

# Ultrasound Augmented Thrombolysis

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**Abstract:** Recent developments in thrombolysis include transcatheter ultrasound augmentation of tissue plasminogen activator (tPA) activity and microbubble augmented ultrasound lysis. While standard thrombolytic drugs are well-known, the increased thrombolytic drug activity with the addition of ultrasound is a new clinical tool early in development. The therapeutic thrombolytic action of ultrasonographic microbubble contrast agents and a beam of ultrasound when in contact with clot is also a technique rapidly developing and not widely appreciated. Both augmentation techniques have progressed to early clinical use. The use of directed ultrasound beams to increase lytic activity in a specific target with either technique may lead to fewer hemorrhagic complications, especially in anatomical areas remote from the target. The combination of intravenous tPA and directed ultrasound is very promising in the treatment of ischemic stroke in human trials, and microbubble augmented ultrasound thrombolysis has been proven effective in several animal models of stroke and clotted dialysis grafts, with phase I/II trials in human dialysis grafts, arteries, and veins ongoing. This paper will review the state-of-the-art in this rapidly progressing field.

**Keywords:** Ultrasound, thrombolysis, stroke.

## INTRODUCTION

Thrombolysis has developed from systemic to localized techniques in the peripheral arteries and veins over the last 30 years. In some areas, such as myocardial infarction and ischemic stroke, systemic techniques persist in emergent situations, but localized techniques show several advantages with better results and lower complications [1-4]. The three major drugs, streptokinase, urokinase, and tissue plasminogen activator (tPA) have been joined by several others and success rates of > 80% are expected. In addition, thrombolysis has teamed up with numerous mechanical devices that can destroy and remove clot in various ways. The use of mechanical devices typically requires extremely high levels of skill and equipment, and these are restricted to major hospital facilities in most cases. The use of thrombolytic drugs has always carried the burden of increased hemorrhagic complications [5]. Though lower doses have decreased this risk, fatal sequelae persist. These techniques are also restricted to a hospital setting, but even in the best situations death can be expected in 0.8% of cases and major bleeding complications in about 6.6%. There are many surgical alternatives for treating peripheral thrombi in veins or arteries that have acceptable success rates but considerable mortality and morbidity as well. The object of all of these techniques is to destroy clot in unwanted locations and promptly restore flow to critical organs.

Thrombolysis has many potential roles to play in such common diseases such as ischemic stroke, myocardial infarction, peripheral artery thrombosis, and deep vein thrombosis [1-4,6,7]. In the United States each year the total medical caseload is well over one million cases. Ischemic

stroke at 600,000 cases per year trails only myocardial infarction in occurrence, yet only minimal improvement has been accomplished in its treatment. Considerable improvement has occurred in the treatment of myocardial infarction with mechanical intervention and thrombolysis. Peripheral arterial and venous thrombosis benefits from well developed localized thrombolytic interventions and surgical procedures. With intravenous tPA therapy of ischemic stroke, a moderate improvement has been demonstrated, but only at the cost of increased intracranial hemorrhagic complications. The room for improvement in ischemic stroke therapy is extremely large. Fewer than 3% of cases are actually treated, and there is a net gain from the treatment of less than 20% at the present time.

This paper will concentrate on the new developments in ultrasonographic augmentation of thrombolysis using two general methods. The best-known of these is the increase in thrombolytic activity when ultrasound is delivered to clot that is being treated with intravenous tPA. A less well-known technique of microbubble augmented thrombolysis has a different mechanism and also shows promise in the treatment of ischemic stroke and other thromboses. We will briefly address the direct application of ultrasound to clot through catheters carrying tiny transducers or vibrating wires to the target which can also destroy clot very rapidly. These require extremely skilled angiographers and therefore are very unlikely to ever have widespread emergent use.

## CURRENT THERAPY

The current treatment of acute ischemic stroke requires delivery of a large dose of tPA intravenously (IV) within 3 hours of symptom onset [1-3]. If therapeutic recanalization of the thrombosed artery is prompt, a favorable outcome is anticipated in about 60% of those with an ischemic stroke compared with spontaneous thrombolysis without therapy, which occurs in up to 20% of patients with variable clinical

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recovery. With tPA treatment a faster return of flow results in moderate clinical improvement. Small increments of delay in treatment decreases recanalization and clinical improvement, supporting the concept "Time is brain!" If treatment is initiated more than 3 hours after symptom onset using the intravenous technique, increased hemorrhagic strokes result, such a devastating problem that delayed treatment cannot be pursued. However, by using catheter directed arterial (IA) delivery of thrombolytic drugs, the treatment window may be extended to 6 hours without excessive bleeding [4,8,9]. This involves a much smaller dose of tPA and is directly delivered to the thrombus and clotted artery. After 6 hours, there is no effective treatment. Indeed, if late reperfusion occurs, the area of ischemic stroke may well convert into the much more severe hemorrhagic stroke with worsened outcomes.

Both IV and IA thrombolytic techniques seem to work by destroying obstructive clot and restoring blood flow. Much of that beneficial effect is in the penumbra of the stroke. This peripheral zone of ischemic brain can include new clot formed at the time of embolization of thrombus and onset of symptoms, and can improve if blood flow resumes promptly. The initial thrombus may be old clot or even other obstructive debris that is entirely insoluble. However, it can cause a considerable amount of fresh clot adjacent to it when it wedges in a small vessel. The thrombolytic treatments may serve to remove only the fresh clot and allow collaterals to develop. However, the net gain by whatever mechanism is significant in this patient population.

Only mechanical devices can actually remove some insoluble bits of debris or thrombus or correct intracranial stenoses at the present time [10]. Thrombolysis, however, can be the emergency step to rapidly reestablish flow through areas of adjacent clot and allow collateral filling to resupply the area at a critical time. Some studies suggest that up to 80% of interarterial clot dissolution or removal is possible.

## ULTRASOUND AND THROMBOLYSIS

### Intravascular Ultrasound Lysis

Intravascular devices such as vibrating wires and transducers can deliver very high levels of local ultrasound to clots [11]. These require great angiographic skill in some locations, especially the brain, but may be easy to use in dialysis grafts and peripheral vessels. These devices operate at very high intensity levels and probably accomplish their clot lysis by causing cavitation and associated mechanical degradation of the target. These energy levels cannot be delivered transcutaneously because of the thermal and mechanical injury encountered at the skin and bony surfaces such as the skull. These levels could also be damaging to the brain and open the blood brain barrier.

### Ultrasound Augmented tPA Thrombolysis

Several studies demonstrate that ultrasound can improve the thrombolytic activity of tPA and similar drugs. The mechanism of this is thought to involve improved penetration of the thrombolytic drug into the clot by a combination of a pumping effect, improved diffusion, cleavage of fibrin polymers to increase the surface for

thrombolytic action, and improved binding of tPA to fibrin [12-23]. It improves lysis from 30% to up to 80% in various studies. Two techniques of delivering ultrasound are in current use. Transcutaneous delivery usually involves placement of a transducer and coupling jell over a window such as the temporal bone or skin overlying a peripheral vessel. The second involves an invasive device such as a transducer tipped catheter.

### Intravascular Ultrasound Augmentation

A specialized ultrasound thrombolytic infusion catheter (EKOS Corporation, Bothell, WA) combines the use of a miniature ultrasound transducer on the tip of the catheter with infusion of thrombolytic agent through the catheter [24,25]. After a bolus of tPA is injected, an infusion of tPA is started with simultaneous ultrasound given for up to 1 hour. Human trials show great promise. Only large vessels can be effectively treated with the ultrasound, but the tPA may lyse peripheral fragments in the area. The delays involved with angiography and demands for very skilled operators, which apply to all mechanical devices, pertain here.

### Transcutaneous Ultrasound Augmentation of Thrombolytic Agents

*In vitro* studies have shown various levels of moderate thrombolytic improvement averaging 30% to 40% and required 1 to 3 hours of insonation to get the effect [26]. Several studies have confirmed increased lytic activity using the technique of delivering ultrasound transcutaneously through the skull, using temporal bone transducer placement much like the trans-cranial Doppler (TCD) techniques require. Lower frequencies penetrate the skull more efficiently than higher frequencies. Frequencies from 20 kHz to 2 MHz have proven to have usable thrombolytic activity. Standard physical therapy devices use 1 MHz for ultrasound delivery while TCD devices used 2 MHz frequency to provide waveform data. The higher frequencies of 3 to 10 MHz used for imaging in standard ultrasound devices do not adequately penetrate the skull. They do not apply here though they produce similar accentuation of the thrombolytic activity and destroy microbubbles effectively [27-29].

Several animal studies also show positive results in various vascular beds including coronary arteries. Living animal systems are much more complex and can show the effect of the animal's own tPA in ischemia. This can produce positive effects with very small amounts of ultrasound. Common frequencies include 27 to 200 kHz when traversing the skull, but 1 and 2 MHz also succeed. The power settings used vary widely. At higher intensity, such as 6.3 W/cm<sup>2</sup>, initial successful thrombolysis was followed rapidly by reocclusion, apparently due to platelet activation or response of the endothelium to the high ultrasound intensity [30]. Lower levels such as 0.6 W/cm<sup>2</sup> to 2.0 W/cm<sup>2</sup> have often proven therapeutic without evidence of safety problems [31].

In human clinical trials, recovery rates higher than expected with simple tPA treatment have been described [32-37]. The temporal window provides adequate insonation in 80% to 90% of adults. As age increases, however, the percentage decreases, and TCD techniques are not useful in 40% of the older population. Better rates of recanalization

have been seen with those treated with continuous ultrasound as well as tPA. Several reports show the bleeding rate with this technique to be the similar to that with simple tPA therapy.

The largest of these studies, the CLOTBUST Phase II study, used a standard transcranial Doppler aimed by a skilled physician-sonographer at middle cerebral artery thrombus in 126 randomized acute ischemic stroke patients [38]. The flow in the artery was observed and intravenous tPA was given. Continuous full power transcranial Doppler remained in use for the next two hours and flow was assessed intermittently. This provided real-time monitoring of treatment which can change management strategies as flow changes. The ultrasound beam is quite narrow, 3 mm in diameter, and requires a highly skilled sonographer to target the occluded segment and keep the beam on target using a specially designed head frame.

The CLOTBUST aims were: 1. To compare recanalization and recovery in patients with standard IV tPA therapy and those receiving additional continuous targeted ultrasound monitoring. 2. Compare safety in the two groups. Patients had to meet standard tPA treatment criteria of symptom onset less than 3 hours prior to treatment and also show middle cerebral occlusion on TCD. The primary end point included clinical recovery or TCD recanalization at 2 hours with 24-hour and 3-month follow up. The safety end point was intracranial hemorrhage with clinical worsening.

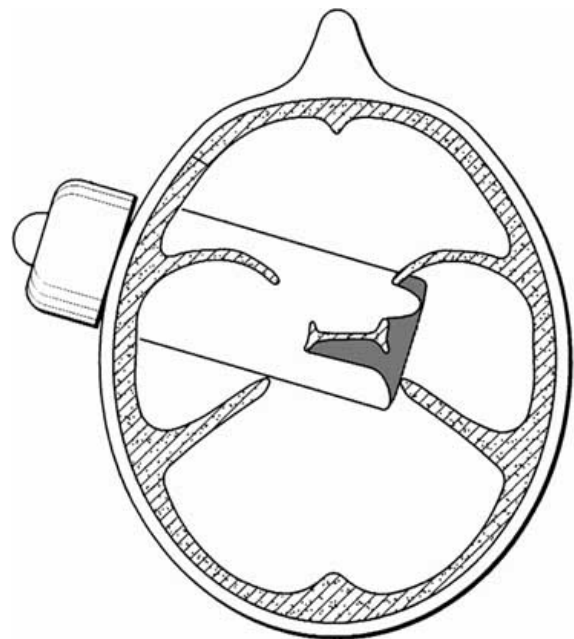
Ninety-six percent of the patients completed the 2-hour procedures and 97% completed follow up. Seventeen percent of controls and 14% of continuous targeted ultrasound groups went on to IA therapy after IV. Symptomatic intracranial hemorrhage (ICH) occurred in 3 in each group, one in each after IA thrombolysis. No hemorrhage occurred during monitoring, only after treatment was complete. The targeted combined endpoint for the target group was met in 49% while controls were 30%,  $p = <0.02$ . Complete recanalization, 46%, plus partial, 27% in the target group compared with 17.5% and 33% in controls,  $p = <0.001$ . At 2 hours sustained complete recanalization was 38% compared with 12%,  $p = 0.003$ . At 2 hours and 24 hours, clinical end points were not significantly different but favored the target group. At 3 months, the trend continued with 41.5% compared with 28% good outcomes,  $p = 0.21$ . The conclusions—first, it is a safe technique and, second, TCD enhances recanalization—will certainly lead to more development in technique and equipment.

### Specific Device Development

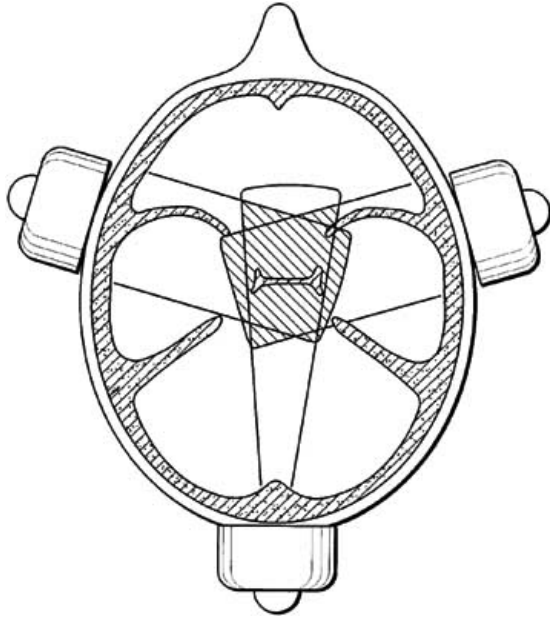
A first generation low frequency device designed specifically for treatment of strokes (NeuroFlow™, Walnut Technologies, Andover, MA, USA) had human trials in Europe [26]. The complex machine uses a hydrophone sensing the ultrasound within the skull to automatically control the input of 300 kHz ultrasound and a large transducer to provide wide distribution of the ultrasound. The better penetration of this frequency allows therapeutic insonation in almost all patients and the lower frequency also has a more favorable ratio of mechanical to thermal effects. Another benefit is the large beam of ultrasound, which further widens within the skull, making aiming a minimal

problem. The increased resonance of the low frequency within the skull also fills the target organ with echoes more completely, while higher frequencies fade out more quickly. This results in a device that can be operated with little training, but it does not give imaging or waveform data for monitoring. The multi-center 48 patient trial at six German university stroke centers was scheduled to be completed by the middle of 2003. The trial was stopped, however, due to increased incidence of clinically important hemorrhage. The final report on this trial is not yet available.

Another first generation specific device developed in our laboratory for treatment of ischemic stroke or other clot lysis consists of multiple large transducers operating at 1 MHz and adjacent frequencies. In the skull, both temporal bone windows are used to transmit ultrasound simultaneously, (Fig. 1a and 1b). In addition, a third transducer can be positioned over the foramen magnum and others where needed, such as over the neck. The multiple transducers use large fields of ultrasound to flood the general area where the energy is needed. Since the therapeutic range of these devices is limited to 6 to 9 cm and actual power in the tissue reduced in the case of temporal sites by the transit of the bone, the effective single transducer range is only a short distance beyond the midline of a typical skull. However, by adding ultrasound from both sides of the skull at once, the central portion of the brain can be more effectively covered at higher levels of energy through an additive effect. In addition, areas of single transducer shadowing around the base of the brain can be effectively filled in by a second or third transducer. This is particularly important in the



**Fig. (1a).** An axial diagram of the skull shows one large transducer in position on the temporal window. The field of effective ultrasound is shown with shadows shaded in beyond structures that block much of the ultrasound.



**Fig. (1b).** The addition of transducers on the opposite temporal window and over the foramen magnum fill in most areas of shadowing and provide increased power in areas of overlap centrally (cross hatch pattern). Areas of reflected waves spread more widely still and fill much of the head, making precise aiming of the beams unnecessary.

posterior fossa, where the inferior aspect of the basilar artery is obscured from temporal ultrasound sources. Posterior transducer placement can supply the inferior aspect of the posterior fossa while the upper portion of the posterior fossa at the bifurcation of the basilar artery is adequately covered



**Fig. (2a).** An angiogram in a pig shows clot placed in the ascending pharyngeal artery, stopping flow and filling much of the rete mirabilis.

from bilateral temporal transducers. Those also fill in critical areas of shadowing around the Circle of Willis and build the total midline sound pressure levels to therapeutic levels without requiring very high skin loads or heating.

The frequency modulation and energy modulated 1 MHz device used here was chosen to avoid the buildup of echoes seen within targets at lower frequencies. Those longer waves penetrate the skull more efficiently, raising the actual power delivered to the brain, and can reflect off structures within the skull more efficiently. The prolonged resonance of low frequencies can produce “rogue waves,” which are exceptionally strong due to echoes from various structures focusing in a standing wave configuration. They may be a cause of localized very high energy sites that could cause damage to the blood brain barrier or other structures. Standing waves of increased energy or nulls of decreased energy may be a special problem at lower frequencies, where the wavelength more closely approximates the dimension of an artery or clot. By avoiding the low frequencies used in other systems and by constantly shifting the frequency of one or more transducers, any standing waves will be small related to the shorter wavelength, and be constantly in motion. This should decrease the chance of localized areas of prolonged excessive or inadequate energy within the skull. The system also uses a pulsed wave format to decrease any excess energy or heat deposition.

Several other task specific devices are in various stages of development.

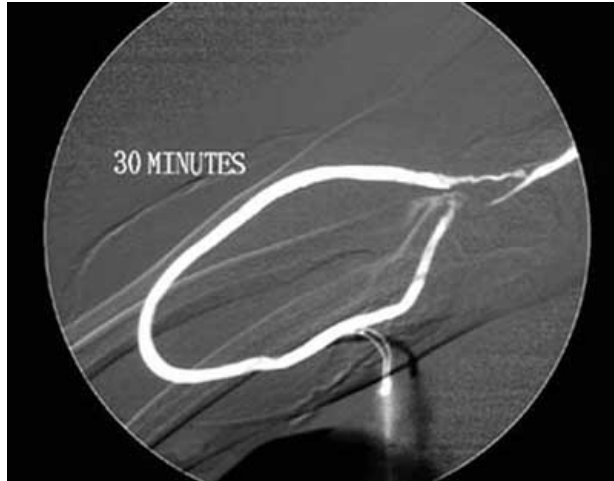
#### **Microbubble Augmented Ultrasonographic Thrombolysis**

The use of microbubble augmented ultrasound thrombolysis has progressed from showing successful lysis of clots within test tubes and skull phantoms to lysis of tiny clots in rabbit arteries and, currently, successful lysis of intracranial clots in pigs, (Fig. 2a and 2b) and large clots in



**Fig. (2b).** Following microbubble augmented ultrasound thrombolysis for 24 minutes, the clot is completely lysed and flow restored. Note complete filling of the rete on both sides of the midline and all cerebral branches of the internal carotids. No tPA was used.

dialysis grafts of dogs and humans [39-45]. In most cases thrombolysis using microbubble augmentation is a fast process ranging from 24 to 30 minutes in animal models. This holds great promise in ischemic stroke therapy, where speed is important. It has moved to Phase I/II human trials of dialysis graft declotting (Fig. 3), and promises to progress further.



**Fig. (3).** A thrombosed human dialysis graft initially showed a large amount of clot and absence of flow. This final image following microbubble augmented ultrasound thrombolysis shows that almost all clot is lysed and flow restored, but the usual stenosis at the venous end of the graft persists and requires angioplasty. No tPA was used.

Microbubbles are tiny spheres of either lipid or human albumin constructed around a gas bubble. Two (Definity, Bristol-Meyers-Squibb Medical Imaging, Inc, Princeton, NJ, USA, and Optison, Amersham Health, Princeton, NJ, USA) are commercially available with FDA approval for use in clarifying the outlines of the ventricle in cardiac ultrasound imaging [46-49]. In addition, they have widely recognized efficacy in identifying vascular structures and tumors in routine diagnostic ultrasound use and have some success and differentiating between malignant and benign masses. Widespread use is anticipated over the next few years in diagnostic ultrasound. The microbubbles are usually from 2 to 5  $\mu$ m and have the ability to go through capillary beds several times before dissolving. Smaller bubbles may be more useful in therapeutic applications and are undergoing testing, (Fig. 4). When ultrasound is added, microbubbles cause increased echogenicity, which gives them their diagnostic use. With enough ultrasound, cavitation and bubble destruction results. The cavitation does not harm most endothelial surfaces but does erode clot wherever it is encountered. Although this might suggest the possibility of localized increased bleeding, it has not been a problem in current use. There is no reason to suggest that bleeding might occur outside the ultrasound beam.

The thrombolysis mechanism is not certain, but in general is thought to be one of ultrasound-induced cavitation that erodes the surface of clots in the ultrasound beam [43,50-54]. Cavitation has been theorized to cause

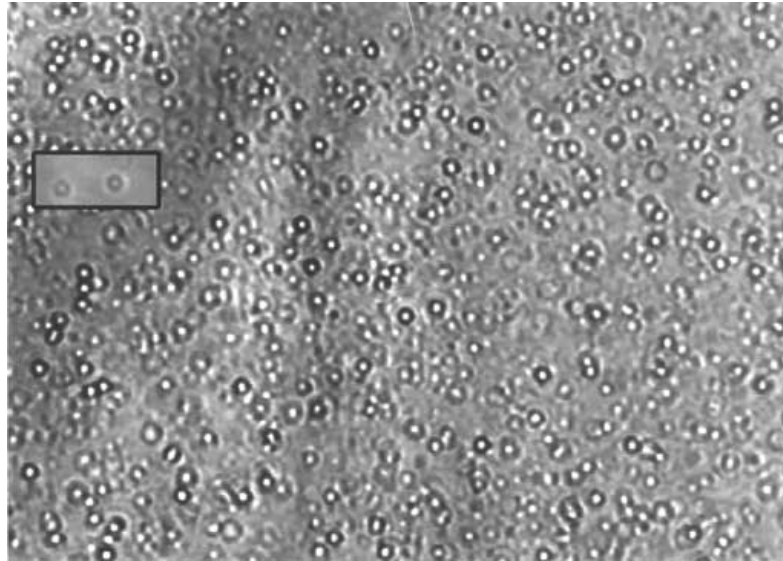
mechanical stress on the surface of adjacent thrombus, leading to its destruction. It can be caused by high power levels of simple ultrasound, but with the addition of microbubbles, the threshold for cavitation is greatly lowered and the effect magnified. Ultrasound causes the microbubble to vibrate and burst. Micro jets and asymmetric collapse of the microbubbles probably contribute to adjacent clot erosion. The average fragment is about 3 microns in size, similar to fragments from standard thrombolysis.

With the destruction of each microbubble the effect is lost, therefore additional microbubbles must be delivered to the target on a continuous basis [52]. Microbubble delivery may be by a number of mechanisms ranging from simple intravenous delivery to tagged intravenous delivery with microbubbles specifically tailored to find clot, to intra arterial direct injection of feeding arteries, or to intraclot injections. The latter is most effective where large volumes are required, such as in thrombosed dialysis grafts, [42] but IV delivery is often adequate in treatment of small clots where the surface area/clot volume ratio is more favorable. However, IV success rates for large clots are lower than in direct injection [43]. Some microbubbles have a specific affinity for clot due to tags of specific drugs or ligands added to the surface. These can be used to greatly improve IV delivery of microbubbles to target clots [45,53].

The exact amount of ultrasound required is widely variable, but pulsed wave mode is usually selected to avoid tissue heating. A 100% declotting success has been demonstrated at levels of 1.2 to 2  $W/cm^2$  in dog dialysis grafts using pulsed wave mode and intra clot microbubble injection [43]. Success rates range down to 50% as power is decreased to 0.06  $W/cm^2$  in the same animal model. In pig models, intracranial lysis was successful at even very low levels of ultrasound after the 1 MHz-2  $W/cm^2$  primary beam had traversed 2 layers of bone [45]. This suggests improved ultrasound transmission in living tissue and raises the possibility of an additive effect with naturally occurring tPA or similar processes in the animal model. Combinations with tPA therapy justify investigation, since the mechanisms are different and may very well be additive [55].

A multi-center Phase I/II human trial in dialysis graft declotting with intra-clot injection of lipid microbubbles (MRX-815, ImaRx Therapeutics, Tucson, AZ, USA) and 30 minutes of variable levels of transcutaneous ultrasound shows a pain-free experience with no serious adverse events in 22 patients (unpublished data). While 100% success has been demonstrated in the 1 to 2 hour old hyperacute thrombus in a dialysis graft model in animals, this has not yet been proven in humans, where the clot is normally 24 to 48 hours old. However, consistent improved luminal filling occurred both in tPA plus microbubble and non tPA plus microbubble groups. Further trials are ongoing.

In the pig model of intracranial rete mirabilis thrombus, successful thrombolysis was first obtained using 1 MHz ultrasound at 2  $W/cm^2$  and arterial delivery of microbubbles [44]. The size of the pig closely approximates human head dimensions. Autogenous clot of 2 to 6 hours age was placed in the rete through an angiographic catheter. Optison microbubbles were injected through the same catheter and transcutaneous ultrasound given through the temporal bone



**Fig. (4).** Experimental lipid microbubbles (MRX-815, ImaRx Therapeutics, Tucson, AZ, USA) developed for therapeutic clot lysis are smaller than most, averaging under one micron in diameter and are true nanoparticles. See the one millimeter standards in the rectangle for reference.

for 24 minutes. Successful lysis was seen in 6 of 7 microbubble tests and in 0 of 7 controls,  $p = 0.03$ . Both lipid based and human albumin microbubbles have been used in this model with excellent success rates. Another system using human albumin microbubbles (PESDA, University of Nebraska, Omaha, NE, USA) tagged with eptifibatid (Integrilin, Key Pharmaceuticals, Kenilworth, NJ, USA) showed successful IV delivery of bubbles and successful clot lysis in the same model [45]. Here 15 pigs completed the protocol with 6 of 8 getting tagged IV microbubbles successfully lysing and 0 of 7 receiving eptifibatid lysing,  $p = 0.007$ . The saline controls showed lysis in 1 of 15,  $p = 0.02$ . This important step may take this technique into clinical use without requiring the delays and risks of arteriography.

#### SAFETY

Ultrasound in the diagnostic range is known to be safe in the usual short-term applications. It is not clear whether this applies to longer-term applications or to the application of lower frequency ultrasound to ischemic brain. It is certainly not clear whether ischemic brain coupled with a thrombolytic drug or microbubble is tolerant of the application of ultrasound. All of these areas of research must be pursued in the near future. However, the application of ultrasound at up to  $2 \text{ W/cm}^2$  in normal rat brain has shown no sign of damage or significant heating, though slight temperature rises have been described. In a rat model, surface temperatures have been demonstrated to rise up to  $8^\circ\text{C}$  after 90 minutes using 185 kHz ultrasound at  $2 \text{ W/cm}^2$  continuous wave [26,31]. The body temperature did not change and there was no disruption of the blood brain barrier. Brain temperature did increase about  $1^\circ\text{C}$ . Other studies using 20 kHz produced a similar result. By switching from continuous to pulsed wave ultrasound transmission, the

temperature rises in the brain disappeared. Therefore it is thought that low intensity of ultrasound of up to  $2 \text{ W/cm}^2$  can be delivered safely during therapy at any of the usual sites. There are also studies which show increased adhesion of leukocytes to the endothelium, but without irreversible damage to the endothelial cells. Also cavitation can cause short-lived gas bubbles, which produce local heating and free radicals and shockwaves on a very localized scale. While much of this is important in the desirable action of microbubble clot lysis, the levels of ultrasound used here typically fall below well-established damage thresholds at which important cavitation can occur. The pulsed wave mode of operation decreases all of these effects.

#### GOALS

Rapid restoration of vascular flow is the initial goal of treatment. Speed (Time is brain!) is a key to stroke therapy and, to a lesser degree, ischemia in other locations caused by thrombus. The presence of ultrasound can increase the rapidity of clot lysis using standard thrombolytic drugs and it offers new thrombolytic mechanisms with the microbubble techniques. Any new system must be simple and safe when widely used. If safety can be proven even in hemorrhagic strokes, it may well be possible to use some technique of microbubble augmented ultrasound lysis or ultrasound augmented thrombolysis in patients who have not yet been transported to the hospital for CT imaging to determine the presence or absence of intracranial hemorrhage. Perhaps microbubble ultrasound treatment or very low tPA dosage with microbubble treatment will be a safe combination that broadens indications. Even if the improvement in outcomes is only moderate with a new technique, the addition of many more patients to therapy within the earliest part of the 3-hour time window will be a service with tremendous impact.

Further research is required to evaluate possible combinations of thrombolytic drugs, microbubbles, and various modes of ultrasound delivery. Once these combinations can be assessed, some new techniques should be ready for application in humans.

As larger numbers of investigators have become involved, the rate of progress has dramatically increased. The critical jump from basic science to clinical science is now underway in several areas. Currently human CLOTBUST studies are progressing rapidly and involve not only thrombolytic drugs, but the addition of microbubbles and the addition of dedicated machines to make ultrasound delivery easier and more reliable. All of these fronts have promise, and the next few years will be filled with many announcements of the various steps and missteps, successes and failures, along the way to improved thrombolysis.

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