Published in final edited form as:

J Ultrasound Med. 2013 September ; 32(9): 1535–1537. doi:10.7863/ultra.32.9.1535.

Evaluation of the Temporal Stability of Definity Using Double Passive Cavitation Detection

Marianne Gauthier, PhD,

Bioacoustics Research Laboratory, University of Illinois at Urbana-Champaign, Urbana, Illinois USA

Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois USA

Daniel A. King, PhD, and

Bioacoustics Research Laboratory, University of Illinois at Urbana-Champaign, Urbana, Illinois USA

Department of Mechanical Science and Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois USA

William D. O'Brien Jr, PhD

Bioacoustics Research Laboratory, University of Illinois at Urbana-Champaign, Urbana, Illinois USA

Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois USA

To the best of our knowledge, no studies have been reported that evaluated the stability of ultrasound contrast agents (UCAs) over time once the vial was opened. Indeed, air injected into the vial via a syringe might interact with the UCAs and degrade them, potentially modifying their physical characteristics. In a clinical context, for example, for diagnosis, therapy, or bioeffect studies, the stability of UCAs once the vial is opened might become critical using either infusion or bolus injection. In particular, for bioeffects studies when the same vial yields UCAs over time, the UCAs' physical characteristics must remain stable during the experimental period to avoid misinterpretation of experimental results.

Analysis of the temporal stability of Definity (Lantheus Medical Imaging, Inc, North Billerica, MA), a second-generation UCA made of microbubbles filled with octafluoropropane (C_3F_8) gas and stabilized by a lipid shell,¹ was performed using double passive cavitation detection, which has been fully described previously.² This method is based on determining the presence or absence of a postexcitation signal occurring a few microseconds after the principle excitation of the UCA; it is assumed that postexcitation signals are emitted by gas bubbles formed after the collapse of the UCA. Double passive cavitation detection experiments give access to the postexcitation curve from which the 50% collapse threshold is extracted and further analyzed²; the temporal stability of the UCA's physical characteristics was assessed by evaluating the 50% collapse threshold over a 2-week period. In addition, to analyze the initial size of the UCA samples, microscope images were acquired (BX51; Olympus Optical Co, Ltd, Tokyo, Japan) and processed using a circle detection routine based on the Hough transform.

This study was performed using 1 vial of Definity (lot 4576U). The vial was reactivated before each set of experiments. Six time points (from day 0 to day 15) were evaluated over a 2-week period. For each time point, 3 parameters were analyzed: the size distribution of the UCA population, the bubble diameter of 100 randomly selected UCAs, and the 50% collapse thresholds based on an average of 1085 double passive cavitation detection response estimates. The 95% confidence intervals (CIs) were estimated for the last 2 parameters.

Figure 1 shows the 6 UCA size distributions. The UCA sizes were compared using a χ^2 test with the Yates correction; no significant difference was detected between the 6 populations ($P = .19$). Figure 2 shows that there was no significant difference between the 6 time points for both the bubble size and the 50% collapse threshold, as all the 95% CIs are overlapping.

The results suggest that the physical characteristics of Definity are stable at least over 2 weeks and following 6 reactivations.

Acknowledgments

We acknowledge the valuable discussions with Douglas G. Simpson, PhD (Department of Statistics, University of Illinois at Urbana-Champaign), on logistic curve fitting. This work was supported by National Institutes of Health grant R37EB002641.

Abbreviations

CI	confidence interval
UCA	ultrasound contrast agent

References

1. Lantheus Medical Imaging, Inc. [Accessed November 19, 2012] Definity. Definity Imaging website. <http://www.definityimaging.com>
2. King DA, Malloy MJ, Roberts AC, Haak A, Yoder CC, O'Brien WD Jr. Determination of postexcitation thresholds for single ultrasound contrast agent microbubbles using double passive cavitation detection. *J Acoust Soc Am*. 2010; 127:3449–3455. [PubMed: 20550244]

Figure 1.
Size distributions of the UCAs for the 6 groups over the 2-week period. D indicates day.

A **B**

Figure 2. Mean UCA diameters (**A**) and 50% collapse thresholds (**B**) with their 95% CIs. The gray rectangles represent the overlapping of the 95% CIs between the 6 groups. D indicates day.