Valsalva maneuver procedures in the diagnosis of right-to-left shunt by contrast-enhanced transcranial doppler using agitated saline solution with blood as a contrast agent

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ABSTRACT

Objective: To compare two different timings for the performance of the Valsalva maneuver (VM) using an infusion of agitated saline solution with blood as contrast agent (CA) to right-to-left shunt (RLS) screening. Method: 42 patients were submitted to a standardized contrast-enhanced transcranial doppler (cTCD) to screen for right-to-left shunt (RLS). cTCD technique was done with two different moments of the VM: [1] the CA injection during the VM (CADuringVM test); [2] the CA injection before the VM (CApreVM test). Results: Positive MCA tests were observed in 47 (56%) CADuringVM tests and in 50 (59.5%) CApreVM tests, p=0.64. There was an almost perfect agreement for the positive tests between the CADuringVM and CApreVM test, r²=0.829 (95% CI 0.61-1.00, p<0.001). Conclusion: The present study demonstrates that there is no significant difference in the results of RLS screening by cTCD when two different moments of VM were done.

Key words: contrast media, paradoxical embolism, microbubbles, transcranial doppler, ultrasonography, Valsalva maneuver.

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Contrast-enhanced transcranial doppler (cTCD) is a reliable and reproducible screening method for right-to-left shunt (RLS) diagnosis12. The Valsalva maneuver (VM) increases the positive results of standardized cTCD studies by 45% by increa-
ing the right atrial pressure to facilitate or reveal an intermittent RLS via a patent foramen ovale (PFO)\(^2,3\). Previous studies have demonstrated that the ideal time to perform the VM is five seconds after contrast agent (CA) infusion, but these studies were done preferentially with agitated saline solution (AS) or a galactose-based CA\(^1,4\). Studies used a small sample of a patient’s own blood to obtain an agitated saline solution with blood (ASb) as a means of increasing the number of microbubbles (MBs) generated compared to AS\(^5\).

The aim of this study was to compare two different timings of the VM with the infusion of ASb as a CA.

**METHOD**

We evaluated 42 patients in the Laboratory of Neurosonology for RLS diagnosis. All of the subjects gave their written informed consent. Clinical and neurological evaluations were done in all of the cases and none patient had an extracranial or an intracranial stenosis evaluated by ultrasonography. There were 32 patients with ischemic stroke, 5 with transitory ischemic attacks, and 5 with migraine with aura. The local ethics committee approved this study.

The cTCD (doppler-Box DWL, Singen, Germany) procedures were performed with the patients in a supine position. Two 2-MHz pulsed doppler transducers were fixed with a head frame (DiaMon DWL, Singen, Germany) and insonated both middle cerebral artery (MCA) main stems through the temporal window at a depth of 50 to 65 mm to capture a small sample volume of 8 mm in length with two spectral gates 8 mm apart and the M-mode (32 sample gates in each channel). A 256-point fast Fourier transform analysis was used.

The CA was composed of a mixture of 8 mL saline, 1 mL air, and 1 mL of the patient’s blood. Before the infusion, the solution was prepared by agitating the mixture between two 10 ml syringes 10 times through a three-way tap connected to an 18 gauge intravenous catheter inserted in a right antecubital superficial vein. The distance from the catheter to the syringes was less than 10 cm. The CA was injected in 5 seconds into the antecubital vein.

All of the tests were 60 seconds in duration, and they were recorded for later interpretation and quantification offline. There was an interval of three minutes between each of the tests.

A test was considered positive when at least one embolus track (ET) with previously defined criteria was detected on both of the spectral gates displays and the M-mode of at least one of the monitored MCAs\(^1,7\). The ET criteria were a unidirectional, typically visible and audible, short duration, high-intensity signal within the doppler flow spectrum with a movement toward the MCA as time progresses and a positively-sloped track in the M-mode image (Fig 1).\(^1,7-9\)

The ET counts were obtained individually for each MCA during an offline analysis. The highest count obtained with ASb in each VM procedure was considered for analysis. The studies were classified based on previous criteria and defined as: negative=no ET observed; grade I=1-10 ETs, and grade II>10 ETs\(^2\).

The latency time, in seconds, between the CA injection and the detection of the first ET were analyzed in each MCA. The duration, in seconds, of the ET passage after the CA injection was evaluated in all of the tests by measuring the time between the first and the last ET in each of the MCAs tested.

The statistical analyses were performed with SPSS 12.0 software (SPSS Inc.). Statistical significance was assessed by a Student's t-test for the parametric variables, and the Chi-square and Mann-Whitney tests were used for the non-parametric variables. The degree of agree-
ment for a positive test (≥1 MB) was tested with the kappa test for agreement. Statistical significance was determined at \( p<0.05 \).

**RESULTS**

For the 42 patients evaluated, the mean age was 41.6±11.9 years old, 52% were female, and a total of 84 MCA tests with the CAduringVM test and 84 MCA tests with the CApreVM test, none of the patients had any adverse events during or after the tests. From all patients evaluated, 28 presented at least one positive CAduringVM test and 27 presented at least one CApreVM test positive (\( p=0.893 \)).

Positive tests were observed in 47 (56%) of the CAduringVM tests and in 50 (59.5%) of the CApreVM test (\( p=0.64 \)). Only two tests were positive with the CAduringVM test and negative with the CApreVM test, while five tests were positive with the CApreVM test and negative with the CAduringVM test. There was an almost perfect agreement for positivity between the CAduringVM test and the CApreVM test, with a correlation \( r_{x}=0.829 \) (95% CI 0.61-1.00, \( p<0.001 \)). The ET grades were similar in both groups: the CAduringVM test demonstrated 37 (44%) negative, 21 (25%) grade I, and 26 (31%) grade II tests, and the CApreVM test demonstrated 34 (40.5%) negative, 24 (28.6%) grade I, and 26 (31%) grade II tests (\( p=0.76 \)) (Fig 2).

The mean number of ET (97.7±125.6 in the CAduringVM test versus 77.3±111.2 in the CApreVM test, \( p=0.40 \)), the latency time in seconds (10.6±9.0 in the CAduringVM test versus 13.5±5.3 in the CApreVM test, \( p=0.56 \)), and the duration time of the ET passage in seconds (18.0±16.8 in the CAduringVM test versus 17.9±16.5 in the CApreVM test, \( p=0.98 \)) were similar in both groups.

**DISCUSSION**

The present study demonstrated that the timing of the VM made no difference when ASb was used as the CA for RLS screening by cTCD. The mean number of ET, the latency time, and the duration did not differ based on the timing of the VM.

Previous studies with different CAs demonstrated that CA infusion during the VM and before the VM showed good sensitivity values compared to contrast-enhanced transesophageal echocardiography (cTEE) for RLS diagnosis, preferentially for PFO diagnosis\(^1\). An international consensus suggested that the VM should start five seconds after the beginning of the CA injection and should be maintained for at least five seconds\(^1\). This procedure was done in the current study (CApreVM test), and the results demonstrated an almost perfect agreement compared to the CA injection during the VM (CAduringVM test) for positivity of RLS with ASb.

Droste et al. demonstrated that at least two different moments of VM must be done if the first procedure was negative\(^1\), these results were confirmed by other studies during the PFO diagnosis\(^1\). In the current study, it was observed that a different procedure changed seven MCA results: two that were negative with the CApreVM test and became positive with the CAduringVM test; five that were negative with the CAduringVM test changed to positive with the CApreVM test.

This study has some limitations. The patients were not submitted to PFO diagnosis by cTEE to identify the sensitivity and specificity for cardiac RLS by this technique. In a previous study, we demonstrated that standardized cTCD is a good method for RLS screening\(^3\). Another limitation was the use of only ASb; the results could be different with other CA, and until now, no previous comparative analysis has been done. We recently demonstrated that ASb is as good as AS for RLS screening by cTCD (unpublished data).

In conclusion, we agree that the VM procedure used in the current consensus for the diagnosis of RLS by cTCD can be accepted when ASb is used as the CA, but if a negative result is observed, the patient should be submitted to a different protocol with a different timing of the VM, which could involve CA injection during VM (CA during VM test).

**REFERENCES**

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