Ear Oximetry: A Noninvasive Method for Detection of Patent Foramen Ovale

A Study Comparing Dye Dilution Method and Oximetry With Contrast Transesophageal Echocardiography

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Background and Purpose—Patent foramen ovale (PFO) may play an important role as a risk factor for ischemic stroke and some other neurological conditions. There is a need for low-cost and noninvasive methods for the detection of PFO. This study evaluates the accuracy of two simple bedside tests, the dye dilution method and ear oximetry, in the detection of PFO.

Methods—Dye dilution curves and ear oximetry recordings with a noninvasive ear densitometer were obtained from consecutive cryptogenic stroke patients referred for contrast transesophageal echocardiography (TEE). All test results were blindly assessed for the presence of PFO. Sensitivity and specificity were calculated with TEE used as a reference method. \( \kappa \) statistics were used to measure interrater agreement.

Results—Dye dilution curves were obtained from 67 patients. Dye dilution correctly diagnosed 35 of the 46 patients who had PFO in TEE and all the 21 patients without PFO. Thus, the sensitivity (95% CI) of the dye dilution method was 76% (61% to 87%) and its specificity 100% (84% to 100%). Ear oximetry was done on 83 patients. Oximetry correctly diagnosed 45 of the 53 patients who had PFO in TEE and all of the 30 patients without PFO. Thus, the sensitivity of ear oximetry was 85% (72% to 93%) and its specificity 100% (88% to 100%). The interrater agreement was excellent (\( \kappa \) value 0.94 for dye dilution and 0.90 for oximetry).

Conclusions—Dye dilution and oximetry are both sensitive and specific methods for the detection of PFO. Oximetry has the following primary advantages over the currently available diagnostic methods: it is noninvasive, safe, and inexpensive and causes no discomfort for the patient. We suggest that oximetry could be used as a first-line screening method for PFO in patients with cryptogenic stroke. Ear oximetry also has potential use in epidemiological studies. (Stroke. 2001;32:448-453.)

Key Words: cerebrovascular disorders ■ echocardiography, transesophageal ■ foramen ovale, patent ■ oximetry

Patent foramen ovale (PFO) is a common finding in the general population and is present in approximately one quarter of adults.\(^1\) There has been increasing interest in the detection of PFO since 2 case-control studies showed that there is a significantly higher prevalence of PFO among young patients with cryptogenic ischemic stroke than in control subjects.\(^2\)\(^3\) This suggested that paradoxical embolism through PFO could play a more important role than was previously believed. PFO has also been shown to be associated with several other conditions, including migraine with aura,\(^4\) decompression sickness and paradoxical gas embolism in scuba diving,\(^5\)\(^6\) platypnea-orthodeoxia syndrome,\(^7\) transient global amnesia,\(^8\) pulmonary embolism,\(^9\) obstructive sleep apnea,\(^10\) chronic obstructive pulmonary disease,\(^11\) and paradoxical embolization and fat embolism syndrome in orthopedic surgery.\(^12\) Because of this growing interest in the role of PFO in different patient groups from an epidemiological point of view, there is a need for a noninvasive and simple diagnostic method that could be used to detect PFO reliably and quickly.

At the moment, contrast transesophageal echocardiography (TEE) is regarded as the gold standard in detecting PFO and is considered superior to transthoracic echocardiography.\(^13\) However, TEE is semi-invasive and has some practical limitations. Transcranial Doppler sonography (TCD) has been suggested as an alternative bedside technique for the detection of PFO,\(^14\)\(^15\) but there are still unsolved problems in the methodology of TCD that limit its use and make the interpretation of the results difficult.\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)

The dye dilution and oximetry techniques were developed as early as in the 1950s for the detection of intracardiac shunts but have been largely overshadowed by the advent of new
diagnostic methods. Our preliminary results of the use of dye dilution and ear oximetry in noninvasive detection of PFO were promising. To date, however, these methods have not been validated against a reference method. In the present study, we evaluated the sensitivity and specificity of the dye dilution method and ear oximetry in the detection of PFO by using contrast TEE as the gold standard. We will discuss the advantages and disadvantages of these simple and inexpensive methods compared with more established techniques and their potential applications.

Subjects and Methods

Patients

The study population consisted of 116 consecutive patients referred to the cardiology unit of Oulu University Hospital for a TEE examination because of lack of a plausible cause for their cerebrovascular ischemic episodes (cryptogenic brain infarction, n=106; TIA, n=10). We excluded 12 patients because the quality of the TEE examination was judged to be inadequate for the determination of PFO. One additional patient was excluded because of the poor technical quality of the dye dilution curves. Thus, the final study population consisted of 103 patients (63 men and 40 women; mean age, 49.9 years; range, 19 to 75 years). In these patients, either dye dilution and ear oximetry or both (n=47) were investigated in the order they were remitted for cardiac investigations. In the beginning of the study we did not have ear oximetry, which became available later on. Therefore, both tests were performed for every patient. Both tests were performed until a sufficient number of studies was reached. All patients gave informed consent, and the study was approved by the Ethics Committee of the Medical Faculty, University of Oulu.

Echocardiography

As a part of the clinical evaluation, all patients underwent a contrast TEE examination, which was performed by trained echocardiographers. We used either a Hewlett-Packard Sonos 500 ultrasonograph with a 5-MHz omniplane esophageal transducer (n=70) or a Toshiba Power Vision model SSA380A ultrasonograph with a 5-MHz multiplane esophageal transducer (n=33). During the examination, the patients were in the left lateral decubitus position. The patients were examined in a fasting state, and they received topical anesthesia of the oropharynx by 10% lidocaine spray or 2% lidocaine gel smeared on the transducer or both. None received intravenous sedation. A 4-chamber view of the atrial septum was obtained before the injection of contrast agent. The contrast material of the study was a mixture of 0.9% NaCl (9 mL) and air (1 mL) agitated vigorously in a syringe. To obtain a good bolus of air microbubbles, the contrast solution was injected immediately after preparation rapidly through a 17-gauge catheter placed into a right antecubital vein. This procedure was performed once during normal breathing and once or more during the end phase of a Valsalva maneuver (VM). All TEE examinations were recorded continuously on S-VHS videotape and later reviewed by a single experienced cardiologist who was blinded to the patient’s clinical data, the initial TEE results, and the dye dilution and oximetry results. A PFO was considered to be present if 1 or more bright microbubbles were seen to cross the atrial septum and to appear in the left atrium within 3 heart cycles after contrast opacification of the right atrium. Positive-contrast TEE studies were classified semiquantitatively into 2 grades by counting the maximum number of microbubbles in the left atrium within 3 heart cycles after contrast media filling of the right atrium. A small shunt was defined as a count of 1 to 25 microbubbles and a large shunt was considered to be present if the count was >25 microbubbles.

Ear Oximetry

The oximetry recordings were obtained by continuous measurement of arterial oxygen saturation with a 2-wavelength earpiece oximeter connected to a personal computer (PC). The signals obtained from the optical sensors, corresponding to 2 photoplethysmograms, were digitized by an analog-to-digital converter inside the oximeter and then transferred to the PC (Figures 1 and 2). The signals were further processed by the PC, and relative oxygen saturation value was continuously displayed as a curve on the screen. For later processing and off-line analysis, the signals were stored on the hard disk. We used special software for data processing and for the elimination of artifacts caused by the large and rapid changes in the blood content of the ear during the VM. To optimize the circulation of blood in the ear, an arterIALIZing warm-up period of 10 minutes was allowed before the measurements were performed. The patients were in a supine position during the recordings. We performed 3 measurements with a VM and 3 measurements with a combined Valsalva and Müller maneuver. The VM consisted of blowing into a mouthpiece attached to a standard blood pressure apparatus. The patients were
able to read the pressure scale of the apparatus during the blowing. The goal was to generate and hold a 40–mm Hg pressure for 15 seconds. The combination of Valsalva and Müller maneuvers was accomplished by asking the patient to inspire rapidly through the closed mouthpiece immediately after the VM. The oximetry recordings were analyzed in a random order by a single investigator who was blinded to the clinical characteristics of the patients and to the results of the contrast TEE. The patient was considered to have PFO when a characteristic transient drop in the oxygen saturation curve was seen after the release of the provocation in ≥2 recordings (Figure 3, A and B). All investigations were well tolerated by the subjects without side effects.

Dye Dilution

Dye dilution curves were recorded with a noninvasive dichromatic earpiece densitometer after intravenous injections of indocyanine green solution (Cardiogreen) at rest and after provocative maneuvers, as reported earlier (Figure 2).25 A PFO was defined as present when an early deflection from the baseline was observed before the main upstroke part of the dye curve (Figure 3, C and D). If there was a characteristic hump in the downslope of the main part of the dye curve, an atrial septal defect (ASD) was diagnosed. The dye dilution recordings were analyzed off-line in a random order by a single investigator who was blinded to the clinical characteristics of the patients and to the results of the contrast TEE. All investigations were well tolerated by the subjects without side effects.

Statistical Methods

Sensitivity, specificity, positive and negative predictive values, and the accuracy of dye dilution and ear oximetry were calculated with contrast TEE used as the gold standard. The 95% CIs were calculated with the exact method of CIA statistical software, version 1.0. To study the interrater agreement, 2 observers independently assessed all dye dilution curves and oximetry recordings blinded to each other and to the results of the TEE. κ statistics was used to measure the amount of agreement. The κ values were calculated with SPSS statistical software, version 9.0, and classified according to Landis and Koch.27 We also calculated the likelihood ratios (LR), which indicate how much a diagnostic test will raise or lower the pretest probability of the target disorder.28 The LR of a positive test was calculated from the formula sensitivity/(1 − specificity). The LR of a negative test was calculated from the formula (1 − sensitivity)/specificity.

Results

There was a total of 103 TEE examinations, of which 61 (59%) were positive for PFO. We also found 1 case of previously undiagnosed ASD, with right-to-left shunting after the VM. This ASD was correctly diagnosed with the dye dilution method. For simplicity, this case is included in the group of PFOs in the overall results. Thus, in the study population as a whole, atrial right-to-left shunting was diagnosed by contrast TEE in a total of 62 (60%) cases. Fifteen (24%) of these cases were classified as small shunts and 47 (76%) were categorized as large shunts.

Dye dilution curves were obtained for 67 patients, and the results are presented in Table 1. A correct diagnosis of PFO...
was made with dye dilution in 35 cases and a false-negative result was made in 11 cases. Thus, the sensitivity of dye dilution was 76%. Because no false-positive results were obtained with dye dilution, specificity was 100%. The positive predictive value of dye dilution was 100%, its negative predictive value 65%, and its accuracy 84%. Of the 11 cases classified as false-negative based on dye dilution, 6 patients had a small shunt and 5 a large shunt. When only the largest shunts were included, the sensitivity of dye dilution was 86% (31 of 36).

Ear oximetry was performed on 83 patients (Table 1). Oximetry diagnosed PFO correctly in 45 patients, and the oximetry result was falsely classified as negative in 8 patients. Thus, the sensitivity of oximetry was 85%. None of the oximeter recordings were falsely classified as positive, and the specificity of oximetry was 100%. The positive predictive value of oximetry was 100%, the negative predictive value 79%, and the accuracy 90%. Of the 8 false-negative cases, 5 patients had a small shunt and 3 patients a large shunt. When only the largest shunts were included, oximetry had a sensitivity of 93% (38 of 41).

We obtained both dye dilution curves and ear oximetry recordings for 47 patients. The results were concordant in 45 cases and discordant in 2. Of the 2 discordant cases, oximetry diagnosed PFO correctly in both, whereas the results of dye dilution tests were false-negative.

The 2 independent observers showed good concordance in their assessments of dye dilution curves (65 of 67, 97%) and ear oximetry recordings (79 of 83, 95%) (Table 2). The respective \( \kappa \) values were 0.94 and 0.90. Thus, the interrater agreement can be interpreted as “almost perfect” on the Landis-Koch scale.

The LR of a positive test result was infinite for both dye dilution and ear oximetry. The LR of a negative test result was 0.24 for dye dilution and 0.15 for ear oximetry.

**Discussion**

The main findings of this study demonstrate that dye dilution and ear oximetry, the two noninvasive methods for the detection of PFO, are both 100% specific when compared with the results obtained by the gold standard, that is, contrast TEE. Both methods also showed high sensitivity, with oximetry being slightly more sensitive (85%) than dye dilution (76%). For the large right-to-left shunts, the corresponding sensitivities were even higher: 93% for oximetry and 86% for dye dilution. The interrater agreement of the test results was excellent in both methods.

At the moment, contrast TEE is considered the most sensitive method in the detection of PFO during life and is hence regarded as the gold standard. However, TEE has several disadvantages. TEE is a semi-invasive method; the transducer must be placed in the esophagus and intravenous administration of an echo-detectable contrast material is necessary. Swallowing the tube is uncomfortable, and in some stroke patients the introduction of the esophageal transducer fails because of a lack of cooperation or because of swallowing difficulties. The detection of PFO by TEE is highly dependent on the experience of the sonographer. There is notable variability between different observers in the detection of PFO unless the TEE technique and the criteria of PFO have been standardized. Also, the correct performance of VM is of vital importance for optimal results. The results may remain false-negative in patients who are not able to perform VM properly either because of a neurological disability or because of intolerance of the probe in the esophagus. With TEE, it is possible to estimate the functional size of PFO. However, this estimate is semiquantitative at best and highly dependent on several variables such as the choice of contrast medium, the volume of the bolus, the rate and site of injection, and the plane used for counting the bubbles.

TCD is an alternative method for the detection of PFO. If only those TCD studies are considered that have used blinding and the same criteria of PFO as we did, the sensitivity of TCD varies from 68% to 89% and its specificity from 92% to 100%. Thus, the sensitivity and specificity of dye dilution, oximetry, and TCD are quite comparable. However, TCD also has some disadvantages. In some persons, the bilateral temporal bone window to the middle cerebral arteries is absent, and evaluation through other arteries has not yet been validated. Several methodological parameters that influence the sensitivity and specificity of TCD are still under debate. These include the patient’s posture during the examination, the choice and volume of contrast medium, and the site and timing of the injection. False-positive results of PFO occur with TCD because of

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**TABLE 1. Sensitivity and Specificity of Dye Dilution and Oximetry for Detection of Patent Foramen Ovale With TEE Used as Gold Standard**

<table>
<thead>
<tr>
<th>TEE</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dye Dilution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>76 (61–87)</td>
<td>100 (84–100)</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sum</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>Oximetry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>85 (72–93)</td>
<td>100 (88–100)</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sum</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>

**TABLE 2. Interrater Agreement Between Two Independent Observers on the Results of Dye Dilution and Oximetry**

<table>
<thead>
<tr>
<th>Observer 1</th>
<th>Positive</th>
<th>Negative</th>
<th>Sum</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dye Dilution, observer 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>34</td>
<td>1</td>
<td>35</td>
<td>0.94</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>31</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>35</td>
<td>32</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Oximetry, observer 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>44</td>
<td>1</td>
<td>45</td>
<td>0.90</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>35</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>47</td>
<td>36</td>
<td>83</td>
<td></td>
</tr>
</tbody>
</table>

Positive indicates detection of PFO; negative, no detection of PFO.
shunting through intrapulmonary routes. Criteria that would discriminate between intrapulmonary and intracardiac shunts have been proposed but have been shown to be useless.\textsuperscript{17} Also, the suggestion that these small intrapulmonary shunts play a role in the cause of stroke has remained unproven. The dye dilution method is based on the detection of intravenously injected dye. In a case of right-to-left shunting, part of the dye enters the left atrium and arterial circulation before the lung passage, thus producing an early deflection from the baseline before the main part of the dye curve.\textsuperscript{21–23,25} The TEE, TCD, and dye dilution methods require intravenous injections of contrast agent or dye. Thus, none of these methods can be considered totally noninvasive. The timing of the injection is critical; if the injection is made too early or too late, the proportion of false-negative findings increases. The site of injection is also important. The sensitivity of TEE and TCD have been reported to increase if the contrast material is injected into the femoral vein instead of the antecubital vein.\textsuperscript{30} This was also demonstrated in the early dye dilution studies.\textsuperscript{21–23} However, injections through the femoral vein cannot be considered very practical. Dye dilution also exposes left-to-right shunting. In fact, in this study, 1 case of ASD was diagnosed, with left-to-right shunting at rest and right-to-left shunting after VM. However, it probably is not always possible to differentiate between a PFO and an ASD by dye dilution method.

The oximeter technique is based on a simple idea. In the case of an ASD or PFO, a right-to-left shunt of desaturated blood occurs across the defect during the first few seconds after the end of VM, creating a transient fall in systemic arterial oxygen saturation, which can be monitored noninvasively from the peripheral circulation.\textsuperscript{24,25} The advantages of TCD, dye dilution method, and ear oximetry over TEE are that the tests can be performed by a single investigator, whereas TEE requires 2 persons. Also, VM is much easier to perform during these examinations than with TEE, and there is no need for fasting or sedation. However, the most important advantage of ear oximetry over the other methods is its simplicity and noninvasiveness. Because no intravenous injections are needed, the results are not sensitive to the choice of contrast, the amount of contrast, the injection site, or the timing of injection. Also, oximetry is very inexpensive because there are no costs for contrast material. Because ear oximetry is safe and there are no known contraindications against its use, the recordings can also be performed by technicians and nurses, and the results can be stored on hard disk or floppy disk and interpreted later off-line. The disadvantages of oximetry include its inability to discriminate between PFO and ASD and the fact that it cannot detect right-to-left shunting without provocative maneuvers. Also, we do not know yet if it is possible to quantify the functional size of a PFO by oximetry.

Our study leaves some unanswered questions. For example, we did not assess the sensitivity and specificity of the dye dilution method and ear oximetry in the detection of PFO in a healthy population. The sensitivity and specificity of these methods may not necessarily be the same in a population with a lower prevalence of PFO and possibly with a larger proportion of minor shunts. Second, both dye dilution and ear oximetry missed some PFOs that belonged to the group of large and possibly clinically more significant shunts. Dye dilution and oximetry should be developed further so that it would be possible to detect smaller changes in the dye curves or the oxygen saturation curves. It should also be studied if it is possible to estimate the functional size of a PFO by dye dilution or oximetry. Importantly, it should be noted that dye dilution and ear oximetry methods demonstrate right-to-left shunting of blood but do not reveal the location of the shunt. Even though the shunt most frequently is at the atrial level and most often through a PFO, there is a possibility for shunting by other routes. Right-to-left shunting can sometimes develop in adults with rare congenital heart diseases through ventricular septal defects and patent ductus arteriosus. Also, patients with pulmonary arteriovenous fistulas can have right-to-left shunting. Small right-to-left pulmonary shunts should not create any changes in the oxygen saturation curves after VM. Also, the passage times of the dye through normal capillaries and through a pulmonary shunt are probably so near each other that we expect to see no signs of shunting in dye curves. However, this should be investigated further. Finally, the high prevalence of PFO in our subjects could be due to referral bias. Clinical suspicion of paradoxical embolism may have been the reason for referral in some patients.

Conclusions
Both dye dilution and ear oximetry were extremely specific and highly sensitive methods in the detection of PFO when compared with TEE. Compared with the currently available methods, ear oximetry has many advantages. Ear oximetry is a truly noninvasive method; it is easy to perform at bedside, safe, and inexpensive. We suggest that ear oximetry could be used as a screening method for PFO in patients with a suspected cryptogenic ischemic stroke. If ear oximetry is performed early in the acute phase of stroke and the test result is positive, venography should be considered to detect occult venous thrombosis. If the oximetry test is negative and paradoxical embolism is still clinically suspected, contrast TEE examination is warranted to exclude PFO. Ear oximetry could also be used to screen PFO in epidemiological studies when studying the true importance of PFO in stroke and other conditions. Before this, oximetry should be validated in a group of healthy volunteers. If the sensitivity and specificity of ear oximetry are found to be also high in populations with a low prevalence of PFO, ear oximetry could be used as a screening tool in large cohort and follow-up studies.

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