Hypersensitivity Cross-Reactivity for Ultrasound-Enhancing Agents and COVID-19 Vaccines

Ultrasound-enhancing agents (UEAs) are an indispensable component of state-of-the-art echocardiography. They also have an excellent safety profile, with serious adverse events (SAEs) occurring in approximately one in 10,000 administrations,[1] the most common of which are hypersensitivity reactions. Based on experience with nanotherapeutics composed of liposomes or lipid emulsions, serious hypersensitivity and other nonserious adverse events (AEs) from lipid-stabilized UEAs have been attributed to complement activation-related pseudoanaphylaxis (CARPA).[2] Ordinarily, blood complement proteins of the immune system interact with microbubble shells and mediate the usually uneventful clearance of UEAs from the circulation.[3,4] CARPA or nonanaphylactic pain responses occur from an exaggerated complement anaphylatoxin response. In early 2021, the MedWatch arm of the United States Food and Drug Administration issued a report on a small number of presumed type I hypersensitivity reactions to UEAs in patients with known allergy to polyethyleneglycol (PEG), thereby suggesting a second mechanism involving adaptive immunity. For some lipid-stabilized UEAs, PEG is a component of the excipient alone (Lumason or Sonovue, Bracco Diagnostics) or is incorporated in the microbubble shell (Definity, Lantheus Medical Imaging). Polyethyleneglycol is also component of many drugs, laxatives, and cosmetics. It is also in the cationic lipid excipient used to stabilize and augment transduction of mRNA COVID-19 vaccines (Pfizer-BioNTech, Moderna). Recent expert consensus statements have outlined new safety recommendations for PEG-containing UEAs and highlighted that the MedWatch report did not change information on the incidence of SAEs.[5] Yet anecdotal reports have raised concern that hypersensitivity reactions to UEAs may have increased after the introduction of COVID-19 vaccines.[6] While it is possible that exposure to PEGylated lipid vaccines could increase type I hypersensitivity to UEAs or CARPA,[7] scientific evidence is lacking and was the aim of this study.

According to power calculations, a prospective study powered at 0.90 to detect a five-fold increase in SAEs to UEAs ($\alpha = 0.05$) based on vaccination status would require a study size of 80,000 subjects. Because of the urgency of the question, we instead examined cross-reactivity through a retrospective survey to assess for mRNA vaccine hypersensitivity in patients exposed to PEG-containing lipid-stabilized UEA within the previous 7 years who either did or did not have a documented reaction to UEAs. A programmed search script of the electronic health record using Cogito Slicer-Dicer (EPIC, Madison, WI) identified subjects with documented AE to Definity or Lumason. Age- and sex-matched control subjects who received UEAs without reaction were identified and recruited in an approximately 2:1 ratio to those with reactions. A scripted phone interview was conducted, and only those with completed COVID-19 vaccination were included. Adverse events were characterized according to symptoms, severity, and need for therapy with SAEs defined using Food and Drug Administration criteria. Vaccine-related AEs qualified only if they occurred within 6 hours.

The search identified 204 subjects with documented AE related to lipid-based UEAs, of whom 62 were alive, could be reached, had completed COVID-19 vaccination, and agreed to participate. Clinical and demographic information is shown in Table 1. The most common AEs to UEAs were nociceptive, followed by dermatologic, dyspnea/throat tightness/lip or tongue swelling, and chest pain/tachycardia. Only six (10%) reactions were classified as SAEs. Vaccine-related AEs occurred in 15 (24%) subjects with a history of UEA reactions and in five (4%) of the control subjects ($n = 120$; χ^2, $P = .0001$, odds ratio = 6.1 [95% CI, 2.4-16.3]). In the former group, vaccine-related reactions were reported in 21%, 17%, and 60% for subjects receiving the Pfizer-BioNTech ($n = 33$), Moderna ($n = 23$), or Johnston and Johnston ($n = 5$) vaccine, respectively. The most common vaccine-related AEs were dyspnea without lip or tongue edema, rash, and chest pain/tachycardia. Flank pain occurred in only one subject. All vaccine-related reactions were nonserious, self-limited, and did not require therapy. In subjects with AEs to both UEAs and vaccines, reaction manifestations to the two were similar in seven subjects, with only rash being perfectly matched when encountered ($n = 3$). In those subjects with UEA and vaccine reactions, 13 had received Definity and two had received Lumason, which is similar to the proportion receiving each agent in general. The median interval between UEA reaction and first vaccination dose was 245 weeks (95% CI, 173-284) and was not related to likelihood for vaccine reaction (Spearman rho = .62).

The aim of this study was to examine whether a link exists between hypersensitivity reactions to lipid-based UEAs that contain PEG and COVID-19 vaccines, in particular the mRNA class of vaccines that have compositional similarity to lipid-stabilized UEAs. The mRNA in these vaccines is complexed with PEGylated cationic lipids, which reduce endonuclease digestion, promote cellular uptake by antigen-presenting cells, and increase translation. The UEAs and the vaccines studied differ in their specific amphipathic lipid moieties, net charge, molar amount of PEG, and whether PEG is incorporated into the lipid membrane. Yet all of them have the potential to stimulate complement activation and CARPA through "non-self" recognition and to sensitize for type I hypersensitivity to PEG through adaptive immunity.[2,7]

This study surveyed for AEs that occurred early after COVID-19 vaccination in subjects who previously received lipid-stabilized UEAs. A greater proportion of vaccine-related AEs were experienced in subjects who also had AEs to UEAs, indicating a modest pattern of cross-reactivity. An important caveat is that we have not investigated the opposite order of exposure, namely, whether those with unexpected AEs to COVID-19 vaccine reactions are more susceptible to UEA reactions. One limitation of our analysis is the inability to confidently differentiate CARPA from type I hypersensitivity reactions. We have also not established a mechanism of sensitization. The finding that vaccine reactions were most common in the few subjects receiving the Johnson and Johnson vaccine, which contains neither lipids nor PEG, implies that mechanisms apart from adaptive immunity can occur. As anticipated, most of the AEs with UEA administration were classified as nonsevere and were nociceptive. For vaccination-related AEs, all were classified as nonsevere. Accordingly, our data do not support the idea that patients with reactions to either lipid-stabilized UEAs or mRNA vaccines should be disqualified from receiving

The study was approved by the Institutional Review Board of Oregon Health and Science University.

Conflicts of Interest: None.

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Table 1 Demographics, clinical characteristics, and AE data

	+AEs to lipid UEA (*n* = 62)	Control subjects (*n* = 120)
Age, years	65 ± 14	65 ± 12
Gender, male/female	32/30	68/52
Cancer history	8 (13)	11 (9)
Chronic kidney disease	2 (3)	8 (7)
Chronic liver disease	6 (10)	4 (3)
Rheumatologic disease	2 (3)	5 (4)
Autoimmune disease	0 (0)	3 (3)
Chronic steroid use	5 (8)	14 (12)
Biologic immunosuppressive use	0 (0)	2 (2)
No. of drug or substance allergies, median (95% CI)	2 (1, 2)	2 (1, 2)
Echocardiography type:		
Resting transthoracic	34 (55)	80 (67)
Stress echocardiography	26 (42)	36 (30)
Research (MCE perfusion)	2 (3)	4 (3)
UEA:		
Definity	58 (94)	95 (79)
Lumason	4 (6)	20 (17)
Both	0 (0)	5 (4)
Vaccine:		
Pfizer-BioNTech	33 (53)	61 (51)
Moderna	23 (37)	49 (41)
Johnston and Johnston	5 (8)	9 (8)
Astra Zeneca	0 (0)	1 (1)
Unknown	1 (2)	0 (0)
AEs with UEAs:		
Total	62 (100)	—
SAE	23 (37)	—
Rash	11 (18)	—
Nociceptive (nonchest pain)	43 (69)	—
Dyspnea/throat tightness/lip or tongue edema	10 (16)	—
Chest pain/tachycardia	7 (11)	—
Fever/dizziness/other	3 (5)	—
AEs with vaccine:		
Total	15 (24)	6 (5)*
Serious AE	0 (0)	0 (0)
Rash	3 (5)	0 (0)
Nociceptive (nonchest pain)	2 (3)	4 (3)
Dyspnea/throat tightness/lip or tongue edema	9 (16)	0 (0)*
Chest pain/tachycardia	3 (5)	1 (1)
Fever/dizziness/other	1 (2)	3 (3)

MCE, myocardial contrast echocardiography.
Data are reported as *n* (%) unless otherwise indicated.
*$P < .05$ by vs + AE cohort.

them. Instead, our findings simply raise awareness that cross-reactivity is possible. While our data indicate that most cross-reactions that occur are expected to be nonsevere, closer monitoring after vaccine or UEA administration is probably warranted in those who have had a prior AE to one or the other. Larger trials will be needed to study SAEs that are infrequent for both classes of agents and to test whether mRNA vaccine exposure increases the likelihood of UEA reactions.

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Comparison of Handheld Ultrasound–Assisted Physical Examination to Physical Examination Alone in Detecting Isolated Severe Tricuspid Regurgitation

Tricuspid regurgitation is a relatively common valve disease that appears to have significant prognostic implications in cohort studies. It represents an area of active research examining the feasibility, indications, and prognostic significance of percutaneous interventions. We aimed at exploring the diagnostic characteristics of handheld ultrasound–assisted physical examination versus physical examination alone in diagnosing isolated severe tricuspid regurgitation.[1]

Conflicts of Interest: None.

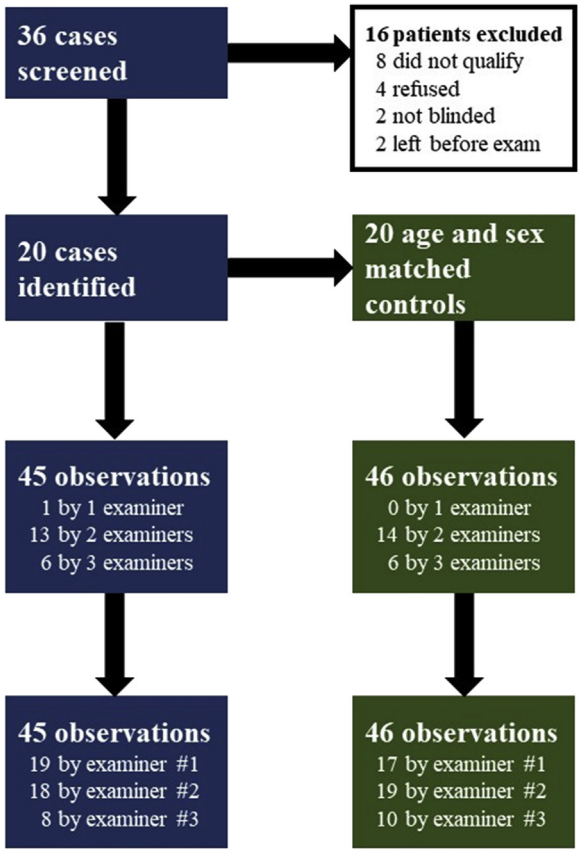

Figure 1 Study flow diagram including case and control selection.

We conducted a prospective, controlled, blinded observational study comparing physical examination alone with ultrasound-assisted physical examination using a handheld device in diagnosing isolated severe tricuspid regurgitation. All study patients (cases and controls) were identified in the echocardiography laboratory (Figure 1). Inclusion criteria for cases were the following: (1) severe isolated tricuspid regurgitation based on the standard echocardiographic criteria,[2] (2) age 18 years or older, and (3) ability to provide informed consent. Controls were matched to cases based on age (±1 year) and gender, and they were free of any significant valve disease.

Three independent examiners performed examinations on study patients. The examiners were cardiology fellows with an equivalent level of training: they had >1 year training in clinical cardiology including ≥4 weeks of formal training in echocardiography. The examiners were blinded to the clinical history and echocardiographic findings of study patients. After informed consent was obtained by the research personnel, physical examination was conducted by the examiner, and the presence or absence of severe tricuspid regurgitation was recorded by the research personnel at bedside using a standardized questionnaire. Subsequently, the examiner used a handheld ultrasound device to confirm or refute his or her initial finding.[3] Ultrasound examination was performed using the VScan, a pocket-sized ultrasound device (General Electric, Wauwatosa, WI). The device