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EDITORIAL COMMENT

The Evolution of Contrast Ultrasound

From Diagnosis to Therapy*

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This issue of the *Journal* features the groundbreaking work of Mathias et al. (1) in which they describe the novel use of contrast-enhanced ultrasound (CEUS) to restore epicardial culprit artery patency and reduce microvascular obstruction, thereby salvaging myocardial tissue and preserving left ventricular (LV) function in patients with acute ST-segment elevation myocardial infarction (STEMI). This study, despite its relatively small sample size, may herald a future therapeutic option for salvaging myocardial tissue in the STEMI setting.

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To contextualize the unique findings, it is helpful to understand the development of CEUS as a novel, multifaceted approach to both diagnostic imaging and therapy. The first ultrasound contrast agents (UCAs) were suspensions of microbubbles created by manual agitation. Although these early microbubbles were relatively large and unstable, their potential use as a tool for enhancing a diagnostic ultrasound (DUS) image was first observed by Claude Joyner and reported in the seminal article of Gramiak and Shah in 1968 (2). Subsequent efforts to stabilize UCAs and achieve unhindered transpulmonary passage were initially met with skepticism (3). Nonetheless, continued research efforts resulted in the development of first-generation commercial UCAs, including Levovist and Albunex.

Early research and development, in the 1960s to 1980s, focused on validation of the UCAs as true intravascular, nondiffusible indicators, providing a firm basis for diagnostic applications. Numerous clinician/scientists contributed to the pioneering effort (4).

In time, the second-generation UCAs offered improved clinical diagnostic utility, given their increased reliability, safety, and diagnostic efficacy (5,6). These second-generation UCAs, described as acoustically active microspheres, were characterized by stabilized shells encasing high molecular weight, low-solubility gases. They are now routinely used for diagnostic imaging in a variety of clinical settings. Currently, third-generation UCAs are in pre-clinical testing as targeted molecular imaging agents (7). Fourth-generation agents are also in development for therapeutic use as platform technologies for targeted delivery of nucleic acids (8–14).

Currently, the clinical uses of second-generation UCAs are expanding and include cardiovascular and whole body imaging of organ anatomy and microvascular perfusion. Newer diagnostic indications include pediatric urology (15), as well as imaging of carotid artery vasa vasorum (16). As experience with second-generation UCAs has matured, numerous international professional societies have endorsed their use and provided guidelines for diagnostic applications.

As diagnostic CEUS expands, therapeutic uses are now also in development. Investigators have recently begun using second-generation UCAs and sonoporation to facilitate the site-specific delivery, without viral mediation, of nucleic acids for treatment of monogenic diseases (11,14) and to treat patients with pancreatic adenocarcinoma (17). Sonoporation induces localized, transient "pores" within thrombi or endothelial cell membranes as intravascularly circulating UCAs are exposed to targeted ultrasound energy. At a microscopic level, the UCAs undergo compression and rarefaction cycles

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that result in stable vibrational effects, inertial cavitation processes, or a combination thereof, depending on the level of locally applied acoustic energy. This sonoporation phenomenon appears to provide a potential platform for more efficient, targeted delivery of a variety of therapeutic compounds.

In addition, the report by Mathias et al. (1) describes the use of second-generation UCAs to lyse intravascular thrombi. Prior in vitro, pre-clinical, and clinical studies demonstrated that externally applied ultrasound energy induces the dissolution of intravascular thrombi (18,19). Several subsequent studies showed that the addition of UCAs to ultrasound thrombolysis therapy may result in more efficient thrombosis lysis (20,21).

The study by Mathias et al. (1) uniquely uses CEUS as both a diagnostic and therapeutic aide. Their diagnostic application used CEUS to evaluate LV myocardial microvascular perfusion during STEMI, on the basis of studies by Ito et al. (22) and Kenner et al. (23), who used intracoronary CEUS to evaluate microvascular reflow more than 2 decades ago. However, their therapeutic application is unprecedented and has the potential to represent a substantial advance in STEMI therapy. Overall, the study represents a successful outgrowth of in vitro and pre-clinical work translated into the clinical domain.

The primary goals of the study were to assess safety and efficacy of using ultrasound therapy and UCAs in patients with a STEMI. The secondary goals were to assess acute patency rates of epicardial arteries, preservation of microvascular perfusion, and LV function at 30 days post-treatment. Importantly, no fibrinolytic therapy was used for the treatment or the control groups.

The study included patients who presented for the first time with a STEMI and were subsequently randomized to DUS. Of the 100 patients that qualified for inclusion, 30 were selected to be in the treatment group due to personnel logistics of performing the treatment protocol. These 30 patients were subdivided into a high acoustic energy DUS group (n = 20) and a low acoustic energy DUS group (n = 10). The other 70 patients served as the controls. All patients received contemporaneous treatment including aspirin, clopdiogrel, heparin, and coronary arteriography and percutaneous coronary intervention. A blinded reader reviewed all diagnostic testing including coronary arteriography and the echocardiographic determinants: wall motion, myocardial perfusion, and LV ejection fraction for the acute treatment and 30-day follow-up time points.

The treatment group exposed to high acoustic energy exhibited an epicardial coronary artery patency rate of 60% (n = 20), compared with 20% in the low acoustic energy group (n = 10) and 23% in the control group (n = 70). At 30 days post-therapy, there was improvement in both microvascular perfusion and LV ejection fraction in the high acoustic energy treatment group. With regard to safety, the authors observed no clinically relevant hemodynamic changes or adverse/allergic reactions and the treatment did not interfere with the door to dilation time.

The authors successfully achieved their goals and introduced a potentially novel method for reducing time to microvascular reperfusion during a STEMI. Significantly, the protocol used did not delay or disrupt the standard clinical therapy protocols.

There were notable limitations of this study, including its small size and the use of a single clinical center; thus, larger, multicenter clinical trials will be required to validate the present findings. However, given the novel, pilot nature of the study, this is to be expected. Further, treated patients with Thrombolysis In Myocardial Infarction flow grades 2 and 3 were combined even though these anatomic markers serve as independent predictors of clinical outcomes (24). Other limitations include the absence of a control cohort (30-day follow-up group); this was acknowledged by the authors. However, using CEUS to monitor both microvascular perfusion and TIMI flow grades may prove to be a powerful predictor of ventricular function (25,26).

Despite the study limitations, the authors are to be commended for their unique approach to a common and potentially life-threatening problem—salvaging myocardial tissue during an acute infarction. Only time will tell whether this approach proves to be reproducible and generalizable, but the initial results are certainly promising.

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