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REFERENCES

1. Pandis D, Anyanwu A, Adams DH. Mitral annular disjunction: a contrary view. J Am Soc Echocardiogr 2022;35:239.
2. Grewal J, Suri R, Mankad S, Tanaka A, Mahoney DW, Schaff HV, et al. Mitral annular dynamics in myxomatous valve disease: new insights with real-time 3-dimensional echocardiography. Circulation 2010;121:1423-31.
3. Dejgaard LA, Skjolsvik ET, Lie OH, Ribe M, Stokke MK, Hegbom F, et al. The mitral annulus disjunction arrhythmic syndrome. J Am Coll Cardiol 2018;72:1600-9.
4. Essayagh B, Sabbag A, Antoine C, Benfari G, Batista R, Yang LT, et al. The mitral annular disjunction of mitral valve prolapse: presentation and outcome. JACC Cardiovasc Imaging 2021;14:2073-87.
5. Essayagh B, Sabbag A, Antoine C, Benfari G, Yang LT, Maalouf J, et al. Presentation and outcome of arrhythmic mitral valve prolapse. J Am Coll Cardiol 2020;76:637-49.

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Ultrasound-Enhancing Agents and Associated Adverse Reactions: A Potential Connection to the COVID-19 Vaccines?

To the Editor:

On April 22, 2021, the federal Food and Drug Administration (FDA) notified health care professionals that ultrasound-enhancing agents (UEA) containing polyethylene glycol (PEG)—Definity (Lantheus Medical Imaging, N. Billerica, MA), Definity RT, and Lumason (Bracco Diagnostics, Monroe Township, NJ)—should not be administered to patients with known or suspected allergies to PEG due to concerns for presumed type I immediate hypersensitivity reactions. The FDA alert reported 11 anaphylactic reactions and two patient deaths after administration of UEA over a reported period of 10 years. These agents contain PEG as a component either in the vehicle or as an inactive ingredient alone (Lumason) or within the microbubble shell and lipid excipient (Definity, Definity RT).[1,2] Polyethylene glycols are commonly used in products including toothpaste, cosmetics, and shampoo and in certain laxatives and bowel preparations as thickeners, solvents, softeners, and moisture carriers.[1] Recently, rare allergic reactions have been reported after administration of the Pfizer and Moderna COVID-19 vaccines. These mRNA vaccines have "PEGylated" lipid nanoparticles for improved stability and delivery of mRNA into human cells.[3,4] We write to inform your readers of adverse reactions after administration of Lumason and Definity across three echocardiography laboratories within the University of Pennsylvania Health System (UPHS) and the Medical University of South Carolina (MUSC) from 2019 to 2021. From January 2019 to July 2021, 10,526 patients at UPHS (including the Hospital of the University of Pennsylvania and Lancaster General Hospital) received Lumason and 9,550 patients received Definity. During this time period, 10,132 patients at MUSC received Lumason. At UPHS, four adverse reactions to Definity occurred in the year 2019, while seven adverse reactions to Lumason occurred after January 2021. At MUSC, three adverse reactions after Lumason administration occurred after January 2021. Adverse reactions included shortness of breath, tongue and throat swelling, abdominal and back pain, hemodynamic instability, arrhythmias, and hypoxia. These adverse reactions were treated with antihistamines and/or steroids, along with supplemental oxygen, intravenous fluids, and/or epinephrine or other vasopressors when oxygenation and hemodynamics were impacted. One patient experienced a cardiac arrest due to pulseless electrical activity after Lumason administration and was resuscitated. The four adverse reactions to Definity were reported in 2019, prior to the initiation of the COVID-19 vaccine program, and occurred over a period of 4 months, with three reactions occurring within the same month. The COVID-19 vaccination program commenced in December of 2020 after emergency use authorization was granted for the Pfizer and Moderna vaccines.[4] The 10 adverse reactions to Lumason at UPHS and MUSC (0.13% of the total Lumason doses administered) were reported after January 1, 2021. Of the 10 patients with adverse reactions to Lumason, six patients were vaccinated (five patients with Moderna, one patient with the Pfizer vaccine) and one patient was unvaccinated, and in three patients vaccination status could not be ascertained. The patient who was resuscitated after cardiac arrest was unvaccinated. These adverse reactions were reported to the UEA manufacturers. We have initiated efforts at UPHS to standardize documentation and reporting of these adverse reactions.

We agree with the expert American Society of Echocardiography consensus statement (April 2021) that echocardiography laboratory personnel should be trained in the recognition and treatment of UEA-related hypersensitivity reactions.[1] We write to your readers to report our institutional observations of a recent increase in adverse reactions to UEAs notably prominent after January 2021, which coincided with the onset of the COVID-19 vaccination program. It is hypothesis generating but certainly not scientifically tested and confirmed that these observed adverse reactions may be potentially related to possible PEG sensitization after vaccination with the COVID-19 vaccines. We also fully acknowledge that the mechanism of these reported adverse reactions is unclear as to whether they were due to a type I hypersensitivity reaction to PEG or due to immune-mediated complement activation-related pseudoallergy.[1] Given our institutional observations, it would be prudent for echocardiography laboratories to remain vigilant for detection of increased UEA-related adverse reactions.

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REFERENCES

1. Lindner JR, Belcik T, Main ML, Montanaro A, Mulvagh SL, Olson J, et al. Expert consensus statement from the American Society of Echocardiography on hypersensitivity reactions to ultrasound enhancing agents in patients with allergy to polyethylene glycol. J Am Soc Echocardiogr 2021; 34:707-8.
2. International Contrast Ultrasound Society. Medical society urges use of ultrasound contrast agents and supports safety record. Available at: icus-society.org/wp-content/uploads/2021/04/ICUS-media-release-contra-indication-4-23-21118089224_3.pdf. Accessed April 23, 2021.
3. Kuehn BM. Rare PEG allergy triggered postvaccination anaphylaxis. JAMA 2021;325:1931.
4. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVD-19 vaccines currently approved or authorized in the United States. Available at: www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Accessed August 31, 2021.

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Findings from Implementation of a Remote Collaboration Solution to Perform Echocardiograms during the COVID-19 Pandemic

The American Society of Echocardiography's recommendations for providing echocardiographic services during the COVID-19 pandemic emphasize performing limited problem-focused examinations with minimal possible scan time.[1] To help operationalize these recommendations, our laboratory employed a remote communication software (Philips Collaboration Live [CL] Feature on EPIQ Ultrasound Machines; Philips Healthcare, Bothell, WA) that allows the physician to connect to the ultrasound machine and provide real-time guidance. We hypothesized that using CL technology during the performance of limited echocardiograms would reduce examination time and image acquisition number without compromising diagnostic quality. To test this hypothesis, we engaged in a quality improvement project prospectively performing 101 limited echocardiograms (CPT 93308) with CL during the COVID-19 pandemic (January through March 2021). This group was compared with limited echocardiograms performed prior to the COVID-19 pandemic without the use of CL technology ($n = 101$, February 2019).

Results are shown in Table 1. All studies in both cohorts were of diagnostic quality. Image acquisition times and numbers analyzed using a two-sample t test and Wilcoxon rank-sum test showed a significant reduction in examination time ($P < .0001$) and image acquisition number ($P \leq .0001$) with CL. These differences remained statistically significant after adjusting for study indication.

Table 1 Clinical characteristics, image acquisition times, and image numbers for CL and noncollaboration live (No-CL) cohorts

	No-CL cohort ($n = 101$)	CL cohort ($n = 101$)	P value
Indication, *n* (%):			<.0001
Evaluate ejection fraction	59 (58.4)	68 (67.3)	
Evaluate for effusion	31 (30.7)	12 (11.9)	
Hypotension	10 (9.9)	5 (5.0)	
Other	1 (1.0)	16 (15.8)	
Body mass index, *n* (%)*:			.9988
≤25	27 (26.7)	26 (25.7)	
>25 to ≤30	28 (27.7)	27 (26.7)	
>30	44 (43.6)	43 (42.6)	
Unknown	2 (2.0)	5 (5.0)	
Duration, minutes:			<.0001
Mean (SD)	12.5 (±5.7)	7.1 (±4.4)	
Median (min-max)	11 (3-28)	6 (2-21)	
No. of images:			.0001
Mean (SD)	37.2 (±12.8)	30.1 (±12.7)	
Median (min-max)	37 (12-78)	27 (10-83)	

*Unknown category not included in testing for statistical difference between groups.

In the CL patient cohort, 43 (42.6%) individuals either had or were suspected of having COVID-19. The average examination time for these patients was 7.4 minutes. This value is important as SARS-CoV-2 transmission risk increases with increasing exposure time.[2]

While CL technology resulted in decreased image acquisition time and number, there were obstacles to the implementation of the technology. Performing examinations required coordination between the physician and sonographer and thus could not be performed on an unscheduled basis. While not formally assessed, it is possible that CL-guided echocardiograms were more physician time intensive than traditional limited echocardiograms since the physician watched the image acquisition in real time. Seventeen percent of the studies performed with CL experienced technological issues such as audio difficulties or lost connection; however, none of these issues limited the ability to complete the examination. Finally, because we used a prepandemic control group, we cannot exclude the possibility that examination time and image acquisition number were affected by pandemic-specific environmental factors, not just CL technology. This is partially refuted by the finding that in the CL cohort there were no statistically significant differences in image acquisition time or number between patients who had or were suspected of having COVID-19 and those who did not ($P = .5708$ and $P = .9244$, respectively).

Our study is the first to report on using a remote communication solution to decrease examination time and image acquisition number during the COVID-19 pandemic. The real-time physician guidance