THE EFFECT OF ULTRASOUND ON THROMBOLYSIS:  
The rationale for EKOS™ Acoustic Pulse Thrombolysis™ Therapy

INTRODUCTION

A small number of recent clinical studies have focused discussion on the efficacy of ultrasound in enhancing thrombolysis. The results and the conclusions they have drawn have raised some debate about the need for ultrasound to enhance thrombolysis, despite the body of research over the past few decades on this topic. One can certainly argue about study design and number of patients, validation of measurement systems, and the finer points of methodology surrounding these studies. However, it is more illuminating to review what has already been firmly established about ultrasound and its effects on fibrinolysis including its mechanism of action and the supporting evidence.

MECHANISM OF ACTION

Ultrasound by itself does not dissolve or disrupt clot, nor does it alter the rate of the plasmin degradation of fibrinogen; dissolving clot requires the presence of a thrombolytic agent (Blinc et al 1993).

Figure 1: The fibrinolytic system in blood vessels showing the physiological mechanisms of tPA activation of plasminogen on fibrin to cause fibrinolysis.


To accelerate thrombolysis, ultrasound has to affect one or a combination of components involved in the thrombolytic process: clot structure, fluid dynamics within the clot structure and exogenous thrombolytic agents (Soltani et al 2008).
With respect to thrombolytic agents, Soltani and Soliday (2007) previously established that low-energy (1 MHz and intensities of 2.5-3.1 W/cm²) ultrasound does not directly increase the potency or biological activity of thrombolytic agents. Although temperature rise due to absorption of ultrasound energy can enhance the biochemical reaction of these enzymes and accelerate the lysis, Sakharov et al (2000) showed the lysis can only be partially attributed to temperature. Further, Blinc et al’s (1993) characterization of ultrasound-potentiated fibrinolysis showed that temperature increases caused by ultrasound exposure were insufficient to account for the increase in thrombolysis. Hence, focusing on the mechanical and physical effects of ultrasound on pressure, stress, and flow in and around the clot, is key to understanding its mechanism of action.

**The effect of ultrasound on clot structure – enhanced thrombus permeability**

Ultrasound increases permeability in thrombus structure by reversibly disaggregating fibrin strands, which exposes more sites to which thrombolytic agents, such as tPA and Urokinase, can bind. The scanning electron microscopy used in Braaten et al’s study (1997) to examine the ultrastructure of fibrin gels before, during, and after exposure to ultrasound provided visual evidence of the reversible disaggregation of fibrin strands. The data collected on fibrin diameter corroborated what the visuals displayed: in the presence of ultrasound, the fibrin fibers thinned approximately 30% in diameter. The resulting fibrin mesh had greater porosity and permeability.

**Figure 2:** Scanning electron micrographs of purified fibrin gels in the absence (A) and presence (B) of 1 MHz ultrasound at an intensity of 4 W/m²

**Source:** Braaten et al. 1997.

Siddiqi et al (1995, 1998) studies suggested that the fibrin structural change shown in Braaten et al’s 1997 study also exposed more tPA binding sites to the thrombolytic agent, thereby enhancing fibrinolysis. Fibrinolysis, after all, depends on the formation of plasmin at the fibrin surface so that the plasmin can dissolve the clot. Siddiqi’s results suggest the structural changes also accelerate tPA binding, alter binding affinity, and increase maximum binding (1998).
The effect of ultrasound on fluid mechanics in thrombus – increased flow and hydrostatic pressure waves

Ultrasound acts to increase fluid flow within thrombus through acoustic streaming, where high-frequency, low-intensity ultrasonic waves mechanically drive lytic into the clot and keep the lytic in close proximity to the binding sites.

In 1995, Francis et al. determined that the rate of tPA uptake in \textit{in vitro} clots was significantly faster in the presence of ultrasound vs. its absence. Uptake of tPA from the surrounding fluid into thrombus has been shown to be 48\% greater at 1 hour, 84\% greater at 2 hours, and 89\% greater at 4 hours in the presence of ultrasound. The study also showed a significantly deeper penetration of tPA into the clot. Blinc et al.’s 1994 study showed flow through clots is an important determinant of the rate of fibrinolysis. The results of both these studies support an acceleration of the thrombolysis.

Ultrasound’s mechanical effect at high-frequency (1-3 MHz) low-intensity (0.5-5 W/cm\(^2\))—that of acoustic streaming--has been characterized as “mild stirring” (Sakharov et al 2000). It is that physical stirring caused by ultrasound’s acoustic pressure waves that led Siddiqi et al (1995) to conclude that ultrasound-induced flow was both intensity dependent—the higher the intensity, the greater the flow--and increased through pressure mediated permeation.

Prokop et al (2007) explored cavitational mechanisms in ultrasound-accelerated fibrinolysis. The study suggested that stable cavitation mechanisms, such as steady microstreaming, could enhance lysis by promoting local mass transfer and thereby increase the rate of penetration of lytic drug into the clot matrix. These acoustic pressure waves help drive the lytic agent into the clot and keep it in proximity to the more exposed binding sites.

It is important to note that the Siddiqi, Prokop, and Francis studies all concluded the ultrasonic enhancement of fibrinolysis was not caused by mechanical disruption or fragmentation of the thrombus. Braaten’s 1997 data, which showed reversible disaggregation of the fibrin structure under ultrasound, also supported this conclusion.

\textbf{Figure 3:} A 360 degree acoustic pressure field map produced by six transducers mounted on an EKOS™ ultrasonic core.

\textbf{Source:} Soltani et al. Ultrasonics 2007
Blinc et al (1993) showed that the acceleration of fibrinolysis by ultrasound was greater at higher intensities and maximum at frequencies between 1 and 2.2 MHz, but decreased at 3.4 MHz. Soltani et al (2008) demonstrated that by varying the ultrasound intensity in a repeating series of different frequencies, thrombolysis was enhanced by 64% compared to thrombolysis with the lytic drug alone. It is this modulated, pulsed pattern of varying ultrasound energy at an optimal 2.2 MHz frequency that is currently used by EKOS™ Acoustic Pulse Thrombolysis™ therapy to accelerate thrombolysis.

SUMMARY

Ultrasound increases permeability in thrombus structure by reversibly disaggregating fibrin strands, which exposes more sites to which thrombolytic agents, such as tPA and Urokinase, may bind. Ultrasound also acts to increase fluid flow within thrombus through acoustic streaming, where high-frequency, low intensity ultrasonic waves mechanically drive lytic into the clot and keep the lytic drug in close proximity to the binding sites. As a result of the increased permeability and increased fluid flow from the ultrasound, transport of the thrombolytic drug into the clot is increased, which in turn accelerates thrombolysis.

REFERENCES


US FDA Clearance: The Ekosonic™ Endovascular System is indicated for the ultrasound-facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified solutions, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries.

Contraindications: Not designed for peripheral vasculature dilation purposes. This system is contraindicated when, in the medical judgment of the physician, such a procedure may compromise the patient’s condition.

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Contraindications: Not designed for peripheral vasculature dilation purposes. This system is contraindicated when, in the medical judgment of the physician, such a procedure may compromise that patient’s condition. Such conditions include but are not limited to: • Tortuous vascular anatomy compromising safe introduction of endovascular equipment • Conditions associated with increased risk of bleeding. See device instructions for use for complete prescribing information.

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