Current Cardiology Reports (2019) 21: 86
https://doi.org/10.1007/s11886-019-1167-z

ECHOCARDIOGRAPHY (JM GARDIN AND AH WALLER, SECTION EDITORS)

Cardiovascular Sonothrombolysis

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Published online: 25 July 2019

Abstract

Purpose of Review This review will provide recent pre-clinical and initial clinical trials exploring the efficacy of sonothrombolysis as an adjunct to current emergent therapies in acute coronary syndromes.

Recent Findings The initial clinical trials examining the efficacy of short pulse duration diagnostic ultrasound (DUS) high mechanical index impulses in patients with ST segment elevation myocardial infarction (STEMI) have demonstrated that there is improved patency of the infarct vessel, and improved microvascular flow following percutaneous coronary intervention. Subsequent randomized prospective trials have confirmed that in patients with acute STEMI receiving an intravenous microbubble infusion, diagnostic high mechanical index impulses applied in the apical windows pre- and post-percutaneous coronary intervention have reduced myocardial infarction size, as assessed by magnetic resonance imaging at 72 h following presentation, and have been associated with better left ventricular systolic function at 6 month follow-up.

Summary Sonothrombolysis has potential for improving early epicardial coronary artery patency and reduce left ventricular remodeling when added to current interventional strategies in STEMI.

Keywords Sonothrombolysis · Perfluorocarbons · Microbubbles · Diagnostic · Ultrasound · Targeted therapy

Abbreviations

DUS	Diagnostic ultrasound
FDA	Food and Drug Administration
IC	Inertial cavitation
STEMI	ST segment elevation myocardial infarction
PWD	Pulsed wave Doppler
PCI	Percutaneous coronary intervention
MI	Mechanical index

This article is part of the Topical Collection on *Echocardiography*

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Introduction

Although the Food and Drug Administration (FDA) has approved microbubbles for only limited diagnostic use, diagnostic ultrasound-induced cavitation of these microbubbles may also have targeted therapeutic applications [1]. One of these applications could be cavitation-induced thrombus dissolution in the absence of a lytic agent, which was first demonstrated in vitro in 1997 [2], and was predicated upon work published just 1 year earlier by Tachibana and Tachibana demonstrating the potential of ultrasound-induced microbubble cavitation to augment the effects of lytic therapy [3]. Subsequent in vivo studies demonstrated, in both acute peripheral artery thrombi and thrombosed arteriovenous grafts, that low frequency transcutaneous ultrasound-induced targeted cavitation could recanalize peripheral vascular thrombi without fibrinolytic agents or heparin [4–6]. More recently, diagnostic ultrasound (DUS) peak negative pressures, despite their short pulse duration, have been shown to be effective at recanalizing intravascular thrombotic occlusions [7]. The effectiveness appears to be related to the use of intermittent high mechanical index impulses, which are capable of causing both stable and inertial cavitation (IC). Stable cavitation is a non-linear microbubble response that is in the ultraharmonic frequency domain,

while IC is a more rapid microbubble growth and collapse that creates a broadband frequency response [8]. The intermittent application is guided by very low mechanical index imaging, to determine when microbubble permeation of the thrombus has occurred. Although both IC and SC have been shown effective in augmenting the effects of fibrinolytic therapy, IC appears to be optimal when using ultrasound alone without lytic agents to recanalize coronary arteries and the microcirculation [9••, 10••]. IC results in fluid jets that erode thrombus both from outside as well as from within the thrombus infrastructure [11, 12]. Intermittent high mechanical index (MI) impulses from a DUS system, which use very low MI pulse sequence schemes to guide the analysis of microbubble replenishment into the thrombus, have been used in both pre-clinical and clinical studies of acute ST segment elevation myocardial infarction (STEMI) and ischemic stroke, achieving successful coronary and cerebral recanalization with improved microvascular flow without the need of fibrinolytic therapy [9••, 10••, 13]. The duration of the high MI impulse (pulse duration) also plays a role in therapeutic effect, with longer pulse duration (20 usec) potentially more effective, but also inducing unwanted bioeffects such as coronary spasm and vasoconstriction [9••] This review will discuss these pre-clinical and ongoing clinical studies which may alter our approach to STEMI and ACS management.

Targeted Thrombolysis with DUS-Preclinical Studies

The potential for thrombolysis-inducing impulses from a DUS transducer was first examined in a canine model of arteriovenous graft thrombosis, where intermittent high MI impulses (all < 1.9 MI) were applied through a 6 cm thick tissue-mimicking phantom only when very low MI imaging detected microbubbles within the thrombus [7]. This presence of microbubbles was used to guide when to apply high MI impulses. The diagnostic low MI ultrasound was also utilized to detect changes in size and flow within the recanalized graft. We observed that over repeated application of the high MI ultrasound impulses, the small channels progressed to larger channels with repeated high MI impulses (Fig. 1). Angiographic recanalization rates improved from 20% (with very low MI imaging alone) to 80% after 30 min of treatment with repeated diagnostic high MI impulses. These grafts recanalized without any adjunctive fibrinolytic, anti-thrombotic, or anti-platelet agents, suggesting that mechanical thrombus dissolution was possible in the absence of pharmacotherapy or invasive percutaneous angioplasty. Furthermore, we observed no downstream embolization with the guided high MI impulse therapy. On further investigation with passive cavitation detectors placed confocal to the DUS beam, the intermittent high MI impulses were shown to induce inertial cavitation within the graft. The results achieved with a DUS

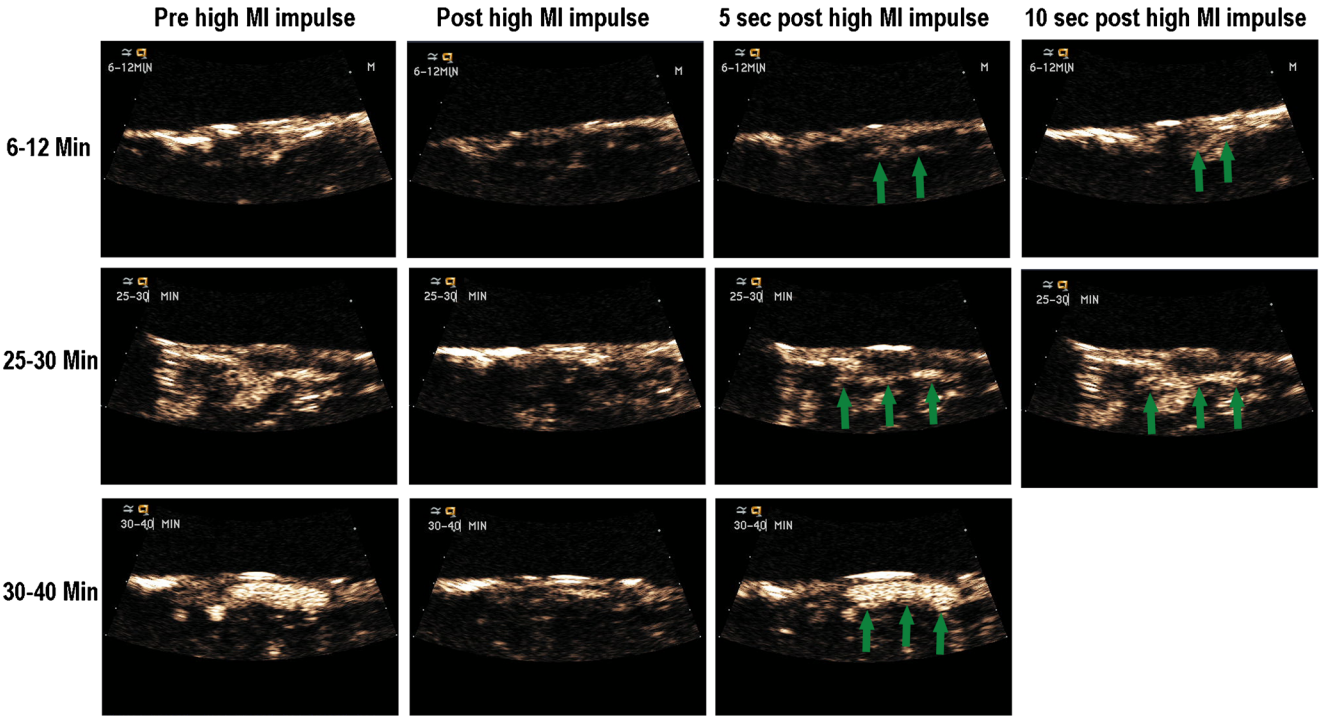

Fig. 1 Very low MI images of a thrombosed arteriovenous graft when applying intermittent application of DUS high MI impulses during an intravenous infusion of lipid encapsulated microbubbles. Small channels (green arrows) that slowly replenish early in therapy (top row at 6–12 min of treatment) eventually become large channels (green arrows middle row at 20–30 min of therapy) and eventually restore flow with rapid replenishment at 30–40 min of therapy (green arrows; bottom row). (Reprinted from Xie F, et.al. [7])

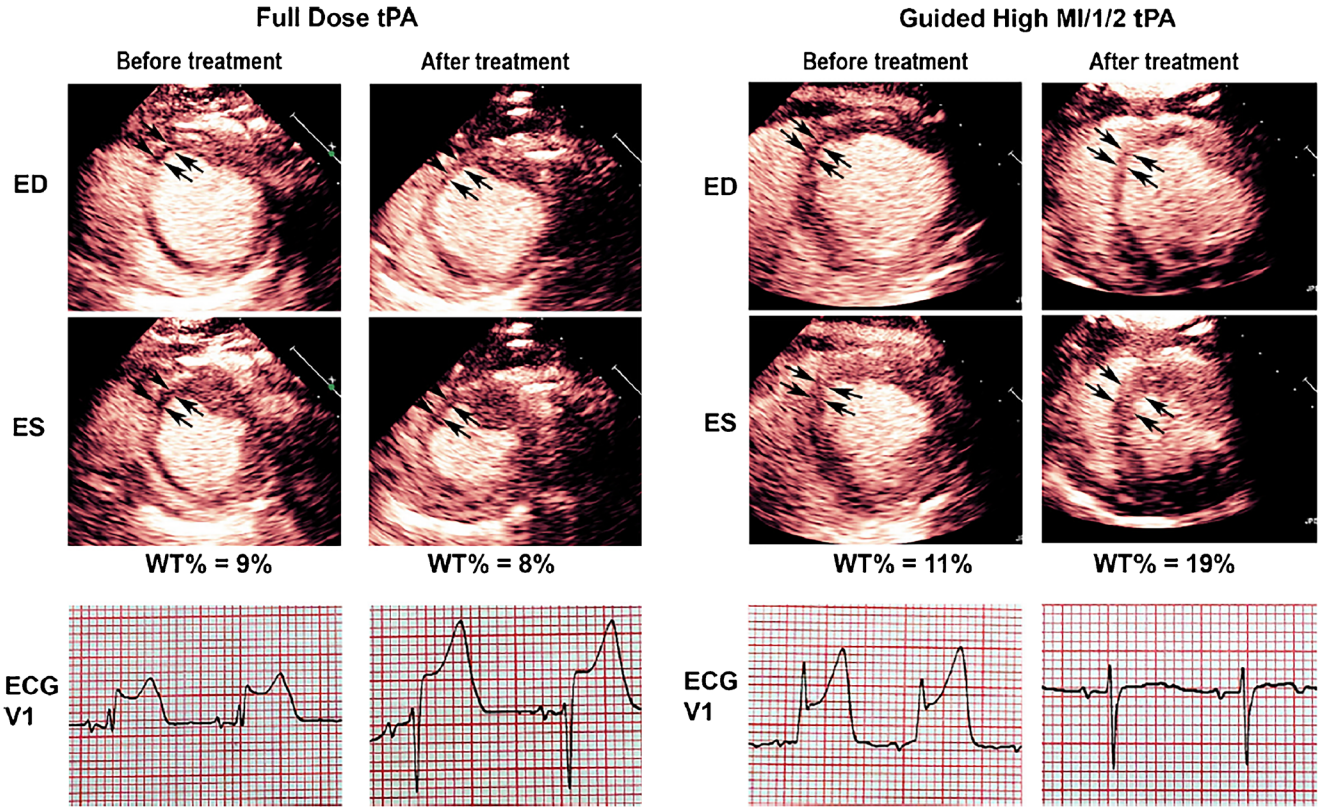

Fig. 2 Parasternal short axis images and corresponding electrocardiogram in acute STEMI due to LAD thrombotic occlusion comparing full dose thrombolytic therapy (left panels) with 1/2 dose thrombolytic therapy and DUS high MI impulses during an intravenous microbubble infusion (right panels). Note that microvascular recovery and ST segment resolution only occurred when high MI impulses were applied; plateau intensity images after therapy demonstrate replenishment of myocardial contrast and ST segment resolution, neither of which are seen after full dose fibrinolytic therapy. Wall thickening (WT) delineated by the black arrows is also restored in the DUS high MI group but not in the full dose tPA group. (reproduced from: Wu J, et.al. [14])

transducer in this study were similar to what had been achieved with non-imaging low frequency therapeutic transducers and microbubbles in acute peripheral artery thrombotic occlusions [5, 6]. Intermittent high MI DUS impulses during an infusion of microbubbles have also been effective for dissolving indwelling catheter-related thrombi and preventing arterial graft thrombosis.

Subsequent investigations examined the efficacy of DUS high MI impulses in restoring microvascular and upstream arterial blood flow in porcine models of acute STEMI [13–16] and ischemic stroke [17]. In these applications, very low MI imaging was also used to guide the applications of high MI impulses. Since coronary arteries are not readily visualized, the presence of microbubbles within the risk area was used to guide the timing of the high MI impulses (Fig. 2). In these studies, two critical outcomes were observed. First, the utilization of guided DUS high MI impulses appeared to restore microvascular flow and function (Fig. 2) even if epicardial recanalization was not achieved. This was further evidenced by ST segment resolution even when epicardial recanalization was not observed. The reason for this could be attributed to either microvascular nitric oxide release from the endothelial cells in response to cavitation induced shear or from microvascular thrombus dissolution. The potential for nitric oxide-induced increases in microvascular blood flow from ultrasound-induced cavitation has been demonstrated in ischemic limb skeletal muscle downstream from a peripheral vessel ligation. In this setting, high MI DUS-induced cavitation of lipid encapsulated microbubbles has resulted in restoration of skeletal microvascular flow which is nearly abolished in the presence of nitric oxide inhibitors [18•].

Subsequent in vitro and in vivo studies have demonstrated that modifying the diagnostic pulse duration may further improve the magnitude of thrombus dissolution. By increasing pulse duration from < 5 to 20 usec on a DUS transducer, a higher epicardial recanalization rate was achieved with DUS guided therapy added to 1/2 dose tissue plasminogen activator [13, 14]. However, both short and longer pulse duration high MI DUS impulses were equally effective in ST segment resolution and improvement in wall thickening within the risk area [13]. Although this slight prolongation of pulse duration appears possible with current DUS transducers, the safety of this longer pulse duration has been brought into question in subsequent pilot clinical trials [9••].

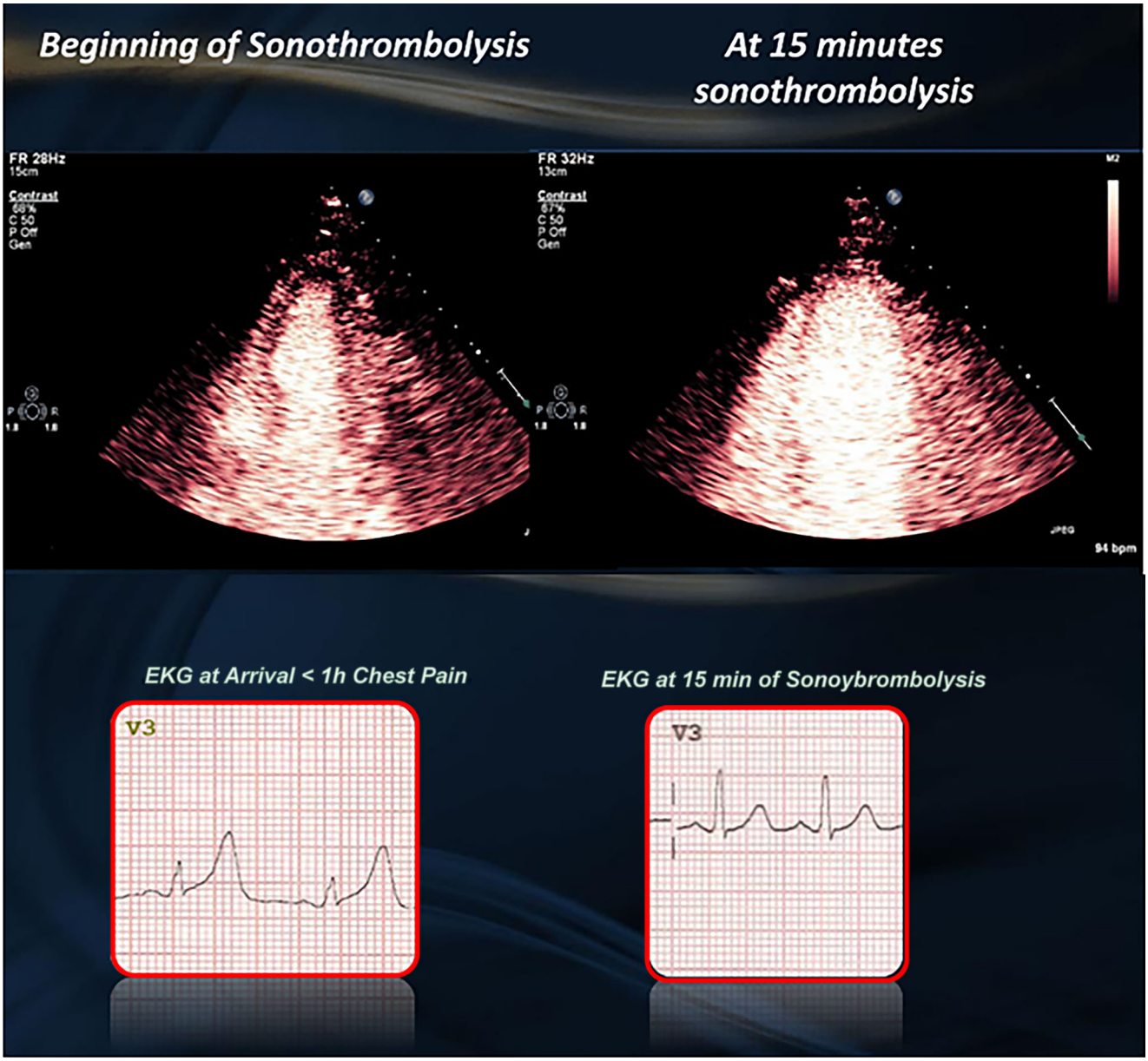

Fig. 3 Example of ST segment resolution and microvascular recovery in a patient treated with DUS intermittent high MI impulses prior to emergent PCI in acute LAD STEMI. Note that with very low MI imaging we see recovery of microvascular flow (top panels), and ST segment resolution (bottom panels) with just 15 min of ultrasound therapy prior to PCI. (images courtesy of Dr. Wilson Mathias, co-author; University of Sao Paulo School of Medicine, Sao Paulo, Brazil)

In ischemic stroke, transcranial DUS-guided high MI impulses and intravenous microbubbles, have recanalized intravascular and microvascular thrombi in a large porcine animal model even in the absence of a fibrinolytic agent [17]. In this model, the DUS high MI impulse had to be 2.4 (pulse duration < 5 usec, 1.7 MHz frequency) to be effective, which is above the FDA limit. Other larger animal models have been utilized to determine the potential for transcranial therapeutic ultrasound-induced cavitation of microbubbles to reduce stroke size [19], but without DUS pulse durations or imaging guidance. Similar to coronary sonothrombolysis studies, longer pulse duration guided high MI impulses that induce inertial cavitation may induce unwanted bioeffects that counter the effectiveness of shorter pulse duration high MI impulses [20].

Preliminary Clinical Results in Sonothrombolysis

The first clinical studies exploring the effectiveness of ultrasound and microbubbles for sonothrombolysis were in acute

Table 1 Future developments that will enhance the clinical effectiveness of DUS-guided sonothrombolysis

Development	Reason
Portable ultrasound systems	Permit ambulance and point of care sonothrombolysis
Feedback cavitation detection	Ensure short pulse duration inertial cavitation achieved at focus
Targeted microbubbles	Ensure greater microbubble adherence to thrombus during cavitation event
Perfluorocarbon droplets	Promote better permeation of the thrombus prior to targeted cavitation.

ischemic stroke. The initial studies, using a pulsed wave Doppler (PWD) and systemically administered microbubbles in humans with acute ischemic stroke, combined microbubbles with full dose fibrinolytic agents [21–23]. In this context, PWD was successful in increasing the speed of intracranial recanalization but did also appear to increase the risk for intracranial hemorrhage. Unfortunately, to date, no human trials of ischemic stroke have examined the effect of targeted ultrasound-induced cavitation alone, without fibrinolytic agents.

The first coronary studies examining the efficacy of DUS-induced microbubble cavitation have demonstrated both safety and potentially enhanced efficacy when combined with emergent percutaneous coronary intervention (PCI) [24]. In these trials, three-dimensional ultrasound at a high MI was aimed at the proximal origins of the coronary arteries during a microbubble infusion to attempt recanalization of the coronary arteries. This study only involved 10 patients and was designed to demonstrate feasibility and safety rather than efficacy. Subsequent trials have aimed the guided high MI impulses at the microvasculature [9••, 10••]. These trials have demonstrated that brief (average 10 min) applications of image-guided high MI impulses, aimed at the microvasculature and at a short pulse duration (< 5 μ), are effective at both restoring epicardial flow and microvascular flow (Fig. 3). However, longer pulse duration (20 μ) high MI impulses may also induce focal areas of vasoconstriction within the infarct vessel [9••]. These important pilot studies have demonstrated the feasibility and safety of DUS high MI impulses at a short pulse duration. Larger randomized studies are forthcoming at the time of this publication.

Future Directions/Conclusions

Sonothrombolysis trials now are either completed or ongoing in three different countries (Canada, The Netherlands, and Brazil). The preliminary data from these investigations indicate that DUS high MI impulses applied to the microvasculature of the infarct zone are effective and safe methods of achieving early coronary patency and reducing myocardial infarction size [25]. Ongoing work is now examining the role of sonothrombolysis pre-PCI and post-PCI to improve microvascular recovery, which remains a serious persistent problem with current treatment methods [26]. The earlier sonothrombolysis is applied, the more effective it may be. Therefore, portable ultrasound systems that could be applied at the point of patient contact have the potential to enhance the efficacy of pre-hospital sonothrombolysis (Table 1). Platelet or fibrin-targeted microbubbles may further improve the efficacy of non-targeted microbubbles [27] but will require FDA approval before such applications could be tested. Equally important for clinical application is the assurance that inertial cavitation is being achieved with the short pulse duration high MI impulses, especially in larger patients. This feedback can be achieved by modifications in transducers which permit the returning radiofrequency spectra to be analyzed for whether inertial or stable cavitation events are occurring at the focus [8]. The MI could then be adjusted if necessary to ensure inertial cavitation was dominant. Finally, better permeation of thrombi prior to a high MI impulse may be possible with nanometer-sized perfluorocarbon droplets, which can be formulated from commercially available agents [28]. These are activated by high MI ultrasound, and the formed microbubbles undergo cavitation within the time period of the same high MI impulse. These modifications in transducer design and microbubble formulation will enhance sonothrombolysis applications not only within the coronary circulation but also for applications in ischemic stroke and peripheral vascular disease.

Acknowledgments The authors want to thank Megan Hoesing for her dedicated work in preparing this manuscript and to the Theodore Hubbard Foundation for funding of costs associated with manuscript preparation.

Authors' Contribution TRP has written the entire paper, whereas WM has assisted with manuscript preparation and figures.

Compliance with Ethical Standards

Conflict of Interest Dr. Porter receives research equipment support from Philips Ultrasound. From Bracco, Dr. Porter receives educational support and he is on their Speaker's Bureau. Dr. Porter also receives salary and research support from the Theodore F. Hubbard Foundation. In addition, Dr. Porter has a patent issued on Thrombolytic Agents and Methods of Treatment for Thrombosis issued to #6,197,345).

Wilson Mathias Jr. declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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