Coronary artery disease is the leading cause of death in the world today, closely followed by cerebrovascular disease, with the incidence of both projected to increase in the next 2 decades. Together, they account for nearly a quarter of all deaths worldwide and almost half the deaths in the United States. This year, 770,000 Americans will suffer a new acute myocardial infarction (AMI), and 430,000 will have a recurrent AMI. Similarly, 600,000 Americans will suffer a new stroke, and 180,000 will experience a recurrent stroke. The treatment approaches for both AMI and stroke are becoming more and more similar. Only a small fraction of these patients will receive timely percutaneous intervention (PI), which is currently the best available therapy for achieving successful reperfusion. Most Americans do not have access to PI, and except for a few wealthy individuals living in urban areas, most people in the developing world, where most of humanity resides, do not have access to PI. If AMI and stroke patients are lucky enough to receive timely treatment, it is likely to be thrombolytic therapy, which has a significantly lower reperfusion rate than PI. Therefore, a noninvasive approach that could improve on thrombolytic therapy and achieve the success rates of PI even in relatively remote locations would have a major impact on public health. Sonothrombolysis is 1 such potential approach.

It has been nearly 30 years since thrombus dissolution with ultrasound was first reported. Research in this area since then has proceeded in fits and starts, with clinical studies performed only recently. More studies have been performed in stroke than AMI. The CLOTBUST (Combined Lysis of Thrombus in Brain Ischemic Tissue Using Transcranial Ultrasound and Systemic t-PA) trial showed an 83% recanalization rate with sonothrombolysis and tissue plasminogen activator compared with 50% with tissue plasminogen activator alone. Other smaller studies in stroke patients have also shown encouraging results, and a larger randomized study has just been completed. There have been only 2 studies using transcutaneous sonothrombolysis in AMI patients. In the first study, 25 patients with ST-elevation AMI were subjected to thrombolytic therapy and sonothrombolysis. Thrombolysis in Myocardial Infarction (TIMI) grade 2 to 3 flow was achieved in 84% of these patients. The second multicenter study randomized 400 patients to tenecteplase alone or to tenecteplase and sonothrombolysis. There was no difference in the arterial patency rate of TIMI grade flow between the 2 groups. However, ST-segment resolution was seen in 76% of patients who received tenecteplase and sonothrombolysis compared with 59% who received tenecteplase alone.

The dissociation between the angiographic and ECG findings should not be surprising and likely represents another benefit of ultrasound treatment not associated with other forms of reperfusion therapy. Low-frequency ultrasound increases tissue blood flow despite total arterial occlusion. The exact mechanism of this phenomenon is not clear, although nitric oxide release by vibrating endothelial cells has been suggested as a probable cause; collateral channel opening also has been implicated. Nitric oxide can directly affect the microvasculature of ischemic tissue independently of its effect on systemic hemodynamics and collateral flow. The augmented blood flow in the ischemic microcirculation occurs in tandem with increased erythrocyte mobility through a change in charge. Formation of S-nitrosothiol in erythrocytes in high-flow states also allows O2 unloading to tissue during low-flow states as a result of a change in hemoglobin configuration. Because necrosis will not ensue until flow is very low, this approach can be used for tissue protection until artery patency is achieved. There are obvious differences between patients with stroke and those with AMI in terms of providing sonothrombolysis. First, unlike the cerebral arteries, the coronary arteries are more difficult to localize with ultrasound. Second, unlike the cerebral arteries, the coronary arteries move during the cardiac and respiratory cycles. These limitations can be overcome if the region surrounding the site of thrombosis can be imaged and ultrasound can be delivered precisely to it. Three-dimensional imaging systems are more suited for this purpose than 2-dimensional imaging and Doppler systems.

There are also ways to improve the efficacy of sonothrombolysis with the use of microbubbles. Rather than using generic microbubbles, one could design microbubbles that can bind to thrombus so that their disruption with ultrasound could cause more effective thrombus fragmentation and loosening. Additionally, the pulsing of ultrasound can be timed in a manner that microbubbles are destroyed only when present in the proximity of the thrombus. Continuous ultrasound pulsing may cause microbubble disruption in...
the ultrasound field and prevent them from coming in proximity to the thrombus or binding effectively to it.

In this issue of *Circulation*, Xie and colleagues\(^6\) have attempted to use these approaches to achieve reperfusion in a porcine acute coronary thrombus model. They combined sonothrombolysis with microbubbles and half-dose recombinant prourokinase and timed their ultrasound pulses when they observed some flow to the risk area, presumably through collaterals. Rates for artery patency, ST-segment resolution, and reperfusion of the risk area flow were higher when they used microbubbles targeted to platelet glycoprotein IIb/IIIa compared with nontargeted microbubbles (53% versus 7%, 82% versus 21%, and 80% versus 40%, respectively). They also observed that regional perfusion and function were enhanced after ultrasound exposure even in pigs that demonstrated persistent coronary occlusion. This dissociation between tissue effect and arterial effect was similar to that seen in clinical studies.

That brings us to another benefit of using microbubbles in both AMI and stroke. In one fourth of ST-elevation AMI patients with an open infarct-related artery after attempted reperfusion therapy, tissue flow is absent (no reflow).\(^{17,18}\) These patients do poorly, with subsequent infarct expansion, left ventricular dilatation, congestive heart failure, and sudden death.\(^{17,18}\) Part of the no reflow is from necrosis and is irreversible, but part of it is from microthromboembolism during PI, microcirculatory spasm, myocardial edema, and in situ platelet aggregation and thrombus formation. Microbubbles can be used very effectively to measure and monitor the no-reflow zones\(^{17,18}\) and to measure collateral flow.\(^{19,20}\) They also can be used to measure the effect of ultrasound on blood flow in ischemic tissue. Thus, microbubbles can provide a more accurate assessment of tissue perfusion and viability than angiography or other methods.

Despite the encouraging results from experimental studies such as the one reported by Xie and colleagues\(^6\) in this journal and the clinical studies in stroke and ST-elevation AMI, much more work needs to be done. Only a handful of investigators are pursuing this kind of research in AMI models. One reason is that most echocardiographers involved in clinical investigation consider ultrasound to be an imaging rather than a therapeutic modality. This is also true for ultrasound companies. The primary reason that Xie et al used the ultrasound frequency they did is that it is available in clinical systems. Even the CLOTBUST study hypothesis was based on a serendipitous observation that higher-than-expected arterial recanalization rates occurred in stroke patients receiving transcranial Doppler to assess arterial recanalization.\(^{21}\) The same transcranial Doppler frequency was subsequently used in the CLOTBUST study because it was available in clinical systems.

We do not have a clear idea of the frequency, power output, duty cycle, or type of pulse (continuous or pulsed wave) that achieves optimal thrombolysis in vivo (with or without thrombolytics) because it is not possible to achieve a wide variety of permutations and combinations of these parameters from commercially available systems because of their relatively narrow bandwidths. We do not even know the ultrasound parameters that provide maximal protection to ischemic tissue and whether they are different from those for thrombolysis. The clinical ST-elevation AMI trials showing beneficial tissue effect used a 27-kHz continuous-wave non-imaging transducer, whereas the porcine study by Xie et al showed this effect with a 1.5-MHz imaging transducer. The heart and brain are 3-dimensional structures, so a combined 3-dimensional imaging and delivery system would improve the chances of locating the sites of thrombus and ischemic tissue and targeting these regions for therapy. Such a system does not exist.

Unless there is an economic benefit downstream, ultrasound companies are not going to invest in developing prototype systems that are not part of their core imaging business. Governmental grants (such as the Small Business Innovation Research Grant that supported the work of Xie et al) are too small to push the technology aggressively. Even larger grants such as Biomedical Research Partnerships that encourage industry and academic collaborations are not large enough to achieve success in a short time. If we believe that sonothrombolysis has promise in stroke and AMI, we need to allocate some serious money for research in this field and provide a timeline for achieving success. We have spent billions of taxpayer dollars on biomedical research, some of which is even interesting, but most of it has failed to benefit human health. It is high time we targeted our 2 top public health problems for some serious funding. The 15 million American survivors of AMI and stroke\(^2\) should not have to resort to political activism and pressure to bring this obvious need to the attention of our leaders, although one wonders whether, without such tactics, taxpayer dollars will ever be allocated rationally.

**Disclosures**

None.

**References**


**Key Words:** Editorials myocardial infarction stroke thrombosis ultrasonics
Sonothrombolysis: A Universally Applicable and Better Way to Treat Acute Myocardial Infarction and Stroke? Who Is Going to Fund the Research?

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_Circulation_. 2009;119:1358-1360; originally published online March 2, 2009;
doi: 10.1161/CIRCULATIONAHA.108.846113

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/119/10/1358

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