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Cognitive Function Following Bubble-Contrast Transcranial Doppler for Evaluation of Right-to-Left Shunt

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for Evaluation of Right-to-Left Shunt

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ABSTRACT

Cognitive Function Following Bubble-Contrast Transcranial Doppler
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Background: Stroke is a leading cause of significant physical, cognitive, and psychiatric morbidity. One risk factor for stroke is paradoxical embolization through a patent foramen ovale (PFO). In cardiac clinical practice, power M-mode Transcranial Doppler (TCD) evaluation is the gold standard for diagnosis of PFO, or right-to-left cardiac shunt (RLS). Brain micro-embolization due to diagnostic bubble contrast echocardiography may cause neurological symptoms in patients with PFO. However, the neurocognitive effects of TCD have not been studied. *Objective:* The purpose of this study was to evaluate cognitive outcomes in patients who undergo routine diagnostic bubble contrast TCD. The aims of the study were (1) to determine if cognitive function declines pre- to post-TCD evaluation and, (2) to assess the relationship between cognitive function and severity of the RLS measured using the Spencer Grading System. *Methods:* One hundred and four participants referred to Sorensen Cardiovascular Group for diagnosis of RLS were evaluated for changes in cognitive functioning at three time points. A dual baseline (pre-test and baseline test) was administered to mitigate practice effects between the first and second administrations. All pre and post-TCD comparisons were analyzed using the baseline test and post-TCD test, controlling for the effects of practice, if present. *Results:* Practice effects were observed for the working memory task, with significant improvement in working memory scores occurring between the first (pre-test) and second (baseline) administrations. The main effect for shunt group (no shunt vs. moderate-to-severe shunt) and the shunt group by time interactions were not significant for processing speed, attention, or working memory, adjusting for practice effects, age, and education. Migraine did not predict group status for mood or shunt variables. *Conclusion:* Cardiac patients with both small and large RLS did not experience a decline in processing speed, attention, or working memory ability following TCD, suggesting that TCD-induced microemboli do not result in immediate cognitive deficits in these domains. These findings support the use of TCD for routine evaluation of PFO, even in patients with severe RLS, although findings are limited to young (30s), medically healthy, predominately Caucasian individuals assessed immediately following TCD. Results do not exclude the possibility of cognitive impairment at follow-up, on other cognitive tests, or in other cognitive domains.

Keywords: patent foramen ovale (PFO), cryptogenic stroke, right-to-left shunt (RLS), cerebral vascular accident (CVA), transcranial Doppler ultrasound (TCD), migraine, cognition

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In the United States, approximately 800,000 people suffer a new or recurrent stroke each year and stroke remains a leading cause of disability and morbidity, accounting for 144,000 deaths in 2005 (Lloyd-Jones et al., 2009). Neurologic disability following cerebral vascular accident (CVA) is one of the greatest fears of patients and their families due to the resulting impaired cognitive function and physical disability, which is often described as worse than death (Solomon, Glick, Russo, Lee, & Schulman, 1994). Stroke also represents an important personal and public health problem due to the cost of care associated with poor physical, psychiatric, cognitive, and functional outcomes. Ischemic stroke affects 15 million people per year (Mackay & Mensah, 2004) and the estimated lifetime economic burden was $90,981 per person in 1996 (Taylor et al., 1996) and is likely considerably higher today. Recognition of the permanence and non-reversibility of stroke, the associated cognitive and physical morbidities, and the economic burden has prompted a shift from post-CVA treatment to early diagnosis and preventative strategies by medical professionals.

Neurological morbidities associated with CVA include cognitive dysfunction, psychiatric disorders, including depression and anxiety (Gas & Lawhorn, 1991), and reduced quality of life. During the acute stages post-stroke 35-60% of patients experience depression, at two years depression persists in 57% of survivors (Bour, Rasquin, Limburg, & Verhey, 2011; Parikh, Lipsey, Robinson, & Price, 1987; Paolucci, 2008) and 28% of survivors meet criteria for generalized anxiety disorder (GAD). Prevalence of depression post-stroke does not differ between men and women and an estimated 26% of men and 39% of women may also experience

comorbid anxiety (Burvill et al., 1995). Depression in stroke patients predicts cognitive decline including deficits in memory, attention, problem solving, and mental speed (Kauhanen et al., 1999), development of dementia (Butters et al., 2000; Li et al., 2001), and poor response to depressive medication (Bour et al., 2011). Psychiatric and cognitive symptoms co-occur in an estimated 22% of patients one month post-stroke (Bour et al., 2011), although there are subsets of patients who experience either psychiatric or cognitive deficits alone. Many studies have demonstrated the dynamic interplay between psychiatric and cognitive symptoms including a bidirectional relationship between depression and executive dysfunction (Mast, Yochim, MacNeill, & Lichtenberg, 2004; Nys et al., 2005), which may result from damage to shared neuroanatomical pathways, such as frontal-subcortical networks (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002; Verdelho, Henon, Lebert, Pasquier, & Leys, 2004). Indeed, lesion characteristics predict depression and anxiety post-stroke, with associations between GAD and right hemispheric lesions and comorbid GAD and depression with left hemispheric involvement (Astrom, 1996). Although cognitive deficits following CVA may also depend on the brain regions affected, common deficits include impaired orientation, problem solving (Weimar et al., 2002), executive functioning (Bour et al., 2011), visuo-perception, language (Nys et al., 2007), memory, and slowed psychomotor speed (Jurate, Krisciunas, & Endezelyte, 2008). Post-stroke psychiatric and cognitive disorders significantly interfere with patients' ability to carry out activities of daily living (Popovich, Fox, & Bandagi, 2007) disrupt social networks and social support (Astrom, 1996) and contribute to poor functional outcome (Freed & Wainapel, 1983; Hermann, Black, Lawrence, Szekely, & Szalai, 1998; Khedr et al., 2009).

The etiologies of CVA are heterogeneous and thus require different prophylactic and interventional strategies. Hemorrhagic strokes may result from anti-coagulant medications,

vascular malformations, including ruptured aneurysms or arterial-venous malformations (AVMs), or neurotrauma, and are often unpredictable. Ischemic strokes, which account for roughly 87% of all strokes annually (Akhondi et al., 2010), may result from pulmonary or cardiac emboli, large or small artery thrombi, or atherosclerosis due to long-standing vascular risk factors (diabetes, hypertension, hyperlipidemia). Prevention of ischemic stroke includes cardiovascular management through exercise, magnetic resonance angiography, pharmacological treatment, and prevention of paradoxical embolization. Paradoxical embolization occurs when a venous emboli reaches the arterial circulation through a low-pressure right-to-left shunt (RLS), such as a patient foramen ovale (PFO), as the venous blood has bypassed the pulmonary filter (Kondapaneni, 2004). Paradoxical embolization is relatively common and may be associated with transient ischemic attacks, stroke, decompression disorders, air and fat embolization, migraine headache, and hypoxemia (Hara et al., 2005). Individuals with large and continuous RLS, such as those with a PFO have a higher risk of such adverse events. In healthy adults, RLS is often asymptomatic and may go unrecognized until paradoxical embolization occurs.

Patent Foramen Ovale

In utero, the septum premium and septum secondum act as a dynamic tunnel (foramen ovale) that enables maternal oxygenated blood to pass directly through the inferior vena cava, bypassing the unaerated fetal lungs (Latson, 2007; Moore & Persaud, 2003; Thomas, Bynevelt, & Price, 2005). Within two years after birth, increased pulmonary vascular resistance and pressure in the left atrium causes the foramen ovale to permanently fuse in 70-75% of individuals, creating the atrial septum which separates the right and left atria of the heart (Thomas et al., 2005). This allows venous (deoxygenated) blood to be filtered by the lungs prior to traveling through the arterial (oxygenated) circulation to the brain (Drighil, Mosalami,

Elbadoui, Chraibi, & Bennis, 2007; Ning et al., 2013). In approximately 20-30% of the adult population the septum does not close, resulting in a PFO (Figures 1 & 2) which permits inter-atrial blood flow when pulmonary pressure increases, such as during Valsalva maneuver, cough, or sexual intercourse (Drighil et al., 2007; Thomas et al., 2005). When pulmonary pressure increases the right atrial pressure exceeds the left and the septum flap opens, allowing dynamic right-to-left blood flow. A PFO accounts for 95% of all RLS (Sathasivam and Sathasivam, 2013), and thus acts as a conduit for paradoxical embolism and potential subsequent stroke due to the passage of thromboemboli through the cerebral arteries to the brain. Indeed, PFO-related strokes affect more than 150,000 people per year in the US and are diagnosed in 40% of patients with cryptogenic stroke and 60% of patients with migraine with aura (Drighil et al., 2007; Hara et al., 2005; Ning et al., 2013). A PFO can also cause non-cerebral, paradoxical systemic events such as coronary artery embolism leading to myocardial infarction (MI), renal infarction, or limb ischemia (Agarwal & Kapadia, 2010; Fazio, 2010; Iwasaki et al., 2011; Ramineni & Daniel, 2010).

Individuals with a PFO are often asymptomatic and unaware of their arterial malformation, unless it is coupled with an atrial septal aneurysm (ASA), which increases the severity of the shunt and is more likely to lead to neurologic symptoms or stroke (Ning et al., 2013). Epidemiological studies of PFO are lacking, making it difficult to predict phenotypic characteristics of PFOs. Prevalence of PFO in the adult population is approximately 25-30%, is equally likely in men and women, and prevalence decreases with age, occurring in 20% in individuals who are greater than 80 years old (Cruz-Gonzalez, Solis, Inglessis-Aziaje, & Palacios, 2008). The small difference in prevalence may reflect the fact that individuals with a PFO are more likely to experience a CVA at younger age and have higher rates of mortality.

Interestingly, the size of the PFO (range of 1 to 19mm) increases with age; in the first 10 years of life mean diameter is 3.4mm compared to a mean diameter of 5.8mm in individuals over 90 years of age (Hagen, Scholz, & Edwards, 1984; Cruz-Gonzalez et al., 2008). Although a larger PFO resulting in greater RLS is more likely in older individuals, large PFOs occur in younger individuals as well. The absence of epidemiological information in individuals with PFOs makes it difficult to predict who will have a PFO prior to the occurrence of stroke.

Patent Foramen Ovale and Stroke

In approximately 40% of individuals the pathogenesis of the stroke cannot be attributed to a specific etiology (e.g. cryptogenic) (Di Tullio, Sacco, Gopal, Mohr, & Homma, 1992; Halperin & Fuster, 2002). Strokes in individuals younger than 60 years of age may be due to arterial septal aneurysm (left-to-right-shunt), atrial fibrillation (Lamy et al., 2002), or PFO. The presence of PFO in younger (aged <55) patients with cryptogenic stroke is estimated at 30-77% and is significantly higher than in patients who have a CVA with an identifiable etiology (Di Tullio et al., 1992; Hagen et al., 1984; Lechat et al., 1988; Mas et al., 2001), suggesting that PFO may be a significant risk factor for CVA in low-risk populations (Bogousslavsky, Garazi, Jeanrenaud, Aebischer, & Van Melle, 1996; Lamy et al., 2002; Zito et al., 2009). The severity of the shunt and size of the PFO are associated with paradoxical embolism in patients who have unexplained CVAs (Hausmann, Mugge, & Daniel, 1995; Homma et al., 1994), although no differences in embolic features have been detected between individuals with large compared to small shunts (Lamy et al., 2002). Valsalva maneuver preceding stroke onset has been reported in PFO-related stroke, with higher incidence in men (>15%) (Langholz, Louie, Konstadt, Rao, & Scanlon, 1991; Ning et al., 2008). A PFO increases the risk of stroke in older individuals as well, especially in the context of critical illness and venous clotting (Handke, Harloff,

Olschewski, Hetzel, & Geibel, 2007; Jacobs, Boden-Albala, Lin, & Sacco, 2002; Petrea et al., 2011; Schneider et al., 2004). Clinical outcomes in PFO patients with stroke and or transient ischemic attacks include unilateral sensory deficits, hemiplegia, hemianopsia, and hearing loss (Komar et al., 2012).

Mechanisms of Ischemic Stroke

Cerebral ischemia reduces oxygen and glucose supply to brain tissue and initiates destructive cellular and molecular mechanisms that impair energy resources required to maintain ionic gradients in the brain. The mechanisms include a series of pathophysiological events, such as cellular depolarization and calcium influx, resulting in excitotoxic cell death, that depend on the duration, severity, and location of the focal ischemic event (Traystman, 2003). Ischemic stroke occurs following a diminution of cerebral blood flow (CBF) to a critical threshold and ischemic polarization occurs when CBF decreases to levels of approximately 18 mL/100g of brain tissue per minute, while apoptosis and necrosis occur if flow reduces to 10 mL/100g or less (Harukuni & Bhardwaj, 2006). Normal CBF ranges from 50 to 75mL/100g of brain tissue per minute and differs between gray and white matter due to cell density.

Focal ischemia is a reduction in blood flow to a very distinct brain region in which no blood flow is found at the core of the event, called the ischemic core. Distal regions of the event are marginally perfused where flow reaches the edges of the affected area via collateral circulation, called the ischemic penumbra (Harukuni & Bhardwaj, 2006). In multifocal ischemia or hypoxia, such as paradoxical cardiac embolism, or hypothetically microembolisation during TCD, there is a patchy pattern of reduced CBF in the middle cerebral artery. This typically affects cortical and striatal regions, although the degree and distribution of flow depends on the degree and duration of the occlusion, site along the middle cerebral artery and the amount of

collateral flow (arising from posterior communicating arteries) into its territory (Traystman et al., 2003; Wholey & El-Merhi, 2011). Striatal (caudate and putamen) and basal ganglia infarcts are most commonly observed following middle cerebral artery occlusion and are thought to be selectively vulnerable due to changes in catecholamine release and metabolism (Harukuni & Bhardwaj, 2006). Damage to these regions result in facial and upper arm weakness in baboons (Symon, Pasztor, & Branston, 1974; Weinstein, Anderson, & Telles, 1986) and impaired learning and memory (Hattori et al., 2000) and altered level of alertness in the rat (Block, 1991). Hattori et al. (2000) observed no cognitive impairment after 60 minutes, impaired learning and memory after 90 minutes, and permanently impaired sensory motor function (skilled motor activity and sensorimotor control) after 120 minutes of middle cerebral artery occlusion, suggesting that lengthy periods of reduced flow are necessary to produce neurological effects, at least in rodents. Other animal models have demonstrated that shorter duration of ischemic events does not produce lasting deficits. Matsui and Kumagae (1991) found that 15 minutes of global ischemia in dogs resulted in permanent cognitive impairments, while 10 minutes of global ischemia did not produce lasting effects. Cipolla, Lessov, Hammer, and Curry (2001) demonstrated that vascular tone in the middle cerebral arteries, an indirect measure of blood perfusion and ischemia, is similar between rats exposed to 15 minutes of ischemia and controls, while significantly reduced tone occurs only after 30-120 minutes (Cipolla et al., 2001). Block (1999) reported that one hour of ischemia results in a 50% reduction in motor functioning in rats (grasping, reflexes, equilibrium) that resolved at 24, 48, and 72 hours. These studies suggest that reductions in blood flow to the middle cerebral arteries of short duration may not result in permanent cognitive effects and that duration and degree of blood flow obstruction are important predictors of impairment in ischemic stroke.

Neural Effects of Patent Foramen Ovale

Individuals with PFOs may develop abnormalities on neuroimaging, with brain lesions occurring in multiple regions (Bonati et al., 2006; Jauss, Wessels, Trittmacher, Allendorfer, & Kaps, 2006) including single non-territorial infarcts (in both cortical and subcortical regions), territorial infarcts, multiple ischemic lesions in the area of the posterior circulation, and peripheral arterial ischemia (renal, axillary, and femoral arteries) (Bonati et al., 2006; Clergeau et al., 2009; Jauss et al., 2006). Ischemic changes are typically found in both the periventricular and deep white matter regions (Adami et al., 2008). High intensity transient signals have been found in middle cerebral and basilar artery regions following stroke and TIA in PFO patients, with significant associations between distribution of air bubbles and clinical symptoms (Telman, Kouperberg, Sprecher, Goldsher, & Yarnitsky, 2005). Interestingly, in individuals with migraine who have prolonged visual-motor aura, reversible cortical abnormalities found on DWI and FLAIR sequences have been described and are thought to be the expression of vasogenic edema (Resnick, Reyes-Iglesias, Carreras, & Villalobos, 2006). Abnormalities on neuroimaging suggest that at least in some cases the presence of a PFO represents a serious risk for neurological injury, although transient effects may also be possible.

Pathological Manifestations of Patent Foramen Ovale

In addition to stroke and paradoxical embolism, an increasing number of medical conditions associated with PFO have been identified. PFO may play a causative role or may be an associated condition predisposing the patient to additional complications including platypnea–orthodeoxia, or shortness of breath and arterial desaturation in the upright position with improvement when lying down (Cheng, 2002; Murray et al., 1991), neurological decompression illness in divers, high altitude pilots and astronauts (Fazio et al., 2010), migraine headache with

aura, transient ischemic attacks, and obstructive sleep apneas (Appelberg, Nordahl, & Janson, 2000; Guerin et al., 2005; Ozdemir, Tamayo, Munoz, Dias, & Spence, 2008; Shanoudy et al., 1998).

Decompression illness. Paradoxical embolism contributes to the neurological symptoms that occur in recreational and commercial divers who develop decompression illness (Gempp, Blatteau, Stephant, & Louge, 2009; Koch, Kirsch, Reuter, Warninghoff, & Deuschl, 2008; Wilmshurst, Pearson, Walsh, Morrison, & Brysons, 2001). Studies have shown that divers with PFO and decompression illness may develop significant neurologic morbidity (Moon, Camporesi, & Kisslo, 1989). The risk of decompression illness and arterial gas embolism is 2.5 times greater in individuals with PFO (Koch et al., 2008). Further, lesions on brain imaging are common in divers with PFO who did not develop decompression illness, with a significant association between the severity of the RLS and number of signal abnormalities on MRI (Knauth et al. 1997). The above findings suggest that PFO is a risk factor for brain injury and supports the association between PFO and neurological injury.

Obstructive sleep apnea and pulmonary dysfunction. In patients with obstructive sleep apnea, there is increased prevalence of PFO and the RLS may worsen their hypoxemia during Valsalva maneuver (Shanoudy et al., 1998). Individuals with severe obstructive sleep apnea have more PFO-related RLS during sleep, as observed by an increased number of microbubbles that pass to the brain, although this does not appear to exert significant influence of the severity of nocturnal oxygen desaturation (Lau et al., 2013). Thus, Valsalva maneuver rather than resting state RLS, may be the mechanism that influences blood oxygenation levels. Treatment of obstructive sleep apnea with continuous positive airway pressure successfully decreases shunting due to PFO (Beelke et al., 2002; Pinet & Orehek, 2005).

Notably, patients with asymptomatic PFO have decreased pulmonary gas exchange efficiency compared to controls (no PFO), and experience more hypoxia (Lovering et al., 2011), although this difference was not observed during exercise. Other studies have shown that one third of patients with PFO-related stroke experience oxygen desaturation during exercise (Devendra, Rane, & Krasuski, 2012), which improves dramatically following PFO closure. The baseline blood oxygenation level differs between individuals with and without PFO along with marked variability between PFO patients, which likely relates to functional outcome and may aid in better identification of those in need of PFO closure.

Migraine. Migraine is a chronic-intermittent neurovascular disorder characterized by severe unilateral headache of pulsating quality and a combination of gastrointestinal (nausea) and autonomic (photophobia and phonophobia) symptoms, and in some patients, transient neurologic dysfunction known as migraine with aura (Kurth & Diener, 2006; Sathasivam and Sathasivam, 2013). Research has demonstrated an association between migraine with aura and increased risk for ischemic stroke (Anzola et al., 1999; Becker et al., 2007; Del Sette et al., 1998; Henrich & Horowitz, 1989; Lamy et al., 2002). The pooled relative risk of ischemic stroke among individuals with migraine is 2.16 (95% CI, 1.89 to 2.48); the risk of stroke for individuals with migraine with aura is 2.27 compared to 1.83 in individuals who have migraine without aura (Etminan, Takkouche, Isorna, & Samii, 2004).

Platelet hyperaggregability and the reduction in cerebral blood flow that may occur in migraine with aura are thought be to potential mechanisms for migraine and stroke (Etminan et al., 2004). Platelet hyperaggregability and reduced cerebral blood flow are likely insufficient to cause ischemic injury (Kurth & Diener, 2006) and thus, the pathophysiology of migraine (i.e., vascular dysfunction) coupled with cardiovascular risk factors (i.e., PFO) likely contribute to the

development of stroke in individuals with migraine. For example, transient focal neurological symptoms due to vasoconstriction occur subsequent to paradoxical embolism via RLS (Domitrz, Mieszkowski, & Kaminska, 2007). Although PFO and migraine with aura may be independent risk factors for stroke, the PFO-migraine relationship is less clear and research to date has been mixed in determining the plausibility of PFO as a cause of migraine.

The estimated prevalence of individuals with PFO who experience migraine with aura is approximately 50% (Caputi et al., 2009; Schwedt, Demaerschalk, & Dodick, 2008) and the rate of PFO in individuals with migraine is twice that of non-migraine controls (Adami et al., 2008). Relationships between migraine and younger age, female sex, and PFO have been reported (Lamy et al., 2002; Post, Thijs, Herroelen, & Budts, 2004; Wilmshurst & Nightingale, 2001;). Possible pathophysiological mechanisms for the PFO-migraine relationship include 1) subclinical emboli (platelet hyperaggregability) and metabolites (serotonin) entering the systemic circulation via PFO and causing irritation of the trigeminal nerve and brain vasculature, and 2) transient hypoxemia (resting and stress) due to RLS induced microinfarcts and irritation in the brain (Botto et al., 2007; Etminan et al., 2004; Naqvi, Rafie, & Daneshvar, 2010). Despite the plausibility of PFO causing migraine, evidence suggests the relationship is complex, including: 1) unpredictability of embolic events in the context of lateralizing and cyclical migraine (Gupta, 2010); 2) migraine onset typically occurring in adolescence, while the PFOs are present from birth; 3) the size of PFO increases with age and while migraine attacks typically subside with age (Gupta et al., 2008); 4) the prevalence of migraine is two times more common in females, alternatively PFO prevalence is equal across genders (Campbell, 1990); 5) propranolol promotes platelet activation and aggregation, but it is effective in migraine prophylaxis (Joseph et al., 1998); 6) migraine is more frequent in younger than older patients with stroke (Hagen et al.,

1984); and 7) RLS is not associated with increased white matter lesion load in individuals with migraine (Adami et al., 2008; Sathasivam & Sathasivam, 2013). Epidemiological studies examining this relationship are mixed and the only randomized controlled trial found improvement of migraine with PFO closure but has failed to support a causative relationship.

Benefits of Patent Foramen Ovale Closure

The conventional medical therapies for patients with stroke or TIA secondary to PFO include long-term anticoagulation, antiplatelet medications, and surgery. Anticoagulants carry a risk of hemorrhage, and data do not support the routine use of anticoagulants in patients with PFO (Furlan, 2004). Recent technological advances have led to low risk, percutaneous device and coil closure options for PFO, thereby making prevention of paradoxical embolic brain and systemic injury feasible. Martin et al. (2002) studied the immediate and long-term clinical effects of transcatheter PFO closure in a cohort of 110 patients. Effective occlusion of the PFO was achieved in 100% of patients, and only two patients had recurrent neurological events due to device misalignment or small shunt two years post-closure (Martin et al., 2002). The rate of serious complications following percutaneous transcatheter PFO closure occurs in less than one percent of patients (Furlan, 2004), suggesting percutaneous transcatheter PFO closure is a safe intervention for CVA prophylaxis.

Several studies have investigated PFO closure as a mechanism to reduce or eliminate migraine. Reisman et al. (2005) found complete resolution of migraine symptoms in 56% of patients who underwent closure of the PFO, and 14% of patients had a significant reduction in migraine frequency. There was an 80% reduction in the mean number of reported migraine episodes per month following PFO closure (Reisman et al., 2005). Patients with cryptogenic stroke had a significant and persistent decrease in the prevalence of migraine with aura six

months after PFO closure (Post et al., 2004). Additionally, patients with migraine with aura had a 54% reduction in the frequency of migraine attacks post PFO closure (Schwerzmann et al. 2004). These studies suggest a strong relationship between PFO and migraine with aura, and lend credence to the benefits of PFO closure above and beyond prevention of stroke.

Diagnosis of Patent Foramen Ovale

The diagnosis of RLS relies upon the visualization of bubbles in the left atrium, which has historically been assessed using either transesophageal echocardiography (TEE) or transthoracic echocardiography (TTE). Power M-mode Transcranial Doppler (TCD) is a more recent technique for RLS evaluation that is reproducible, low cost, timely (15-20 minutes), and semi-quantitative. Transcranial Doppler has excellent concordance with TEE and studies have found 100% sensitivity, specificity, and diagnostic accuracy for TCD compared with TEE for detection of inter-atrial RLS (Belvis et al., 2006; Nemec et al., 1991; Sastry, Daly, Chengodu, & McCollum, 2007). Evaluation of shunt severity, shunt duration (resting flow) and shunt variation with postural change make TCD an optimal test for diagnosis, quantification and risk stratification of patients with neurological conditions and RLS (Giardini et al., 2007; Jesurum et al., 2007; Sastry et al., 2006; Spencer et al., 2004). The Spencer Logarithmic Grading Scale is a TCD grading system used to quantify severity of RLS that has equal sensitivity but superior specificity and diagnostic accuracy compared with other TCD grading techniques (Lao et al., 2008), and is considered the gold standard for quantification of RLS.

Despite the benefits of using TCD to diagnose RLS, the putative effects of TCD on cognition are unclear. While neurological symptoms have been reported in patients with larger RLS (i.e., Spencer Grades 2-5+) during or following routine diagnostic bubble TCD (Anzola, 2009; Sorensen et al., 2010), no studies to date have evaluated cognitive outcomes using

standardized neuropsychological tests pre- and post-routine diagnostic bubble TCD.

Additionally, the minimal microembolic signals suggest clinically relevant RLS has not yet been

established (Jauss & Zanette, 2000).

Purpose of the Current Study

The purpose of this study was to evaluate cognitive outcomes in patients who undergo

routine diagnostic bubble contrast TCD. The aims of the study were (1) to determine if cognitive

function declined pre- to post-TCD evaluation and, (2) to assess the relationship between

cognitive function and severity of the RLS, as measured by the Spencer Grading system.

Aims and Hypotheses

The first aim is to assess the relationship between diagnostic bubble contrast TCD and

cognitive functioning. The first hypothesis is that participants undergoing diagnostic bubble

contrast TCD will experience a significant decline in cognitive functioning, irrespective of shunt

size.

The second aim is to assess the effect of shunt size on cognition following TCD. The

second hypothesis predicts that participants with a moderate-to-severe shunt will have

significantly slower reaction times and decreased attention and working memory ability

following TCD compared to the participants with little to no shunting.

Method

Participants

Individuals referred to Sorensen Cardiovascular Group for diagnostic Power M-mode

TCD for the presumed diagnosis of RLS were evaluated for the study. Study inclusion criteria

were age ≥ 18 and < 60 years and undergoing diagnostic TCD as part of their routine clinical

care. Study exclusion criteria were prior cognitive impairment that prevented the subject from

living independently at study enrollment (e.g., mental illness requiring institutionalization, acquired or congenital mental retardation, traumatic brain injury, stroke with severe cognitive deficits, Parkinson's disease, Huntington's disease, dementia), pregnancy, atrial septal aneurysm, or prior cardiac surgery. This study had IRB approval and informed consent was obtained from all participants prior to their participation in the study.

Procedures

Two independent review boards, Western Institutional Review Board and the institutional review board at Brigham Young University, approved the study protocol. All data was collected and de-identified at Sorensen Cardiovascular Group, Murray, UT on all participants who had provided written informed consent. Participant demographic and medical information was collected prior to cognitive evaluation and Power M-mode TCD testing. Demographic and medical information was collected by questionnaire and included age, education, ethnicity, sex, prior psychiatric diagnosis of depression or anxiety, and medications. Patients were also administered a brief headache questionnaire and cognitive tests.

Measures

Cognitive testing. Participants completed an eight minute computerized CogState® battery to assess cognitive function. The CogState® computerized battery was designed to detect the presence or absence of cognitive change when performance is repeatedly measured over short retest intervals (Maruff et al., 2008). The CogState® uses computer-administered stimuli in the form of standard playing cards that are familiar to most cultures and education levels and measure a wide range of cognitive function (e.g., psychomotor speed, reaction time, working memory, attention). The CogState® allows for nearly unlimited combinations (i.e., alternate forms) of item presentation in a random order, as well as an extensive range of

continuous data (Collie et al., 2005; Falleti, Maruff, Collie, Darby, & McStephen, 2003; Maruff, 2005). CogState® data metric properties that aid in detecting cognitive change in individuals include interval level outcome data, lack of range restrictions, and normal distributions (Collie, Maruff, Darby, & McStephen, 2003b; Mollica, Maruff, & Vance, 2004; Snyder et al., 2005a). The tests have good reliability (test-retest between .84 to .91 at 10 minutes) and validity (Collie et al., 2003a; Maruff, 2005), as well as good sensitivity and specificity for detecting even mild cognitive impairment (Cysque, Maruff, Darbie, & Brew, 2006; Darby et al., 2004).

The construct validity of the CogState® is demonstrated by its significant association with comparator neuropsychological tests (Maruff et al., 2009). Measures specific to this study, psychomotor speed, attention, and working memory, correlate well (r=.78-.81) with established neuropsychological measures (Maruff et al., 2009). Cogstate® subtests selected from the overall battery were chosen due to their measurement of domains that are sensitive to brain injury, including processing speed (Caine & Watson, 2000), working memory, and attention (Armengol, 2000).

Due to observed practice effects between the first and second administrations of each test, a dual baseline is recommended. Practice effects are stabilized subsequent to the second administration and test performance remains stable at retest intervals of 10 minutes to one week (Faletti, Maruff, Collie & Darby, 2006). The Cogstate® battery was administered initially after which the battery was immediately administered a second time to obtain their baseline test (using alternate forms). Participants then underwent clinical diagnostic bubble TCD procedure (described above), done by trained cardiology technicians under the supervision of a physician. Immediately following TCD (within five minutes), participants were administered the post-test using the same eight minute computerized CogState® test battery, using alternate forms.

Three tests from the CogState® battery were administered: the Detection Task (psychomotor function and speed of processing, test time = two minutes), Identification Task (visual attention and vigilance, test time = two minutes), and the Two Back Task (working memory, test time = two minutes). The total time for the pre-test was 16 minutes (one practice and one baseline test) and eight minutes for the post-test administration. Laptop computers were used to run the CogState® battery using the Windows XP operating system.

At the beginning of each task, written instructions were presented on the screen and the task instructions were read aloud to each participant. Each task requires selection of a Yes or No response using the right and left mouse pad keys on the laptop track board. The buttons were labeled "Yes" and "No" and each participant was given an active demonstration and about one minute to familiarize them with the buttons prior to the administration of the test battery.

The Detection task is a simple reaction time test in which the participant must attend to the task in the center of the screen and select the Yes key following the rule "Has the card turned face up?" The task continued until the two-minute time limit had elapsed. The primary outcome measure is speed of correct responses in milliseconds. The Identification Task is a choice reaction time task in which the participant must attend to the card in the center of the screen and select either "Yes" or "No" following the prompt "Is the face-up card red?" The task was continued until the two-minute time limit has elapsed. The primary outcome measure is the speed of correct responses in milliseconds. The Two-Back task (Figure 7) requires the participant to attend to the card in the center of the screen and respond according to the rule "Is this card the same as the card shown before the previous card? In other words, is the card two cards back the same as the one currently presented?" The task continued until the two-minute time period has elapsed. The primary outcome measure is accuracy of performance, or the

number of correct responses (percent correct of the total trials). After participants completed the post-test cognitive battery, their participation in the study was complete.

Headache. Diagnosis of migraine was made using the International Headache Society's structured migraine history questionnaire. Diagnostic criteria includes the following: A) at least two headache attacks lasting four to 72 hours (untreated or successfully treated), B) migraine aura that occurs with criterion A, and includes at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, and C) not attributable to another disorder (Olesen, 2005). Patients were also asked if their physician had previously diagnosed them with migraine or migraine with aura. Patients with physician-diagnosed migraine and/or participants who meet diagnostic criteria according to the IHS Headache Classification Subcommittee (migraine questionnaire) were considered as having active migraine.

Depression and anxiety. Participants were asked whether or not they had a formal diagnosis of depression or anxiety made by either a physician or psychiatrist.

Bubble-contrast transcranial doppler evaluation. Clinical Power M-mode TCD was performed as previously described (Spencer et al., 2004). All TCD studies were done as part of the patient's routine clinical care by medical personnel. TCD is widely used to evaluate intra-cranial blood flow. Power M-mode TCD is a newer application of this technology to evaluate right-to left shunting through intra-cranial bubble detection that displays the power and the velocity/frequency of the Doppler signal. Bilateral middle cerebral arteries were located using a hand-held 2-megahertz probe prior to affixing bilateral 2-megahertz ball probes using a secure head frame (Spencer Technologies).

Transducers were adjusted by angulation and depth control (60-70 mm usually) and minimal (ALARA) power to obtain optimal power M-mode windows, representing flow in the middle and anterior cerebral arteries, and spectrogram windows, representing the blood velocity profile of the selected power M-mode depth (Figure 3). Imaging was performed using a PM-100 (Spencer Vascular, Seattle, Washington) in the resting state and after contrast injection at rest and with calibrated respiratory strain. Insonation was performed with 33 gates placed at 2 mm intervals along the ultrasound beam permitting selection of gate depth for the spectral analysis. The middle cerebral artery was used for bilateral spectral analysis. Contrast injection was performed following rapid mixing of 8 cc of bacteriostatic saline, ½ cc of withdrawn blood, and ½ cc of air using two syringes and a stopcock with a minimum of 10 agitations. Calibrated strain (valsalva maneuver) utilized a mouthpiece connected directly to a dial manometer viewed by the patient with strain calibrated to 40 mm mercury pressure.

Cerebral microembolic events were quantified by an automatic embolic detection program (Spencer Vascular Laboratories) that separates artifact from embolic events and counts emboli (micro-bubbles) at depths of 30 mm to 81 mm. This technique results in emboli that appear as brightly colored embolic events in the arteries. Embolic events (micro-bubbles) also appear on the spectrogram as embolic signals (Figure 3). All data was recorded continuously and saved for visual review and confirmation using the automated detection system.

Calibrated respiratory strain RLS was graded using the Spencer Logarithmic Grading Scale. The scale is as follows:

Grade 0: No embolic events.

Grade 1: 1-10 cerebral embolic events.

Grade 2: 11-30 cerebral embolic events.

Grade 3:   31-100 cerebral embolic events

Grade 4:   101-300 cerebral embolic events.

Grade 5:   Greater than 300 countable discrete events.

Grade 5+: Overwhelming events (so called "curtain" effect).

The number of embolic events represents the detection of bubble conductance by RLS to the middle cerebral arteries. The conductance is the result of intra-cranial arterial distribution, the size of the intra-cardiac defect (ASD, PFO, p-AVM) while permitting flow, right-to-left pressure gradient of the defect, and the duration of flow. Grades 0 to 1 indicate no shunt, Grades 2 and 3 indicate moderate shunt, and grades 4, 5, and 5+ represent severe shunt based upon previous validation and definition studies (Jesurum et al., 2007; Lao et al., 2008; Sastry et al., 2006; Spencer et al., 2004).

Statistical Analyses

Descriptive statistics were conducted for demographic, medical, psychiatric history (e.g. depression and anxiety), and cognitive data (e.g., working memory, processing speed, and attention), including: distributions, means, medians, variances, standard deviations, skewness, kurtosis, ranges, and quartiles. Data were also examined for homogeneity of variance. Continuous data are presented as means ± standard deviations (*SD*), while categorical variables are presented as proportions. Continuous data was analyzed by independent samples t-tests and categorical data by chi-square analysis; relationships between variables were analyzed with ANOVA and its variants. All analyses were performed using SPSS version 22. All repeated measures ANOVAs were two-tailed, where applicable, with an alpha level of .05 ($\alpha = .05$).

A grouping variable was created to test hypothesis 2, that participants with a moderate-to-severe shunt will have significantly slower reaction times and decreased attention and working

memory ability following TCD compared to the participants who have little to no shunting. The two groups were created based upon previous validation and definition studies for shunt size and severity; Grades 0-1 indicate no shunt, Grades 2-3 indicate moderate shunt, and Grades 4-5 indicate severe shunt (Jesurum et al., 2007; Lao et al., 2008; Sastry et al., 2006; Spencer et al., 2004), as well as on the distribution of the sample. Spencer grades 3-5 are highly sensitive and specific in predicting whether a functional PFO is present and whether it can be determined with catheterization (Lao et al., 2008).

Data were screened for missing data and violations of assumptions of parametric statistical analyses, including outliers, non-normality, non-linearity, and heteroscedasticity. Notably, data had not been previously corrected for age or education. One participant had missing baseline data for all cognitive variables that was replaced with their initial test, as there were no significant effects of practice for either the processing speed or attention variables for the whole sample (see results below).

Outliers. All quantitative data (per shunt group per time point) were inspected for outliers using boxplots. A few outliers were identified on some of the variables; however, none were extreme (±3 *SD*; Tabachnick and Fidel, 2007). Outliers were inspected for accuracy in raw data by verification with source documents. Outliers were considered to accurately reflect reasonable variability in scores on each of the variables (Tabachnick and Fidel, 2007), and were fenced using an operational definition [median ± (2 x interquartile range)] to decrease the probability of type I and/or II errors and to improve the generalizability of the data.

Normality. Normality was assessed (per group per time point) on each of the variables. Data was assessed visually (e.g., histograms) and statistically, using a cutoff of $z = \pm 3$ for determining significant skewness and kurtosis (Tabachnick and Fidel, 2007). Two kurtotic

distributions (working memory baseline for the no-shunt group $z = 3.705$ and processing speed post-test for the shunt group $z = 3.267$) and two skewed distributions were identified (processing speed baseline for the shunt group $z = 3.643$; processing speed posttest for the shunt group $z = 3.347$), even after outliers were fenced. Data transformations appropriate for moderate positive skewness (square root, log10, natural log) were applied, with no effect on the skewness or kurtosis of the data, likely due to the fact that the data were previously log10 transformed. Non-transformed data (original log10 transformed data) were used due to the mild nature of non-normality and failure of transformed data to be normalized.

Hypothesis 1. To evaluate whether patients undergoing diagnostic bubble contrast TCD had a decline in cognitive function, irrespective of shunt group membership, three separate repeated-measures analysis of variance (ANOVAs) were performed for each of the cognitive variables (processing speed, attention and working memory), with two time points, pre-TCD (baseline) and post-TCD (post-test), as the within-subjects factor and no grouping factor in the model. Covariates included in the model were age, education, and practice effects for working memory only.

Hypothesis 2. To evaluate the effect of shunt size on cognition following TCD, three separate repeated measures ANOVAs were performed for each of the cognitive variables, with two time points, pre-TCD (baseline) and post-TCD (post-test), as the within subjects factor and one grouping factor of presence or absence of shunt as the between-subjects factor accounting for covariates (age, education and practice effects for working memory).

Exploratory analyses. A practice test was administered prior to the baseline and post-test to mitigate practice effects that may occur with repeated assessment. To evaluate whether there were practice effects for any of the three cognitive tests, three separate repeated-measures

ANOVAs were performed with two time points, practice test and pre-TCD (baseline test), as the within-subjects factor.

To evaluate whether demographic variables or depression or anxiety were associated with cognitive functioning three separate repeated-measures ANOVAs were run for each of the dependent cognitive variables, with age, education, depression, and anxiety as the between-subjects factor.

To evaluate whether individuals with no shunting (SG = 0) differed from those with only severe shunt (SG = 5) three separate repeated-measures ANOVAs were run for each of the dependent cognitive variables, with two time points, pre-TCD (baseline) and post-TCD (post-test), as the within subjects factor and one grouping factor of presence or absence of shunt as the between-subjects factor accounting for covariates (age, education, and practice effects for working memory).

Results

One hundred and five participants referred to Sorensen Cardiovascular Group for diagnostic Power-M-mode TCD for the presumed diagnosis of RLS were enrolled in the study. One participant dropped out of the study after the practice cognitive assessment due to time limitations needed to complete her clinical care. Therefore, 104 participants (mean age 36.8±11.3 years) who underwent diagnostic TCD for evaluation of RLS completed all cognitive data. The sample was predominately Caucasian ($n = 99$), female ($n = 77$), highly educated ($M = 14.2±2.3$ years; range 8-19 years), right handed ($n = 88$), and had migraines ($n = 98$) (Table 1).

Descriptive statistics for demographic and medical data are shown in Table 1. Migraine was diagnosed in 94% of the sample ($n = 98$) and migraine status did not significantly differ by shunt group ($\chi^2 = 0.01$); individuals with migraine comprised 94% of the no shunt group and

94% of the shunt group. Sixteen percent of participants had comorbid medical diagnoses (i.e., stroke, concussion, heart disease), 15% of no shunt and 18% of shunt participants had comorbid medical diagnoses; this difference was not significant ($\chi^2 = 0.19$). Six participants were diagnosed with a premorbid stroke or TIA, one had a history of concussion, three had multiple sclerosis (MS), and two had heart disease. Thirty-eight percent of participants reported taking one or more medications; 43% of the no shunt group and 32% of the shunt group; this difference was not significant ($\chi^2 = 3.99$). Additionally, benzodiazepine ($\chi^2 = 2.89$) and antidepressant ($\chi^2 = 0.05$) prescriptions did not significantly differ by shunt group (Table 1).

For hypothesis two participants were separated into two groups based on 1) no shunt (Grade 0-1; $n = 54$) and 2) moderate-to-severe shunt (Grades 2-5; $n = 50$), based on previous validation studies (Lao et al., 2008) and on the distribution of the sample ($n = 37$ for SG = 0; $n = 17$ for SG = 1; $n = 0$ for SG = 2; $n = 6$ for SG = 3; $n = 5$ for SG = 4; and $n = 39$ for SG = 5). When comparing the no shunt (SG = 0-1) and shunt (SG = 3-5) groups, there were no differences for age, $t(104) = 0.99$, $p = .326$ or education, $t(99) = 1.45$, $p = .150$. The participants were predominantly female with males comprising only 31% of the no shunt group and 20% of the shunt group; this difference was not significant ($\chi^2 = 1.78$).

Table 1. *Descriptive Statistics for Demographic and Medical Variables.*

Variable	Total Sample ($n = 104$) Mean ± *SD*	No Shunt ($n = 54$) Mean ± *SD*	Shunt ($n = 50$) Mean ± *SD*	No Shunt vs. Shunt t	p
Age (years)	36.8±11.3	37.8±11.4	35.7±11.1	0.99	0.33
Education (years)	14.2±2.3	14.5±2.4	13.8±2.1	1.45	0.15

Variable	n	n (% within group)	n (% within group)	χ^2	p
Females	77	37 (69)	40 (80)	1.78	0.18
Males	27	17 (31)	10 (20)	1.78	0.18
Comorbid Conditions	17	8 (15)	9 (18)	0.19	0.66
Migraine	98	51 (94)	47 (94)	0.01	0.92
Medicated	39	23 (43)	16 (32)	3.99	0.26
Anti-Depressants	26	13 (24)	13 (26)	0.05	0.82
Anti-Psychotics	1	1 (2)			
Benzodiazepines	12	9 (16)	3 (6)	2.89	0.09
Psychiatric History				χ^2	p
Depression	33	18 (33)	15 (30)	0.13	0.71
Anxiety	30	19 (35)	11 (22)	2.19	0.14

Practice Effects

Data for the practice effects are shown in Table 2. When all participants were analyzed in one group, there was no significant difference between practice and baseline for processing speed or attention. However, there was a significant difference for working memory ($p = .000$, partial $\eta^2 = .22$), with participants performing more accurately at baseline (second test administration) than on the initial test. After adjusting for education and age the practice effect for working memory did not remain significant $F(1, 104) = .12$, $p = .73$, partial $\eta^2 = .001$.

Table 2. *Practice Effects (pre-test to baseline assessment) collapsed across group.*

Variable	Practice (*n* = 104) Mean ± *SD*	Baseline (*n* = 104) Mean ± *SD*	*F*	*p*	*Partial Eta²*
PSI	2.56±.079	2.57±.081	.893	.347	0.009
Attention	2.75±.079	2.75±.068	.188	.666	0.002
WM	1.21±.169	1.29 ±.164	28.6	.000	0.217

Abbreviations are as follows: PSI = processing speed; WM = working memory

Hypothesis 1

There were no main effects of time for processing speed or attention comparing baseline to post-test scores when analyses were collapsed across shunt groups (no shunt and moderate-to-severe shunt), adjusting for age and education. There was a main effect for working memory when comparing baseline and post-test scores, indicating significant improvement in working memory scores from baseline to post-test even after adjusting for practice effects, age, and education (*p* = .04; See Table 3). Table 3 shows change in cognitive function from baseline to post-test.

Effect of Depression, Anxiety, Age, and Education

There was a main effect for depression (history of depression) on processing speed (*p* = .01; Appendix A; Table A6). Participants diagnosed with depression had significantly slower processing speed than individuals who did not have a diagnosis of depression, after adjusting for age and education. No main effects of depression were observed for attention or working memory and no interaction of depression and time was observed for any of the cognitive variables, adjusting for practice effects, age, and education. There was no main effect of anxiety (history of anxiety) and no interaction between anxiety and time on processing speed, attention, or working memory, adjusting for the effects of practice, age, and education (Appendix B; B7).

There were no main effects for gender, age, or education and there was no time by gender or time by education interactions for any of the cognitive variables, even after adjusting for the effects of practice. There were no time by age interaction effects for processing speed or attention, however, there was an age by time interaction effect for working memory ($p = 0.02$), adjusting for the effects of practice and education. In order to examine the interaction, age was analyzed using a median split. The main effect of age group on working memory score, using median split (younger and older than 35), was significant $F(1, 104) = 4.82$, $p = 0.03$, η^2 of .047, adjusting for practice effects and education. There was a significant two-way interaction, where individuals older than 35 had improved working memory scores from baseline to post-test and those younger than 35 had stable working memory performance across the two time points.

Hypothesis 2

Hypothesis two assessed the effect of shunt size on cognition following TCD. There was no main effect of shunt and no significant two-way interactions of shunt group by time for processing speed, attention, or working memory, adjusting for working memory practice effects, age, and education (Table 4). The age by time by shunt interaction effect was not significant for working memory, $F(1,104) = 0.01$, $p = 0.92$, η^2 of .000.

Table 3. *Baseline and post-TCD test Cognition.*

Variable	Baseline (*n*=104) Mean ± *SD*	Posttest (*n*=104) Mean ± *SD*	F	df	p	Partial Eta^2
Main Effect of Time						
Processing Speed	2.57±.007	2.57±.007	0.47	1	0.49	0.005
Attention	2.75±.007	2.75±.008	0.05	1	0.83	0.000
Working Memory	1.29±.013	1.32±.016	4.50	1	0.04	0.044
Main Effect of Age						
Processing Speed			3.56	1	0.06	0.035
Attention			1.76	1	0.18	0.018
Working Memory			2.94	1	0.09	0.029
Main Effect of Education						
Processing Speed			0.12	1	0.73	0.001
Attention			0.85	1	0.36	0.009
Working Memory			0.20	1	0.65	0.002
Main Effect of Gender						
Processing Speed			0.60	1	0.44	0.006
Attention			0.09	1	0.75	0.001
Working Memory			3.37	1	0.07	0.034
Age x Time Interaction						
Processing Speed			1.59	1	0.21	0.016
Attention			0.76	1	0.38	0.008
Working Memory			6.12	1	0.02	0.059
Under 35 years	1.33±.019	1.33±.024				
Over 35 years	1.25±.019	1.31±.023				
Education x Time Interaction						
Processing Speed			0.00	1	0.98	0.000
Attention			0.14	1	0.71	0.001
Working Memory			2.12	1	0.15	0.021
Gender x Time Interaction						
Processing Speed			0.10	1	0.75	0.001
Attention			1.36	1	0.25	0.014
Working Memory			2.35	1	0.13	0.024

*p < .05, two-tailed. **p < .01, two-tailed. ***p <.001, two-tailed

Table 4. *Baseline and post-TCD test Cognition by Shunt Group.*

Variable	No Shunt (*n* = 54) Mean ± *SD*	Shunt (*n* = 50) Mean ± *SD*	*F*	*df*	*p*	Partial Eta^2
Main Effect of Shunt						
Processing Speed	2.58±.010	2.56±.010	1.87	1	0.17	0.019
Attention	2.75±.009	2.74±.010	1.79	1	0.18	0.018
Working Memory	1.31±.019	1.30±.019	0.84	1	0.77	0.001
	Baseline (*n* = 104) Mean ± *SD*	Posttest (*n* = 104) Mean ± *SD*	*F*	*df*	*p*	Partial Eta^2
Shunt x Time Interaction						
Processing Speed			0.28	1	0.87	0.000
No Shunt	2.58±.010	2.58±.011				
Shunt	2.57±.010	2.56±.011				
Attention			0.93	1	0.34	0.010
No Shunt	2.76±.009	2.76±.011				
Shunt	2.73±.009	2.74±.011				
Working Memory			1.84	1	0.19	0.019
No Shunt	1.29±.019	1.33±.023				
Shunt	1.30±.019	1.31±.023				

*p < .05, two-tailed. **p < .01, two-tailed. ***p <.001, two-tailed

Alternate Shunt Groups (Spencer Grade 0 vs. 5)

An alternative shunt group was created excluding those participants with mild to moderate shunt (Spencer Grades 1-4) to evaluate the second hypothesis in participants who experienced no microbubbles and those with the highest microbubble load. Therefore, participants were re-grouped according to those with no shunt (SG = 0; *n* = 37) and large shunt (SG = 5; *n* = 39) only. Descriptive statistics for demographic and medical data for the no shunt and large shunt groups found no difference for age, $t(74) = 1.265$, $p = .210$, or educations, $t(72) = .956$, $p = .343$ (Table 5). The sample was predominantly female with males comprising only 35% of the no shunt group and 18% of the large shunt group; this difference was not significant

(χ^2=2.89). Consistent with findings using the original grouping method, the shunt by time interactions for processing speed, attention, and working memory were not significant, even after adjusting for practice effects, age, and education. Individuals with migraine accounted for 95% of the no shunt (SG 0; $n = 37$) group, while 92% of patients with large shunt (SG 5; $n = 39$) were diagnosed with migraine, and this difference was not statistically significant ($\chi^2 = 0.16$).

Table 5. *Baseline and post-TCD test Cognition, by Alternate Shunt Group (Spencer Grade 0 and 5).*

Variable	No Shunt ($n = 37$) Mean ± SD	Shunt ($n = 39$) Mean ± SD	F	df	p	Partial Eta^2
Main Effect of Shunt						
Processing Speed	2.58±.012	2.56±.012	1.21	1	0.27	0.017
Attention	2.75±.012	2.74±.011	0.43	1	0.51	0.006
Working Memory	1.30±.024	1.30±.022	0.03	1	0.86	0.000
	Baseline Mean ± SD	Posttest Mean ± SD				
Main Effect of Time						
Processing Speed	2.57±.009	2.58±.010	0.11	1	0.74	0.002
Attention	2.74±.008	2.75±.009	0.06	1	0.79	0.001
Working Memory	1.29±.016	1.31±.019	2.05	1	0.16	0.029
Shunt x Time Interaction						
Processing Speed			0.09	1	0.76	0.001
Attention			0.04	1	0.83	0.001
Working Memory			1.30	1	0.26	0.019
	n (% within group)	*n* (% within group)				χ^2
Migraine	35 (95)	36 (92)				0.16

Discussion

The current study assessed the effects of diagnostic bubble contrast TCD on cognitive function in participants with and without a PFO. We found a high prevalence of large shunt (38%) in our sample, which is higher than the estimated incidence of 2.4-4.9% of large PFO size in the general population (Hagen et al., 1984; Wilmshurst et al., 2001). The high prevalence of large RLS in our sample may reflect the pre-selection of patients visiting this office due to significant cryptogenic neurological events, and severity of shunt is consistent with the high rates of migraine headache among these individuals (94% in the current sample).

Practice Effects

Practice effects were found for working memory (small effect size) but not for processing speed or attention tasks. However, practice effects for working memory did not remain significant after controlling for the effects of age and education suggesting that years of education may, in part, account for improvements from practice to baseline. Research conducted using the CogState® battery has demonstrated variability in the effects of practice across each task, which may depend on sample characteristics, such as medical or psychiatric disorders. The mean education level of our participants was 14 years, which is higher than previous investigations. Collie et al. (2003) found in neurologically normal individuals (mean education level of 13.1 years) the positive effects of practice on simple reaction time tasks (SRT) were most evident between the first and second administrations. Although stable performance was achieved after the second, third, and fourth SRT assessments within a 15-minute time period, no significant improvements in performance were observed after the second administration for the SRT test. This is not consistent with our findings, as participants did not demonstrate practice effects for attention or processing speed after the first assessment. Differences in our findings

compared to Collie et al. (2003) may be related to age, as participants in Collie and colleagues' study mean age was 63.7 years, while our sample was younger, with a mean age of 36.8 years. It may be that older individuals benefit more from practice, at least on some CogState® tests, than younger adults, as previous research has shown that aging results in declines in processing speed (Burgmans et al., 2011). Consistent with our findings, however, Pietrzak, Snyder, and Maruff (2010) found that individuals with schizophrenia (mean age 40 years; mean education level 10 years) showed no evidence of improvement in scores with repeated assessment on a SRT measure. Taken together, the above findings support the proposition that age may play a role in practice effects for simple reaction time tasks.

On an executive functioning task (Grotton Maze Learning Task), significant and large practice effects (d = 2.05) were observed across four practice sessions (Pietrzak et al., 2010), suggesting that more difficult tasks may elicit significant practice effects even in younger cohorts. This is consistent with our findings of practice effects on a working memory test. One potential explanation for the improvement from practice to baseline for working memory is task difficulty and demand. Attention and processing speed tasks are simple, have few rules, and require less mental effort than working memory tasks. The Two-Back working memory task requires a participant to hold multiple pieces of information (card number, color, and suit) in short-term memory in the correct sequence (two cards back), and to discriminate between novel and previously learned stimuli. Anecdotally, participants in our study reported more difficulty learning the Two-Back working memory task suggesting that rule acquisition instead of simple rule implementation may in part account for these effects (Pietrzak et al., 2008; Snyder et al., 2008). After controlling for age and education, working memory practice effects were not significant suggesting that academic achievement had some impact on working memory.

Pietrzak et al. (2010)'s sample was less educated (mean of 10 years of education) compared to 14 years in our sample, suggesting that these effects may reflect differences in education level and task. This is consistent with research that demonstrates a significant effect of education on CogState® task performance; although the effect of education was found on speeded and choice reaction time tasks (Lim et al., 2012).

The findings of the current study provide additional support for the stability of the Cogstate detection and identification tasks at multiple test-retest intervals within a very brief period of time (30 minutes for 3 trials) in middle-aged, predominately Caucasian, highly educated adults. Practice effects were observed for the Two-Back task, and age and education level were shown to influence working memory on this test.

Hypothesis 1

There was no change in attention or processing speed abilities from baseline to post-test, suggesting that irrespective of shunt size, participants' attention and processing speed ability were unaffected by the TCD procedure. The putative effects of TCD on cognition are thought to depend on the presence of microemboli passing to the brain and causing ischemia or hypoxia, which may produce a decline in cognitive ability. Thus, when participants with no shunt and moderate-to-severe shunts were analyzed together cognition did not decline following the TCD procedure, as only about 50% of participants had microbubbles passing to the brain. Participants' working memory ability improved from baseline to post-test, adjusting for practice effects, age, and education. Although this effect was small to medium in size (partial η^2 of 0.44), it suggests that the positive effects of practice for working memory persisted at the third (post-test) assessment, above and beyond the initial improvement from practice to baseline.

There were no main effects of age, education, or gender on processing speed, working memory, or attention, when collapsed across group. Null findings of age on the three cognitive tests may be due to the younger age of our sample (mean age of 36.8 years; range 18-60), as prominent declines in cognitive function begin around sixth decade of life (Salthouse, 2009). Although an age by time interaction effect was observed on working memory, those participants older than 35 years working memory improved from baseline to post-test, while individuals younger than 35 years working memory performance did not change over time. Thus, age did not have a deleterious effect on executive performance in our relatively young sample. Gender differences in cognitive ability have not been demonstrated for speed or accuracy of performance across CogState® tasks, including Detection (processing speed), Identification (Attention), and One-Back (working memory) tasks (Lim et al., 2012), consistent with the current findings.

Hypothesis 2

Unexpectedly, the presence of moderate to severe shunt did not result in a decline from baseline to post-test for processing speed, attention, or working memory compared to the no shunt group, although this study's power to detect a difference was low. Cohen (1988) suggests that a power of 0.80 is considered acceptable. Power calculations for a 2x1 Factorial ANOVA indicate that for a small effect size (.25), observed power would have to be 0.39 with a sample size of n= 90 per group. Although the sample size in the current study was relatively large (n= 104), only half those patients were included in the moderate-to-severe shunt group, suggesting that the effect of microbubbles on cognitive function, if it exists, must be small and require at least double the number of participants with large and no shunt in order to detect an effect.

Alternate Shunt Groups (Spencer Grade 0 vs. 5)

In order to explore whether previously described methods for grouping PFO into no shunt (SG = 0-1) vs. moderate-to-severe shunt (SG = 3-5) (Lao et al, 2008) were obscuring findings we compared participants who had no shunt (SG = 0) to severe shunt (SG = 5). Findings were consistent with the initial results, suggesting that even in patients with the largest shunt (SG 5), who experience between 300-500 embolic events during TCD, processing speed, attention, and working memory ability did not decline post-TCD. Thus, TCD appears to demonstrate no immediate effect for individuals who undergo TCD testing whether or not they have a shunt, at least in these domains of cognition and as measured by CogState® tests. However, due to the low power these results should be interpreted with caution, as it is possible that increased power to detect change in cognition may yield a significant effect.

Literature describing the link between cognitive functioning and microembolic load in patients undergoing cardiac surgery has been mixed. Of 15 studies that evaluated the association between TCD-detected microemboli and neuropsychological outcome, only five studies found a relationship between high-intensity transient signals (HITS) and cognitive impairments (Kruis, Vlasveld, & Van Dijk, 2010). In most studies, the correlation between microemboli and cognitive dysfunction was observed one week post-surgery and did not persist over time, occurred in only one cognitive domain, in a small subgroup, and often did not reflect the large percentages of patients that improved from pre to post-test (Kruis et al., 2010). Across these studies, cognitive dysfunction was present in patients who experienced a high microembolic load during the procedure (greater than 500) and occurred in the domains of memory, attention, processing speed, and motor functioning (Fearn et al., 2001; Pugsley et al. 1994). In ten studies, no association was found between emboli and cognitive impairment. Thus, in more severe

medical patients, such as those undergoing coronary artery bypass surgery, there are mixed findings regarding the effect of microemboli on cognition. Indeed, some studies indicate that cognitive impairments are present only in subtypes of cardiac patients (e.g., valve replacement) with microembolisation (Braekken, Reinvang, Russel, Brucher, & Svennevig, 1998). This is consistent with findings demonstrating neurological symptoms following TCD or Valsalva-like activity, such as hemiparesis and transient ischemic attack, in patients who have multiple additional vascular (stenosis), cardiologic (ASA), and embolic risks (Anzola, 2002; Khaffaf, Karnik, Winkler, Valentin, & Slany, 1994; Sander et al., 2000). Overall, the preponderance of studies suggests that microemboli are not neuropsychologically significant in high-risk cardiac surgery patients. This is consistent with the lack of association between TCD-induced microemboli and cognition in the current sample of young and relatively healthy patients who have a PFO.

Other putative reasons for the null findings include time between TCD and post-test (approximately 5-10 minutes), TCD related measurement error, and the possibility of missed cognitive or neurological effects associated with the TCD procedure, which may be identified using neuroimaging, neurologic examination, or other standardized neuropsychological tests. It is possible that brief and transient cognitive effects occurred either during or immediately after (i.e., within a few minutes) the TCD procedure and that cognitive assessment at earlier or the cognitive effects may not appear until later time points, which were not assessed in this study. The lack of cognitive decline at 5-10 minutes post-TCD test suggests that if cognitive deficits are present immediately following TCD testing, they are transient and resolve quickly. Alternatively, it may take time for neuronal injury to occur after microemboli. One study has demonstrated an effect of microbubbles on cognition at one week following TCD (Kruis,

Vlasveld, & Van Dijk, 2010), thus it is possible that the effects of microembolisation may not produce cognitive deficits for days to weeks following TCD. Sorensen et al., (2010) described self-reported neurological symptoms (e.g., loss of vision, hemi-sensory weakness, vertigo/imbalance, migraine, or aura) in one fifth (21%) of their sample ($n = 455$) of post-TCD shunt patients. Although symptoms occurred during and immediately following TCD in this study (within 30 minutes) (Sorensen et al., 2010), the authors did not assess cognitive function. The authors reported that those with induction of headache had symptoms that persisted after they left the office, but that no permanent effects were observed. A timeline for resolution of the observed neurological symptoms was not provided. It is possible that patients experiencing neurological symptoms do not have concomitant cognitive changes, that cognitive deficits are present only in a select sub-set of patients, and/or that effects may be observed at follow-up.

It is also possible that the cognitive domains assessed or neuropsychological tests used in the present study were not sensitive to the effects of neuronal damage due to transient hypoxia. One study evaluating a variety of cognitive domains, including attention, short-term recall, comprehension, and visuoconstruction, failed to detect any effect of TCD microembolisation on cognition. Ferrari et al. (2004) found that during transcatheter closure of PFO in patients under 65 with cryptogenic ischemic stroke, the highest rates of cerebral microembolism did not result in neurological or cognitive deficits. Additionally, the CogState® measures used in the current study correlate well ($r = .78-.81$) with established neuropsychological measures, such as Digit Span and Trail Making Test B (Maruff et al., 2009). These findings make it unlikely that an effect would be detected in other cognitive domains or by using gold standard neuropsychological measures. However, alternative domains of cognition, such as executive and

motor functioning, should be assessed in order to rule out the possibility that a lack of task complexity may contribute to the current findings.

Another reason for the lack of microembolic effect in shunt patients may include an insufficient degree of hypoxia necessary to induce pathophysiological dysfunction, as bubbles are microscopic $26.7 \pm 7.4\mu$ and have half-lives estimated at 4.6 seconds (Jeon et al., 2002). It is possible that microembolisation disrupts blood flow but does not altogether occlude the passage of blood through the arteries and that bubbles are present for a short duration of time prior to dissolution of the air and saline mixture. Therefore, such minor disruptions in flow are unlikely to reach levels necessary for ischemic polarization (18 mL/100g of brain tissue per minute; CBF reductions of 40-45% of normal values) and neuroinflammation (Welch & Barkley, 1986).

Individual variability in vascular health, PFO characteristics, and/or neurovascular protective factors may also influence the effect of TCD on cognition. Medically complex patients and those with continuous RLS (PFO and ASA) have increased frequency of multiple ischemic lesions on MRI, previous stroke history and embolism, and more frequent migraine than those with Valsalva-induced shunt only (Rigatelli et al., 2011). Therefore, they may represent a subset of patients who may experience cognitive decline following TCD. Alternatively, protective factors, such as "ischemic preconditioning," may be present in which transcription factors (HIF-1) activate vasculogenesis, increased glucose transport, and improved CBF in hypoxia-prone individuals (Dirnagl, Simon, & Hallenbeck, 2003). It is possible that individuals who have a large shunt have experienced multiple hypoxic events over the lifespan and thus, may be less susceptible to transient hypoxemia, or that the previous events have already resulted in cognitive decline. However, these suggestions are speculative, were not

evaluated in the current study, and may only suggest future populations in which to evaluate the effects of TCD on cognition.

Overall, the lack of shunt by time interaction in the current study suggests that TCD-induced microembolisation does not pose cognitive risk for individuals with even large shunt and is consistent with studies demonstrating the general safety of TCD. Despite systematic documentation of changes in blood pressure and heart rhythm, studies have not found adverse events in numerous TCD bubble studies, even in patients with large PFO and concomitant ASA, intracardiac thrombi, and cerebral ischemia (Lao et al., 2007; Lao et al. 2008; Tsvigoulis et al., 2009; Tsvigoulis et al., 2010). Our study adds to this literature by providing additional information about the lack of immediate cognitive effect of TCD in patients with and without shunt.

Strengths and Limitations

To our knowledge, this was the first study to evaluate cognitive functioning in RLS patients following TCD provocation, a procedure performed frequently as a part of routine cardiac care. Results demonstrated the feasibility and utility of the CogState® as a brief cognitive assessment battery in a medical setting. There were no practice effects for processing speed and attention, thereby decreasing administration times for these tasks. Practice effects were found for working memory at each of the three time points, although this finding may depend, in part, on age and education variables.

Limitations of the current study include relatively small sample size (n=104) with low power to detect an effect, limited assessment of cognitive domains (processing speed, attention, and working memory only) and a lack of task complexity, lack an independent marker of brain health, such as neuroimaging, and homogeneous sample restrictions, which limit generalizability

of findings. An additional limitation is the inability in this study to follow patients in the weeks to months after TCD to determine if there were any long-term cognitive effects.

Conclusion

Our findings suggest that TCD, administered as part of a cardiology patient's routine diagnostic care, does not produce any immediate cognitive effects in the domains of processing speed, attention, or working memory, even for individuals with large RLS. Importantly, these findings are restricted to young, relatively healthy, Caucasian individuals assessed immediately following the TCD procedure and this finding should be replicated at other cardiac centers with larger sample sizes at multiple time points following the bubble test.

Future Directions

Future research would benefit from assessment of a larger and more heterogeneous sample, including inclusion of medically complex patients for study, multi-site studies, collection of patient data related to vascular risk factors (diabetes, hypertension, hyperlipidemia), the use of neuroimaging as an independent marker of brain injury, assessment of additional cognitive domains, including executive functioning, and assessment of cognition at multiple time points (1 week and 1 month post-TCD).

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Appendix A

Effect of Depression on Cognition as a Function of Shunt Group and Time.

A main effect of depression on processing speed and a shunt group by depression interaction was found on baseline attention. However, these findings become insignificant when adjusting for multiple comparisons.

Table A6. *History of Depression by Shunt Group.*

Variable	Dx ($n = 33$) Mean ± *SD*	No Dx ($n = 70$) Mean ± *SD*	F	df	p	Partial Eta^2
Main Effect of Depression						
Processing Speed	2.58±.012	2.56±.008	8.11	1	0.01	0.077
Attention	2.76±.012	2.74±.008	2.74	1	0.10	0.028
Working Memory	1.29±.024	1.31±.016	0.91	1	0.34	0.010
Depression x Time Interactions						
Processing Speed			2.99	1	0.09	0.031
Attention			0.34	1	0.55	0.004
Working Memory			0.27	1	0.60	0.003
	No Shunt Mean ± *SD*	Shunt Mean ± *SD*	F	df	p	Partial Eta^2
Shunt x Depression Interactions						
Processing Speed						
Baseline			5.09	1	0.02	0.051
Depressed	2.59±.016	2.62±.018				
Not Depressed	2.57±.012	2.53±.012				
Posttest			1.99	1	0.16	0.021
Depressed	2.58±.018	2.59±.019				
Not Depressed	2.57±.013	2.55±.013				
Attention						
Baseline			6.75	1	0.01	0.066
Depressed	2.75±.015	2.78±.017				
Not Depressed	2.76±.011	2.71±.011				
Posttest			2.82	1	0.09	0.029
Depressed	2.75±.018	2.77±.020				
Not Depressed	2.76±.013	2.73±.013				
Working Memory						
Baseline			0.17	1	0.68	0.002
Posttest			0.12	1	0.72	0.001
Shunt x Depression x Time Interactions						
Processing Speed			0.68	1	0.41	0.007
Attention			0.51	1	0.46	0.005
Working Memory			0.00	1	0.98	0.000

Appendix B

Effect of Anxiety on Cognition as a Function of Shunt Group and Time.

A shunt x anxiety x time interaction was found for working memory, although this effect becomes insignificant when correcting for multiple comparisons.

Table B7. *History of Anxiety by Shunt Group*.

Variable	No Shunt (n = 54) Mean ± SD	Shunt (n = 50) Mean ± SD	F	df	p	Partial Eta²
Main Effect of Anxiety						
Processing Speed			0.92	1	0.34	0.010
Attention			0.09	1	0.76	0.001
Working Memory			0.16	1	0.68	0.002
Anxiety x Time Interactions						
Processing Speed			1.20	1	0.29	0.011
Attention			0.02	1	0.89	0.000
Working Memory			0.37	1	0.54	0.004
Shunt x Anxiety Interactions						
Processing Speed						
Baseline			1.89	1	0.17	0.020
Posttest			0.29	1	0.86	0.000
Attention						
Baseline			3.69	1	0.06	0.037
Posttest			1.52	1	0.22	0.016
Working Memory						
Baseline			0.86	1	0.36	0.009
Posttest			2.31	1	0.13	0.024
Shunt x Anxiety x Time Interactions						
Processing Speed			2.13	1	0.15	0.022
Attention			0.36	1	0.55	0.004
Working Memory			7.96	1	0.01	0.078
Baseline						
Anxious	1.30±.032	1.27±.041				
Not Anxious	1.28±.039	1.30±.022				
Posttest						
Anxious	1.27±.037	1.33±.049				
Not Anxious	1.36±.029	1.30±.026				

Appendix C

Benzodiazepines and Cognition by Shunt Group.

No significant main effects or interactions were found.

Table C8. *Benzodiazepines and Cognition by Shunt Group.*

Variable	No Benzo (*n* = 11) Mean ± *SD*	Benzo (*n* = 90) Mean ± *SD*	*F*	*df*	*p*	*Partial Eta²*
Gender x Shunt Interactions						
Processing Speed			0.45	1	0.50	0.005
Attention			0.71	1	0.40	0.007
Working Memory			0.16	1	0.68	0.002
Gender x Shunt x Time Interactions						
Processing Speed			0.01	1	0.92	0.000
Attention			2.68	1	0.10	0.028
Working Memory			0.05	1	0.82	0.000
Main Effect of Benzodiazepines						
Processing Speed	2.57±.007	2.56±.021	0.52	1	0.47	0.005
Attention	2.75±.007	2.73±.020	1.42	1	0.23	0.015
Working Memory	1.30±.014	1.31±.041	0.05	1	0.81	0.001
Benzodiazepines x Time Interactions						
Processing Speed			0.39	1	0.53	0.004
Attention			2.25	1	0.12	0.023
Working Memory			0.12	1	0.67	0.002