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iCONCEPTS

TECHNOLOGY TOWARD TRANSLATION

# Treatment of Acute Intravascular Thrombi With Diagnostic Ultrasound and Intravenous Microbubbles

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The purpose of this study was to determine whether high mechanical index (MI) impulses from diagnostic ultrasound (DUS) could dissolve intravascular thrombi using intravenous microbubbles. Using a canine model, DUS was applied during a continuous intravenous infusion of microbubbles. Completely thrombosed grafts were assigned to 2 treatment regimens: low-MI (<0.5-MI) ultrasound alone; or intermittent high-MI impulses (1.9-MI) guided by low-MI ultrasound (contrast pulse sequencing). A 20-MHz cavitation detector was placed confocal to the ultrasound transducer to make intravascular cavitation measurements in 1 dog. Intravascular cavitational activity was detected when an MI of >0.5 was applied. In grafts treated with intermittent high-MI ultrasound, angiographic success was 71% at 30 min and 79% at 45 min, compared with 20% and 30% at these times in the low-MI ultrasound alone group ($p < 0.05$). We conclude that a commercially available DUS transducer can successfully recanalize acute intravascular thrombi during a continuous microbubble infusion. (J Am Coll Cardiol Img 2009;2:511–8) © 2009 by the American College of Cardiology Foundation

Low-frequency (<2 MHz) therapeutic ultrasound and intravenous microbubbles are able to recanalize acutely thrombosed vessels (1,2). One established mechanism in in-vitro studies is ultrasound-induced cavitation (3), which results in thrombus dissolution during the microbubbles' rapid growth and collapse within the ultrasound field. The utilization of ultrasound and microbubbles for this application has significant clinical potential in that it can be accomplished without requiring systemic anticoagulation or fibrinolysis. In vivo studies have applied the ultrasound over the affected vessel without knowledge of whether microbubbles were present within the thrombus. The frequencies and peak negative pressures required to induce thrombus dissolution are similar to those used with diagnostic transducers, with

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the added advantage that diagnostic devices can detect whether microbubbles are present within the thrombus before application of cavitation-inducing peak negative pressures. Despite these potential advantages, insufficient research has been published to determine whether a diagnostic imaging ultrasound transducer could recanalize intravascular thrombi, and whether a mechanical index (MI) that induces cavitation would be required to recanalize the vessel. The purpose of this study was to determine whether diagnostic ultrasound, in the presence of microbubbles, would be capable of recanalizing deeply located intravascular thrombi without the need for fibrinolysis or systemic anticoagulation.

## Methods

**Diagnostic ultrasound system measurements.** A diagnostic ultrasound (DUS) system with a 4C1 transducer (ACUSON Sequoia 512, Siemens Medical Solutions, Mountain View, California) was used for all studies. The peak negative pressures (PNP) generated by this DUS transducer at different MI settings were measured using a calibrated 0.5-mm diameter needle hydrophone (Precision Acoustics Ltd., Dorchester, England). All measurements were made at 6 cm from the transducer face through a custom-designed 6-cm–thick tissue-mimicking phantom (attenuation 0.49 dB/cm/MHz; Computerized Imaging Reference Systems, Inc., Norfolk, Virginia). The image depth was set to 9 cm. This transducer has dual focal zones, which were placed at 4.5 and 8.0 cm within the field. The pulse repetition frequency for the transducer was set to 5 KHz. The transducer was clamped to a stand so that it was in a fixed position perpendicular to the phantom surface. The hydrophone was placed on the opposite side of the phantom, and aligned with the ultrasonic axis of the transducer by positioning the hydrophone at the location of the highest peak root mean square pressure amplitude. The MI setting on the diagnostic transducer was incrementally decreased from 1.9 down to 0.3 in 0.2- to 0.3-MI increments. All peak negative pressure measurements were made in triplicate for each MI setting. The same tissue-mimicking phantom used for these peak negative pressure measurements in the water bath was also used for in vivo studies.

Both high-MI impulses (1.5 MHz, 1.9 MI) and low-MI contrast-specific imaging (contrast pulse sequencing [CPS] using a 2.0-MHz center frequency and <0.4 MI) were possible using the same DUS transducer. For in vivo studies, high-MI impulses at a 7-cycle pulse length were delivered for 5 to 7 s whenever microbubbles were observed transiting through the thrombi within the graft.

**Intravenous microbubble infusion.** The intravenous microbubbles used for continuous infusion in this study were MRX-801 (ImaRx Therapeutics, Inc., Tucson, Arizona). These are lipid-encapsulated microbubbles containing a perfluorocarbon gas. The mean diameter of the microbubbles was analyzed using a Particle Sizing System Model 770 (Particle Sizing Systems, Santa Barbara, California), and were measured to be 1.0 ± 0.1 $\mu$m, with <1% of the microbubbles being >5.0 $\mu$m. Microbubble concentration was 1.5 to 3.0 × $10^{10}$/ml. The microbubble infusion was prepared, as previously described, by diluting 2 ml of the MRX-801 in 100 ml of 0.9% saline, and administering at a rate of 1.8 ml/min for 45 min. All infusions were through a peripheral intravenous line placed in the front leg.

**Surgical procedures.** All animal protocols were approved by the Institutional Animal Care and Use Committee of the University of Nebraska Medical Center. Three mongrel dogs weighing 25 ± 1 kg underwent surgical placement of an arteriovenous graft in the left groin under inhalation anesthesia with 1.2% to 3.0% isoflurane. A 6-mm diameter by 25-cm long dialysis graft (Gore-Tex, W.L. Gore & Associates, Flagstaff, Arizona) was implanted between the femoral artery and femoral vein bilaterally, in a loop configuration. The graft was allowed to mature for 4 weeks. After the maturation period, the dogs were anesthetized at 1-week intervals, at which time thrombotic occlusions of the grafts were created. One graft was used for in vivo cavitation measurements, whereas the other 2 dogs had repeated thrombotic occlusions (16 in 1 dog, 8 in the second dog) for comparisons of different ultrasound treatments.

**In vivo cavitation measurements.** To determine whether intravascular cavitation was occurring during DUS application to a thrombotic occlusion, we measured inertial cavitational activity in 1 of the grafts of 1 dog using a 20-MHz single-crystal transducer that was positioned confocal to the diagnostic transducer (Fig. 1). The 20-MHz transducer passively monitored the presence of cavitational activity during the microbubble infusion, whereas the MI on the diagnostic transducer was incrementally decreased from 1.9 down to 0.3 in 0.2- to 0.3-MI increments. Cavitational activity was recorded at these MI settings at a time period

**ABBREVIATIONS AND ACRONYMS**

**CPS** = contrast pulse sequencing
**DUS** = diagnostic ultrasound
**MI** = mechanical index
**PNP** = peak negative pressures

when microbubbles were visualized channeling through the thrombosed graft. For these experiments, the diagnostic transducer and overlying 6-cm–thick phantom with cavitation monitoring device were submerged in a water bath to accommodate the cavitation monitor.

**Study protocol.** After anesthesia induction, the skin site overlying the graft was sterilized, and a 4-F cannula was placed percutaneously in the arterial proximal limb of the graft. Angiograms using 2-ml to 3-ml injections of Iohexol 300 (Ominipaque 300, Nycomed Princeton, New Jersey) were performed to assess patency. Then, a percutaneous double-suture ligature distal to the tip of the indwelling cannula was used to produce thrombosis of the graft. Thirty minutes of manual occlusive pressure was also applied to the graft proximal to the cannula to assist in thrombus formation. After a median period of 4 h, the suture was removed and thrombotic occlusion confirmed by angiography.

Based on the results of the in vivo cavitation experiments, 2 treatments were compared: (A) intravenous MRX-801 plus low-MI ultrasound (<0.4) that was below the experimentally determined cavitational threshold of the DUS transducer (low-MI DUS); and (B) intravenous MRX-801 plus intermittent high-MI (1.9) ultrasound impulses delivered when low-MI CPS detected microbubbles within the thrombus. This treatment was termed high-MI/low-MI DUS. All DUS transmissions were applied through the 6-cm tissue-mimicking phantom placed on the skin overlying the graft, as shown in Figure 1.

In the MRX-801 plus high-MI/low-MI DUS group, high-MI ultrasound was applied over the graft only when low-MI DUS imaging with CPS confirmed that microbubbles were present within the graft. An example of this technique is shown in Figure 2. The duration of high-MI applications was approximately 5 s. The duration of low-MI DUS in between high-MI applications varied depending on how rapid replenishment of contrast was observed within the graft. In the low-MI DUS group, the MI was maintained at <0.4 and continuously applied over the graft during the treatment period. Angiograms of graft patency were repeated at 6, 12, 20, 25, 30, 40, and 45 min of treatment to characterize flow through the graft. Patency of the 4-F cannula for angiograms was maintained by small quantities of intragraft heparin (cumulative dose: 1,000 U over the 45-min treatment period).

Flow scores were used to characterize angiographic flow in the graft as previously described.

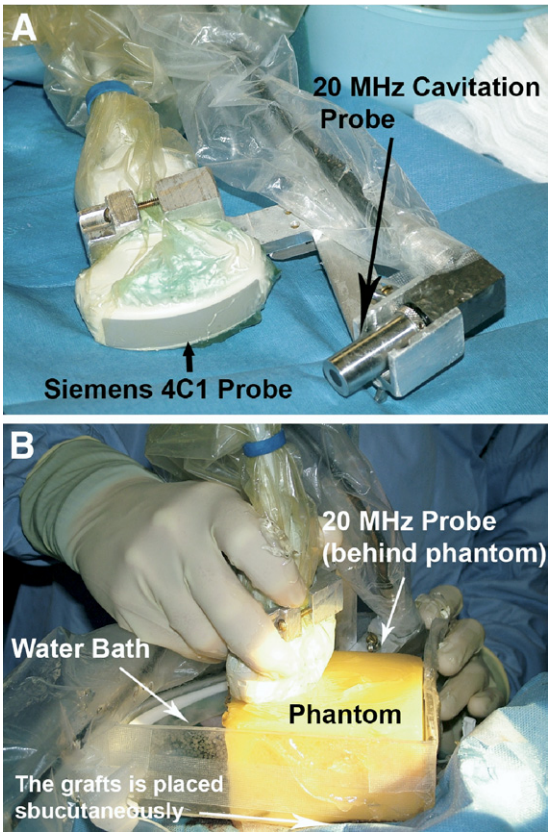


**Figure 1. The Set-Up of the 20-MHz Listening Device**

**(A)** Siemens Acuson Sequoia 4C1 probe with a 20-MHz cavitation detector mounted on it. **(B)** A 4C1 probe insonifying subcutaneous graft through 6-cm–thick phantom with cavitation monitoring device submerged in water bath.

The absence of visible flow was graded as 0. Flow beyond the obstruction that did not completely fill the graft and was associated with delayed clearance (when compared with the adjacent femoral artery) was graded as 1. When flow beyond the obstruction did completely fill the graft but clearance was delayed, the score was 2. Complete filling of the graft beyond the obstruction with rapid clearance was graded as 3. Success was defined as a flow score of 3.

At the completion of each procedure, any residual thrombosis in the graft was removed with intravenous heparin (100 U/kg) and balloon dilatation. The graft was reused for a subsequent randomized treatment at weekly intervals.

**Statistical analysis.** No corrections were made for multiple correlated observations in the same animal. Therefore, the thrombotic occlusion, not the animal, was the unit of analysis to permit statistical evaluation. Eight low-MI/high-MI DUS studies

were performed in the first canine and 6 in the second canine, whereas the 10 low-MI DUS studies were performed in the second canine. The study assignments were randomized in both canines, with the statistical comparisons in the first canine being low-MI/high-MI DUS versus a therapeutic transducer, and the randomized comparison in the second canine being low MI/high DUS versus low-MI DUS alone. Continuous data are expressed as mean ± SD and were compared using the Student unpaired *t* test. A chi-square test was used to compare differences between 2 groups in the proportion of grafts that achieved flow grade 3 at 20, 30, and 45 min. A p value <0.05 was considered statistically significant. The relationship between the peak negative pressure and MI was analyzed using linear regression analysis. All statistics were calculated using SigmaStat version 3.1 (Systat Software, Inc., San Jose, California).

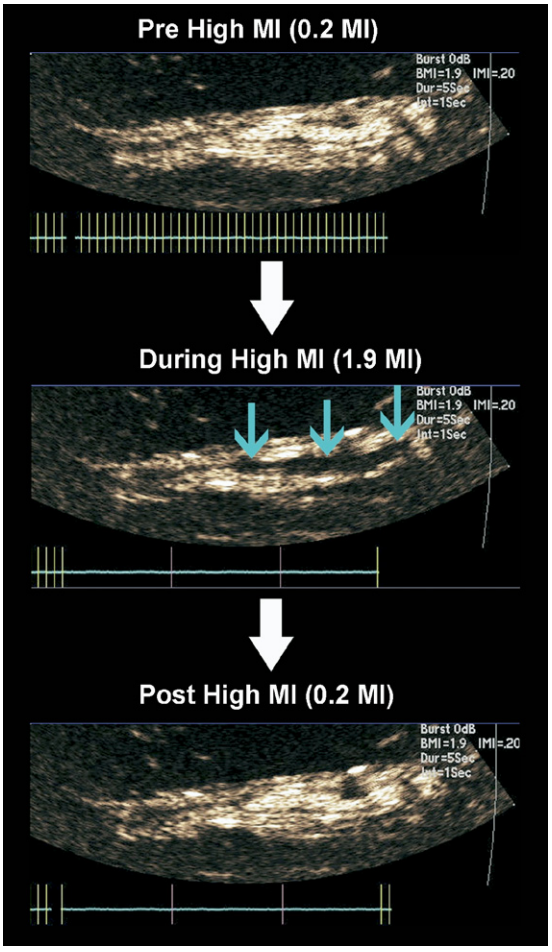


**Figure 2. Demonstration of Low-MI CPS-Guided Applications of High-MI Impulses Using the DUS Transducer**

When microbubbles seemed to maximally penetrate the thrombus (**top**), high-MI impulses were applied over the graft and this immediately destroyed the microbubbles (**middle, blue arrows**). After a programmed period, the transducer switched to low-MI imaging again to examine for microbubble replenishment (**bottom**). CPS = contrast pulse sequencing; DUS = diagnostic ultrasound; MI = mechanical index.

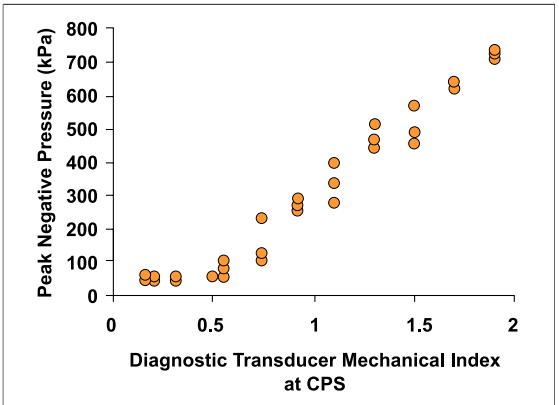


**Figure 3. Peak Negative Pressure at Different Mechanical Indexes**

The measurements were obtained through the tissue-mimicking phantom from the diagnostic ultrasound transducer at different mechanical indexes. There was a linear relationship between the peak negative pressure and mechanical indexes. CPS = contrast pulse sequencing.

## Results

**Peak negative measurements.** Figure 3 shows the PNP measurements at the different MI settings. There was a linear relationship between the PNP and MI ($r^2 = 0.96$, $p < 0.0001$). The PNP obtained for 1.9 MI was 723 ± 12 KPa, and decreased with decreasing MI down to 50 ± 7 KPa at the 0.31-MI setting.

**Intravascular cavitation activity within the thrombosed vessel.** Cavitational activity within the graft was detectable only when microbubbles were visualized with CPS moving through channels within the thrombus. Figure 4 depicts the plot of cavitational activity (root mean square voltage of passive 20-MHz detector) on the y-axis plotted as a function of the applied MI on the x-axis. The recordings were obtained when there was evidence of microbubbles channeling through the thrombus and angiographic flow grade 3 within the graft. As can be seen, cavitational activity was recorded all the way down to 0.5 MI, below which there was an abrupt decrease of cavitational activity within the graft.

**Recanalization of occluded grafts.** Of the 24 acute graft occlusions, 14 were treated with low-MI/

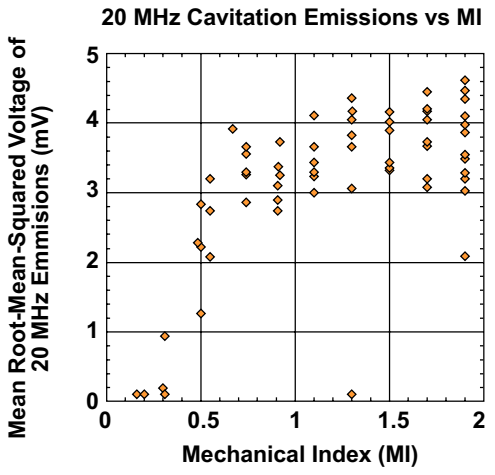


**Figure 4. Cavitation Emissions at Different Mechanical Indexes**

Plot of intravascular cavitational activity within the recanalized arteriovenous graft during a microbubble infusion as a function of mechanical index (MI) setting on the 1.5-MHz diagnostic transducer. Note that cavitation was not observed below 0.5 MI.

high-MI DUS, and 10 with low-MI DUS. Figure 5 is an example of one of the images obtained through the tissue-mimicking phantom in a dog receiving low-MI/high-MI DUS. During low-MI imaging, CPS showed microbubbles filling channels within the thrombus (top panel). When a high-MI impulse was applied (middle panel), the microbubbles were immediately cleared from the channels within the thrombus. After the return to low-MI DUS, there was replenishment of microbubbles (bottom panel). In the first 10 min of treatment, the time intervals between high-MI ultrasound applications were 21 ± 19 s (ranging up to as long as 121 s), reflecting slower microbubble replenishment because of slower flow through smaller channels within the thrombus early on in treatment. At subsequent treatment intervals, there were progressively shorter time intervals (8 ± 8 s at 40 min into treatment) between high-MI treatments as low-MI CPS detected more rapid microbubble replenishment within the thrombosed graft as the channels enlarged. These short time replenishment intervals were seen only in the dogs in whom flow grade 3 by angiography (6 ± 5 s replenishment interval in grafts with flow grade 3 vs. 12 ± 6 s replenishment interval in grafts with flow grade <3; $p < 0.001$) was achieved.

**Table 1. Recanalization Rates at Different Time Intervals of Treatment**

| | MRX-801 + Low-MI DUS | MRX-801 + Low-MI/High-MI DUS |
|---|---|---|
| 20 min | 10% | 29% |
| 30 min | 20% | 71%* |
| 45 min | 30% | 79%* |

DUS = diagnostic ultrasound; MI = mechanical index. *$p < 0.05$ compared with MRX-801 + low-MI DUS.

The angiographic flow scores in the 2 treatment groups at the different time intervals of treatment are presented in Table 1. As can be seen, after 30

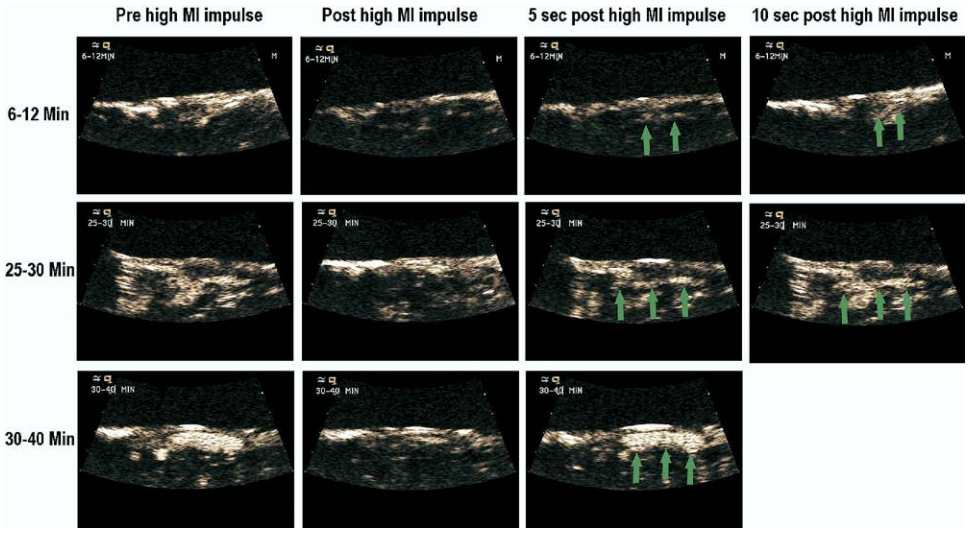


**Figure 5. An Example of Receiving Low-MI/High-MI DUS Treatment**

The increase in channel size **(green arrows)** within the thrombus as a function of treatment time. Note the rapidity with which replenishment of microbubbles occurred within the channels of the thrombus as a function of treatment time. Abbreviations as in Figure 2.

and 45 min of treatment, the successful recanalization rates in the grafts treated with low-MI/high-MI DUS were significantly larger than those treated with low-MI alone. The majority of grafts treated with intermittent high-MI diagnostic impulses already showed flow grade 3 at 30 min. A flow score of 3 at 45 min was achieved in 11 of 14 grafts treated with low-MI/high-MI DUS ($p < 0.05$ compared with low-MI DUS). In the canine in which randomized comparisons between low-MI/high-MI DUS and low-MI alone were made, 5 of the 6 thrombi treated with low-MI/high-MI recanalized at 30 min, compared with 2 of 10 in the low-MI group ($p = 0.02$). There were no statistically significant differences between groups in activated clotting times after the different ultrasound treatments (110 ± 16 s vs. 122 ± 1 s).

## Discussion

Tachibana and Tachibana (4) first described the impact of a nonimaging low-frequency ultrasound transducer and microbubbles on the effectiveness of fibrinolytic agents. These investigators observed, in an in vitro model, that the combination of urokinase, low-frequency ultrasound, and microbubbles resulted in an increased rate of fibrinolysis when compared with urokinase plus ultrasound or urokinase alone. In vitro studies have also indicated that cavitation plays an important role in ultrasound-induced thrombolysis (3). These cavitation thresholds have been shown to be lowered in the presence of microbubbles. Our study documents the importance of cavitation for producing thrombolysis with ultrasound in vivo, in that only when we applied the cavitation-producing high-MI impulses did we achieve a high degree of success in recanalizing the acutely thrombosed grafts.

Ultrasound, used alone or in combination with microbubbles, has potentiated the clinical effect of fibrinolytic agents in the treatment of stroke in humans (1,2). The CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and systemic TPA) trial showed that a nonimaging continuous transcranial Doppler ultrasound transducer augments t-PA–induced middle cerebral arterial recanalization. Molina et al. (1) showed that administration of microbubbles augmented the effectiveness of continuous-wave ultrasound-enhanced thrombolysis in acute stroke. More recently, Pagola et al. (2) reported that this same ultrasound technique and microbubbles with t-PA leads to early recanalization in acute basilar artery occlusion. None of these clinical studies, however, assessed the efficacy of ultrasound and microbubbles alone. Furthermore, because they applied the therapeutic ultrasound in an uninterrupted fashion, this procedure may have reduced the effectiveness of the microbubbles by prohibiting replenishment of microbubbles within the field of interest that would serve as nuclei for the desired cavitation effect.

Microbubble-mediated thrombus dissolution without fibrinolytic agents has been shown in animal studies using a variety of echo-contrast agents in combination with nonimaging therapeutic ultrasound devices. These studies were primarily performed in peripheral vessel thromboses where there was minimal attenuation of the ultrasound beam. In the present study, we showed that intravascular cavitational activity occurs within a deeply located thrombosed vessel when high-MI impulses were applied after replenishment of the insonified field with microbubbles. We have previously shown that thrombus dissolution was more effective when a nondestructive imaging transducer was used to guide when to apply the high-MI impulses. In the present study, we showed that a diagnostic transducer has the capability of simultaneously being both the guiding transducer (at a low MI) and the therapeutic transducer (brief 1.9-MI impulses). In the absence of a fibrinolytic agent or systemic anticoagulation, the angiographic success rate with intermittent high-MI DUS and microbubbles was 71% at 30 min and 79% at 45 min, compared with only 20% at 30 min and 30% at 45 min in the low-MI ultrasound-alone group. Thus, an imaging-guided approach has the potential to both improve recanalization of thrombosed vessels, and also limit the duration in which high-MI ultrasound needs to be applied. The low-MI-alone setting played a minimal role in facilitating sonolysis because the angiographic success rates in the grafts receiving low MI alone were not different from what we have observed in thrombosed grafts treated with unguided therapeutic ultrasound and microbubbles in this setting. Therefore, we propose that it is not just the induction of cavitation that improves ultrasound's success rate in recanalizing the thrombosed vessel, but an imaging-guided approach that maximizes the presence of microbubbles within the vessel before the application of the cavitation-inducing impulses.

**Study limitations.** One of the limitations in the study was that only 2 dogs were used to test the hypothesis. The multiple thromboses were created in each group to overcome the variable that different grafts pose in influencing outcome. Differences in

surgical graft positions and geometry may affect the ability of any pharmacologic or mechanical therapy in recanalizing the thrombosed grafts. This is why we chose a model in which repetitive thromboses (n = 24) were created in just 2 grafts of 2 dogs, so that any variations in graft geometry or position would not affect our comparison of the 2 different ultrasound settings compared in this study. Although the age of the thrombus used in this study may not be similar to the situation seen in a clinical graft thrombosis, our goal was more to create an acute thrombosis in a deeply located vessel, similar to what may be seen in acute cerebral or coronary thromboses. In these situations, the thrombus is more often of the age used in this study, and we expect the findings of our study to be applicable to these situations more than a clinical graft thrombosis.

We did not have a separate group testing what effect diagnostic ultrasound alone (without microbubbles) may have in recanalizing the graft thromboses. However, we have previously examined what effect therapeutic ultrasound alone has in recanalizing thrombosed arteriovenous grafts like the one in this study, and the success rate was only 12.5%.

Although the mechanical index setting on a given ultrasound system serves as a guide for the peak negative pressure reaching the insonified region, how this value is determined varies among different manufacturers. Thus the mechanical index value can only serve as an estimation of the peak negative pressure reaching tissue, and the actual MI setting that induces cavitation may vary depending on the type of diagnostic system that is being used. For example, the high-MI pulses used in this study (machine setting 1.9) produced a peak negative pressure of 0.723 MPa as measured by the hydrophone through the tissue phantom material. The true MI, therefore, would be calculated as 1.0 based on the tissue derating criterion published by the U.S. Food and Drug Administration (5).

Although we did formally evaluate the safety of ultrasound- and microbubble-mediated thrombus dissolution in this study, we have previously examined whether there was evidence that this technique resulted in pulmonary embolization and found no evidence of this when using a diagnostic ultrasound-guided technique. Furthermore, we have not seen any evidence that ultrasound and microbubble–induced recanalization altered right ventricular systolic function or pressures.

We did not determine what additional effects systemic anticoagulation or lysis therapy may have on this technique. It would be assumed that such additional therapies would be additive because the effects of ultrasound and microbubbles seem to be mostly mechanical dissolution and not activation of lytic enzymes.

**Clinical implications.** We have shown that a diagnostic ultrasound transducer, operating within U.S. Food and Drug Administration peak negative pressure limits (4), has the capability to induce intravascular thrombus dissolution when used in combination within intravenous microbubbles. This imaging transducer must also be used to detect when microbubbles are present within the thrombus, and to guide when to apply the high-MI impulses. Furthermore, recanalization in this study was achieved without the need for systemic fibrinolysis or systemic anticoagulation. Because these results were achieved when the DUS was applied through a 6-cm–thick tissue-mimicking phantom, they indicate that this method of treatment may be a noninvasive alternative for treating acute thrombotic occlusions within the coronary or cerebral circulation. Microbubbles very similar in structure to the ones used in this study are already commercially available today. Although concerns regarding the safety of ultrasound contrast agents like the one used in this study have recently been raised by the U.S. Food and Drug Administration, subsequent safety studies have shown that such concerns are not clinically significant. The cumulative doses of MRX-801 used in this animal study were only slightly above one commercially available vial of Definity (Lantheus, Inc., North Billerica, Massachusetts), and were given repetitively to the same animal without evident side effects. In addition, the diagnostic transducer used for this study is commonly used for transthoracic imaging in patients. Therefore, we conclude that this technique should be explored as a method of treating acute intravascular thrombosis in conjunction with anticoagulation or fibrinolytic therapy, or as an alternative therapy in patients who have contraindications to anticoagulants or fibrinolytic agents.

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**Key Words:** cavitation ■ microbubbles ■ ultrasound ■ thrombolysis.