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Nathan Eller

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Ideal Practices for Optimizing Results of Agitated Saline Studies Within Echocardiography: A
Literature Review

Nathan Eller

Seattle University

Abstract

Objective. This literature review will summarize evidence of improved accuracy in patients suspected of right to left shunts using unconventional practices in agitated saline (bubble) studies compared to traditional methods.

Methods and Materials. PubMed, CINAHL, and ClinicalKey were utilized to find studies since 2012 using the key words bubble studies, patent foramen ovale, right to left shunts, agitated saline study, and atrial septal defect.

Results. Using six sources, this study will provide background about uses of bubble studies. Using four more, there will be discussion about best practices in bubble studies including: 1) agitating the saline twenty times compared to the traditional ten agitations 2) using 6 mL of sodium bicarbonate and 4 mL of vitamin B6 and if not possible 3) using 8 mL of water, 1 mL of air, and 1 mL of blood 4) a combination of transcranial, transthoracic, and transesophageal echocardiography produces the most thorough analysis of right to left shunts.

Conclusion. Based on review and results, studies suggest that there are many uncommon, yet ideal methods for performing a maximally diagnostic agitated saline study.

Keywords

Echocardiography, Valsalva Maneuver, Patent Foramen Ovale, Stroke, Microbubble

Introduction

Agitated saline studies are commonly used in both transthoracic and transesophageal echocardiography to find right to left shunts within the interatrial septum in the form of patent foramen ovals or atrial septal defects. Visually, one can tell that there is a right to left shunt if

bubbles cross over from the right atrium into the left atrium. This is indicative of a positive bubble study. On the contrary, if one does not see any bubbles appear in the left heart following injection, then that is a negative bubble study. In 2012, a study concluded that there is high prevalence of right to left shunting in patients with obstructive sleep apnea¹. In said study, it says patent foramen ovals and atrial septal defects are known to cause neurological and respiratory complications, such as transient ischemic attacks, stroke, paradoxical peripheral or coronary embolization. Given recent findings, like those proving the value of bubble studies in patients with obstructive sleep apnea, many push for more widespread use due to the ease and effectiveness in diagnosing right to left shunts. The push for a broadened scope of bubble study use can be seen through a paper written in 2023 urging the benefits of having bubble studies performed on patients with hypoxemic respiratory failure². With the expanded use of bubble studies, it is important to recognize the best practices and ideal indications for their use.

Materials and Methods

To yield the research necessary for this literature review, PubMed, CINAHL, and Clinical Key have been consulted. The keywords used to find the sources are agitated saline study, bubble study, patent foramen ovale, right to left shunt, and atrial septal defect. From the sources that matched these key words, only sources published since 2012 are being used to keep research as up to date and relevant as possible. Out of the hundreds of works published, those that best exemplify the best practices of an agitated saline study within echocardiography are the ones in

¹ Guchlerner M, Kardos P, Liss-Koch E, et al. PFO and Right-to-Left Shunting in Patients with Obstructive Sleep Apnea. *J Clin Sleep Med*. 2012;8(4):375-380. doi:10.5664/jcsm.2026

² Millington SJ, Mayo-Malasky H, Koenig S. Agitated Saline Contrast Injection in Patients with Severe Hypoxemia. *J Intensive Care Med*. 2023;38(5):479-486. doi:10.1177/08850666231159019

this literature review that will dictate the proper way to perform a bubble study. For the sources used to dictate results, the studies must be tested and proven in large sample populations. This is to prevent the use of research that may have flaws or any level of unreliability.

Results

Agitated saline studies are more common than they have ever been with their use spanning so many different indications. With this increase of bubble studies, it is essential to recognize that there are right and wrong ways to conduct the study. Many echocardiographers use an agitated air-saline mixture, but in 2020, Dr. Ali and his colleagues proved that using an agitated blood-saline mixture provides clearer images and more definitive studies. This result is especially evident when it comes to transthoracic echocardiograms where almost twice the number of “excellent-quality” studies were completed with agitated blood-saline³. Taken a step further, however, Dr. Zhao and colleagues examined how a mixture of eight mL saline, one mL air, and one mL blood would compare to a mixture of four mL vitamin B6 and six mL sodium bicarbonate. While less readily available, it is evident that the vitamin B6 and sodium bicarbonate mixture is more successful in identifying right to left shunts⁴.

Another common practice is using the Valsalva maneuver to induce a more accurate result in proving right to left shunts. The practicality of this maneuver was proven by Dr. Yang and

³ Ali M, Hepinstall M, Cassidy C, et al. Agitated Blood-Saline Rather Than Agitated Air-Saline for Echocardiographic Shunt Studies - ClinicalKey. Accessed December 6, 2023. <https://www-clinicalkey-com.proxy.seattleu.edu/#!/content/journal/1-s2.0-S0894731720301668?scrollTo=%231-s2.0-S0894731720301668-gr1>

⁴ Zhao E, Cheng G, Zhang Y, Li Y, Wang Y. Comparison of Different Contrast Agents in Detecting Cardiac Right-to-Left Shunt in Patients with a Patent Foramen Ovale during Contrast-Transthoracic Echocardiography. *Biomed Res Int*. 2017;2017:6086094. doi:10.1155/2017/6086094

colleagues in a study aimed at finding which doppler study is most beneficial for finding patent foramen ovals and atrial septal defects. They established that, while not entirely practical, the best practice for identifying and assessing the operability of a right to left shunt is using transcranial doppler to identify the shunt, transthoracic echo to quantify the severity of the shunt, and transesophageal echo to identify the morphologies of the shunt in the case of a planned closure procedure⁵. Even more specifically, Dr. Wang and colleagues determined that when agitating saline, twenty agitations is preferable to ten. In the case of both saline mixtures and blood-saline mixtures, the samples agitated twenty instead of ten times had higher duration times, more bubbles, and lower transit times⁶.

Discussion

To begin discussion, it is important to analyze the practicality of the aforementioned results about best practices of agitated saline studies. So far, it is established that optimal bubble studies use four mL of vitamin B6 and six mL of sodium bicarbonate, and if that is not available, eight mL saline, one mL air, and one mL of blood⁴. On top of that, one must use twenty agitations of the bubble study mixture and use the Valsalva maneuver in order to best identify right to left shunts⁶. Finally, to best identify a right to left shunt and close the shunt, if necessary, the best practice would be to start with transcranial doppler, then use transthoracic echocardiography, then finish the evaluation with a transthoracic echocardiography⁵. Unfortunately, however, these

⁵ Yang X, Wang H, Wei Y, Zhai N, Liu B, Li X. Diagnosis of Patent Foramen Ovale: The Combination of Contrast Transcranial Doppler, Contrast Transthoracic Echocardiography, and Contrast Transesophageal Echocardiography. *Biomed Res Int*. 2020;2020:8701759. doi:10.1155/2020/8701759

⁶ Wang Y, Zeng J, Yin L, Zhang M, Hou D. Modified Right Heart Contrast Echocardiography Versus Traditional Method in Diagnosis of Right-to-Left Shunt: A Comparative Study. *Pol J Radiol*. 2016;81:428-433. doi:10.12659/PJR.897388

best practices are not practical. Echocardiographers do not often have access to vitamin B6 or sodium bicarbonate, which requires us to use a saline-blood mixture. Additionally, transcranial doppler is very uncommon for identification of right to left shunts, so for the most part, the diagnosis process only uses transthoracic and transesophageal echocardiography. The last less-than-feasible option for these agitated saline studies is that many stroke patients are ventilated and TEE exams require patients to be sedated. As a result, the Valsalva maneuver often takes the form of pushing on a patient's stomach as opposed to a proper, formal Valsalva maneuver.

In addition to finding RTL shunts, agitated saline studies have the benefit of illuminating the right ventricle. From the idea of a bubble study came the concept of ultrasound enhancing agents, which are used to rule out thrombi, determine an accurate ejection fraction, and check for wall motion abnormalities in the left ventricle. With that said, it is important to discuss the benefits of ultrasound enhancing agents, such as Definity and Lumason. One less common use of contrast is in interventional oncology, where Dr. Gummadi has proven that it can be beneficial for lymph node mapping, sentinel lymph node localization, biopsy guidance, and ablation therapy⁷. With this being a comprehensive paper about bubble studies, one must acknowledge the rare circumstance when a typical, antecubital or peripheral injection is not ideal. Dr. Koh's study analyzes the idea of using a femoral vein to inject agitated saline instead of an antecubital vein. In the case of a persistent eustachian valve, it is proven that a transesophageal echocardiogram can result in a false-negative for right to left shunt when the agitated saline is

⁷ Gummadi S, Eisenbrey JR, Lyshchik A. Contrast-enhanced ultrasonography in interventional oncology. *Abdom Radiol (NY)*. 2018;43(11):3166-3175. doi:10.1007/s00261-018-1581-5

injected into the antecubital vein. Instead, it is best to inject into a femoral vein. While rare, this is an important distinction of the best practices of bubble studies⁸.

With any medical intervention, there are certain risks associated. Before ending the discussion of bubble studies, one must be aware of risks outside common knowledge. Any healthcare professional should know that injecting air into a patient's bloodstream can have adverse effects, if large quantities of air are injected. In a traditional bubble study, there should not be more than one mL of air, so in theory, there should be no problems. That is unless the patient in question already has a known right to left shunt, in which case the FDA states that an agitated saline study is contraindicated⁹. The safety of agitated saline studies should not, however, be confused with the safety of ultrasound enhancing agents. Despite the similarities between bubble studies and ultrasound enhancing agents, there is no evidence to suggest that the microbubbles within enhancers have any negative effects on the body or pose any threat to the patient, even in the case of a right to left shunt¹⁰.

Conclusion

⁸ Koh TW. When to use femoral vein injection for diagnosis of patent foramen ovale-Effect of a persistent eustachian valve on right atrial flow patterns during contrast transesophageal echocardiography. *ECHOCARDIOGRAPHY*. 2017;34(5):768-772. doi:10.1111/echo.13511

⁹ Loncar G, Payot L. Obscurum Per Obscurius. Which Contrast Agent Should Be Contraindicated for Cardiac Shunt Detection (Agitated Saline Agent vs. Ultrasound Contrast Agent)?...Vallurupulli, S. What's in a name? Confusing agitated saline contrast with ultrasound contrast agents. *Echocardiography* 2015; 33(1):164. *ECHOCARDIOGRAPHY*. 2016;33(1):167-167. doi:10.1111/echo.13137

¹⁰ Main ML, Feinstein SB, Feinstein LM, Grayburn PA, Wilson SR. Transient Ischemic Attack Caused by Contrast Echocardiography in a Patient with Platypnea-Orthodeoxia...Loncar G, Payot L, Dubois M: TIA caused by contrast echocardiography in patient with platypnea-orthodeoxia. *Echocardiography* 2015;32:1585 – 1587. *ECHOCARDIOGRAPHY*. 2016;33(1):165-166. doi:10.1111/echo.13138

An ideal agitated saline study uses the following techniques to yield the most accurate results in determining the presence of a right to left shunt. First, one must use four mL of vitamin B6 and six mL of sodium bicarbonate, but if those are not available, eight mL of saline, one mL of air, and one mL of blood. Second, it is best practice to use the Valsalva maneuver if possible, because it gives the best chance of giving an accurate result. Third, when agitating the mixture, it is best to agitate twenty times, as it results in the most bubbles, higher duration times, and lower transit times than ten agitations. Finally, if possible, it is best practice to use transcranial doppler first to find the right to left shunt, then use transthoracic echo to identify the severity of the shunt, and last use transesophageal echo to study the anatomy of the shunt. While these are the best practices, some are more practical than others and it is recognized that all of this cannot be achieved with every patient.

Key Takeaways

Refer to the conclusion for a comprehensive list of the best practices when conducting an agitated saline study within echocardiography. It is important to note that these recommendations are not fully exhaustive and are not always practical for use in a clinical setting. As an echocardiographer, it is one's responsibility to do their best to perform as many of these best practices with as many patients as they can.

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