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Permalink

<https://escholarship.org/uc/item/5jz99693>

Journal

Echocardiography (Mount Kisco, N.Y.), 33(8)

ISSN

0742-2822

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Publication Date

2016-08-01

DOI

10.1111/echo.13231

Peer reviewed

ORIGINAL INVESTIGATION

Transcranial Doppler: Does Addition of Blood to Agitated Saline Affect Sensitivity for Detecting Cardiac Right-to-Left Shunt?

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Background: Transcranial Doppler (TCD) with agitated saline has been shown to be an alternative for the detection of right-to-left shunts (RLS) with similar diagnostic accuracies as transesophageal echocardiography (TEE). It is hypothesized that the addition of blood to agitated saline increases the sensitivity of TCD for the detection of RLS. The aim of this meta-analysis was to determine whether agitated saline with blood increases the sensitivity of TCD for the detection of RLS compared to agitated saline alone and other contrast agents. **Method:** A systematic review of Medline, Cochrane, and Embase was performed to look for all prospective studies assessing intracardiac RLS using TCD compared with TEE as the reference; both tests were performed with a contrast agent and a maneuver to provoke RLS in all studies. **Results:** A total of 27 studies (29 comparisons) with 1,968 patients met the inclusion criteria. Of 29 comparisons, 10 (35%) used echovist contrast during TCD, 4 (14%) used a gelatin-based solution, 12 (41%) used agitated saline, and 3 (10%) utilized 2 different contrast agents. The addition of blood to agitated saline improved the sensitivity of TCD to 100% compared to agitated saline alone (96% sensitivity, $P=0.161$), echovist (94% sensitivity, $P=0.044$), and gelatin-based solutions (93% sensitivity, $P=0.041$). **Conclusion:** The addition of blood to agitated saline improves the sensitivity of TCD for the detection of RLS to 100% when compared to other conventional contrast agents; these findings support the addition of blood to agitated saline during TCD bubble studies. (Echocardiography 2016;00:1–9)

Keywords: right-to-left shunt, patent foramen ovale, transcranial Doppler, transesophageal echocardiogram

Patent foramen ovale (PFO) is a congenital heart defect that is a result of incomplete fusion of the septum primum and septum secundum.¹ Through transient right-to-left shunting (RLS), a PFO may serve as a conduit for paradoxical embolic strokes or transient ischemic attacks.² Although the CLOSURE,³ RESPECT,⁴ and PC⁵ trials failed to meet their primary endpoints by intention-to-treat analysis,

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recent meta-analyses of these trials and observational studies suggest that PFO occluding devices may reduce the recurrence of stroke and transient ischemic attack compared to medical treatment in patients with cryptogenic stroke.^{6,7} While contrast transesophageal echocardiogram (TEE) is considered by many as the gold standard for diagnosing PFO,⁸ contrast transcranial Doppler (TCD) is an alternative for the detection of RLS with similar diagnostic accuracies as TEE.⁹

It is hypothesized that TCD using agitated saline with blood produces a higher sensitivity for the detection of RLS compared to agitated saline alone.¹⁰ Utility of agitated saline with

Figure 1. Selection of studies.

blood has also been observed to increase the sensitivity of TTE harmonic imaging compared to agitated saline alone for the detection of RLS.¹¹ The Consensus Conference of Venice has outlined certain key guidelines for performing a TCD bubble study including use of an 18-gauge needle in

the cubital vein, preferential utilization of agitated saline as the contrast

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agent, and application of the
Valsalvamaneu-ver as the
provocation maneuver for
greater than ten
seconds.¹² While these
guidelines are based on data
derived from older
observational studies,
institutional variations in
methodology continue to
exist. The Consensus
Conference of Venice and
newer practice
guidelines for TCD¹³ have not de
lineated a difference

between use of agitated saline with or without blood.

In a recent meta-analysis, a review of 27 studies was conducted to determine the accuracy of TCD for the detection of RLS. This analysis demonstrated that there was no significant difference in sensitivity or specificity when different contrast agents (agitated saline, echovist and gelatin-based solutions) were utilized.⁹ The aim of the current review was to expand on our prior meta-analysis of TCD to determine whether agitated saline with blood produces a higher sensitivity compared to agitated saline alone and other contrast agents.

Methods:

A comprehensive systemic search of Medline, Cochrane, and Embase was conducted by the authors to look for all the prospective studies assessing for intracardiac RLS using TCD bubble study with subsequent confirmation by TEE bubble study as the reference standard. The search was completed in August 2013. Identified studies were analyzed by 3 independent reviewers for preset inclusion criteria which encompassed (1) original prospective studies, (2) subjects' age greater than 18 years, (3) studies with at least 20

subjects, (4) utilization of a contrast agent and provocation maneuver to calculate TCD and TEE accuracies, and (5) availability of completed data to calculate diagnostic accuracies (Fig. 1). For studies that compared different TCD protocols (such as comparing accuracy of different types of contrast) and also provided the variables to calculate the different accuracies (i.e. true positive, false positive, false negative, and true negative), then each methodology was considered a separate comparison in the final analysis. A sensitivity analysis was then performed to demonstrate the effect of varying methodologies on accuracy of TCD. The methods of the study are described in more detail elsewhere.⁹

Statistical Analysis:

Meta-analysis of diagnostic accuracy variables was performed using Meta-DiSc software (version 1.4).¹⁴ Cochran Q statistic and inconsistency index (I^2) were calculated to assess between-study heterogeneity and between-study inconsistency with statistical significance defined by $P < 0.10$. Due to anticipated inter-study heterogeneity, a random effects analysis model (DerSimonian-Laird estimator)¹⁵ was utilized because it provides more conservative estimates.

TABLE I
Sensitivity Analysis of TCD Stratifying for Agitated Saline with
and without Blood

Parameter	No. of Studies	No. of Patients	Sensitivity (95% CI)	Specificity (95% CI)	*LR+ (95% CI)	*LR- (95% CI)
1: Saline-blood versus saline only						
Saline-blood	3	139	1 (0.90, 1.00)	0.83 (0.74, 0.89)	6.55 (1.70, 25.29)	0.05 (0.01, 0.24)
Saline only	9	73	0.96 (0.93, 0.98)	0.84 (0.80, 0.88)	5.798 (3.00, 11.19)	0.049 (0.02, 0.12)
P-value		1	0.16	0.82	0.91	0.99
2: Saline-blood versus echovist						
Saline-blood	3	13	1 (0.90, 1.00)	0.83 (0.74, 0.89)	6.55 (1.70, 25.29)	0.05 (0.01, 0.24)
echovist	10	61	0.94 (0.90, 0.96)	0.87 (0.83, 0.90)	9.98 (4.00, 24.92)	0.114 (0.07, 0.18)
P-value		6	0.04	0.34	0.67	0.32
3: Saline-blood versus gelatin						
Saline-blood	3	13	1 (0.90, 1.00)	0.83 (0.74, 0.89)	6.55 (1.70, 25.29)	0.05 (0.01, 0.24)
gelatin	4	26	0.93 (0.87, 0.96)	0.93 (0.87, 0.97)	10.190 (4.57, 22.72)	0.103 (0.054, 0.20)

P-value			0.04	0.03	0.63	0.44
4: Saline only versus echovist						
Saline only	9	73	0.96 (0.93, 0.98)	0.84 (0.80, 0.88)	5.80 (3.01, 11.19)	0.05 (0.02, 0.12)
echovist	10	61	0.94 (0.90, 0.96)	0.87 (0.83, 0.90)	9.98 (4.00, 24.92)	0.11 (0.07, 0.18)
P-value			0.32	0.27	0.47	0.08
5: Saline only versus gelatin						
Saline only	9	73	0.96 (0.93, 0.98)	0.84 (0.80, 0.88)	5.80 (3.01, 11.19)	0.05 (0.02, 0.12)
gelatin	4	26	0.93 (0.87, 0.96)	0.93 (0.87, 0.97)	10.19 (4.57, 22.72)	0.10 (0.05, 0.20)
P-value			0.25	0.01	0.39	0.23

*LR = positive likelihood ratio; LR = negative likelihood ratio; CI = confidence interval.

Figure 2. A,B. Sensitivity and specificity forest plots for studies that utilized agitated saline with blood.

of the pooled data. Subgroups were constructed only when ≥ 3 studies could be included. Heterogeneity of diagnostic accuracy between sub-groups was assessed by Cochran's Q test and inconsistency index (I^2) with a random effect model.¹⁵ The "Metan" package in Stata, version 12 (StataCorp LP, College Station, TX, USA) was used in the subgroup analysis. Values of 95% confidence intervals (CI) were used for all pooled data, all P-values are two tailed, and an adjusted P-value of < 0.05 was considered statistically significant unless otherwise specified.

Results:

Of 174,961 articles identified, 27 studies met the inclusion criteria.¹⁶⁻⁴² Two studies compared 2 different TCD protocols; the final meta-analysis therefore consisted of 29 comparisons. Of the 29 comparisons, 10 (35%) used echovist contrast during TCD,^{20,21,24-26,29-33} 4 (14%) used a gelatin-based solution,^{18,20,27,40} 12 (41%) used agitated saline,^{16,18,23,32,34,37,38,40-42} and 5 (17%) utilized 2 different contrast agents.^{22,27,28} A further review of the 12 studies that used agitated saline

revealed that 3 of 12 utilized agitated saline with blood^{16,38,41} and 9 of 12 utilized agitated saline without blood. Figure 1 describes the study selection method with breakdown of the included studies by contrast used.

A total of 731 patients (mean age 50; 53% male) received agitated saline alone, 139 patients (mean age 46; 50% male) received agitated saline with blood, 616 patients (mean age 46; 59% male) received echovist, and 266 patients (mean age 50.5; 55% male) received gelatin-based solutions. Before stratifying for agitated saline contrast with and without blood, there was no significant difference in diagnostic accuracies when agitated saline, echovist, and gelatin-based solutions were compared.⁹

Table I describes the results of the sensitivity analysis after stratifying for agitated saline with and without blood. Although the addition of blood to agitated saline increased the sensitivity of TCD for the detection of RLS compared to agitated saline alone (from 96% to 100%), this was not statistically significant ($P=0.16$). There was no significant difference in specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) comparing agitated saline with and without blood ($P=NS$). Agitated saline with blood increased the sensitivity of TCD when compared to echovist (from 94% to 100%, $P=0.04$) without compromising specificity, LR+, and LR- ($P=NS$). Compared to gelatin-based solutions, agitated saline with blood had a superior sensitivity (100% vs. 93%, $P=0.041$) but an inferior specificity (83% vs. 93%, $P=0.03$);

Figure 3. A,B.Sensitivity and specificity forest plots for studies that utilized saline only.

there was no difference in LR+ and LR when comparing the two contrast agents (P=NS). There was no difference in sensitivity, specificity, LR+, and LR when comparing agitated saline alone to echovist (P=NS). Compared to gelatin-based solutions, agitated saline alone had an inferior specificity (84% versus 93%, P=0.006) for the detection of RLS; there was, however, no difference in sensitivity, LR+, and LR (P=NS). Figures 2-5 illustrate the sensitivity and specificity forest plots for the different contrast agents utilized.

Discussion:

Our study demonstrates that the addition of blood to agitated saline contrast improves the sensitivity of TCD

to 100% compared to agitated saline alone (96% sensitivity, P=0.16), echovist

(94% sensitivity, $P=0.044$), and gelatin-based solutions (93% sensitivity, $P=0.041$). This increased sensitivity was not countered by a compromise in specificity, LR+, or LR when agitated saline with blood was compared to agitated saline alone and echovist; however, there was a decreased specificity when compared to gelatin. To our knowledge, this is the first meta-analysis that compares the diagnostic accuracy of TCD for the detection of RLS using agitated saline with blood compared to agitated saline alone and other contrast agents.

Lange et al. demonstrated that a TCD bubble study utilizing agitated saline with blood generates more positive tests with higher shunt grades and longer embolic tract duration than agitated saline alone when middle cerebral arteries were considered independently.⁴³ However,

Figure 4. A,B.Sensitivity and specificity forest plots for studies that utilized echovist.

the study was limited as it did not compare the diagnostic accuracies of the two contrast mixtures to a reference standard such as TEE bubble study or right heart catheterization. Prior studies have demonstrated that combining the patient's blood with the contrast agent increases the number of microbubbles within a given volume, which maintain a constant size when visualized using a hemocytometer.¹⁰ The increased number of microbubbles detected at the level of the middle cerebral arteries with TCD may explain the increased sensitivity when utilizing agitated saline with blood. In this meta-analysis, we observed an increased sensitivity of TCD to 100% using saline with blood

which is supportive of this hypothesis. Compared to other contrast agents, agitated saline has the advantage of its low cost and easy

availability. The addition of patients' own blood (ranging from a drop to 4 ml)^{16,38,41} to the agitated saline mixture is safe and inexpensive, allowing the detection of a larger number of microbubbles during the bubble study. Given that the increased sensitivity of agitated saline with blood has been demonstrated in both this study utilizing TCD and in other studies using TTE,¹¹ saline with blood may be the superior contrast in all bubble studies.

TTE is the most commonly used modality for detecting intracardiac RLS due to its cost-effectiveness and easy availability. Due to the posterior location of the atria, TTE images of the septum often have a low resolution. For enhanced imaging, the subcostal (subxyphoid) four-chamber view is often utilized. However,

Figure 5. A,B.Sensitivity and specificity forest plots for studies that utilized gelatin-based solutions.

during a Valsalva maneuver, the inflating lungs and shifting diaphragm often lead to a brief loss of image, usually when the agitated saline has already been introduced and bubbles are crossing the septum. Although cost-effective and commonly used for diagnosing intracardiac RLS, TTE has a low sensitivity.^{44,45} In addition, the differentiation between intracardiac and intrapulmonary RLS can be difficult using the standard TTE technique. A recent meta-analysis of prospective studies comparing fundamental TTE to TEE as the reference demonstrated a sensitivity of 46% and specificity of 99%.⁴⁶ The use of second harmonic imaging with TTE has now become standard in most centers. Harmonic imaging allows better visualization of a PFO and differentiation of the source of RLS (interatrial septum vs. pulmonary veins). In one recent study, TTE with second harmonic imaging increased the sensitivity of TTE to 90.5%.¹¹ However, even with enhanced TTE imaging, TCD bubble study has a superior sensitivity of 97% for the detection of intracardiac RLS⁹ as TCD is not limited by

potential poor echo windows and possible loss of imaging during the Valsalva maneuver.

TCD is limited by its inability to visualize the atrial septal anatomy and inability to differentiate

between cardiac and pulmonary RLS.^{11,44} Due to its low cost, good safety profile, and high sensitivity, we recommend TCD bubble study using agitated saline with blood as an initial screening test for suspected RLS followed by TEE bubble study as a confirmatory test.

Limitations:

Limitations of this meta-analysis include the heterogeneity of the included studies and the lack of studies utilizing power M-mode TCD. Power M-mode TCD has been reported to have a higher sensitivity than older single-gated TCDs for the diagnosis of RLS when catheterization was used as the reference.⁴⁷ In addition, the higher sensitivity of agitated saline with blood compared to agitated saline alone was not found to be statistically significant; this may have been due to a lack of statistical power considering there were fewer studies utilizing agitated saline with blood (only 3 studies compared to 9 studies using saline alone) with fewer patients (139 patients compared to 731 patients using saline alone). Finally, as the sensitivity of the other methods is already high, it would be difficult to show a statistical difference, even though saline with blood had 100% sensitivity.

Conclusion:

Utility of agitated saline with blood improves sensitivity of TCD to 100% when compared to other contrast agents. Considering that the addition of a patient's blood to the agitated saline mixture is easy to perform, does not increase cost, and adds minimal to no extra time to the procedure, our findings support the addition of blood to agitated saline during TCD bubble studies.

Disclosures:

Dr. Tobis is a consultant for St. Jude Medical, Inc. and W.L. Gore, Inc. All other authors have nothing to disclose.

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