plexus. All catheters had 90-100% of holes unblocked and normal flow rates after treatment.

FIGURE 4. Post-mortem hemotoxylin and eosin stained sections of rat brain. *A*, showing the effects of shunt insertion without ultrasonic cavitation. *B*, showing the effect of shunt insertion plus ultrasonic cavitation treatment. In both cases, the catheter was inserted into the left hemisphere. No difference was seen between the pairs.

FIGURE 5. Low power histological sections from pig brain. *A* & *C* from animals receiving treatment with ultrasonic cavitation. *B* & *D* from control specimens. In *A* & *B* the catheter tract is seen in the white matter with resultant demyelination. There was no difference between sides when reviewed by a pathologist blinded to use of the cavitation device.

FIGURE 6. *A* & *B* preoperative CT images for patient # 2. *C* & *D* immediate postoperative images that show no evidence of hemorrhage. The ventricles are slightly smaller. The patient has remained well for one year.

Figure 1a
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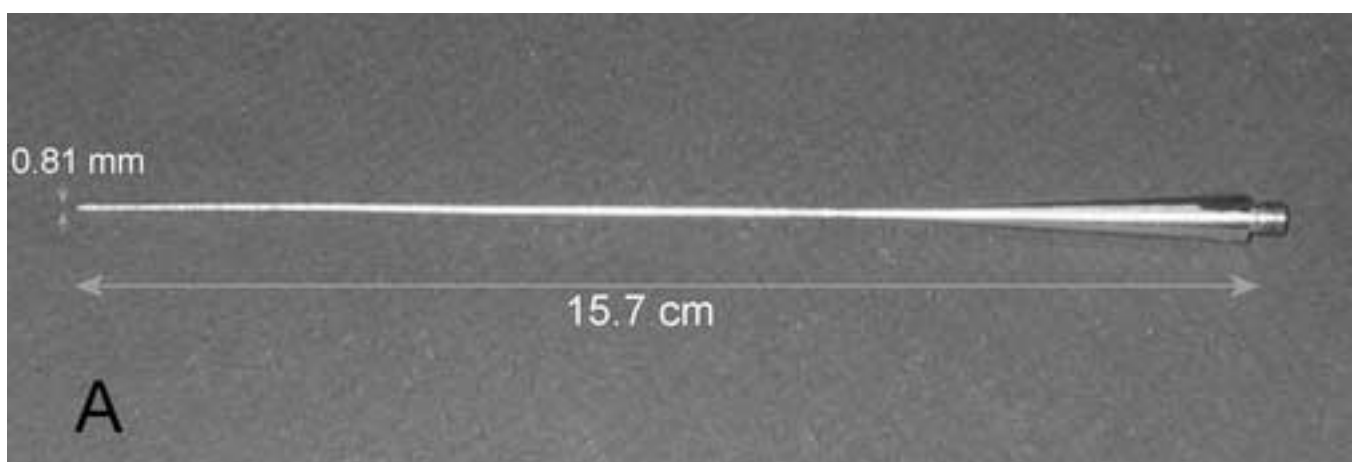


Figure 1b
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Figure 2a

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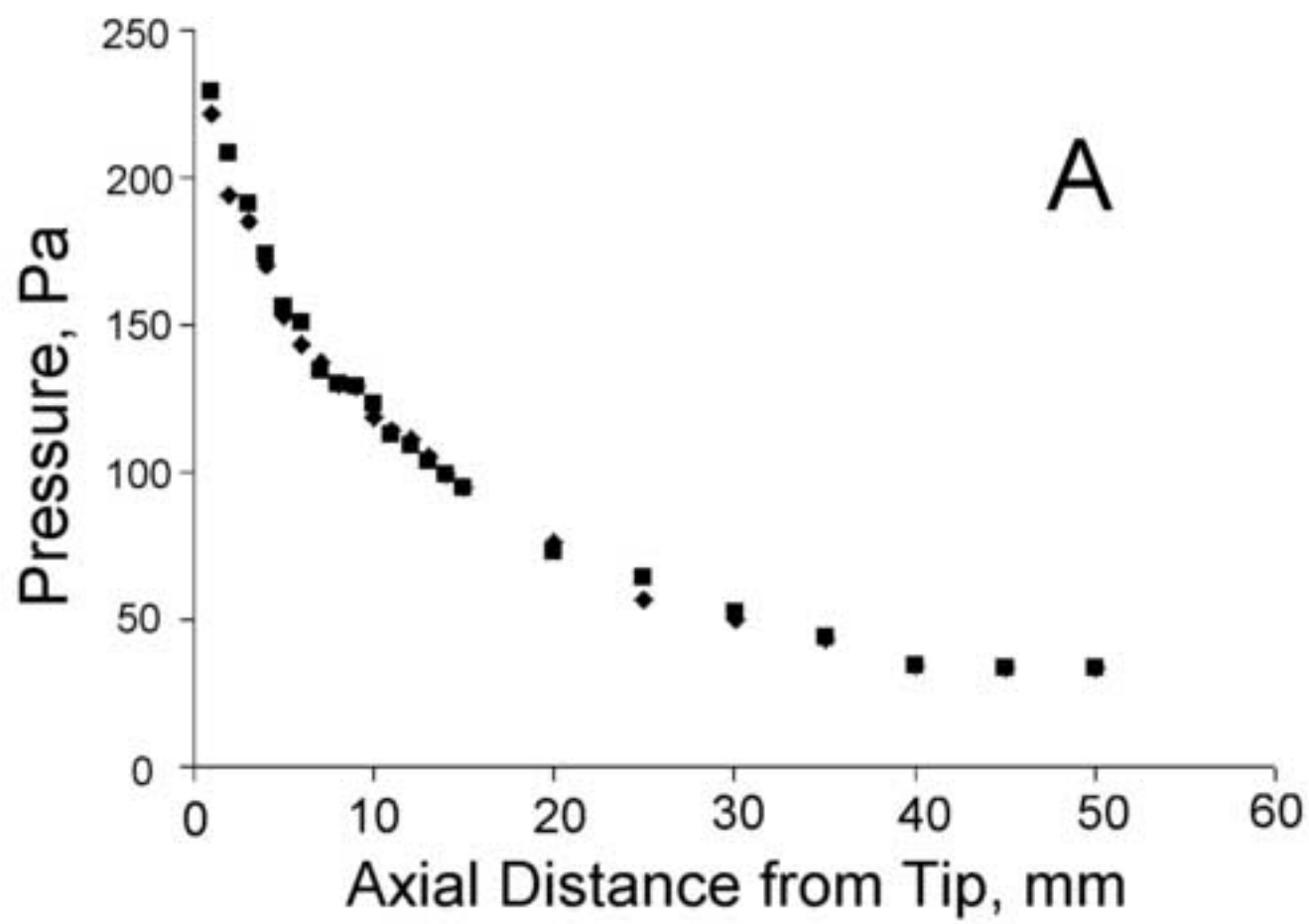
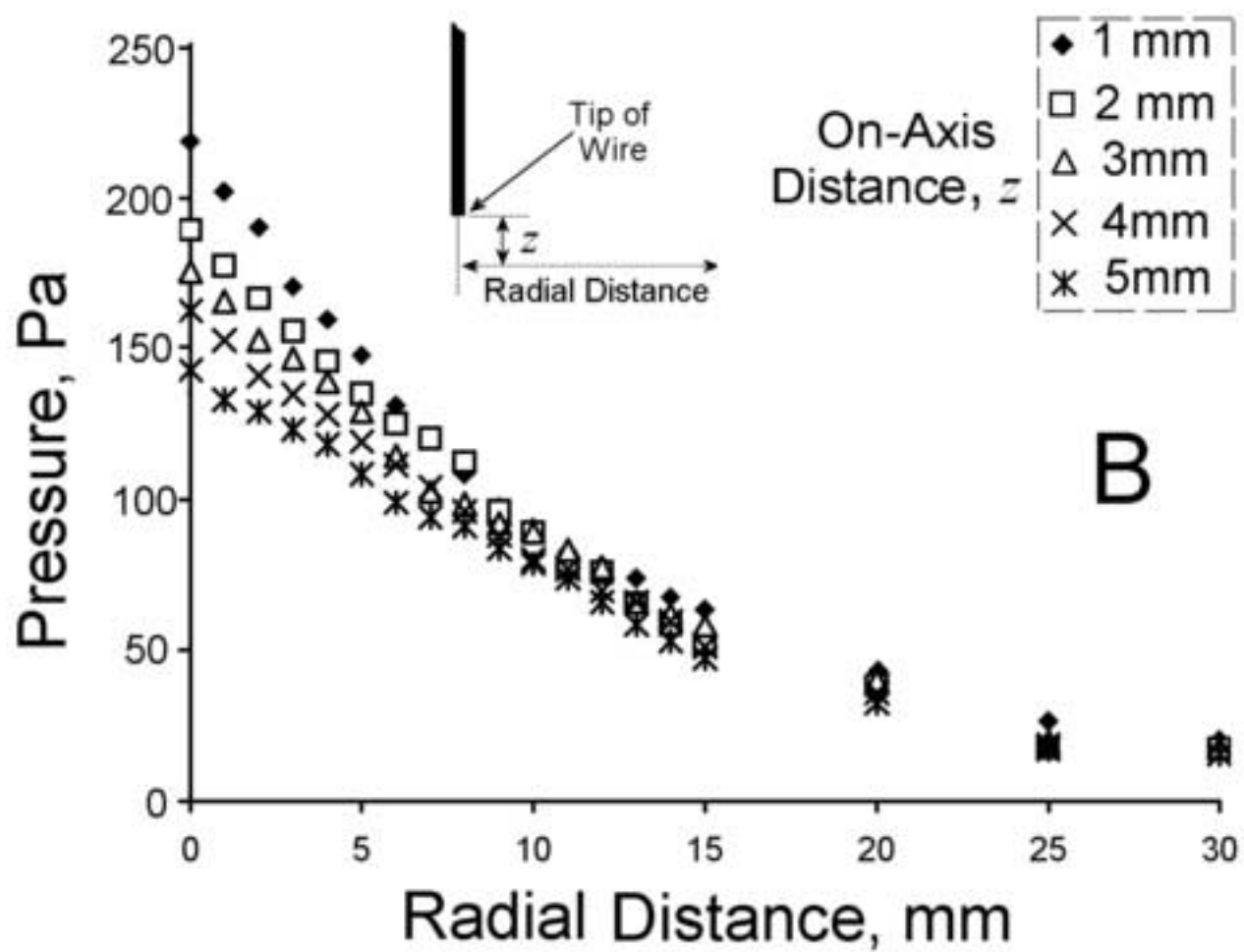
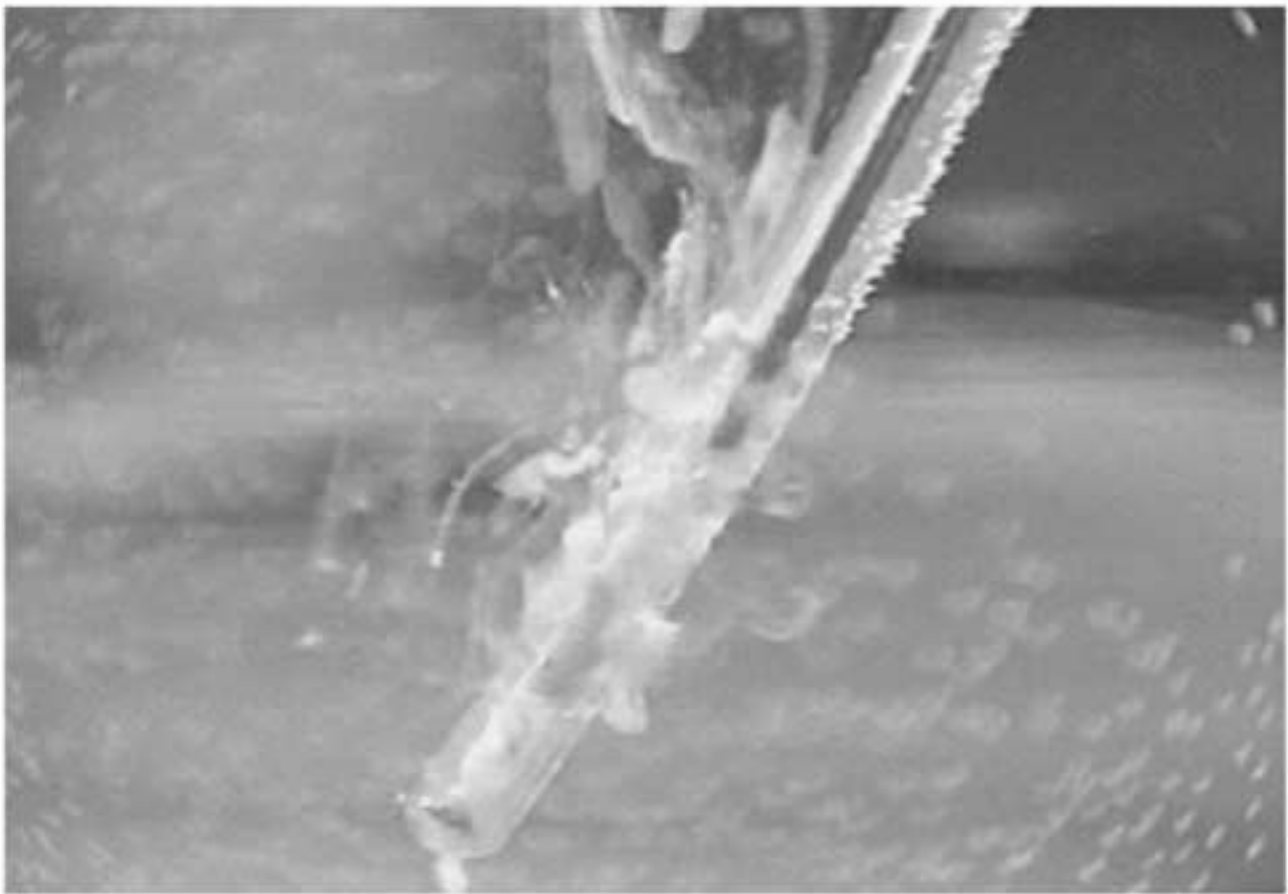
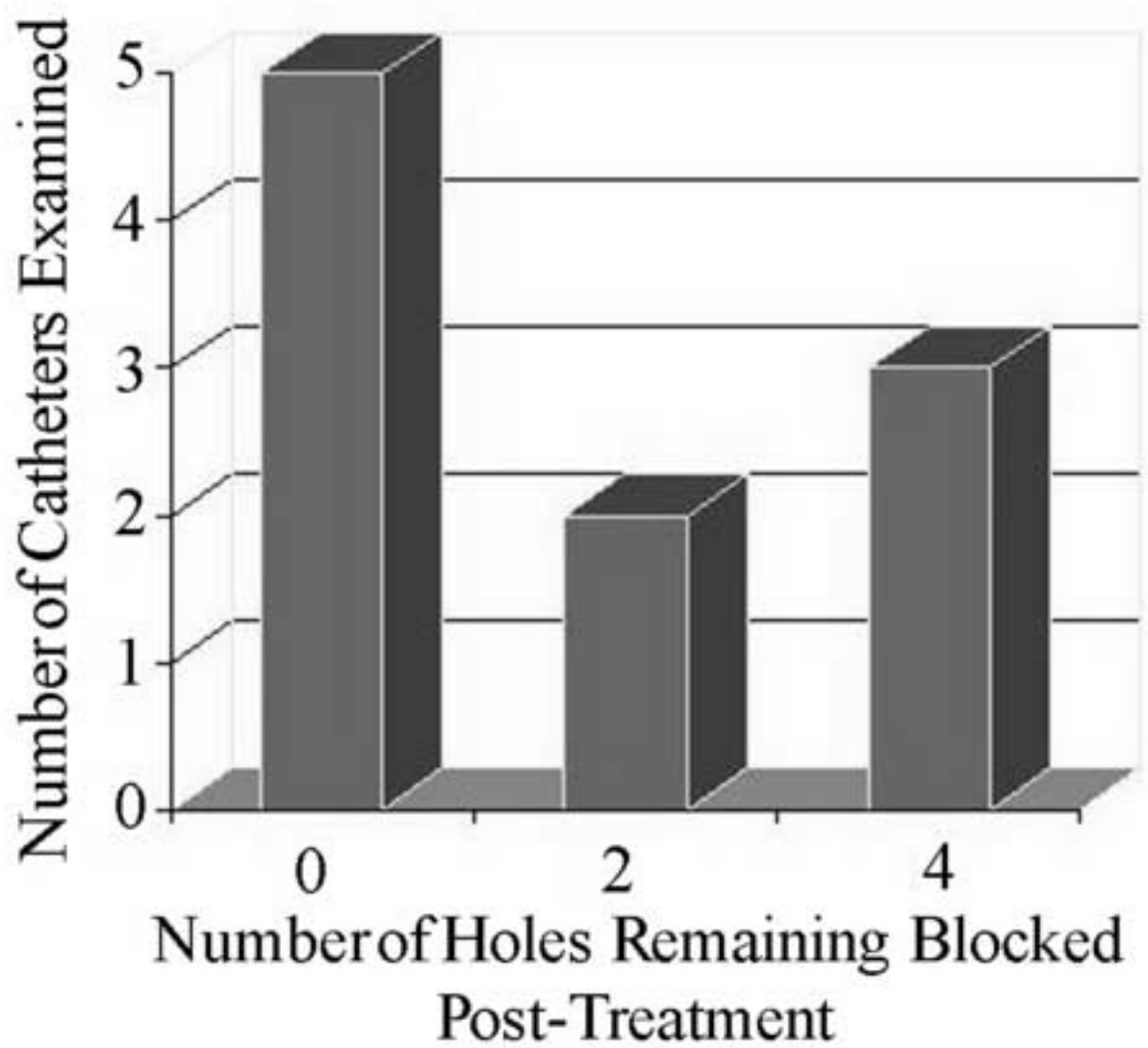


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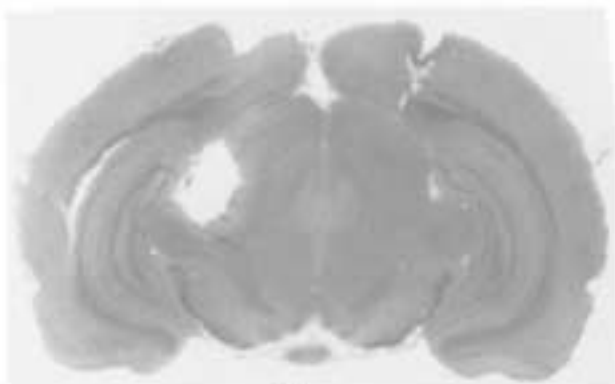




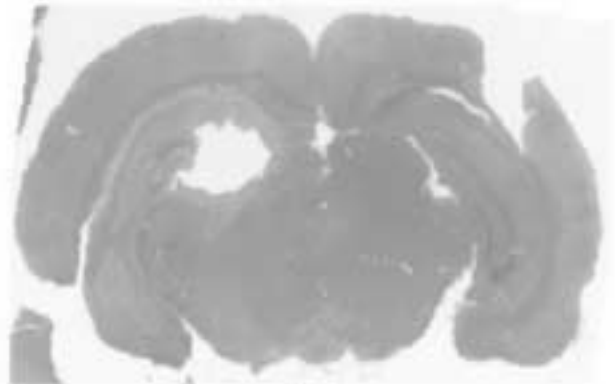
A



B



A



B

Figure 5abcd

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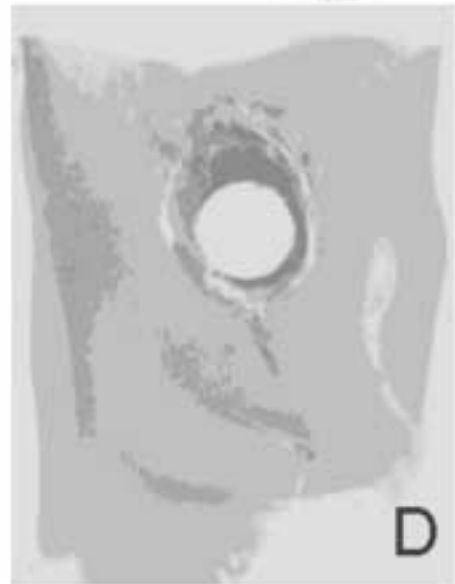
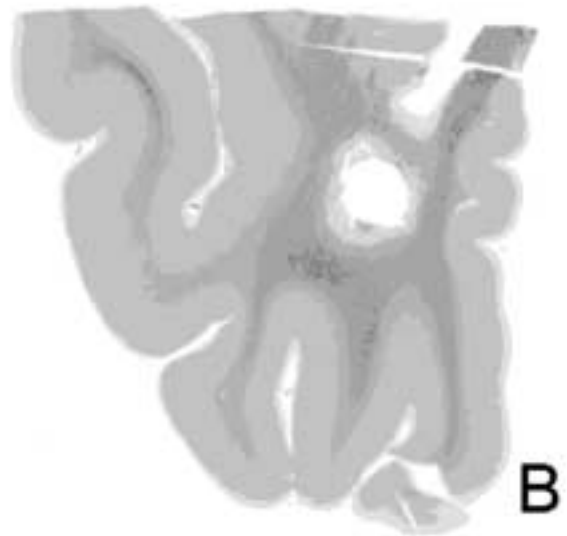


Figure 6abcd
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Table 1. Preliminary Clinical Study; Details of patients and outcome.

Patient	Etiology of Hydrocephalus	Age	Sex	Site of Ventricular Catheter	Unblocked with Electrocautery	Freed with electrocautery	Unblocked with Cavitation	Freed with Cavitation	Post OP CT Scan	Complications	Outcome
1	Multiples cavernomas, hemorrhage	7	M	Post fossa	No	No	Yes	Partial	Small amount of blood along catheter tract	None	Returned to baseline status
2	Intraventricular hemorrhage of prematurity	17	M	Left lateral ventricle	No	No	Yes	No	No hemorrhage	None	Remained well
3	Post meningitic hydrocephalus	11	F	Left lateral ventricle	No	No	Yes	Yes	No hemorrhage	48 hr post op respiratory distress unrelated to shunt malfunction	Returned to baseline status
4	Intraventricular hemorrhage of prematurity	7	F	Left lateral ventricle	Yes	No	Unblocked by cautery	No	Small subdural hemorrhage from ventricular decompression	None	Remained well

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