Clinical Neurology and Neurosurgery 125 (2014) 9–14

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Patent foramen ovale and asymptomatic brain lesions in military fighter pilots

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ARTICLE INFO

Article history:
Received 14 May 2014
Received in revised form 3 July 2014
Accepted 7 July 2014
Available online 18 July 2014

Keywords:
Patent foramen ovale
Right-to-left shunt
White matter lesion
Pilot

ABSTRACT

Background and purpose: Previous studies have reported higher incidence of white matter lesions (WMLs) in military pilots. The anti-gravity straining maneuver, which fighter military pilots perform numerously during a flight is identical to the valsalva maneuver. We sought to investigate the prevalence of right-to-left shunt (RLS) associated with WMLs in military pilots.
Methods: A prospective study was performed involving military pilots who visited the Airomedical Center. The pilots underwent brain magnetic resonance imaging (MRI) scan and transcranial Doppler (TCD) with intravenous injection of agitated saline solution for the detection of RLS. Periventricular WMLs (PVWMLs) on MRI were graded using Fazeka's scale, and deep WMLs (DWMLs) were graded using Scheltens's scale.
Results: This study included 81 military pilots. RLS on TCD was observed less frequently in non-fighter pilots than in fighter pilots (35.5% vs. 64.5%, $p = 0.011$). Fighter pilot was an independently associated factor with RLS on the TCD. DWMLs were independently associated with RLSs through a patent foramen ovale (PFO) (OR 3.507, 95% CI 1.223–10.055, $p = 0.02$).
Conclusion: The results suggest that DWMLs in military pilots may significantly be associated with RLS via PFO. Additional investigations are warranted.

1. Introduction

Compared to the past, advances in neuroimaging have brought attention to incidentally detected abnormalities in brain magnetic resonance imaging (MRI). Among these abnormalities, only white matter lesions (WMLs) show hyperintense MRI signals on both fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequence located in periventricular areas (periventricular WMLs, PVWMLs) and deep white matter (deep WMLs, DWMLs) [1]. WMLs are associated with dementia, migraine, neurologic decompression sickness, stroke, and other neurologic disorders [2–6]. In particular, migraineurs have a 2- to 4-fold higher risk of developing WMLs than nonmigraine controls [7]. However, clinical implications and causes of these WMLs remain controversial and incomplete.

Recent studies have reported that right-to-left shunts (RLSs) via patent foramen ovale (PFO) are associated with WMLs in patients with migraine and dementia [8–11]. Purandare et al. [11] found that the presence of a significant RLS is associated with severe DWMLs in patients with Alzheimer's disease. Also, a retrospective study has shown that migraineurs with RLS have a higher frequency of small DWMLs compared with those without RLS [12]. Moreover, in a systematic review and meta-analysis investigating the role of trans-catheter closure of PFO in the occurrence of migraine, percutaneous closure of PFO showed some benefit in migraineurs [13]. Thus, microembolization, thrombosis, and vasoactive chemicals through PFO are thought to contribute to the pathophysiology of migraine in addition to the development of WMLs [14–16].

In a previous case-control study of military pilots with WMLs, we found that the Korean military pilot group displayed a tendency toward a higher prevalence of WMLs compared with the nonflying personnel group and presumed that the etiology of these phenomena was decompression sickness [17]. However, applying this hypothesis to all military pilots may need more investigations.

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http://dx.doi.org/10.1016/j.clineuro.2014.07.011
0303-8467/

As with migraine, we presumed that RLS via PFO could lead to WMLs in Korean military pilots.

Military pilots perform the antigravity straining maneuver (AGSM) several times to prevent gravity-induced loss of consciousness (G-LOC) due to cerebral vascular collapse because they are subjected to multiple events of head-to-foot inertial force that is maximal 9 times their own body weight (9 G) during centrifuge training and flight missions. The AGSM is isometric straining of the legs, buttocks, and arm muscles to hinder venous pooling of blood and simultaneous straining of the stomach muscles for increasing abdominal cavity pressure. The maneuver is almost identical to Valsalva's maneuver enhancing the PFO detection rate by increasing right atrial (RA) pressure [18,19].

However, only a few studies have investigated the etiology of WMLs by using MRI in pilots. In this study, we identified the etiology of subcortical WMLs in healthy young pilots who lack common risk factors for recognized cerebrovascular disease. We hypothesized military pilots with WMLs would exhibit a significantly higher prevalence of PFO than those without.

2. Subjects and methods

2.1. Study population

This is a prospective study of male pilots visiting the Aeromedical Center, Republic of Korea Air Force between May and October of 2012. The subjects in this study were healthy pilots who (1) visited our hospital for routine checkups, (2) aged 20–40 years, and (3) gave written informed consent. Exclusion criteria through a questionnaire were as follows: (1) history of decompression sickness, hypertension, cardiac arrhythmia, diabetes mellitus, hyperlipidemia, migraine, cerebral arteriovenous malformations, stroke, or other serious structural brain diseases and (2) suspicious current infection signs, such as fever, increased ESR, and leukocytosis affecting the brain lesion.

2.2. Methods

2.2.1. Clinical assessment

The pilots were consistently evaluated according to our biannual medical checkup protocol, and the following clinical data were obtained from all pilots: age and stroke-related risk factors, including blood pressure, fasting blood sugar, total cholesterol, triglyceride, and low-density lipoprotein. Also, we obtained the following data through the questionnaire: flight-related factors, such as flight hour in pilot's lifetime (total flight hour), aircraft type (fighter vs. nonfighter), the mean frequency of AGSM performance per month (monthly number of AGSM), the maximum possible G-acceleration of the current aircraft type (Gmax), the mean number of exposed Gmax per month (number of Gmax), the mean time of a single exposure to Gmax (Gmax exposure time, second), the presence or absence of experience with gray-out (phenomenon which is a transient loss of vision characterized by perceived dimming of light and color) during performance of flight missions (experience of gray-out), and the number of lifelong gray-out (number of gray-out). Each pilot gave written informed consent. The research ethical committee of the Aeromedical Center, Repiblic of Korea Air Force approved this study.

2.2.2. Detection and rating of WMLs on magnetic resonance imaging

Brain MRI was performed by using a 1.5-T magnetic resonance scanner (Achieva, Philips Medical systems, Best, The Netherlands) equipped with a head coil. All examinations included axial sections of conventional spin-echo T1-weighted (TR = 609.1 ms, TE = 12 ms), turbo-spin-echo T2-weighted (TR = 5586.6 ms, TE = 100 ms), and fluid-attenuated inversion recovery (FLAIR; TR = 11,000 ms, TI = 2800 ms, TE = 140 ms) sequences to improve differentiation between widened Virchow-Robin spaces and true brain lesions. Images were obtained using a 230 × 230-mm FOV, 328–384 × 199–305 matrix, and slice thickness was 5 mm without any interslice gap.

All MRI scans were rated by a single neurologist who was blinded to clinical data and RLS grade. WMLs were defined as punctuate or confluent hyperintense lesions without mass effects located in periventricular areas or deep white matter. They had to be present on both standard and FLAIR T2-weighted sequences and had to be absent on T1-weighted sequence. A T2-hyperintense lesion that was not hyperintense on FLAIR T2-wighted images were considered a widened Virchow-Robin space and excluded from WMLs [20,21]. We used Fazeka's scale to score periventricular WMLs and the Scheltens scale to score deep WMLs [22,23]. Fazeka's scale applied to periventricular WMLs was rated from 0 to 3 as follows: 0 (absence), 1 (punctate foci), 2 (beginning confluence of foci), and 3 (large confluent area). The severity of deep WMLs according to the Scheltens scale was defined by aggregated scores of cortical regions (frontal, parietal, occipital, and temporal lobes), basal ganglia (caudate nucleus, putamen, globus pallidus, thalamus, and internal capsule), and infratentorial regions (cerebellum, mesencephalon, pons, and medulla). Each of these regions was rated on a 7-point severity scale (0–6) [23].

2.2.3. Detection of RLS

Transcranial Doppler (TCD) ultrasonography was performed on pilots in the supine position according to the standardized International Consensus Protocol [24–26]. Briefly, we used a 2-MHz pulsed Doppler transducer (Doppler-Box DWL, Singen, Germany) generating simultaneous digital power M-mode and spectral TCD displays and 1-min recording time. An appropriate temporal window was identified with a standard hand-held technique prior to the procedure. A probe was fixed manually to monitor blood flow and insonated unilateral middle cerebral artery (MCA) main stems through the temporal window at a depth of 45–65 mm to capture a small sample volume of 8 mm.

The agitated saline contained 10 mL of air-mixed saline solution (9 mL of normal saline plus 1 mL of air). Before infusion, the solution was prepared by sufficiently agitating the mixture between two 10-mL syringes several times through a 3-way tap connected to an 18- or 20-gauge intravenous catheter inserted into the antecubital superficial vein. The agitated saline was injected as a bolus for 5 s into the antecubital vein before the AGSM. Monitoring was started just prior to agitated saline injection and continued for 1 min after bolus injection. The AGSM was performed for 5 s starting at 5 s after intravenous injection of agitated saline, and its effectiveness was monitored by a 25% decrease of MCA flow velocity.

TCD ultrasonography was performed during the AGSM by 2 experienced flight surgeons who were blinded to clinical data. The pilots were asked to perform the AGSM, as previously practiced. After 1 session of exercise, the pilots were instructed to start the AGSM. Micro-embolic signal (MES) was defined as a short click sound (<300 ms) of high intensity that was visible as a white streak within the Doppler flow spectrum. RLSs were considered present if ≥1 MES was recorded during monitoring time window. The magnitude of RLSs was classified according to the Spencer grading scale: negative (no microbubbles), gade I (1–5 MES), grade II (6–15 MES), grade III (16–50 MES), grade IV (51–150 MES), and grade V/V+ (>150 MES, 'curtain or shower effect') [27]. All of the test results were recorded for later interpretation and quantification.