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High prevalence of right-to-left shunt in patients with symptomatic great saphenous incompetence and varicose veins

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Background: Varicose veins are common and increasingly are being treated by less invasive endoscopic methods such as foam sclerotherapy. Patent foramen ovale (PFO) is also common, present in approximately one-quarter of adults. PFO allows bubbles introduced by foam sclerotherapy to cross into the general circulation, potentially causing cerebral artery gas embolization with unexplained consequences.

Methods: Men and women aged 18 to 60 years with symptomatic varicose veins (CEAP C3-5) responded to an advertisement to recruit volunteers for a study on endovenous microfoam ablation (EMA). Participants’ veins were screened by duplex ultrasound imaging, and those with isolated great saphenous vein (GSV) incompetence were tested for right-to-left (R-L) vascular shunt using transcranial Doppler (TCD) of the middle cerebral artery to detect the presence of bubble emboli after an injection of an agitated saline, blood, and air mixture as a contrast at rest and with the Valsalva maneuver.

Results: Of 221 participants tested for R-L shunt, 85 (38.5%) were positive at rest (95% confidence interval [CI], 32.5-45.2) and 114 (51.8%) were positive after the Valsalva maneuver (95% CI, 45.4-58.5). A total 130 patients (58.8%) were positive for R-L shunt at rest or after Valsalva (95% CI, 52.5%-65.1%). This is significantly higher than the reported 26% prevalence of PFO in the general population (95% CI, 24.4-30.1).

Conclusions: The prevalence of R-L shunt in patients with GSV incompetence CEAP C3-5 in this study was higher than expected in the general population. TCD does not differentiate between intracardiac shunts and intrapulmonary shunts, so this observation needs further investigation. This link between R-L shunt and varicose veins is novel and, whether etiologic or functional, may improve the understanding of both conditions. The findings have importance in the treatment of varicose veins with foam sclerotherapy and EMA. (J Vasc Surg 2010;51:104-7.)

Patent foramen ovale (PFO) is common in the general population: in 11 studies totalling 9262 autopsies, the prevalence was 26% (range, 15%-32%).1 Although PFO has been considered a benign congenital cardiac abnormality that is rarely associated with any adverse consequences, it is known to be associated with cryptogenic stroke in adults aged <55 years, with a prevalence of up to 56%.2 The prevalence decreases with age from 35% in the first 3 decades, 25% in the next 5 decades, and approximately 20% in age >80 years,3 suggesting that either that PFOs close in adult life or that they are associated with premature death.

As the diagnosis of PFO has been facilitated by the use of contrast ultrasound imaging methods, PFO has been found to be associated with migraine,5,6 dementia,7 and an increased number of brain lesions on magnetic resonance imaging in recreational divers.8,9 all postulated to be caused by microemboli crossing through a venous (R) to arterial (L) circulation (R-L) shunt. Repair of the PFO has been proposed to reduce migraine attacks,10 but not all studies have been supportive.11

Endovenous microfoam ablation (EMA) for the treatment of varicose veins caused by trunk vein incompetence has been rapidly adopted in Europe after early publications by Cabrera et al.12 Millions of small bubbles are introduced into the venous circulation during EMA. If the foam or microfoam is prepared with room air,13 most of the gas is nitrogen, which is sparingly soluble and may embolize to the brain through a R-L shunt.

In a series of patients treated with a proprietary microfoam under United States Food and Drug Administration (FDA) Investigation of New Drug (IND) regulations, bubbles were detected by transthoracic echocardiography in the right side of the heart in all patients. In one patient, bubbles were seen to cross into the left circulation and were identified by continuous-wave Doppler ultrasound imaging in the carotid artery.14 Transesophageal echocardiography (TEE) showed this patient had a small PFO.
MATERIALS AND METHODS

Ethics. The study was conducted under the standards of the International Conference on Harmonisation, Good Clinical Practice. All sites obtained local Investigational Review Board approval for the protocol, and all participants signed approved informed consent. An independent Data Safety and Monitoring Board was established to review adverse events.

Patients. Between March 2007 and May 2008, 545 patients were recruited at five investigational sites and underwent screening. Entry criteria, including symptomatic varicose veins (CEAP C4-6), duplex ultrasound (DU) venous examination confirming isolated symptomatic GSV incompetence, and completion of TCD examination, were fulfilled by 221 patients. Their demographics were typical of varicose vein patients presenting for treatment, with a mean age of 46.2 years (range, 21-61 years) and 95% of patients between 30 and 60 years old, 76% women, and 92% white.

Shunt investigation. The test was administered by Registered Vascular Technologists (RVT) who had been prequalified by a TCD expert (A. R.) before the start of the study. The R-L shunt investigation was performed in a semi-recumbent position at rest and after a standardized Valsalva maneuver. Unilateral middle cerebral artery monitoring using a 2-MHz probe held in a head frame (Doppler-Box, Compumedics, GmbH, Singen, Germany) was used to detect the presence of bubble emboli as high-intensity transient signals (HITS). Agitated saline for the contrast TCD test was prepared by rapidly transferring 8 mL of normal saline, 1 mL of room air, and 1 mL of the patient’s blood between two 10-mL syringes, connected by an open three-way tap, before injecting it into an antecubital vein as a bolus. An R-L shunt was confirmed if the patient had one or more HITS within 15 cardiac cycles of injection at rest or after release of Valsalva. The Valsalva strain was started 5 seconds after contrast injection and maintained for 10 seconds at 40 mm Hg before release and resumption of normal breathing according to the Consensus Conference. Unsatisfactory or equivocal tests were repeated at the discretion of the investigator. The timing of the arrival and the number of HITS was recorded, and a modified Spencer grading was used to categorize the severity of the shunt at rest and after Valsalva.

Microfoam administration. Patients subsequently received treatment with polidocanol endovenous microfoam, up to a maximum of 20 mL, 1% polidocanol, O2/CO2 microfoam (Varisolve under FDA IND). The GSV was cannulated in the middle thigh, the leg was elevated, and an initial proximal injection was made. When microfoam was seen on ultrasound imaging 5 cm from the saphenofemoral junction, the GSV was compressed using ultrasound probe, and the injection was stopped. Further injections, up to a maximum of 20 mL, were made to fill the distal GSV trunk and varicosities. TCD monitoring of the middle cerebral artery was continuously maintained during the procedure and continued for three 10-minute periods: after treatment, immediately before, and after two 10-minute periods of ambulation.

RESULTS

Of the 224 patients entered for TCD screening, three had no temporal bone window, leaving 221 patients with TCD data. Of these, 85 (38.5%) were positive at rest (95% CI, 32.5-45.2), and 44 were classified Spencer grade 1 (1-5 HITS), declining in frequency to nine (4%) at grade 5 (>150 HITS). After the Valsalva maneuver, 114 (51.8%) were positive (95% CI, 45.4-58.5), 29 were grade 1, 25 were grade 4, and 29 were grade 5 (Table 1).

The R-L shunt test was positive in 130 patients (58.9%), either at rest or after Valsalva (95% CI, 52.5-65.1), 91 patients were negative both at rest and with Valsalva, and 15 were grade 1 at rest but negative on
Table II. Right-to-left shunt severity by Spencer grading at rest and with Valsalva

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*One patient grade 5 at rest was not retested with Valsalva.*

Valsalva. At rest, 136 were negative, and 45 were positive with Valsalva. Most of these were low-grade shunts, but nine of 136 (6.6%) had grade 4 or 5 shunts with Valsalva (Table II). Most patients had more severe shunting after Valsalva, and all patients who were classified as grade 5 at rest were also grade 5 after Valsalva.

EMA was then performed using Varisolve in 82 patients, and 61 had an R-L shunt. After Varisolve injection (median volume, 18 mL; range, 6-24 mL), 54 of the patients (89%) with an R-L shunt had HITS compared with six of 21 patients (29%) without an R-L shunt on TCD (*P* < .001, Fisher’s exact test). No patients had symptoms or signs of cerebral embolization. Despite the large volumes of microfoam injected, the number of bubbles was similar to that during the diagnostic test.

**DISCUSSION**

In this study in patients with varicose veins due to GSV incompetence (CEAP C3,4), R-L shunting was detected at more than twice the anticipated prevalence, 58.8% (95% CI, 52.5-65.1). The presence of R-L shunting on TCD was, unsurprisingly, a strong predictor of HITS during subsequent EMA, even though Valsalva and coughing were discouraged. This high prevalence is unlikely to be accounted for by false-positive results, and only a small proportion of these shunts are likely to have resulted from the transpulmonary passage of contrast.

The previous gold standard for PFO diagnosis has been TEE with contrast; however, contrast TCD as used in this study has been shown to be as sensitive as TEE26 while being less invasive and expensive, quantitative, and more patient-friendly. It was impossible to apply in only three patients (<2%) due to absence of a temporal bone window. Agitated saline with a small amount of the patient’s own blood was used as the ultrasound contrast. Although not documented in the literature, the blood acts as a surfactant to improve bubble stability and create contrast of sufficient duration, and it minimizes false-negative results.

The inclusion of a well-performed standardized Valsalva maneuver is equally important, as demonstrated by finding an additional 45 shunts, of which nine were higher-grade shunts. Although 15 patients were grade 1 (1 to 5 emboli) at rest and were subsequently negative on Valsalva, this could have resulted from chance, a very small shunt, a false-positive embolus identification at rest, or a shunt that was inhibited by Valsalva, which might be the case of a transpulmonary shunt or the surge of blood free of contrast from the inferior vena cava impinging on the PFO aperture.

TCD has the disadvantage, however, of being incapable of differentiating the location of the shunt, whether intracardiac or intrapulmonary. In the diagnostic part of this study, only bubbles reaching the middle cerebral artery within 15 cardiac cycles were counted, reducing the potential effect of any transpulmonary passage. Reliable differentiation between a PFO and a pulmonary shunt is not possible, however,21 and the transit times associated with pulmonary shunts are comparable with those of cardiac shunts.22 Transpulmonary passage may account for some patients having HITS after treatment. In one study, transpulmonary shunt was found in four of 49 patients (8%), whereas a PFO was present in 19 (38%).23

During EMA for varicose veins, bubbles released into the circulation will flow to the heart through the inferior vena cava and will be streamed against the intra-atrial septum. This route of introduction of contrast has been shown to increase the sensitivity of R-L shunt detection24 and could account for other shunt-negative patients having cerebral bubble emboli through a previously missed PFO.

**CONCLUSION**

The high prevalence of R-L shunt seen in this population of CEAP C3-5 patients was 58.9% and confirms earlier study observations18 and that of Neuhardt et al,25 in which the prevalence of cardiac and cerebral HITS was >30% in an unselected varicose vein population. The high prevalence of R-L shunt in patients with symptomatic GSV incompetence and varicose veins is important because it indicates that more than half of the symptomatic varicose vein patients being treated with foam sclerotherapy are likely to be exposed to cerebral bubble embolization. Continued caution is indicated because bubble emboli are the presumed cause of neurologic symptoms and stroke in published case reports after foam sclerotherapy.15,16 The results from this study will be compared with the prevalence of an age- and sex-matched control population, and in parallel, common genetic markers are being sought to shed further light on this observation. This association, if confirmed, is very intriguing as to its mechanism, and if it is genetic, might shed light on the cause of one or both conditions.

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**AUTHOR CONTRIBUTIONS**

Conception and design: DW, JR
Analysis and interpretation: DW, JB
REFERENCES


