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Detection of Right-to-Left Shunt with Ultrasound Contrast Agent and Transcranial Doppler Sonography

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Key Words

Right-to-left shunt · Ultrasound contrast agent · Transcranial Doppler sonography · Patent foramen ovale · Valsalva maneuver

Abstract

An international Consensus Meeting to determine a standard in the examination technique for the detection of right-to-left shunt (RLS) using contrast transcranial Doppler sonography (TCD) led to the following recommendations to standardize the examination procedure: The patient should be prepared with an 18-gauge needle inserted into the cubital vein and should be in the supine position. Insonation of at least one middle cerebral artery (MCA) using TCD is performed. The contrast agent is prepared using 9 ml isotonic saline solution and 1 ml air mixed with a three-way stopcock by exchange of saline/air mixture between the syringes and injected as a bolus. In case of little or no detection of microbubbles (MB) in the MCA under basal conditions, the examination will be repeated using the Valsalva maneuver (VM). Contrast agent will be injected 5 s before the start of the VM; the overall VM duration should be 10 s. The patient should start the VM on examiner's command. The strength of the VM can be controlled by peak flow velocity of the Doppler curve. The time when the first MB appears at the MCA level will be noted. A four-level categorization according to the MB count should be applied: (1) 0 MB (negative result); (2) 1–10 MB; (3) >10 MB and no curtain, and (4) curtain. ('Curtain' refers to a shower of MB, where a single bubble cannot be identified.) The results should be documented for basal condition and VM testing separately. The clinical significance of the diagnosis of a RLS in a particular patient is not fully evaluated and requires further studies. A minimum amount of MB suggestive of a clinical relevant RLS is not yet established. It probably depends on interindividual differences in hemodynam-

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ics that are currently not fully understood. Transesophageal echocardiography remains the gold standard for detection of a patent foramen ovale or an atrial septum defect. However, TCD with a contrast agent has been turned out as a potential method to diagnose a RLS in several studies which have been published during the last years, and a RLS other than at the atrial level may be detected only by this method. Furthermore, the VM can be applied more comfortably and more reliably during Doppler examination than during transesophageal echocardiography.

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Introduction

The main purpose of this meeting was to develop a standard examination protocol for detection of right-to-left shunt (RLS) using transcranial Doppler sonography (TCD) and an ultrasonic contrast agent (CA).

It is expected, that a standardization of the examination technique leads to the following benefits: (1) wider acceptance of the method and facilitation of its use; (2) using comparable methods in detection of RLS as a prerequisite of multicenter studies, and (3) the process of consensus finding stimulates studies in order to answer unsettled questions.

To be qualified as a member of the consensus conference, the invited experts had to be authors of at least one study using TCD and CA for the detection of RLS published in an international journal and were selected according to personal contacts and a Medline research in December 1998. Other contributors with expertise in neurovascular ultrasound field have been included at a consulting level.

In preparation of the Consensus Meeting, a proposal with a current review of the literature and preliminary recommendations according to the level of evidence[1] had been distributed to experts as a base for further discussion. Consensus on controversial items was achieved by voting of the members of the consensus on meeting. This method closely resembles Glaser's approach [1, 2] that has been successfully applied in smaller expert panels on different subjects, first to describe the current knowledge of chronic obstructive pulmonary disease [3].

Features of this approach are an initial position paper with current state of the literature subjected to a series of rounds and critiques by experts and redrafted according to the contributions. A second step includes a conference to find a consensus on controversially discussed points. It results in a final draft written by a member of the core group, including points where agreement could be achieved and items where further research is needed.

Background and Objective

An incidence of a cardiac RLS – i.e., patent foramen ovale or atrial septum defect – of 40% in stroke patients compared with 10% in a control group [4**] led to the consideration of cardiac RLS as a risk factor in cryptogenic stroke, especially in young patients with no additional risk factors.

Transesophageal echocardiography (TEE) remains the gold standard for the detection of cardiac RLS, and diagnostic yield is enhanced using CA. Additional risk factors like an atrial septum aneurysm or an increased mobility of the foramen ovale membrane can only be detected with the use of TEE.

TCD has proved to be a sensitive and specific method to diagnose cardiac RLS regardless of location as documented by several studies which have been published during the last years. The method has been widely used, but results of tests vary considerably, depending on methodological factors such as CA, injection mode, and timing with respect to Valsalva maneuver (VM) [5***, 6***, 7**]. The relevance of cardiac RLS is related to size and functional factors [8**, 9***, 10**] that require quantification of RLS during the examination.

This paper presents recommendations on a standardized approach for cardiac RLS detection using TCD according to the data available and consensus in case of lacking data. Furthermore, unsettled questions are addressed.

Recommendations

Choice of the CA

Recent publications focused on agitated saline solution or *D*-galactose microparticle solution (Echovist®; Schering, Berlin, Germany) as ultrasonic CA, whereas few

[1] Several studies cited in text are rated according to the level of evidence: *** well-designed clinical study of a diverse population using a 'gold standard' reference in a blinded evaluation with an experimental setting appropriate for the relevant question and with control of all probable bias factors; ** well-designed clinical study of a restricted population with an experimental setting appropriate for the relevant question and with control of several bias factors, and * evidence provided by expert opinion, nonrandomized historical controls, or observations from case series.

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Table 1. Sensitivity and specificity compared to the gold standard for different CA and different dosage patterns according to recent studies

Authors	Year of publication	Dosage per injection and CA type	Sensitivity %	Specificity %
Chimowitz et al. [29]	1991	saline/air/gelatine	100	100
Teague and Sharma [24][1]	1991	5 ml saline, 0.2 ml air	100	76
Nemec et al. [27]	1991	6 ml saline, 0.2 ml air	100	–
Karnik et al. [28]	1992	gelatine	87	100
Di Tullio et al. [25]	1993	10 ml saline, 0.5 ml air	68	100
Jauss et al. [12]	1994	5 ml Echovist	93	100
Job et al. [11]	1994	Oxypolygelatine	89	92
Klötzsch et al. [21]	1994	5 ml Echovist	91	94
Schminke et al. [7]	1995	5 ml Echovist	91	81
Anzola et al. [14]	1995	20 ml saline agitated	90	100
Zanette et al. [6][2, 3]	1996	10 ml air/saline	79	–
Devyust et al. [13]	1997	9 ml saline, 0.2 ml air	100	100
Horner et al. [22]	1997	10 ml Echovist	97	70
Hamann et al. [23][4]	1998	2.5 ml Echovist	75	100
Schwarze et al. [5]	1999	5–10 ml Echovist	100	97
Droste et al. [15]	1999	9 ml saline, 1 ml air	95	75
Droste et al. [15]	1999	5 ml Echovist	95	75
Droste et al. [16][5]	1999	10 ml Echovist	90	85

1 Gold standard was transthoracic echocardiography instead of TEE.
2 Injection of CA before VM was considered.
3 Only patients with positive TEE were included in the study.
4 Injection of CA at the antecubital site was considered.
5 A time window <22 s was used.

authors used other media such as Oxypolygelatine 10® [11**]. A sensitivity of 100% was achieved by using both Echovist [12**] and saline solution [13**]. A specificity of 100% for agitated saline solution [14**] and one of 93.8% for Echovist [12] was reported (table 1). Echovist and agitated saline are, therefore, reliable CA with respect to sensitivity and specificity when used with VM and are proven in several studies with high numbers of patients. A direct comparison of saline/air mixture and Echovist was currently performed [15***, 16***] and demonstrated no superiority of any CA concerning sensitivity. However, in both studies more microbubbles (MB) were detected using Echovist even when applied at a smaller dose than saline (5 ml Echovist as compared with 10 ml air/saline). Echovist contains more MB than air/saline. This may be an advantage when quantifying an RLS.

The Consensus Meeting proposes the use of agitated saline/air mixture, since its availability is not restricted to local approval rules that vary between the countries and since it has been proven as effective in numerous studies (table 1). No side effects have been reported. Nevertheless, the bubble size is not standardized, and complications (e.g., occlusion of retinal arteries in case of large cardiac RLS) are possible on theoretical grounds. With regard to safety aspects and to decrease MB load, the VM should be limited to patients in whom no or only a mild RLS is present on testing without VM.

Usage of air/saline in countries where Echovist is approved has to be considered according to local legal regulation. Extensive safety testing of Echovist [17***] revealed no safety concerns. At the dose recommended there are currently no reports on side effects after air/saline administration.

Preparation of the CA

Since the sensitivity for the detection of an RLS is influenced by the amount of CA [5, 18***], a generally accepted standard dose, mode of preparation, and mode of injection are desirable, as was stated by the following consensus:

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Table 2. Sensitivity and specificity compared to gold standard for different time intervals for evaluation of TCD test result according to recent studies

Authors	Year of publication	Number of MB and time window when MB in the MCA are considered positive	Sensitivity %	Specificity %
Teague and Sharma [24][1]	1991	≥1 MB, no time window	100	76
Jauss et al. [12]	1994	≥1 MB, 25 s	93	100
Job et al. [11]	1994	≥1 MB, 4–15 s	89	92
Klötzsch et al. [21]	1994	≥1 MB, 6 heartbeats	91	94
Anzola et al. [14]	1995	≥1 MB, 10 s	90	100
Zanette et al. [6][2, 3]	1996	≥1 MB, 22 s	79	–
Devyust et al. [13]	1997	>3 MB, 10 s	100	100
Hamann et al. [23][4]	1998	>10 MB, 10 s	75	100
Droste et al. [16]	1999	≥1 MB, 22 s	90	85
Droste et al. [15]	1999	≥1 MB, 25 s	95	75

1 Gold standard was transthoracic echocardiography instead of TEE.
2 Injection of CM before VM was considered.
3 Only patients with positive TEE where included in the study.
4 Injection of CA at the antecubital site was considered.

(1) The amount of CA per injection should be 10 ml of air/saline solution (using 1 ml air and 9 ml saline). If Echovist is used, an amount of 5 ml/injection is recommended. To minimize bacterial contamination, aspiration of air should be through a bacterial filter. Injection of the air/saline solution immediately after the preparation is important to prevent formation of large air bubbles.

(2) Preparation of agitated saline should be performed as follows: using a three-way stopcock connected to a 10-ml syringe I (containing 9 ml of 0.9% saline) and to syringe II (containing 1 ml air aspirated through a bacterial filter) and to the patient with a short flexible tube (<10 cm) to minimize patient discomfort during manipulation. 1 ml air (syringe I) and 9 ml saline (syringe II) should be rapidly and energetically exchanged between the syringes at least ten times. Echovist should be prepared according to the instructions given by the manufacturer.

(3) Bolus injection is recommended.

Further Details of the Examination

As stated recently, RLS detection is influenced by numerous details of the examination technique [5, 15, 18***], some of them were recommended by the consensus group: (1) supine position, the arm used for injection in the horizontal position; (2) an 18-gauge needle should be preferred over a 20-gauge needle to increase the sensitivity, according to the results of Khan et al. [19**]; (3) injection into the right cubital vein, and (4) recording of the middle cerebral artery (MCA) Doppler signal (bilaterally if available).

Repeated testing may increase the sensitivity [15]. Most investigators use single testing without VM and a second test with VM, while in some studies [9, 20*] repeated tests were performed. In case of discrepancies, the positive test is considered. Whether this approach reduces the specificity and facilitates false-positive results has not been tested yet. In case of different results during repeated testing or during bilateral testing, the test with the highest number of MB is considered.

Diagnostic Time Window for MB Appearance

The specificity for an RLS shunt at the atrial level may be increased by using a defined time of MB appearance considered as evidence for crossing of MB at the atrial level. A general agreement for a cutoff interval does not exist, and, therefore, a wide range from six heartbeats [21**] to 25 s for Echovist [12] and to 22 s for agitated saline solution [6] has been applied (table 2). The passage time from the cubital injection site to the MCA through an intracardiac shunt is about 11 s and about 14 s for passage from the cubital injection site to the MCA in case of pulmonary passage [22**]. Therefore, an overlap interval for intrapulmonary passage and passage at the atrial level

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Table 3. Sensitivity and specificity compared to gold standard for different VM methods according to recent studies

Authors	Year of publication	Injection mode	Sensitivity, %		Specificity, %	
			with VM	without VM	with VM	without VM
Teague and Sharma [24][1]	1991	D	100	100	76	79
Jauss et al. [12]	1994	B	93	47	100	100
Zanette et al. [6][2, 3]	1996	B, D, A	79	53	–	–
Hamann et al. [23][4]	1998	B	75	40	100	100
Droste et al. [16][5]	1999	B	90	55	85	88

Studies are listed when separate values for testing with and without VM were given in the particular reference. D = Injection of CA *during* VM; B = injection of CA *before* start of VM; A = injection of CA *after* release of VM.

1 Gold standard was transthoracic echocardiography instead of TEE.

2 Injection of CA before VM was considered.

3 Only patients with positive TEE where included in the study.

4 Injection of CA at the antecubital site was considered.

5 Using 22 s as time window.

must be assumed. Moreover, an exact definition of the time window is difficult, since the VM introduces an additional variance into hemodynamic parameters. A direct comparison of different cutoff limits with respect to concordant or discordant findings as compared with TEE was given by Droste et al. [16] and further supports the conclusion that a rigid diagnostic time window does not exist.

The consensus group agreed that a time window cannot differentiate between RLS at the atrial level and RLS at different sites of the vascular system. It is, therefore, of no value to consider any cutoff limit in the assessment of the MB test result. Clinical relevance of the MB test can be achieved by quantitative analysis.

Valsalva Maneuver

The time of CA injection in relation to VM varies in different studies. Injection before the VM [11, 12, 23**] during the VM [22**, 24**, 25**], or after release of the Valsalva strain [14] has been applied. A comparison between different injection modes [6] found an increased sensitivity using injection before VM for air/saline as a CA. A similar study using Echovist revealed comparable results [18]. Different methods for control of the VM like the use of a sphygmomanometer [14] or a decrease of the TCD envelope have been proposed [21]. The sphygmomanometer has the advantage of a quantitative assessment of the VM strength and allows visible feedback for the patient [9]. Since the sphygmomanometer alone does not detect direct circulatory effects, it may erroneously indicate sufficient VM when a high pressure is maintained by palatal closure rather than by elevated intrathoracic pressure. Simultanous monitoring of Doppler spectrum and sphygmomanometer indications allows optimal control of the VM. The VM should be trained with the patient before injection of CA.

General consensus was achieved that a VM is necessary to increase the sensitivity (table 3). In case of detection of massive MB without a VM ('curtain pattern'), one should not perform a VM to prevent possible air embolism.

The VM should start 5 s after the beginning of the CA injection and should be maintained for at least 5 s.

Quantitative Assessment of RLS

Recent imaging studies [8] emphasized the need to quantify the size of the cardiac RLS using TEE. Assessment of the RLS size can be achieved by TCD in a semiquantitative manner by counting the MB after injection [9]. The number of MB is affected by several methodological variations, including position of patient and dosage of CA [5, 18], and several factors like the adhesion of the CA to brachial veins, interindividual differences in hemodynamics, and CA composition that cannot be controlled completely. Quantitative assessment of the RLS size requires a strict standardization of the diagnostic procedure, as stated above, in order to generate comparable results.

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Table 4. Summary of test procedures

Preparation of the patient
Supine position, insert 18-gauge needle into (right) cubital vein; insonate (both if possible) MCA
Preparation of CA and injection
Syringe I: 9 ml saline, syringe II: 1 ml air
Connect both syringes with three-way stopcock connected with a short flexible line to an intravenous line of 18 gauge with the patient
Exchange air/saline mixture vigorously between the syringes at least ten times
Inject immediately as a bolus
In case of little or no detection of MB at the MCA level: repeat the examination with VM
Application of VM
CA will be injected
The patient should start with VM on examiner's command 5 s after injection of CA; control of VM will be performed by reduction of peak flow velocity of TCD curve
Overall VM duration should be 10 s
Evaluation of test results
Categorization: 0 MB (negative result), 1–10 MB, > 10 MB and no curtain, curtain
Separate evaluation will be performed for basal condition and VM

A four-level categorization was accepted according to MB appearance in the TCD spectrum using unilateral MCA monitoring (values for bilateral monitoring in parentheses): (1) no occurrence of MB; (2) 1–10 (1–20) MB; (3) >10 (>20) MB, but no curtain, and (4) curtain, where a single MB cannot be discriminated within the TCD spectra.

Quantitative assessment requires documentation for off-line evaluation that can be performed by video or by recording Doppler spectra, as possible with many computer-based TCD devices. The MB count must be documented and evaluated both for baseline condition and VM separately. An outline of the procedure is given in table 4.

Open Questions

Contrast TCD is commonly used in the assessment of stroke patients to reveal RLS as a possible cause of stroke. However, the clinical significance of the diagnosis of a proven RLS in a particular patient is not yet clear. Criteria for the clinical relevance of a given RLS do not depend on the results of TCD testing alone and are not yet established. More research is needed in this field. Modification of examination techniques may be applied especially in research fields. Recent studies showed evidence for different distributions of MB among vascular territories according to site of ischemic lesion [26**]. Assessment of different vascular territories or at least bilateral recording of MCA [6, 22] for RLS testing might lead to more relevant results, but must be subject of further validation.

Concluding Remarks

TEE serves as a reference for the detection of cardiac RLS, and the diagnostic yield is enhanced by the use of a CA. Additional risk factors like an atrial septum aneurysm or an increased mobility of the foramen ovale membrane can be detected only with TEE. However, TCD has turned out to be a highly sensitive and specific method to study the *functional* impact of cardiac RLS and other RLS. Main advantages of contrast TCD as compared with TEE in the detection of RLS are: (1) the VM can more comfortably be applied during TCD than during TEE, and (2) size and functional relevance of RLS can more easily be assessed using TCD than using TEE.

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