

Patent Foramen Ovale in Obstructive Sleep Apnoea and Chronic Obstructive Pulmonary Disease

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Abstract of Thesis

Title

**Patent Foramen Ovale in Obstructive Sleep Apnoea and
Chronic Obstructive Pulmonary Disease**

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The objective of this thesis was to determine the impact of right to left shunting (RLS) through patent foramen ovale (PFO) on oxygen saturation in obstructive sleep apnoea (OSA) and chronic obstructive pulmonary disease (COPD).

The first aim was to determine the prevalence of PFO in severe OSA and whether PFO closure improves nocturnal oxygen saturation. The data showed that PFO with large shunts were more prevalent, however overall prevalence was not statistically different when compared to healthy controls. PFO closure did not reduce nocturnal desaturation.

The second aim was to determine whether severe COPD patients with $\text{PaO}_2 \leq 7.3\text{kPa}$ had a higher prevalence of PFO compared to patients with $\text{PaO}_2 > 8\text{kPa}$, additionally to compare the prevalence of PFO in COPD with healthy controls. The data showed no difference in PFO prevalence in patients with $\text{PaO}_2 \leq 7.3\text{kPa}$ compared to patients with $\text{PaO}_2 > 8\text{kPa}$, however, intrapulmonary shunts were more prevalent in hypoxaemic patients. Similar to OSA, PFO with large shunts were more prevalent in severe COPD, however overall prevalence was not statistically different to healthy controls.

The final aim was to determine whether patients with COPD and PFO developed RLS during exercise and whether this was associated with reduced oxygen saturation, reduced exercise endurance and increased intrathoracic pressure swings. The data showed that RLS through PFO increased from baseline during exercise and this was associated with increased swings in intrathoracic pressure. There was no difference in desaturation or exercise endurance when compared to patients with no PFO.

In summary, this thesis shows that PFO with large shunts are more prevalent in both OSA and COPD. PFO closure in OSA did not reduce nocturnal desaturation. Furthermore, the presence of a PFO in COPD did not influence resting or exercise oxygen saturation despite the observed increase in RLS with exercise.

Declaration

I hereby declare that this thesis has been composed by me and is based on work done by me and that this thesis has not been presented for assessment in any previous application for a degree, diploma or other similar award. I also declare that all sources of information have been specifically acknowledged.

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Dedication

I would like to dedicate this thesis to my parents. Their love, encouragement, support and guidance has been the reason that I can complete this PhD. They are my inspiration.

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Abbreviations

Abbreviations

A/D	Analogue to digital
ABG	Arterial blood gases
AHI	Apnoea / hypopnoea index
ANOVA	Analysis of variance
ASA	Atrial septal aneurysm
ASDA	American Sleep Disorders Association
BMI	Body mass index
CF	Cystic fibrosis
CI	Confidence interval
CO	Carbon monoxide
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CVA	Cerebrovascular accident
DCI	Decompression illness
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth sleepiness scale
ETCO ₂	End-tidal carbon dioxide
FEV ₁	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
HAPE	High altitude pulmonary oedema
HIT6	Headache impact test 6 questionnaire
ICE	Intracardiac echocardiography
IVC	Inferior vena cava
KCO	Carbon monoxide transfer coefficient
LED	Light emitting diode
LTOT	Long term oxygen therapy
MCA	Middle cerebral artery
NPSG	Nocturnal polysomnography
NREM	Non rapid eye movement sleep
O ₂	Oxygen
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
OSLER	The Oxford SLEep Resistance test
OR	Odds ratio
PaCO ₂	Arterial carbon dioxide tension
PaO ₂	Arterial oxygen tension

PAP	Pulmonary artery pressure
P_{di}	Transdiaphragmatic pressure ($P_{gas} - P_{oes}$)
PEEPi	Intrinsic positive end expiratory pressure
PFO	Patent foramen ovale
P_{gas}	Gastric pressure
P_{oes}	Oesophageal pressure
RAP	Right atrial pressure
REM	Rapid eye movement sleep
RER	Respiratory exchange ratio
RLS	Right to left shunt/right to left shunting
RR	Relative risk
RV	Residual volume
RVSP	Right ventricular systolic pressure
SaO ₂	Arterial oxygen saturation
SD	Standard deviation
SF36v2	Short form 36 questionnaire version 2
TCD	Transcranial Doppler
TIA	Transient ischaemic attack
TLC	Total lung capacity
TLCO	Carbon monoxide transfer factor
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
VCO ₂	Carbon dioxide production
VD	Dead space
VE	Minute ventilation
VO ₂	Oxygen consumption
VQ	Ventilation perfusion
VT	Tidal volume
6MWT	Six minute walk test

Chapter 1

Introduction

Chapter 1 introduces the themes and aims of the thesis. The first section describes patent foramen ovale (PFO) embryology, developmental anatomy, prevalence and detection. Relevant clinical associations are then discussed followed by an evaluation of the current knowledge of the association of PFO with hypoxaemia. This leads on to the second section that describes obstructive sleep apnoea (OSA), a condition associated with nocturnal hypoxaemia. Knowledge of studies investigating PFO in OSA are discussed and questions raised from that research are given. The third section describes chronic obstructive pulmonary disease (COPD). The causes of hypoxaemia at rest are examined. The exercise physiology that may precipitate shunting through a PFO is described and finally studies investigating PFO in COPD are discussed. Again, possible research questions regarding PFO in COPD are raised. The overall aims of the thesis are given and the hypotheses listed.

1.1 Patent foramen ovale

1.1.1 Embryology

A patent foramen ovale is a common cardiac defect prevalent in over 25% of healthy adults (Hagen et al., 1984). The foramen ovale is a unidirectional valve formed from the septum primum and secundum in utero. It allows oxygenated blood returning to the right atrium from the mothers placenta to bypass the dormant foetal lungs and enter the left atrium.

The embryological sequence that results in the formation of the foramen ovale is shown in Figure 1.1.

At approximately 4 weeks gestation the single atrium is divided by the septum primum (Sadler, 1990). The septum primum grows from the atrial roof towards the endocardial cushions (Figure 1.1A). The endocardial cushions develop from the anterior and posterior aspects of the atrioventricular canal and as they grow, both sides eventually fuse dividing the canal into right and left halves. The foramen primum is formed (Figure 1.1B). As the septum primum develops programmed cell death in the central area forms multiple small perforations (Figure 1.1B). These enlarge and coalesce eventually forming the foramen secundum (Figure 1.1C). The septum primum continues to grow towards the endocardial cushions and fuses with them, closing the foramen primum (Figure 1.1D). The septum secundum then develops from the right ventrocranial atrial wall (Figure 1.1E). As it grows, it overlaps the foramen secundum leaving a flap like opening between the right and left atria (Figure 1.1F, G). This is the foramen ovale, an integral component and vital route for oxygenated blood to traverse the foetal circulation (Figure 1.1H).

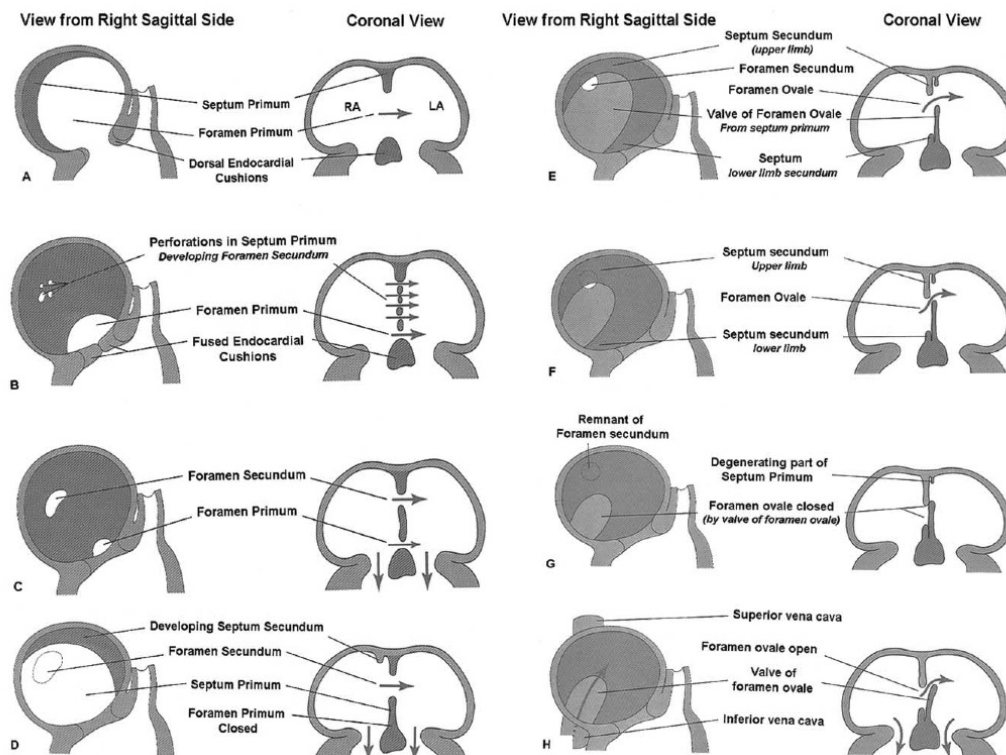


Figure 1.1: Development of the foramen ovale, taken from Hara et al, 2005, Figure 1. Right sagittal and coronal views. LA: left atrium, RA: right atrium. A) The single atrium is divided by the septum primum. B) The septum primum grows towards the endocardial cushions which develop from the anterior and posterior aspects of the atrioventricular canal. Both sides eventually fuse dividing the canal into right and left halves. The foramen primum is formed. As the septum primum develops multiple small perforations enlarge. C) The perforations eventually form the foramen secundum. D) The septum primum fuses with the endocardial cushions closing the foramen primum. At approximately day 37, the septum secundum then develops from the right ventrocranial atrial wall. E, F, G) As it grows, it overlaps the foramen secundum leaving a flap like opening between the right and left atria. H) By day 55, the foramen ovale has formed which provides a vital route for oxygenated blood to traverse the foetal circulation.

As oxygenated blood enters the umbilical vein, the inferior vena cavae and the right atrium, high pulmonary pressures in the developing foetal lungs prevent blood from entering the pulmonary circulation. Instead, it is shunted through the foramen ovale which preferentially directs this oxygen rich blood to the developing brain. Blood is also directed around the foetus and eventually returns to the placenta via the umbilical arteries.

At birth, lung inflation, decreasing pulmonary vascular resistance and initialisation of a pulmonary circulation result in a decrease in right atrial and increase in left atrial pressure. This reverses the pressure gradient and seals the valve shut. Fibrosis with complete fusion of the foramen ovale occurs within the first 2 years of life. Incomplete fusion creates a PFO, an interatrial connection which is the most common cause of a systemic right to left shunt (RLS).

1.1.2 Prevalence

The overall prevalence of PFO in an autopsy study of 965 normal adult hearts was 27.3% (Hagen et al., 1984), of note, the frequency decreased from 34% in the first 3 decades, to 20% in those aged over 80 years. Interestingly, as the prevalence decreased, the mean size of the PFO tunnel increased from 3.8mm in the first 3 decades to 5.4mm over 80 years. A suggested theory is that smaller PFO seal shut with increasing age.

A prospective, population based study of 581 adults using transoesophageal echocardiography reported a similar PFO prevalence of 25.6% (Meissner et al., 1999).

1.1.3 Anatomy of patent foramen ovale

There are considerable variations in the morphology of PFO and its associated anatomy (Rana et al., 2010). The size of the PFO tunnel and its anatomical position can be strikingly different. In some patients the septum primum and secundum are quite closely opposed leading to a thin, long tunnel. In others, the 2 flaps are separate leading to a wide PFO opening. PFO can be held open in patients where the 2 septae fail to meet resulting in continuous left

to right shunting. In these cases, PFO can be difficult to distinguish from a secundum atrial septal defect (Figure 1.2). An atrial septal aneurysm (ASA)

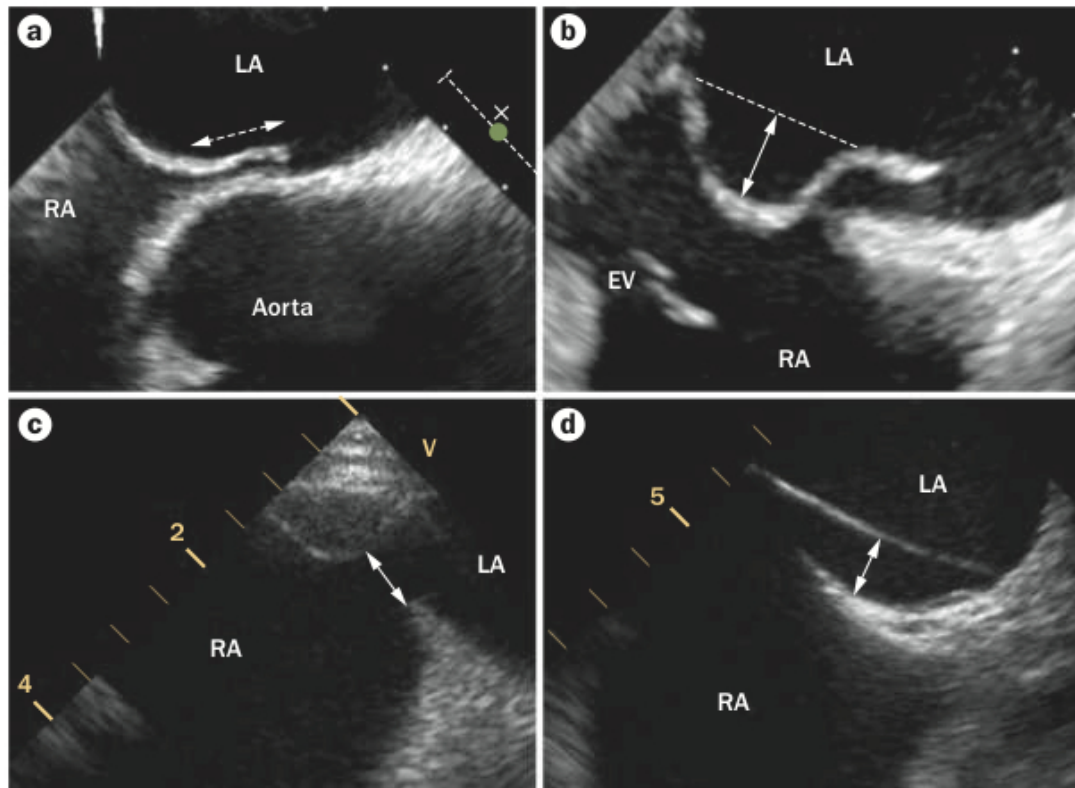


Figure 1.2: *Anatomical variations in PFO anatomy is taken from Calvert et al. (2011). Images were obtained using transoesophageal echocardiography. a) Long tunnel PFO (arrow). b) PFO associated with atrial septal aneurysm (arrow). c) Spontaneous retraction of primum septum resulting in widely opening PFO (arrow). d) Held open PFO with permanent separation of the primum and secundum septa (arrow). Abbreviations: EV, Eustachian valve; LA, left atrium; PFO, patent foramen ovale; RA, right atrium*

is a hypermobile interatrial septum which bows $>10\text{mm}$ from the right to left atrium, (Figure 1.2). Lack of a consistent definition of what constitutes an ASA has prohibited accurate estimates, however they have been detected in 1% of consecutive autopsy studies (Silver and Dorsey, 1978) and in 5% of patients undergoing transoesophageal echocardiography (Pearson et al., 1991). It is thought they are rarely a separate clinical entity, instead coexisting with PFO and increasing both the magnitude of shunt and the thrombogenic

risk especially in cryptogenic stroke (Overell et al., 2000).

A eustachian valve is a remnant of the primordial valve of the inferior vena cava. In utero, it directs oxygen rich blood from the umbilical vein through the foramen ovale. It persists in 55.8% to 80% of adults (Schuchlenz et al., 2004; Rigatelli et al., 2008) but has no function after birth. Again, there is great variation in the morphology of the persisting eustachian valve, some being barely visible and in rare cases being large enough to divide the right atrium. In the presence of a PFO, the persisting valve can direct blood flow onto the atrial septum and cause right to left shunting (RLS) in the absence of elevated right atrial pressure.

All the anatomical variants of PFO described above have implications for the type of PFO closure device used and the success of the procedure.

1.1.4 Detection of patent foramen ovale

PFO have been detected using many methods including CT (Kim et al., 2009; Saremi et al., 2007, 2008), MRI (Mohrs et al., 2007), nuclear lung perfusion scans (Weissmann et al., 1980) and ear oximetry (Karttunen et al., 2001). However, the most commonly used methods rely on the ultrasound detection of right-to-left shunting of microbubble contrast using contrast transthoracic echocardiography (TTE), transoesophageal echocardiography (TOE) or transcranial Doppler (TCD). TTE and TOE allow direct visualisation of contrast crossing from right to left heart whereas TCD detects microbubbles in the middle cerebral artery after they have crossed a RLS. Since gas is 100 000 times less dense than blood, the acoustic impedance between the two is high and microbubble contrast is clearly identifiable.

The study by Lynch et al in 1984 was the first to employ a Valsalva manoeuvre

as a technique to improve detection of PFO (Lynch et al., 1984). The Valsalva manoeuvre increases intrathoracic pressure, which precipitates a fall in venous return and a drop in blood pressure. On release of the manoeuvre, sudden deep inspiration augments venous return and transiently elevates right atrial pressure. This reverses the atrial pressure gradient and in the presence of a PFO will unmask a RLS. All clinical ultrasound protocols now incorporate testing both at rest and during the release phase of a Valsalva manoeuvre to identify RLS.

Historically, contrast TOE was regarded as the gold standard investigation (De Belder et al., 1992). However, this semi-invasive, time-consuming method is limited by an inability of patients to generate an effective Valsalva. TTE was previously disadvantaged by image quality; however, newer machines with second harmonic imaging have significantly improved sensitivity. Detection rates using TTE are now comparable to TOE (Daniels et al., 2004; Trevelyan and Steeds, 2006; Madala et al., 2004). A multicentre trial of 256 patients concluded that TTE is as accurate and identifies important and early shunting more often than TOE (Daniels et al., 2004). Compared to TOE, TTE with second harmonic imaging has been shown to have a sensitivity of 91 to 100% and specificity of 82 to 100% (Van Camp et al., 2000; Daniels et al., 2004; Madala et al., 2004).

Transcranial doppler (TCD) detection of PFO is also highly sensitive and specific compared with contrast TOE. Compared to TOE, contrast TCD has been shown to have a sensitivity of 89 to 97% and specificity of 78 to 94% (Klotzsch et al., 1994; Karnik et al., 1992; Job et al., 1994; Caputi et al., 2009). It provides the additional benefits of monitoring the effectiveness of the Valsalva manoeuvre by observing a decrease in cerebral blood flow and it also permits semi-quantification of embolic contrast material (Job et al., 1994). The advent

of multi-gated Power M Mode machines has further enhanced the detection of microbubble signals (Saqqur et al., 2004; Spencer et al., 2004). Spencer et al studied 100 patients undergoing cardiac catheterisation with Power M mode contrast TCD and used a 6 point logarithmic scale (0 to 5) to grade shunt size. Using the McNemar change test they found that the diagnostic capability of TCD corresponded with anatomical findings at catheterisation, $p = 0.69$ (Spencer et al., 2004). This technique is invaluable to neurologists who can diagnose PFO without referring for echocardiographic assessment.

Gonzalez-Alujas et al compared TTE, TCD and TOE in 134 patients (Gonzalez-Alujas et al., 2011). They found TTE and TCD to be more sensitive: 100% and 97% respectively compared to TOE, which was 86% sensitive, $p < 0.001$. They concluded that TTE allowed improved diagnosis and quantification of shunt size.

The use of 3D real time TTE is a promising new technique that can identify PFO without the need for a contrast injection with results comparable to contrast TOE (sensitivity 83%, specificity 100%, positive predictive value 100%, negative predictive value 88%) (Monte et al., 2010). With increasing expertise, this may overtake contrast TTE as the diagnostic method of choice.

In this thesis I used the combination of contrast TTE and TCD.

1.1.5 Clinical associations

Stroke

Cohnheim originally linked PFO to an unexplained fatal stroke in a young woman in 1877 (Cohnheim, 1877). Since this early description the association with PFO and cryptogenic stroke, which accounts for 40% of ischaemic strokes

in people younger than 55, has been firmly established (Lechat et al., 1988; Webster et al., 1988; Cabanes et al., 1993; Job et al., 1994; DiTullio et al., 1992; Yeung et al., 1996; Overell et al., 2000; Handke et al., 2007). A metaanalysis conducted by Overell et al calculated that for people under 55 years, the odds ratio of suffering an ischaemic stroke compared to control subjects was 3.10 (95% CI: 2.29 - 4.21) in the presence of PFO, 6.14 (95% CI: 2.47 - 15.22) in the presence of an ASA and 15.59 (95% CI: 2.83 - 85.87) if both PFO and ASA were present (Overell et al., 2000).

Various mechanisms have been proposed to explain the increase in cryptogenic stroke risk. Paradoxical embolism of a venous thrombus through a PFO occurring after a Valsalva manoeuvre or in relation to chronically elevated pulmonary artery pressure is the most popular hypothesis (Choong et al., 2008; Kim et al., 2009; Madani and Ransom, 2007; Ahmed et al., 2003; Cramer et al., 2004). The lurking clot theory hypothesises that a clot forms within the PFO tunnel and embolises when right atrial pressure is transiently elevated. An increased propensity for atrial arrhythmias and the generation of spontaneous echo contrast has also been postulated (Rigatelli et al., 2009).

Studies evaluating the magnitude of RLS have found that as the PFO shunt size increases, so does stroke risk (Anzola et al., 2003; Giardini et al., 2007; Paciaroni et al., 2011). Schuchlenz et al studied the impact of PFO diameter on stroke risk (Schuchlenz et al., 2000). They used multiplane TOE to measure PFO size in 121 patients (< 60 years) with cryptogenic stroke and 123 control subjects. Mean PFO diameter was larger in stroke patients compared to controls (4 (2) mm versus 2 (1) mm, $p < 0.0001$) and PFO greater than 4mm were associated with an increased risk of transient ischaemic attack (TIA) (OR: 3.4, 95% CI: 1.0 to 11, $p = 0.04$), ischaemic stroke (OR: 12, 95% CI: 3.3 to 44, $p = 0.0001$) and having evidence of 2 or more strokes (OR: 27, 95% CI: 4.7 to 160,

$p = 0.0002$).

Steiner et al evaluated 95 patients with first ischaemic stroke (over age 39) using TOE for a cardiac source of embolism (Steiner et al., 1998) and had similar findings to that of Schuchlenz et al (Schuchlenz et al., 2000). They compared patients with medium to large PFO (≥ 2 mm) to patients with small (< 2 mm) or no PFO. Thirty-three percent of patients had a PFO. The frequency of PFO in patients with cryptogenic infarcts was 45% (19/42) compared to 23% (12/53) in patients with determined cause of stroke, $p = 0.02$. Medium to large PFO were found in 26% of cryptogenic strokes compared to 6% among infarcts of determined cause, $p = 0.04$. Patients with moderate to large PFO had evidence of an increased number of superficial infarcts, occipital and infratentorial strokes and showed more brain imaging features of embolic infarcts than those with small PFOs. In addition, PFO shunt size has also been associated with increased stroke recurrence. Harrer et al investigated 124 cryptogenic stroke patients over a period of 10 years (Harrer et al., 2006). They found that large shunts were more frequent in patients with recurrent strokes (OR = 5.0, CI: 1.02 to 23.69, $p < 0.05$). Taken together, these data suggest that PFO diameter is a risk factor for cerebral ischaemic events.

Not all studies have found a positive association between PFO and stroke. The PFO in cryptogenic stroke study (Homma et al., 2002) followed 630 stroke patients (265 cryptogenic and 365 known stroke subtype) for 2 years with the combined endpoint of recurrent ischaemic stroke or death. All patients were medically treated with either warfarin or aspirin. They did not find any significant difference between those with and without PFO in the time to primary endpoints (hazard ratio: 0.96; 95% CI: 0.62 to 1.48; 2-year event rates 14.8% versus 15.4%, $p = 0.16$). Furthermore, there was no difference in stroke rates for those with no, small and large PFO shunts (2-year event rates:

15.4%, 18.5%, and 9.5%, respectively).

Feurer et al studied 639 patients with a diagnosis of cerebral ischaemia. Using contrast TCD, a RLS was detected in 140 (28%) men and in 114 (42%) women at baseline. Ten shunt carriers (1.6%) and 32 patients (5.0%) without RLS had suffered a recurrent stroke. The hazard ratio of RLS for stroke recurrence was 0.86 (95% CI: 0.41 to 1.79) suggesting PFO was not associated with an increased risk of stroke recurrence (Feurer et al., 2010). The Spanish RLS multicenter study included 486 patients with cryptogenic stroke. They also found no association between massive RLS and recurrent stroke (OR: 0.94, 95% CI: 0.36 to 2.40, $p = 0.89$) (Serena et al., 2008).

Given the lack of agreement in studies outlined above, it is unsurprising that despite PFO closure being one of the most common structural procedure in the cardiac catheterisation laboratory, it remains one of the most controversial. Currently there are no data from randomised controlled trials to suggest a benefit, although these studies are ongoing.

The study on which justification of PFO closure for cryptogenic stroke rests was performed by Windecker et al (Windecker et al., 2004). This non-randomised trial followed patients with at least 1 paradoxical embolic event for 6.5 years. Patients were divided into those who had undergone PFO closure ($n = 150$) and those who had been medically treated ($n = 158$: $n = 79$ with oral anticoagulants and $n = 79$ with antiplatelet agents). Age, gender, cardiovascular risk factors were similar amongst groups. Complete PFO closure was achieved in 83% of patients undergoing closure. At 4 years follow up the combined endpoint of death, stroke or TIA was 8.5% in the PFO closure group compared to 24.3% in the medically treated group (RR: 0.48, 95% CI: 0.23 to 1.0, $p = 0.05$). This non-significant trend towards a lower risk of the combined endpoint is the justification for current PFO closure protocols.

The risk of recurrent stroke or TIA also showed a trend towards benefit in the PFO closure group but was not statistically different when compared to medical treatment: 7.8% versus 22.2% (RR: 0.51, 95% CI: 0.23 to 1.11, $p = 0.08$). There was no difference in outcomes between patients on anticoagulants or antiplatelets.

The CLOSURE I trial is the first and only randomised controlled trial of PFO closure for stroke/TIA. The results have recently been presented (Furlan, 15th November 2010) and are likely to have a significant impact on PFO closure for cryptogenic stroke. The CLOSURE I study enrolled 909 patients and randomised to PFO closure (with 6 months clopidogrel and 24 months aspirin) or best medical therapy (aspirin or warfarin or both). The composite primary endpoint was stroke or TIA at 2 years, all cause mortality at 30 days, and neurological mortality between 31 days and two years. The results of this study showed no difference in both arms (5.9% in closure arm versus 7.7% in medical therapy arm, $p = 0.30$). Procedural success was good with 86.7% PFO closed at 1 year. Major vascular complications and atrial fibrillation were significantly greater in the intervention arm and all other safety endpoints showed no difference. Since the announcement of these findings there has been much debate with regards to implications for PFO closure. The investigators state that when assessed over 30 days, most patients had underlying causes for their ischaemic event and the strokes were therefore not strictly cryptogenic. There is also controversy with regards to duration of the trial, 2 years perceived by some as too short to show any difference in endpoints.

Four other trials are still ongoing: the CLOSE and PC trials in France and Switzerland, respectively, plus St Jude Medical's/ AGA's RESPECT trial and Gore's REDUCE trial. Results from these studies will further inform practice.

Migraine

Migraine is estimated to affect approximately 13% of people aged 26 to 64 years (Lipton et al., 2003). One in three sufferers have associated transient focal neurologic symptoms or aura (Lipton et al., 2001). Many studies have found associations between migraine and PFO (Anzola et al., 1999; Sztajzel et al., 2002; Caputi et al., 2010). A cross-sectional case-control study of 93 patients with migraine with aura reported a prevalence of 47% compared to 17% in healthy controls. Highlighting the importance of shunt size, the presence of a moderate to large shunt increased the odds of having migraine by 7.78 (95% CI: 2.53 to 29.3, $p < 0.001$) (Schwerzmann et al., 2005). It is thought that interatrial passage of microemboli or vasoactive compounds reaching the cerebral circulation which would otherwise be filtered by the lung may be the mechanism for the migraine.

There is, however a distinct dichotomy in study findings. A large case-control study examined 144 patients with migraines and 144 healthy controls (Garg et al., 2010). PFO prevalence was similar in case and control subjects (26.4% versus 25.7%; OR: 1.04, 95% CI: 0.62 to 1.74, $p = 0.90$). In patients with migraine with aura there was also no difference in prevalence compared to patients without aura (26.8% versus 26.1%; OR: 1.03, 95% CI: 0.48 to 2.21, $p = 0.93$).

The Migraine Intervention With STARFlex Technology (MIST) trial pioneered a robust study design for multicentre, prospective, randomised, sham-controlled PFO closure studies. The study randomised 147 patients who suffered from migraine with aura, experienced frequent migraine attacks, had previously failed 2 or more classes of prophylactic treatments, and had moderate or large RLS consistent with the presence of a PFO to PFO closure or to a sham procedure. Patients were followed up for 6 months with the

ambitious primary end point of complete cessation of migraine headache 91 to 180 days after the procedure. The investigators found no difference in primary endpoint between the closure and sham groups. Post hoc analysis (excluding 2 outliers) showed that the closure group demonstrated a greater reduction in total migraine headache days, $p = 0.027$ which in itself is an important outcome. MIST II, a larger follow-on study from MIST I was terminated prematurely when funding was withdrawn. PFO closure for migraine headache is a contentious issue and further trials are awaited before conclusions can be drawn.

Decompression illness

Decompression illness (DCI) in divers results from locally expanding gas nuclei or arterial gas embolism during ascent following a dive.

A study performed in 230 scuba divers revealed that the presence of TOE detected PFO was related to an absolute risk of suffering approximately 5 major DCI events per 104 dives. This was 5 times that of divers without a PFO (Torti et al., 2004). Similar to both stroke and migraine, the risk of a major DCI increased as PFO shunt size increased. Divers with a small shunt had a similar risk as divers without PFO (1.1, 95% CI: 0.14 to 8.4). However, compared to divers without PFO, the risk of major DCI in those with a moderate shunt was 4.4-fold (95% CI: 1.8 to 10.7) and large shunt was 6.6-fold (95% CI: 2.8 to 15.5).

Wilmshurst et al performed a case-control study using contrast TTE in 100 divers with neurological DCI and 123 unaffected divers (Wilmshurst and Bryson, 2000). They found that divers who had suffered neurological DCI had a higher prevalence of PFO with large shunts and PFO that were present at rest, $p < 0.001$. Moderate to large size shunts were present in 52% of affected divers and 12% controls, $p < 0.001$.

The proposed mechanism behind the association between DCI and PFO is that paradoxical gas embolism with expansion of nitrogen bubbles occurs on ascent from a dive. Divers with moderate to large PFO often undergo PFO closure to prevent further DCI episodes despite the lack of randomised trial data.

Acute pulmonary embolism

In the event of an acute pulmonary embolism, it is reasonable to assume that part of a clot, on its course to the pulmonary arteries, can pass through a PFO. In fact, elevated right ventricular pressures may provide a favorable environment for this to occur. Konstantinides et al tested the hypothesis that a PFO is an important prognostic indicator for mortality and the occurrence of cardiovascular complications in major pulmonary embolism (Konstantinides et al., 1998). In a prospective study of 139 patients they found that having a PFO was an independent predictor of mortality (33% death rate versus 14%) with an odds ratio of 11.35 (CI: 2.89 to 44.52). Patients with PFO were also more likely to have a complicated clinical course with a significantly higher incidence of ischaemic stroke (13% versus 2.2%, $p = 0.02$) and peripheral arterial embolism (15% versus 0, $p < 0.001$). Interestingly, risk of death was independent of pulmonary artery pressures. Moreover, patients with systolic PAP > 60 mmHg had a lower mortality compared with those with mild to moderate pulmonary hypertension. This may reflect the fact that the patients with severe pulmonary hypertension were likely to have had chronically raised right sided pressures and could therefore tolerate the haemodynamic effects of a pulmonary embolus. Konstantinides et al recommended that on the basis of their findings, patients with a PFO should be considered for aggressive therapy such as thrombolysis or catheter thrombus fragmentation.

1.1.6 Clinical associations with hypoxaemia

PFO have been implicated in exacerbating hypoxaemia in a number of studies (Kerut et al., 2001; Gelernter-Yaniv et al., 2008). The studies are smaller and fewer in number than those conducted for stroke or migraine, however, they raise interesting questions about not only the prevalence of PFO but also the physiological consequences of a RLS in hypoxic conditions. Furthermore, it is a theoretical possibility that failure of PFO closure may be a marker for a related behaviour that leads to the development of the conditions described below and that this can only be conclusively resolved with surgery.

Platypnoea-orthodeoxia syndrome

Platypnoea-orthodeoxia syndrome is a condition where desaturation occurs in the sitting position and resolves with lying down (Varsano et al., 2011; Toffart et al., 2008). Numerous case reports demonstrate an associated PFO and resolution of hypoxaemia following PFO closure (Desouza et al., 2009; Gurin et al., 2005; Ilkhanoff et al., 2005; Rao et al., 2001; Varkul et al., 2001; Waight et al., 2000; Yalonetsky et al., 2006). The mechanism for these findings is thought to be that the anatomical configuration of the interatrial septum is modified with age-related changes, including elongation of the aortic root, diaphragm paralysis and scoliosis (Sanikommu et al., 2009); or following pneumonectomy (Bakris et al., 1997; Mercho et al., 1994; Bellato et al., 2008) such that a RLS develops in the upright position. It is speculated that the development of this RLS causes further arterial hypoxaemia.

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive condition which is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. It has an incidence of approximately 1 in 2000 newborns and is a multisystem disorder affecting predominantly the lungs and gastrointestinal tract. Recurrent pulmonary infections and airway obstruction precipitate progressive hypoxaemia (Davis, 2006). Case reports of PFO in CF have focused primarily on presumed paradoxical embolism through PFO in patients with implantable venous access devices and right atrial thrombus causing TIA and strokes (Al Lawati and Wilcox, 2007; Davidson et al., 1990; Espiritu and Kleinhenz, 2000; Playfor and Smyth, 1999; Sritippayawan et al., 2003; Simmonds et al., 2009). Simmonds et al reported an improvement in baseline SaO₂ from 90% to 95% in a young CF woman following PFO closure (Simmonds et al., 2009). Davidson et al described a series of hypoxaemic CF patients with PFO and speculated the PFO may contribute to hypoxaemia (Davidson et al., 1990). Although inconclusive, these reports suggest that PFO may exacerbate hypoxaemia in CF patients.

High altitude pulmonary oedema

High altitude pulmonary oedema (HAPE) is a life threatening condition that requires immediate descent from high altitude. The pathophysiology is incompletely understood, but pulmonary hypertension and arterial hypoxaemia are characteristic features. In a study of 19 mountaineers resistant to HAPE and 16 participants who were susceptible, PFO frequency was 4 times higher in HAPE susceptible individuals both at low altitude (56% versus 11%, $p = 0.004$) and high altitude (69% versus 16%, $p = 0.001$) (Allemann et al., 2006). In the HAPE susceptible group, participants with a large PFO had

lower SaO₂ (65 (6)% versus 77 (8) %, $p = 0.001$) compared to those with smaller or no PFO. This suggests right to left shunting through PFO does exacerbate arterial hypoxaemia and HAPE.

Obstructive sleep apnoea and chronic obstructive pulmonary disease

Obstructive sleep apnoea and chronic obstructive pulmonary disease are both common diseases currently increasing in prevalence that have significant associated morbidity. Hypoxaemia is a significant feature in both. The question that arises is could right to left shunting through PFO exacerbate arterial desaturation in these patients?

1.2 Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is estimated to be present in 4% of men and 2% of women (Young et al., 1993). It is characterised by repetitive, intermittent episodes of partial or complete collapse of the upper airway (Guilleminault et al., 1976) leading to a reduction (hypopnoea) or cessation (apnoea) of airflow. This causes episodic oxyhaemoglobin desaturation and recurrent arousals from sleep. This sleep fragmentation causes daytime somnolence, which if left untreated leads to significant impairments in quality of life, cognitive function and mood (Finn et al., 1998; Akashiba et al., 2002; Engleman and Douglas, 2004). Obesity is the main risk factor for developing OSA (Young et al., 1993; Peppard et al., 2000a) and with the current obesity epidemic, the prevalence of OSA is likely to rapidly increase.

1.2.1 Diagnosis

Obstructive sleep apnoea commonly presents as excessive daytime somnolence, a partner history of witnessed apnoeas or excessive snoring. Other symptoms may include a combination of excessive snoring, choking or gasping during sleep, nocturia, changes in personality or mood and morning headaches. In essence, the presentation is heterogeneous and as many other sleep disorders present with sleepiness, symptoms of OSA do not always correlate with disease severity as measured by the apnoea hypopnoea index (Deegan and McNicholas, 1996; Viner et al., 1991). Diagnosis is often by a combination of clinical features and sleep study results.

The gold standard investigation for OSA is full nocturnal polysomnography (ASDA, 1997; Kushida et al., 2005). This provides nocturnal measures of airflow, saturation, respiratory effort, SaO_2 , EEG/EOG/EMG recording of sleep and arousals and snoring. More limited respiratory sleep studies that do not monitor sleep, but do monitor breathing during sleep are also validated for the diagnosis of OSA (Dingli et al., 2003a).

An obstructive apnoea is defined as a cessation of airflow with ongoing respiratory effort and a hypopnoea as reduction in airflow to less than 50% of baseline for greater than 10 seconds (Iber et al., 2007). The total number of apnoeas and hypopnoeas are divided by sleep time to give an apnoea-hypopnoea index (AHI) of events/hour.

The current, widely utilised grading system is based on a report of a task force of the American Academy of Sleep Medicine (AASM, 1999). An AHI of up to 5 events/hour is considered normal. In the presence of symptoms, OSA is graded as:

- AHI 5 – 15 events/hour: Mild OSA
- AHI 15 – 30 events/hour: Moderate OSA
- AHI > 30 events/hour: Severe OSA

1.2.2 Pathophysiology

There has been considerable interest in the role of OSA as an independent risk factor for cardiovascular diseases including hypertension (Peppard et al., 2000b; Barbe et al., 2010), cerebrovascular disease (Martnez-Garcia et al., 2009; Arzt et al., 2005; Yaggi et al., 2005) and cardiac arrhythmias (Mehra et al., 2006). Although causative associations are hard to identify, observational studies have suggested strong associations and further data from longitudinal cohort and randomised controlled trials is accumulating. It is thought that the following pathophysiological disturbances are responsible for this increase in cardiovascular risk.

Arousals from sleep

Sleep is broadly divided into non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM is further subdivided into stages 1, 2, 3 and 4 depending on the depth of sleep. Stage 1 and 2 represent light sleep and stage 3 and 4 (previously 2 distinct stages and now recognised as one entity) represent deep sleep (AASM, 1999). Sleep architecture in a typical

healthy adult comprises 90 minute blocks of light, deep and REM sleep which cycle throughout the night.

In OSA patients the restorative qualities of sleep are fragmented by brief EEG arousals that terminate apnoeic events. The fragmented and reduced percentage of deep sleep and REM can cause daytime sleepiness. Arousals also activate the sympathetic nervous system (Somers et al., 1989) and suppress parasympathetic activity (Horner et al., 1995) causing blood pressure surges and tachycardia (Tun et al., 1999; O'Driscoll et al., 2004; Okabe et al., 1995). The cumulative effect impairs vagally mediated heart rate variability (Narkiewicz et al., 1998) and may be implicated in the pathogenesis of hypertension in OSA (Arabi et al., 1999).

Negative intrathoracic pressure

Continued respiratory effort against an obstructed airway generates negative intrathoracic pressure. This increases transmural cardiac pressures increasing left ventricular afterload and myocardial oxygen demand (Stoohs and Guilleminault, 1992; Buda et al., 1979) which may in turn increase the risk of cardiovascular disease.

Intermittent hypoxaemia

An important mechanism underlying the association between OSA and cardiovascular disease is chronic intermittent hypoxia. Intermittent hypoxia is currently believed to promote the formation of reactive oxygen species (Christou et al., 2003) and thus oxidative stress; stimulate sympathetic activity (Somers et al., 1991; Cutler et al., 2004a,b); decrease availability of nitric oxide (Jelic et al., 2008) and propagate inflammatory cascades (Minoguchi

et al., 2005). It is thought that these processes precipitated by intermittent hypoxia enhance vascular dysfunction and ultimately result in increased cardiovascular disease.

1.2.3 Patent foramen ovale in obstructive sleep apnoea

To date there have been 3 studies investigating PFO in OSA and 2 that have specifically addressed the PFO prevalence in OSA. Shanoudy et al studied 48 males with a respiratory disturbance index of 33.9 (3.1) events/hour and 24 male controls with contrast TOE (Shanoudy et al., 1998). The prevalence of PFO in OSA was 69% (33/48) compared to 17% (4/24) in controls. The OSA group were significantly younger than the control group (57 (12) years compared to 65 (10) years respectively, $p = 0.004$) and therefore may have been expected to have a higher prevalence. The authors also measured the SaO_2 drop during the Valsalva manoeuvre and found those with OSA and a PFO desaturated by 2.4 (1.5)% versus 1.3 (0.6)% in those with OSA and no PFO, $p = 0.007$. This observed difference is within the error range of a standard oximeter, however it does lend support to the theory that PFO influence SaO_2 . Beelke et al conducted a study using contrast TCD only (Beelke et al., 2003). They studied 78 OSA patients with an AHI of 52 (25) events/hour and 89 controls. A RLS was identified in 27% (21/78) of OSA patients and 15% (13/89) of controls, only just reaching statistical significance at $p < 0.05$. Taken together, the data suggest PFO are more prevalent in OSA.

Johannsen et al studied 30 OSA patients with varying severity of OSA and stratified them according to their ODI/AHI ratio (Johansson et al., 2007). This was done as a surrogate for the amount of desaturation for a given respiratory disturbance; a higher ratio indicative of greater desaturation. Overall PFO prevalence was 47% (14/30) and 11 patients had large PFO shunts. They

found that in 15 patients with an ODI/AHI > 0.66 , the prevalence of large PFO was 60% (9/15) compared to 13% (2/15) in those with ODI/AHI < 0.33 , $p < 0.05$. These data suggest that there is an association between nocturnal desaturation and PFO in OSA; this also highlights again that it is the PFO with larger shunts that are associated with the clinical findings. My study will be the first to characterise the size of shunts associated with PFO in OSA.

A single case report describes PFO closure in a 42 year old man with severe OSA (AHI 44 events/hour) who remained dyspnoeic despite CPAP treatment. Following PFO closure there was complete resolution of exertional symptoms.

Research questions based on the above data include: if PFO are more prevalent in OSA what is the magnitude of associated shunt? Also, if PFO contribute to nocturnal desaturation, would percutaneous closure of the defect in OSA improve overnight SaO₂? I will answer these questions in this thesis.

1.3 Chronic obstructive pulmonary disease

COPD is a disease state characterised by progressive airflow limitation that is at best, partially reversible; and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The estimated prevalence of COPD in adults over the age of 40 years is 10% and it causes 30,000 deaths per year in England and Wales. In developed countries it is one of the only common causes of death to be increasing.

1.3.1 Hypoxaemia in chronic obstructive pulmonary disease

Hypoxaemia in COPD is a poor prognostic marker independent of FEV₁ (Schols et al., 1998). Chronic hypoxaemia that remains untreated is associated with many of the adverse sequelae of COPD. These include systemic inflammation (Fitzpatrick et al., 2011; Takabatake et al., 2000), skeletal muscle dysfunction (Koechlin et al., 2005), neurocognitive decline (Dodd et al., 2010; Thakur et al., 2010) and although less of a current issue, historically with the development of polycythaemia (Epstein, 1912; Chambellan et al., 2005).

Two landmark trials conducted in the 1970s provide evidence for the mortality benefit of long-term oxygen therapy (LTOT) in hypoxaemic COPD patients with PaO₂ < 8kPa. The British Medical Council long-term domiciliary oxygen trial randomised 87 hypoxaemic COPD patients (FEV₁ 0.58 to 0.75L) to 2L O₂ via nasal cannulae for at least 15 hours per day or no oxygen, with follow up over a period of 5 years (MRC, 1981). Nineteen of the 42 treated with LTOT died compared to 30 of the 45 who were not given LTOT. The nocturnal oxygen therapy trial enrolled 203 COPD patients and compared nocturnal oxygen for 12 hours with continuous oxygen (NOTT, 1980). Follow up was conducted over an average period of 19.3 months during which 41 patients in the nocturnal O₂ arm died versus 23 in the continuous O₂ arm. These trials form the basis of current O₂ prescription guidelines. Since publication, the expense of domiciliary oxygen has substantially increased and it now constitutes one of the largest medical expenses. What are the causes of hypoxaemia in COPD?

The principal contributor to hypoxaemia is ventilation perfusion (VQ) mismatch (Gibson, 2009). In mild disease prior to the onset of significant airway obstruction, there is often moderate VQ mismatch (Barbera et al.,

1990). This observation is thought to be related to small airways disease and structural abnormalities that are present despite only a small reduction in FEV₁. The greatest amount of VQ mismatching occurs in severe disease (Sandek et al., 2001). Despite this, there is a large variation from almost normal VQ relationships to very abnormal. Rodrigues-Roisin et al studied 150 COPD patients with a range of severity spread across GOLD 1 to 4 and found the VQ inequality from stage 1 through to stage 4 increased by only a modest amount (Rodriguez-Roisin et al., 2009). This suggests that the underlying contributors to hypoxaemia may differ from those causing airflow obstruction.

In addition to VQ mismatch, other causes of inadequate gas exchange include: impaired alveolar-end capillary diffusion to oxygen, inadequate alveolar ventilation and a true anatomical shunt. Extrapulmonary factors also contribute and they include cardiac output (Barr et al., 2010), inspired oxygen concentration and the metabolic oxygen demands of the body.

This list is extensive. However, the contribution of intracardiac shunting to hypoxaemia has not been previously studied. The question "does a RLS through PFO contribute to hypoxaemia?" will be investigated in this thesis.

1.3.2 Exercise in chronic obstructive pulmonary disease

There are numerous pathophysiological changes that affect exercise in COPD patients and all play a role, albeit to different extents in limiting exercise in COPD. These include reduced ventilatory capacity (O'Donnell et al., 1999; Babb et al., 1991), increased work of breathing, deconditioning and systemic inflammation with subsequent skeletal muscle dysfunction (Yende et al., 2006; Broekhuizen et al., 2006; Pinto-Plata et al., 2006) and destruction of the pulmonary capillary bed by emphysema. Treatment strategies that have been studied include bronchodilator therapy (O'Donnell et al., 2004b,a; Cukier

et al., 2007), supplemental oxygen (O'Donnell et al., 2001a), helium-oxygen mixtures (Laude et al., 2006), rehabilitation (Porszasz et al., 2005) and lung volume reduction (Hopkinson et al., 2005).

In a study of 576 COPD patients followed up over a period of 3 years, exercise desaturation predicted mortality (relative risk: 2.63, 95% CI: 1.53 to 4.51, $p < 0.001$) (Casanova et al., 2008). Desaturation occurs largely as a result of increased VQ mismatching, increased peripheral muscle oxygen extraction (Dantzker and D'Alonzo, 1986), and alveolar hypoventilation (O'Donnell et al., 2002). The effects of intracardiac shunting have not been studied. This raises the question, could a RLS develop through a PFO and could this then contribute to exercise hypoxaemia? For a RLS to develop through a PFO, the atrial pressure gradient would have to reverse. Pathophysiological changes during exercise in COPD could, theoretically allow this.

COPD is characterised by expiratory flow limitation secondary to airway obstruction and reduced pulmonary elastic recoil. As the respiratory rate increases during exercise, expiratory time is reduced leading to incomplete lung emptying prior to the onset of the next breath. End-expiratory lung volume is increased, inspiratory capacity is reduced and alveolar pressure remains positive at end expiration known as: intrinsic positive end-expiratory pressure (PEEPi). As exercise continues, this cycle of incomplete lung emptying causes progressive dynamic hyperinflation (O'Donnell et al., 2001b). In order to assist lung emptying, abdominal muscles are recruited, further increasing intrathoracic pressure and PEEPi, effectively producing a Valsalva manoeuvre (Kyroussis et al., 2000). This increases right ventricular afterload and right ventricular end-diastolic pressure (Mahler et al., 1984). The next inspiratory breath has to generate sufficient negative pressure to overcome PEEPi. This exaggerated pleural pressure swing will draw venous

blood into the right atrium and in the face of increases in right heart pressure, could reverse the atrial pressure gradient. In addition, pulmonary artery pressure is known to increase during exercise in COPD causing further increases in right ventricular afterload and therefore promoting right to left shunting through a PFO (Raeside et al., 2002).

1.3.3 Patent foramen ovale and chronic obstructive pulmonary disease

The prevalence of PFO in COPD has been investigated in 2 studies. Soliman et al studied 20 patients with COPD (FEV₁ 27.2 (8.4)% predicted) and 20 healthy controls with contrast TOE and detected PFO in 70% (14/20) versus 35% (7/20) respectively, $p < 0.05$ (Soliman et al., 1999). COPD patients had significantly higher systolic pulmonary artery pressures (38.3 (7.3) mmHg versus 21 (2.4) mmHg, $p < 0.05$). COPD patients with PFO desaturated by 2.6 (1.4) % during the Valsalva manoeuvre compared to 1.1 (0.9) % in COPD patients without PFO, $p < 0.005$. Hacievliyagil et al studied 52 COPD patients (FEV₁ 44.7 (13.4)% predicted) with contrast TTE and also found a higher prevalence of PFO compared to controls: 44% (23/52) versus 20% (10/50) respectively, $p = 0.001$ (Hacievliyagil et al., 2006). The COPD group was a heterogeneous group, however it appeared that those with PFO at rest had more functional impairment with significantly shorter 6 minute walk test distances, lower SaO₂, lower PaO₂ and higher MRC dyspnoea scores.

These data suggest that PFO are more prevalent in COPD and that they may contribute to hypoxaemia.

1.4 Overall aims of thesis

PFO are common in healthy adults and under physiological conditions which elevate right atrial pressure, allow right to left shunting of deoxygenated blood. PFO have been associated with hypoxaemia and numerous case reports exist that describe resolution of hypoxaemia following PFO closure.

Studies have identified a higher prevalence of PFO in OSA and COPD, both common diseases in which intermittent and chronic hypoxaemia respectively cause significant morbidity. The aim of the research in this thesis was to examine both these conditions and to investigate the impact of right to left shunting through PFO on oxygenation.

In severe OSA patients, the aim was to determine the prevalence of PFO and magnitude of associated shunt and to investigate the impact of PFO closure on nocturnal oxygenation. The aim in severe COPD patients was to determine whether hypoxaemic patients have a higher prevalence of PFO compared to those who are less hypoxaemic with similar lung function impairment. Furthermore, to determine whether a RLS develops during exercise and the impact this may have on SaO₂ and exercise endurance.

1.5 Hypotheses

The following hypotheses were tested:

1. Severe OSA patients have a higher prevalence of PFO compared to healthy controls of similar age
2. Severe OSA patients have a higher prevalence of PFO with large shunts compared to healthy controls of similar age
3. Percutaneous closure of PFO with large shunts in patients with severe OSA reduces nocturnal desaturation
4. Patients with severe COPD and $\text{PaO}_2 \leq 7.3 \text{ kPa}$ have a higher prevalence of PFO with a greater magnitude of RLS compared to others with a similar lung function impairment and $\text{PaO}_2 > 8 \text{ kPa}$
5. Severe COPD patients have a higher prevalence of PFO compared to healthy controls of similar age
6. Right to left shunting through PFO increases from baseline during exercise in COPD
7. During exercise, patients with severe COPD and a PFO experience greater desaturation and have reduced exercise endurance compared to those without a PFO
8. During exercise in severe COPD, increased swings in intrathoracic pressure are associated with increased right to left shunting through a PFO

Chapter 2

Methods

2.1 Ethical approval and study overview

The Kings College Hospital Ethics Committee approved the studies contained in Chapter 3. The Brompton and Harefield Ethics Committee approved the studies contained in Chapters 4 and 5. All patients gave written informed consent.

Chapter 3 is an observational study investigating the prevalence of PFO and magnitude of associated shunt in severe OSA compared to healthy age matched controls. A prospective, interventional study has also been carried out testing the effect of PFO closure on nocturnal oxygenation in patients with severe OSA and large PFO.

Chapter 4 is an observational study examining the prevalence of PFO in COPD patients who are hypoxic compared to those with higher PaO₂ levels.

Chapter 5 is an observational study carried out to determine whether there is increased right to left shunting compared to baseline during exercise in COPD patients with PFO and if so, whether this correlates with swings in intrathoracic pressure and results in greater desaturation and reduced exercise endurance.

2.2 Contributions

The following tests that are described in this Chapter were performed with contributions from staff members at the Royal Brompton Hospital as detailed below.

Contrast transthoracic echocardiography requires 2 people to perform. I performed them with help from the echocardiography technicians and when

they were not available, with help from the research fellows in the muscle laboratory or sleep department.

The 6 minute walk tests on 25 COPD patients were performed by the research physiotherapists in the muscle laboratory.

Lung function tests were performed by the physiologists in the lung function department.

Cardiopulmonary exercise tests were performed by myself with help from Julia Kelly, research physiotherapist.

All other tests were performed and analysed by myself.

2.3 Subject information

2.3.1 Obstructive sleep apnoea patients

Patients were recruited from the OSA clinic at the Royal Brompton Hospital.

The inclusion criteria were:

- Age $\geq$ 18 years
- Severe OSA: AHI $>$ 30/hour on a respiratory sleep study
- Weight $<$ 150 kg
- FVC $\geq$ 70% predicted
- FEV₁/FVC ratio $\geq$ 70%

2.3.2 Chronic obstructive pulmonary disease patients

Patients were recruited from the advanced COPD clinic at the Royal Brompton Hospital. Inclusion criteria were:

- Age > 40 years
- Severe COPD measured according to the Global initiative for chronic Obstructive Lung Disease (GOLD) $\geq$ Stage III
- No evidence from either clinical notes or subjective assessment of OSA/obesity-hypoventilation syndrome
- No active infections
- No evidence of other cardiac disease (valve disease, cardiomyopathy, left ventricular failure, congenital heart disease)
- No previous PFO closure device
- No evidence of severe, uncontrolled hypertension
- No untreated coronary artery disease

2.3.3 Healthy control subjects

Healthy volunteers were recruited from a departmental database of controls that had participated in other studies. Advertising in local newspaper was used to recruit additional people. The advert is shown in Appendix A

2.4 Assessment of PFO: Contrast transthoracic echocardiography

Contrast TTE scans were performed with the help of echocardiography technicians at the Royal Brompton Hospital. Standard echocardiographic image planes were acquired with ECG monitoring. OSA patients and healthy controls were scanned with Sonos 7500 (Philips, Netherlands) and COPD patients were scanned with Vivid 7 (GE Healthcare, Chalfont St Giles, UK). All scans were performed with second harmonic imaging. The recordings were stored anonymised for offline analysis on the Medcon system (McKesson, San Francisco, USA).

2.4.1 Measurement of systolic pulmonary artery pressure

Systolic pulmonary artery pressure was measured using continuous wave Doppler to localise tricuspid regurgitation. The maximum velocity of the transtricuspid jet (V_{TR}) reflects the right ventricular (RV) to right atrial (RA) pressure difference as described by the Bernoulli equation:

$$\Delta P_{RV-RA} = 4(V_{TR})^2$$

Right ventricular systolic pressure (RVSP) is obtained by adding ΔP_{RV-RA} to the estimated right atrial pressure (RAP).

$$RVSP = \Delta P_{RV-RA} + RAP$$

In the absence of pulmonary stenosis, RVSP is equal to the systolic pulmonary artery pressure ($PAP_{systolic}$):

$$PAP_{systolic} = \Delta P_{RV-RA} + RAP$$

Right atrial pressure is estimated by measuring the diameter of the inferior vena cava (IVC) in the subcostal view on expiration and assessing the percentage by which it collapses on inspiration as described in Table 2.1.

Table 2.1: Estimating right atrial pressure from the inferior vena cava

IVC diameter expiration (cm)	Collapse on inspiration (%)	RAP estimate (mmHg)
< 2	complete	0 – 5
< 2	> 50	5 – 10
> 2	25 – 50	10 – 15
> 2	< 25	15 – 20

Adapted from Rimmington and Chambers, (Rimington and Chambers, 1998)

2.4.2 Measurement of right to left shunting

Agitated saline contrast

An intravenous cannula was inserted into an antecubital vein and a 3-way tap attached. 8ml normal saline and 1ml air was drawn up into a 10ml luer lock syringe and attached to the 3-way tap. An empty 10ml luer lock syringe was attached to the second port of the 3-way tap. One ml blood was drawn back into the empty syringe. The valve on the 3-way tap was turned off to the subject and on to the 2 syringes. The saline, air and blood mixture was agitated between the 2 syringes at least 10 times forming a suspension of microbubbles that was used for contrast injection (Lange et al., 2010; Dowson et al., 2008).

Contrast TTE

Contrast studies were performed in accordance with previously published guidelines (Attaran et al., 2006). The four chamber view, with the probe at the apex was obtained and depth and sector width adjusted to optimise the image. The rest injection was performed with the patient breathing normally. Agitated saline contrast was injected in a single push, the right heart was seen to opacify and the left heart was observed for 10 to 15 beats for evidence of shunting. The Valsalva injection was performed with the following standard instructions for a Valsalva manoeuvre: the subject was asked to take a normal breath in, a normal breath out, then at functional residual capacity, they were asked to hold their breath and push their stomach in (similar to being constipated) for 10 seconds.

The injection was timed to coincide with the interatrial septum bowing to the left and/or reduction of heart size (due to reduction of venous return). As soon as contrast was seen in the right heart, the subject was instructed to release the VSM quickly and the left heart was observed for 10 to 15 beats for evidence of shunting. The Valsalva injection was repeated twice and in patients with poor views repeated until a good image was obtained.

PFO versus Pulmonary shunts

Both intracardiac shunting through PFO and intrapulmonary shunting can be detected as a RLS with contrast TTE. A PFO was detected if bubbles were seen in the left heart within 5 cardiac cycles of right heart opacification. A pulmonary shunt was present if bubbles entered the left heart after 5 cardiac cycles and continued to enter in a steady stream.

2.4.3 Data analysis: Grading of PFO shunt size

PFO shunt size was graded visually (Figure 2.1) according to the following criteria:

Negative	No bubbles on left side
Small	A few scattered bubbles seen in left heart
Moderate	Obvious shunt with > 10 bubbles at any one time seen in the left heart but not sufficient to completely opacify any section or all of the left heart
Large	Large obvious shunt, with contrast that completely opacifies a section or all of the left heart.

A PFO was detected if bubbles were seen in the left heart within 5 cardiac cycles of right heart opacification. A pulmonary shunt was present if bubbles entered the left heart after 5 cardiac cycles and continued to enter in a steady stream.

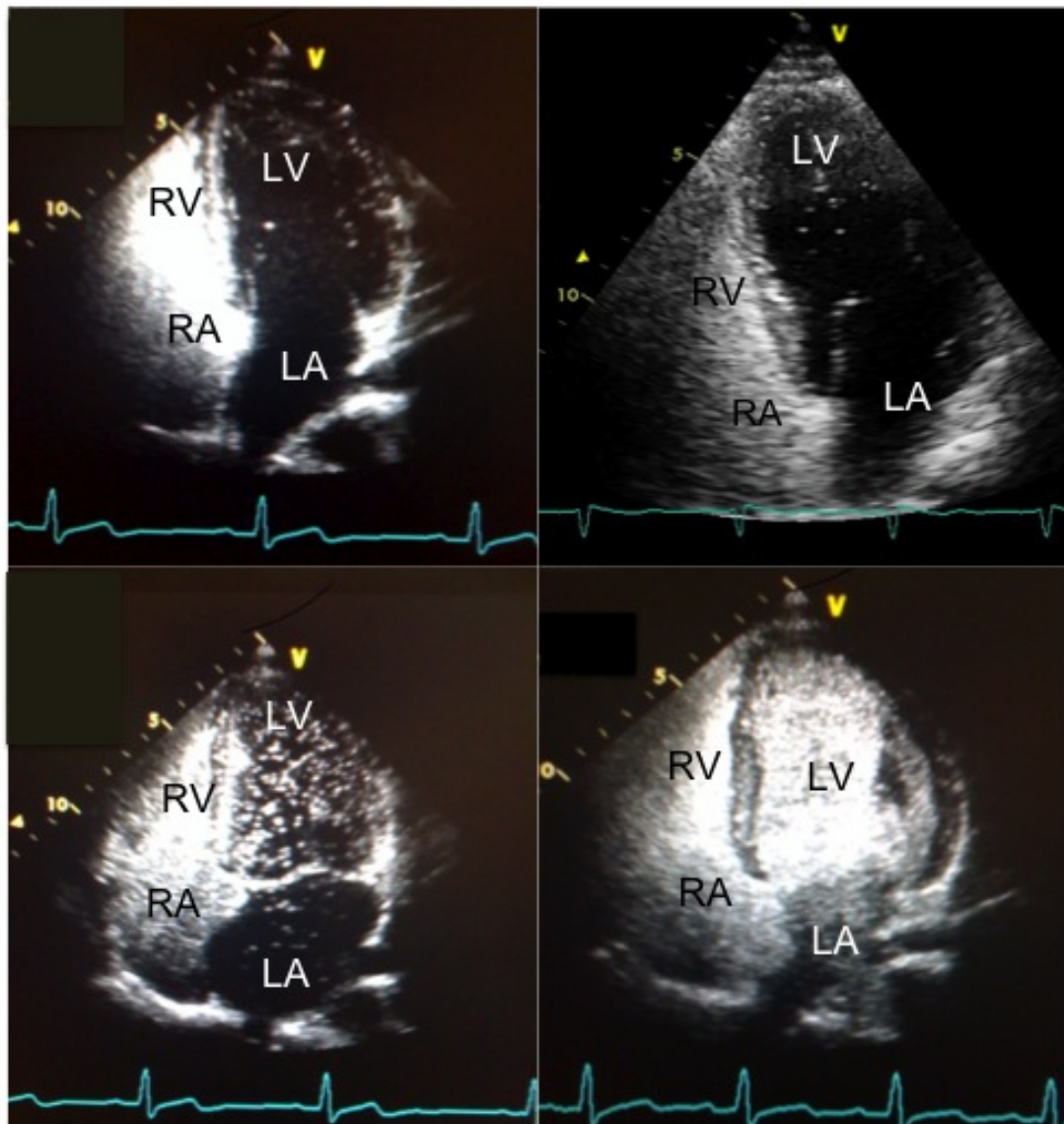


Figure 2.1: RA: right atrium; RV: right ventricle; LA: left atrium; LV: left ventricle. These 4 chamber images are all taken from contrast studies. Top left: bright, white contrast is seen in the RA and RV, however no contrast is detected in the left heart. This patient does not have a PFO. Top right: a few microbubbles can be seen in the LV. This is a small PFO. Bottom left: contrast is clearly detected in the left heart, but not enough to completely opacify any chamber. This is a moderate size PFO. Bottom right: contrast can be seen in all four chambers, completely filling the left heart. This is a large PFO)

2.4.4 Interobserver agreement of TTE scoring of PFO shunt size

The interobserver agreement between the grades of shunt assigned to contrast TTE examinations by myself and another independent echocardiographer were assessed. This was performed to ensure the absence of observer bias. 50 contrast studies chosen at random were analysed. The results are given in Table 2.2.

Table 2.2: Interobserver agreement with TTE scoring

Grade of shunt assigned by me	Grade of shunt assigned by echocardiographer			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	21	1		
Small shunt	1	10	1	
Moderate shunt			5	
Large shunt				11

The kappa statistic was 0.91 indicating good interobserver agreement.

2.5 Assessment of PFO: Contrast transcranial Doppler

2.5.1 Measurement of right to left shunting

Instrumentation and signal processing

Contrast transcranial Doppler (TCD) was performed using a 2 MHz Power M-Mode digital TCD system (ST3/PMD150, Spencer Technologies, Seattle, WA). Power M mode images (Figure 2.2a) were calculated and displayed above the single gate spectrogram image (Figure 2.2b) sharing the same horizontal time axis. The 13mm circular transducer was set to emit 16 cycles at 2MHz with a pulse repetition frequency of 8kHz in one transmit burst. The received ultrasound waves were amplified, converted from analogue to digital and processed. Doppler shift values were low pass filtered to reject any noise not within the frequency bandwidth of the transmit burst and resampled. The Power M Mode display comprised 33 sample gates with one gate every 2mm from a depth of 24 to 88mm. Axial extension of sample volume was set at 6mm. A red line depicted flow towards the probe and a blue line flow away from the probe. The spectral display below was obtained from a 34th sample gate, the depth of which was controlled by moving the yellow horizontal line in the Power M Mode display (Figure 2.2a and b). The spectrogram was calculated by applying a 128 point fast fourier transformation with 50% overlap at 8 kHz pulse repetition frequency with a Hanning window. The high pass filter was set at 200Hz. The spectrogram velocity accuracy assuming a zero Doppler angle was $\pm 1\%$ or $\pm 1\text{cm/s}$.

Microbubbles are detected by measuring backscatter. The backscatter of

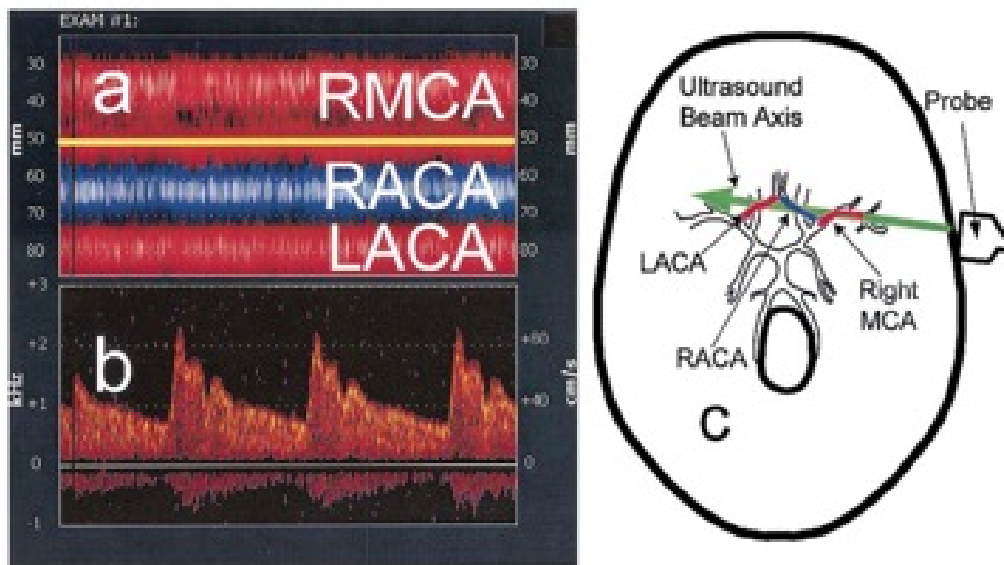


Figure 2.2: Contrast transcranial Doppler (From Moerhing MA et al, 2002) a) Power M-mode Doppler display of cerebral blood flow with beam alignment with the right middle cerebral artery (RMCA), the right anterior cerebral artery (RACA), and the left anterior cerebral artery (LACA). (b) Concurrent spectrogram from 50-mm gate depth (MCA). (c) Representation of ultrasound beam direction and intersection with intracranial vessels shown in (a)

ultrasound from normal flowing blood is less than that from gaseous emboli. Multiple gates of Power M mode allow emboli to be tracked and identified in arteries not in the line of the spectral display.

Middle cerebral artery insonation

With the subject in the supine position, the middle cerebral artery (MCA) was insonated bilaterally through the temporal bone windows. The MCA projects laterally from the circle of Willis and is the only artery that will produce a signal towards the probe at a depth of 35 to 60mm in the temporal area. The MCA responds to ipsilateral carotid vibration, has reduced velocities with ipsilateral carotid compression and does not respond to contralateral carotid compression. Once located on the Power M Mode display, the Doppler

signal gain and depth was adjusted to optimize flow detection. The probes were secured using an adjustable head frame (Marc 600 head frame, Spencer Technologies, Seattle, WA).

Contrast study

Agitated saline contrast was prepared as in Section 2.4.2. Injections were performed at rest and 5 seconds into the start of a Valsalva manoeuvre. Automatic signal detection was used to detect microemboli in the cerebral circulation for 1 minute following contrast injection (Figure 2.3). The Valsalva injection was performed twice. Data were recorded onto an external hard drive for analysis of PFO shunt size blinded to patient group.

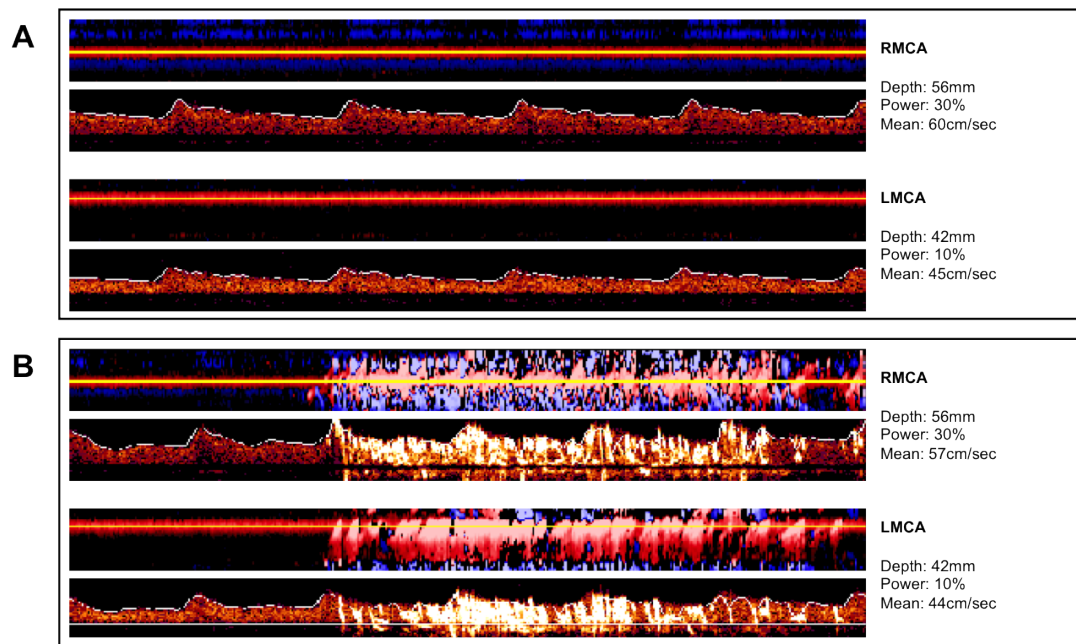


Figure 2.3: Contrast TCD recording A: at rest and B: following a Valsalva manoeuvre. The bright signals in panel B represent bubble contrast arriving in the middle cerebral artery. LMCA: left middle cerebral artery, RMCA: right middle cerebral artery, Depth: depth of Doppler sample volume in mm, Power: transmitting Doppler output power, Mean: mean cerebral blood flow velocity in cm/second

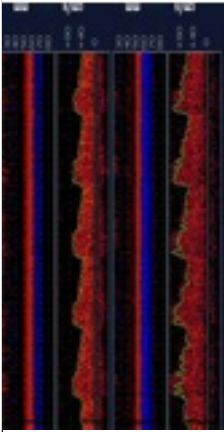
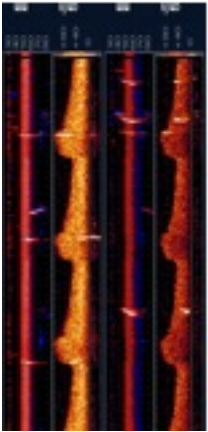
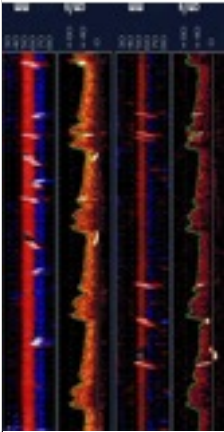
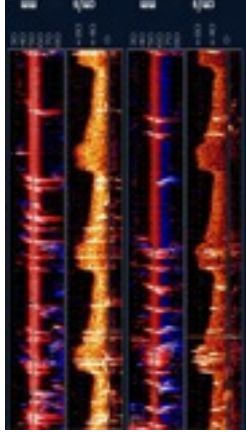
2.5.2 Measurement of right to left shunting during exercise

Contrast TCD for the detection of RLS is reliably performed in the sitting position (Stendel, 2000). A cycle ergometer was therefore used for the exercise platform. The middle cerebral arteries were insonated bilaterally as in Section 2.5.1. An intravenous cannula was sited in the left antecubital fossa and agitated saline contrast was prepared as in Section 2.4.2. Contrast was injected at 2 minute intervals during the continuous work rate exercise protocol (described in Section 2.11.2) to assess the degree of RLS.

2.5.3 Data analysis: Grading of PFO shunt size

PFO grade was scored using the criteria of Spencer (Spencer et al., 2004) in Table 2.3. In Chapters 3 and 4 PFO shunt sizes were graded as no shunt, small, moderate or large. In Chapter 5, in order to detect smaller differences in shunting during exercise the Grade 0 to Grade 5 scale was used.

Table 2.3: Criteria for grading contrast TCD studies (Spencer et al., 2004)

Grade 0	Grade 1	Grade 2
		
0 – 3 bubbles	4 – 10 bubbles	11 – 30 bubbles
No shunt	Small shunt	Small shunt
Not clinically significant	Not clinically significant	Not clinically significant
Grade 3	Grade 4	Grade 5
		
30 – 100 bubbles	> 100 bubbles	Curtain of indistinguishable tracks
Moderate shunt	Large shunt	Large shunt
R–L conductance may be sufficient to produce paradoxical embolism	R–L conductance sufficient to produce paradoxical embolism	R–L conductance sufficient to produce paradoxical embolism

Images are adapted from scoring examples produced by Spencer Ltd, Seattle, WA (Spencer et al., 2004)

2.5.4 Interobserver agreement of TCD scoring of PFO shunt size

The interobserver agreement between the grades of shunt assigned to contrast TCD examinations by myself and another independent scorer were assessed. This was performed to ensure the absence of observer bias. 69 contrast studies were analysed. The results are given in Table 2.4.

Table 2.4: Interobserver agreement with TCD scoring

Grade of shunt assigned by me	Grade of shunt assigned by independent scorer					
	0	1	2	3	4	5
0	15	3				
1		8				
2			10			
3			1	9		
4				3	10	
5					2	8

The kappa statistic was 0.84 indicating good interobserver agreement.

2.6 Blood testing

2.6.1 Arterial blood gas analysis

Resting arterial blood gas tensions were measured from an arterial blood sample taken from the radial artery and analysed with the Radiometer ABL 30 (Radiometer, Denmark).

2.6.2 Venous blood tests

Venous blood samples were taken for full blood count and brain natriuretic peptide (BNP) measurement. In a study of 176 patients with a combination of obstructive and restrictive disease BNP was measured in conjunction with right heart catheter derived pulmonary artery pressure and patients were followed up for a year. BNP identified high pulmonary artery pressure with a sensitivity of 0.85 and a specificity of 0.88 and was found to be an independent predictor of death (Leuchte et al., 2006). BNP may therefore be a prognostic marker in lung disease.

2.7 Respiratory function testing

2.7.1 Measurement of respiratory function

Spirometry

Spirometry was performed with the Vitalograph 2120 (Vitalograph Ltd, Buckinghamshire) according to standard criteria using a pneumotachograph with integration of flow to derive volume (Miller et al., 2005b). The device

was calibrated regularly with a 1L syringe ensuring an accuracy of within 3% of the calibration volume.

Subjects were asked to take a deep inhalation, completely filling the lungs and then to perform a maximal forced exhalation through a disposable mouthpiece with attached filter using the greatest effort possible. The procedure was repeated until 3 consistent attempts within 5% difference of each other were obtained and the best FEV₁ and FVC results recorded.

The measurement of lung volume and gas transfer

The lung function technicians at the Royal Brompton Hospital performed these pulmonary function tests. Lung volumes were measured using body plethysmography (Wanger et al., 2005). Gas transfer was obtained by inhaling a known concentration of carbon monoxide (CO), measuring end expiratory CO concentration after a single breath hold and adjusting for alveolar volume (Compact Master lab system, Jaeger, Germany) (Macintyre et al., 2005). All tests were performed and interpreted in accordance with ATS/ERS guidelines (Miller et al., 2005a; Pellegrino et al., 2005). Data obtained from the European Coal and Steel community (Quanjer et al., 1993a,b; Cotes et al., 1993) were used to calculate predicted values. Calibrations on all equipment were undertaken regularly.

2.7.2 Data analysis

COPD was graded according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging criteria (Table 2.5) (Rabe et al., 2007).

Table 2.5: GOLD staging of COPD severity (Rabe et al., 2007)

Stage	Description	Findings (based on postbronchodilator FEV ₁)
0	At risk	Risk factors and chronic symptoms but normal spirometry
I	Mild	FEV ₁ /FVC < 70% FEV ₁ > 80% of predicted value May have symptoms
II	Moderate	FEV ₁ /FVC < 70% FEV ₁ 50% – 80% of predicted value May have chronic symptoms
III	Severe	FEV ₁ /FVC < 70% FEV ₁ 30% – 50% of predicted value May have chronic symptoms
IV	Very severe	FEV ₁ /FVC < 70% FEV ₁ < 30% of predicted value or FEV ₁ < 50% of predicted value plus severe chronic symptoms

2.8 Questionnaires

2.8.1 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) was used to measure subjective sleepiness (Johns, 1991) (Appendix B). This self-administered, validated questionnaire presents 8 different situations commonly encountered in daily life and asks for a score from 0 to 3 depending on the likelihood of dozing (0: no chance of dozing, 3: high chance of dozing). Scores can range from 0 to 24 and a cut-off of 11 or more is used to indicate significant sleepiness.

2.8.2 HIT6 headache test

The HIT-6 questionnaire (Appendix C) (Kosinski et al., 2003), based on the computerised headache impact test (DynHAHIT) was developed to provide a shorter, paper form of the internet test that was equally valid as a means of assessing headache impact and for monitoring response to treatment. It comprises 6 questions and asks to rate them as never (6 points), rarely (8 points), sometimes (10 points), very often (11 points) and always (13 points). The score ranges from 36 to 78 with the following cut-offs:

- Over 60: headaches having severe impact on life
- 56 to 59: headaches having substantial impact on life
- 50 to 55: headaches having some impact on life
- Less than 49: Headaches having little or no impact on life

2.8.3 SF36v2 quality of life questionnaire

The SF36v2 (Appendix D) (Hawthorne et al., 2007) is the second version of the short form 36 questionnaire, designed as a generic, short, acceptable survey to assess subjective wellbeing. The second version was developed in response to issues with the two role functioning scales. The SF36v2 has been validated over a range of disease conditions and the scores are more reliable than the first version (Garratt et al., 1993). The test yields 2 summary measures: a physical component and mental component, which will be used in Chapter 3. The average score for the US population is 50 and all results are compared to this benchmark.

2.9 Assessments during sleep

Full attended nocturnal polysomnography (NPSG) was performed in the Research Sleep Laboratory at the Royal Brompton Hospital using the SomnoScreen system (S-Med UK, SOMNOmedics). Measurement of sleep and wakefulness, respiratory effort, airflow, arterial oxygen saturation, snoring, body position and electrocardiography (ECG) were obtained as described below. Probes and electrodes were attached to the SOMNOscreen box containing the amplifiers and filters for all physiological signals, which were transmitted via telemetry to a computer with SOMNOscreen software.

Respiratory polygraphy was performed at the subjects home using the SomnoScreen system (S-Med UK, SOMNOmedics). Measurement of respiratory effort, airflow, arterial oxygen saturation, snoring and body position were obtained as described below. The set up was demonstrated to the subject after which they took the equipment home for the nocturnal

recording and then returned it the following day. During home studies, signals were stored on a flashcard.

2.9.1 Measurement of sleep and wakefulness

Pairs of electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG) electrodes were used to measure sleep and wakefulness.

EOG, EEG and EMG position

EEG electrodes were placed according to standard 10-20 system of electrode placement (Harner and Sannit, 1974). The system identifies 4 landmarks:

- the nasion: the indentation between the forehead and nose
- the inion: the occipital ridge felt as the finger is run from the back of the neck up to the skull
- the left and right preauricular points: the indentations bilaterally just superior to the tragus

Once identified, electrodes were placed either 10 or 20% of the distance between these landmarks (Figure 2.4). EEG electrodes were placed in the left central C3 and right central C4 areas and referred to the contralateral mastoid electrode A2 and A1 respectively (C3:A2 and C4:A1). A vertex CZ electrode and a central forehead ground electrode were placed. A left occipital O1 electrode was referred to the contralateral A2 mastoid electrode (O1:A2).

EOG electrodes were placed 1cm lateral and superior to the left outer canthus: F7 and 1cm lateral and inferior to the right outer canthus: F8. F7 and F8 electrodes were both referred to the right mastoid process A2 (F7:A2 and F8:A2).

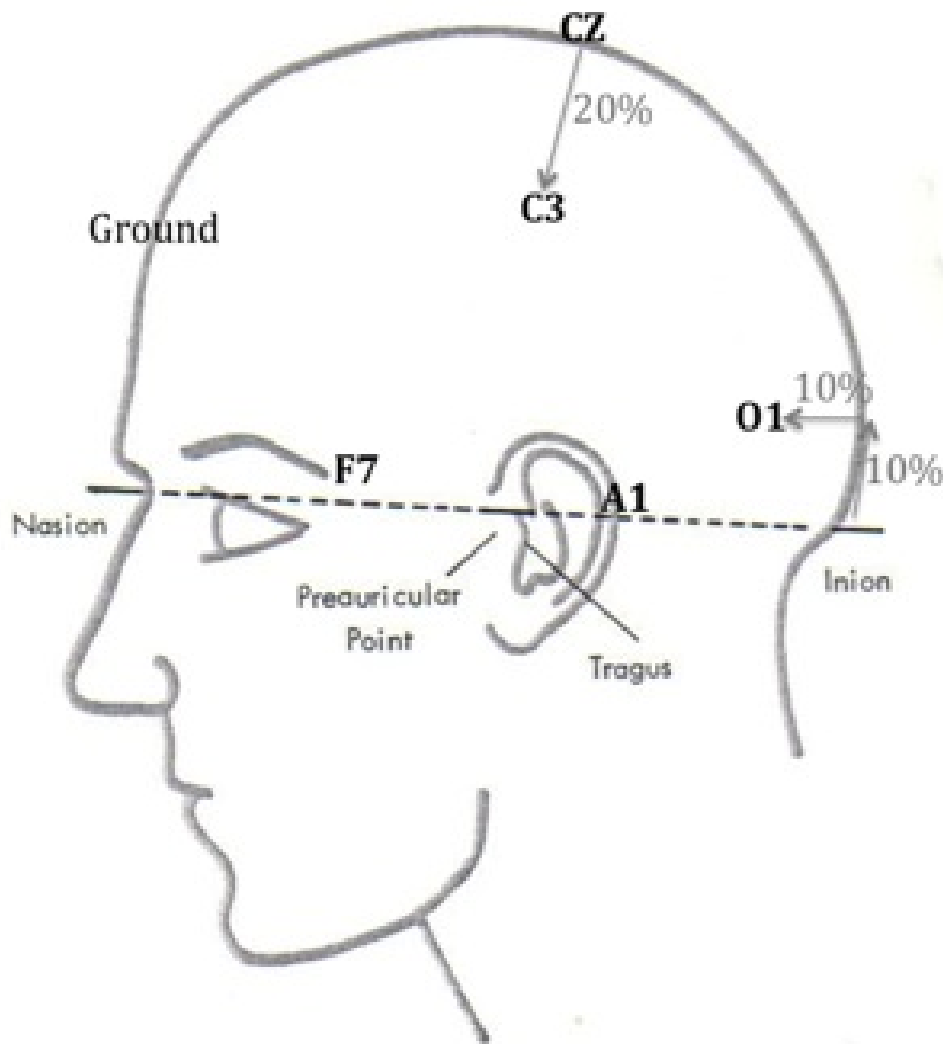


Figure 2.4: (adapted from Harner and Sannit, 1974) The landmarks from which EEG electrode placement is based are the nasion, inion and preauricular points. O1 is placed superior (10% of the distance from nasion to inion) and left lateral (10% of the circumference of the left side) to the inion. CZ is positioned at the intersection of a line joining the left to right preauricular points and the nasion to the inion. C3 is positioned 20% of the distance between preauricular points to the left of CZ. A1 is positioned on the left mastoid process and the ground EEG on the central forehead. EOG F7 is attached 1cm lateral and superior to the outer canthus of the left eye. These positions are replicated on the right side (not shown) as C4, F8 and A2.

EMG electrodes were positioned on the chin over the submental muscle and on the legs over the anterior tibialis muscle.

EEG, EMG and EOG electrode attachment

Landmarks and electrode positions were marked with a china graph pencil. To minimize electrode impedance, the areas were cleaned with Nuprep abrasive gel (D.O. Weaver and Co., USA) and alcohol swabs (Universal Hospital Supplies Ltd., UK). Gold cup EEG electrodes (Grass Instruments Division, Astro-Med Inc.,) were placed in the hairline (C3, C4 and CZ). The gold cups were filled with Ten20 EEG conductive paste (D.O. Weaver and Co., USA) and secured using Colloidian glue (S.L.E. diagnostics Ltd., UK). Disposable silver-silver chloride electrodes on self-adhesive patches (Neuroline, Ambu Ltd., UK) were used for all other EEG, EOG and EMG positions.

EEG, EMG and EOG signal acquisition and calibration

Electrodes were attached to the SOMNOScreen system, amplified and transmitted to a computer via telemetry as well as recorded to a flashcard.

Recordings were made in AC mode. High pass and low pass filters were set at 0.2 and 35Hz respectively for EEG, 0.3 and 10Hz respectively for EOG and 10 and 100Hz respectively for EMG. Sampling rate was 500Hz for EEG, EOG and EMG. An additional notch filter was set at 50Hz to remove artefact from electronic power sources.

Electrode to skin impedance was maintained below 5k Ω to ensure adequate signals. Biological calibrations were performed to check signal quality. Patients were asked to perform a series of instructions to check each channel in turn.

1. Please keep your eyes open and look straight ahead

2. Please look from left to right
3. Please look up and down
4. Please blink
5. Please close your eyes
6. Please open your jaw and clench your teeth in turn

2.9.2 Measurement of respiratory effort via respiratory inductance plethysmography

Respiratory effort was measured using respiratory inductance plethysmography. The technique uses an elastic belt with a wire sewn into it in a zig-zag arrangement to allow for chest/abdominal expansion. One belt is attached as a loop around the chest at the level of T4 vertebrae and one around the abdomen at the umbilicus. An alternating current is applied to the wire, which generates a magnetic field (Faradays law). As the area within the loop changes, an opposing current is set up which is measured as a change in frequency of the applied current. The change in frequency is proportional to the change in area. This signal is displayed graphically for interpretation. The low pass filter was set at 15Hz and the high pass filter at 0.1Hz. Signals were sampled at 100Hz.

Biological calibration was performed by asking the patient to:

1. Take big, deep breaths in and out
2. Take small, shallow breaths in and out
3. Stop breathing for 10 seconds

2.9.3 Measurement of arterial oxygen saturation via pulse oximetry

Oximetry provides a measure of the arterial oxygen saturation of haemoglobin. The technique relies on 2 basic principles:

1. The absorption of light at two different wavelengths by haemoglobin differs depending on the degree of oxygenation of Hb.
2. The light signal following transmission through the tissues has a pulsatile component, resulting from the changing volume of arterial blood with each pulse beat and is distinguishable by the microprocessor from the non-pulsatile component resulting from venous, capillary and tissue light absorption.

Within the probe are 2 light emitting diodes one in the visible red spectrum (660nm) and the other in the infrared spectrum (940nm). The beams of light pass through the tissues to a photodetector. During passage, some light is absorbed depending on the concentration of haemoglobin. The amount absorbed at each frequency depends on the degree of oxygenation of haemoglobin. The microprocessor selectively analyses the pulsatile fraction of blood.

The microprocessor calculates the ratio of absorbed light at each frequency and then compares them to standardised measurements within its memory (derived from previous human experiments) to arrive at a percentage oxygen saturation.

Oxyhaemoglobin saturation was measured with a finger probe oximeter. The margin of error for SaO_2 measurement between 70 and 100% was $\pm 2\%$ standard deviations. Each value was averaged over 4 heartbeats and updated

after every heartbeat.

2.9.4 Measurement of airflow

Nasal airflow was measured with a nasal cannula connected to a pressure transducer with a range of ± 24 mbar. Pressure was taken to be proportional to airflow and the corresponding signal was processed, converted from analogue to digital and displayed on screen. Recordings were made in DC mode with a low pass filter of 1 Hz.

A thermistor was also used in addition to a nasal cannula. Thermistors detect temperature oscillations between warm, expired air and cooler, room temperature inhaled air. Absence of temperature variation implies no airflow and was detected as an apnoea.

2.9.5 Measurement of sleep position and snoring

An inbuilt sensor within the amplifier box was used to discriminate between supine, left, right, prone and upright positions.

A tracheal microphone recorded snoring sampling at a rate of 256 Hz. The low pass filter was set at 100 Hz and the high pass filter at 10 Hz.

2.9.6 Data analysis

Sleep and wakefulness

Sleep stages were scored in 30 second epochs by analyzing EEG, EOG and EMG signals according to the American Academy of Sleep Medicine guidelines (Iber et al., 2007) as outlined in Table 2.6. If more than one stage



Figure 2.5: *Patient with standard NPSG monitors attached (Received permission from participant to print photo)*

existed in an epoch, the predominant stage was assigned (i.e. more than 50% of the 30 second epoch).

Table 2.6: Scoring of sleep stages

	EEG	EOG	EMG
Wake	Low amplitude Alpha activity 8 – 13 Hz Beta activity >13 Hz	Reading eye movements Eye blinks REM	Variable
NREM Stage 1	Low amplitude Theta activity 4 – 7 Hz Vertex sharp waves	Slow rolling eye movements	Reduced compared to wake
NREM Stage 2	Low amplitude Theta activity 4 – 7 Hz K complexes, spindles	No eye movement	Reduced compared to wake
NREM Stage 3/4	High amplitude > 75 μ V Delta activity 0.5 – 2 Hz for > 20% of epoch	No eye movement	Reduced compared to wake
REM	Low amplitude Mixed frequency Saw tooth waves	Bursts of REM	Further, marked reduction compared to NREM

Respiratory events

Respiratory events were scored according to the AASM 2007 guidelines (Iber et al., 2007). An apnoea was defined as complete cessation of airflow for at least 10 seconds (obstructive: paradoxical thoraco-abdominal movements, central: absence of discernable respiratory effort). A hypopnoea was defined as a reduction in airflow of $\geq 30\%$ from baseline for 10 seconds or more, associated with EEG arousal or a $\geq 4\%$ desaturation in SaO_2 from baseline. The apnoea hypopnoea index (AHI) was calculated as the average number of apnoeas and hypopnoeas per hour of sleep. The oxygen desaturation index (ODI) was calculated as the average number of dips in oxygen saturation $\geq 4\%$ per hour of sleep.

Interobserver agreement of sleep stage scoring

The interobserver agreement of sleep scoring was assessed by scoring 25 randomly selected epochs of sleep and comparing the sleep stages assigned to each epoch with 3 other independent scorers using the kappa statistic. This was performed to ensure the absence of observer bias. The range of experience amongst the scorers was approximately 1 to 4 years. The scoring results are given in Table 2.7.

Compared to my sleep scoring the kappa statistic for scorer 1 was 0.81, scorer 2 was 0.86 and for scorer 3 was 0.81. These results indicate good agreement between my scoring and that of the 3 other independent scorers.

Table 2.7: Interobserver sleep scoring agreement

Epoch	My scoring	Scorer 1	Scorer 2	Scorer 3
1	W	W	W	W
2	1	1	2	1
3	R	R	R	R
4	3	3	3	3
5	W	W	W	W
6	R	R	R	R
7	1	W	1	W
8	2	2	2	R
9	4	4	4	4
10	1	1	1	1
11	R	R	R	R
12	2	2	2	2
13	2	2	2	2
14	2	2	2	3
15	3	2	3	3
16	2	2	2	2
17	1	1	1	1
18	4	3	4	4
19	W	W	W	W
20	3	3	3	3
21	R	R	1	R
22	4	4	4	4
23	R	R	R	R
24	4	4	4	4
25	2	R	W	R

W: wake, R: REM, 1: stage 1, 2: stage 2, 3: stage 3, 4: stage 4

2.10 The Oxford sleep resistance test

The Oxford SLeeP Resistance test (OSLER, Stowood Scientific Instruments, Oxford, UK) is a behavioural maintenance of wakefulness test. It has been validated as a simple, easy, reliable method of assessing daytime somnolence (Priest et al., 2001).

The subject was positioned semi-recumbent in a dark, quiet room alone and instructed to stay awake for 40 minutes. A small LED was placed at eye level 2m from the head of the subject. The LED was lit for 1 in every 3 seconds and the subjects responded by removing their thumb or finger from a button to cancel the LED. The LED was controlled by software that stored the response. If the subject failed to respond for 21 seconds (7 LED flashes), it was assumed they had fallen asleep and the test was stopped. The LCD display showed the test termination timing and the number of missed events (Figure 2.6). The OSLER was performed 4 times at 2 hour intervals during the day.



Figure 2.6: *The OSLER test equipment (Stowood Scientific Instruments, Oxford, UK)*

2.11 Exercise testing

Exercise tests provide information on functional capacity, response to treatment and causes of exercise limitation. They range from simple stair climbing to cardiopulmonary exercise testing. The six-minute walk test (6MWT) was used in Chapters 3 and 4 and cardiopulmonary exercise testing in Chapter 5. These will be explained in more detail below.

2.11.1 Six-minute walk test

The 6MWT provides a global estimate of pulmonary, cardiac and muscular integrated function and reflects daily functional activity. A single 6MWT was performed with oxygen saturation monitoring according to ATS guidelines (ATS, 2002).

A 30m calibrated route marked at 3m intervals in a quiet corridor of the Royal Brompton Hospital was used for all tests. Subjects sat down for 10 minutes before starting the route. Pre-test SaO₂ and heart rate were recorded with an N-200E Nellcor oximeter (Nellcor, Covidien-Nellcor™ and Putitan Bennett™, Boulder, USA). Standard instructions were given to each patient. Subjects were taken to the start point and instructed to walk as far as they could as fast as they could without running or jogging. Laps were manually counted and the test was timed with a stopwatch. Standard prompts were provided. Tests were terminated prematurely for extreme dyspnoea, chest pain, leg pain or diaphoresis. At the end of the six minutes, subjects were asked to stop. Heart rate and SaO₂ were measured and the distance walked calculated to the nearest metre. Cote et al followed 1,379 COPD patients for 55 ± 30 months and found mortality was increased in those with 6 minute walk distance < 350m (Cote et al., 2008).

A single test was undertaken as in the ATS guidelines (ATS, 2002). without a prior practice walk.

2.11.2 Cardiopulmonary exercise test

Exercise equipment

Tests were performed in the Exercise Laboratory in the Lung Function Department at the Royal Brompton Hospital. A cycle ergometer (Jaeger ergoline 800, Wrzburg, Germany) was used instead of a treadmill as this provided a stable platform for contrast TCD. In addition, cycle ergometry permitted more accurate quantification of work rate. The cycle was electrically braked allowing resistance to be controlled electromagnetically, hence for any given work rate, moderate changes in cadence (40 to 70 rpm) did not influence work performed.

Gas analyser

A nose clip was attached and a snorkel mouthpiece fitted through which the subject took breaths. Respiratory gases were sampled from polymer Nafion tubing that absorbed water so that water vapour did not introduce errors into gas concentration analysis. This was attached to an Oxycon Device (Jaeger, Wrzburg, Germany) for analysis and real time computerisation. Oxygen concentration was obtained by using an electrochemical fuel cell analyser that measured high temperature reactions between O₂ and substrate. Carbon dioxide concentration was analysed by passing infrared light through the sampled gas onto a sensor. Infrared light at 4.3 μ m was absorbed by CO₂, the amount absorbed proportional to its concentration in the sample. The corresponding reduction in light hitting the sensor, changed its voltage in the circuit. The CO₂ concentration was obtained by comparing observed values to reference standards.

Airflow transducer

A turbine spirometer was fitted into the snorkel mouthpiece. It employed a lightweight impeller in the flow stream to interrupt a light beam. The interruptions were counted by the computerised Oxycon Device (Jaeger, Wrzburg, Germany) and flow rates generated. These were integrated to calculate volume and obtain measurement of tidal volume (VT), ventilation (VE) and respiratory rate.

Breath by breath gas exchange measurement and analysis

Oxygen uptake (VO_2) and CO_2 output (VCO_2) under steady state conditions are equal to O_2 consumption and CO_2 production. Breath by breath analysers sample expired airflow, fractional concentrations of CO_2 and O_2 more than 50 times/second. Each breath is split into these smaller sections and VO_2 and VCO_2 calculated for each interval as follows:

$$\begin{aligned}\text{VO}_2 &= \Sigma (\text{FIO}_2 - \text{FEO}_2) \times \text{VE} \times \Delta t \\ \text{VCO}_2 &= \Sigma \text{FECO}_2 \times \text{VE} \times \Delta t\end{aligned}$$

Where FIO_2 and FEO_2 are equal to O_2 concentration in inhaled and mixed exhaled gas respectively, FECO_2 is equal to CO_2 concentration in exhaled gas and t is the time period of gas volume measurement. Inspired room air CO_2 concentration is nearly zero and hence is ignored. The measurements from each small section are added to get a total per breath and extrapolated for every minute.

Breath by breath data was averaged over 8 breaths for each analysis period. Values derived from coughs, swallows, etc were not included.

Physiologic dead space to tidal volume ratio

The ratio of physiologic dead space to tidal volume (VD/VT) was calculated using the following equation:

$$VD/VT = [(PaCO_2 - PeCO_2) / PaCO_2] \times V_{\text{mouthpiece deadspace}}$$

PaCO₂ was measured directly from earlobe capillary blood gas analysis, PeCO₂ represented the mixed expired value of alveolar and dead space CO₂ derived from breath by breath data and mouthpiece deadspace was 60ml. A normal VD/VT at rest is 0.3 to 0.45 (Harris et al., 1973).

Electrocardiograph

A 12 lead ECG was monitored throughout the exercise tests. Heart rate was calculated from the R–R interval.

Pulse oximetry

Pulse oximetry was measured throughout the exercise protocol. The principle is described in Section 2.9.3.

Calibration

Prior to each exercise test automated gas and volume calibrations were performed and in addition, barometric pressure and temperature were updated. Regular calibration of parameters with biological controls was performed to ensure that measurements remained consistent for each person.

2.12 Intrathoracic, gastric and transdiaphragmatic pressure

2.12.1 Measurement of intrathoracic and gastric pressure

The oesophageal balloon catheter sits in the mid to lower third of the oesophagus. As the oesophagus is a passive structure, pressure transmitted from the intrapleural space to the catheter closely approximates that in the pleural cavity in the upright posture (Mead et al., 1955; Cherniack et al., 1955). Similarly, gastric balloon catheter measurements provide a close surrogate for intraabdominal pressure (Tzelepis et al., 1996). The transdiaphragmatic pressure is the calculated difference between the gastric and oesophageal measurements (Agostoni and Torri, 1962).

2.12.2 Pressure analysis equipment

Balloon catheters comprised an 86cm closed-ended polyethylene tube with an internal diameter of 1mm and an external diameter of 2mm (Ackrad Laboratories Inc, Cranford, NJ, USA). The end of the catheter had 4 pairs of holes to transmit pressure and these were covered with a 9.5cm long balloon. A non-compliant 24cm extension tube and 3-way tap connected the end of the catheters to the differential pressure transducers (range ± 300 cmH₂O; Validyne MP45, Validyne, Northridge, Ca, USA). The signals were amplified (P.K. Morgan) and converted from analogue to digital with a 12-bit NB-MIO-16 A/D board (National Instruments, USA). These were transferred to a Macintosh Quadra Centris 650 personal computer (Apple Computer Inc.) running LabviewTM Software (National Instruments) sampling at 100Hz. The

computer displayed oesophageal pressure (P_{oes}), gastric pressure (P_{gas}) and transdiaphragmatic pressure (P_{di} derived from $P_{\text{gas}} - P_{\text{oes}}$).

2.12.3 Balloon catheter insertion protocol

Patients were positioned comfortably in a chair. Lignocaine gel BP 2% (Biorex Laboratories Ltd, London, UK) was used to lubricate the catheters and anaesthetize the nasal mucosa. Both catheters were advanced through one nostril. When the tips reached the pharynx, the patients were asked to take small sips of water through a straw. This enabled safe passage into the oesophagus. The full length of the catheters was inserted. One catheter was then withdrawn to sit in the oesophagus. The guidewires were removed, the distal ends were attached to the appropriate pressure transducers and the catheters were taped into position.

The balloons were both inflated with 5ml air to allow creases to be smoothed out. 4.5ml air was removed from the oesophageal balloon leaving 0.5ml, a volume sufficient to prevent occlusion of the holes and to maintain a column of air for pressure transmission, but small enough so that peristalsis was not stimulated and discomfort was minimised. 3ml air was removed from the gastric balloon leaving 2ml, a slightly larger volume to withstand the higher abdominal pressures.

2.12.4 Calibration of Equipment

A 2 point calibration of pressure transducers was performed prior to each exercise study with a BioTek handheld digital pressure meter (BioTek, Winooski, USA). The BioTek meter was regularly calibrated in the laboratory against a mercury manometer and pressure readings were accurate and linear.

The pressure transducer was connected to a non-compliant tube and the 1st port of a 3-way tap. The 2nd port of the 3-way tap was connected to the BioTek meter. The system was opened to air and atmospheric pressure was calibrated as zero. A 5ml syringe was attached to the third port of the 3-way tap creating a closed system. Using the 5ml syringe, air was withdrawn and injected to create negative and positive pressures of approximately 150cmH₂O to calibrate the oesophageal and gastric transducers respectively.

Biological calibrations were performed when the balloons were in position and measurements transmitted to computer. The recording was observed for negative inspiratory P_{oes} and with corresponding positive P_{gas} . Patients were asked to cough (positive P_{oes} and P_{gas}), sniff (sharp negative P_{oes} and positive P_{gas}) and to take large breaths in and out (augmented negative P_{oes} and positive P_{gas}).

2.12.5 Data analysis of pressure signals

Pressure signals were recorded during each exercise study and analysed offline from the raw pressure traces (Figure 2.7, Figure 2.8). Measurements from 8 breaths were averaged starting from the point of microbubble injection.

The following conventions were followed:

- The point where P_{di} increased indicating diaphragmatic contraction was taken to signify the start of inspiration
- The point where P_{oes} crossed zero cmH₂O was taken to signify the end of inspiration

The following measurements were recorded:

- Peak and trough P_{oes} , P_{gas} and P_{di}

- Intrathoracic pressure swing: peak P_{oes} – trough P_{oes}
- End expiratory intrathoracic pressure
- Abdominal muscle recruitment: the difference between peak expiratory P_{gas} and P_{gas} at the start of expiration. If there was no recruitment, a value of 0 was assigned

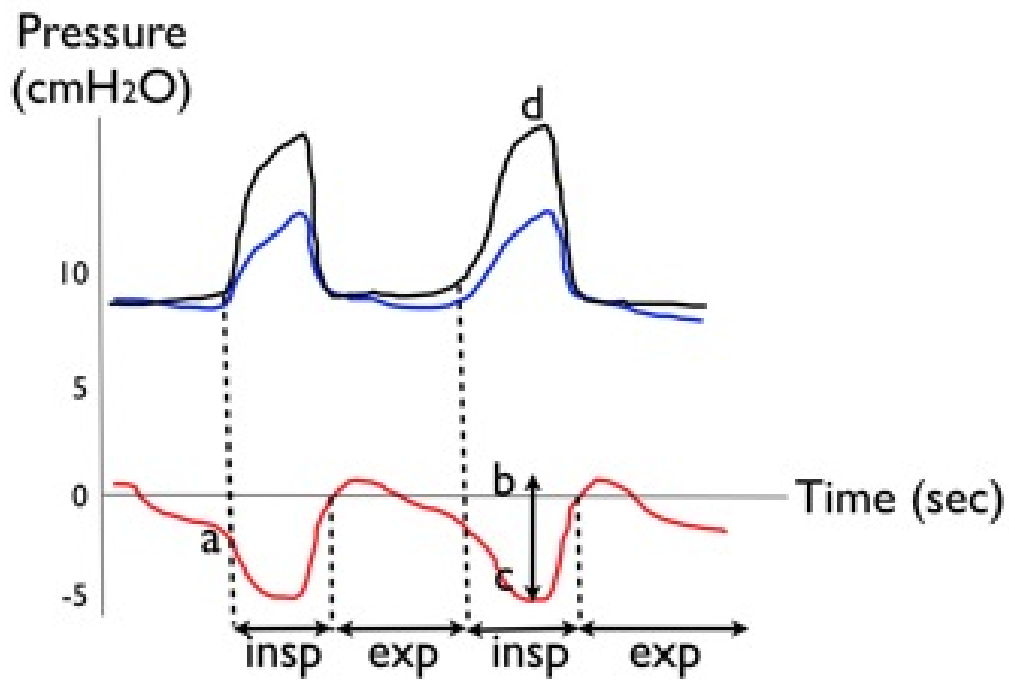


Figure 2.7: Pressure traces at rest. Red line: P_{oes} , blue line: P_{gas} , black line: P_{di} . Start of inspiration is the point at which the P_{di} increases (diaphragmatic contraction) and end inspiration is the point where P_{oes} crosses 0 cmH₂O. a: end expiratory P_{oes} ; b: peak P_{oes} ; c: trough P_{oes} ; b – c: intrathoracic pressure swing; d: peak P_{di}

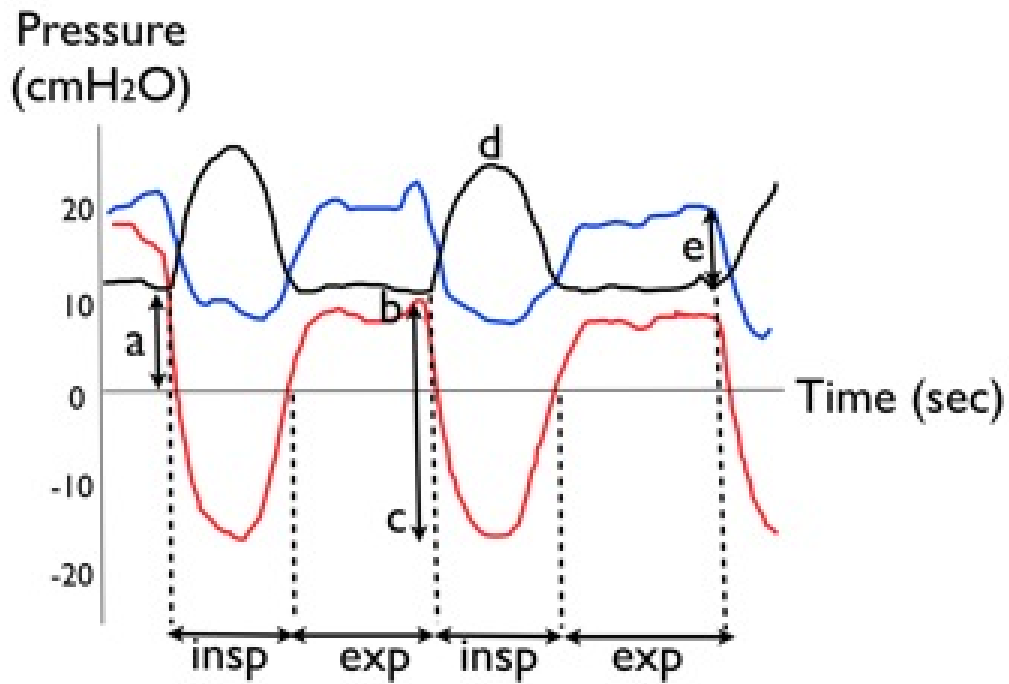


Figure 2.8: Pressure traces during exercise. Red line: P_{oes} , blue line: P_{gas} , black line: P_{di} . Start of inspiration is the point at which the P_{di} increases (diaphragmatic contraction) and end inspiration is the point where P_{oes} crosses 0 cmH₂O. a: end expiratory P_{oes} ; b: peak P_{oes} ; c: trough P_{oes} ; b – c: intrathoracic pressure swing; d: peak P_{di} ; e: abdominal muscle recruitment: peak expiratory P_{gas} – end inspiratory P_{gas}



Figure 2.9: Exercise study set up with TCD headset, oesophageal and gastric balloon catheters, metabolic cart testing on a cycle ergometer

2.13 Statistical analysis

Power calculations and statistical analysis is described in each of the experimental chapters (Chapter 3, 4 and 5).

Chapter 3

Patent foramen ovale in severe obstructive sleep apnoea

Study A: prevalence and associated shunt size

**Study B: effect of patent foramen ovale closure on
nocturnal hypoxaemia**

3.1 Introduction

Severe OSA is a condition, which if inadequately treated is associated with increased cardiovascular morbidity and mortality (Marin et al., 2005). Studies have shown that the mechanisms underlying this increased risk include the cumulative long term effect of negative intrathoracic pressure on left ventricular transmural pressure and cardiac afterload during an apnoeic event (Tkacova et al., 1998), sympathetic nervous system activation inducing tachycardia and blood pressure surges at the termination of an apnoea (Horner et al., 1995) and the impact of intermittent hypoxaemia. Data from studies investigating the effect of intermittent hypoxaemia on the cardiovascular system suggest that stimulation of vascular dysfunction underpins this association (Somers et al., 1991; Christou et al., 2003; Cutler et al., 2004a,b; Minoguchi et al., 2005; Jelic et al., 2008; Belaidi et al., 2009).

PFO allow the passage of mixed venous blood from the right atrium directly into the left atrium and hence the systemic circulation (see Section 1.1 for more details). The presence of a PFO in patients with OSA, could exacerbate hypoxaemia if a RLS is induced during an apnoea, therefore promoting further vascular dysfunction and eventually increasing cardiovascular morbidity.

The relationship between OSA and PFO has been explored in three previous studies discussed in Section 1.2.3. Two of these were prevalence studies that identified a higher prevalence of PFO in OSA compared to healthy controls: 69% versus 17%, $p < 0.001$ (Shanoudy et al., 1998) and 27% in OSA versus 15% in controls, $p < 0.05$ (Beelke et al., 2003).

Since these studies were undertaken, the advent of Power M Mode TCD and TTE with second harmonic imaging (Spencer et al., 2004; Daniels et al., 2004)

have allowed the definition of associated shunt size with greater levels of accuracy.

The aim of this study was to examine the prevalence of PFO in severe OSA compared to healthy controls and furthermore, to accurately determine the associated shunt size. Study A was an observational study conducted to test the hypotheses that:

1. severe OSA patients have a higher prevalence of PFO compared to healthy controls
2. severe OSA patients have a higher prevalence of PFO with large shunts compared to healthy controls

In the study by Johanssen et al, 11 OSA patients with large shunts through PFO were found to have higher ODI/AHI ratios than 19 OSA patients without large shunts: 0.75 (0.27) versus 0.37 (0.3) respectively, $p = 0.001$ (Johansson et al., 2007). This suggests that OSA patients with large shunts experience more nocturnal desaturation for a given level of respiratory disturbance and supports the notion that PFO with large shunts exacerbate nocturnal intermittent hypoxaemia.

Clinical experience suggests that PFO can be safely closed percutaneously, and that where there is substantial right to left shunting, waking arterial oxygen tensions can be improved (Remy-Jardin et al., 1990; Allan et al., 1997; Piechaud, 2001; Shnaider et al., 2004; Kuch et al., 2006; Mottram et al., 2006). However, data on the effect of PFO closure in OSA are limited to one case report which documented resolution of exercise induced dyspnoea following PFO closure; no nocturnal data were reported (Agnoletti et al., 2005).

The second aim of this study was to examine the effect of percutaneous PFO closure on nocturnal hypoxaemia in OSA patients who were found to

have PFO with large RLS. Study B was a prospective, interventional, proof of concept study to test the hypothesis that percutaneous closure of PFO with large shunts in patients with severe OSA reduces nocturnal desaturation.

3.2 Methods for Study A

3.2.1 Subjects

Severe OSA patients (AHI > 30 events/hour) were recruited from the sleep clinic at the Royal Brompton Hospital. Age and gender matched healthy controls were recruited as described in Chapter 2, Section 2.3.3. The sample size calculation is given in the statistical analysis in Section 3.2.5. Inclusion and exclusion criteria are detailed in Chapter 2, Section 2.3. All participants met the specified criteria.

3.2.2 Protocol

All participants attended for baseline assessments including resting arterial blood gas tensions, spirometry and a six minute walk test. Subjects completed the Epworth Sleepiness Score to assess subjective sleepiness (Johns, 1991), the HIT6 questionnaire to assess headache (Kosinski et al., 2003) and the SF36v2 questionnaire to assess quality of life (Ware et al., 2000). Contrast TTE and TCD were performed to determine the presence of PFO and size of the associated shunt. Healthy control subjects underwent respiratory polygraphy prior to enrolment to ensure they did not have undiagnosed OSA.

3.2.3 Measurements

Respiratory polygraphy

Nocturnal measures of nasal and oral airflow (nasal cannula and thermistor), thoracic and abdominal respiratory effort (respiratory inductance plethys-

mography), cardiac frequency and arterial oxygen saturation (finger pulse oximetry), snoring and body position were recorded in all patients. (Further details of polygraphy measurements are in Chapter 2, Section 2.9.)

Contrast transthoracic echocardiography

Standard echocardiographic image planes were acquired with ECG monitoring (Sonos 7500, Philips, Netherlands). Contrast studies were performed in the four-chamber view with the subject in the left lateral position. Agitated saline (8ml saline, 1ml autologous blood, 1ml air) contrast was injected in a single push via a cannula in an antecubital vein. Injections were performed at rest and during a Valsalva manoeuvre. (Further details of contrast TTE measurement are in Chapter 2, Section 2.4.)

Contrast transcranial Doppler

A 2MHz Power M-mode digital TCD system (ST3/PMD150, Spencer Technologies, Seattle, USA) was used to insonate the middle cerebral arteries bilaterally through the temporal bone windows. The probes were secured using an adjustable head frame with the patient lying in the supine position. The Doppler signal gain and depth were adjusted to detect flow. Signals were recorded for 1 minute following contrast injections at rest and after 2 Valsalva manoeuvres. Studies were analysed offline and PFO shunt size was graded using the criteria of Spencer (Spencer et al., 2004) (Further details in Chapter 2, Section 2.5.1.)

3.2.4 Data analysis

Respiratory polygraphy traces for OSA patients were scored using automated criteria. Respiratory polygraphy studies performed on healthy control subjects were manually scored offline. Scoring was performed in accordance with the AASM 2007 guidelines (Iber et al., 2007). Details of scoring criteria are given in Chapter 2, Section 2.9.6.

A PFO was defined as present if a shunt of any magnitude was detected following a Valsalva manoeuvre. PFO shunt capacity was graded as small, moderate or large in accordance with validated criteria (Spencer et al., 2004; Saqur et al., 2004; Dowson et al., 2008). The size of shunt assigned to each PFO was the maximum shunt detected following a Valsalva manoeuvre. Pulmonary shunts were defined as present if a RLS developed after 5 cardiac cycles following right heart opacification. Where there was a disagreement between TTE and TCD, the larger detected shunt was recorded. Further details of scoring criteria are in Chapter 2, Sections 2.4.2, 2.4.3 and 2.5.3.

OSA patients were divided into 2 groups for analysis 1) those with moderate and large shunts following a Valsalva manoeuvre and 2) those with small shunts following Valsalva and those without PFO. The rationale behind this was that moderate to large shunts have been associated with clinical manifestations of PFO (Schwerzmann et al., 2005; Torti et al., 2004; Schuchlenz et al., 2000; Harrer et al., 2006).

3.2.5 Statistical analysis

The aim of Study A was to examine the prevalence of PFO in OSA and to determine the size of the associated shunt. There have been two previous studies investigating the prevalence of PFO in OSA. They have shown a

prevalence of 69% and 27% in OSA, and 17% and 15% in healthy controls (Beelke et al., 2003; Shanoudy et al., 1998). The 2 studies were used in combination to obtain a mean PFO prevalence of 48% in OSA and 16% in controls. Exercising caution a lower PFO prevalence was assumed in OSA and a higher prevalence in controls. A prevalence of 45% in OSA and 20% in healthy controls yielded a sample size, in a ratio of 2:1, of 96 OSA patients and 48 controls at 80% power and a significance level of 0.05. These values were then rounded to 100 and 50 respectively. A ratio of 2:1 allowed us to study more OSA patients so enlarging the pool of potential recruits for the percutaneous closure study. Sample size was calculated using STATA version 10.1 (StataCorp LP, Texas, USA).

Remaining statistical analysis was performed using SPSS (version 16.0, SPSS Inc., Chicago, Illinois, USA). Parametric data are presented as mean (SD) and non-parametric as median (range). Categorical variables were compared using the Chi-squared test. Students t test was used to compare measurements in OSA patients versus healthy controls. Patients with OSA were divided into 2 groups: those with no PFO or a small shunt, and those with a moderate to large shunt. Measurements between the 2 groups were compared using the unpaired Students t test (parametric) or Mann-Whitney U test (non-parametric). Receiver operating characteristic curve analysis was performed to determine the ability of the ODI/AHI ratio to predict moderate to large shunts. Statistical significance was defined as $p < 0.05$.

3.3 Methods for Study B

3.3.1 Subjects

Six OSA patients with large shunts suitable for PFO closure were recruited from Study A. Additional exclusion criteria were: FVC < 80% predicted, active infections, serum creatinine > 115 micromol/L, known or suspected pregnancy, predisposition to haemorrhage, sensitivity to porcine material, road traffic accident or near miss related to sleepiness, sensitivity to aspirin, clopidogrel or heparin, baseline thrombocytopenia, thrombus visualised within the heart, seizure disorder, other cardiac disease (valve disease, known cardiomyopathy, left ventricular failure, known coronary disease, known congenital heart disease), previous atrial septal closure device, known pulmonary arteriovenous malformation, pulmonary hypertension (tricuspid regurgitation maximum velocity > 3 metres/second), atrial fibrillation or flutter.

3.3.2 Protocol

Baseline visit

Patients discontinued CPAP for 3 nights prior to the baseline visit. They were advised not to drive in this period. On the day of the visit, patients were asked to abstain from caffeine and alcohol. Dinner was provided at 19.00 and attachment of the NPSG electrodes was commenced at 21.00. On the day following the NPSG, patients carried out 4 OSLEP tests. During the natural intervals in the OSLEP test, they completed a 6 minute walk test, a blood sample was taken for resting ABG analysis, an ECG was carried

out, blood tests for full blood count, urea and electrolytes and BNP were taken and the Epworth Sleepiness Score, the HIT6 headache test and the SF36v2 questionnaire were completed. At 17.00, the patients were able to go home and CPAP was restarted that evening. Percutaneous PFO closure was performed as described below on a separate occasion.

PFO closure

Pre-Procedure

Patients were admitted to the Royal Brompton Hospital. CPAP was continued throughout the visit. All patients were given aspirin 300 mg and clopidogrel 300 mg within the 24 hours prior to the procedure.

Procedure

PFO closure was performed percutaneously using the BioSTAR device (NMT Medical, Inc., Boston, USA) as previously described (Nugent et al., 2006; Carminati et al., 2001; Mullen et al., 2006). Procedures were performed in the cardiac catheterization laboratory by a single investigator using a combination of fluoroscopic and intracardiac echocardiographic (ICE) imaging. ICE imaging is performed by directing an ultrasound probe into the heart to visually assist percutaneous atrial septal closure procedures.

Following sterile preparation, local anaesthesia was administered to the right groin and two venous sheaths were positioned in the right femoral vein. An ICE catheter was passed through the first sheath and advanced to the right atrium. The second sheath was used to implant the BioSTAR device. All patients were awake during the implant procedure. Patients received 100 units/kg intravenous heparin during the procedure to keep the activated coagulation time > 200 seconds and a single dose of antibiotic prophylaxis.

The PFO were crossed with a multipurpose catheter and soft tipped guidewire. Anatomy and size of PFO was defined by balloon interrogation (PTS balloon, NuMed). A balloon was inflated in the PFO to assess the defect size and to enable selection of an appropriately size PFO closure device. An appropriate size device was chosen based on the size of PFO. The device was deployed as below.

The BioSTAR device was deployed using the Rapid Transport™ Delivery Catheter. The Rapid Transport™ Delivery Catheter facilitates device attachment and transfer from the QwikLoad Plus to a previously placed and irrigated transeptal introducer sheath. Once the BioSTAR implant was placed through the defect, the operator advanced the device and the distal umbrella was opened in the left atrium. The operator then retracted the sheath, while maintaining gentle pressure to hold the distal umbrella against the left atrial wall of the septum, releasing the proximal side of the device against the right atrial wall of the septum. The device position was monitored by fluoroscopy and ICE and once the operator determined that the device was properly in place, the delivery system was activated to release the device, and the delivery system and transeptal sheath were removed.

Post-procedure

Patients received 75 mg aspirin daily for 6 months and clopidogrel 75 mg daily for 90 days following the procedure date. Endocarditis prophylaxis was given for any invasive or dental procedure 6 months following implant of the device.

Discharge from Hospital

An ECG and TTE were performed prior to discharge to confirm placement of the study implant. Patients were discharged within 24 hours of the procedure.

Follow up visits

Follow up NPSG studies were undertaken at 1, 6 and 12 months post closure. The protocol was the same as for the baseline visit. In addition, contrast TTE and TCD were performed to detect residual shunting post closure.

3.3.3 Measurements

Attended nocturnal polysomnography (NPSG) was performed in patients undergoing closure of PFO in the hospital sleep laboratory (SomnoScreen system, SOMNOmedics, S-Med UK). Electroencephalograms (C3/A2 and C4/A1) were placed according to standard 10-20 system of electrode placement (See Chapter 2, Section 2.9.1). Left and right electrooculograms (EOG) and submental electromyograms (EMG) were recorded. EEG, EOG and submental EMG were used to assess sleep/wake status. Bilateral anterior tibialis EMG were recorded to detect periodic limb movements. A 2 lead ECG was recorded throughout. Chest and abdominal respiratory effort were monitored using respiratory inductance plethysmography. Oxyhaemoglobin saturation was monitored with a finger probe oximeter. Nasal pressure was monitored with a nasal cannula connected to a pressure transducer, oral and nasal temperature changes were monitored as an index of airflow using a thermistor. A tracheal microphone recorded snoring (further details of NPSG set up are given in Chapter 2 Section 2.9).

The OSLER test was performed in accordance with standard criteria. Further details regarding NPSG and OSLER testing are in Chapter 2, Section 2.9 and 2.10 respectively. Contrast TTE and TCD were performed as described in Section 3.2.3.

3.3.4 Data analysis

Sleep/wake status, arousals from sleep and respiratory events were scored offline, visually using standard criteria (Iber et al., 2007) with scorer blinded to status of patient. (Further details on scoring criteria are in Chapter 2, Section 2.9.6.) Contrast TTE and TCD were analysed as described in Section 3.2.4.

3.3.5 Statistical analysis

The effects of PFO closure on measured parameters in OSA patients were compared using one-way ANOVA on repeated measures (parametric) or the Kruskal Wallis test (non-parametric). A probability value of < 0.05 was considered statistically significant.

3.4 Results

3.4.1 Study A: Baseline characteristics of participants

One-hundred and sixty-one severe OSA patients were approached; 46 declined to participate in the study. Of the 115 patients who were screened, 15 did not meet the inclusion criteria, therefore 100 patients were included in the study (Figure 3.1). One-hundred and seventeen healthy volunteers were recruited from the general population. Fifty-five were subsequently not studied as they had a high pre-test probability of OSA (snoring or history of witnessed apnoeas); 62 volunteers were studied with respiratory polygraphy; 12 did not meet the inclusion criteria; therefore data for 50 healthy controls was included in the study (Figure 3.1).

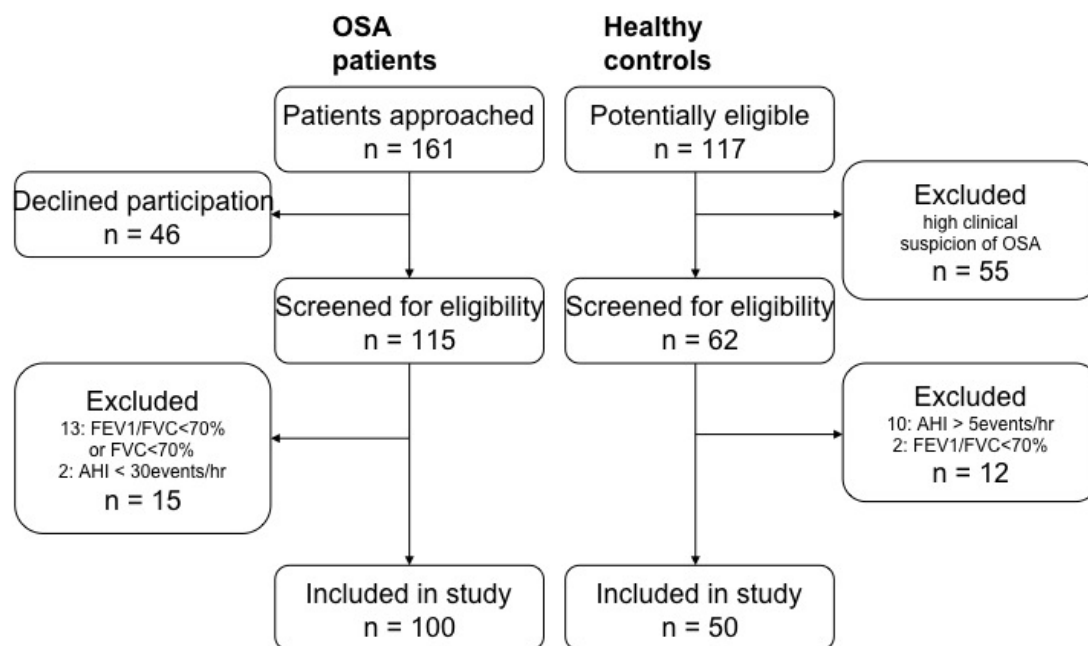


Figure 3.1: Diagram illustrating recruitment of severe OSA patients and healthy controls in Study A

Details of comorbidities of OSA patients and healthy controls are given in

Table 3.1. The median time from diagnosis of OSA to the study visit was 70 (IQR: 28 to 160, range: 0 to 805) days. There was no significant weight change in any OSA patient from diagnosis to the study visit: 104.4 (18.3) kg to 104.8 (19.0) kg, $p = 0.19$. Data on compliance with CPAP was available for 55 patients from machine smartcards. Median compliance was 6 hours (range: 1.4 to 8.8 hours). Five patients were not using CPAP.

Table 3.1: Comorbidities of OSA patients (n = 100) and controls (n = 50)

Comorbidity	OSA (n)	Controls (n)
No cormorbidity identified	21	45
Ischaemic heart disease	11	
Hypertension	43	3
Atrial fibrillation/flutter	4	
Hypercholesterolaemia	12	
Previous stroke/transient ischaemic attack	3	
Diabetes (type I and II)	16	2
Migraine	5	
Cluster headache	1	
Normal spirometry, previous mild airflow obstruction	4	
Gastroenterological	10	
Musculoskeletal	14	2
Chest infection between OSA diagnosis and study visit	2	
Other	19	

Baseline characteristics for OSA patients and healthy controls are given in Table 3.2. OSA patients had a mean AHI of 53.9 (17.8) events/hour and ODI of 49.5 (21.0) events/hour. All healthy controls had an AHI < 5 events/hour. There were no significant differences in age ($p = 0.83$), gender ($p = 0.41$) and FEV₁/FVC ratio ($p = 0.22$) between the OSA patients and healthy controls. OSA patients had higher body mass indices (BMI) ($p < 0.001$), lower predicted FEV₁ ($p < 0.001$) and FVC ($p < 0.001$), lower resting PaO₂ ($p = 0.004$) and PaCO₂ ($p = 0.01$), higher ESS ($p < 0.001$) and HIT6 ($p = 0.02$) scores and lower SF36v2 physical component ($p < 0.001$) and mental health component ($p < 0.001$) quality of life scores.

Table 3.2: Baseline characteristics of OSA patients and healthy controls

	OSA patients n = 100	Healthy controls n = 50	p value
Age (years)	52 (10)	52 (11)	0.83
Male/ female	87 / 13	42 / 8	0.41
BMI (kg/m ²)	34.5 (6.4)	24.3 (2.7)	< 0.001
FEV ₁ (% predicted)	93 (2)	101 (13)	< 0.001
FVC (% predicted)	94 (11)	104 (13)	< 0.001
FEV ₁ /FVC	80 (5)	79 (6)	0.22
PaO ₂ (kPa)	11.6 (1.3)	12.3 (1.4)	0.004
PaCO ₂ (kPa)	5.3 (0.5)	5.6 (0.5)	0.011
Epworth sleepiness score	9 (5)	5 (4)	< 0.001
HIT 6 headache score	45 (9)	42 (7)	0.02
SF36v2: Physical component	47 (11)	57 (5)	< 0.001
SF36v2: Mental component	48 (10)	53 (8)	< 0.001
AHI (events/hour)	53.9 (17.8)	2.0 (1.9)	
ODI (events/hour)	49.5 (21.0)	1.9 (1.8)	
CPAP duration (months)*	2 (0 – 24)		

*Values are expressed as mean (SD), * median (range)*

3.4.2 Study A: PFO prevalence

The prevalence of PFO in OSA patients and healthy controls is shown in Figure 3.2. There was no significant difference in the overall prevalence of PFO in severe OSA patients compared to healthy controls: 43% (43/100) versus 30% (15/50), $p = 0.16$. OSA patients had a higher prevalence of large shunts following Valsalva manoeuvre compared to healthy controls: 18% (18/100) versus 6% (3/50), $p = 0.049$. Full details of shunt size at rest and following a

Valsalva manoeuvre are given in Table 3.3. OSA patients and healthy controls had a similar prevalence of small and moderate size shunts. Intrapulmonary shunts were detected in 4% (4/100) OSA patients and 12% (6/50) healthy controls, $p = 0.08$.

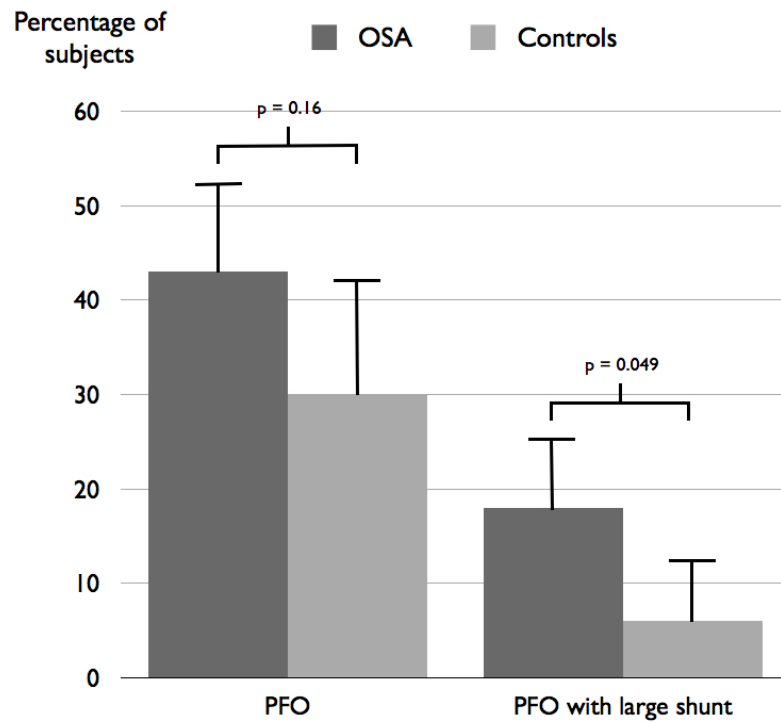


Figure 3.2: Prevalence of PFO in OSA (dark grey bars) compared to healthy controls (light grey bars). Error bars represent 95% confidence intervals. PFO were detected in 43% of OSA patients compared to 30% of healthy controls, $p = 0.16$. PFO with large shunts were detected in 18% of patients with OSA compared to 6% of healthy controls, $p = 0.049$

Table 3.3: PFO shunt size in OSA patients and healthy controls

	At rest			Following Valsalva manoeuvre		
	OSA	Controls	p value	OSA	Controls	p value
	n = 100	n = 50		n = 100	n = 50	
No shunt	79	44	0.26	57	35	0.16
Small shunt	11	4	0.77	17	8	1.00
Moderate shunt	10	1	0.34	8	4	1.00
Large shunt	0	1	0.33	18	3	0.049

The p value was calculated using the Chi squared and Fishers Exact test

3.4.3 Study A: OSA patients with moderate to large shunts

Measurements in OSA patients with and without moderate to large shunts are compared in Table 3.4. OSA patients with moderate to large shunts had a lower AHI: 46.8 (14.3) versus 56.5 (18.3) ($p = 0.01$), and a higher ODI/AHI ratio: 1.05 (0.27) versus 0.86 (0.26) ($p = 0.004$) compared to those with no clinically significant shunt. PaCO_2 was lower in the moderate to large shunt group: 5.1 (0.5) kPa versus 5.4 (0.5) kPa ($p = 0.02$) despite similar PaO_2 . In patients with moderate to large shunts there were trends towards a shorter 6 minute walk test distance, higher ESS, higher HIT6 headache scores and lower SF36v2 scores (all $p \leq 0.1$). Age, BMI, spirometry, ODI, 6 minute walk test distance, ESS, HIT6 headache scores and SF36v2 scores were similar across groups.

Table 3.4: Comparison of OSA patients with and without moderate to large shunts through PFO

	Moderate to large shunt	Small/ no shunt	p value
	n = 26	n = 74	
Age (years)	54 (9)	51 (10)	0.20
BMI (kg/m ²)	34.2 (7.2)	34.6 (6.1)	0.77
FEV ₁ (% predicted)	92 (16)	93 (11)	0.67
FVC (% predicted)	93 (13)	94 (11)	0.63
FEV ₁ /FVC	81 (6)	80 (5)	0.65
AHI (events/hour)	46.8 (14.3)	56.5 (18.3)	0.01
ODI (events/hour)	48.6 (16.1)	49.8 (22.5)	0.78
ODI/AHI	1.05 (0.27)	0.86 (0.26)	0.004
6MWT distance (metres)	511 (138)	564 (83)	0.07
PaO ₂ (kPa)	11.8 (1.4)	11.6 (1.2)	0.43
PaCO ₂ (kPa)	5.1 (0.5)	5.4 (0.5)	0.02
Epworth sleepiness score	11 (6 – 15)	7 (4 – 12)	0.08
HIT 6 headache score	48 (38 – 55)	40 (36 – 50)	0.09
SF36v2: physical	43 (13)	48 (10)	0.10
SF36v2: mental health	45 (12)	50 (9)	0.08

Values expressed as mean(SD) or median (range)

3.4.4 Study A: ODI/AHI as a predictor of a moderate to large shunt

Receiver operating characteristic curve analysis of the ODI/AHI ratio as a predictor of a moderate to large shunt showed that the area under the curve was 0.66 (95% CI: 0.55 to 0.78). An ODI/AHI ratio > 0.92 has a sensitivity of 75%, a specificity of 53% and a likelihood ratio of 1.6 for predicting the presence of a moderate to large shunt (Figure 3.3). An ODI/AHI of 0.92 was the optimum cut off for sensitivity and specificity obtained by the coordinates on the ROC curve at the greatest perpendicular distance from the diagonal line.

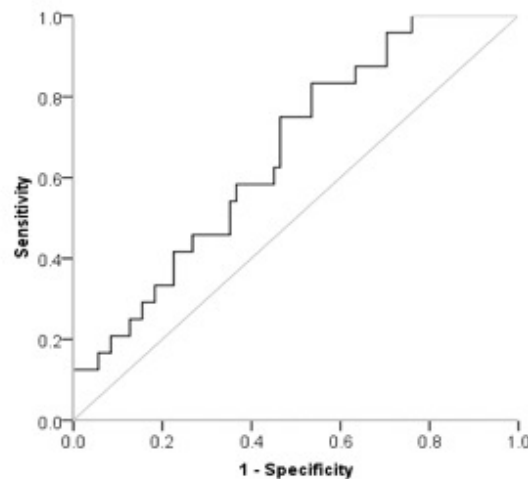


Figure 3.3: Receiver operating characteristic curve analysis of the ODI/AHI ratio as a predictor of a moderate to large shunt

3.4.5 Study A: CPAP compliance according to shunt size

CPAP compliance (55 patients with compliance data and 5 patients who were not on CPAP) was similar in patients with and without PFO. Furthermore, it was the same in patients with different magnitudes of shunt (Table 3.5).

Table 3.5: CPAP compliance (hours/night) in OSA patients with different shunt sizes

PFO SHUNT SIZE AT REST					
	No shunt	Small	Moderate	Large	p value
	n = 48	n = 7	n = 5		
Compliance (hrs)	6 (0–8.8)	5.3 (1.4–7.3)	5.2 (0–7.5)		0.85
PFO SHUNT SIZE FOLLOWING VALSALVA					
	No shunt	Small	Moderate	Large	p value
	n = 36	n = 9	n = 4	n = 11	
Compliance (hrs)	5.8 (0–8.8)	5.5 (0–8.5)	6.6 (5.3–7)	5.2 (0–7.5)	0.76

Values expressed as median(range), p value obtained from Kruskal Wallis test

3.4.6 Study B: Recruitment of OSA patients

Eighteen OSA patients were found to have PFO with associated large shunts after Valsalva; 6 declined to participate, and 6 did not meet the inclusion criteria (Figure 3.4). Therefore, 6 OSA patients (5 male, age: 35 – 66 years) underwent percutaneous PFO closure.

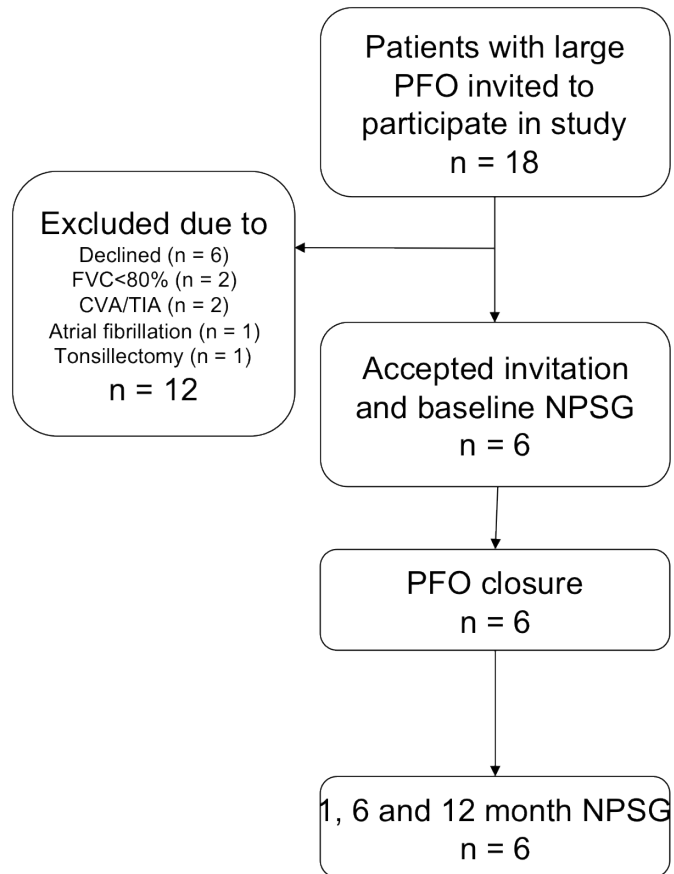


Figure 3.4: Diagram illustrating recruitment of severe OSA patients for PFO closure, Study B. NPSG: nocturnal polysomnography, CVA: cerebrovascular accident, TIA: transient ischaemic attack

3.4.7 Study B: PFO closure procedure details

Table 3.6 provides details on the PFO closure procedures and adverse events.

Table 3.6: PFO closure procedure details, outcomes and complication

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	66	59	56	47	35	60
Procedure time (min)	58	29	37	28	71	40
Device size (mm)	28	28	23	23	23	28
Follow up Shunt size*						
– 1 month	Large	Small	No shunt	Large	No shunt	Large
– 6 months	Large	Small	Small	Large	No shunt	Small
– 12 months	Large	No shunt	Small	Large	No shunt	No shunt
Procedure complications	Nil reported	Nil reported	Nil reported	Nil reported	Nil reported	Left foot bruising, palpitations, blood in stools

* shunt sizes given are those detected following a Valsalva manoeuvre

Early follow-up evaluations at 1 month following the PFO closure procedure revealed ongoing shunting after Valsalva in 3 out of 6 patients. At the 12-month evaluation, 3 PFO were sealed, 1 had a small, clinically insignificant residual shunt and 2 patients had persisting large shunts after Valsalva (Table 3.6).

3.4.8 Study B: Effect of PFO closure

PFO closure was not associated with a significant change in ODI or percentage of time spent with $\text{SaO}_2 < 90\%$. ODI at baseline was 47.7 (18.4) events/hour and post closure was 47.3 (19.0) events/hour at 1 month, 45.8 (21.2) events/hour at 6 months and 50.9 (18.6) events/hour at 12 months, $p = 0.93$ (Figure 3.5). Percentage of time with $\text{SaO}_2 < 90\%$ at baseline was 22.8 (16.0)% and post closure was 11 (10)% at 1 month, 20.1 (16.9)% at 6 months and 19.9 (22.2)% at 12 months, $p = 0.35$ (Figure 3.6).

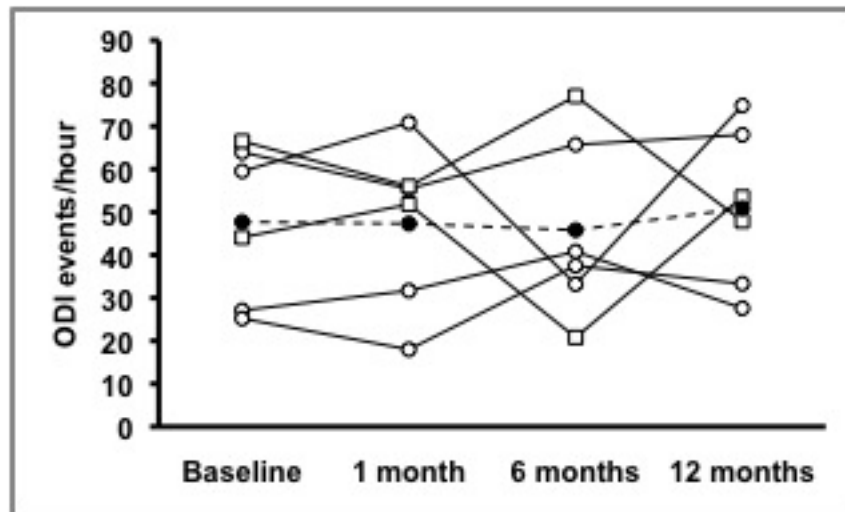


Figure 3.5: ODI at baseline and 1, 6 and 12 months following PFO closure. Open circles: individual values for 3 patients with completely sealed PFO and 1 patient with insignificant residual shunt, open squares: individual values for patients with residual large shunts, closed circle: mean value

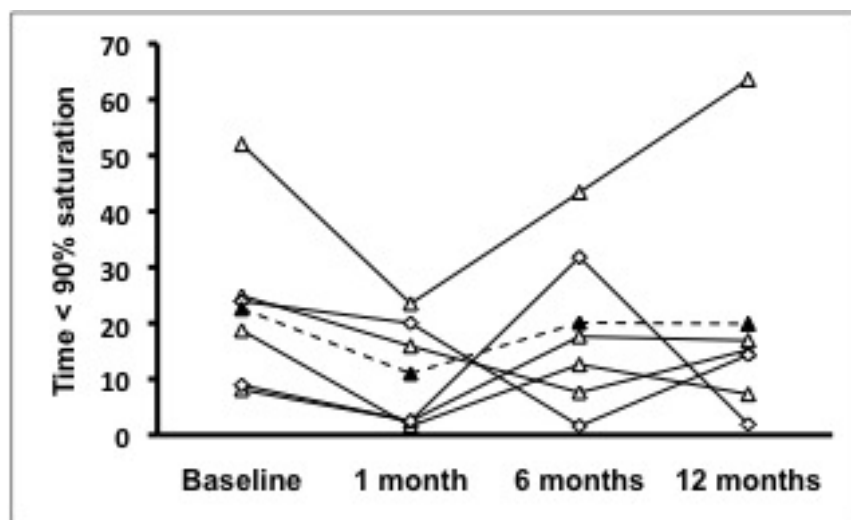


Figure 3.6: Percentage of time with $SaO_2 < 90\%$ at baseline and 1, 6 and 12 months following PFO closure. Open triangles: individual values for 3 patients with completely sealed PFO and 1 patient with insignificant residual shunt, open diamonds: individual value for patients with residual large shunts, closed triangle: mean value

Closure was not associated with any significant changes in PaO₂ (p = 0.23), PaCO₂ (p = 0.74), AHI (p = 0.99), ODI/AHI ratio (p = 0.28), BMI (p = 0.06), 6 minute walk test distance (p = 0.17), ESS (p = 0.14), HIT 6 questionnaire (p = 0.28), SF36v2 physical component (p = 0.08) or SF36v2 mental health component (p = 0.43). For individual values, see Table 3.7. During the 12-month follow up period in the 4 patients using CPAP, nocturnal use was 5 (3.5 – 7) hours per night.

An additional analysis examining the desaturation associated with each apnoea pre and post closure is detailed in Appendix F.

Table 3.7: Results at baseline and 1, 6 and 12 months following PFO closure

	Baseline	1 month	6 months	12 months	p value
PaO ₂ (kPa)	11.2 (0.7)	11.8 (0.5)	10.7 (0.7)	10.8 (1.5)	0.23
*PaCO ₂ (kPa)	5.6 (4.5–5.8)	5.6 (5.0–5.8)	5.6 (5.3–6.1)	5.5 (4.7–6.1)	0.74
AHI (events/hour)	67.2 (24.9)	67.7 (21.9)	66.6 (31.0)	68.5 (31.0)	0.99
*ODI/AHI	0.73 (0.34–0.87)	0.73 (0.53–0.87)	0.70 (0.44–0.90)	0.85 (0.40–1.01)	0.28
BMI (kg/m ²)	33.7 (3.5)	32.8 (3.5)	34.3 (3.2)	33.2 (3.4)	0.06
6MWT distance (m)	558 (102)	578 (81)	584 (69)	593 (79)	0.17
Epworth sleepiness score	13 (3)	11 (4)	10 (5)	11 (5)	0.14
*Headache Impact Test 6	42 (40–59)	43 (36–46)	37 (36–52)	41 (38–65)	0.28
SF36v2: physical	47 (9)	48 (7)	52 (7)	46 (9)	0.08
SF36v2: mental health	51 (5)	52 (4)	47 (8)	49 (7)	0.43

*Values are expressed as mean (SD) or *median (range). p value obtained from ANOVA or Kruskal Wallis test*

3.5 Discussion

Patients with severe OSA were found to have a significantly higher prevalence of PFO with large shunts than healthy controls. However, overall PFO prevalence was not found to be significantly different from the control population. PFO closure did not reduce nocturnal desaturation, nor did it improve resting arterial blood gas tensions, 6 minute walk test distance, Epworth Sleepiness Score or quality of life.

Two previous studies have reported a higher prevalence of PFO in patients with OSA. Shanoudy et al., detected PFO in 69% of OSA patients compared to 17% in controls (Shanoudy et al., 1998). They studied 48 male OSA patients undergoing elective transoesophageal echocardiography for other reasons and in doing so may have selected a group likely to have a PFO. This could explain the particularly high prevalence of PFO in their study.

Beelke et al., detected PFO in 27% of OSA patients compared to 15% of controls (Beelke et al., 2003). The lower prevalence of PFO in OSA patients in their study may be a consequence of using an older TCD machine without Power M Mode, which has been shown to improve PFO detection rates (Spencer et al., 2004). Smaller shunts which contribute the majority of PFO in controls may have therefore been missed.

Both studies used saline and air contrast to detect PFO, which is not as effective as the saline, blood and air mixture used in the present study (Sastry et al., 2007), therefore, again, smaller PFO in the healthy controls may have been missed.

3.5.1 PFO detection

Contrast TTE and TCD were used to detect and size PFO. Both tests have good sensitivity and specificity and are comparable to contrast transoesophageal echocardiography, the commonly regarded gold standard (Daniels et al., 2004; Saqqur et al., 2004). Obese OSA patients have poor echo windows, therefore combining echocardiography with TCD enabled us to detect and estimate the size of each PFO shunt accurately (Zito et al., 2009). Further details of grades of shunt assigned by TCD and TTE are given in Appendix E.

3.5.2 Mechanisms for the higher prevalence of large PFO in OSA

The increased prevalence of large PFO may be explained by mechanisms that alter the anatomical configuration of the interatrial septum, ultimately stretching pre-existing PFO and increasing the size of shunt. An obstructive apnoea can cause a large increase in pulmonary artery pressure primarily due to hypoxic pulmonary vasoconstriction (Tilkian et al., 1976; Nijima et al., 1999). This increases right ventricular afterload, promoting right ventricular diastolic dysfunction leading to an increase in right atrial pressure. Combined with this, obstructive apnoeas generate increased respiratory effort against a closed airway to produce negative intrathoracic pressure, which increases venous return and augments right ventricular preload. This augmented venous return leads to further increases in right atrial pressure with resulting strain on the interatrial septum. The generation of negative intrathoracic pressure is an important mechanism to be considered as it also causes elevations in transmural pressure further increasing right atrial pressure. Termination of obstructive apnoeas is followed by a reflex hyperventilatory

response. The inspiratory phase of this response increases venous return. In patients with persistent eustachian valves or anatomy that streamlines inferior vena caval flow towards the atrial septum, this venous return is directed through a PFO. In combination with elevated right atrial pressure, we speculate over time that this may stretch a PFO and increase its shunt capacity.

Beelke et al., used TCD to investigate nocturnal shunting through PFO. They studied OSA patients with shunts present only after Valsalva manoeuvre (not at rest), and found that apnoeas of 17 seconds or more, were associated with shunting (Beelke et al., 2002). Interestingly, the magnitude of shunt detected following a Valsalva correlated positively with the magnitude of shunt induced by an apnoea. Hypopnoeas did not induce significant shunting, nor did apnoeas of shorter duration.

3.5.3 Nocturnal desaturation in patients with moderate to large shunts

The ODI/AHI was increased in patients with moderate to large shunts compared to those with no or small shunts. Johanssen et al are the only group that have used the ODI/AHI ratio as an index of the amount of desaturation for a given level of respiratory disturbance (Johansson et al., 2007). They found that in OSA patients with a high ratio of > 0.66 , PFO prevalence was 60% (9/15) versus 13% (2/15) in OSA patients with a low ratio of < 0.33 .

The ODI/AHI values for the OSA dataset in this chapter were obtained from respiratory polygraphy studies that were scored automatically. The ratios obtained were higher than in the study by Johansson. Only 1 OSA patient out of 100 had an ODI/AHI < 0.33 of 0.23 and the remainder were higher.

This may reflect the method by which the ratio was derived e.g. NPSG versus polygraphy with respiratory analysis only, or it may reflect the severity of OSA in the patients studied.

In patients that ultimately underwent PFO closure, the median ratio was 0.73 (0.34 – 0.87) at baseline and 0.85 (0.40 – 1.01) 12 months post procedure. These values were scored by NPSG and more comparable to the study by Johansson. However, ODI/AHI was not affected by PFO closure. In addition, the ratio was unaffected by whether or not there was residual shunting post closure. It is therefore difficult to draw any firm conclusions on the significance of the ODI/AHI findings. It remains an interesting, yet unvalidated measure of quantifying the magnitude of nocturnal desaturation.

The ODI itself was no different between the moderate to large shunt and no/small shunt groups.

The combined effect of increased pulmonary artery pressure, negative intrathoracic pressure and post-apnoeic hyperventilation could increase right to left shunting through a PFO. Delivery of mixed venous blood to the systemic circulation through a large PFO, could, theoretically lead to a reduction in arterial oxygen saturation, However, the data in this study does not conclusively support this notion.

3.5.4 PFO closure

PFO closure was successful in 3/6 patients and left only a very small residual shunt in 1 patient. Two patients were left with a large residual shunt. Percutaneous PFO closure was not associated with a reduction in ODI or percentage of time with $\text{SaO}_2 < 90\%$ even in patients who had complete PFO closure. These data suggest that the predominant cause of desaturation even

in patients with large PFO remains the apnoea. The PFO closure procedures that were performed in this subset of OSA patients were technically difficult due to body habitus. Therefore, based on these data, PFO closure cannot be recommended as a means of improving nocturnal oxygenation.

3.5.5 Critique of methods

There was a trend towards a higher prevalence of PFO in OSA, although no statistically significant difference was detected. The number of OSA subjects in this study was greater than in any previous study, however, may not have been sufficient to detect a difference in prevalence. If this were the case, assuming a prevalence of PFO in OSA of 43% and in healthy controls of 30%, a sample size of 214 patients in each group would give 80% power to detect a difference at a significance level of 0.05.

OSA patients were recruited on the basis of sleep studies that were performed and scored using automated algorithms. Studies comparing automated with manual scoring have shown manual scoring to be more accurate (Ayappa et al., 2004; Cirignotta et al., 2001; Dingli et al., 2003b; Yin et al., 2006). Calleja et al compared respiratory polygraphy to full NPSG and found that the mean difference between the AHI obtained from both methods was smaller when the respiratory polygraphy data were scored manually (4 ± 14) than when using an automated algorithm (24 ± 30) (Calleja et al., 2002). However, automated scoring has been shown to have good correlation with manual scoring for severe OSA ($r = 0.949$; $p < 0.001$), but poor correlation for mild and moderate OSA (Yin et al., 2005). Therefore, the AHI generated from automated scoring of respiratory polygraphy studies from OSA patients were taken to be representative of severe OSA.

This study was limited to severe OSA patients, the pattern of PFO prevalence

and associated nocturnal desaturation may be different in those with mild to moderate OSA.

A possible confounding factor is the use of CPAP. OSA patients had been using CPAP for a median of 2 months (0 – 24 months). The longer duration of use may be associated with a reduction in upper airway oedema, hence reduce the severity of OSA. This may have influenced the frequency of PFO and size of shunt detected.

Six patients out of 18 identified with large PFO underwent closure. This small sample size may have limited the ability to detect a significant change in primary outcomes of ODI and percentage of time with $\text{SaO}_2 < 90\%$. Nevertheless, this is the first PFO closure study in severe OSA and it demonstrates that although technically difficult (successful closure was not achieved in 2 of 6 participants), the procedure can be safely performed in this group of patients, although it does not improve OSA.

3.5.6 Summary and conclusions

Study A demonstrated that the overall prevalence of PFO is not significantly increased in patients with severe OSA. However, a higher prevalence of PFO with large shunts was found compared to the control subjects. This may represent a pathophysiological consequence of increased right heart pressure. In patients with moderate to large shunts greater nocturnal desaturation was noted for a given respiratory disturbance however, there was no benefit from PFO closure. Based on these data, PFO closure cannot be recommended for treating intermittent hypoxaemia in OSA.

Chapter 4

Patent foramen ovale in severe chronic obstructive pulmonary disease

4.1 Introduction

Hypoxaemia in COPD is a consequence of both intrapulmonary factors including VQ mismatch, alveolar hypoventilation, impaired alveolar-end capillary diffusion to oxygen and intrapulmonary shunting; and extrapulmonary factors including cardiac output, inspired oxygen concentration and the metabolic oxygen demands of the body. The development of resting hypoxaemia is a poor prognostic marker independent of FEV₁ (Schols et al., 1998).

Currently, the only treatment which reduces mortality in severe, hypoxaemic COPD is long-term oxygen therapy (LTOT) (MRC, 1981; NOTT, 1980). This is prescribed for patients in whom resting PaO₂ on air is ≤ 7.3 kPa tested twice, 3 weeks apart, or ≤ 8 kPa with clinical evidence of cor pulmonale or sleep disordered breathing. Above these cut offs, there is no evidence to suggest that LTOT provides a mortality benefit (Gorecka et al., 1997). Despite the improvements in survival, pulmonary haemodynamics and cognitive function with LTOT, studies have indicated that this may be at the expense of deterioration in quality of life (Janssens et al., 1997). Perhaps as a consequence, treatment compliance is variable (Pepin et al., 1996). Furthermore the cost of oxygen therapy in the UK has been increasing since the 1980s (Calverley, 2000). The importance of finding alternative methods to control hypoxaemia in this patient group cannot be overstated. It may be possible that closure of PFO offers an adjunct treatment in these patients.

There have been 2 studies that have investigated the prevalence of PFO in COPD as discussed in Chapter 1. Both identified a higher prevalence of PFO in COPD compared to healthy controls: 70% versus 35%, $p < 0.05$ (Soliman et al., 1999) and 44% versus 20% (Hacievliyagil et al., 2006) $p < 0.01$. In addition,

Haceivliyagil and colleagues found that compared to COPD patients without PFO, those with PFO at rest had lower PaO₂ (6.8 (1.1) kPa versus 8.4 (1.5) kPa, $p < 0.001$), higher systolic pulmonary artery pressures (64.2 (25.5) mmHg versus 46.6 (13.8) mmHg, $p < 0.001$) and were also functionally impaired with shorter 6 minute walk test distances (246 (127) m versus 386 (156) m, $p < 0.001$). If this is the case, then it raises the question: in patients with severe COPD could identifying and closing PFO improve not only arterial oxygen tensions, but also functional status? Furthermore, could it reduce the requirement for LTOT? Prior to closing PFO in COPD, it is important to determine whether the presence of a RLS contributes to hypoxaemia and furthermore to understand the pathophysiology and phenotypic presentation of those patients with and without PFO in COPD.

The first aim of this chapter was to determine whether the prevalence of PFO in severe COPD (GOLD stage III or above) is higher in patients who are hypoxaemic compared to those with higher arterial oxygen tensions and a similar amount of lung function impairment. The second aim was to determine the prevalence of PFO in severe COPD and to accurately quantify the magnitude of associated shunt.

I conducted an observational study to test the hypotheses that:

1. Patients with severe COPD and PaO₂ ≤ 7.3 kPa have a higher prevalence of PFO with a greater magnitude of RLS compared to others with a similar degree of lung function impairment and PaO₂ > 8 kPa
2. Severe COPD patients have a higher prevalence of PFO compared to healthy controls

4.2 Methods

4.2.1 Subjects

COPD patients were recruited from the advanced COPD clinics at the Royal Brompton Hospital. Validation for the total number of patients recruited is given in the power calculation in Section 4.2.5. All recruited COPD patients met the inclusion criteria previously detailed in Chapter 2, Section 2.3.2. The data collected from healthy controls studied in Chapter 3 was also used for comparison in this study.

4.2.2 Protocol

Participants attended for one visit during which the following assessments were undertaken. Arterial blood samples were taken for resting ABG analysis (on air), a 6 minute walk test with oxygen saturation monitoring (ATS, 2002) was performed and full respiratory function tests involving spirometry, carbon monoxide gas transfer and whole body plethysmography were performed according to ATS/ERS guidelines (Macintyre et al., 2005; Miller et al., 2005a,b; Pellegrino et al., 2005; Wanger et al., 2005). Venous blood samples for full blood count and natriuretic peptides (Bozkanat et al., 2005; Leuchte et al., 2006) were taken. Contrast TTE and TCD were then performed on all patients.

4.2.3 Measurements

Contrast transthoracic echocardiography

Details of contrast TTE studies are given in Chapter 2, Section 2.4. In brief, standard echocardiographic image planes were acquired with ECG monitoring (Vivid 7, GE Healthcare, Chalfont St Giles, UK). Systolic pulmonary artery pressure was measured when possible. Contrast studies were performed in the four chamber view with the subject in the left lateral position. Agitated saline (8ml saline, 1ml autologous blood, 1ml air) contrast was injected in a single push via a cannula in an antecubital vein. Injections were performed at rest and during a Valsalva manoeuvre.

Contrast transcranial Doppler

Details of contrast TCD studies are given in Chapter 2, Section 2.5. In brief, the middle cerebral arteries were insonated bilaterally through the temporal bone windows and the probes secured in place. Contrast was injected at rest and during 2 Valsalva manoeuvres. Signals were recorded for 1 minute following contrast injection.

4.2.4 Data analysis

A PFO was defined as present if a shunt of any magnitude was detected following a Valsalva manoeuvre. PFO shunt capacity was graded as small, moderate or large in accordance with validated criteria (Spencer et al., 2004; Saqqur et al., 2004; Dowson et al., 2008). The size of shunt assigned to each PFO was the maximum shunt detected following a Valsalva manoeuvre. Pulmonary shunts were defined as present if a RLS developed after 5 cardiac

cycles following right heart opacification. Where there was a disagreement between TTE and TCD, the larger detected shunt was recorded (further details in Chapter 2, Section 2.4 and 2.5).

4.2.5 Statistical analysis

The aim of Study 2 was to examine the prevalence of RLS in COPD patients who are hypoxaemic ($\text{PaO}_2 \leq 7.3\text{kPa}$) compared to COPD patients who are less hypoxaemic ($\text{PaO}_2 > 8\text{kPa}$) with similar lung function impairment. Two studies investigating the prevalence of PFO in COPD detected PFO in 70% and 44% of COPD patients and 35% and 20% of healthy controls (Soliman et al., 1999; Hacievliyagil et al., 2006). The 2 studies were used in combination, to obtain a mean PFO prevalence of 57% in COPD and 27.5% in controls. It was assumed that the PFO prevalence in less hypoxaemic COPD patients was 27.5% and in hypoxaemic COPD patients was 57%, in a ratio of 2:1, a sample size of 63 patients with $\text{PaO}_2 > 8\text{kPa}$ and 31 patients with $\text{PaO}_2 \leq 7.3\text{kPa}$ was needed to achieve a power of 80% at a significance level of 0.05. A ratio of 2:1 enabled more patients who were potentially eligible for the exercise study in Chapter 5 to be recruited.

The same estimates of prevalence were used to calculate the sample size needed to compare COPD patients with healthy controls. Assuming PFO prevalence was 57% in COPD and 27.5% in healthy controls, 49 subjects were needed in each group to achieve 80% power to detect a difference at a significance level of 0.05. This was rounded up to 50 subjects.

Statistical analysis was performed using SPSS (version 16.0, SPSS Inc., Chicago, Illinois, USA). Parametric data are presented as mean (SD) and non-parametric as median (range).

Comparisons were made between data from hypoxaemic ($\text{PaO}_2 \leq 7.3\text{kPa}$) and less hypoxaemic ($\text{PaO}_2 > 8\text{kPa}$) COPD groups. Healthy volunteers were compared to the 50 youngest COPD patients (age 41 to 61 years) in order to ensure that the mean age of the two groups was not significantly different, since the prevalence of PFO is age dependent. The frequency and size of RLS between 1) hypoxaemic and less hypoxaemic groups and 2) COPD and healthy controls were compared using the Chi Squared test. Measurements between these groups were compared using the Student's t test (parametric data) or the Mann Whitney U test (non-parametric data).

A further subgroup analysis was performed by dividing all patients with COPD into 4 groups according to the type of RLS:

1. patients with no PFO or a small shunt through PFO,
2. patients with a moderate to large shunt through a PFO,
3. patients with only a pulmonary shunt,
4. patients with both a PFO and pulmonary shunt combined.

Analysis of variance (ANOVA) or the Kruskal Wallis test were used for continuous data and the Chi Squared test was used for categorical variables. This was an exploratory analysis. The study was not powered to answer this question.

Statistical significance was defined as $p < 0.05$.

4.3 Results

4.3.1 Subject characteristics

Two-hundred and seven severe COPD patients were approached; 17 declined to participate in the study and 5 patients did not attend more than 3 appointments and were not rescheduled. Of the 185 patients who were screened, 72 did not meet the inclusion criteria, therefore 113 (60%) patients were included in the study (Figure 4.1). Fifty healthy controls also studied in Chapter 3 were used for comparison (Section 3.2.1). Details of comorbidities of COPD patients are given in Table 4.1.

Baseline characteristics of COPD patients are given in Table 4.2. The mean age was 63 (8) years with a male predominance (70 male, 43 female). All patients had severe COPD with a mean FEV₁ 30.1 (9.8) % predicted. Gas exchange was impaired with mean TLCO of 31.9 (12.9) % predicted and patients were hyperinflated with TLC 128.2 (17.3) % predicted.

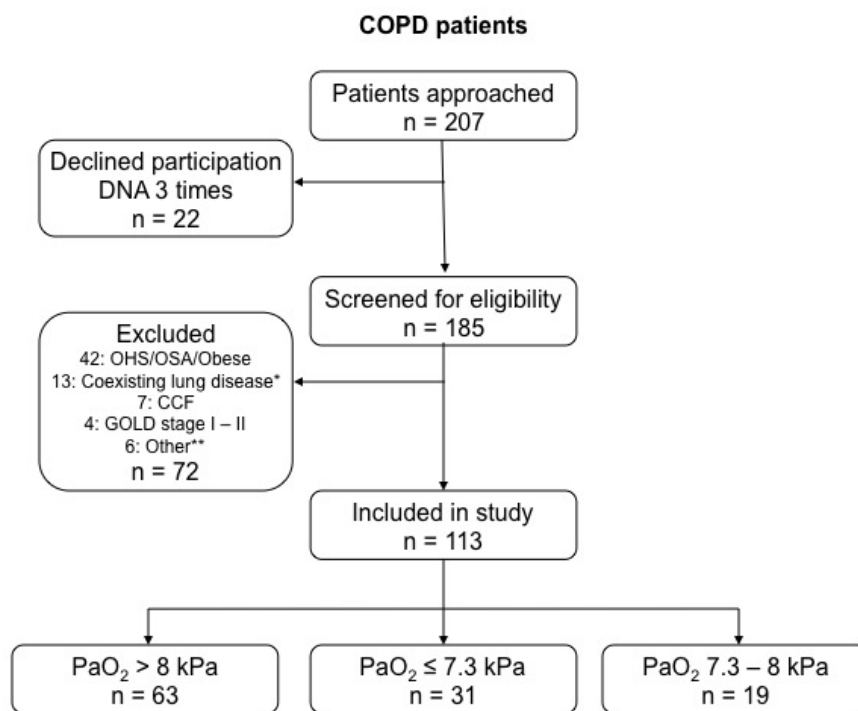


Figure 4.1: Diagram illustrating recruitment of severe COPD patients. DNA: did not attend, OHS: obesity hypoventilation, OSA: obstructive sleep apnoea, CCF: congestive cardiac failure. *5: unable to take oxygen off to take blood gas, 2: asthma, 1: tuberculosis, 1: diaphragm paralysis, 1: obliterative bronchiolitis, 1: asbestosis, 2: lung transplant. **5: $\text{PaO}_2 > 8\text{kPa}$ and group had reached recruitment target, 1: ABG phobia

Table 4.1: Comorbidities of COPD patients (n = 113)

Comorbidity	n
No identified cormorbidity	59
Ischaemic heart disease	8
Hypertension	16
Atrial fibrillation/flutter	6
Peripheral vascular disease	3
Previous stroke/transient ischaemic attack	3
Diabetes (type I and II)	2
Migraine	1
Depression	4
Osteoporosis	6
Gastroenterological	7
Musculoskeletal	6
Neurological	4
Other *	8

* *Prostate conditions (n = 3), hypothyroidism (n = 2), goitre (n = 1), cancer (n = 2)*

Table 4.2: Baseline characteristics of COPD patients

Characteristic	n = 113
Age (years)	63 (8)
Gender (male/female)	70 / 43
FEV ₁ (% predicted)	30.1 (9.8)
FVC (% predicted)	83.0 (19.5)
FEV ₁ /FVC	28.2 (7.5)
TLCO (% predicted)	31.9 (12.9)
KCO (% predicted)	43.1 (17.4)
TLC (% predicted)	128.2 (17.3)
RV (% predicted)	210.6 (49.9)
RV/TLC	61.9 (16.0)
FRC (% predicted)	182.2 (33.6)
BMI (kg/m ²)	24.5 (4.4)
PaO ₂ (kPa)	8.5 (1.6)
PaCO ₂ (kPa)	5.7 (1.1)

Values are expressed as mean (SD)

4.3.2 Prevalence of RLS in COPD patients with $\text{PaO}_2 \leq 7.3\text{kPa}$ and $> 8\text{kPa}$

The baseline characteristics of the hypoxaemic and less hypoxaemic group are given in Table 4.3. All COPD patients in the hypoxaemic group were on LTOT. Mean PaO_2 was 6.5 (0.7) kPa in the hypoxaemic group and 9.7 (1.0) kPa in the less hypoxaemic group. PaCO_2 was higher in the hypoxaemic group: 6.6 (1.4) kPa versus 5.2 (0.7) kPa, $p < 0.001$. There was no significant difference in age, gender, FEV_1 , FVC, FEV_1/FVC , TLC, RV, RV/TLC, FRC and BMI between the 2 groups. TLCO and KCO were lower in the hypoxaemic group at 24.6 (12.7) versus 34.4 (11.5) % predicted, $p = 0.001$ and 35.5 (15.3) versus 44.3 (14.2) % predicted, $p = 0.02$ respectively.

There was no difference in the prevalence of PFO or the magnitude of associated shunt at rest (Figure 4.2) or after Valsalva manoeuvre (Figure 4.3) in the hypoxaemic and less hypoxaemic groups.

The overall prevalence of PFO in the group with $\text{PaO}_2 \leq 7.3\text{kPa}$ compared to the group with $\text{PaO}_2 > 8\text{kPa}$ was 29% (9/31) versus 27% (17/63), $p = 0.99$ at rest and 39% (12/31) versus 52% (33/63), $p = 0.27$ after Valsalva manoeuvre. The overall prevalence of large shunts in the group with $\text{PaO}_2 \leq 7.3\text{kPa}$ compared to the group with $\text{PaO}_2 > 8\text{kPa}$ was 6% (2/31) versus 6% (4/63) at rest and 26% (8/31) versus 25% (16/63) after Valsalva manoeuvre.

Table 4.3: Baseline characteristics of COPD patients with $\text{PaO}_2 \leq 7.3\text{kPa}$ and $> 8\text{kPa}$

Characteristic	$\text{PaO}_2 \leq 7.3\text{kPa}$ n = 31	$\text{PaO}_2 > 8\text{kPa}$ n = 63	p value
Age (years)	63 (8)	62 (9)	0.42
Gender (male/female)	21 / 10	39 / 24	0.65
FEV ₁ (% predicted)	27.8 (11.9)	30.8 (9.1)	0.23
FVC (% predicted)	77.0 (21.9)	85.7 (19.4)	0.07
FEV ₁ /FVC	28.4 (7.5)	28.0 (7.9)	0.80
TLCO (% predicted)	24.6 (12.7)	34.4 (11.5)	0.001
KCO (% predicted)	35.5 (15.3)	44.3 (14.2)	0.02
TLC (% predicted)	127.3 (16.3)	130.6 (16.4)	0.40
RV (% predicted)	217.3 (50.9)	214.7 (50.0)	0.83
RV/TLC	67.7 (27.3)	60.0 (9.3)	0.18
FRC (% predicted)	187.1 (35.5)	184.6 (32.2)	0.75
BMI (kg/m^2)	25.3 (4.5)	24.0 (4.3)	0.22
PaO_2 (kPa)	6.5 (0.7)	9.7 (1.0)	< 0.001
PaCO_2 (kPa)	6.6 (1.4)	5.2 (0.7)	< 0.001

Values are expressed as mean (SD)

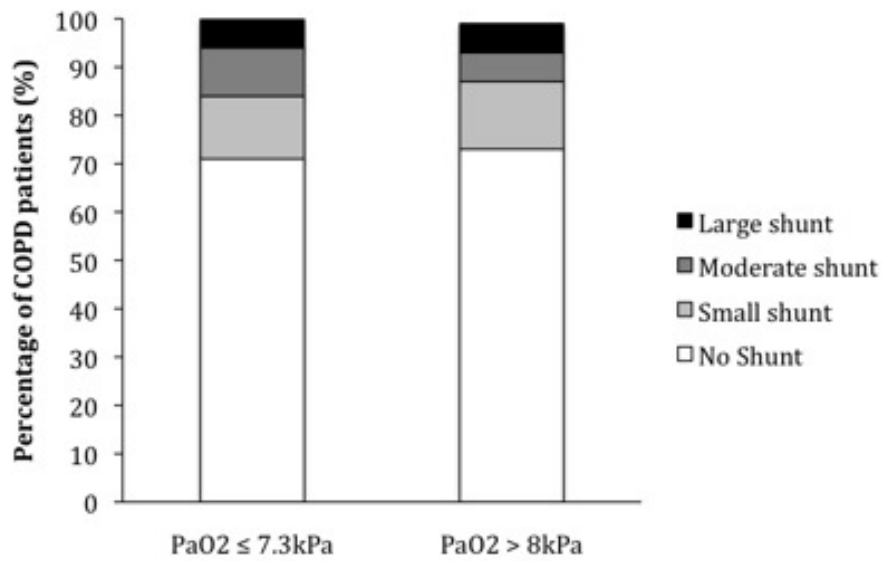


Figure 4.2: The percentage of COPD patients with PFO and the magnitude of associated shunt in patients with PaO₂ ≤ 7.3kPa and > 8kPa at rest. White bar: no shunt, light grey bar: small shunt, dark grey bar: moderate shunt and black bar: large shunt

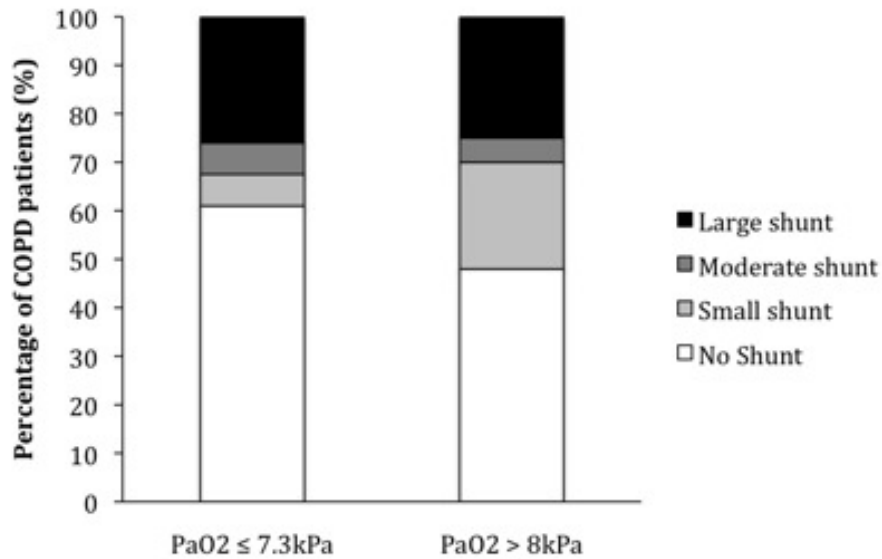


Figure 4.3: The percentage of COPD patients with PFO and the magnitude of associated shunt in patients with PaO₂ ≤ 7.3kPa and > 8kPa after Valsalva. White bar: no shunt, light grey bar: small shunt, dark grey bar: moderate shunt and black bar: large shunt

Forty-eight percent (15/31) of the hypoxaemic group had a pulmonary shunt compared to 24% (15/63) of the less hypoxaemic group, $p = 0.02$ (see Figure 4.4).

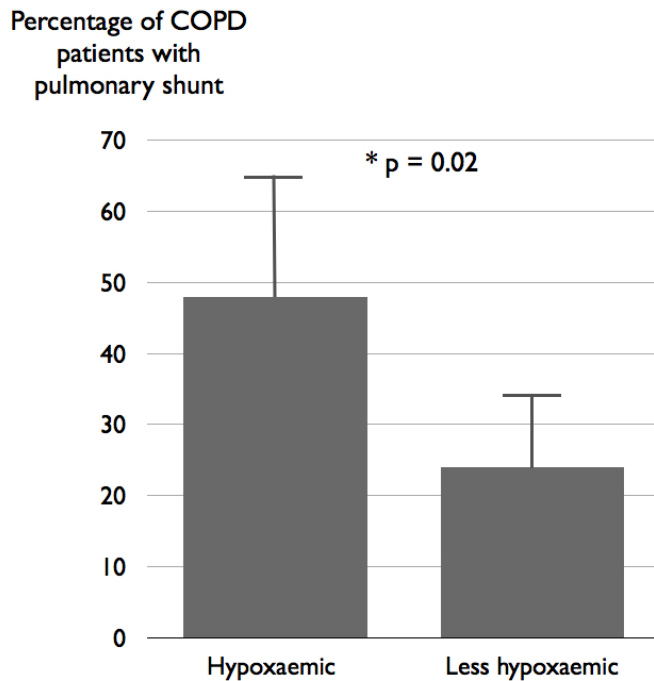


Figure 4.4: *Percentage of hypoxaemic ($\text{PaO}_2 \leq 7.3\text{kPa}$) and less hypoxaemic ($\text{PaO}_2 > 8\text{kPa}$) COPD patients with pulmonary shunts. Error bars represent 95% confidence intervals.*

4.3.3 Prevalence of RLS in COPD versus age matched control subjects

The baseline characteristics of the 50 youngest COPD patients studied and 50 healthy controls are given in Table 4.4.

Healthy controls and the youngest COPD patients had similar age, BMI and PaCO_2 . COPD patients had a higher proportion of female subjects, lower

Table 4.4: Baseline characteristics of COPD patients and healthy controls

	COPD n = 50	Healthy controls n = 50	p value
Age (years)	55 (5)	52 (11)	0.07
Gender (male/female)	27 / 23	42 / 8	0.002
FEV ₁ (% predicted)	29.4 (11.4)	101.4 (13.4)	< 0.001
FVC (% predicted)	81.0 (19.9)	104.2 (13.4)	< 0.001
FEV ₁ /FVC	28.6 (8.0)	78.8 (6.4)	< 0.001
BMI (kg/m ²)	24.3 (4.4)	24.3 (2.7)	0.98
PaO ₂ (kPa)	8.4 (1.7)	12.3 (1.4)	< 0.001
PaCO ₂ (kPa)	5.6 (1.3)	5.6 (0.5)	0.58

Values are expressed as mean (SD)

FEV₁, FVC, FEV₁/FVC and PaO₂.

The prevalence of PFO was not statistically different in COPD and healthy volunteers both at rest: 26% (13/50) versus 12% (6/50), $p = 0.12$ (Figure 4.5) and following Valsalva manoeuvre: 46% (23/50) versus 30% (15/50), $p = 0.15$ (Figure 4.6). The prevalence of large shunts following Valsalva was significantly higher in COPD patients compared to healthy controls: 26% (13/50) versus 6% (3/50), $p = 0.01$.

The prevalence of pulmonary shunt in COPD patients was numerically twice that in healthy controls but was not statistically significant: 24% (12/50) versus 12% (6/50), $p = 0.19$.

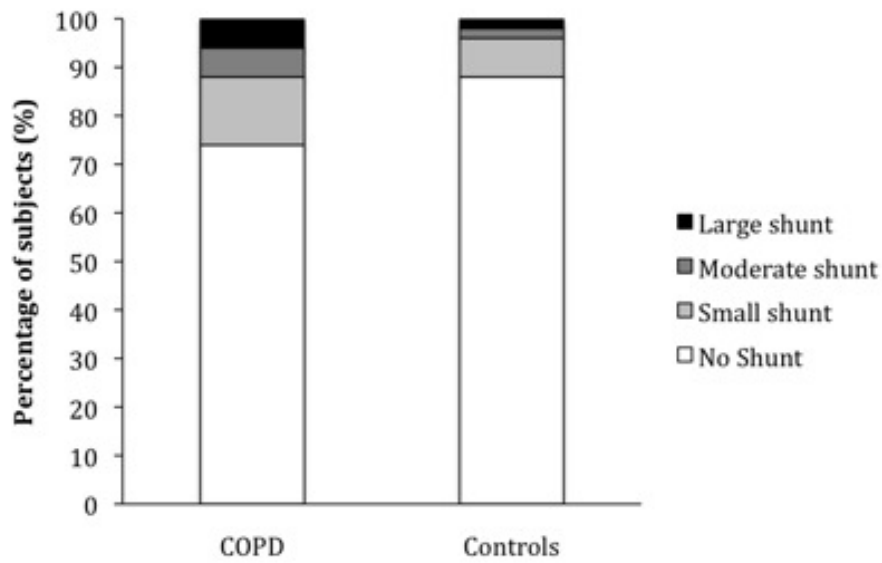


Figure 4.5: The percentage of subjects with PFO and the magnitude of associated shunt in COPD patients and healthy controls at rest. White bar: no shunt, light grey bar: small shunt, dark grey bar: moderate shunt and black bar: large shunt

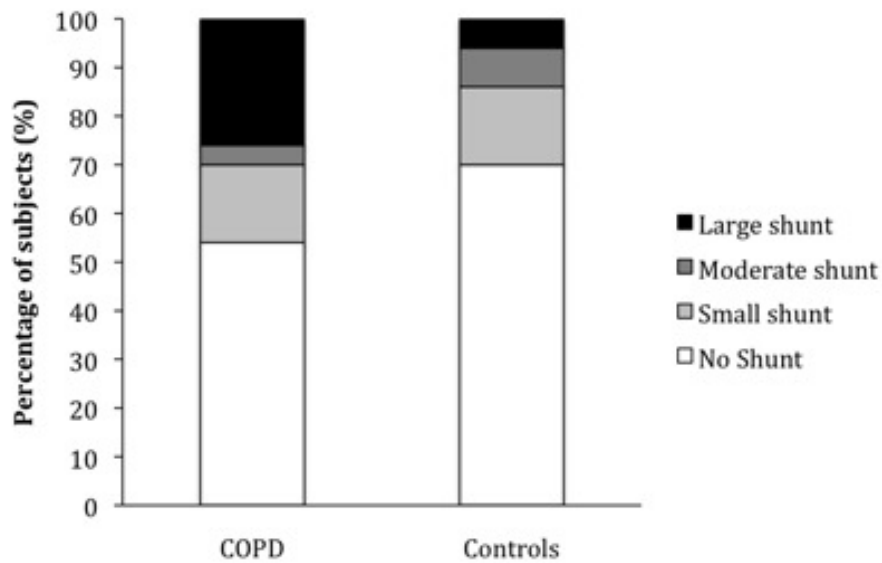


Figure 4.6: The percentage of subjects with PFO and the magnitude of associated shunt in COPD patients and healthy controls following Valsalva manoeuvre. White bar: no shunt, light grey bar: small shunt, dark grey bar: moderate shunt and black bar: large shunt

4.3.4 Overall prevalence of PFO in 113 COPD patients studied

Table 4.5 gives the PFO shunt sizes in the 113 COPD patients.

Table 4.5: PFO shunt size in COPD patients

	Magnitude of shunt through PFO (n (%))			
	No shunt	Small shunt	Moderate shunt	Large shunt
At rest	80 (71)	14 (12)	11 (10)	8 (7)
After Valsalva	54 (48)	22 (19.5)	6 (5)	31 (27.5)

If all 113 COPD patients studied were compared to healthy controls, the prevalence of PFO both at rest and following Valsalva manoeuvre was higher in COPD (rest: 29% (33/113) versus 12% (6/50), $p = 0.02$ and Valsalva: 52% (59/113) versus 30% (15/50), $p = 0.01$).

The prevalence of pulmonary shunts was 30% (34/113) which was also significantly higher than in healthy controls: 12% (6/50), $p = 0.02$.

4.3.5 Clinical features in COPD patients with different types of RLS

Forty-six COPD patients had no or small shunts through PFO, 33 had moderate to large shunts through PFO, 25 had pulmonary shunts and 9 had both PFO and pulmonary shunts. Clinical features of the patients in these groups are shown in Table 4.6.

The clinical features did not differ between the no/small shunt, moderate to large shunt and PFO plus pulmonary shunt groups. The pure pulmonary shunt group when compared to no/small shunt and moderate to large shunt groups had a lower PaO₂: $p = 0.002$ and $p = 0.02$, TLCO: $p = 0.005$ and $p = 0.001$ and KCO: $p = 0.002$ and $p = 0.002$ respectively.

Pulmonary artery pressure (PAP) measurement was possible in 41 COPD patients. The distribution of systolic PAP across the 4 groups with different types of RLS is shown in Figure 4.7. Systolic PAP was significantly higher in the pulmonary shunt group at 60 (33 – 115) mmHg when compared to the no/small PFO shunt group: 44 (29 – 72) mmHg, $p = 0.04$ and the moderate to large PFO shunt group: 38 (28 – 56) mmHg, $p = 0.003$.

Table 4.6: Clinical features in COPD patients with different RLS

	Type of RLS			
	No/small shunt n = 46	Moderate to large shunt n = 33	Pulmonary shunt n = 25	PFO and pulmonary shunt n = 9
Age (years)	62 (7)	62 (11)	63 (7)	67 (8)
FEV ₁ (% predicted)	28.1 (9.1)	31.9 (9.9)	30.0 (9.9)	34.0 (11.6)
FVC (% predicted)	81.6 (20.6)	82.8 (20.2)	84.0 (13.2)	88.5 (26.7)
FEV ₁ /FVC	26.9 (5.9)	30.6 (8.7)	27.2 (8.1)	29.0 (7.5)
TLCO (% predicted)	33.8 (10.8)	36.5 (13.1)	24.1(13.3)*	27.8 (11.7)
KCO (% predicted)	45.2 (11.6)	49.7 (21.6)	32.8 (16.0)*	37.9 (17.0)
TLC (% predicted)	127.9 (15.9)	123.9 (17.3)	134.0 (19.6)	129.0 (15.4)
RV (% predicted)	212.1 (50.8)	199.0 (46.5)	226.5 (53.3)	202.0 (42.3)
RV/TLC	63.9 (22.9)	59.1 (9.1)	62.2 (8.9)	61.2 (8.8)
FRC (% predicted)	182.7 (32.3)	173.0 (29.6)	194.7 (39.3)	178.1 (31.3)
BMI (kg/m ²)	25.0 (4.2)	25.4 (4.9)	22.7 (4.1)	23.3 (3.2)
6MWT distance (m)	275 (139)	304 (104)	237 (126)	331 (159)
PaO ₂ (kPa)	8.9 (1.7)	8.6 (1.4)	7.6 (1.6)*\$	8.5 (1.4)
PaCO ₂ (kPa)	5.6 (1.2)	5.8 (1.0)	5.9 (1.4)	5.4 (0.8)
BNP	11 (26)	11 (10)	9 (8)	8 (7)

Values are expressed as mean (SD)

* $p < 0.01$ compared to no/small shunt and moderate to large shunt groups, \$ $p = 0.02$ compared to moderate to large shunt group

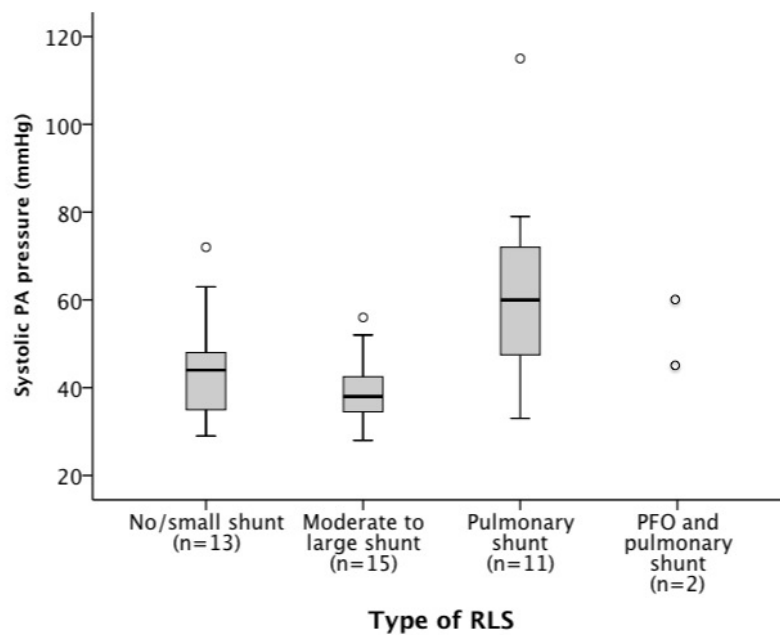


Figure 4.7: *Systolic pulmonary artery pressure measured in COPD patient with different types of RLS. ○ represent outliers*

4.4 Discussion

This study shows that PFO prevalence was similar between hypoxaemic and less hypoxaemic COPD patients. This result implies that severe COPD patients with normal left ventricular function are hypoxaemic primarily due to pulmonary factors. The second main finding is that intrapulmonary shunts were more prevalent in the hypoxaemic group compared to those with higher PaO_2 . Interestingly, it was the pulmonary shunt group and not those with moderate to large shunting through PFO that had higher systolic pulmonary artery pressures (PAP). In keeping with the elevated PAP, carbon monoxide gas transfer was also worse. PFO with large shunts were more prevalent in COPD patients than healthy controls.

4.4.1 Significance of patent foramen ovale in COPD

The findings of this study do not support the hypothesis that hypoxaemic COPD patients have a higher prevalence of PFO than those with higher PaO₂. Furthermore, all magnitudes of shunt size, both at rest and after Valsalva, were similar amongst both groups. Soliman et al studied 20 patients with severe COPD and found that baseline SaO₂ in 14 patients with PFO was similar to the 6 patients without PFO: 93.9 (2.1) % versus 93.8 (2.3) %, $p > 0.05$ (Soliman et al., 1999). Kilic et al studied 20 mild COPD patients (FEV₁ > 50%) who were found to have disproportionate hypoxaemia in relation to their lung disease with resting PaO₂ < 10.7kPa and SaO₂ < 95% (Kilic et al., 2010). PFO were detected in only 20% (4/20) of patients and PaO₂ was similar to those without PFO 7.7 (0.9) kPa versus 6.2 (1.8) kPa, $p > 0.05$. Although these are small studies, taken together, they suggest that the amount of RLS of mixed venous blood is insufficient to significantly decrease resting PaO₂ in patients with COPD.

The findings of the present study are also inconsistent with the hypothesis that the overall PFO prevalence is greater in COPD patients than in the general population. My findings showed overall prevalence was not statistically different. However, PFO with large shunts were more prevalent in COPD patients than in healthy controls, suggesting that existing PFO tunnels are being "stretched" and enlarged. The intermittent elevations in PAP causing right ventricular diastolic dysfunction and elevations in right atrial pressure could offer an explanation for this finding. Estimates of the prevalence of pulmonary hypertension in COPD vary considerably depending on the population studied and the method used to detect elevated PAP (Chaouat et al., 2005; Christensen et al., 2004; Scharf et al., 2002; Kessler et al., 2001; Thabut et al., 2005). Severe elevations are uncommon and if present, point to

other precipitating diagnoses. In general, PAP in COPD is mildly elevated with intermittent increases during exacerbations (Abraham et al., 1969) or with exercise (Butler et al., 1988; Horsfield et al., 1968; Fletcher et al., 1989). Nevertheless, these chronic, intermittent increases in right ventricular afterload and ensuing right heart strain could be enough to promote RLS with the PFO enlarging as a consequence of the increased blood flow through it. Another important explanation is the effect of significant swings in intrathoracic pressure during exercise as described in Section 1.3.2. The exaggerated pleural pressure swings increase transmural pressure gradients across the thin walled atria. This should affect left and right atria equally, however when accompanied by the increase in venous return to the right atrium and the increases in right ventricular afterload, it is possible that the pressure within the right atrium increases more than that of the left, therefore increasing the RLS and stretching a PFO.

The data presented in this Chapter showed patients with moderate to large shunts had similar 6 minute walk test distances to those with no/small shunts. Furthermore, the clinical features were similar in the 2 groups with the greatest functional impairment detected in patients with intrapulmonary shunts. Haceivliyagil et al suggested that COPD patients with PFO at rest are functionally impaired with lower 6MWT, lower PaO₂ and higher systolic PAP compared to those with no PFO shunt at rest. The methodology in their study clearly defined the criteria for contrast TTE detection of PFO, but provided no criteria for intrapulmonary shunt detection, hence they did not report any pulmonary shunts in their cohort of 52 severe COPD patients. By definition, intrapulmonary shunts are present at rest and unaffected by Valsalva. Thirty percent (34/113) of COPD patients studied in this chapter had evidence of pulmonary shunting, therefore, it may be possible that patients with PFO at rest in the study by Haceivliyagil et al included patients with pulmonary

shunts. This could explain the inconsistency with their findings and the data presented above.

The findings in this chapter show that PFO do not exacerbate hypoxaemia, do not increase functional impairment and may offload the right heart at times of stress; rather than worsen outcomes as suggested in previous studies, which raises the question: could the presence of a PFO be beneficial?

Zierer et al conducted a study in 8 dogs whereby a pulmonary artery band was progressively inflated over the course of 3 months to induce chronic pulmonary hypertension (Zierer et al., 2009). An 8mm shunt prosthesis was inserted between the atria, which was controlled to obtain 3 models of atrial septostomy: 1) no shunt, 2) a low flow shunt directing 15% cardiac output through to left atrium and 3) a high flow shunt directing 29% cardiac output through the septum. The authors found that compared to no shunt, the low flow state increased right atrial compliance, increased cardiac output and despite a decline in oxygen content due to the RLS, there was a trend towards improved systemic oxygen delivery. The high flow state also reversed the beneficial effects suggesting 29% cardiac output exceeded the ideal shunt fraction. The presence of a PFO in conditions causing elevations in PAP such as COPD could mimic the low flow state improving cardiac haemodynamics and systemic oxygenation.

4.4.2 Prevalence and significance of intrapulmonary shunts in COPD

The prevalence of intrapulmonary shunts was significantly higher in the hypoxaemic patients compared to the less hypoxaemic patients. Furthermore, patients with pulmonary shunts had lower PaO₂, higher systolic PAP and

lower transfer factors compared to those with moderate to large shunts.

Intrapulmonary shunts in healthy humans are well described but relatively understudied. In healthy humans, there is evidence that pulmonary shunts are dynamic in nature, opening up at maximal exercise (Eldridge et al., 2004; Lovering et al., 2008; Stickland et al., 2004) and when moving from the upright to supine position (Stickland et al., 2004). In addition, breathing hypoxic air opens inducible arteriovenous shunts in a dose dependent manner with increased shunting as the oxygen concentration of the inhaled gas mixtures decreases (Laurie et al., 2010); complete cessation of shunting occurs on return to breathing room air. Furthermore, hyperoxia prevents arteriovenous shunting during exercise in healthy humans (Lovering et al., 2008). It is unclear why this occurs, but several theories exist. The first postulates that opening the pathway results in a true shunt that worsens arterial hypoxemia. The second is that intrapulmonary shunts behave like the ductus arteriosus which remains patent in utero in conditions where PvO_2 is approximately 17 Torr (Siggaard-Andersen and Huch, 1995) and seals shut when breathing room air increases the PvO_2 to 40 Torr. The uterine conditions are replicated by exercise, which lowers PvO_2 , therefore opening intrapulmonary shunts. The third is that arteriovenous connections open with elevated PAP to allow passage of blood through an increasingly fixed pulmonary circulation (Laurie et al., 2010).

The COPD patients with intrapulmonary shunts in this chapter had lower PaO_2 and higher PAP. This supports the above mechanisms that suggest pulmonary arteriovenous connections are modulated by arterial hypoxaemia and elevations in PAP.

4.4.3 Methodological considerations

Although prevalence of PFO in COPD appeared greater when compared to controls, this did not reach statistical significance; thus the sample size in this study may have been too small. If PFO prevalence is 46% in COPD and 30% in healthy controls, 143 subjects are needed in each group to have 80% power to detect a difference at a significance level of 0.05.

The NOTT trial showed that LTOT is associated with modest improvements in pulmonary haemodynamics (NOTT, 1980). This could be a potential source of bias in the hypoxaemic patients on oxygen therapy. To minimise any influence from this potential confounder, all ABG and contrast measurements and where possible 6MWT were performed off oxygen.

4.4.4 Summary

This study has shown that in severe COPD, hypoxaemic patients have a similar prevalence of PFO to COPD patients who are less hypoxemic, but have a higher prevalence of intrapulmonary shunts. COPD patients with intrapulmonary shunts have lower PaO₂, decreased carbon monoxide transfer factor and higher PAP. These data do not address the question of whether the intrapulmonary shunt is a consequence of more severe COPD or a cause.

Chapter 5

Patent foramen ovale in severe chronic obstructive pulmonary disease during exercise

5.1 Introduction

As COPD progresses, the inability to perform the activities of daily living through exercise intolerance forms one of the most distressing symptoms and frequently leads to social isolation and immobility. Reduction in the 6 minute walk distance is an independent predictor of mortality (Pinto-Plata et al., 2004). Although ventilatory limitation is the main contributing factor, little is understood of the pathophysiology of cardiopulmonary interactions during exercise in COPD, in particular, the effect of right to left intracardiac shunting through a PFO. The presence of a PFO in COPD has been associated with shorter 6 minute walk distances and higher dyspnoea scores (Hacievliyagil et al., 2006). Notably, a PFO with shunting at rest conferred the greatest compromise. This suggests the physiological consequences of a RLS in COPD decrease exercise capacity.

In healthy humans, RLS during exercise is unlikely as left atrial pressure exceeds right atrial pressure. In COPD, there are several factors which lead to a reversal of this pressure gradient. Firstly, during exercise, pulmonary vascular resistance and pulmonary artery pressure rise (Schonhofer et al., 2001; Raeside et al., 2002). Right ventricular end-diastolic volume increases; however, right ventricular ejection fraction remains static (Mahler et al., 1984; Light et al., 1984). The exercise induced increase in right ventricular preload and afterload lead to an elevated right atrial pressure. In the presence of a PFO, this could result in a RLS. It is thought that this potentially offloads the right heart by acting as a pressure-release valve and maintains cardiac output albeit at the expense of systemic desaturation.

Secondly, because lung emptying in COPD requires more time due to the effects of increased airways resistance and reduced elastic recoil; gas trapping

and dynamic hyperinflation is a well recognised phenomenon. Because the chest wall cannot fully recoil towards functional residual capacity there is continuous intrinsic positive expiratory pressure (PEEPi). The negative pressure generated in the following inspiratory breath needs to overcome this PEEPi and in doing so will promote venous return, deliver a volume load to the right ventricle and potentially increase RLS through a PFO. A RLS results in the addition of deoxygenated, acidaemic, and hypercapnic rich blood to the systemic circulation. In order to maintain pH and PaCO₂ homeostasis, arterial chemoreceptors in the carotid bodies are stimulated to increase ventilation. This would in turn increase dynamic hyperinflation and cause further shunting.

Thirdly, abdominal muscle recruitment during exercise is common in patients with COPD (Kyroussis et al., 2000). Contraction of these muscles in expiration may lead to pleural pressures in excess of 40 cmH₂O effectively producing a Valsalva manoeuvre. The negative pressure that is generated to overcome this mini-Valsalva during inspiration would increase venous return and could promote RLS.

The aim of this study was to conduct a physiological investigation during exercise in patients with COPD firstly to determine whether right to left shunting increases during exercise, secondly to investigate the impact of a RLS through PFO on oxygen saturations and exercise endurance and thirdly to examine the effect of intrathoracic pressure swings on the magnitude of the RLS.

I tested the following hypotheses:

1. Right to left shunting through PFO increases from baseline during exercise in COPD
2. During exercise, patients with severe COPD and a PFO experience greater desaturation and have reduced exercise endurance compared to those without a PFO
3. During exercise in severe COPD, increased swings in intrathoracic pressure are associated with increased right to left shunting through a PFO

5.2 Methods

5.2.1 Subjects

Patients meeting the inclusion criteria from those studied in Chapter 4 were invited to take part. The power calculation is given in Section 5.2.5. All subjects met the inclusion criteria specified in Section 2.3.2.

5.2.2 Protocol

The protocol outlined below took 6 hours, patients attended for one day. Patients were asked to rest for one hour prior to the study. A symptom limited, incremental work rate cardiopulmonary exercise test was undertaken on a cycle ergometer to determine 60% peak work rate (further details of the incremental work rate test are in Chapter 2, Section 2.11.2). This work rate, determined for each individual, was maintained for the 2nd exercise test.

Participants then had a break of one hour. During this time, oesophageal and gastric balloon catheters were inserted (further details of balloon catheters are in Chapter 2, Section 2.12), the TCD headset was secured, the probes were positioned (further details regarding TCD are in Chapter 2, Section 2.5.2) and an intravenous cannula was inserted in the left antecubital fossa.

Prior to starting the exercise protocol, agitated saline was injected at rest and during a Valsalva manoeuvre to record the magnitude of baseline RLS. The patients then undertook a continuous work rate cardiopulmonary exercise test on a cycle ergometer with metabolic testing to record breath by breath gas exchange measurements, ECG and oximetry (further details of the continuous work rate test are in Chapter 2, Section 2.11.2). Oesophageal (P_{oes}) and gastric

(P_{gas}) pressure measurements were recorded throughout the test. The exercise protocol comprised 2 minutes of rest, 2 minutes of unloaded cycling and then continuous exercise at 60% peak work rate. Agitated saline contrast was injected at 2 minute intervals during the protocol. Earlobe capillary blood samples were taken before and at the end of exercise.

Patients were then free to have lunch. Following this after a break of at least one hour, full respiratory function tests including spirometry, carbon monoxide gas transfer and whole body plethysmography were performed according to ATS/ERS guidelines (Macintyre et al., 2005; Miller et al., 2005a,b; Pellegrino et al., 2005; Wanger et al., 2005).

5.2.3 Measurements

Cardiopulmonary exercise test

A snorkel mouthpiece connected to an Oxycon device (Jaeger, Germany) was used for breath by breath metabolic measurements. Metabolic data, heart rate and pulse oximetry data were measured throughout exercise.

Contrast transcranial Doppler measurements

TCD measurements were obtained as outlined in Chapter 2, Section 2.5.2. In brief, the middle cerebral arteries were insonated bilaterally through the temporal bone windows and the probes were secured using an adjustable head frame. Agitated saline contrast was injected into the left antecubital vein at 2 minute intervals during exercise and recovery.

Pressure catheter measurements

Oesophageal and gastric pressures (P_{oes} and P_{gas}) were recorded to investigate the relationship between intrathoracic pressures, transdiaphragmatic pressure ($P_{di} = P_{gas} - P_{oes}$), expiratory abdominal muscle recruitment and RLS. This was performed as described in Chapter 2, Section 2.12. In brief, 2 balloon catheters were inserted via the nose into the oesophagus and stomach (Kyroussis et al., 2000; Hopkinson et al., 2005). The catheters were connected to differential pressure transducers, the signals were amplified and converted from analogue to digital then displayed graphically on a computer for analysis.

5.2.4 Data analysis

60% peak work rate

The peak work rate was defined as the maximum work rate in Watts maintained for greater than 8 breaths on the incremental work rate cardiopulmonary exercise test. 60% peak wattage was calculated and rounded to the nearest multiple of 5 Watts. This rate was used for the continuous exercise test.

Magnitude of right to left shunt

PFO shunt size was graded in accordance with validated criteria detailed in section 2.5.3. In order to detect small increases in shunting, the original 5 point grading scale described by Spencer et al was used (Spencer et al., 2004). The time of each microbubble injection was noted and shunt size was analysed offline after the test.

Pressure data

Pressure data were analysed as outlined in Chapter 2, Section 2.12.5. All measurements were averaged for eight breaths starting at the time when the microbubbles were injected. Measurements were made offline from the raw exercise pressure traces. Peak and trough P_{oes} , P_{gas} and P_{di} , were recorded. In addition, swing in P_{oes} (peak P_{oes} – trough P_{oes}) was calculated. Abdominal muscle recruitment was measured as the difference between peak expiratory P_{gas} and P_{gas} at the start of expiration. If there was no recruitment, a value of 0 was assigned.

5.2.5 Statistical analysis

The aim of this study was to investigate whether shunting increased during exercise and the impact of this on exercise endurance. Using data from the study by O'Donnell et al (O'Donnell et al., 2001a) the exercise time in COPD patients with a PFO was estimated to be 4.1 minutes (± 3.6) and in those with no PFO it was estimated to be 8.8 minutes (± 3.6). These values yielded sample sizes of 10 patients in each group to achieve 80% power to detect a difference at a significance level of 0.05.

The change in RLS, oxygen saturations, exercise duration and intrathoracic pressure between the PFO and no RLS groups was compared using the Student's t test for parametric data and Mann Whitney U test for non-parametric data. Spearman's rank correlation coefficient was calculated to determine whether the measured respiratory variables correlated with the amount of RLS during exercise.

5.3 Results

5.3.1 Subject characteristics

COPD patients were recruited from those studied in Chapter 4. Twenty-nine COPD patients with no evidence of RLS and 33 COPD patients with significant shunts through PFO were approached. Of those with no RLS, 10 declined, 2 did not have adequate TCD signals and 7 did not meet the inclusion criteria. Ten patients completed the exercise protocol, however 1 patient was excluded due to the development of a significant pulmonary shunt with subsequent detection of multiple pulmonary emboli. Two patients developed a grade 1 shunt but were included as the amount of shunting was negligible. Nine patients were included in the final analysis. Of the 33 patients with PFO, 13 patients declined, 2 patients did not have adequate TCD signals and 7 patients did not meet the inclusion criteria. One had a pulmonary shunt coexisting with a PFO and one patient felt faint during the exercise protocol, which was terminated prematurely. Nine patients completed the exercise protocol and were included in the study. Details of patient selection are shown in Figure 5.1.

Assessments made on COPD patients recruited for the exercise study in this chapter compared to those made when initially studied in Chapter 4 are given in Appendix G, Table G.1. No significant differences were found.

The baseline characteristics of patients studied in the exercise tests are given in Table 5.1. All baseline characteristics including age, gender, spirometry, gas transfer, lung volumes, PaO₂ and PaCO₂ were similar ($p > 0.05$) in both patients with PFO and patients with no significant RLS.

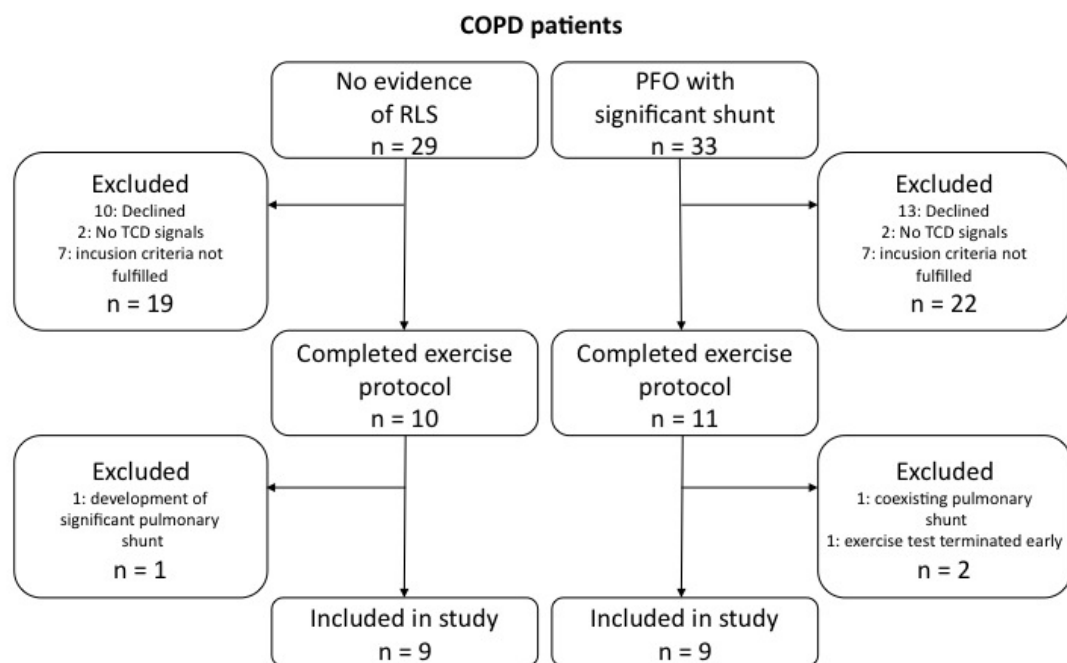


Figure 5.1: *Diagram illustrating recruitment of COPD patients for the exercise study. TCD: transcranial Doppler*

Table 5.1: Baseline characteristics of no significant RLS and PFO groups

	No significant RLS	PFO	Student t test
	n = 9	n = 9	p value
Age (years)	61 (6)	65 (9)	0.29
Gender (male/female)*	6 / 3	4 / 5	0.64
FEV ₁ (% predicted)	32.8 (14.1)	34.8 (10.6)	0.75
FVC (% predicted)	94.0 (12.9)	90.8 (16.6)	0.66
FEV ₁ /FVC	26.9 (8.9)	30.2 (8.6)	0.44
TLCO (% predicted)	40.2 (14.1)	40.3 (10.5)	0.99
KCO (% predicted)	49.0 (15.3)	51.9 (18.3)	0.72
TLC (% predicted)	131.4 (18.1)	126.0 (18.6)	0.54
RV (% predicted)	212.3 (62.4)	190.8 (46.1)	0.42
RV/TLC (%)	56.1 (7.6)	57.4 (7.6)	0.74
FRC (% predicted)	184.4 (47.6)	170.8 (36.3)	0.51
BMI (kg/m ²)	27.1 (5.4)	26.6 (6.5)	0.85
PaO ₂ (kPa)	9.7 (1.0)	9.6 (1.3)	0.90
PaCO ₂ (kPa)	5.1 (0.4)	5.2 (0.4)	0.50

*Values are expressed as mean (SD), *Chi squared test used*

5.3.2 RLS at baseline, during continuous work rate exercise and in recovery

PFO group

There was a significant increase in shunt size during exercise from minute 1 to 3: grade 1(1) to grade 2 (2), $p = 0.008$; minute 1 to 5: grade 1(1) to grade 3(2), $p = 0.001$; minute 1 to 7: grade 1(1) to 3(2), $p = 0.003$ and from minute 3 to 5: 2(2) to 3(2), $p = 0.023$ (Figure 5.2). Shunt size peaked in the 5th minute and reached a plateau for the remaining duration of exercise. There was no significant difference between shunt size during the final stage of exercise and the first minute of recovery ($p = 0.59$). Shunt size appeared to gradually decline for the remainder of recovery, however this did not reach statistical significance.

Right to left shunting increased during exercise in 8 out of 9 patients (see Table 5.2, Figure 5.4). The remaining patient (Table 5.2, Figure 5.4, PFO group, patient 7) had no shunt at rest, a grade 5 shunt after Valsalva and did not develop any shunt during exercise. Interestingly, a grade 3 shunt developed in the first minute of recovery, which eventually decreased to a grade 2 shunt with the last recovery injection. Patient 6 in Table 5.2 (PFO group) and Figure 5.4 also experienced an increase in shunt size in the first recovery injection.

No significant RLS group

There was no increase in shunting beyond an insignificant, grade 1 shunt during exercise in 7 out of 9 patients, which persisted into recovery in 3 patients. Shunt size was not significantly different from baseline to exercise to recovery (Table 5.2, Figure 5.3 and Figure 5.5).

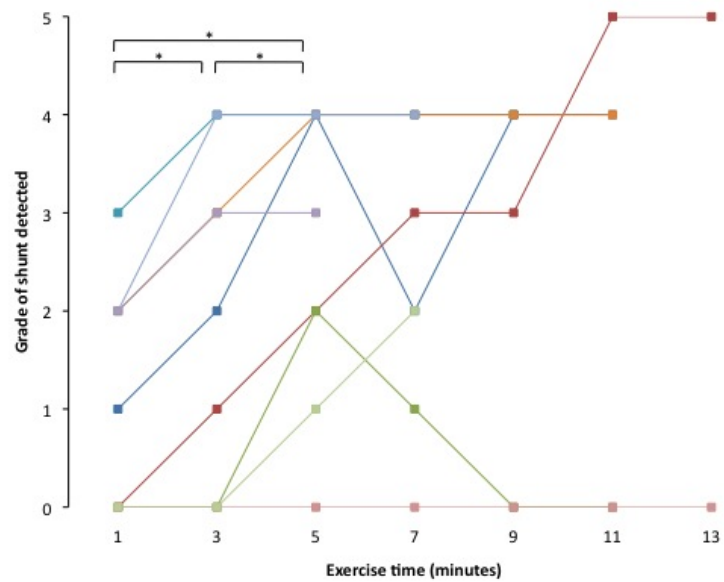


Figure 5.2: Grade of shunt detected by contrast TCD during continuous work rate exercise in the PFO group. Minute 1 is rest and minute 3 is unloaded cycling.
* $p < 0.05$

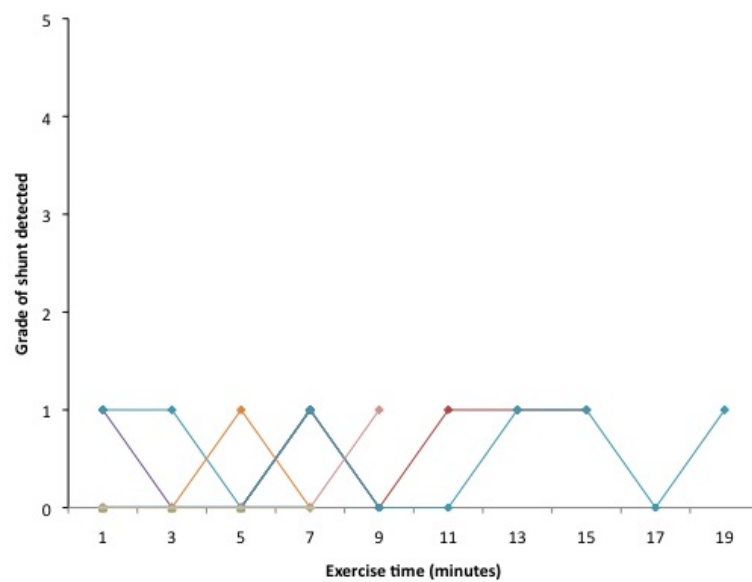


Figure 5.3: Grade of shunt detected by contrast TCD during continuous work rate exercise in the no significant RLS group. Coloured diamonds are individual values. Minute 1 is rest and minute 3 is unloaded cycling.

Table 5.2: Individual values for shunt size at baseline, during exercise and in recovery

	Grade of shunt PFO group n = 9										Grade of shunt No significant RLS group n = 9									
Patient	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9		
Baseline																				
Rest	2	0	0	3	3	1	0	0	0	0	0	0	0	0	0	0	0	0		
Valsalva	5	5	5	5	4	5	5	2	4	0	0	0	0	1	1	0	0	0		
Exercise time (mins)																				
1	1	0	0	3	2	2	0	0	2	0	0	0	1	1	0	0	0	0		
3	2	1	0	4	3	4	0	0	3	0	0	0	0	1	0	0	0	0		
5	4	2	2	4	4	4	0	1	3	0	0	0	0	0	1	0	0	0		
7	2	3	1	4	4	4	0	2		1	1	1	1	1	0	0	0	0		
9	4	3	0	4	4		0			0	0			0			1	0		
11	4	5	0		4		0				1			0						
13		5					0				1			1						
15											1			1						
17														0						
19														1						
Recovery (mins)																				
1	4	5	0	4	3	5	3	2	2	0	0	0	0	1	1	0	0	0		
3	4	1	0	3	2	4	0	1	3	0	0	0	0	1	0	0	0	0		
5	2	0	1		3	3	1	1	2	0	0	0	1	0	0	0	0	0		
7	3				3	2	2	0	2	0					0		0			
9									2											

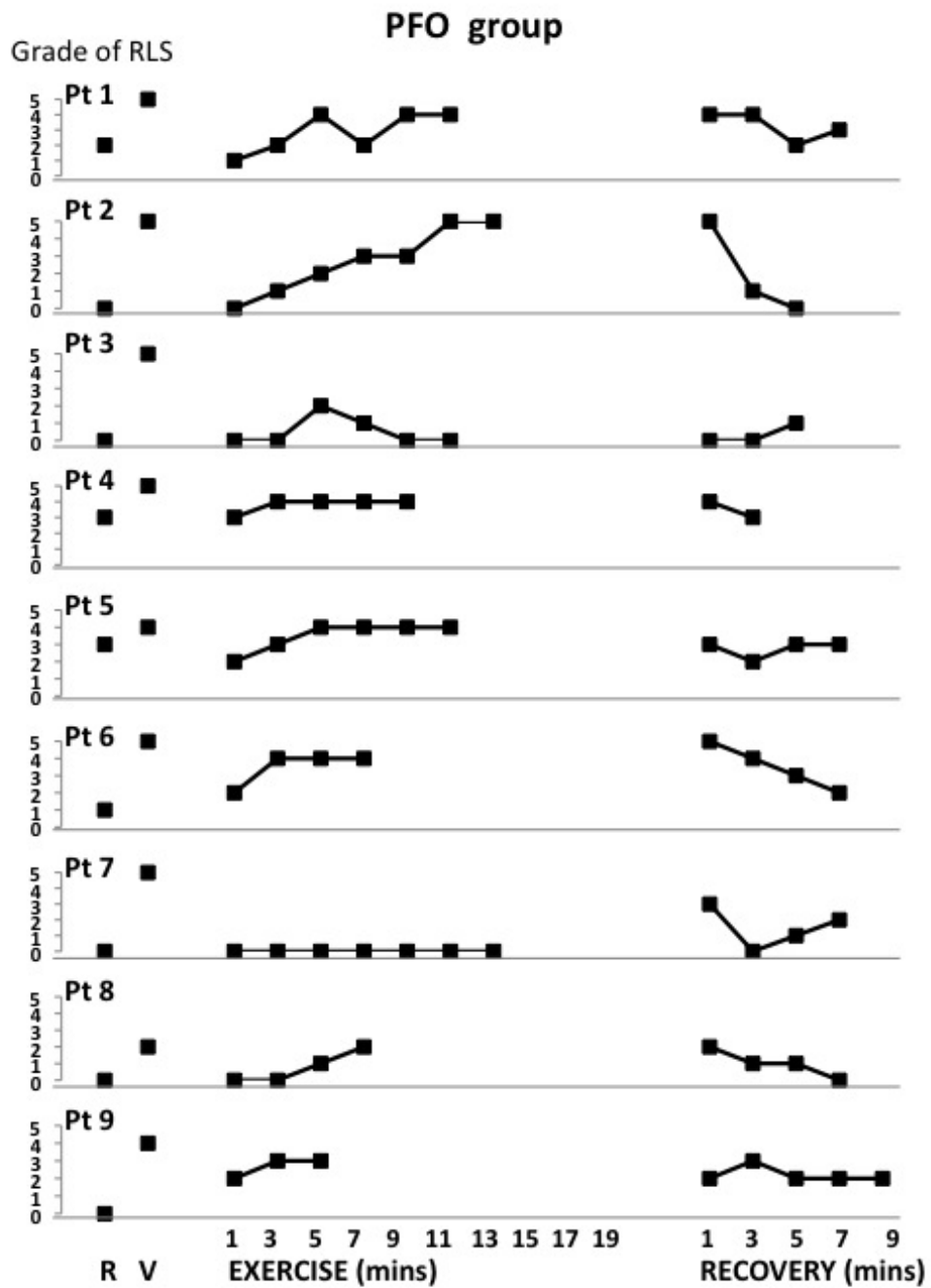


Figure 5.4: Grade of shunt detected by contrast TCD during continuous work rate exercise in the PFO group. Black squares are individual values, Minute 1 is rest and minute 3 is unloaded cycling. R: rest, V: Valsalva

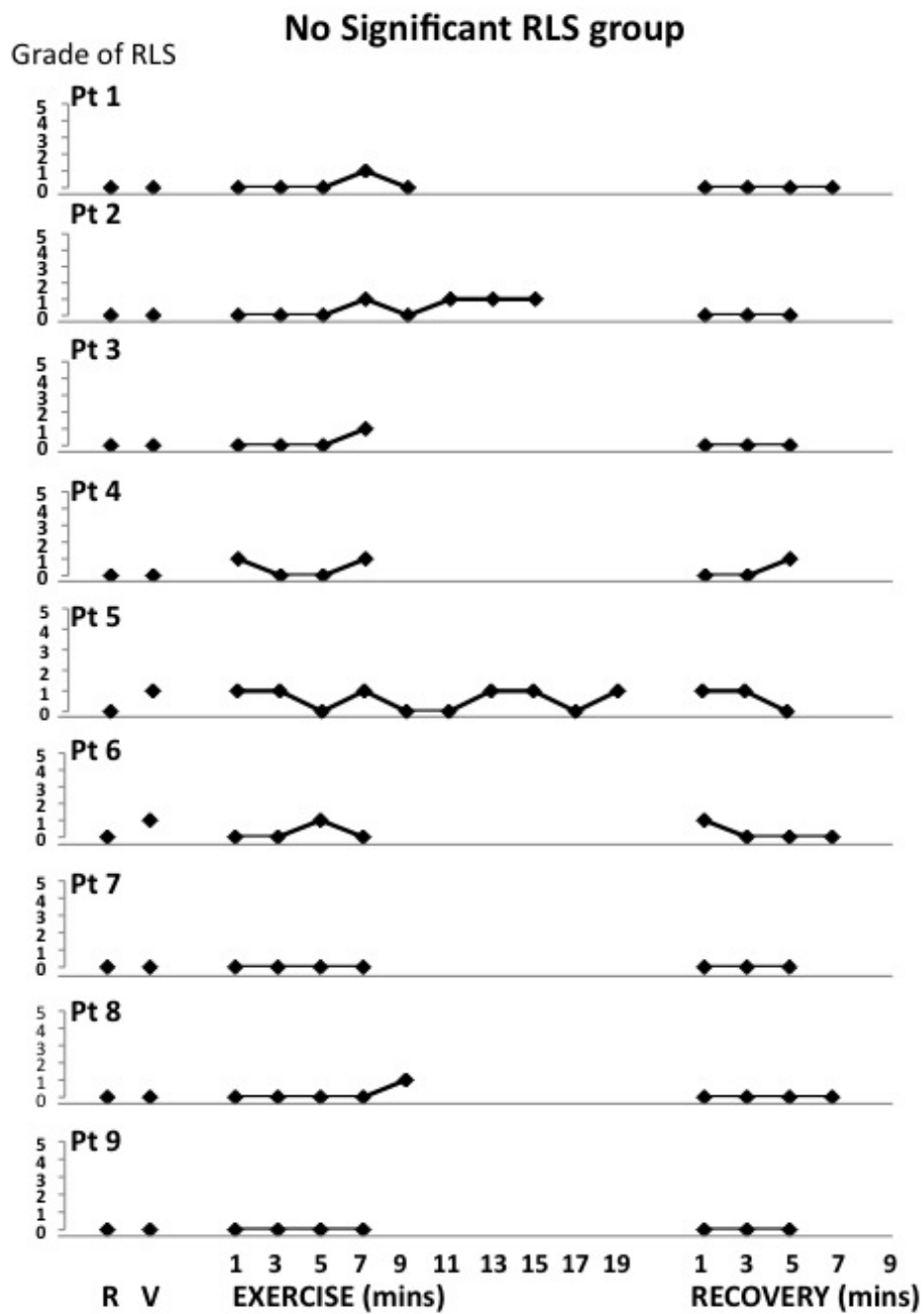


Figure 5.5: Grade of shunt detected by contrast TCD during continuous work rate exercise in the no significant RLS group. Black diamonds are individual values, Minute 1 is rest and minute 3 is unloaded cycling. R: rest, V: Valsalva

5.3.3 Exercise measurements

Initial incremental exercise test

Baseline and peak exercise measurements for the initial incremental exercise test from which the work rate for the continuous tests were derived are given in Table 5.3. Patients with PFO achieved a maximum load of 26 (10) Watts compared to 33 (12) Watts in patients with no significant RLS, $p = 0.22$. Patients with PFO and patients with no significant RLS had similar heart rate (rest: $p = 0.96$, peak exercise: $p = 0.62$), VE (rest: $p = 0.07$, peak exercise: $p = 0.58$), VO_2 (rest: $p = 0.86$, peak exercise: $p = 0.52$) and VCO_2 (rest: $p = 0.68$, peak exercise: $p = 0.50$), for individual values, see Table 5.3.

Table 5.3: Baseline and peak incremental exercise test measurements

	No significant RLS n = 9	PFO n = 9	Student t test p value
Load (Watts)	33 (12)	26 (10)	0.22
Pulse (beats/min) rest	89 (13)	90 (14)	0.96
Pulse (beats/min) peak	116 (14)	113 (15)	0.62
VE rest (L/min)	14.3 (5.5)	10.1 (3.0)	0.07
VE peak (L/min)	38.7 (13.1)	41.1 (9.6)	0.58
VO_2 rest (L/min)	0.29 (0.15)	0.28 (0.10)	0.86
VO_2 peak (L/min)	1.06 (0.28)	0.97 (0.30)	0.52
VO_2 /kg rest (ml/min/kg)	3.7 (1.6)	3.7 (1.3)	0.94
VO_2 /kg peak (ml/min/kg)	12.9 (2.1)	13.0 (3.4)	0.95
VCO_2 rest (L/min)	0.31 (0.09)	0.29 (0.10)	0.68
VCO_2 peak (L/min)	0.91 (0.29)	0.82 (0.27)	0.50

Values are expressed as mean (SD)

Continuous work rate exercise test

There was no difference in exercise endurance between the group with no significant RLS and the PFO group: 10:00 (04:18) mins versus 10:08 (03:10) mins, $p = 0.94$. The drop in SaO_2 from the beginning to end of exercise was 5 (4) % in the PFO group and 5 (4) % in the group with no significant RLS, $p = 1.00$ (Table 5.4). There was no difference in SaO_2 at 5 minutes exercise in both groups: 91 (5)% versus 91 (4)%, $p = 0.80$. The 2 groups also had similar A-a gradients, VD/VT measurements and $\text{Pa}-\text{ETCO}_2$ at the start and end of exercise. Individual values are given in Table 5.4.

Table 5.4: Measurements during exercise

	No significant RLS	PFO	Student t test
	n = 9	n = 9	p value
Exercise time (mins)	10:00 (04:18)	10:08 (03:10)	0.94
SaO ₂ (%)			
start of exercise	95 (2)	95 (2)	0.59
5 mins into exercise	91 (4)	91 (5)	0.80
end of exercise	90 (5)	90 (3)	0.79
difference in SaO ₂ (%)	5 (4)	5 (3)	1.00
A-a gradient (kPa)			
start of exercise	3.9 (0.9)	3.8 (1.3)	0.85
end of exercise	4.7 (1.8)	4.5 (1.7)	0.82
VD/VT			
start of exercise	0.49 (0.07)	0.43 (0.05)	0.07
end of exercise	0.33 (0.20)	0.35 (0.15)	0.79
difference in VD/VT	0.16 (0.20)	0.08 (0.14)	0.33
Pa-ETCO ₂ (kPa)			
start of exercise	1.01 (0.57)	0.85 (0.46)	0.52
end of exercise	0.38 (1.09)	0.58 (0.63)	0.67

Values are expressed as mean (SD)

5.3.4 Intrathoracic pressure during exercise: relation to RLS

Baseline pressure measurements are given in Table 5.5. All pressure measurements were similar between the 2 groups. During exercise, intrathoracic pressure swings, end inspiratory P_{oes} (PEEPi), abdominal muscle recruitment and transdiaphragmatic pressure all increased and returned back to baseline during recovery (Table 5.6).

Table 5.5: Baseline pressure measurements

Pressure measurement (cmH ₂ O)	No sig RLS n = 9	PFO n = 9	Student t test p value
Peak P_{oes}	5.7 (3.4)	5.7 (3.3)	0.98
Trough P_{oes}	-5.3 (2.7)	-4.8 (2.8)	0.71
Intrathoracic pressure swing	11.0 (2.4)	10.5 (4.3)	0.75
End expiratory P_{oes}	2.3 (3.4)	2.3 (2.8)	0.98
Abdominal muscle recruitment	2.4 (2.5)	1.2 (1.5)	0.29
Peak P_{di}	20.7 (7.2)	22.3 (9.6)	0.70
Trough P_{di}	7.8 (5.4)	10.1 (4.1)	0.38
Valsalva P_{oes}	77.7 (38.4)	55.8 (30.3)	0.22
Valsalva P_{gas}	112.3 (65.0)	103.9 (51.4)	0.78

Values are expressed as mean (SD)

Table 5.6: Exercise pressure measurements

	No sig RLS n = 9	PFO n = 9	Student t test p value
Intrathoracic pressure swing (cmH₂O)			
Baseline	13 (4.0)	8.5 (5.0)	0.052
Peak Exercise	32.8 (7.2)	42.1 (25.6)	0.32
End recovery	13.8 (4.6)	13.0 (5.4)	0.73
Abdominal muscle recruitment (cmH₂O)			
Baseline	2.6 (3.2)	3.2 (3.5)	0.72
Peak Exercise	18.0 (13.1)	23.5 (25.5)	0.58
End recovery	2.5 (3.2)	3.3 (2.9)	0.58
Peak Pdi (cmH₂O)			
Baseline	22.9 (7.3)	22.9 (9.9)	0.99
Peak Exercise	32.2 (12.1)	33.5 (12.0)	0.84
End recovery	24.7 (5.5)	24.7 (9.7)	0.99

Values are expressed as mean (SD)

The size of the RLS during exercise was significantly correlated with intrathoracic pressure swings, $r_s = 0.67$, $p < 0.001$ (Figure 5.6). RLS size also correlated with peak transdiaphragmatic pressure $r_s = 0.56$, $p < 0.001$, $p < 0.001$. There was no correlation between RLS size and abdominal muscle recruitment $r_s = 0.07$, $p = 0.54$.

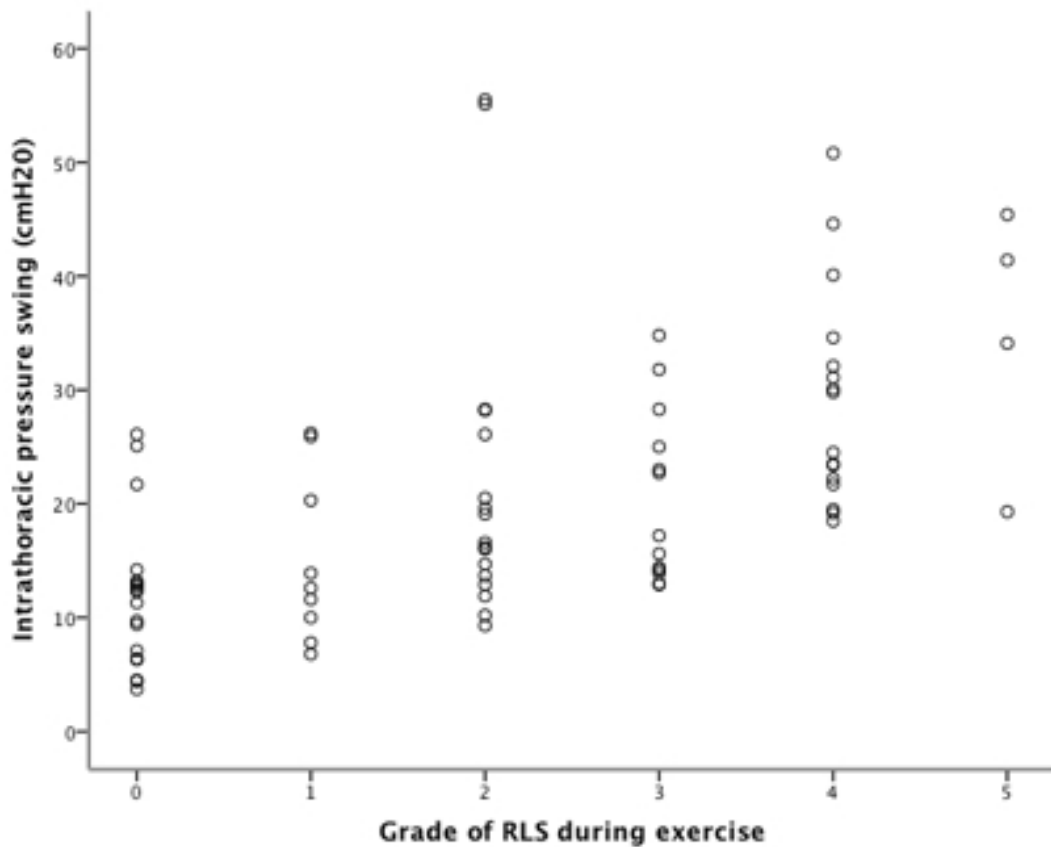


Figure 5.6: *Grade of shunt during exercise and intrathoracic pressure swing*

5.4 Discussion

The main finding from this study is that in severe COPD, right to left shunting through PFO increases from baseline during exercise, however the magnitude of shunt is insufficient to decrease SaO₂, compared to patients without a RLS. Exercise endurance was also similar in those with and without PFO. Increasing amplitude of inspiratory P_{oes} effort was associated with increasing right to left shunting.

5.4.1 Pattern of RLS through PFO during exercise

These data support the hypothesis that RLS through PFO increases during exercise in COPD. The pattern of RLS detected with TCD implies that at the start of submaximal exercise, right atrial pressure is elevated beyond that of the left atrium. In those patients with PFO, shunting commences. As exercise continues, this pressure gradient increases precipitating more shunting. As patients exercise further, the magnitude of RLS reaches a plateau. In recovery RLS continues, in fact an increase was observed with the first post-exercise injection in 2 patients. It then gradually returns to baseline as patients relax.

5.4.2 Mechanism of RLS through PFO during exercise

The findings in this study are consistent with the hypothesis that increased RLS is associated with increasing intrathoracic pressure swings. Furthermore, positive correlations were also detected between RLS and transdiaphragmatic pressure.

Dynamic hyperinflation during exercise in COPD is a well recognized phenomenon (O'Donnell et al., 2001b). Expiratory flow limitation results in air

trapping and PEEPi. Isolated PEEPi decreases venous return (Cournand et al., 1948) however during exercise in COPD it is accompanied by large increases in inspiratory intrathoracic pressure swings. These pressures need to generate enough force to overcome the opposite recoil pressure to stimulate inspiratory flow. It is speculated PEEPi has some similarities with the Valsalva manoeuvre with the onset of inspiration being similar to the release phase. The resulting negative pleural pressure generation, augments venous return increasing right atrial pressure and promoting RLS. As exercise continues, abdominal muscles are recruited to help expel the trapped pulmonary air and this increases intrathoracic pressure further (Kyroussis et al., 2000). Additionally, transdiaphragmatic pressure increases and hence so does the gradient for venous return (Permutt, 1988). Recovery prompts a gradual return to normal ventilatory mechanics and thus the RLS decreases.

The explanation outlined above does not explain the mechanism behind the biphasic pattern of RLS exhibited by the 2 patients in whom the magnitude of RLS increased in recovery. One possible theory is at maximal exercise, intraabdominal pressures compress abdominal blood vessels decreasing venous return (Moreno et al., 1967). In addition, as inspiratory capacity declines and PEEPi continues to increase, the respiratory pump becomes increasingly inefficient and may further impede return of blood to the right atrium (Cournand et al., 1948). The onset of recovery releases the mechanical constraints on inspiratory flow augmenting venous return and increasing RLS through PFO.

Pulmonary artery pressure elevations during exercise could also explain the increase in RLS as discussed in Chapter 4.4.1.

5.4.3 Significance of RLS through PFO during exercise

The findings of this study do not support the hypothesis that patients with severe COPD and PFO have reduced exercise endurance and greater exercise induced hypoxia. Not only was exercise endurance similar in patients with PFO and patients without RLS, the drop in exercise SaO₂ during exercise was the same. Extending the work in Chapter 4, this suggests that the amount of shunting through PFO is not sufficient to cause systemic desaturation, either at rest or during exercise. The exercise induced shunt may stretch the PFO accounting for the findings of Chapter 4 of a higher prevalence of PFO with large shunts.

Atrial RLS during exercise in COPD has not previously been studied, however experiments in pulmonary hypertension report physiological improvements in those with shunts. Austen et al studied dogs with pulmonary hypertension and found that RLS improved exercise capacity and cardiac output (Austen et al., 1964). Kawaguchi et al studied 74 rats with monocrotaline induced pulmonary hypertension with weekly cardiopulmonary exercise testing for 2 months. The 22 rats with an atrial level shunt had higher levels of O₂ uptake and CO₂ production compared to the 52 rats with no shunt. Additionally, those with shunts had vastly improved survival at 27% compared to 0% of those with sealed interatrial septae, $p < 0.05$ (Kawaguchi et al., 1993). Extrapolating these studies to COPD, PFO may improve cardiac haemodynamics by decompressing the right heart with resulting functional benefit. This notion directly contradicts current published findings. Future studies are needed to assess the impact of RLS on right heart function.

A fascinating study by Faul et al examined the effect of an ileofemoral arteriovenous fistula on exercise capacity in 12 patients with severe COPD.

They found that the 6 minute walk distance increased from 217 (63) m at baseline to 272 (18) m at 6 weeks and 276 (25) m at 12 weeks post surgery. Cardiac output also increased. Patients that responded initially to supplemental oxygen received most therapeutic benefit. It was speculated that the creation of a shunt increases mixed venous oxygen content and hence exercise performance. It is clear that the interactions are more complex than previously imagined and future studies are needed to investigate the importance of arteriovenous shunts at different levels in patients with COPD (Faul et al., 2010).

5.4.4 Methodological considerations

This study is restricted to patients with severe COPD and cannot be generalized to patients with milder disease. This is, however an area for future research.

The exercise tests were invasive and technically difficult in COPD patients with marked morbidity. The addition of pulmonary pressure monitoring was not feasible, therefore no comment is possible on the influence of pulmonary haemodynamics on RLS in this study.

Due to the complexity of the protocol, many patients studied in Chapter 4 were either unsuitable or unwilling to participate in the study presented in this chapter. The sample size of 10 in each group was not attained. However, it is unlikely that one additional patient in each arm would have changed the study outcome.

5.4.5 Summary

Right to left shunting through PFO increases during exercise in COPD. The magnitude of increase is associated with raised intrathoracic pressure swings. RLS does not influence arterial oxygenation or exercise endurance.

Chapter 6

Discussion

6.1 Discussion

The data presented in this thesis provides the following original contributions to PFO research:

- PFO with large shunts are more prevalent in both OSA and COPD patients compared to healthy controls
- PFO closure in six patients with severe OSA did not improve nocturnal oxygenation
- The prevalence of PFO in hypoxaemic COPD patients is similar to that which occurs in patients with higher PaO₂
- There is a higher prevalence of pulmonary shunts in hypoxaemic COPD patients compared to those with higher PaO₂
- RLS through PFO in COPD patients increases from baseline during exercise and is associated with increases in intrathoracic pressure swings and transdiaphragmatic pressure

The data suggest that RLS through PFO such as that seen during exercise in COPD can stretch a PFO, increasing shunt magnitude, however, the volume of shunted blood is insufficient to produce significant desaturation.

6.1.1 Critique of methods

The calculated sample sizes derived from the power calculations were attained in both COPD and OSA. Despite this, in both conditions overall PFO prevalence appeared to be greater than in healthy controls, but did not reach statistical significance. If the prevalence is higher in OSA and COPD,

a difference may have become apparent if more patients had been recruited. The studies on which the power calculations were based employed older, less sensitive PFO detection techniques and therefore may have underestimated PFO prevalence in control subjects. Based on the data in this thesis (as calculated in the discussion sections of chapters 3 and 4), the OSA and COPD studies require 214 and 143 patients respectively in the patient and healthy control groups to achieve 80% power to detect a difference at a significance level of 0.05.

Recruitment of OSA patients for PFO closure (Chapter 3, Study B) was difficult owing to lack of evidence of a benefit, the risks of percutaneous PFO closure and the intense follow up required. Out of 161 patients initially approached, 18 were suitable and 6 participated. Feasibility of the technique in OSA was demonstrated, however there was no improvement in ODI or percentage of time with $\text{SaO}_2 < 90\%$. The percentage of time with $\text{SaO}_2 < 90\%$ was 22.8 (16.0)% pre closure and 19.9 (22.2)% at 12 months. Based on this data, any further trial addressing a similar question would have to approach approximately 14,785 patients to recruit 551 patients for PFO closure in order to achieve 80% power to detect a difference at a significance level of 0.05. A trial of this magnitude cannot be recommended on the basis of data presented in this thesis. Additionally, there is little clinical significance in improving the percentage of time with $\text{SaO}_2 < 90\%$ from 22.8% to 19.9% .

Recruitment of severe COPD patients into the exercise study was also difficult. Patients well enough to exercise that did not have pulmonary shunts were all approached and many declined participation due to the invasive nature of the study. Ultimately data from 18 patients was included. This did not meet the power calculation of 10 patients with PFO and 10 without PFO, however, it is unlikely that one extra patient in each group would change the outcome.

Agreement between TCD and TTE shunt grades is detailed in Appendix E. Agreement was good in controls both at rest and following Valsalva. This is not surprising as controls have good acoustic windows and transtemporal bone windows. Agreement was only moderate at rest in both OSA and COPD and increased to substantial following Valsalva. The majority of discordance was secondary to the detection of smaller shunts by TCD that were not visible using TTE. The use of TCD in the respiratory setting proved invaluable. Obese patients and those with hyperinflated lungs have very poor acoustic windows for TTE and TCD provided a complementary method for assessing shunt presence and magnitude. TCD also allowed assessment of shunt size during upright exercise in COPD. This would not have been possible with other available techniques.

6.1.2 Functional significance of results

PFO and hypoxaemia

Previous data from PFO studies in respiratory disease have lead to the conclusion that PFO contribute to hypoxaemia and increased functional limitation (Konstantinides et al., 1998; Kerut et al., 2001; Allemann et al., 2006; Shanoudy et al., 1998; Johansson et al., 2007; Soliman et al., 1999; Hacievliyagil et al., 2006). The only finding from data in this thesis that lends some support to this assertion is that the ODI/AHI was greater in OSA patients with PFO than those without. However due to the reasons stated in the discussion in Chapter 3 (Section 3.5.3), this is an inconclusive finding. In COPD patients, the presence of a PFO was not associated with lower resting PaO₂. Furthermore despite experiencing increases in RLS, the PFO group had similar exercise endurance and SaO₂ compared to COPD patients without PFO. The absence of

an association with hypoxaemia means the volume of shunted blood in severe OSA and severe COPD is insufficient to cause systemic desaturation.

Magnitude of PFO shunt

In both OSA and COPD, large shunts were more prevalent than in healthy controls but overall prevalence was statistically similar. Repetitive stretching of the PFO tunnel in both OSA and COPD could lead to PFO enlargement therefore rendering them easier to detect. Individual mechanisms are described in the Discussion sections of Chapters 3, 4 and 5.

Pulmonary shunts

Interestingly the COPD group had a higher prevalence of pulmonary shunts compared to healthy controls. This finding was not replicated in OSA patients. These COPD patients were more hypoxaemic at rest compared to OSA patients and controls. In addition, they had high pulmonary artery pressures compared to the rest of the COPD group. It is therefore reasonable to speculate that pulmonary shunting is modulated by hypoxaemia and/or pulmonary hypertension. This is discussed further in the Discussion in Chapter 4. As OSA patients were not hypoxaemic at rest, pulmonary shunt frequency was low.

6.1.3 The role of PFO closure in respiratory disease

This thesis highlights implications for assessing patients for PFO closure. Patients with OSA and COPD who do not have resting pulmonary hypertension, but instead experience intermittent increases in PAP, may benefit from the presence of PFO. A single PAP measurement at rest may not

be sufficient to identify suitability for closure and sealing off the “pressure release valve” may increase the longterm risk of cor pulmonale. Although 6 OSA patients underwent PFO closure, they were all subsequently treated with CPAP therefore minimising nocturnal right heart strain.

Prior to undertaking larger PFO closure trials on hypoxaemic patients with respiratory disease, invasive physiological exercise studies in the cardiac catheterisation laboratory are warranted. Right heart catheterisation performed during supine exercise in patients with PFO could accurately define cardiac haemodynamics. By occluding the PFO with a balloon, and repeating the same supine exercise with invasive monitoring any changes in the 2 conditions could be identified. This would help define the role of PFO and the safety of any subsequent closure procedure. Until further data on the physiological implications are available, PFO closure assessment and risk-benefit analysis in respiratory disease must be undertaken on an individual basis.

6.1.4 Further research

The findings from the studies presented in this thesis lead to many different research questions.

PFO in healthy subjects

A PFO was identified in 30% of control subjects. Considering the high prevalence of the congenital defect, there are very few studies that assess the physiological implications of PFO in health. A small study of 16 healthy humans, 8 with and 8 without PFO, showed an asymptomatic PFO did not contribute to arterial-alveolar oxygen difference during exercise. Surprisingly,

a significant difference between subjects with and without PFO was detected at rest (5.9 (5.1) versus 0.5 (3.5) mmHg, $p < 0.05$), (Lovering et al., 2011). A longitudinal cohort study could assess the prevalence and natural history of shunts, both PFO and intrapulmonary. The exercise study from Chapter 5 performed under normoxic, hyperoxic and hypoxic conditions would determine whether findings in COPD are replicated in health. Another interesting study would investigate RLS in healthy people that perform repetitive strain manoeuvres such as musicians that play wind instruments or weight lifters. Investigating PFO in the other end of the spectrum i.e. athletes would provide an insight into whether there is a selection bias into different sports (long distance versus sprint) depending on interatrial septal physiology.

PFO in respiratory diseases

Small studies and isolated case reports on the influence of PFO in respiratory diseases are discussed in Chapter 1, Sections 1.1.5 and 1.1.6. It is possible that the findings of the studies in this thesis can be extrapolated to other respiratory diseases such as interstitial lung disease, bronchiectasis and cystic fibrosis, however, further work in this area is needed. The data in this thesis does not cover people with less severe OSA and COPD. It is possible that shunt size and exercise physiology is different to that of severe disease. COPD exacerbations place a similar amount of stress on the body to that of exercise. It is possible that RLS through PFO increases. Studies to investigate whether or not this is a protective mechanism are needed.

The question of paradoxical emboli has not been assessed in this thesis. The risk of stroke and myocardial infarction is increased in both OSA (Yaggi et al., 2005; Arzt et al., 2005; Marin et al., 2005) and COPD (Arboix et al., 2000;

Feary et al., 2010). Given that the magnitude of shunt was larger in both OSA and COPD compared to controls, and that larger shunts are associated with increased stroke risk (Anzola et al., 2003; Giardini et al., 2007; Paciaroni et al., 2011; Schuchlenz et al., 2000; Steiner et al., 1998; Harrer et al., 2006), studies investigating whether PFO increase the cardiovascular risk in COPD and OSA are required.

Pulmonary shunting

An interesting finding from Chapter 4 was the prevalence of pulmonary shunts in COPD. Pulmonary shunts have been studied in health but not in respiratory disease. From the data presented it is likely that they open up as a response to hypoxaemia. However, studies are needed to identify the natural history, anatomy and exercise physiology of these shunts.

Right heart function and PFO

There is evidence that both OSA (Koshino et al., 2010; Virolainen et al., 1995) and COPD (Burgess et al., 2002; Vitarelli et al., 2006; Tayyareci et al., 2009) can cause right heart dysfunction. One of the most important questions yet unanswered is: do PFO protect the right heart in respiratory disease? Further work looking at right heart function in those with and without PFO is needed. The TTE studies performed in this thesis did not adequately investigate global right heart function, nor did they assess right ventricular end diastolic dysfunction. A cardiac MR study or 3D ECHO may provide better assessment (Nesser et al., 2006; Caudron et al., 2011).

6.2 Overall summary

PFO are more prevalent, cause functional impairment and significant desaturation in respiratory disease. This formed the underlying premise on which the hypotheses in this thesis were based. OSA was used to model intermittent nocturnal hypoxaemia and COPD to model resting and exercise hypoxaemia. Through the course of data collection and evaluation, it was found that PFO prevalence was similar between OSA, COPD and healthy controls, patients with PFO did not experience more desaturation, nor were they functionally impaired as a consequence of shunting. Further work should be directed at investigating PFO in health and the role of PFO in protecting right heart function in respiratory disease.

Appendix A

Healthy volunteer advert

Healthy volunteers needed

Healthy (not on any medication) non-smoking males aged 40 to 70 years required to help with research into lung disease and holes in the heart

Volunteers will have breathing tests, a blood test, a 6 minute walking test, ultrasound tests and an overnight home sleep study.

We offer paid compensation for your time.

For more information please contact:
Zarrin Shaikh
Clinical Research Fellow
Academic Unit of Sleep and Breathing
Royal Brompton Hospital

020 7352 8121 (ext 4183)
Email: z.shaikh07@imperial.ac.uk

This research project has been approved by King's College Hospital Research Ethics Committee

Appendix B

Epworth sleepiness scale

Please rate how likely you are to fall asleep in the following situations. Your answers should reflect how you have been in the past week:

- 0= Would never doze
- 1= Slight chance of dozing
- 2= Moderate chance of dozing
- 3= High chance of dozing

Situation	Score
Sitting and reading	
Watching television	
Sitting inactive in a public place e.g. theatre, meeting	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon	
Sitting and talking to someone	
Sitting quietly after lunch (when you've had no alcohol)	
In a car, while stopped at traffic	
Total	

Appendix C

HIT 6 Headache questionnaire

HIT-6™



This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please fill in a bubble for each question.

Name: _____ Email Address: _____

1. When you have headaches, how often is the pain severe?

Never	Rarely	Sometimes	Very Often	Always	
☐ O ₁	☐ O ₂	☐ O ₃	☐ O ₄	☐ O ₅	HIT6A

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never	Rarely	Sometimes	Very Often	Always	
☐ O ₁	☐ O ₂	☐ O ₃	☐ O ₄	☐ O ₅	HIT6B

3. When you have a headache, how often do you wish you could lie down?

Never	Rarely	Sometimes	Very Often	Always	
☐ O ₁	☐ O ₂	☐ O ₃	☐ O ₄	☐ O ₅	HIT6C

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never	Rarely	Sometimes	Very Often	Always	
☐ O ₁	☐ O ₂	☐ O ₃	☐ O ₄	☐ O ₅	HIT6D

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never	Rarely	Sometimes	Very Often	Always	
☐ O ₁	☐ O ₂	☐ O ₃	☐ O ₄	☐ O ₅	HIT6E

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never	Rarely	Sometimes	Very Often	Always	
☐ O ₁	☐ O ₂	☐ O ₃	☐ O ₄	☐ O ₅	HIT6F

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Appendix D

SF36v2 Quality of life questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐	☐	☐	☐	☐

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐	☐	☐	☐	☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
a. <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports.....	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs.....	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs.....	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping.....	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself.....	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
a. Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the <u>kind of</u> work or other activities.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort).....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
a. I seem to get ill more easily than other people.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix E

Agreement between contrast TCD and TTE

E.1 Overall agreement of contrast TCD and TTE

The agreement between the grades of shunt assigned by contrast TCD and TTE examinations were assessed in all subjects (OSA, COPD and healthy controls). The results are given in Table E.1 for rest studies and Table E.2 for studies with Valsalva.

The kappa statistic for studies at rest was 0.57 indicating moderate agreement between TCD and TTE. The kappa statistic for studies with Valsalva was 0.76 indicating substantial/good agreement between TCD and TTE.

Table E.1: Overall agreement between TCD and TTE at rest

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	190	12	5	
Small shunt	2	13	4	1
Moderate shunt		6	7	4
Large shunt	1			2

Table E.2: Overall agreement between TCD and TTE after Valsalva

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	137	14	2	1
Small shunt	1	29	4	2
Moderate shunt		4	8	6
Large shunt		1		37

E.2 Agreement between contrast TCD and TTE in controls

The agreement between the grades of shunt assigned by contrast TCD and TTE examinations were assessed in healthy control subjects. The results are given in Table E.3 for rest studies and Table E.4 for studies with Valsalva.

The kappa statistic for studies at rest was 0.82 indicating good agreement between TCD and TTE. The kappa statistic for studies with Valsalva was 0.83 indicating good agreement between TCD and TTE.

Table E.3: Agreement between TCD and TTE at rest: controls

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	44			
Small shunt		4		
Moderate shunt		1		1
Large shunt				

Table E.4: Agreement between TCD and TTE after Valsalva: controls

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	35			
Small shunt		8	2	
Moderate shunt		2		
Large shunt				3

E.3 Agreement between contrast TCD and TTE in OSA

The agreement between the grades of shunt assigned by contrast TCD and TTE examinations were assessed in OSA patients. The results are given in Table E.5 for rest studies and Table E.6 for studies with Valsalva.

The kappa statistic for studies at rest was 0.53 indicating moderate agreement between TCD and TTE. The kappa statistic for studies with Valsalva was 0.68 indicating substantial agreement between TCD and TTE.

Table E.5: Agreement between TCD and TTE at rest: OSA

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	77	5	2	
Small shunt	2	3	1	
Moderate shunt		3	4	
Large shunt				

Table E.6: Agreement between TCD and TTE after Valsalva: OSA

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	55	11	1	1
Small shunt	1	5		
Moderate shunt		2	5	
Large shunt		1		15

E.4 Agreement between contrast TCD and TTE in COPD

The agreement between the grades of shunt assigned by contrast TCD and TTE examinations were assessed in COPD patients. The results are given in Table E.7 for rest studies and Table E.8 for studies with Valsalva.

The kappa statistic for studies at rest was 0.53 indicating moderate agreement between TCD and TTE. The kappa statistic for studies with Valsalva was 0.79 indicating substantial/good agreement between TCD and TTE.

Table E.7: Agreement between contrast TCD and TTE at rest: COPD

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	69	7	3	
Small shunt		6	3	1
Moderate shunt		2	3	3
Large shunt	1			2

Table E.8: Agreement between contrast TCD and TTE after Valsalva: COPD

Grade of shunt assigned by TTE	Grade of shunt assigned by TCD			
	No shunt	Small shunt	Moderate shunt	Large shunt
No shunt	47	3	1	
Small shunt		16	2	2
Moderate shunt			3	6
Large shunt				19

E.5 Summary of agreement between contrast TCD and TTE

Table E.9 shows the kappa values for the agreement between contrast TCD and TTE studies. Studies in control subjects had the best agreement. Agreement of contrast TCD and TTE was better following Valsalva manoeuvre than at rest. This is discussed in Chapter 6, Section 6.1.1.

Table E.9: Summary of agreement between contrast TCD and TTE

	Kappa value	
	Rest	After Valsalva
Overall	0.57	0.76
Controls	0.82	0.83
OSA	0.53	0.68
COPD	0.53	0.79

Appendix F

SaO₂ in OSA patients before and after PFO closure

An additional analysis was conducted on NPSG studies in OSA patients who had undergone PFO closure. It was undertaken to determine whether the drop in SaO_2 or ΔSaO_2 (baseline SaO_2 – nadir SaO_2) associated with each apnoeic event decreased following PFO closure.

The baseline and 6 month post closure studies were analysed for each patient. Each apnoeic event that was clearly associated with one single desaturation was included. Measurements recorded for each event were: apnoea length, baseline SaO_2 , ΔSaO_2 . Apnoeas were divided according to sleep stage: NREM or REM, and position: lateral or supine. Hypopnoeas were not included due to the varying amount of airflow limitation that they produce. Analysis was blinded to pre and post closure.

Table F.1 below gives a summary of the findings.

Table F.1: Apnoea and SaO₂ in OSA patients before and after PFO closure

		Number of apnoeas		Baseline SaO ₂ (%)		Apnoea length (seconds)		Δ SaO ₂ (%)	
		BL	6mth	BL	6mth	p	BL	6mth	p
NREM	Lat	411	465	95 (2)	94 (3)	< 0.001	22 (7)	20 (8)	< 0.001
	Sup	792	807	95 (2)	95 (2)	0.19	26 (9)	26 (8)	0.06
REM	Lat	163	159	94 (3)	96 (4)	< 0.001	33 (13)	36 (14)	0.08
	Sup	127	130	95 (4)	94 (4)	< 0.001	33 (15)	32 (15)	0.80
							13 (6)	14 (8)	0.14
							12 (8)	14 (9)	0.15

Values are expressed as mean (SD) Lat: lateral, Sup: supine, BL: baseline, 6mth: 6 months post closure

At 6 months, 2 patients had large residual shunts, 3 had small shunts and only 1 patient had complete closure. It appears that ΔSaO_2 decreases following PFO closure in NREM. However, apnoea length is shorter and this could also account for the findings. It is difficult to draw conclusions based on this analysis.

Appendix G

Characteristics of COPD patients in Chapter 5

Table G.1 compares assessments made on COPD patients (n = 18) recruited for the exercise study in Chapter 5 to those made when initially studied in Chapter 4. The median time between the 2 visits was 278 (74 – 498) days .

Table G.1: Assessments in 18 COPD patients at exercise study (Chapter 5) compared to baseline (Chapter 4)

	Baseline (Chapter 4)	Exercise study (Chapter 5)	Paired Student t test p value
FEV ₁ (% predicted)	33.8 (11.1)	33.7 (12.2)	0.93
FVC (% predicted)	90.2 (17.4)	92.5 (14.4)	0.44
FEV ₁ /FVC	28.7 (7.1)	28.4 (8.6)	0.81
TLCO (% predicted)	38.0 (15.8)	40.2 (12.1)	0.34
KCO (% predicted)	47.1 (19.6)	50.5 (16.4)	0.20
TLC (% predicted)	119.5 (33.3)	128.7 (18.1)	0.25
RV (% predicted)	189.9 (73.1)	201.6 (54.4)	0.37
RV/TLC (%)	53.2 (15.6)	56.8 (7.4)	0.38
FRC (% predicted)	164.3 (54.6)	177.6 (41.7)	0.26
BMI (kg/m ²)	26.6 (5.5)	26.9 (5.8)	0.45
PaO ₂ (kPa)	9.3 (0.9)	9.7 (1.1)	0.23
PaCO ₂ (kPa)	5.4 (0.5)	5.2 (0.4)	0.04

Values are expressed as mean (SD)

PFO shunt sizes in COPD patients in the PFO group were similar to baseline except one patient in whom the shunt was initially TCD grade 3 and when studied for the exercise test, was TCD grade 2.

In the patients with no significant RLS, all patients initially had no detectable shunt and when studied for the exercise test, 2 out of 9 had very small, TCD grade 1 shunts. These were too small to influence the exercise study and the patients remained in the group with no significant RLS for analysis.

References

- AASM. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. the report of an american academy of sleep medicine task force. Sleep, 22(5): 667–89, 1999.
- A. S. Abraham, R. B. Cole, I. D. Green, R. B. Hedworth-Whitty, S. W. Clarke, and J. M. Bishop. Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure studies by serial observations during recovery. Circ Res, 24(1):51–60, 1969.
- G. Agnoletti, L. Iserin, A. Lafont, D. Sidi, and M. Desnos. Obstructive sleep apnoea and patent foramen ovale: successful treatment of symptoms by percutaneous foramen ovale closure. J Interv Cardiol, 18(5):393–5, 2005.
- E. Agostoni and G. Torri. Diaphragm contraction as a limiting factor to maximum expiration. J Appl Physiol, 17:427–8, 1962.
- S. Ahmed, A. Sadiq, A. K. Siddiqui, E. Borgen, and J. Mattana. Paradoxical arterial emboli causing acute limb ischemia in a patient with essential thrombocytosis. Am J Med Sci, 326(3):156–158, Sep 2003.
- T. Akashiba, S. Kawahara, T. Akahoshi, C. Omori, O. Saito, T. Majima, and T. Horie. Relationship between quality of life and mood or depression in

- patients with severe obstructive sleep apnea syndrome. Chest, 122(3):861–5, 2002.
- N. M. Al Lawati and P. Wilcox. Paradoxical embolization in an adult cystic fibrosis patient. Can Respir J, 14(5):293–4, 2007.
- J. J. Allan, C. Marinelli, K. C. Dellsperger, and M. D. Winniford. Percutaneous balloon catheter closure of a patent foramen ovale in a patient with pulmonary disease, profound hypoxemia, and normal right heart pressures. Clin Cardiol, 20(3):307–9, 1997.
- Y. Allemann, D. Hutter, E. Lipp, C. Sartori, H. Duplain, M. Egli, S. Cook, U. Scherrer, and C. Seiler. Patent foramen ovale and high-altitude pulmonary edema. Jama, 296(24):2954–8, 2006.
- G. P. Anzola, M. Magoni, M. Guindani, L. Rozzini, and G. Dalla Volta. Potential source of cerebral embolism in migraine with aura: a transcranial doppler study. Neurology, 52(8):1622–1625, May 1999.
- G. P. Anzola, P. Zavarize, E. Morandi, L. Rozzini, and G. Parrinello. Transcranial doppler and risk of recurrence in patients with stroke and patent foramen ovale. Eur J Neurol, 10(2):129–135, Mar 2003.
- Y. Arabi, B. J. Morgan, B. Goodman, D. S. Puleo, A. Xie, and J. B. Skatrud. Daytime blood pressure elevation after nocturnal hypoxia. J Appl Physiol, 87(2):689–698, Aug 1999.
- A. Arboix, C. Morcillo, L. Garca-Eroles, M. Oliveres, J. Massons, and C. Targa. Different vascular risk factor profiles in ischemic stroke subtypes: a study from the "sagrat cor hospital of barcelona stroke registry". Acta Neurol Scand, 102(4):264–270, Oct 2000.

- M. Arzt, T. Young, L. Finn, J. B. Skatrud, and T. D. Bradley. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med, 172(11):1447–51, 2005.
- ASDA. Practice parameters for the indications for polysomnography and related procedures. polysomnography task force, american sleep disorders association standards of practice committee. Sleep, 20(6):406–422, Jun 1997.
- ATS. Ats statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med, 166(1):111–7, 2002.
- R. R. Attaran, I. Ata, V. Kudithipudi, L. Foster, and V. L. Sorrell. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. Echocardiography, 23(7):616–22, 2006.
- I. Ayappa, R. G. Norman, M. Suryadevara, and D. M. Rapoport. Comparison of limited monitoring using a nasal-cannula flow signal to full polysomnography in sleep-disordered breathing. Sleep, 27(6):1171–1179, Sep 2004.
- T. G. Babb, R. Viggiano, B. Hurley, B. Staats, and J. R. Rodarte. Effect of mild-to-moderate airflow limitation on exercise capacity. J Appl Physiol, 70(1):223–230, Jan 1991.
- N. C. Bakris, A. J. Siddiqi, C. D. Fraser, and A. C. Mehta. Right-to-left interatrial shunt after pneumonectomy. Ann Thorac Surg, 63(1):198–201, Jan 1997.
- F. Barbe, J. Duran-Cantolla, F. Capote, M. de la Pena, E. Chiner, J. F. Masa, M. Gonzalez, J. M. Marn, F. Garcia-Rio, J. D. de Atauri, J. Teran, M. Mayos, C. Monasterio, F. del Campo, S. Gomez, M. S. de la Torre, M. Martinez, J. M. Montserrat, Spanish Sleep, and Breathing Group. Long-term effect

- of continuous positive airway pressure in hypertensive patients with sleep apnea. Am J Respir Crit Care Med, 181(7):718–726, Apr 2010.
- J. A. Barbera, J. Ramirez, J. Roca, P. D. Wagner, J. Sanchez-Lloret, and R. Rodriguez-Roisin. Lung structure and gas exchange in mild chronic obstructive pulmonary disease. Am Rev Respir Dis, 141(4 Pt 1):895–901, Apr 1990.
- R. G. Barr, D. A. Bluemke, F. S. Ahmed, J. J. Carr, P. L. Enright, E. A. Hoffman, R. Jiang, S. M. Kawut, R. A. Kronmal, J. A. C. Lima, E. Shahar, L. J. Smith, and K. E. Watson. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med, 362(3):217–227, Jan 2010.
- M. Beelke, S. Angeli, M. Del Sette, F. De Carli, P. Canovaro, L. Nobili, and F. Ferrillo. Obstructive sleep apnea can be provocative for right-to-left shunting through a patent foramen ovale. Sleep, 25(8):856–62, 2002.
- M. Beelke, S. Angeli, M. Del Sette, C. Gandolfo, M. E. Cabano, P. Canovaro, L. Nobili, and F. Ferrillo. Prevalence of patent foramen ovale in subjects with obstructive sleep apnea: a transcranial doppler ultrasound study. Sleep Med, 4(3):219–23, 2003.
- E. Belaidi, M. Joyeux-Faure, C. Ribuot, S. H. Launois, P. Levy, and D. Godin-Ribuot. Major role for hypoxia inducible factor-1 and the endothelin system in promoting myocardial infarction and hypertension in an animal model of obstructive sleep apnea. J Am Coll Cardiol, 53(15):1309–17, 2009.
- V. Bellato, S. Brusa, J. Balazova, S. Marescotti, D. De Caria, and G. Bordone. Platypnea-orthodeoxia syndrome in interatrial right to left shunt postpneumonectomy. Minerva Anesthesiol, 74(6):271–275, Jun 2008.
- E. Bozkanat, E. Tozkoparan, O. Baysan, O. Deniz, F. Ciftci, and M. Yokusoglu.

- The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease. J Int Med Res, 33(5):537–44, 2005.
- R. Broekhuizen, E. F M Wouters, E. C. Creutzberg, and A. M W J Schols. Raised crp levels mark metabolic and functional impairment in advanced copd. Thorax, 61(1):17–22, Jan 2006.
- A. J. Buda, M. R. Pinsky, N. B. Ingels, G. T. Daughters, E. B. Stinson, and E. L. Alderman. Effect of intrathoracic pressure on left ventricular performance. N Engl J Med, 301(9):453–459, Aug 1979.
- M. I. Burgess, N. Mogulkoc, R. J. Bright-Thomas, P. Bishop, J. J. Egan, and S. G. Ray. Comparison of echocardiographic markers of right ventricular function in determining prognosis in chronic pulmonary disease. J Am Soc Echocardiogr, 15(6):633–9, 2002.
- J. Butler, F. Schrijen, A. Henriquez, J. M. Polu, and R. K. Albert. Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. Am Rev Respir Dis, 138(2):350–4, 1988.
- L. Cabanes, J. L. Mas, A. Cohen, P. Amarenco, P. A. Cabanes, P. Oubary, F. Chedru, F. Gurin, M. G. Bousser, and J. de Recondo. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. a study using transesophageal echocardiography. Stroke, 24(12):1865–1873, Dec 1993.
- J. M. Calleja, S. Esnaola, R. Rubio, and J. Durn. Comparison of a cardiorespiratory device versus polysomnography for diagnosis of sleep apnoea. Eur Respir J, 20(6):1505–1510, Dec 2002.
- P. M. Calverley. Supplementary oxygen therapy in copd: is it really useful? Thorax, 55(7):537–8, 2000.

- P. A. Calvert, B. S. Rana, A. C. Kydd, and L. M. Shapiro. Patent foramen ovale: anatomy, outcomes, and closure. Nat Rev Cardiol, 8(3):148–160, Mar 2011.
- L. Caputi, M. R. Carriero, C. Falcone, E. Parati, P. Piotti, C. Materazzo, and G. P. Anzola. Transcranial doppler and transesophageal echocardiography: comparison of both techniques and prospective clinical relevance of transcranial doppler in patent foramen ovale detection. J Stroke Cerebrovasc Dis, 18(5):343–348, 2009.
- L. Caputi, S. Usai, M. R. Carriero, L. Grazzi, D. D’Amico, C. Falcone, G. P. Anzola, M. Del Sette, E. Parati, and G. Bussone. Microembolic air load during contrast-transcranial doppler: as trigger for migraine with aura? Headache, 50(8):1320–1327, Sep 2010.
- M. Carminati, M. Chessa, G. Butera, R. M. Bini, S. Giusti, P. Festa, I. Spadoni, S. Redaelli, and G. Hausdorf. Transcatheter closure of atrial septal defects with the starflex device: early results and follow-up. J Interv Cardiol, 14(3): 319–24, 2001.
- C. Casanova, C. Cote, J. M. Marin, V. Pinto-Plata, J. P. de Torres, A. Aguirre-Jame, C. Vassaux, and B. R. Celli. Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with copd. Chest, 134(4):746–752, Oct 2008.
- J. Caudron, J. Fares, P. H. Vivier, V. Lefebvre, C. Petitjean, and J. N. Dacher. Diagnostic accuracy and variability of three semi-quantitative methods for assessing right ventricular systolic function from cardiac mri in patients with acquired heart disease. Eur Radiol, May 2011.
- A. Chambellan, E. Chailleux, Similowski. T, and A. N. T. A. D. I. R. Observatory Group. Prognostic value of the hematocrit in patients with

- severe copd receiving long-term oxygen therapy. Chest, 128(3):1201–1208, Sep 2005.
- A. Chaouat, A. S. Bugnet, N. Kadaoui, R. Schott, I. Enache, A. Ducolone, M. Ehrhart, R. Kessler, and E. Weitzenblum. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 172(2):189–94, 2005.
- R. M. Cherniack, L. E. Farhi, B. W. Armstrong, and D. F. Proctor. A comparison of esophageal and intrapleural pressure in man. J Appl Physiol, 8(2):203–11, 1955.
- C. K. Choong, P. A. Calvert, F. Falter, R. Mathur, D. Appleton, F. C. Wells, P. M. Schofield, and R. Crawford. Life-threatening impending paradoxical embolus caught “red-handed”: successful management by multidisciplinary team approach. J Thorac Cardiovasc Surg, 136(2):527–528.e8, Aug 2008.
- C. C. Christensen, M. S. Ryg, A. Edvardsen, and O. H. Skjonsberg. Relationship between exercise desaturation and pulmonary haemodynamics in copd patients. Eur Respir J, 24(4):580–6, 2004.
- K. Christou, N. Markoulis, A. N. Moulas, C. Pastaka, and K. I. Gourgoulanis. Reactive oxygen metabolites (roms) as an index of oxidative stress in obstructive sleep apnea patients. Sleep Breath, 7(3):105–10, 2003.
- F. Cirignotta, S. Mondini, R. Gerardi, B. Mostacci, and E. Sancisi. Unreliability of automatic scoring of mesam 4 in assessing patients with complicated obstructive sleep apnea syndrome. Chest, 119(5):1387–1392, May 2001.
- J Cohnheim. Thrombose und Embolie: Vorlesung uber allgemeine Pathologie. Berlin, Germany: Hirschwald, 1877.

- C. G. Cote, C. Casanova, J. M. Marin, M. V. Lopez, V. Pinto-Plata, M. M. de Oca, L. J. Dordelly, H. Nekach, and B. R. Celli. Validation and comparison of reference equations for the 6-min walk distance test. Eur Respir J, 31(3): 571–8, 2008.
- J. E. Cotes, D. J. Chinn, P. H. Quanjer, J. Roca, and J. C. Yernault. Standardization of the measurement of transfer factor (diffusing capacity). report working party standardization of lung function tests, european community for steel and coal. official statement of the european respiratory society. Eur Respir J Suppl, 16:41–52, 1993.
- A. Cournand, H. L. Motley, and et al. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol, 152(1):162–74, 1948.
- S. C. Cramer, G. Rordorf, J. H. Maki, L. A. Kramer, J. C. Grotta, W. S. Burgin, J. A. Hinchey, C. Benesch, K. L. Furie, H. L. Lutsep, E. Kelly, and W. T. Longstreth. Increased pelvic vein thrombi in cryptogenic stroke: results of the paradoxical emboli from large veins in ischemic stroke (pelvis) study. Stroke, 35(1):46–50, Jan 2004.
- A. Cukier, C. A. S. Ferreira, R. Stelmach, M. Ribeiro, F. Cortopassi, and P. M. A. Calverley. The effect of bronchodilators and oxygen alone and in combination on self-paced exercise performance in stable copd. Respir Med, 101(4):746–753, Apr 2007.
- M. J. Cutler, N. M. Swift, D. M. Keller, W. L. Wasmund, J. R. Burk, and M. L. Smith. Periods of intermittent hypoxic apnea can alter chemoreflex control of sympathetic nerve activity in humans. Am J Physiol Heart Circ Physiol, 287(5):H2054–60, 2004a.
- M. J. Cutler, N. M. Swift, D. M. Keller, W. L. Wasmund, and M. L. Smith.

- Hypoxia-mediated prolonged elevation of sympathetic nerve activity after periods of intermittent hypoxic apnea. J Appl Physiol, 96(2):754–61, 2004b.
- C. Daniels, C. Weytjens, B. Cosyns, D. Schoors, J. De Sutter, B. Paelinck, L. Muyldermans, and G. Van Camp. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. Eur J Echocardiogr, 5(6):449–52, 2004.
- D. R. Dantzker and G. E. D’Alonzo. The effect of exercise on pulmonary gas exchange in patients with severe chronic obstructive pulmonary disease. Am Rev Respir Dis, 134(6):1135–1139, Dec 1986.
- A. Davidson, K. Chandrasekaran, L. Guida, and Jr. Holsclaw, D. S. Enhancement of hypoxemia by atrial shunting in cystic fibrosis. Chest, 98(3):543–5, 1990.
- P. B. Davis. Cystic fibrosis since 1938. Am J Respir Crit Care Med, 173(5): 475–482, Mar 2006.
- M. A. De Belder, L. Tourikis, M. Griffith, G. Leech, and A. J. Camm. Transesophageal contrast echocardiography and color flow mapping: methods of choice for the detection of shunts at the atrial level? Am Heart J, 124(6):1545–50, 1992.
- P. C. Deegan and W. T. McNicholas. Predictive value of clinical features for the obstructive sleep apnoea syndrome. Eur Respir J, 9(1):117–124, Jan 1996.
- K. A. Desouza, S. Saraswat, S. A. DeSouza, V. Rajaram, P. C. Reddy, L. Mosley, and N. Tandon. Platypnea-orthodeoxia syndrome: a diagnostic challenge. South Med J, 102(10):1046–1048, Oct 2009.
- K. Dingli, E. L. Coleman, M. Vennelle, S. P. Finch, P. K. Wraith, T. W. Mackay,

- and N. J. Douglas. Evaluation of a portable device for diagnosing the sleep apnoea/hypopnoea syndrome. Eur Respir J, 21(2):253–9, 2003a.
- K. Dingli, E. L. Coleman, M. Vennelle, S. P. Finch, P. K. Wraith, T. W. Mackay, and N. J. Douglas. Evaluation of a portable device for diagnosing the sleep apnoea/hypopnoea syndrome. Eur Respir J, 21(2):253–259, Feb 2003b.
- M. DiTullio, R. L. Sacco, A. Gopal, J. P. Mohr, and S. Homma. Patent foramen ovale as a risk factor for cryptogenic stroke. Ann Intern Med, 117(6):461–465, Sep 1992.
- J. W. Dodd, S. V. Getov, and P. W. Jones. Cognitive function in copd. Eur Respir J, 35(4):913–922, Apr 2010.
- A. Dowson, M. J. Mullen, R. Peatfield, K. Muir, A. A. Khan, C. Wells, S. L. Lipscombe, T. Rees, J. V. De Giovanni, W. L. Morrison, D. Hildick-Smith, G. Elrington, W. S. Hillis, I. S. Malik, and A. Rickards. Migraine intervention with starflex technology (mist) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with starflex septal repair implant to resolve refractory migraine headache. Circulation, 117(11):1397–404, 2008.
- M. W. Eldridge, J. A. Dempsey, H. C. Haverkamp, A. T. Lovering, and J. S. Hokanson. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. J Appl Physiol, 97(3):797–805, 2004.
- H. M. Engleman and N. J. Douglas. Sleep. 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax, 59(7):618–22, 2004.
- A. A. Epstein. A contribution to the study of the chemistry of blood serum. J Exp Med, 16(6):719–731, Dec 1912.

- J. D. Espiritu and M. E. Kleinhenz. Paradoxical embolization in an adult patient with cystic fibrosis. Mayo Clin Proc, 75(10):1100–2, 2000.
- John L Faul, Juan Galindo, Rodolfo Posadas-Valay, Guillermo Elizondo-Riojas, Angel Martinez, and Christopher B Cooper. An arteriovenous fistula increases exercise capacity in patients with copd. Chest, 138:52–58, 2010.
- J. R. Feary, L. C. Rodrigues, C. J. Smith, R. B. Hubbard, and J. E. Gibson. Prevalence of major comorbidities in subjects with copd and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. Thorax, 65(11):956–962, Nov 2010.
- R. Feurer, S. Sadikovic, D. Sepp, L. Esposito, M. Schleef, A. Bockelbrink, J. Schwarze, B. Hemmer, D. Sander, and H. Poppert. Patent foramen ovale is not associated with an increased risk of stroke recurrence. Eur J Neurol, 17(11):1339–1345, Nov 2010.
- L. Finn, T. Young, M. Palta, and D. G. Fryback. Sleep-disordered breathing and self-reported general health status in the wisconsin sleep cohort study. Sleep, 21(7):701–6, 1998.
- S. F Fitzpatrick, M. M. Tambuwala, U. Bruning, B. Schaible, C. C. Scholz, A. Byrne, A. O’Connor, W. M. Gallagher, C. R. Lenihan, J. F. Garvey, K. Howell, P. G. Fallon, E. P. Cummins, and C. T. Taylor. An intact canonical nf- κ b pathway is required for inflammatory gene expression in response to hypoxia. J Immunol, 186(2):1091–1096, Jan 2011.
- E. C. Fletcher, C. Costaragos, and T. Miller. The rate of fall of arterial oxyhemoglobin saturation in obstructive sleep apnea. Chest, 96(4):717–22, 1989.
- A. J. Furlan. Closure 1 investigators. a prospective, multicenter, randomized controlled trial to evaluate the safety and efficacy of the starflex septal

closure system versus best medical therapy in patients with a stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. presented at the american heart association meeting. 15th November 2010.

P. Garg, S. J. Servoss, J. C. Wu, Z. H. Bajwa, M. H. Selim, A. Dineen, R. E. Kuntz, E. F. Cook, and L. Mauri. Lack of association between migraine headache and patent foramen ovale: results of a case-control study. Circulation, 121(12):1406–1412, Mar 2010.

A. M. Garratt, D. A. Ruta, M. I. Abdalla, J. K. Buckingham, and I. T. Russell. The sf36 health survey questionnaire: an outcome measure suitable for routine use within the nhs? BMJ, 306(6890):1440–1444, May 1993.

L. Gelernter-Yaniv, A. Khoury, Y. Schwartz, and A. Lorber. Transcatheter closure of right-to-left interatrial shunts to resolve hypoxemia. Congenit Heart Dis, 3(1):47–53, 2008.

A. Giardini, A. Donti, R. Formigari, L. Salomone, G. Palareti, D. Guidetti, and F. M. Picchio. Spontaneous large right-to-left shunt and migraine headache with aura are risk factors for recurrent stroke in patients with a patent foramen ovale. Int J Cardiol, 120(3):357–62, 2007.

G. J. Gibson. Clinical Tests of Respiratory Function. London: Hodder Arnold, 3rd ed. edition, 2009.

T. Gonzalez-Alujas, A. Evangelista, E. Santamarina, M. Rubiera, Z. Gmez-Bosch, J. F. Rodriguez-Palomares, G. Avegliano, C. Molina, J. Alvarez-Sabn, and D. Garca-Dorado. Diagnosis and quantification of patent foramen ovale. which is the reference technique? simultaneous study with transcranial doppler, transthoracic and transesophageal echocardiography. Rev Esp Cardiol, 64(2):133–139, Feb 2011.

- D. Gorecka, K. Gorzelak, P. Sliwinski, M. Tobiasz, and J. Zielinski. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax, 52(8):674–9, 1997.
- C. Guilleminault, A. Tilkian, and W. C. Dement. The sleep apnea syndromes. Annu Rev Med, 27:465–84, 1976.
- P. Gurin, V. Lambert, F. Godart, A. Legendre, J. Petit, F. Bourlon, B. De Geeter, A. Petit, B. Monrozier, A. M. Rossignol, M. Jimenez, D. Crochet, A. Choussat, C. Rey, and J. Losay. Transcatheter closure of patent foramen ovale in patients with platypnea-orthodeoxia: results of a multicentric french registry. Cardiovasc Intervent Radiol, 28(2):164–168, 2005.
- S. S. Hacievliyagil, H. Gunen, F. M. Kosar, I. Sahin, and T. Kilic. Prevalence and clinical significance of a patent foramen ovale in patients with chronic obstructive pulmonary disease. Respir Med, 100(5):903–10, 2006.
- P. T. Hagen, D. G. Scholz, and W. D. Edwards. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc, 59(1):17–20, 1984.
- M. Handke, A. Harloff, M. Olschewski, A. Hetzel, and A. Geibel. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med, 357(22):2262–2268, Nov 2007.
- P. F. Harner and T. Sannit. A Review of the International Ten-Twenty System of Electrode Placement. Grass Instrument Company, 1974.
- J. U. Harrer, T. Wessels, A. Franke, S. Lucas, P. Berlit, and C. Klotzsch. Stroke recurrence and its prevention in patients with patent foramen ovale. Can J Neurol Sci, 33(1):39–47, 2006.

- E. A. Harris, M. E. Hunter, E. R. Seelye, M. Vedder, and R. M. Whitlock. Prediction of the physiological dead-space in resting normal subjects. Clin Sci Mol Med, 45(3):375–386, Sep 1973.
- S. Homma, R. L. Sacco, M. R. Di Tullio, R. R. Sciacca, J. P. Mohr, and PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in cryptogenic stroke study. Circulation, 105(22):2625–2631, Jun 2002.
- N. S. Hopkinson, T. P. Toma, D. M. Hansell, P. Goldstraw, J. Moxham, D. M. Geddes, and M. I. Polkey. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Respir Crit Care Med, 171(5):453–60, 2005.
- R. L. Horner, D. Brooks, L. F. Kozar, S. Tse, and E. A. Phillipson. Immediate effects of arousal from sleep on cardiac autonomic outflow in the absence of breathing in dogs. J. Appl. Physiol., 79:151–62, 1995.
- K. Horsfield, N. Segel, and J. M. Bishop. The pulmonary circulation in chronic bronchitis at rest and during exercise breathing air and 80 per cent oxygen. Clin Sci, 34(3):473–83, 1968.
- C. Iber, S. Ancoli-Israel, A. L. Chesson, and S. F. Quan. The aasm manual for the scoring of sleep and associated events: Rules, terminology and technical specifications, 2007.
- L. Ilkhanoff, S. S. Naidu, S. Rohatgi, M. J. Ross, F. E. Silvestry, and H. C. Herrmann. Transcatheter device closure of interatrial septal defects in patients with hypoxia. J Interv Cardiol, 18(4):227–232, Aug 2005.
- J. P. Janssens, T. Rochat, J. G. Frey, N. Dousse, C. Pichard, and J. M. Tschopp. Health-related quality of life in patients under long-term oxygen therapy: a home-based descriptive study. Respir Med, 91(10):592–602, 1997.

- S. Jelic, M. Padeletti, S. M. Kawut, C. Higgins, S. M. Canfield, D. Onat, P. C. Colombo, R. C. Basner, P. Factor, and T. H. LeJemtel. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation, 117(17):2270–8, 2008.
- F. P. Job, E. B. Ringelstein, Y. Grafen, F. A. Flachskampf, C. Doherty, A. Stockmanns, and P. Hanrath. Comparison of transcranial contrast doppler sonography and transesophageal contrast echocardiography for the detection of patent foramen ovale in young stroke patients. Am J Cardiol, 74(4):381–4, 1994.
- M. C. Johansson, P. Eriksson, Y. Peker, J. Hedner, L. Rastam, and U. Lindblad. The influence of patent foramen ovale on oxygen desaturation in obstructive sleep apnoea. Eur Respir J, 29(1):149–55, 2007.
- M. W. Johns. A new method for measuring daytime sleepiness: the epworth sleepiness scale. Sleep, 14(6):540–5, 1991.
- R. Karnik, C. Stollberger, A. Valentin, W. B. Winkler, and J. Slany. Detection of patent foramen ovale by transcranial contrast doppler ultrasound. Am J Cardiol, 69(5):560–2, 1992.
- V. Karttunen, M. Ventil , M. Ik lheimio, M. Niemel , and M. Hillbom. Ear oximetry: a noninvasive method for detection of patent foramen ovale: a study comparing dye dilution method and oximetry with contrast transesophageal echocardiography. Stroke, 32(2):448–453, Feb 2001.
- A. T. Kawaguchi, Y. Kawashima, H. Ishibashi-Ueda, M. Yanase, T. Murakami, T. Yagihara, and T. Kunieda. Right-to-left interatrial shunt in rats with progressive pulmonary hypertension. J Thorac Cardiovasc Surg, 106(6):1072–80, 1993.

- E. K. Kerut, W. T. Norfleet, G. D. Plotnick, and T. D. Giles. Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol, 38(3):613–623, Sep 2001.
- R. Kessler, A. Chaouat, P. Schinkewitch, M. Faller, S. Casel, J. Krieger, and E. Weitzenblum. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest, 120(2):369–76, 2001.
- H. Kilic, M. M. Balci, M. N. Aksoy, E. Bilgin, K. G. Gulsoy, E. Yeter, S. Acikel, and R. Akdemir. Patent foramen ovale among patients with mild chronic obstructive pulmonary disease and unexplained hypoxia. Echocardiography, 27(6):687–90, 2010.
- Y. J. Kim, J. Hur, C-Y. Shim, H-J. Lee, J-W. Ha, K. O. Choe, J. H. Heo, E-Y. Choi, and B. W. Choi. Patent foramen ovale: diagnosis with multidetector ct– comparison with transesophageal echocardiography. Radiology, 250(1): 61–67, Jan 2009.
- C. Klotzsch, G. Janssen, and P. Berlit. Transesophageal echocardiography and contrast-tcd in the detection of a patent foramen ovale: experiences with 111 patients. Neurology, 44(9):1603–6, 1994.
- C. Koechlin, F. Maltais, D. Saey, A. Michaud, P. LeBlanc, M. Hayot, and C. Prefaut. Hypoxaemia enhances peripheral muscle oxidative stress in chronic obstructive pulmonary disease. Thorax, 60(10):834–841, Oct 2005.
- S. Konstantinides, A. Geibel, W. Kasper, M. Olschewski, L. Blumel, and H. Just. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. Circulation, 97(19):1946–51, 1998.
- Y. Koshino, H. R. Villarraga, M. Orban, C. J. Bruce, G. S. Pressman, P. Leinveber, H. K. Saleh, T. Konecny, T. Kara, V. K. Somers, and F. Lopez-

- Jimenez. Changes in left and right ventricular mechanics during the mueller maneuver in healthy adults: a possible mechanism for abnormal cardiac function in patients with obstructive sleep apnea. Circ Cardiovasc Imaging, 3(3):282–9, 2010.
- M. Kosinski, M. S. Bayliss, J. B. Bjorner, Jr. Ware, J. E., W. H. Garber, A. Batenhorst, R. Cady, C. G. Dahlof, A. Dowson, and S. Tepper. A six-item short-form survey for measuring headache impact: the hit-6. Qual Life Res, 12(8):963–74, 2003.
- B. Kuch, M. Riehle, and W. von Scheidt. Hypoxemia from right-to-left shunting through a patent foramen ovale in right ventricular infarction: treatment by revascularization, preload reduction, and, finally, interventional pfo closure. Clin Res Cardiol, 95(12):680–4, 2006.
- C. A. Kushida, M. R. Littner, T. Morgenthaler, C. A. Alessi, D. Bailey, J. Coleman, L. Friedman, M. Hirshkowitz, S. Kapen, M. Kramer, T. Lee-Chiong, D. L. Loube, J. Owens, J. P. Pancer, and M. Wise. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep, 28(4):499–521, Apr 2005.
- D. Kyroussis, M. I. Polkey, C. H. Hamnegard, G. H. Mills, M. Green, and J. Moxham. Respiratory muscle activity in patients with copd walking to exhaustion with and without pressure support. Eur Respir J, 15(4):649–55, 2000.
- M. C. Lange, V. F. Zetola, E. J. Piovesan, and L. C. Werneck. Saline versus saline with blood as a contrast agent for right-to-left shunt diagnosis by transcranial doppler: Is there a significant difference? J Neuroimaging, Oct 2010.
- E. A. Laude, N. C. Duffy, C. Baveystock, B. Dougill, M. J. Campbell, R. Lawson,

- P. W. Jones, and P. M. Calverley. The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease: a randomized crossover trial. Am J Respir Crit Care Med, 173(8):865–870, Apr 2006.
- S. S. Laurie, X. Yang, J. E. Elliott, K. M. Beasley, and A. T. Lovering. Hypoxia-induced intrapulmonary arteriovenous shunting at rest in healthy humans. J Appl Physiol, 109(4):1072–9, 2010.
- P. Lechat, J. L. Mas, G. Lascault, P. Loron, M. Theard, M. Klimczak, G. Drobinski, D. Thomas, and Y. Grosgogeat. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med, 318(18):1148–52, 1988.
- H. H. Leuchte, R. A. Baumgartner, M. E. Nounou, M. Vogeser, C. Neurohr, M. Trautnitz, and J. Behr. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. Am J Respir Crit Care Med, 173(7):744–50, 2006.
- R. W. Light, H. M. Mintz, G. S. Linden, and S. E. Brown. Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. Am Rev Respir Dis, 130(3):391–5, 1984.
- R. B. Lipton, W. F. Stewart, S. Diamond, M. L. Diamond, and M. Reed. Prevalence and burden of migraine in the united states: data from the american migraine study ii. Headache, 41(7):646–657, 2001.
- R. B. Lipton, J. N. Liberman, K. B. Kolodner, M. E. Bigal, A. Dowson, and W. F. Stewart. Migraine headache disability and health-related quality-of-life: a population-based case-control study from england. Cephalalgia, 23(6):441–450, Jul 2003.
- A. T. Lovering, M. K. Stickland, M. Amann, J. C. Murphy, M. J. O’Brien, J. S. Hokanson, and M. W. Eldridge. Hyperoxia prevents exercise-induced intrapulmonary arteriovenous shunt in healthy humans. J Physiol, 586(Pt 18):4559–65, 2008.

- A. T. Lovering, M. K. Stickland, M. Amann, M. J. O'Brien, J. S. Hokanson, and M. W. Eldridge. Effect of a patent foramen ovale on pulmonary gas exchange efficiency at rest and during exercise. J Appl Physiol, 110(5):1354–1361, May 2011.
- J. J. Lynch, G. H. Schuchard, C. M. Gross, and L. S. Wann. Prevalence of right-to-left atrial shunting in a healthy population: detection by valsalva maneuver contrast echocardiography. Am J Cardiol, 53(10):1478–1480, May 1984.
- N. Macintyre, R. O. Crapo, G. Viegi, D. C. Johnson, C. P. van der Grinten, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, P. Enright, P. Gustafsson, J. Hankinson, R. Jensen, R. McKay, M. R. Miller, D. Navajas, O. F. Pedersen, R. Pellegrino, and J. Wanger. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J, 26(4):720–35, 2005.
- D. Madala, J. G. Zaroff, L. Hourigan, and E. Foster. Harmonic imaging improves sensitivity at the expense of specificity in the detection of patent foramen ovale. Echocardiography, 21(1):33–6, 2004.
- H. Madani and P. A. Ransom. Paradoxical embolus illustrating speed of action of recombinant tissue plasminogen activator in massive pulmonary embolism. Emerg Med J, 24(6):441, Jun 2007.
- D. A. Mahler, B. N. Brent, J. Loke, B. L. Zaret, and R. A. Matthay. Right ventricular performance and central circulatory hemodynamics during upright exercise in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis, 130(5):722–9, 1984.
- J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. Agusti. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea

- with or without treatment with continuous positive airway pressure: an observational study. Lancet, 365(9464):1046–53, 2005.
- M. A. Martnez-Garcia, J. J. Soler-Cataluna, L. Ejarque-Martinez, Y. Soriano, P. Roman-Sanchez, F. B. Illa, J. M. M. Canal, and J. Duran-Cantolla. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. Am J Respir Crit Care Med, 180(1):36–41, Jul 2009.
- J. Mead, I. M. Mc, N. J. Selverstone, and B. C. Kriete. Measurement of intraesophageal pressure. J Appl Physiol, 7(5):491–5, 1955.
- R. Mehra, E. J. Benjamin, E. Shahar, D. J. Gottlieb, R. Nawabit, H. L. Kirchner, J. Sahadevan, and S. Redline. Association of nocturnal arrhythmias with sleep-disordered breathing: The sleep heart health study. Am J Respir Crit Care Med, 173(8):910–6, 2006.
- I. Meissner, J. P. Whisnant, B. K. Khandheria, P. C. Spittell, W. M. O’Fallon, R. D. Pascoe, M. Enriquez-Sarano, J. B. Seward, J. L. Covalt, J. D. Sicks, and D. O. Wiebers. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the sparcs study. stroke prevention: Assessment of risk in a community. Mayo Clin Proc, 74(9):862–9, 1999.
- N. Mercho, J. K. Stoller, R. D. White, and A. C. Mehta. Right-to-left interatrial shunt causing platypnea after pneumonectomy. a recent experience and diagnostic value of dynamic magnetic resonance imaging. Chest, 105(3): 931–933, Mar 1994.
- M. R. Miller, R. Crapo, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, P. Enright, C. P. van der Grinten, P. Gustafsson, R. Jensen, D. C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O. F. Pedersen, R. Pellegrino,

- G. Viegi, and J. Wanger. General considerations for lung function testing. Eur Respir J, 26(1):153–61, 2005a.
- M. R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C. P. van der Grinten, P. Gustafsson, R. Jensen, D. C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O. F. Pedersen, R. Pellegrino, G. Viegi, and J. Wanger. Standardisation of spirometry. Eur Respir J, 26(2): 319–38, 2005b.
- K. Minoguchi, T. Yokoe, T. Tazaki, H. Minoguchi, A. Tanaka, N. Oda, S. Okada, S. Ohta, H. Naito, and M. Adachi. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med, 172(5):625–30, 2005.
- O. K. Mohrs, S. E. Petersen, D. Erkapic, A. Victor, T. Schlosser, B. Nowak, G. Kauffmann, T. Voigtlaender, and H-U. Kauczor. Dynamic contrast-enhanced mri before and after transcatheter occlusion of patent foramen ovale. Am J Roentgenol, 188(3):844–849, Mar 2007.
- I. Monte, S. Grasso, S. Licciardi, and L. P. Badano. Head-to-head comparison of real-time three-dimensional transthoracic echocardiography with transthoracic and transesophageal two-dimensional contrast echocardiography for the detection of patent foramen ovale. Eur J Echocardiogr, 11(3):245–249, Apr 2010.
- A. H. Moreno, A. R. Burchell, R. Van der Woude, and J. H. Burke. Respiratory regulation of splanchnic and systemic venous return. Am J Physiol, 213(2): 455–65, 1967.
- P. M. Mottram, D. J. McGaw, I. T. Meredith, R. E. Peverill, and R. W. Harper. Profound hypoxaemia corrected by pfo closure device in carcinoid heart disease. Eur J Echocardiogr, 2006.

- MRC. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. report of the medical research council working party. Lancet, 1(8222):681–6, 1981.
- M. J. Mullen, D. Hildick-Smith, J. V. De Giovanni, C. Duke, W. S. Hillis, W. L. Morrison, and C. Jux. Biostar evaluation study (best): a prospective, multicenter, phase i clinical trial to evaluate the feasibility, efficacy, and safety of the biostar bioabsorbable septal repair implant for the closure of atrial-level shunts. Circulation, 114(18):1962–7, 2006.
- K. Narkiewicz, N. Montano, C. Cogliati, P. J. van de Borne, M. E. Dyken, and V. K. Somers. Altered cardiovascular variability in obstructive sleep apnea. Circulation, 98(11):1071–1077, Sep 1998.
- H. J. Nesser, W. Tkalec, A. R. Patel, N. D. Masani, J. Niel, B. Markt, and N. G. Pandian. Quantitation of right ventricular volumes and ejection fraction by three-dimensional echocardiography in patients: comparison with magnetic resonance imaging and radionuclide ventriculography. Echocardiography, 23(8):666–680, Sep 2006.
- M. Niijima, H. Kimura, H. Edo, T. Shinozaki, J. Kang, S. Masuyama, K. Tatsumi, and T. Kuriyama. Manifestation of pulmonary hypertension during rem sleep in obstructive sleep apnea syndrome. Am J Respir Crit Care Med, 159(6):1766–72, 1999.
- NOTT. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. nocturnal oxygen therapy trial group. Ann Intern Med, 93(3):391–8, 1980.
- A. W. Nugent, A. Britt, K. Gauvreau, G. E. Piercey, J. E. Lock, and K. J. Jenkins. Device closure rates of simple atrial septal defects optimized by the starflex device. J Am Coll Cardiol, 48(3):538–44, 2006.

- D. E. O'Donnell, M. Lam, and K. A. Webb. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 160(2):542–549, Aug 1999.
- D. E. O'Donnell, C. D'Arsigny, and K. A. Webb. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 163(4):892–8, 2001a.
- D. E. O'Donnell, S. M. Reville, and K. A. Webb. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 164(5):770–7, 2001b.
- D. E. O'Donnell, C. D'Arsigny, M. Fitzpatrick, and K. A. Webb. Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. Am J Respir Crit Care Med, 166(5):663–668, Sep 2002.
- D. E. O'Donnell, T. Flge, F. Gerken, A. Hamilton, K. Webb, B. Aguilaniu, B. Make, and H. Magnussen. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in copd. Eur Respir J, 23(6):832–840, Jun 2004a.
- D. E. O'Donnell, N. Voduc, M. Fitzpatrick, and K. A. Webb. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. Eur Respir J, 24(1):86–94, Jul 2004b.
- D. M. O'Driscoll, G. E. Meadows, Corfield. D. R., A. K. Simonds, and M. J. Morrell. Cardiovascular response to arousal from sleep under controlled conditions of central and peripheral chemoreceptor stimulation in humans. J Appl Physiol, 96(3):865–870, Mar 2004.

- S. Okabe, W. Hida, Y. Kikuchi, O. Taguchi, H. Ogawa, A. Mizusawa, H. Miki, and K. Shirato. Role of hypoxia on increased blood pressure in patients with obstructive sleep apnoea. Thorax, 50(1):28–34, Jan 1995.
- J. R. Overell, I. Bone, and K. R. Lees. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology, 55(8):1172–9, 2000.
- M. Paciaroni, G. Agnelli, A. Bertolini, A. Pezzini, A. Padovani, V. Caso, M. Venti, A. Alberti, R. A. Palmiero, P. Cerrato, G. Silvestrelli, A. Lanari, P. Previdi, F. Corea, A. Balducci, R. Ferri, F. Falcinelli, E. Filippucci, P. Chiochi, F. C. Grandi, L. Ferigo, R. Musolino, A. Bersano, I. Ghione, S. Sacco, A. Carolei, A. Baldi, W. Ageno, and F. O. R. I. (Foramen Ovale Registro Italiano) Investigators. Risk of recurrent cerebrovascular events in patients with cryptogenic stroke or transient ischemic attack and patent foramen ovale: the fori (foramen ovale registro italiano) study. Cerebrovasc Dis, 31(2):109–116, 2011.
- A. C. Pearson, A. J. Labovitz, S. Tatinenja, and C. R. Gomez. Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. J Am C, 17:66 – 72, 1991.
- R. Pellegrino, G. Viegi, V. Brusasco, R. O. Crapo, F. Burgos, R. Casaburi, A. Coates, C. P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. C. Johnson, N. MacIntyre, R. McKay, M. R. Miller, D. Navajas, O. F. Pedersen, and J. Wanger. Interpretative strategies for lung function tests. Eur Respir J, 26(5):948–68, 2005.
- J. L. Pepin, C. E. Barjhoux, C. Deschaux, and C. Brambilla. Long-term oxygen therapy at home. compliance with medical prescription and effective use of

- therapy. antadir working group on oxygen therapy. association nationale de traitement a domicile des insuffisants respiratoires. Chest, 109(5):1144–50, 1996.
- P. E. Peppard, T. Young, M. Palta, J. Dempsey, and J. Skatrud. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA, 284(23):3015–3021, Dec 2000a.
- P. E. Peppard, T. Young, M. Palta, and J. Skatrud. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med, 342(19):1378–84, 2000b.
- S. Permutt. Circulatory effects of weaning from mechanical ventilation: the importance of transdiaphragmatic pressure. Anesthesiology, 69(2):157–60, 1988.
- J. F. Piechaud. Hypoxemia related to right-to-left shunting through a patent foramen ovale: successful percutaneous treatment with the cardioseal device. J Interv Cardiol, 14(1):57–60, 2001.
- V. M. Pinto-Plata, C. Cote, H. Cabral, J. Taylor, and B. R. Celli. The 6-min walk distance: change over time and value as a predictor of survival in severe copd. Eur Respir J, 23(1):28–33, 2004.
- V. M. Pinto-Plata, H. Mllerova, J. F. Toso, M. Feudjo-Tepie, J. B. Soriano, R. S. Vessey, and B. R. Celli. C-reactive protein in patients with copd, control smokers and non-smokers. Thorax, 61(1):23–28, Jan 2006.
- S. D. Playfor and A. R. Smyth. Paradoxical embolism in a boy with cystic fibrosis and a stroke. Thorax, 54(12):1139–40, 1999.
- J. Porszasz, M. Emtner, S. Goto, A. Somfay, B. J. Whipp, and R. Casaburi. Exercise training decreases ventilatory requirements and exercise-induced

- hyperinflation at submaximal intensities in patients with copd. Chest, 128 (4):2025–2034, Oct 2005.
- B. Priest, C. Brichard, G. Aubert, G. Liistro, and D. O. Rodenstein. Microsleep during a simplified maintenance of wakefulness test. a validation study of the osler test. Am J Respir Crit Care Med, 163(7):1619–25, 2001.
- P. H. Quanjer, G. J. Tammeling, J. E. Cotes, L. M. Fabbri, H. Matthys, O. F. Pedersen, R. Peslin, J. Roca, P. J. Sterk, W. T. Ulmer, and et al. Symbols, abbreviations and units. working party standardization of lung function tests, european community for steel and coal. Eur Respir J Suppl, 16:85–100, 1993a.
- P. H. Quanjer, G. J. Tammeling, J. E. Cotes, O. F. Pedersen, R. Peslin, and J. C. Yernault. Lung volumes and forced ventilatory flows. report working party standardization of lung function tests, european community for steel and coal. official statement of the european respiratory society. Eur Respir J Suppl, 16:5–40, 1993b.
- Klaus F Rabe, Suzanne Hurd, Antonio Anzueto, Peter J Barnes, Sonia A Buist, Peter Calverley, Yoshinosuke Fukuchi, Christine Jenkins, Roberto Rodriguez-Roisin, Chris van Weel, Jan Zielinski, and Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Gold executive summary. Am J Respir Crit Care Med, 176:532–555, 2007.
- D. A. Raeside, A. Brown, K. R. Patel, D. Welsh, and A. J. Peacock. Ambulatory pulmonary artery pressure monitoring during sleep and exercise in normal individuals and patients with copd. Thorax, 57(12):1050–3, 2002.
- B. S. Rana, L. M. Shapiro, K. P. McCarthy, and S. Y. Ho. Three-dimensional imaging of the atrial septum and patent foramen ovale anatomy: defining

- the morphological phenotypes of patent foramen ovale. Eur J Echocardiogr, 11(10):i19–i25, Dec 2010.
- P. S. Rao, I. F. Palacios, R. G. Bach, S. R. Bitar, and E. B. Sideris. Platypnea-orthodeoxia: management by transcatheter buttoned device implantation. Catheter Cardiovasc Interv, 54(1):77–82, Sep 2001.
- M. Remy-Jardin, J. Remy, and B. Wallaert. Right-to-left shunting through a patent foramen ovale without pulmonary hypertension. transient improvement after balloon catheter closure. Chest, 97(5):1250–2, 1990.
- G. Rigatelli, F. Dell’Avvocata, P. Cardaioli, M. Giordan, G. Braggion, S. Aggio, L. Roncon, and M. Chinaglia. Migraine-patent foramen ovale connection: Role of prominent eustachian valve and large chiari network in migrainous patients. American Journal of the Medical Sciences, 336(6):458–461, 2008.
- G. Rigatelli, S. Aggio, P. Cardaioli, G. Braggion, M. Giordan, F. Dell’avvocata, M. Chinaglia, G. Rigatelli, L. Roncon, and J. P. Chen. Left atrial dysfunction in patients with patent foramen ovale and atrial septal aneurysm: an alternative concurrent mechanism for arterial embolism? JACC Cardiovasc Interv, 2(7):655–662, Jul 2009.
- H. Rimington and J. Chambers. Echocardiography A Practical Guide for Reporting. The Parthenon Publishing Group, 1998.
- R. Rodriguez-Roisin, M Drakulovic, D. A. Rodrguez, J. Roca, J. A. Barbera, and P. D. Wagner. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. J Appl Physiol, 106(6):1902–1908, Jun 2009.
- T.W. Sadler. Langmans Medical Embryology. Lippincott Williams & Wilkins, Philadelphia, 6th edition edition, 1990.

- K. Sandek, T. Bratel, G. Hellström, and L. Lagerstrand. Ventilation-perfusion inequality and carbon dioxide sensitivity in hypoxaemic chronic obstructive pulmonary disease (copd) and effects of 6 months of long-term oxygen treatment (ltot). Clin Physiol, 21(5):584–593, Sep 2001.
- V. Sanikommu, D. Lasorda, and I. IPoornima. Anatomical factors triggering platypnea–orthodeoxia in adults. Clin Cardiol, 32(11):E55–E57, Nov 2009.
- M. Saqqur, N. Dean, M. Schebel, M. D. Hill, A. Salam, A. Shuaib, and A. M. Demchuk. Improved detection of microbubble signals using power m-mode doppler. Stroke, 35(1):e14–7, 2004.
- F. Saremi, S. F. Attai, and J. Narula. 64 multidetector ct in patent foramen ovale. Heart, 93(4):505, Apr 2007.
- F. Saremi, S. Channal, A. Raney, S. V. Gurudevan, J. Narula, S. Fowler, A. Abolhoda, and J. C. Milliken. Imaging of patent foramen ovale with 64-section multidetector ct. Radiology, 249:483–492, 2008.
- S. Sastry, K. Daly, T. Chengodu, and C. McCollum. Is transcranial doppler for the detection of venous-to-arterial circulation shunts reproducible? Cerebrovasc Dis, 23(5-6):424–9, 2007.
- S. M. Scharf, M. Iqbal, C. Keller, G. Criner, S. Lee, and H. E. Fessler. Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med, 166(3):314–22, 2002.
- A. M. Schols, J. Slangen, L. Volovics, and E. F. Wouters. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 157(6 Pt 1):1791–7, 1998.
- B. Schonhofer, T. Barchfeld, M. Wenzel, and D. Kohler. Long term effects

- of non-invasive mechanical ventilation on pulmonary haemodynamics in patients with chronic respiratory failure. Thorax, 56(7):524–8, 2001.
- H. W. Schuchlenz, W. Weihs, S. Horner, and F. Quehenberger. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. Am J Med, 109(6):456–62, 2000.
- H. W. Schuchlenz, G. Saurer, W. Weihs, and P. Rehak. Persisting eustachian valve in adults: relation to patent foramen ovale and cerebrovascular events. J. Am. Soc. Echocardiogr., 17:231233, 2004.
- M. Schwerzmann, K. Nedeltchev, F. Lagger, H. P. Mattle, S. Windecker, B. Meier, and C. Seiler. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology, 65(9):1415–8, 2005.
- J. Serena, J. Marti-Fabregas, E. Santamarina, J. J. Rodriguez, M. J. Perez-Ayuso, J. Masjuan, T. Segura, J. Gallego, A. Davalos, Right-to-Left Shunt in Cryptogenic Stroke Study CODICIA, and Stroke Project of the Cerebrovascular Diseases Study Group. Recurrent stroke and massive right-to-left shunt: results from the prospective spanish multicenter (codicia) study. Stroke, 39(12):3131–3136, Dec 2008.
- H. Shanoudy, A. Soliman, P. Raggi, J. W. Liu, D. C. Russell, and N. F. Jarmukli. Prevalence of patent foramen ovale and its contribution to hypoxemia in patients with obstructive sleep apnea. Chest, 113(1):91–6, 1998.
- H. Shnaider, A. Shiran, and A. Lorber. Right ventricular diastolic dysfunction and patent foramen ovale causing profound cyanosis. Heart, 90(6):e31, 2004.
- O. Siggaard-Andersen and R. Huch. The oxygen status of fetal blood. Acta Anaesthesiol Scand Suppl, 107:129–35, 1995.

- M. D. Silver and J. S. Dorsey. Aneurysms of the septum primum in adults. Arch Pathol Lab Med, 102(2):62–65, Feb 1978.
- N. J. Simmonds, H. Wyatt, R. Patel, M. E. Hodson, and K. M. Gyi. A woman with cystic fibrosis, severe hypoxaemia, an atrial thrombus and a patent foramen ovale: a case report. J Med Case Reports, 3:8582, 2009.
- A. Soliman, H. Shanoudy, J. Liu, D. C. Russell, and N. F. Jarmukli. Increased prevalence of patent foramen ovale in patients with severe chronic obstructive pulmonary disease. J Am Soc Echocardiogr, 12(2):99–105, 1999.
- V. K. Somers, A. L. Mark, D. C. Zavala, and F. M. Abboud. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. J. Appl. Physiol., 67:2101–2106, 1989.
- V. K. Somers, A. L. Mark, and F. M. Abboud. Interaction of baroreceptor and chemoreceptor reflex control of sympathetic nerve activity in normal humans. J Clin Invest, 87(6):1953–7, 1991.
- M. P. Spencer, M. A. Moehring, J. Jesurum, W. A. Gray, J. V. Olsen, and M. Reisman. Power m-mode transcranial doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. J Neuroimaging, 14(4):342–9, 2004.
- S. Sritippayawan, E. F. MacLaughlin, and M. S. Woo. Acute neurological deficits in a young adult with cystic fibrosis. Pediatr Pulmonol, 35(2):147–51, 2003.
- M. M. Steiner, M. R. Di Tullio, T. Rundek, R. Gan, X. Chen, C. Liguori, M. Brainin, S. Homma, and R. L. Sacco. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. Stroke, 29(5):944–948, May 1998.

- M. K. Stickland, R. C. Welsh, M. J. Haykowsky, S. R. Petersen, W. D. Anderson, D. A. Taylor, M. Bouffard, and R. L. Jones. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. J Physiol, 561(Pt 1): 321–9, 2004.
- R. Stoohs and C. Guilleminault. Cardiovascular changes associated with obstructive sleep apnea syndrome. J Appl Physiol, 72(2):583–589, Feb 1992.
- R. Sztajzel, D. Genoud, S. Roth, B. Mermillod, and J. Le Floch-Rohr. Patent foramen ovale, a possible cause of symptomatic migraine: a study of 74 patients with acute ischemic stroke. Cerebrovasc Dis, 13(2):102–106, 2002.
- N. Takabatake, H. Nakamura, S. Abe, S. Inoue, T. Hino, H. Saito, H. Yuki, S. Kato, and H. Tomoike. The relationship between chronic hypoxemia and activation of the tumor necrosis factor-alpha system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 161(4 Pt 1): 1179–1184, Apr 2000.
- Y. Tayyareci, G. Tayyareci, C. P. Tastan, P. Bayazit, and Y. Nisanci. Early diagnosis of right ventricular systolic dysfunction by tissue doppler-derived isovolumic myocardial acceleration in patients with chronic obstructive pulmonary disease. Echocardiography, 26(9):1026–1035, Oct 2009.
- G. Thabut, G. Dauriat, J. B. Stern, D. Logeart, A. Levy, R. Marrash-Chahla, and H. Mal. Pulmonary hemodynamics in advanced copd candidates for lung volume reduction surgery or lung transplantation. Chest, 127(5):1531–6, 2005.
- N. Thakur, P. D. Blanc, L. J. Julian, E. H. Yelin, P. P. Katz, S. Sidney, C. Iribarren, and M. D. Eisner. Copd and cognitive impairment: the role of hypoxemia and oxygen therapy. Int J Chron Obstruct Pulmon Dis, 5:263–269, 2010.

- A. G. Tilkian, C. Guilleminault, J. S. Schroeder, K. L. Lehrman, F. B. Simmons, and W. C. Dement. Hemodynamics in sleep-induced apnea. studies during wakefulness and sleep. Ann Intern Med, 85(6):714–9, 1976.
- R. Tkacova, F. Rankin, F. S. Fitzgerald, J. S. Floras, and T. D. Bradley. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation, 98(21):2269–75, 1998.
- A. C. Toffart, H. Bouvaist, V. Feral, D. Blin, and C. Pison. Hypoxemia-orthodeoxia related to patent foramen ovale without pulmonary hypertension. Heart Lung, 37(5):385–389, 2008.
- S. R. Torti, M. Billinger, M. Schwerzmann, R. Vogel, R. Zbinden, S. Windecker, and C. Seiler. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. Eur Heart J, 25(12):1014–20, 2004.
- J. Trevelyan and R. P. Steeds. Comparison of transthoracic echocardiography with harmonic imaging with transoesophageal echocardiography for the diagnosis of patent foramen ovale. Postgrad Med J, 82(971):613–4, 2006.
- Y. Tun, S. Okabe, W. Hida, H. Kurosawa, M. Tabata, Y. Kikuchi, and K. Shirato. Nocturnal blood pressure during apnoeic and ventilatory periods in patients with obstructive sleep apnoea. Eur Respir J, 14(6):1271–1277, Dec 1999.
- G. E. Tzelepis, L. Nasiff, F. D. McCool, and J. Hammond. Transmission of pressure within the abdomen. J Appl Physiol, 81(3):1111–4, 1996.
- G. Van Camp, P. Franken, P. Melis, B. Cosyns, D. Schoors, and J. L. Vanoverschelde. Comparison of transthoracic echocardiography with

- second harmonic imaging with transesophageal echocardiography in the detection of right to left shunts. Am J Cardiol, 86(11):1284–7, A9, Dec 2000.
- M. Varkul, T. Robinson, E. Ng, and R. Hyland. Orthodeoxia and platypnea secondary to a patent foramen ovale despite normal right-sided cardiac pressures. Can Respir J, 8(2):105–107, 2001.
- S. Varsano, Y. Neuman, and R. Hirsch. [posture-dependent refractory hypoxemia]. Harefuah, 150(1):21–4, 69, Jan 2011.
- S. Viner, J. P. Szalai, and V. Hoffstein. Are history and physical examination a good screening test for sleep apnea? Ann Intern Med, 115(5):356–359, Sep 1991.
- J. Virolainen, M. Ventilä, H. Turto, and M. Kupari. Influence of negative intrathoracic pressure on right atrial and systemic venous dynamics. Eur Heart J, 16(9):1293–1299, Sep 1995.
- A. Vitarelli, Y. Conde, E. Cimino, S. Stellato, S. D’Orazio, I. D’Angeli, B. L. Nguyen, V. Padella, F. Caranci, A. Petroianni, L. D’Antoni, and C. Terzano. Assessment of right ventricular function by strain rate imaging in chronic obstructive pulmonary disease. Eur Respir J, 27(2):268–75, 2006.
- D. J. Waight, Q. L. Cao, and Z. M. Hijazi. Closure of patent foramen ovale in patients with orthodeoxia-platypnea using the amplatzer devices. Catheter Cardiovasc Interv, 50(2):195–198, Jun 2000.
- J. Wanger, J. L. Clausen, A. Coates, O. F. Pedersen, V. Brusasco, F. Burgos, R. Casaburi, R. Crapo, P. Enright, C. P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. Johnson, N. Macintyre, R. McKay, M. R. Miller, D. Navajas, R. Pellegrino, and G. Viegi. Standardisation of the measurement of lung volumes. Eur Respir J, 26(3):511–22, 2005.

- J. E. Ware, M. A. Kosinski, and J. E. Dewey. How to score version 2 of the sf-36 health survey, 2000.
- M. W. Webster, A. M. Chancellor, H. J. Smith, D. L. Swift, D. N. Sharpe, N. M. Bass, and G. L. Glasgow. Patent foramen ovale in young stroke patients. Lancet, 2(8601):11–2, 1988.
- H. S. Weissmann, R. M. Steingart, T. M. Kiely, L. A. Sugarman, and L. M. Freeman. Myocardial visualization on a perfusion lung scan. J Nucl Med, 21(8):745–746, Aug 1980.
- P. Wilmshurst and P. Bryson. Relationship between the clinical features of neurological decompression illness and its causes. Clin Sci (Lond), 99(1): 65–75, Jul 2000.
- S. Windecker, A. Wahl, K. Nedeltchev, M. Arnold, M. Schwerzmann, C. Seiler, H. P. Mattle, and B. Meier. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. J Am Coll Cardiol, 44(4):750–758, Aug 2004.
- H. K. Yaggi, J. Concato, W. N. Kernan, J. H. Lichtman, L. M. Brass, and V. Mohsenin. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med, 353(19):2034–41, 2005.
- S. Yalonetsky, A. B. Nun, Y. Shwartz, and A. Lorber. Transcatheter closure of a patent foramen ovale prior to a pneumonectomy to prevent platypnea syndrome. Eur J Cardiothorac Surg, 29(4):622–624, Apr 2006.
- S. Yende, G. W. Waterer, E. A. Tolley, A. B. Newman, D. C. Bauer, D. R. Taaffe, R. Jensen, R. Crapo, S. Rubin, M. Nevitt, E. M. Simonsick, S. Satterfield, T. Harris, and S. B. Kritchevsky. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. Thorax, 61(1):10–16, Jan 2006.

- M. Yeung, K. A. Khan, and A. Shuaib. Transcranial doppler ultrasonography in the detection of venous to arterial shunting in acute stroke and transient ischaemic attacks. J Neurol Neurosurg Psychiatry, 61(5):445–449, Nov 1996.
- M. Yin, S. Miyazaki, Y. Itasaka, Y. Shibata, T. Abe, A. Miyoshi, K. Ishikawa, and K. Togawa. A preliminary study on application of portable monitoring for diagnosis of obstructive sleep apnea. Auris Nasus Larynx, 32(2):151–156, Jun 2005.
- M. Yin, S. Miyazaki, and K. Ishikawa. Evaluation of type 3 portable monitoring in unattended home setting for suspected sleep apnea: factors that may affect its accuracy. Otolaryngol Head Neck Surg, 134(2):204–209, Feb 2006.
- T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med, 328(17):1230–5, 1993.
- A. Zierer, S. J. Melby, R. K. Voeller, and M. R. Moon. Interatrial shunt for chronic pulmonary hypertension: differential impact of low-flow vs. high-flow shunting. Am J Physiol Heart Circ Physiol, 296(3):H639–44, 2009.
- C. Zito, G. Dattilo, G. Oreto, G. Di Bella, A. Lamari, R. Iudicello, O. Trio, G. Caracciolo, S. Coglitore, F. Arrigo, and S. Carerj. Patent foramen ovale: comparison among diagnostic strategies in cryptogenic stroke and migraine. Echocardiography, 26(5):495–503, 2009.