

Menstrual cycle dependent right-to-left shunting: A single-blinded transcranial Doppler sonography study.

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¹Department of Neurology, University Hospital Innsbruck, Austria (S.K., M.S., K.E., C.S., E.S.), ²Institute of Biostatistics and Documentation, University Innsbruck, Austria (H.U.), ³Department of Neuroradiology University Hospital Mannheim, Clinical Faculty University of Heidelberg, Germany (M.D.), ⁴Clinic for Cranio-Maxillofacial Surgery, University Hospital Zurich, Switzerland (T.M.)

Klien S, Spiegel M, Engelhardt K, Schmidauer C, Ulmer H, Diepers M, Mutzbauer T, Schmutzhard E. Menstrual cycle dependent right-to-left shunting: A single-blinded transcranial Doppler sonography study. *Undersea Hyperb Med* 2005; 32(6): 403-407. Background and purpose: Menstruation has been described as risk factor for neurological decompression sickness in divers. In considering this for paradoxical gas embolism, we hypothesized that there may be a link between cycle-dependent hormonal changes and the manifestation of a right-to-left shunt (RLS). Methods: 40 women with a regular cycle of 28 days underwent transcranial Doppler sonography examinations (TCD) on day 1 and on day 15 of the menstrual cycle. Cerebral high intensity transient signs (HITS) proved a RLS. Results: We found a 25% RLS incidence consistent with the literature. In 7 of 10 shunt-positive women it was detected mainly or exclusively on day 15. This difference in PFO detection rate is statistically significant ($p=0.031$), indicating more RLS during the peri-ovulatory period. Conclusions: Our results do not support menstruation as a risk factor for neurological decompression sickness. The peri-ovulatory estrogen peak, which leads to systemic vasodilation, may explain our data. Factors that increase the risk for developing a RLS and thereby paradoxical embolism should be avoided, perhaps including diving during the peri-ovulatory period of the menstrual cycle. Furthermore, contrast PFO testing in fertile females may be most sensitive if conducted mid-cycle.

INTRODUCTION

In humans, the postnatal closure of the foramen ovale is often incomplete, leading to a patent foramen ovale (PFO), which may be opened by increasing right atrial pressure (1). The prevalence of a PFO is estimated to be 25-35% (2). However, larger foramina (6-10mm diameter), leading to a right-to-left shunt (RLS) even at rest, occur only in 5% of the population (3). This is in contrast to usually clinically silent foramina with a size of 2-6 mm. A prevalence of PFO of more than 40% has been found in patients with brain infarcts, especially those with cryptogenic stroke (4-5).

A PFO usually does not cause disease.

Depending on size, the direction of flow, and the inter-atrial pressure gradient, this defect is the most important cause of RLS (6). Alternatively, RLS can develop through pulmonary arteriovenous malformations (P-AVM), which are rare vascular anomalies (7). The pathogenic potential of PFO varies with the degree of RLS and associated cardiac abnormalities (8, 9), but the greatest concern is as pathway for a paradoxical arterial embolism (5). In patients with RLS, it is surmised that >50% of paradoxical emboli end up in intracranial vessels (10). Frequently paradoxical arterial embolism results in a large

territorial infarction (11); however, transient ischemic attack, transient global amnesia (12), migraine with aura (13) and occlusion of retinal arteries (14) have also been reported. A PFO in divers may enhance the risk for cerebral manifestation of decompression sickness (15), and in surgery, a PFO can be detrimental by promoting peri-operative hypoxemia or paradoxical gas embolism (6). Moreover PFO in mountaineers increases the risk of cerebral hypoxia or paradoxical arterial embolism (16). Similarly, in patients with permanently increased right atrial pressure (e.g. caused by chronic lung disease (17)) as well as in patients with pulmonary embolism (18) or asthma (19), the presence of a PFO increases mortality.

The diagnostic certainty of paradoxical embolism rests mainly on the exclusion of other causes and proof of a PFO, and can usually only be given a high probability (20). Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and transcranial Doppler (TCD) sonography with the administration of contrast medium are accepted means to diagnose a PFO, each with a specificity of 100% (21). The non-invasive TTE has low sensitivity (57-76%); the “gold standard” semi-invasive TEE has up to 99% sensitivity (22). Relevant cardiac or pulmonary shunts have been shown by TCD with a sensitivity of more than 93%; even the smallest emboli in the brain may be detected with this non-invasive method (23).

Recently, menstruation has been described as a potential risk factor for neurological manifestations of decompression sickness in scuba divers when diving is performed during the menstrual cycle (24). Scuba diving adds to RLS because exertion and the Valsalva manoeuvre increase pulmonary pressure, thus cycle-dependent vasoactive substances may increase the significance of a PFO. The aim of this study was to provide evidence for cycle-dependent changes of RLS

via a PFO or the pulmonary circulation, thus possibly allowing the assessment of additional risk of air embolism in fertile women planning to scuba dive, go to altitude, or undergo certain surgical or diagnostic procedures.

SUBJECTS AND METHODS

This study was approved by the ethical committee of the University Hospital Innsbruck, Austria. It was performed as a prospective, single-blinded cross over cohort study. Forty healthy female patients, aged 18-40 years, without oral contraceptive use or other hormonal medication and a regular cycle of 28 days were included. Pregnancy, breastfeeding and a history of cerebro-vascular ischemia were exclusion criteria. The subjects were recruited by a non-blinded coordinator (S.K), and were informed of the significance of the study, the possible risks, and the sequence of examinations. Written informed consent was obtained from every test person in accordance to the University Hospital's procedures. The subjects, who had a median age of 30.5 years (range 18-40 years), were chosen at least two weeks before the first of two scheduled TCD examinations. One examination was planned on the first day of menstruation and the second during the peri-ovulatory period.

Both TCD examiners (M.S, C.S.) were unaware of the day of the menstrual cycle for the examinations. Each subject was examined by the same TCD examiner on both occasions. TCD was carried out with a transcranial Doppler system (Multi-Dop-X2, DWL) with a 2 MHz probe. Signal detection was always performed unilaterally in the right middle cerebral artery (MCA). A mixture of 9ml NaCl and 1ml air (agitated saline) injected into an antecubital vein through a Venflon (18 GA) was used as the sonographic contrast medium. The first recording was done under resting conditions, to allow evaluation of spontaneous passage

of the contrast medium. The examination was repeated while the subject performed a Valsalva manoeuvre 5 seconds after the contrast medium had been injected that lasted at least 10 seconds. The recordings differentiated between single bubbles (<10) and a shower of bubbles (>10) in the MCA. The procedure was repeated 14 days later. After completion of both TCD for all 40 test persons, the results were documented by the coordinator (S.K.). The case report forms were statistically evaluated by three of the authors (K.E., T.M., H.U.), who were also blinded with respect to the day of the menstrual cycle of the examined subject. Statistical analysis was carried out using Mc Nemar's test, a non-parametric test to evaluate two related variables.

RESULTS

One hundred and five women were screened for entry into the study. Sixty-five were excluded for not meeting the inclusion criteria. Forty women were randomized by a sequence generated by our statistician, and all received both examinations. In 10/40 (=25%) females a RLS was identified on at least one examination. As shown in Table 1, a shunt was detectable in these 10 subjects on day 15 of the cycle, i.e. during the periovulatory phase. Four of these women had a detectable RLS on day 1 of the cycle as well.

Seven shunt-positive women showed high intensity transient signs (HITS) mainly on the day 15 examination: In 6 women the RLS was detected on day 15, exclusively. One person showed single bubbles on day 1, but a shower of bubbles on the day 15 examination. The cycle-dependent difference in the frequency of a RLS in these 18-40 year old women with a regular menstrual cycle was significant by Mc Nemar's test ($p=0,031$), i.e. during the periovulatory phase significantly more females displayed a RLS than on the first day of the

menstrual cycle.

DISCUSSION

In accordance with the prevalence of a PFO of 20-30% in the normal population (2), a RLS was demonstrated in 10/40 (=25%) healthy fertile women at least once during the menstrual cycle. In this cohort a significant variation was found in the frequency of RLS throughout the menstrual cycle. In literature, a possible relationship has been reported between altitude decompression sickness and the menstrual cycle (24) but diving studies that support such findings are rare (25). Most reports suggest women may be at greater risk of developing decompression sickness at the beginning of the menstrual cycle. However, this idea was not supported by the findings of our cohort study. A RLS by recording high intensity transient signs (HITS) on transcranial Doppler sonography with contrast medium was detected significantly more often during the periovulatory period than on day 1 of the menstrual cycle. Scuba diving adds to RLS by increasing the intrathoracic pressure, e.g. by Valsalva manoeuvre (26) or by immersion (27), through possible PFO or pulmonary shunts. Vasoactive substances in the blood are subject to variable concentrations. Dilatation of systemic vessels induced by these substances (e.g. estrogen), may increase RLS by loosening the PFO frame. Since scuba diving favours a RLS, the presence of vasoactive substances may increase the clinical relevance of a RLS.

Estrogen is the dominant hormone in the female cycle in the follicular phase, particularly during ovulation. One of the effects of estrogen is systemic vasodilation. The exact mechanism of this systemic vasodilation by estrogen has not been fully explained; cycle dependent increases of systemic vasodilators like certain prostaglandins (28) or nitric oxide (NO) (29) may execute this estrogen effect.

Table 1. Patent persistent foramen ovale on day 1 and day 15 in a cohort of 40 healthy females, objectivised by transcranial Doppler sonography.

	Day 1		Day 15	
	At rest	With Valsalva	At rest	With Valsalva
Test person 1			Single bubbles	Shower
Test person 2			Single bubbles	Shower
Test person 3			Single bubbles	Shower
Test person 4			Single bubbles	Shower
Test person 5				Single bubbles
Test person 6				Shower
Test person 7		Single bubbles		Single bubbles
Test person 8		Single bubbles		Single bubbles
Test person 9	Single bubbles		Shower	Shower
Test person 10	Shower			Single bubbles

Furthermore, estrogen-induced vasodilation was found to be regulated by calcium-activated potassium channels and nitric oxide (30). Beside that, estrogen is reported to suppress the vasoconstrictor, endothelin (31). These reports (28-31) support our findings, as a higher frequency of a RLS was observed during the high estrogen periovulatory phase.

Our findings showed that the presence of RLS in fertile women may be subject to cyclical fluctuations. In the periovulatory phase, the risk of a potential paradoxical embolism may be higher than in the initial phase of the menstrual cycle. Under conditions of increased risk of paradoxical embolism, special care taken to avoid the arterialisation of venous emboli in young females during the periovulatory period may reduce the risk of central nervous system manifestations. It is also prudent to recommend appropriate timing of PFO examinations in fertile females in the periovulatory period of the cycle. In scuba diving, conservative diving profiles are highly recommendable for these

individuals during the periovulatory phase.

In conclusion, factors that increase the basic risk of development of RLS and thereby paradoxical embolism should be avoided, if possible, during the periovulatory period of the menstrual cycle. Furthermore, contrast PFO tests in females of fertile age may be most sensitive if conducted mid cycle.

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