Shunt volume dynamics in stroke patients with patent foramen ovale

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1University Giessen Lung Center, University Hospital Giessen, Giessen, Germany; 2Department of Neurology, University Hospital Giessen, Giessen, Germany; and 3Department of Pneumology, Asklepios Lung Center, Munich-Gauting, Germany

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Reichenberger F, Kaps M, Seeger W, Tanislav C. Shunt volume dynamics in stroke patients with patent foramen ovale. J Appl Physiol 115: 704–707, 2013. First published June 6, 2013; doi:10.1152/japplphysiol.00507.2012.—A variation in right atrial and pulmonary arterial pressure might result in a shunt dynamic across a patent foramen ovale (PFO). In the present study we tested if peak exercise facilitates a restoration of right to left shunt (RLS) in stroke patients who demonstrated a functional PFO closure (no evidence of RLS across an initially demonstrated PFO). In stroke patients with PFO demonstrating a functional closure, the RLS was reassessed on peak exercise using contrast-enhanced transcranial Doppler sonography. The exercise procedure consisted of a cardiopulmonary exercise test with supplementary stress echocardiography for assessment of pulmonary circulation. Four stroke patients with initially PFO curtain pattern and a subsequent functional PFO closure (no evidence for RLS) underwent the procedure. In all four patients a RLS could be resurrected during peak physical exercise after a Valsalva strain. While in two patients peak exercise led to an RLS in a countable range of microembolic signals, in two patients a curtain pattern was obtained. One patient showed evidence for reoccurrence of RLS on peak exercise without a Valsalva strain. The patients with curtain pattern had a better peak exercise performance. Although the systolic pulmonary arterial pressure increased during exercise in all patients, there was no direct correlation with the detected RLS. After a functional PFO closure peak exercise combined with a Valsalva strain facilitates the reoccurrence of RLS in stroke patients.

In patients with patent foramen ovale (PFO) there is evidence supporting the hypothesis of variation in right to left shunt (RLS) (1, 4, 6, 10, 21, 25). As demonstrated by Zerio and coworkers after the normalization of the right atrial pressure in the course of a pulmonary emboli, a RLS across a previously demonstrated PFO was no longer detected (25). This observation indicates the mechanism of a functional PFO closure. A potential factor involved in the mechanism of shunt dynamic across a PFO is obviously the fluctuation in right atrial and pulmonary arterial pressure (25). This occurs physiologically during intense physical activity (1, 7, 10). Therefore we tested in stroke patients demonstrating a functional PFO closure whether the RLS across a PFO could be resurrected during peak exercise, which might induce an increase in right atrial and pulmonary arterial pressure.

Patients and Methods

Patients. We examined patients with PFO, who presented during the acute stroke with a large RLS and showed a functional PFO closure (no evidence of RLS across an initially demonstrated PFO) on follow-up. The PFO was initially diagnosed by transesophageal echocardiography and contrast-enhanced transcranial Doppler sonography (ce-TCD) (21). For physical exertion an exercise bicycle was used; a comprehensive cardiopulmonary monitoring was continuously undertaken. To prove the RLS a ce-TCD was performed according to a standardized protocol described elsewhere in detail (11). The instrumentation and the study settings are demonstrated in Fig. 1. The study protocol was reviewed and approved by the ethical committee of the medical faculty of the Justus Liebig University Giessen (protocol no. 153/07).

c-TCD. A 2-MHz probe (Multi-Dop T digital; Compumedics DWL, Singen, Germany) was used to carry out the c-TCD. The contrast agent Echovist (Bayer Vital, Berlin, Germany) was prepared according to the manufacturer’s instructions and injected into a large cubital vein of the left arm. The contrast agent was administered in two separate boluses of 5 ml each; the first dose was injected during normal respiration and the second dose during a Valsalva strain lasting 10 s. The number of microembolic signals (MES) that appeared in the cerebral circulation (insonation of the proximal part of the left middle cerebral artery) was precisely documented; a curtain pattern was considered in case an individual count of MES was not possible (11). The examination was performed at rest and repeated at peak physical performance.

Exercise procedure and cardiopulmonary monitoring. Before the procedure the following examinations were performed: spirometry, body plethysmography, measurement of diffusion capacity for carbon monoxide, blood gas analysis from an arterialized earlobe sample, ECG, and transthoracic echocardiography at rest. Standard transthoracic echocardiography (SSD 4000; Aloka, Meersbusch, Germany) at rest included measurements of dimension and function of left and right heart chambers and assessment of valvular changes by Doppler echocardiography. The systolic pulmonary arterial pressure (sPAP) was calculated using the tricuspid valve pressure gradient and adding estimated central venous pressure, predicted by assessment of inferior vena cava diameters in end inspiration as previously described elsewhere (24).

All patients underwent unencouraged cardiopulmonary exercise test (Vmax 229 Sensormedics; Viasys Healthcare, Hoechberg, Germany). Patients were asked to exercise up to their individual limit on an exercise bicycle in a semisupine position tilted 30 degrees toward the left side to obtain an optimal echocardiographic window (Ergoline, Bitz, Germany). The exercise protocol included an increase in exercise load of 30 watts every two minutes. The echocardiographic sPAP, heart rate, ECG, and oxygen saturation were recorded continuously. The blood pressure was measured every two minutes, and blood gas analyses from arterialized earlobe samples were retrieved at rest and at peak exercise to calculate alveolar-arterial oxygen difference. For assessment of individual exercise capacity, we determined the maximum oxygen uptake, \( \dot{V}O_2 \) peak (ml·kg\(^{-1}\)·min\(^{-1} \) and %predicted, respectively), and the individual heart rate reserve at peak exercise (predicted maximum heart rate 220-age). For individual assessment of adaption of pulmonary circulation during exercise, we considered the ratio between systolic pulmonary artery pressure and \( \dot{V}O_2 \) peak (%predicted) (5, 17, 18).

Results

In a previous investigation, we identified six patients with a functional PFO closure being eligible for inclusion in the present study (21). Four patients were investigated according

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to the protocol. In these patients, the index stroke event was
classified as cryptogenic stroke. One patient suffered from a
transient ischemic attack, and in the remaining three patients a
brain infarction was evident (Table 1). Before the exercise
procedure, the functional closure of the PFO was confirmed by
ce-TCD in two consecutive examinations.

All patients showed a significant cardiocirculatory response
to exercise with an increase in heart rate and blood pressure.
The individual peak performance ranged from 120 to 250
watts. In all patients, there was an obvious increase in sPAP
(from 16–20 to 22–39 mmHg) (Table 2). The detected param-
ters at rest and peak exercise are summarized in Table 2.
While testing the RLS on peak exercise in one patient a shunt
could be detected (patient 3; 5 MES), whereas in the other
patients a RLS was not evident. After performing the Valsalva
strain during peak exercise, in all four patients, a consid-

erable RLS could be detected. Whereas in patients 1 and 4 an
RLS in countable range was evident (17 and 30 MES), in
patients 2 and 3 a significant RLS with curtain pattern was
induced by the Valsalva strain during peak exercise. The two
patients with a curtain pattern had a better peak exercise perfor-

cance and achieved a higher heart rate with a maximal consump-
tion of heart rate reserve; both patients achieved a higher \( \dot{V}_O^2_{\text{peak}} \)
compared with the other two patients. Although the sPAP in-

creased during exercise in all patients, there was no evident
association between the increase in sPAP or the sPAP-to-\( \dot{V}_O^2_{\text{peak}} \)
ratio and RLS detected at rest and on peak exercise (Table 2).

**DISCUSSION**

In a small number of subjects, we demonstrated the resur-

duction of the RLS across a PFO; in all cases, a history of

**Table 1. Baseline data on index event and shunt evaluation on follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
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<td>Age, yr</td>
<td>38.4</td>
<td>55.2</td>
<td>32.2</td>
<td>55.1</td>
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<tr>
<td>Sex</td>
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<td>Stroke</td>
<td>Stroke</td>
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<td>Cryptogenic</td>
<td>Cryptogenic</td>
<td>Cryptogenic</td>
<td>Cryptogenic</td>
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<tr>
<td>ce-TCD findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt size without Valsalva, MES</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Shunt size with Valsalva, MES</td>
<td>Curtain</td>
<td>Curtain</td>
<td>Curtain</td>
<td>Curtain</td>
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<tr>
<td>TEE findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shunt size without Valsalva, microbubbles</td>
<td>&lt;30</td>
<td>0</td>
<td>0</td>
<td>&lt;30</td>
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<tr>
<td>Shunt size with Valsalva, microbubbles</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
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<tr>
<td>ASA</td>
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<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HAS</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
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<td>No</td>
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<tr>
<td>Shunt evaluation on follow-up</td>
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<td></td>
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<tr>
<td>Time delay to index event, mo</td>
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<td>6</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>ce-TCD shunt size without Valsalva, MES</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>ce-TCD shunt size with Valsalva, MES</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

TIA, transient ischemic attack; ce-TCD, contrast-enhanced transcranial Doppler sonography; MES, microembolic signals; TEE, transesophageal echocardiography; ASA, atrial septum aneurysm; HAS, hypermobile atrial septum; DVT, deep vein thrombosis.
stroke and a previous functional PFO closure was evident. Whereas the peak physical exercise alone might not be sufficient to induce a RLS, in this condition the peak exercise combined with a Valsalva strain seems to be most effective in facilitating a RLS. In all included patients, a RLS was resurrected by peak exercise in addition to a Valsalva.

As suggested in previous investigations, a variation in shunt volume across a PFO might be determined by different pressure conditions in the right heart and pulmonary arterial system (1, 10, 25). In the presented study, physical exercise led to an increase of sPAP within normal limits in all patients. However, a direct relationship between the increase in sPAP and the detected RLS volume was not obvious. In contrast, the increase in cardiac output during physical exercise seems to be of higher relevance. For inducing a RLS across a PFO, a pressure difference on the atrial level is necessary to open the PFO.

In stroke patients with unknown etiology, this finding is of particular interest (13, 15, 16). It seems likely that a considerable number of PFO might be missed using routine diagnostic procedures. In this context, screening for PFO in the exercise condition could be beneficial, potentially unveiling PFO shunts that otherwise remain hidden when investigated at rest.

In summary, the results presented in this study suggest that PFO diagnostic procedures in stroke patients with evidence for a functional closure of a PFO may be enhanced by adding peak exercise combined with a Valsalva strain. In this circumstance, shunt resurrection may be induced with peak exercise plus the addition of the Valsalva, particularly when the Valsalva fails to resurrect the RLS at rest. When considering patients with

### Table 2. Hemodynamic parameters and PFO shunt evaluation before and during peak exercise

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maximal individual performance, watts</th>
<th>sPAP, mmHg</th>
<th>Peak exercise</th>
<th>At rest</th>
<th>V˙O2peak, ml/kg</th>
<th>%predicted</th>
<th>V˙O2peak, %predicted</th>
<th>sPAP/V˙O2</th>
<th>sPAP/V˙O2</th>
<th>Blood pressure, mmHg</th>
<th>Heart rate, /min</th>
<th>ce-TCD at rest, MES</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>16</td>
<td>20</td>
<td>17</td>
<td>18</td>
<td>8</td>
<td>33</td>
<td>0.38</td>
<td>0.41</td>
<td>100/50</td>
<td>61</td>
<td>0</td>
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<td>24</td>
<td>39</td>
<td>22</td>
<td>25</td>
<td>9</td>
<td>32</td>
<td>0.41</td>
<td>0.41</td>
<td>145/85</td>
<td>64</td>
<td>0</td>
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<tr>
<td>3</td>
<td>150</td>
<td>86</td>
<td>82</td>
<td>80</td>
<td>25</td>
<td>25</td>
<td>16</td>
<td>0.24</td>
<td>0.24</td>
<td>120/80</td>
<td>84</td>
<td>0</td>
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<tr>
<td>4</td>
<td>120</td>
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<td>78</td>
<td>98</td>
<td>96</td>
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<td>61</td>
<td>0.48</td>
<td>0.48</td>
<td>180/90</td>
<td>84</td>
<td>0</td>
</tr>
</tbody>
</table>

sPAP, systolic pulmonary arterial pressure; Pvo2, partial pressure of oxygen in the arterialized blood sample from the earlobe; AaDO2, alveolar–arterial oxygen difference; V˙O2, oxygen uptake; MES, microembolic signals.
functional closure of the PFO, reopening with RLS may occur under various conditions when significant pressure gradients are induced right-to-left across the PFO. This may occur during exercise but appears to be more likely when additionally straining maneuvers like the Valsalva are performed.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES