MEETING REPORT

The 34th Annual Advances in Contrast Ultrasound International Bubble Conference, Chicago 2019: synopsis and take-home messages

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Abstract

The 34th annual Advances in Contrast Ultrasound (ACU) International Bubble Conference convened in Chicago, IL, USA, on September 5–6, 2019 to feature new directions of research, preclinical and first-in-man clinical trials, and novel clinical applications highlighting the diversity and utility of contrast enhanced ultrasound (CEUS). An expert group comprising clinicians, engineers, basic scientists, government officials, attorneys, and industry partners convened to collaborate on cutting-edge ultrasound enhancement technology. Utilizing this information, the International Contrast Ultrasound Society (ICUS) continues to have cause to advocate for the safe and appropriate use of CEUS with expanding indications and applications.

Key Words

- contrast echocardiography
- image quality
- preclinical
- ultrasonography

Contrast-enhanced ultrasound in clinical trials

The conference opened with world-renowned panelists presenting updates on current clinical trials that investigate the important uses of CEUS, including contrast enhancement and sonoporation via acoustic cavitation. Novel applications of CEUS included motion-resistant (MORE) microvascular mapping. The MORE technique, presented by Dr Alfred Yu, eliminates excess motion, thus allowing improved visualization of the microvasculature (Fig. 1). It integrates three key principles, plane wave imaging, pixel-based motion correction, and accumulative bubble localization to accentuate the microvasculature, utilizing the choroidal blood flow as a developmental model.

Dr Misun Hwang from the Children's Hospital of Philadelphia demonstrated the utility of CEUS in critically ill neonates. CEUS is a superior imaging modality in this patient population, Dr Hwang contended, due to the lack of ionizing radiation, performance without sedation, portability in the critical care setting, and excellent reproducibility. She presented her work on evaluating hypoxic ischemic brain injury, where perfusion using CEUS is more sensitive than conventional MRI in predicting outcomes. She showed that CEUS is more sensitive in tracking microvascular flow dynamics than MRI due to better resolution on a pixel by pixel basis. Dr Hwang additionally exhibited

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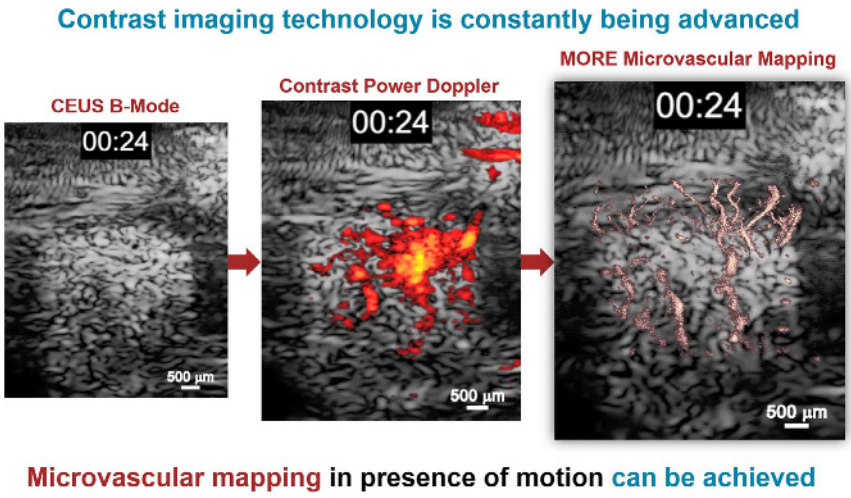

Figure 1
Motion-resistant (MORE) microvascular mapping technique used to eliminate excess motion, thus allowing improved visualization of the microvasculature. Presented by Dr Alfred Yu, University of Waterloo, Ontario, Canada.

that the role of CEUS in the early detection of ischemia extends beyond the brain and to the gut. Early studies presented at the ICUS meeting showed that CEUS was potentially superior in flow assessment to color Doppler in the detection of necrotizing enterocolitis in neonates.

Another use of CEUS in an even more vulnerable population was shown by Dr Dirk Clevert, who presented on the use of CEUS in assessing hepatic lesions in pregnant women. Conventional imaging with CT and MRI are limited by concerns about safety to the mother and developing fetus. Due to its excellent safety profile and inability to cross the placenta into the fetal circulation, CEUS is a useful imaging modality for the pregnant woman. Knowledge of CEUS applications continue to evolve through such studies and through regular workshops for training and education, in the pediatric population as detailed by Dr Kassa Darge from Children's Hospital of Philadelphia.

Gene and drug therapy

Imaging is only the beginning. Research presented at the ACU meeting highlighted the use of ultrasound-enhancing agents as a robust platform for targeted drug and gene delivery. Microbubbles loaded with therapeutic agents can be targeted and delivered to specific locations in the presence of ultrasound waves. Dr Kullervo Hynynen demonstrated this concept, showing how CEUS aids in the delivery of glioma cancer drug therapy to brain tumors while minimizing damage to healthy surrounding tissues (Fig. 2). Dr Paul Grayburn presented on the use of ultrasound targeted microbubble destruction (UTMD) to target glucagon-like-peptide-1 (GLP-1) receptors, which exist in the atria but not ventricles, leading to myocyte regeneration in rodents. Still the importance of further research was emphasized, including optimization of microbubble formulation, fine-tuning ultrasound parameters, and importance of duration/timing of therapy

Figure 2
Use of contrast enhanced ultrasound (CEUS) in delivering brain cancer drug therapy to tumors while minimizing damage to healthy surrounding tissues. Presented by Dr Kullervo Hynynen, University of Toronto, Toronto, Canada.

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as an aid in the prevention of chemotherapy-induced cardiomyopathy. Additional uses of UTMD were shown by Dr Pinton Huang, where UTMD gene therapy with GLP-1 stimulated proliferation of functional pancreatic insulin-producing B cells resulting in improved fasting glucose levels in cynomolgus macaque with type 2 diabetes for 6 months.

The use of therapeutic ultrasound-targeted microbubble cavitation to deliver gene therapy was also described by Dr Liza Villanueva. Microbubble-targeted delivery of a microRNA inhibitor to the heart was shown to suppress cardiac hypertrophy and preserve cardiac function in a mouse model. The ultrasound technology increases the bioavailability of the administered gene therapy. Targeted drug and gene delivery remain a rich area of research, ripe for translation from bench to clinical practice.

Preclinical and clinical trials: novel applications

Dr Luciano Agati of La Sapienza University of Rome, Italy, described the use of CEUS to assess intraventricular flow patterns before and after MitraClip implantation. Contrast-enhancing agents allowed investigation of the revised valve anatomy, a double or multi-orifice configuration after MitraClip implantation, demonstrating altered intraventricular flow patterns in diastole. Findings showed that MitraClip produces non-physiologic changes that may have a greater impact in more compromised ventricles. This provides pathophysiologic and mechanistic insights into understanding the recent discrepant clinical trial results (CoAPT and MitraFR) and an explanation why patients with severe left ventricular dilation and dysfunction appear to experience diminished benefits from the MitraClip procedure, re-emphasizing that adequate patient selection is mandatory before intervention.

The utility of CEUS in clinical cardiology was underscored by the work of Dr Wilson Mathias Jr. He reviewed his randomized clinical trial work on sonothrombolysis, using high mechanical index pulses from a diagnostic ultrasound transducer during an IV microbubble infusion, to restore epicardial and microvascular flow in patients with acute ST-elevation myocardial infarction (Fig. 3). Impressively, at 6-month follow-up, patients receiving sonothrombolysis emergently before percutaneous coronary intervention (PCI) were more likely to have decreased infarct size, greater improvement in left ventricular ejection fraction, and decreased rate of implantable cardioverter defibrillator placements compared to those who had not received sonothrombolysis. Given these positive results, this exciting work will continue into the next phase as a larger multicenter, multinational trial in the High Ultrasound mechanical index and microbuBBLEs to reduce acute myocardial infarction burden I (HUBBLE-I) study.

Advanced clinical applications

The emerging role of contrast in the assessment of neovascularization in carotid arterial plaques for cardiovascular risk stratification was presented by Dr Amer Johri. Use of contrast is important in identifying the activity (neovascularization) and anatomical quantity of plaque (Fig. 4). The study found that CEUS of carotid artery plaque may be a valuable predictor in cardiovascular risk stratification, as presence of increased neovascularization was sensitive and specific for association with significant coronary artery disease, and a lower neovascularization score was associated with lower short-term (30-day) adverse cardiovascular outcomes after coronary

Figure 3
The use of sonothrombolysis using high mechanical index and pulses from a diagnostic ultrasound transducer during an IV microbubble infusion to restore epicardial and microvascular flow. Presented by Dr Wilson Mathias Jr, University of São Paulo, Medical School, São Paulo, Brazil.

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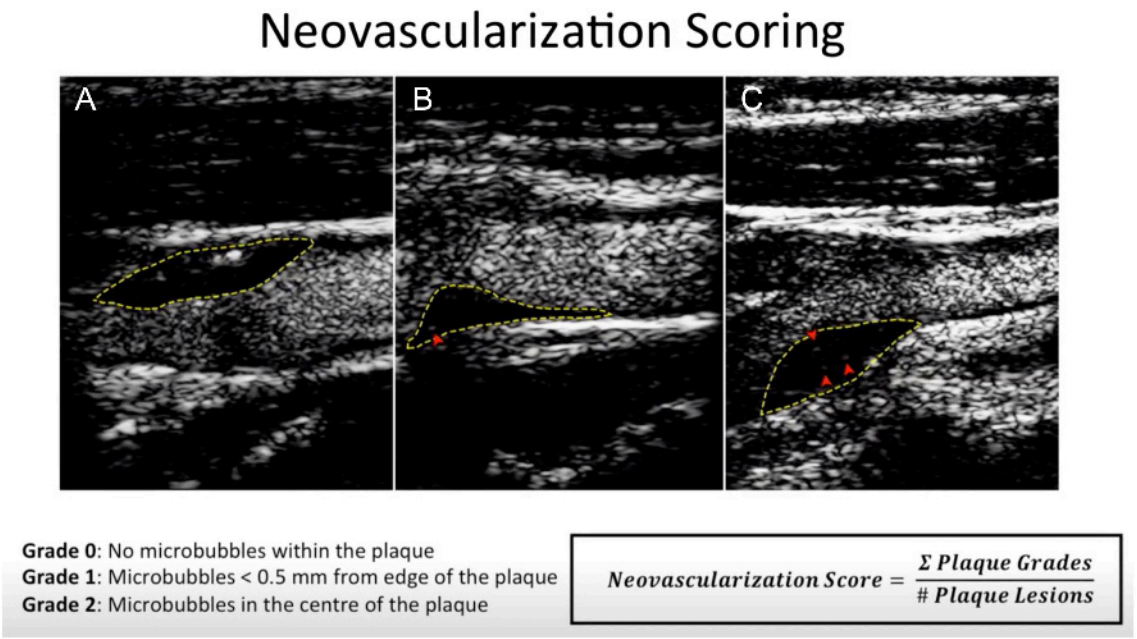

Figure 4
The use of contrast in assessment of neovascularization in carotid arterial plaque activity (neovascularization) and anatomical quantity. Presented by Dr Amer Johri, Queen's University, Kingston, Ontario, Canada.

angiography. Application of CEUS to characterize carotid plaque morphology in stable patients with chronic peripheral arterial disease and unstable patients with acute myocardial infarctions is being studied by Dr Henrik Sillesen.

Novel acoustic imaging

Further developments in microbubble technology to optimize sonothrombolysis were also discussed during the conference. Dr Evan Unger presented on the use of sonothrombolysis using nanodroplets in place of microbubbles to disrupt thrombi. Nanodroplets are smaller than microbubbles and may be able to better detect, penetrate, and disrupt fibrin clots (Fig. 5) than conventional microbubbles. Ongoing research is underway to improve the stability of nanodroplet formulation, determine optimal ultrasonic frequency, and pulse duration for coronary thrombus disruption and understand the relative microvascular and epicardial effects on clinical outcomes.

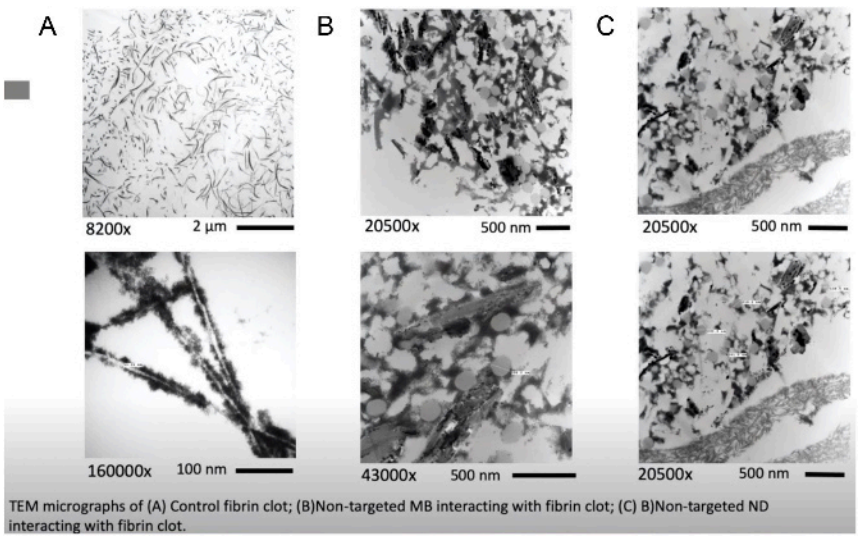

Figure 5
The use of sonothrombolysis using nanodroplets (ND) in place of microbubbles to disrupt thrombi. ND are smaller than microbubbles, which are postulated to better detect, penetrate, and disrupt fibrin clots. Presented by Dr Evan Unger, University of Arizona, Tuscon, Arizona, USA.

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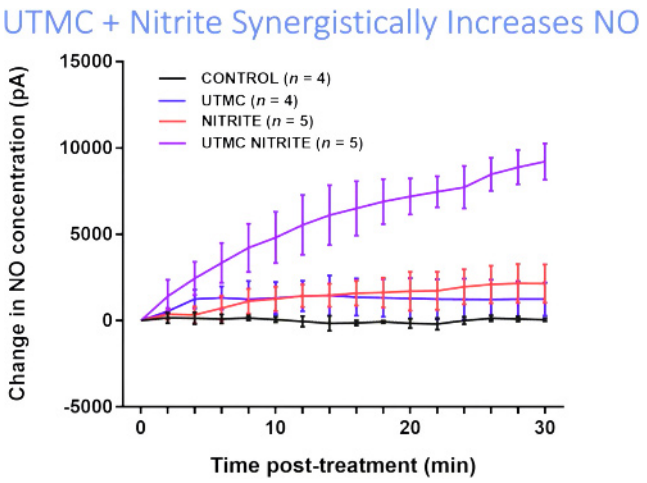

Figure 6
Intravenous microbubble-mediated ultrasound therapy, or ultrasound-targeted microbubble cavitation (UTMC), with sodium nitrite synergistically enhanced exogenous nitric oxide (NO) production and microvascular reperfusion in a healthy rat hindlimb model. Presented by Dr John Pacella, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

CEUS cellular physiology

The mechanism of therapeutic effects of CEUS remains a topic of ongoing investigation. The combination of microbubbles with ultrasound technology cause cellular effects, including membrane poration, cell-cell contact opening, and cytoskeleton changes to facilitate drug release and uptake. Dr Klazina Kooiman presented on the relationship between sonoporation and the opening of intracellular junctions for microbubble-mediated vascular drug delivery.

The use of sonoreperfusion for the treatment of microvascular obstruction after PCI was exhibited by Dr John Pacella. Intravenous. microbubble-mediated ultrasound therapy, or ultrasound-targeted microbubble cavitation (UTMC), with sodium nitrite synergistically enhanced exogenous nitric oxide (NO) production and microvascular reperfusion in a healthy rat hindlimb model (Fig. 6). NO bioavailability is important in mitigating both the occurrence and sequelae of microvascular occlusions post PCI in acute myocardial infarction. UTMC provides intravascular shear stress through microbubble oscillations, which activate pathways yielding greater NO production and bioavailability. Further studies are underway and needed for better understanding and development of CEUS technology and its physiologic impact on the NO pathway at a cellular level in this model.

Final remarks

In summary, the 34th Annual ACU Meeting objectives were more than satisfied: (1) recognition of CEUS as a safe, radiation-free economical diagnostic tool for cardiovascular and whole body imaging with positive impact on patient care, (2) understanding the use and interpretation of diverse clinical CEUS applications in accordance with established international professional guidelines, (3) awareness of clinical and preclinical CEUS trials for diagnostic applications, and (4) reviewing emerging investigational applications of CEUS for targeted delivery of gene and drug therapies. CEUS education, research, and applications continue to show robust growth and development. ICUS continues to engage with the clinicians, engineers, basic scientists, sonographers, nurses, government officials, attorneys, and industry and patient partners for advancement in ultrasound contrast technology and applications, and the annual ACU meetings provide an excellent resource for the broad spectrum of individuals and organizations involved in and/or interested in the field. Next year's meeting is on September 10–11, 2020 in Chicago, IL, USA; be sure to save the date on your calendar!

Declaration of interest
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