The Need to Quantify Right-to-Left Shunt in Acute Ischemic Stroke
A Case-Control Study

Joaquín Serena, MD; Tomás Segura, MD; Maria Jesús Perez-Ayuso, MD; Joan Bassaganyas, MD; Albert Molins, MD; Antoni Dávalos, MD

Background and Purpose—Although right-to-left shunt (RLSh) has been reported to be significantly more frequent in young stroke patients with cryptogenic stroke, its relevance in a nonselected population of acute ischemic stroke is not well known. The aim of this study was to determine the importance of the RLSh magnitude as a risk factor for stroke in nonselected patients.

Methods—Two hundred eight patients hospitalized consecutively with transient ischemic attack or acute cerebral infarction and 100 healthy control subjects were studied. Transcranial Doppler ultrasonography (TCD) was performed in both middle cerebral arteries (MCAs) after intravenous application of agitated saline solution. The magnitude of RLSh was quantified by counting the number of signals in 1 MCA during a Valsalva maneuver. RLSh was classified as “no shunt,” “small” (<10 signals), and “large” (>10 signals), with the latter including the “shower” (>25 signals) and “curtain” (uncountable signals) patterns. Extensive investigations, including contrast transesophageal echocardiography, were carried out on patients diagnosed as suffering from stroke of an uncertain etiology. The importance of RLSh for stroke was assessed by logistic regression analysis.

Results—Contrast TCD detected a large RLSh in 40 (19.7%) patients and in 21 (21%) control subjects, all with cardiac RLSh characteristics. A large RLSh was present in 4.7% of atherothrombotic strokes, 10.5% of cardioembolic strokes, 15.4% of lacunar strokes, and 45.3% of cryptogenic strokes ($P<0.001$). Although the overall frequency of RLSh was not significantly different between patients and control subjects, the detection of curtain or shower patterns by contrast TCD was associated with a higher risk of stroke (odds ratio, 3.5; 95% confidence interval, 1.29 to 9.87), particularly with cryptogenic stroke (odds ratio, 12.4; 95% confidence interval, 4.08 to 38.09) after adjustment for concomitant vascular risk factors.

Conclusions—It is essential to quantify RLSh by contrast TCD during the Valsalva maneuver given that only those with shower and curtain patterns are associated with a higher risk of ischemic stroke in a nonselected population. (Stroke. 1998;29:1322-1328.)

Key Words: echocardiography, transesophageal stroke, acute

I

schemic strokes represent the third greatest cause of death and the greatest cause of functional incapacity in the western world. Despite exhaustive investigations, the origin of ischemic strokes is undetermined in 40% of cases according to conventional etiologic criteria, and this is even higher in young stroke patients. PFO has been suggested as a potential source of paradoxical embolism, but this has been questioned by some experts. Most authors agree that there is greater prevalence of RLSh in ischemic stroke of undetermined etiology, although most studies have been carried out using only TEE or in relatively small groups of selected patients, which does not allow for firm conclusions in the general population. Recent studies have suggested the superiority of contrast TCD over TEE both in its ability to diagnose RLSh and to distinguish between cardiac and pulmonary shunt.

The aim of this study was to compare the prevalence of RLSh in a nonselected group of patients consecutively admitted for cerebral infarction and TIA with a group of healthy control subjects.

The subjects and Methods

Our department of neurology is a reference facility for 4 community hospitals, covering an area with a population of about 500 000...
Both MCAs were simultaneously monitored using a monitoring device (Multi DOP X-4; TCD 8 manufactured by DWL Elektronische Systeme). Both MCAs were simultaneously monitored with transcranial Doppler ultrasonography with injection of agitated saline solution (TCD). Contrast transcranial Doppler ultrasonography (contrast TCD) was performed. Patients were divided into 3 different groups on the basis of the maximum number of microbubble signals in the MCA within 7 seconds of the injection. Potential cardiac sources for embolism, including the fossa ovalis, were examined. The TCD protocol was approved by the ethical committee of our hospital, and informed consent was given by control subjects, patients, or the patients’ relatives.

The protocol was approved by the ethical committee of our hospital, and informed consent was given by control subjects, patients, or the patients’ relatives. All patients were submitted to the following examinations: medical history recording potential precipitant stroke factors, clinical examination, blood and coagulation tests, 12-lead ECG, noncontrast CT scan, color-coded duplex sonography of supra-aortic trunks, cerebral microemboli monitoring, and detection of RLSH by contrast TCD. In the control group, vascular risk factors were recorded, and Doppler examination of supra-aortic trunks, basal TCD, cerebral microemboli monitoring, and contrast TCD were performed. Extensive investigations, including contrast TEE, were carried out on patients diagnosed as suffering from stroke of uncertain etiology. The type of stroke was classified using the criteria of the Stroke Data Bank of the Spanish Neurological Society (BADISEN). Briefly, the BADISEN classification system includes 5 categories: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel disease, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology. A diagnosis of infarction caused by large-artery atherosclerosis was made if the patient did not have a lacunar stroke and ipsilateral duplex or arteriography showed a stenosis of >50% of an appropriate intracranial or extracranial artery with hemodynamically significant stenosis.

Cardioembolism included patients with arterial occlusion presumably due to an embolus arising in the heart. Potential cardiac sources for embolism were based on the evidence of their relative propensities for embolism. Potential large-artery atherosclerotic sources of thrombosis or embolism were excluded.

Small-vessel disease was diagnosed if the patient had one of the characteristic clinical lacunar syndromes, no evidence of cerebral cortical dysfunction, and normal CT scan or a focal deep infarction with a diameter of <1.5 cm. Potential cardiac sources for embolism and a stenosis of greater than 50% in an ipsilateral artery were excluded. Acute stroke of other determined etiology included patients with rare causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis were excluded.

Finally, we considered the category of cryptogenic stroke if no etiology was determined despite an extensive evaluation.

Contrast TCD Protocol
Transcranial Doppler examination was carried out using a TCD monitoring device (Multi DOP X-4; TCD 8 manufactured by DWL Elektronische Systeme). Both MCAs were simultaneously monitored through the temporal window by the use of 2-MHz probes. TCD probes were fitted in a light metal frame that was firmly fixed to the head with 2 ear pieces and an adjustable nose saddle (DWL). The contrast of the study was obtained by a mixture of saline solution (9 mL) and air (1 mL), agitated between two 10-ml syringes, connected by a 3-way stopcock. The solution was immediately injected with a 20-gauge/32-mm catheter placed in the antecubital vein to obtain a bolus of air microbubbles. This procedure was performed 3 times during normal breathing and the same number of times during a Valsalva maneuver. The Valsalva maneuver was standardized by having the subjects blow into a manometer until 50 to 60 mm Hg of pressure was reached and asking them to maintain it for a period of at least 5 to 7 seconds. The bolus of air microbubbles was injected in 1 to 2 seconds when this 7-second period ended. The subjects had been previously instructed in performance of the Valsalva maneuver, the efficacy of which was shown by a reduction in the mean velocity of the MCA of at least 25%. To reduce the risk of misclassifying intrapulmonary shunt as intracardiac shunt, only the appearance of air-embolism signals in the MCA within 7 seconds of the injection was considered positive for intracardiac shunt. We quantified the importance of RLSH by counting the number of signals in 1 MCA. Special software for counting emboli was used to record and count high-intensity transient signals from each MCA after air microbubble infusion. Patients were divided into 3 different groups on the basis of the maximum number of microbubble signals in the MCA in any single frame after intravenous injection of agitated saline solution: “normal” TCD study (if 0 signals were detected), “small” RLSH (<10 signals), and “large” degree of shunt (>10 signals). In this last group, “shower” (>25 microbubbles) and “curtain” (uncountable microbubbles) were identified (Figure 1).
Statistical Analysis

Proportions between groups were compared by the \( \chi^2 \) test. The importance of RLSh for all types of stroke and cryptogenic stroke was assessed by logistic regression analysis controlling for age, sex, smoking habit, history of diabetes, hypertension, high cholesterol levels, and cardiac diseases (myocardial infarction, angina pectoris, and atrial fibrillation). Results were expressed as ORs and 95% CIs.

Results

Two hundred sixty-three patients and 117 control subjects were evaluated. Despite the fact that TCD detected RLSh in carotid siphon by ophthalmic window or in the basilar artery by the suboccipital approach, we excluded 55 patients (14 men and 41 women, with a mean age of 72.4 years) and 17 control subjects from the analyses because of absent temporal bone window in order to maintain a standardized method in RLSh detection. Therefore, 208 patients (156 men and 52 women, with a mean age of 64.8 ± 12.3 years) and 100 control subjects (61 men and 39 women, with a mean age of 63.6 ± 12.5 years) were included in the study. Arterial hypertension was registered in 49.3% of patients and 25% of control subjects; diabetes mellitus in 23.9% and 13%, respectively; hypercholesterolemia in 18.7% and 13%, respectively; cigarette smoking in 52.6% and 35%, respectively; and coronary heart disease or atrial fibrillation in 22% and 10%, respectively. Brain infarction was the initial event in 148 patients (71.2%) and TIA in 60 (28.8%). The etiology of ischemic events was large-artery atherosclerosis in 45 patients (21.6%), cardioembolism in 39 (18.8%), small-vessel disease in 65 (31.3%), stroke of other determined etiology in 4 (1.9%), and cryptogenic stroke in 55 (26.4%), with cryptogenic stroke being the stroke subtype particularly frequent in patients under 50 years old (14 of 30, 46.7%). The suspected causes of TIA and cerebral infarction were similar. Territorial infarction occurred in 4 patients with both atrial fibrillation and significant carotid disease. Two of them were classified as atherothrombotic stroke after detection of ipsilateral microembolic signals by TCD monitoring and impaired ipsilateral cerebrovascular reactivity by acetazolamide test, and the other 2 as cardioembolic strokes. The onset of stroke coincided with physical activity in 48 patients, but a Valsalva maneuver and a strong physical exertion were recorded in only 6 and 5 patients, respectively.

The mean time between stroke onset and TCD examination was 71 ± 50 hours. Valsalva maneuver during the procedure could not be achieved in 5 patients and was suboptimal in 18 because of their severe neurological deficit. Among 203 patients, and in all control subjects, who all performed the Valsalva maneuver, contrast TCD detected RLSh in 68 patients (33.5%) and in 32 control subjects (32%), all with cardiac-RLSh characteristics. The RLSh was large in 40 patients (19.7%) compared with 21 control subjects (21%). None of the differences was statistically significant. However, RLSh, both in basal conditions and during the Valsalva maneuver, was found to be significantly more frequent in patients with cryptogenic stroke than in those with stroke of known etiology (Table 1). Moreover, the prevalence of RLSh in cryptogenic strokes was higher not only in young people but in all age groups (Figure 2).

Contrast TCD during the Valsalva maneuver showed an increase in the number of signals when the examination was conducted under basal conditions (Table 2). The quantification of RLSh by TCD during the Valsalva maneuver is shown.
An interesting finding was that the curtain pattern was detected only in the patient group and only in those with cryptogenic stroke. As with the curtain pattern, the shower pattern was detected essentially in cryptogenic stroke. The detection of curtain or shower patterns was associated with a higher risk of stroke (OR, 3.5; 95% CI, 1.29 to 9.87), particularly with cryptogenic stroke (OR, 12.4; 95% CI, 4.08 to 38.09), after adjustment for concomitant risk factors. Potential precipitant stroke factors were not significantly different between patients with and those without large RLSh. Among patients with cryptogenic stroke, a previous Valsalva maneuver or strong physical exertion was registered in 2 patients with \( P < 0.001 \) and in 3 without large RLSh. TEE examination was performed in 44 of 55 patients with cryptogenic stroke (in 4 patients the poor general conditions contraindicated TEE, and in 7 patients TEE was not completed because they did not tolerate the procedure). TEE showed PFO in 22 (50%) patients with cryptogenic stroke and revealed other potential cardioembolic sources in 9 (atrial septal aneurysm in 5 patients, proximal aortic plaques in 3, and atrial spontaneous contrast in 1). TCD showed RLSh in all patients in whom PFO was detected by TEE. An RLSh with intracardiac characteristics shown by contrast TCD was not observed by TEE in 4 patients (3 with small and 1 with large RLSh). All patients with atrial septal aneurysm had a massive RLSh by TCD (curtain pattern in 3 and shower pattern in 2), although it was interpreted by TEE as small in 3 of them and moderate in 2. When TCD was the reference test used to detect RLSh, the sensitivity, specificity, and diagnostic accuracy of TEE were 80.9%, 100%, and 89.4%, respectively.

### Discussion

The role of PFO as a cerebrovascular risk factor is controversial. Previous medical studies in stroke patients, frequently without a control group, have investigated the prevalence of PFO in heterogeneous populations (such as small series of patients,2,3,8,9,17,26,33 selected young patients,2,3,5,8,9,13,17 or patients referred for a TEE study of potential cardiac sources of embolism10,12 ) using different methods for detection, which would explain the variability of the results (Table 4). Most of these investigations showed a higher prevalence of PFO in patients with cryptogenic stroke than in those with stroke of known etiology, suggesting that RLSh may be a risk factor particularly in the first group. However, the frequent identification of PFO among patients with strokes of known cause

**Figure 2.** Frequency of detection of large RLSh by age group. Histogram shows the percentage of large RLSh detected during the Valsalva maneuver in the group of cryptogenic stroke (3), in stroke of known etiology (2), and in the control group (1) in each age group, and in the total population. Numbers inside the bars represent the number of patients studied in each group. Probability values representing the differences between groups are shown at the top of the bars.

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**TABLE 1. Prevalence of RLSh by TCD in Patients by Stroke Subtype and in the Study Population**

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Patients</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atherosclerotic</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>RLSh basal</td>
<td>11 (24.4%)</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>RLSh Valsalva*</td>
<td>11 (25.6%)</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>Large RLSh basal</td>
<td>2 (4.4%)</td>
<td>2 (5.1%)</td>
</tr>
<tr>
<td>Large RLSh Valsalva*</td>
<td>2 (4.7%)</td>
<td>4 (10.5%)</td>
</tr>
</tbody>
</table>

RLSh basal and RLSh Valsalva include all RLSh detected, independent of the size of RLSh. Large RLSh subgroup contains patients with more than 10 microbubbles (including those with shower and curtain patterns).

*Proportions have been calculated from 203 patients who performed the Valsalva maneuver.
†Cryptogenic vs stroke of known etiology, \( P < 0.0001 \).
‡Control group vs cryptogenic, \( P = 0.001 \); ‡‡ \( P = 0.01 \).
§Whole group of patients vs control group, \( P = NS \).
and the unusual coexistence of factors that support a paradoxical embolism (such as previous history of phlebothrombosis; clinical, ECG, or echocardiographic criteria of pulmonary hypertension; and, especially, stroke onset after maneuvers that increase the pressures in the right-sided heart cavities such as coughing or defecation) in patients with PFO and cerebral infarction,12,17,34 raises doubts about the etiopathogenic role of PFO, particularly in older patients, the group most at risk from stroke.

To clarify these contradictory results, we undertook a large-scale study that evaluated 263 consecutive, nonselected patients submitted to an extensive standardized diagnostic protocol and 117 control subjects. Contrast TCD was used for the detection of RLSh because of its high reliability and its relatively noninvasive procedure. The prevalence of RLSh in healthy control subjects (32%) was similar to the prevalence of PFO in autopsy studies,35,36 supporting a high degree of accuracy of TCD in the detection of cardiac shunt. Although the prevalence of RLSh in stroke patients was similar to that seen in the control group, it was extremely high in those with cryptogenic stroke. These findings agree with those from previous studies that demonstrate a higher prevalence of PFO in young patients with stroke of unexplained etiology than in previous studies that demonstrate a higher prevalence of PFO, particularly in older patients, the group most at risk from stroke.

The importance of the size of RLSh detected by TEE was previously stressed by De Castro et al.40 These authors found that patients with cryptogenic stroke and PFO showing ischemic brain lesions on CT had a higher number of air microbubbles in the left atrium than those without CT ischemic lesions and PFO.40 In the present study we investigated whether the size of RLSh quantified by TCD during the Valsalva maneuver was a determinant of the association of RLSh with cryptogenic stroke observed in previous studies. To the best of our knowledge, only 1 study on nonselected patients with acute ischemic stroke evaluated the size of RLSh11 (Table 4). Although the etiopathogenic and therapeutic implications of the size of RLSh are still not clear, our results stress the need to quantify RLSh during the Valsalva maneuver. First, the detection of a large RLSh during the Valsalva maneuver was not infrequent in patients with minimal or absent RLSh under basal conditions, a fact that may lead to the misclassification of relevant RLSh as minimal shunts. Among 68 patients with RLSh detected during the Valsalva maneuver, 9 had a minimal or absent RLSh under basal conditions that were in turn detected as massive (shower or curtain pattern) during the Valsalva maneuver (Table 2). Second, we have observed that the greater the magnitude of the RLSh the greater the significant association with cryptogenic stroke; this is not surprising if we assume that the larger the RLSh the higher the risk of paradoxical embolism. Third, the clinical relevance of small RLSh is questionable. We have found no significant association between small RLSh detected during the Valsalva maneuver and the risk of stroke, not only in patients with <10 signals but also in those with >10 signals and no shower or curtain pattern (Table 3). Previously published studies and the present study have shown a higher frequency of RLSh in patients with cryptogenic stroke than in the control group; nevertheless, we have demonstrated that this significant difference was because of the presence of massive RLSh with shower or curtain characteristics in the patient group. These patterns were associated with a 3.5-fold increase in the risk of stroke and a 12-fold increase in the risk of cryptogenic stroke.

In our study the quantification of RLSh was more sensitive and reliable with TCD than TEE. In fact, 6 cryptogenic strokes with large RLSh defined as shower or curtain by TCD were classified by TEE as small PFO in 5 and as no RLSh in 1. Although TEE may detect a concomitant atrial septal

### TABLE 2. Distribution of Patients According to the Degree of RLSh Detected by TCD Under Basal Conditions and During Valsalva Maneuver

<table>
<thead>
<tr>
<th>RLSh During Valsalva Maneuver</th>
<th>No</th>
<th>&lt;10 Signals</th>
<th>&gt;10 Signals</th>
<th>Shower</th>
<th>Curtain</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>134</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>&lt;10 signals</td>
<td>11</td>
<td>17</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>&gt;10 signals</td>
<td>1</td>
<td>10</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Shower</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Curtain</td>
<td>...</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

### TABLE 3. RLSh Detected by TCD During Valsalva Maneuver Classified by Its Magnitude in Cryptogenic Stroke, Stroke of Known Etiology, and Control Group

<table>
<thead>
<tr>
<th>RLSh</th>
<th>Cryptogenic Stroke</th>
<th>Stroke of Known Etiology</th>
<th>All Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=53)</td>
<td>(n=150)</td>
<td>(n=203)</td>
<td>(n=100)</td>
</tr>
<tr>
<td>&lt;10 signals</td>
<td>6 (11.3%)*</td>
<td>22 (14.7%)†</td>
<td>28 (13.8%)§</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>10-25 signals</td>
<td>5 (9.4%)*†</td>
<td>13 (8.7%)‡</td>
<td>18 (9.0%)§</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Shower pattern</td>
<td>10 (18.9%)**</td>
<td>3 (2%)††</td>
<td>13 (6.4%)§</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Curtain pattern</td>
<td>9 (17%)***</td>
<td>9 (4.4%)††</td>
<td>4 (4.0%)‡‡</td>
<td>0</td>
</tr>
</tbody>
</table>

Cryptogenic vs control group, *P=NS; **P=0.01; ***P=0.0001.
Stroke of known etiology vs cryptogenic stroke, †P=NS; ††P=0.0001.
Whole group of patients vs control group, ‡P=NS; ‡‡P=0.03.
an aneurysm (a defect that has been identified as a minor potential source of cardiac embolism),\textsuperscript{1,41–43} which occurred in 5 patients in the present study, in our experience all of them are associated with shower or curtain RLSh patterns. This fact suggests that these contrast TCD patterns may be used as potential markers of atrial septal aneurysm and that they may be useful in selecting those patients in whom TEE should be performed. The TEE is an invasive test that frequently requires the patient to be sedated and is problematic in patients with swallowing difficulties, and the Valsalva maneuver is difficult to perform and standardize. In our opinion, TCD represents the ideal method to assess the cerebral consequences of PFO and is the only technique capable of detecting the passage of emboli across the brain arteries in real time. The number and size of air microbubbles is not standardized in our method. Nevertheless, ischemic symptoms in patients with large RLSh (shower or curtain) due to presumed embolus blockage of small brain arteries by air infusion were not detected in this series or in our daily clinical practice. Despite this, to reduce the number of intravenous air injections, the basal examination should be avoided in cooperative patients. TCD is more sensitive in the detection of RLSh than transthoracic\textsuperscript{9,22,44} and transesophageal\textsuperscript{23} contrast echocardiography, as we observed in our series of patients, because it is simple to use, noninvasive, relatively inexpensive, and repeatable without adverse consequences. Moreover, it allows the magnitude of the RLSh to be quantified more easily. These characteristics make TCD an excellent routine diagnostic tool for the assessment of intracardiac RLSh in all patients with an acute ischemic stroke or TIA.

We conclude that it is essential to quantify the magnitude of RLSh by contrast TCD during the Valsalva maneuver, given that only those with shower and curtain patterns are associated with a higher risk of ischemic stroke in a nonselected population. Contrast TCD is more sensitive than contrast TEE and should be routinely used in the evaluation of RLSh in acute ischemic stroke.

**Acknowledgments**

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**References**


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