Mechanisms of Obstructive Sleep Apnoea in Congestive Heart Failure

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Declaration of Originality

I, Thomas William Carlisle, hereby declare that this thesis contains the results of my own work except where otherwise acknowledged. The studies presented in this thesis were conceived and designed with the assistance of my supervisors, Professor Morrell, Professor Simonds and Professor Cowie. In addition, the research carried out in Detroit, USA during a 6 month collaboration was conceived and designed with the assistance of my collaborators and supervisors, Professor Badr and Professor Sankri-Tarbichi. I acknowledge the invaluable assistance from Mr. Vitor Roldao and Dr Angela Atalla who analysed some of the polysomnography sleep studies. I also acknowledge the inventiveness of Mr Eric Grieg of GM Instruments Ltd who helped to design the mouthpiece used in acoustic reflection measurements. Statistical support was received from Mr Winston Banya of the Clinical Trials and Evaluation Unit, Royal Brompton Hospital and Imperial College London. Information derived from the work of others and discussed in this thesis is referenced in the text and listed in the bibliography. No part of this thesis has previously been submitted in application for a higher degree. Publications in the form of abstract presentations arising from this work are listed on Page 4.

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Abstract

Approximately 50% of chronic heart failure (CHF) patients have obstructive sleep apnoea (OSA); however the mechanisms associated with OSA in CHF patients are incompletely understood. The overall aim of this thesis was to characterise upper airway phenotypes that may contribute to OSA in patients with CHF. Specifically, I sought to test the hypothesis that CHF patients with OSA have overnight rostral fluid shift. Pharyngeal phenotypes were measured non-invasively; pharyngeal calibre was measured using acoustic reflection, pharyngeal collapsibility using the passive critical closing pressure (Pcrit) technique, and changes in pharyngeal compliance during sleep using oesophageal pressure manometry combined with direct visualisation of the pharynx using bronchoscopy. Chapter 5 investigated differences in pharyngeal anatomy and morphology in healthy younger and older male volunteers using acoustic reflection, testing the hypothesis that older healthy males have similar pharyngeal dimensions to younger healthy males.

The findings of this thesis showed that CHF patients with OSA have similar pharyngeal cross-sectional areas to CHF patients without OSA and healthy controls (Chapter 3). Pharyngeal collapsibility was also similar between groups (Chapter 4). CHF patients may be predisposed to pharyngeal collapse due to overnight attenuation of normal pharyngeal dilation during inspiration (Chapter 6). Finally, it was demonstrated that there may be differences in pharyngeal dimensions and morphology in older males compared to younger males (Chapter 5).

The implications of the studies presented in this thesis are that fluid shift may be a contributing factor to OSA in CHF but the findings in this thesis suggest that its role is not likely to be dominant over more established mechanisms of OSA. Moreover, there may be no special features of CHF that explain the high prevalence of OSA in CHF.
Publications Arising from this Thesis

Presented Abstracts


Tom Carlisle, Abdul Ghani Sankri-Tarbichi, Amy Bascom, Mark Pohlman, Mary J Morrell and Safwan Badr. Overnight Pharyngeal Narrowing in Patients with Congestive Heart Failure and Sleep Disordered Breathing. Sleep 2011, Minneapolis, USA.


Tom Carlisle, Neil Ward, Angela Atalla, Martin Cowie, Anita K Simonds and Mary J Morrell. Postural And Overnight Changes In Pharyngeal Calibre And Neck Circumference In Heart Failure Patients With Obstructive Sleep Apnoea. ATS 2012, San Francisco, USA.
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<th>Description</th>
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<tbody>
<tr>
<td>AHI</td>
<td>Apnoea hypopnoea index</td>
</tr>
<tr>
<td>APmean</td>
<td>Mean pharyngeal area</td>
</tr>
<tr>
<td>AR</td>
<td>Acoustic Reflection</td>
</tr>
<tr>
<td>BI</td>
<td>Beginning inspiration</td>
</tr>
<tr>
<td>BiPAP</td>
<td>Bi-level positive airway pressure</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CHF-only</td>
<td>Congestive heart failure without obstructive sleep apnoea</td>
</tr>
<tr>
<td>CHF-OSA</td>
<td>Congestive heart failure with obstructive sleep apnoea</td>
</tr>
<tr>
<td>CHF-CSA</td>
<td>Congestive heart failure with central sleep apnoea</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>CSA</td>
<td>Central sleep apnoea</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized tomography</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>E-DC</td>
<td>Expiratory dynamic pharyngeal compliance</td>
</tr>
<tr>
<td>EE</td>
<td>End expiration</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>EI/BE</td>
<td>End inspiration/beginning expiration</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyogram</td>
</tr>
<tr>
<td>EOG</td>
<td>Electrooculogram</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GA</td>
<td>Glottis area</td>
</tr>
<tr>
<td>I-DC</td>
<td>Inspiratory dynamic pharyngeal compliance</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NREM</td>
<td>Non rapid eye movement</td>
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<tr>
<td>NYHA</td>
<td>New York heart association</td>
</tr>
<tr>
<td>ODI</td>
<td>Oxygen desaturation index</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive sleep apnoea</td>
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<tr>
<td>PE</td>
<td>Peak expiration</td>
</tr>
<tr>
<td>PI</td>
<td>Peak inspiration</td>
</tr>
<tr>
<td>PLM</td>
<td>Periodic limb movement</td>
</tr>
<tr>
<td>Pmask</td>
<td>Mask pressure</td>
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<tr>
<td>Perit</td>
<td>Critical closing pressure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement</td>
</tr>
<tr>
<td>RIP</td>
<td>Respiratory inductance plethysmography</td>
</tr>
<tr>
<td>VP</td>
<td>Pharyngeal volume</td>
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</table>
Chapter 1: General Introduction
1.1. General Introduction

Obstructive sleep apnoea (OSA) is a respiratory disorder characterised by repetitive episodes of pharyngeal narrowing and collapse during sleep. These episodes result in cessation of ventilation and hypoxia, despite ongoing efforts to breathe. The airway reopens and ventilation is restored following arousal from sleep. The symptoms of OSA can include daytime somnolence, although this is not always present, witnessed apnoeas (e.g. by a bed partner), and snoring. If these symptoms are not recognised then OSA can remain undetected for many years.

The prevalence of OSA syndrome (≥5 apnoeas or hypopnoeas per hour of sleep with daytime symptoms of somnolence) in the general population is estimated to be approximately 4% in males and 2% in females (Young et al., 1993). However the prevalence of OSA irrespective of daytime symptoms is even higher, rising to 24% in males and 9% in females (Young et al., 1993). As well as being more common in males than females, the prevalence of OSA tends to increase with age (Bixler et al., 2001, 1998; Durán et al., 2001; Young et al., 1993), although there is some evidence to suggest that it plateaus or decreases over the age of 65 (Ancoli-Israel et al., 2001). In the general population the strongest predictors of OSA are high body mass index (BMI) and large neck circumference (for a review see Young et al., 2002). Some individuals may also be predisposed to OSA by their cranio-facial morphology (Dempsey et al., 2002).

Sleep apnoea is more common in congestive heart failure (CHF) than in the general population. The prevalence is estimated to be approximately 50%, with approximately half having OSA and half having central sleep apnoea (CSA), though estimates vary depending on the criteria used to define sleep apnoea and the population studied (Bitter et al., 2009; Ferrier et al., 2005; Javaheri, 2006; Javaheri et al., 1998; Lanfranchi et al., 2003; MacDonald et al.,
2008; Oldenburg et al., 2007; Schulz et al., 2007; Vazir et al., 2007). Unlike typical OSA patients, the prevalence of obesity in CHF patients is similar to the general population (approximately 25%; Johansson et al., 2001; The NHS Information Centre, 2004), and CHF patients with OSA tend not to present with daytime somnolence (Hastings et al., 2006). It is not currently known what causes such a high prevalence of OSA in CHF or whether different daytime symptoms indicate a different underlying aetiology.

The overall aim of this thesis was to investigate the pathophysiology of OSA in CHF and to determine whether the underlying mechanisms of OSA differ in CHF patients compared to the general population. In the following sections I will describe the aetiology of OSA and CHF.

1.2. Mechanisms of Obstructive Sleep Apnoea

Obstructive sleep apnoea is defined as repetitive narrowing and collapse of the pharynx during sleep. The pharynx is a muscular region of the upper airway composed of the nasopharynx, oropharynx, and laryngopharynx. It is unsupported by any bone or cartilage attachments except at its inferior border with the larynx and its superior border with the nasal and oral cavities. Due to the pharynx lacking any rigid support or bony attachments along most of its length, its patency is determined by a balance of factors that act on the pharyngeal lumen. These factors are discussed further in the following sections.

1.2.1. Site of Pharyngeal Collapse

A number of studies have attempted to localise the site of airway collapse. Due to the dynamic nature of the pharynx there are a number of regions in the pharynx that may be susceptible to collapse. The majority of papers report that pharyngeal collapse occurs in most people with OSA in the retro-palatal region of the oropharynx (the most narrow region of the pharynx), and to a lesser extent, the retro-glossal and hypopharyngeal regions (Rama et al., 2002). It is
interesting to note that several studies identify multiple sites of collapse within the same individual, suggesting that in some individuals the whole airway may be susceptible to collapse and that it simply collapses at its most susceptible region (see Rama et al., 2002 for a meta-analysis and full review of this topic).

1.2.2. Pharyngeal Critical Closing Pressure

Obstructive sleep apnoea is traditionally thought to be a consequence of negative intrathoracic pressure generating a sub-atmospheric upper airway intra-luminal pressure, coupled with insufficient upper airway muscle tone to maintain patency, resulting in pharyngeal narrowing and closure (Remmers et al., 1978). However, this paradigm only takes account of collapsing intra-luminal forces and does not account for extra-luminal forces, which may also contribute to upper airway resistance and collapsibility. The importance of extra-luminal forces can be demonstrated by observations of collapse occurring at pressures equal to or greater than atmospheric pressure under conditions of pharyngeal hypotonia (Schwartz et al., 1998), and of the upper airway closing passively during central apnoea (Badr et al., 1995; see Figure 1.1). Neither of these observations can be explained by a paradigm where negative intra-luminal pressure is the only collapsing force acting on the upper airway.
Images show the pharyngeal lumen becoming progressively narrower during a period of absent airflow and oesophageal pressure swings (a surrogate for respiratory effort). The pharynx is completely occluded in image 4 and 5. Passive pharyngeal collapse cannot be explained by a model of the pharynx that relies exclusively on negative intra-luminal pressure being the only collapsing force (Badr et al., 1995).

A comprehensive paradigm for understanding upper airway collapse is to model the upper airway as a Starling resistor (Knowlton and Starling, 1912). A Starling resistor consists of a collapsible tube attached at each end (upstream and downstream) to rigid tubes and surrounded by a sealed box (Figure 1.2).
The collapsible segment represents the pharynx, the upstream segment represents the airway opening, the downstream segment represents the trachea, and the sealed box represents extra-luminal tissue. The collapsible segment can be induced to collapse when pressure inside the segment (Pin) is equal to or less than the pressure outside the segment (Pout). See text for further description (Gold and Schwartz, 1996; Dempsey et al., 2010).

Flow of fluid through the collapsible segment of the tube (above) is dependent upon the pressure of the upstream segment (Pus) and downstream segment (Pds), the pressure of the rigid box outside the collapsible segment (Pout), and the pressure inside the collapsible segment itself (Pin) (Gold and Schwartz, 1996). In the human airway, the collapsible segment is the pharynx, Pus is equal to atmospheric pressure, Pds is equal to the pressure in the trachea, and Pout is the sum of tissue pressures surrounding the pharynx. Therefore pharyngeal patency can be subject to negative intra-luminal pressure generated by inhalation, and to positive extra-luminal pressures exerted by surrounding tissue (Schwartz et al., 1988). Under the Starling resistor model, the patency of the collapsible segment is maintained as long as Pin is greater than Pout. The collapsible segment will close if Pin is ever equal to, or less than Pout. The Pin at which collapse occurs is defined as the critical closing pressure (Pcrit).

The pharyngeal Pcrit is subject to additional physiological factors that are not represented by
the Starling resistor model. Pharyngeal Pcrit can be modified by increasing or decreasing the stiffness of the pharyngeal wall. This can be achieved by increasing or decreasing neuromuscular tone of pharyngeal dilator muscles. It can also be achieved by varying the caudal traction on the pharynx generated by changes in lung volumes (see Section 1.2.5). The Pcrit can also be modified by increasing or decreasing pharyngeal size (see Section 1.2.3).

The pharyngeal Pcrit has been studied extensively in OSA patients and healthy subjects during wake and sleep. The Pcrit of OSA patients is consistently found to be greater (more positive) than healthy controls, indicating that the pharynx is more collapsible in OSA patients (Kirkness et al., 2008). As predicted by the Starling resistor model, the Pcrit of OSA patients is often found to be greater than atmospheric pressure (Patil et al., 2007). A Pcrit of -5cmH₂O has been suggested as an important threshold for Pcrit, as the risk of OSA increases markedly when Pcrit is higher than this threshold (Kirkness et al., 2008). Pcrit also correlates with a number of risk factors for OSA including obesity, neck circumference, soft palate length, and a narrow retro-palatal pharynx (Kirkness et al., 2008; Sforza et al., 2000).

**Pharyngeal Pcrit in Heart Failure**

The Pcrit of CHF patients has never been measured before, therefore it is unclear whether the pharynx of CHF patients is more collapsible than healthy controls (see Chapter 4). However, there is some evidence to suggest that CHF patients may be prone to a more collapsible airway due to their age. Eikermann et al. (2007) measured pharyngeal collapsibility in healthy subjects aged 18-75 years old using the Pclose technique. This technique is not directly comparable with Pcrit, however it offers a useful indication of the correlation between pharyngeal collapsibility and age. It was found that Pclose positively correlated with age, suggesting that the pharynx became more collapsible with age. Another study that did use the Pcrit technique found that there was a positive correlation between age and Pcrit when
regression models were adjusted for BMI and gender. Pcrit was estimated to increase 0.52 cmH₂O per decade (95% CI: 0.1 – 0.93 cmH₂O per decade) (Kirkness et al., 2008). This notion led me to conclude that it would be necessary for me to control my studies for age.

Neither of these studies were able to explain the possible mechanism for the age-related increase in pharyngeal collapsibility. The possible mechanisms may be predicted using the Starling resistor model as a framework. It is possible that there is an age-related increase in the pressure surrounding the pharynx, perhaps due to increasing body fat with age (see Section 1.2.6). Alternatively, the pharynx may undergo changes to its dimensions due to age that result in a narrower or more collapsible airway (see Section 1.2.3).

1.2.3. Anatomical Determinants of Pharyngeal Calibre

According to Poiselle's law of fluid dynamics, flow of a fluid (such as air) through a conduit is proportional to radius raised to the 4th power (radius⁴), assuming flow is laminar. Therefore the radius of a conduit has a very large influence on the flow of fluid through it. Under the Starling resistor model of the pharynx, maximum airflow through the collapsible segment (the pharynx) can be described by the equation:

\[ V_{\text{max}} = \frac{P_{\text{us}} - P_{\text{crit}}}{R_{\text{us}}} \]

*(Gold and Schwartz, 1996)*

Where \( V_{\text{max}} \) = maximal flow; \( P_{\text{us}} \) = pressure upstream of collapsible segment; \( P_{\text{crit}} \) = critical closing pressure of collapsible segment; \( R_{\text{us}} \) = resistance upstream of collapsible segment.

According to this equation, maximum airflow through the collapsible segment is inversely proportional to upstream resistance, which itself is largely determined by radius. This demonstrates the important role that pharyngeal calibre has on pharyngeal resistance, pharyngeal collapse, and the pathogenesis of OSA.
Pharyngeal calibre in OSA patients is consistently found to be narrower than healthy controls (Bradley et al., 1986; Ciscar et al., 2001) and in particular, the minimum cross-sectional area of the pharynx is smaller (Ciscar et al., 2001). It has also been demonstrated that the shape of the pharyngeal lumen may be different in OSA patients compared to healthy controls (Ciscar et al., 2001). In healthy people the shape of the pharynx in the retro-glossal region is an ellipse in the lateral plane. In OSA patients the shape of the pharynx in the same region is more circular or elliptical in the transverse plane. It has been suggested that this may result in the pharynx being less resistant to collapsing forces exerted on its lateral walls by surrounding tissue.

**Influence of Bone Structures and Cranio-Facial Morphology**

The reasons for OSA patients having a narrower pharynx are multi-factorial. Cephalometric studies examining the bone structures that surround the pharynx have identified a number of key anatomical features that appear to be more common in OSA patients than in the general population. OSA patients have been found to have a relatively short distance between the spine and the anterior portion of the mandible and the maxilla which may be associated with a narrower retro-palatal pharyngeal lumen (Dempsey et al., 2002). These findings are not universal however, as some studies have failed to find a correlation between cranio-facial morphology and OSA (Battagel and L’Estrange, 1996). There may be some impact of ethnicity on the prevalence of cranio-facial abnormalities in OSA, as some authors have noted a higher proportion of cranio-facial bony restriction in east Asian OSA patients than in Caucasian or African OSA patients (Sutherland et al., 2012). Taken together, the literature to date suggests that cranio-facial features may be a key factor in some individuals and in certain populations, but that they cannot be assumed to be a universal mechanism for an anatomically narrow pharynx.
Influence of Soft Tissue Structures

In addition to skeletal restrictions on the pharynx, there may be a number of soft tissue structures that restrict pharyngeal patency. The soft palate and tongue are among the muscles that comprise the oropharynx, therefore any variation in their size and shape could be expected to have a direct impact on pharyngeal patency. This has been found to be the case in several respects for each muscle. The soft palate length is greater in OSA patients compared to healthy controls (Sforza et al., 2000). The soft palate volume is also increased in OSA patients (Schwab et al., 2003). These effects combined seem to result in significant encroachment of the soft palate on the retro-palatal pharyngeal lumen in OSA patients (Schwab et al., 2003). This could represent a significant compromise to pharyngeal patency, given that the retro-palatal region of the pharynx is the most common site of pharyngeal collapse in OSA (Rama et al., 2002; see Section 1.2.1).

The tongue may encroach on the retro-glossal region of the pharynx either due to skeletal limitations imposed by the length of the mandible and maxilla (Dempsey et al., 2002) or due to enlargement of the tongue volume. In the case of skeletal restriction, the tongue may be a normal size but forced into a more posterior position relative to the posterior pharyngeal wall. Alternatively, the tongue volume may be enlarged in OSA patients, which may result in retro-glossal narrowing (Schwab et al., 2003), irrespective of skeletal structures. Given that another common site of pharyngeal collapse is the retro-glossal region (Rama et al., 2002; see Section 1.2.1), tongue encroachment on the pharynx may also represent an important compromise to pharyngeal patency in OSA.

Other soft tissue structures may also act directly or indirectly on the pharyngeal wall to cause narrowing of the pharynx. In particular, fat deposits lateral of the pharynx appear to be larger in OSA patients than healthy controls (Horner et al., 1989; Schwab et al., 2003). These enlarged fat deposits may exert lateral forces on the pharynx, causing it to narrow, particularly
in the retro-palatal region (Schwab et al., 2003). This may offer an explanation for the observation that the pharyngeal lumen appears to narrow in the lateral plane, leading to a more rounded pharyngeal shape in OSA patients (Ciscar et al., 2001).

**Pharyngeal Calibre in Heart Failure**

As with pharyngeal collapsibility, the pharyngeal calibre and cranio-facial morphology of CHF patients has not been specifically studied. There are several large cohort studies that have investigated the clinical and physiological risk factors for OSA in CHF. These studies suggest that the risk factors for OSA in CHF and the general population may be similar. Obesity is associated with OSA in CHF, as is age and male gender (Yumino et al., 2009). Given that the risk factors for OSA are similar in the CHF population and the general population it could be assumed that pharyngeal patency may be an underlying mechanism for OSA in CHF as it appears to be in the general population. The lack of specific research investigating the pharyngeal calibre of CHF patients with OSA is surprising, given that the high prevalence of OSA in CHF has been established for some time (Javaheri et al., 1998; Sin et al., 1999). In Chapter 3 I have attempted to address this gap in the literature by measuring the pharyngeal calibre of CHF patients with OSA and comparing it to the pharyngeal calibre of CHF patients without OSA and healthy age matched controls.

Ageing is associated with decreased facial height, and a more inferiorly located hyoid bone in relation to a number of anatomical reference points (Kollias and Krogstad, 1999a). Changes in hyoid bone location associated with age may also be mediated by facial morphology; people with a relatively acute angle of the mandible relative to the horizontal plane tend to have a greater inferior relocation of the hyoid bone associated with age than people with a more shallow mandible angle (Pae et al., 2008). The location of the hyoid bone may act as a surrogate of pharyngeal dimensions, particularly pharyngeal length. Pharyngeal length may be
an additional pharyngeal dimension that increases the risk of OSA in older people, and because CHF patients are older I considered it important to take this mechanism into account.

Changes in pharyngeal calibre associated with ageing are complex and there is no firm consensus in the literature. Five studies found that pharyngeal calibre is decreased in older age (Brown et al., 1986; Huang et al., 1998; Kollias and Krogstad, 1999b; Martin et al., 1997; Shigeta et al., 2008b), compared to 4 studies that showed pharyngeal calibre was increased in older age (Brooks and Strohl, 1992; Burger et al., 1992; Mayer et al., 1996; Tagaya et al., 2011), and one study only just failed to show a significant increase with age (p=0.08; Malhotra et al., 2006). The characteristics of all of these studies are presented in Chapter 5, Table 5.3. It is possible that the reported age-related decrease in pharyngeal calibre in some studies was due in part to unknowingly including asymptomatic and undiagnosed OSA patients in their “healthy” cohorts. Therefore the reported effect was not necessarily due to ageing alone.

Overall, the consensus from these studies is that the pharyngeal calibre is probably increased in older age, however, given the contrasting findings in the literature, this consensus is a tentative one. In Chapter 5 I aimed to investigate the putative differences in pharyngeal calibre between younger and older males. The groups were very well matched for key predictors of OSA including BMI and neck circumference. Groups were screened for OSA using polysomnography or respiratory polygraphy to ensure both groups were healthy and free of OSA. I tested the hypothesis that pharyngeal length and calibre would be similar in healthy older and younger males.

1.2.4. Rostral Fluid Shift

In addition to the factors influencing pharyngeal calibre described in the sections above, there is evidence to suggest that pharyngeal patency may be influenced by rostral fluid shift. This
idea was first postulated in 1996 by Shepard et al., however the theory did not gain wider recognition until a later series of studies was conducted by a group in Toronto on healthy volunteers (Chiu et al., 2006; Redolfi et al., 2009; Shiota et al., 2007; Su et al., 2008), and later on OSA patients (Redolfi et al., 2009) and CHF patients (Yumino et al., 2010). Under normal conditions inspiration is associated with an increase in pharyngeal calibre and expiration is associated with a decrease in pharyngeal calibre. Shepard et al. (1996) found that mean pharyngeal cross-sectional area during inspiration was significantly smaller when subjects lay in a supine posture with their legs tilted 33º up, compared to when they lay in a supine posture with their legs flat. The authors proposed a physiological model whereby an increase in central venous pressure (as would be imposed by elevating the legs) results in increased jugular vein volume, thus preventing normal inspiratory pharyngeal dilation (Figure 1.3).

![Figure 1.3. Model for attenuation of inspiratory pharyngeal dilation due to raised central venous pressure.](image)

Baseline central venous pressure (CVP) in the supine posture is illustrated by the CVPnl condition. At low central venous pressure (CVP-) venous volume is also low, making jugular veins collapsible and able to compress as the upper airway dilates during inspiration. At high CVP (CVP+) venous volume is also high, making jugular veins more resistant to collapse and resistant to compression as the upper airway dilates during inspiration. Thus inspiratory pharyngeal dilation is attenuated under conditions of high CVP (Shepard et al., 1996).
Subsequent studies have confirmed that rostral fluid shift is associated with increased pharyngeal resistance (Chiu et al., 2006), decreased pharyngeal calibre (Shiota et al., 2007), and increased pharyngeal collapsibility (Su et al., 2008) in healthy volunteers subjected to lower body positive pressure. Furthermore, rostral fluid shift has been associated with an increased apnoea-hypopnoea index (AHI) in non-obese OSA patients (Redolfi et al., 2009), and the AHI of sedentary OSA patients can be reduced by wearing compression stockings during the day; theoretically reducing the fluid available for rostral fluid shift during the night (Redolfi et al., 2011a). However, Jafari and Mohsenin (2011) found that only 65 of 135 OSA patients (48%) had any detectable rostral fluid shift. Moreover, of those that did have rostral fluid shift, there was no correlation between fluid shift and AHI. This finding was replicated by Fischer et al. (2012) who found no correlation between overnight changes in neck circumference and AHI, but who did find a correlation between postural changes in neck circumference and AHI. Overall, these studies suggest that rostral fluid shift may contribute to OSA severity but that this contribution may be relatively small.

**Influence of Rostral Fluid Shift in Heart Failure**

The effects of rostral fluid shift may be more significant in disease states where excess fluid is retained, as more fluid would be expected to accumulate in dependent veins and extra-cellular compartments during the day, making more fluid available for rostral fluid shift during the night. In people with hypertension, overnight decreases in leg fluid volume and increases in neck circumference correlate with AHI (Friedman et al., 2010). Furthermore, people with drug-resistant hypertension had more severe OSA to begin with and experienced a greater overnight decrease in leg fluid volume and increase in neck circumference than people with controlled hypertension (Friedman et al., 2010). In people with chronic venous insufficiency, wearing compression stockings during the day resulted in significant reductions in AHI when compared to not wearing compression stockings (Redolfi et al., 2011b). In renal disease there
does not seem to be a strong association between OSA severity (according to the AHI) and rostral fluid shift (Elias et al., 2012); nevertheless, nocturnal renal dialysis appears to be more effective at reducing AHI than ambulatory daytime dialysis in patients with chronic renal disease, suggesting that fluid clearance during sleep is of added benefit for reducing AHI in these patients (Tang et al., 2006).

In CHF patients, rostral fluid shift correlates with AHI in patients with both obstructive-dominant and central-dominant sleep apnoea (Yumino et al., 2010). Also, as in other fluid-loaded states, treatment of fluid retention may result in improvement of OSA severity. Bucca et al. (2007) hospitalised CHF patients with OSA for 3 days of intensive diuresis using furosemide and spironolactone. This resulted in significant reduction in AHI and an increase in pharyngeal cross-sectional area (measured at the oro-pharyngeal junction). However, there are several limitations to consider in interpreting this study. First, the CHF patients in this study also had drug-resistant hypertension. As discussed above, people with drug-resistant hypertension are prone to more severe nocturnal rostral fluid shift than people with controlled hypertension. Therefore it is not clear whether fluid overload in these patients was due to hypertension or CHF, and whether removal of excess fluid using diuretics had additional ameliorative effects on their hypertension (such as reduced blood pressure and central venous pressure) beyond simple fluid volume reduction. Second, patients in this study were not receiving any diuretics as part of their normal CHF treatment prior to entering this study. Therefore it is not clear whether CHF patients with OSA who are on optimal treatment, including optimally titrated diuretics, would receive the same reduction in AHI and increase in pharyngeal calibre as the diuretic-naive patients of this study.

The literature to date strongly suggests that rostral fluid shift is a potential mechanism for OSA in CHF. However, there remain uncertainties around how strong the impact of fluid shift is on OSA severity in CHF and whether targeting of fluid retention for treatment is of benefit
to patients already using diuretics to control extra-cellular fluid overload. Furthermore, the mechanisms by which rostral fluid shift may increase the risk of OSA in CHF have not been adequately explored, with only one physiological model being proposed but not tested in over 15 years of research. In Chapters 3 and 4 I present two studies performed in the same groups of participants that measure overnight rostral fluid shift (using changes in neck circumference as a surrogate) in CHF patients with OSA. In Chapter 3 overnight changes in pharyngeal calibre were measured, and I tested the hypothesis that overnight fluid shift would result in overnight narrowing of the pharynx. In Chapter 4 overnight changes in Perit were measured to test the hypothesis that overnight fluid shift would result in an overnight increase in the collapsibility of the pharynx.

1.2.5. Caudal Traction, Lung Volumes and Pharyngeal Length

Another determinant of pharyngeal collapsibility (Section 1.2.2) and calibre (Section 1.2.3) is the longitudinal tension of the pharyngeal walls, created by caudal traction. Caudal traction is generated when the pharynx is pulled caudally towards the thorax. This occurs either by activation of upper airway dilator muscles located caudally of the pharynx, and/or by expansion of the lungs during inspiration, causing the trachea to be tugged further into the thorax. It is thought that expansion of the lungs generates caudal traction in two ways: 1) contraction of the diaphragm causes it to flatten and descend within the thoracic cavity. This caudal movement is transmitted to the pharynx via the lungs, trachea and other mediastinal structures; 2) Contraction and flattening of the diaphragm generates negative intra-thoracic pressure which inflates the lungs and also sucks the trachea further into the thoracic cavity. This motion is transmitted to the pharynx. Therefore, by a combination of mechanisms, caudal traction is increased during inspiration and decreased during expiration (Van de Graaff, 1988). An increase in end-expiratory lung volume has been shown to result in decreased pharyngeal resistance (Begle et al., 1990; Van de Graaff, 1988), increased pharyngeal calibre.
(Hoffstein et al., 1984) and decreased pharyngeal collapsibility (Eastwood et al., 2002; Jordan et al., 2010; Owens et al., 2010; Squier et al., 2010; Stanchina et al., 2003; Tagaito et al., 2007). Lung volume-dependent changes in caudal traction appear to be independent of upper airway muscle activation, based on studies in an isolated dog trachea model (Van de Graaff, 1988) and in humans whose lung volumes are passively manipulated using an iron lung (Sériès et al., 1990). Therefore, it is likely that these effects are directly related to mechanical changes imposed on the pharynx due to caudal traction. These mechanical effects may include: pharyngeal unfolding; reduced pharyngeal wall compliance; decreased pharyngeal compression from surrounding tissue; and hyoid bone repositioning (Van de Graaff, 1988; see Figure 1.4).

![Figure 1.4](image_url)

**Figure 1.4.** Mechanisms by which caudal traction may improve pharyngeal patency, resistance and collapsibility. Solid lines represent the configuration of the pharynx without caudal traction; dotted lines represent the configuration with caudal traction applied (Van de Graaff, 1988).

It has been suggested that pharyngeal length may act as an additional mechanism for OSA (see Section 1.2.3). Pharyngeal length correlates significantly with OSA severity (Segal et al., 2008) and is increased significantly when moving from an upright to supine posture in OSA.
patients but not in control subjects (Pae et al., 1997). Pharyngeal length is also greater in males than females, which may be one of the causes of the higher prevalence of OSA in males than females (Malhotra et al., 2002). It is thought that a longer pharynx is more prone to collapse than a shorter pharynx due to increased negative intra-luminal pressure. During inspiration, airflow through a longer pharynx must necessarily travel faster than airflow through a shorter pharynx, assuming that lung volumes, pharyngeal calibre and inspiratory time are constant. Faster airflow would require a more negative intra-luminal pressure which would increase the collapsibility of the pharynx (Pae et al., 1997; see Figure 1.5).

![Figure 1.5. Mechanism by which a longer pharynx may be more collapsible than a shorter pharynx. Assuming that pharyngeal calibre and inspiratory time are constant and that airflow is laminar, a longer pharynx (A) would require faster airflow during tidal breathing to inflate the same lung volume than a shorter pharynx (B). This would generate a more negative intra-luminal pressure and increase the collapsing forces acting on the pharyngeal lumen (Pae et al., 1997).](image)

1.2.6. Body Composition and Neck Circumference

Obesity is a consistent predictor of OSA (Kirkness et al., 2008). A high body fat percentage is associated with increased fat deposits lateral of the pharynx (Horner et al., 1989) and
increased tongue volume and pharyngeal wall thickness may be associated with increased deposition of intra-muscular fat (Nashi et al., 2007). The increase in tissue volumes surrounding the pharynx may increase its collapsibility by increasing extra-luminal pressure (see Section 1.2.2). Given that the soft tissues of the upper airway occupy a finite space that is bounded by fixed skeletal structures, increased soft tissue volumes may also contribute to the observation that the pharyngeal lumen is narrowed in obese subjects (Martin et al., 1997; Mayer et al., 1996; Shigeta et al., 2008a). Obesity may also promote pharyngeal collapse by causing reduced lung volumes in a supine posture. Reduced lung volumes may promote pharyngeal collapse by reducing caudal traction on the pharynx (as discussed in Section 1.2.5).

The prevalence of obesity increases with age, therefore the contribution of obesity to the risk of developing OSA may increase with age. Obesity is also associated with OSA in the CHF population (Yumino et al., 2009), however obesity is no more prevalent in the CHF population than in the general population (Johansson et al., 2001; The NHS Information Centre, 2004). Therefore obesity is likely to contribute to OSA in the CHF population, but probably cannot alone account for the increased prevalence of OSA in CHF patients.

1.2.7. Control of Breathing

It has been documented previously in our laboratory as well as others, that the type of SDB that presents in individuals with CHF can vary; both central and obstructive events can be observed in the same patient in a single night, and across several nights (Tkacova et al., 2001; Vazir et al., 2008). It has been demonstrated in OSA patients who do not have CHF that AHI correlates with greater centrally-mediated breathing instability (loop gain, discussed below). This relationship was found in patients with severe OSA and whose Pcrit occurred above atmospheric pressure (Wellman et al., 2004). Furthermore, passive pharyngeal collapse can be
observed in as many as 90% of central apnoeas (Badr et al., 1995; see Section 1.2.2). These studies together demonstrate the notion that OSA and CSA are not independent of each other but rather interact and may in fact promote one another. Therefore in order to understand the high prevalence of OSA in CHF, it is also necessary to appreciate the mechanisms of central respiratory control and how instability in this system during sleep may lead to CSA. Ventilation during sleep can be modelled as a negative feedback system using an engineering concept called loop gain. Loop gain can be used as a framework to understand the ability of a negative feedback system to maintain a given output with minimal oscillation. Under the typical model of loop gain (Figure 1.6), a negative feedback system is composed of a controller, a plant, and a feedback sensor. The controller sets the input to the plant based on achieving a pre-set, desired output. The plant performs work that produces an output. The output of the system is measured by the feedback sensor and this information is fed back to the controller. The controller compares the sensed output to the desired output and modulates the input to the plant to bring the sensed output closer to the desired output. In the respiratory control system, the chemoreceptors represent the controller, the lungs represent the plant, and the circulation represents the feedback sensor. The system is modulated by an increase or decrease in respiratory drive with reference to maintaining a desired homeostatic upper and lower limit of the partial pressure of arterial CO$_2$ (PaCO$_2$). For example, a transient hyperventilation due to an arousal from sleep would result in a decrease in the PaCO$_2$; this would be detected by central and peripheral chemoreceptors, which would then decrease sympathetic tone and ventilatory drive. Decreased ventilation would subsequently increase PaCO$_2$ back towards resting levels. This system would result in stability if all signals between components of the loop were instantaneous. However, in ventilation there are delays at each stage of the loop; there is a delay between a change in alveolar gas tensions being translated to a change in arterial gas tensions; there is a delay between a change in arterial gas tensions and
these changes being detected at the chemoreceptors; and there is a delay between the chemoreceptor response and the resultant change in ventilation (Khoo, 2000). These delays are exacerbated in CHF due to decreased cardiac output and increased circulation time when in a supine posture (Gibbs et al., 1989; Tkacova et al., 2001). By the time the feedback loop has detected and responded to the original perturbation (the transient hyperventilation) the ventilatory perturbation itself may have ended. Thus the response to the original perturbation may result in an overshoot and become a new perturbation in itself. This would result in a transient hypopnoea, increase in PaCO₂ and increase in chemoreceptor output; these responses themselves would be subject to delay and thus an oscillating pattern would be established (Khoo, 2000). Therefore for any given perturbation, a stable ventilatory control system requires a response (or gain) that is large enough to maintain blood gas tensions within desirable limits, but not so large that it results in an oscillating pattern of ventilation that prevents reaching a stable equilibrium. In CHF an oscillating pattern of ventilation is often observed (both Cheyne-Stokes respiration and periodic breathing). In addition to circulatory delay, this may also be explained by a high hypercapnic ventilatory response (Javaheri et al., 1998), resulting in increased controller gain and an overall increase in loop gain. The combination of increased loop gain and circulatory delay have been modelled mathematically and shown to be sufficient to create a self-sustaining oscillatory pattern of ventilation; furthermore, these mathematical models have been tested in a population of CHF patients which confirmed the high loop gain and ventilatory instability produced by circulatory delay and high controller (i.e. chemoreceptor) gain (Pinna et al., 2000).
VE (system input) is set by the chemoreceptors (controller) based on achieving an acceptable range of PaCO₂ (reference). The lungs (plant) perform ventilation and gas exchange, producing a given PaCO₂ (system output). This determines the PaCO₂ (measured output) which is transmitted to the chemoreceptors, subject to circulatory delay. If the PaCO₂ exceeds acceptable limits, the chemoreceptors respond by modifying VE in order to bring PaCO₂ back within desirable limits. This system is subject to ventilatory disturbance which may cause the feedback loop to destabilise and assume an oscillatory pattern of ventilation. See text for further description (Figure adapted from Khoo, 2000 and Wellman et al., 2003).

Compared to OSA, central sleep apnoea (CSA) occurs when PaCO₂ falls below a threshold (the hypocapnic apnoeic threshold; Skatrud and Dempsey, 1983). As illustrated in Figure 1.7, the apnoeic threshold itself is not a fixed PaCO₂, but is influenced by neural respiratory drive and the hypercapnic ventilatory response (HCVR), which in turn is influenced by conscious state (Douglas et al. 1982b). In CHF, ventilatory drive is often chronically elevated due to pulmonary oedema, which stimulates pulmonary J receptors resulting in chronic hyperventilation and decreased PaCO₂ (Hanly et al., 1993). If the slope of the ventilatory response to CO₂ were to remain constant (Figure 1.7A), chronic hyperventilation could
actually protect against apnoea by increasing the required transient hyperventilation necessary to drive PaCO$_2$ below the apnoeic threshold. CHF patients have a high prevalence of CSA, therefore it is likely that other factors offset the protection against apnoea conferred by chronic hyperventilation. One such factor could be that CHF patients have an elevated HCVR during wake (Javaheri 1999) which could mean that a relatively smaller transient hyperventilation would drive PaCO$_2$ below the apnoeic threshold (Figure 1.7B). However, this prediction does not take account of the findings that the slope of the HCVR changes from wake to sleep (Douglas et al. 1982b) and above and below eupnoea (Casey et al. 1987). A more robust explanation for CSA in CHF is based on the observation that in healthy subjects transition from wake to sleep is associated with a decrease in ventilation and an increase in PaCO$_2$ of 2-4 mmHg (Douglas et al. 1982a), whereas in CHF patients, the increase in PaCO$_2$ during sleep is attenuated (Tkacova et al. 2001; Xie et al. 2002). This means that transition to sleep is associated with a relatively low PaCO$_2$ and a relative shortfall of ventilatory drive in CHF (Xie et al. 2002). Sleep is also associated with a decrease in cardiac output in CHF patients due to assuming a supine posture (Gibbs et al., 1989; Tkacova et al., 2001) which in turn leads to an increase in circulation time. This increases the delay between a change in ventilation and the resulting change in alveolar and arterial gas tensions being fed back to the chemoreceptors via the circulation. This could make ventilatory overshoots more likely, resulting in an oscillating pattern of breathing (i.e. periodic breathing and Cheyne-Stokes respiration). Therefore, it is possible that in CHF patients, the protection against CSA conferred by chronic hyperventilation and hypocapnia during wake is offset by a high waking HCVR (and thus a higher, less stable controller gain), an attenuated rise in PaCO$_2$ and ventilatory drive when transitioning from wake to sleep (thus causing them to ventilate close to their apnoeic threshold), and circulatory delay during sleep (thus destabilising the ventilatory feedback loop). These factors may all contribute to a higher loop gain and unstable
ventilatory control. They also offer mechanisms for some of the features that typify SDB in some CHF patients; namely a tendency towards an oscillatory breathing pattern during sleep (Cheyne-Stokes respiration and/or periodic breathing) and increased risk of developing CSA.

![Diagram](image)

**Figure 1.7.** Metabolic hyperbola for ventilatory response to CO\(_2\) below eupnoea. Eupnoea is represented by the hyperbolic line on both graphs. The apnoeic threshold is the \(P_{a}CO_2\) at which ventilation is zero. A: Effect of hyperventilation or hypoventilation when the slope of the ventilatory response to \(CO_2\) is constant below eupnoea. Under conditions of chronic hyperventilation (towards the left on the metabolic hyperbola) a relatively greater transient hyperventilation is required to drive \(P_{a}CO_2\) down to the apnoeic threshold. Under conditions of chronic hypoventilation (towards the right on the metabolic hyperbola) a relatively small transient hyperventilation is sufficient to drive \(P_{a}CO_2\) down to the apnoeic threshold. B: Effect of changing the \(CO_2\) response below eupnoea. If the slope of the \(CO_2\) response changes, the transient hyperventilation required to drive \(P_{a}CO_2\) to the apnoeic threshold is altered (Dempsey et al., 2010).
1.3. Obstructive Sleep Apnoea in Heart Failure

1.3.1. Pathophysiology of Heart Failure

CHF is a clinical syndrome that may result from a number of cardiovascular conditions affecting the structure and function of the heart. Due to its often heterogeneous and multifactorial disease progression it can be defined according to any number of signs or symptoms but is most simply and broadly defined as any structural or functional cardiac disorder that impairs the ability of the heart to function effectively as a pump (Cowie and Zaphiriou, 2002). CHF occurs in approximately 1% of the UK population but increases markedly with age, occurring in approximately 13% of people aged ≥75 years (Scarborough et al., 2011). Its prevalence is expected to rise as the average age of the UK population increases (Scarborough et al., 2011).

Clinical diagnosis of CHF is based on manifestation of symptoms (e.g. breathlessness at rest or during exercise), fatigue, signs of fluid retention (e.g. pulmonary or peripheral oedema), and objective evidence of structural or functional abnormality of the heart (e.g. abnormal echocardiogram; raised brain natriuretic peptide) (Dickstein et al., 2008). Approximately two-thirds of CHF patients present with an impaired left ventricular ejection fraction (LVEF; <40% although there is no diagnostic threshold per se) (Aurigemma and Gaasch, 2004). This is referred to as systolic heart failure because it suggests a dysfunction in the systolic phase of the cardiac cycle. A reduced LVEF results in a high left-ventricular after-load and reduced volume of blood passing through the aorta to the systemic circulation which is insufficient to meet the oxygen requirements of the body.

When patients present with signs and symptoms of CHF but with a normal ejection fraction this is called diastolic heart failure and is associated with impaired relaxation of the myocardium. This results in impaired filling of the chambers of the heart and raised end-
diastolic pressure that ultimately prevents adequate venous return of blood to the right atrium (Aurigemma and Gaasch, 2004). Although systolic and diastolic heart failure can be conceptualised as separate entities, they often occur simultaneously in patients either at rest or during exercise and the clinical consequences and symptoms often overlap. Treatment is also the same regardless of whether a patient's CHF is systolic or diastolic in origin; therefore the distinction between these differing aetiologies could be considered to be more academic than clinically relevant.

In normal physiology there are a number of challenges to the maintenance of cardiac output that operate on both acute and chronic time-scales. For example, blood pressure can be reduced due to acute challenges such as orthostatic stress, or chronic and gradual challenges such as dehydration. Both of these may result in decreased venous return and reduced cardiac output, however this is prevented by activation of sympathetic systems to constrain fluid loss. These can include transient increase in heart rate and cardiac contractility, vasoconstriction, and fluid re-uptake at the kidneys via the renin-angiotensin-aldosterone system. All of these responses serve to maintain blood pressure, increase venous return and maintain cardiac output.

These normal physiological responses to reduced cardiac output are also activated in CHF as cardiac output is reduced in this condition. During an acute decompensation of CHF these processes work to transiently attenuate cardiac output reduction. However, these adaptive mechanisms become maladaptive in CHF over a longer period of time and contribute to the symptoms that typify the condition. Vasoconstriction increases the transmural pressure in capillary beds, resulting in increased diffusion of fluid from the blood plasma into interstitial space. This is one of the causes of peripheral and pulmonary oedema often observed in CHF. Normally excessive fluid in the interstitial space is drained by the lymphatic circulation and filtered by the kidneys to be excreted. However, vasoconstriction also occurs at the kidney,
and combined with increased fluid reabsorption due to activation of the renin-angiotensin-aldesterone system, this contributes to increased extra-cellular oedema (Levick, 2003).

Vaso- and veno-constriction may also impair cardiac function by increasing the stroke volume required to eject blood from the left ventricle against constricted arteries, and by excessive cardiac dilation due to atrial filling. Combined, these mechanisms can result in cardiac remodelling and hypertrophy (Levick, 2003). Remodelling and hypertrophy of the myocardium may also be caused by chronic elevation of the sympathetic nervous system, resulting in chronically elevated heart rate and cardiac contractility. Initially this allows the heart to contract with greater force but remodelling in the long term results in impaired filling and emptying of the chambers of the heart. Therefore mechanisms that are effective in normal physiology for attenuating transient falls in cardiac output interact chronically in CHF to produce a fluid-loaded state and a net-detriment to cardiac function.

1.3.2. Treatment and Prognosis

The aim of CHF treatment is to prevent, reverse or attenuate the maladaptive processes underpinning its pathogenesis (described above). Treatment and management incorporate one or more of the following types of intervention (Dickstein et al., 2008):

Non-pharmacological treatment: Consisting of education and behavioural modification that allows patients to recognize worsening signs and symptoms and respond appropriately (e.g. self-adjustment of diuretics, contacting healthcare professionals).

Pharmacological treatment: Consisting of ACE inhibitors, diuretics and beta blockers, unless poorly tolerated. In severe cases aldosterone antagonists and angiotensin receptor blockers may also be prescribed.

Surgical treatment: Surgery is recommended when the underlying cause of CHF is correctable by surgery (e.g. coronary artery disease). Heart transplantation is also an accepted treatment
for CHF when indicated by careful screening of candidates. It is believed to improve survival, exercise capacity and quality of life.

Device treatment: Devices are usually used in patients whose symptoms persist despite optimum treatment. Cardiac resynchronisation therapy is recommended for severe patients (NYHA III-IV; LVEF <40%) who have prolonged QRS width. Implantable cardioverter defibrillators are recommended for patients who have previously had ventricular fibrillation.

Prognosis in CHF remains relatively poor, despite continuing advances in treatment and management. In the UK in 2010, 32% of all patients admitted for CHF died within one year (The NHS Information Centre, 2009). Prognosis for individuals is complex and determined by a number of factors including disease severity and progression, age, co-morbidities and course of treatment (Dickstein et al., 2008).

1.3.3. Mechanisms of Obstructive Sleep Apnoea in Heart Failure

Despite the high prevalence of OSA in CHF, there have been surprisingly few studies investigating the pathophysiological interactions between these two diseases. It is relatively well established that OSA may be a contributing mechanism for CHF. OSA that is undetected and untreated for many years may contribute to CHF progression by sympathetic nervous system activation, decreased left ventricular pre-load and increased after-load and increased hypertension (Bradley and Floras, 2003). Despite this well established causative relationship between OSA and CHF, there is surprisingly little data on the reverse relationship whereby CHF may cause OSA.

In the preceding sections, the mechanisms of OSA were discussed in light of their specific effects in CHF where this data was available, and also in light of their effects in older age. Older age was used as a surrogate of CHF where specific data could not be found for CHF because CHF is predominantly a disease of older age. Review of the literature reveals that
there are several mechanisms by which OSA may be increased in older age and CHF. These include changes in cranio-facial morphology (Section 1.2.3), decreased pharyngeal calibre (Section 1.2.3), increased pharyngeal collapsibility (Section 1.2.2), and increased pharyngeal length (Section 1.2.5). Given that all of these factors are affected in some way by ageing, all of these could be potential mechanisms for OSA in CHF, however, no studies of any of these factors have been conducted in CHF patients to date. The one exception to this is in the case of rostral fluid shift.

Rostral fluid shift correlates with AHI in CHF patients with OSA and reduction of fluid overload by diuresis may increase pharyngeal calibre and decrease AHI. The theory that rostral fluid shift contributes to OSA in CHF is very attractive, as it proposes a direct mechanism by which CHF may cause OSA. However, the mechanisms by which rostral fluid shift may cause OSA have not themselves been adequately explored and there are still large gaps in our understanding of the pathophysiological causes of OSA in CHF. The experiments presented in this thesis are designed to address some of these gaps in our present knowledge.

1.4. Aims of Thesis

The aim of this thesis was to investigate the mechanisms of OSA in CHF. Specifically, I have investigated the contribution of fluid shift to the pathogenesis of OSA in CHF. This was done by investigating pharyngeal phenotypes of CHF patients relating to pharyngeal collapsibility and pharyngeal calibre.

In Chapter 3, changes in pharyngeal calibre were measured in CHF patients with OSA, CHF patients without OSA and healthy controls. Measurements were performed in a seated and supine posture and in the evening and morning. The aim of this study was to determine the effects of rostral fluid shift and postural change on pharyngeal calibre during wake. The hypotheses were that neck circumference would be greater and pharyngeal calibre would be
smaller in CHF patients with OSA than CHF patients without OSA and healthy age-matched controls; and that neck circumference would increase and pharyngeal calibre would decrease overnight in CHF patients with OSA more than CHF patients without OSA and healthy age-matched controls.

In Chapter 4, the same cohort of participants from Chapter 3 had their pharyngeal collapsibility measured in the early and late part of the night. The aim of this study was to investigate whether overnight rostral fluid shift results in the pharynx becoming more collapsible overnight. The hypotheses were that CHF patients with OSA would have a more collapsible pharynx than CHF patients without OSA and healthy age-matched controls; and that the pharynx would become more collapsible overnight in CHF patients with and without OSA but not healthy age-matched controls.

CHF patients studied in Chapters 3 and 4 were older, and so in Chapter 5 I investigated whether ageing had any impact on pharyngeal calibre. Two groups of healthy older and younger males were recruited for this study and were very carefully matched for BMI, neck circumference, AHI and ODI. I tested the hypothesis that pharyngeal calibre and length would be similar between older and younger healthy males.

In Chapter 6 a study is presented that was conducted during a 6 month sabbatical in Detroit, USA. CHF patients with CSA were recruited in order to investigate passive pharyngeal collapse in CHF patients with CSA. The study also aimed to investigate any effects of rostral fluid shift on pharyngeal calibre during sleep. The pharynx was visualised during sleep using a fibre-optic bronchoscope. I tested the hypotheses that CSA is associated with passive pharyngeal collapse in CHF patients with CSA; and that pharyngeal calibre would reduce progressively overnight.
Chapter 2: General Methods
2.1. Participants

Three of the studies presented in this thesis were conducted at the Royal Brompton Hospital, London, UK, and one study was conducted during a 6 month sabbatical in Detroit, USA. The studies presented in Chapters 3 and 4 involved the recruitment of CHF patients and healthy volunteers. The study presented in Chapter 5 involved the recruitment of two groups of healthy volunteers: younger males, and older males. The study presented in Chapter 6 involved the recruitment of CHF patients with CSA.

For Chapters 3 and 4, CHF patients were recruited from heart failure clinics at the Royal Brompton Hospital from March 2009 to March 2012. Patients were screened for OSA using polysomnography (see Section 2.2). They were assigned to groups of CHF patients with OSA (CHF-OSA; AHI \( \geq 10 \) events/hour with \( >50\% \) of apnoeas defined as obstructive) or CHF patients without OSA (CHF-only; AHI <10 events/hour).

For Chapter 5, healthy volunteers were recruited from the general population using advertising placed in local newspapers and by contacting local charity groups, sports and social clubs from January 2010 to March 2012. Healthy volunteers were screened for OSA using polysomnography or respiratory polygraphy (see Section 2.2). Volunteers with an AHI \( \geq 5 \) events/hr were excluded from further studies. Those with an AHI \( \geq 5 \) events/hr and with daytime symptoms of sleepiness were referred for further clinical assessment and follow-up via their GP.

For Chapter 6, CHF patients with CSA (CHF-CSA) were identified by screening of hospital records for the 5 years preceding the start of the study (February 2005 – August 2010) and by screening sleep apnoea clinic lists at the John D Dingell Veterans Affairs Hospital, Detroit, USA. Patients who had CHF and CSA (AHI \( \geq 10 \) events/hr with \( >50\% \) of apnoeas defined as central) confirmed by polysomnography were invited to participate in the study.
2.1.1. Inclusion Criteria

Individual inclusion criteria are listed in each chapter – they are also listed below for completeness. All studies received ethical approval from local ethics committees and all participants gave written informed consent. The studies presented in Chapters 3 and 4 were reviewed by the Brompton Harefield and NHLI Research Ethics Committee and received ethical approval (REC number 09/H0708/24). The study presented in Chapter 5 was reviewed by the London-Chelsea Research Ethics Committee (previously the Brompton Harefield and NHLI Research Ethics Committee) and received ethical approval (REC number 09/H0708/24). Ethical approval for the study presented in Chapter 6 was granted locally in Detroit, USA by the John D. Dingell Veterans Affairs Medical Center and the Wayne State University Institutional Review Board (IRB number 081596MP4F).

On their first visit to the research sleep laboratory all participants were screened to assess their general health by answering a questionnaire on their medical history and undergoing spirometry and blood pressure measurements.

Chapters 3 and 4:

Both groups of CHF patients:

- Age 18-85
- CHF severity of class II-III according to New York Heart Association criteria
- Clinically stable condition, having had no hospital admissions in the 3 months preceding testing and no change in medication 4 weeks preceding testing (except minor dose changes to diuretics).

CHF patients with sleep apnoea (all the above, with the addition of):

- Apnoea-Hypopnoea Index (AHI) ≥10 events/hr.

Healthy volunteers:
• Age 18-85
• AHI <10 events/hr and no known history of sleep disorders

Chapter 5:

• Male
• Age 18-40 years (younger) or Age 60-85 years (older)
• No sleep disorders
• No upper airway surgery
• No ferrous metal in body
• AHI <5 events/hr

Chapter 6:

• 18-85 years old
• AHI ≥10 events per hour with >50% of events classified as central
• Left ventricular ejection fraction <40%
• In a clinically stable condition, having had no heart failure-related hospital admission in the 3 months prior to recruitment.
• No previous upper airway surgery, uncontrolled or treatment-resistant hypertension or recent or current problems with opioid abuse.

2.2. Experimental Techniques

In Chapters 3, 4 and 6 participants were monitored throughout the night using polysomnography. In Chapter 5 participants were screened for OSA using unattended respiratory polygraphy.
2.2.1. Polysomnography

A commercial polysomnography system was used for OSA screening studies in Chapter 3 and 4 (SOMNOscreen, Somnomedics GmbH, Germany). Data were recorded onto an integral micro computer and flash card and transmitted in real time to a personal computer for online review. In Chapter 4 sleep was monitored using an analogue polysomnography system (Model 12 Neurodata acquisition system, Grass Instruments, USA). Signals were collected via an analogue to digital converter (Micro 1401, Cambridge Electronic Design, UK) and recorded using data acquisition software (Spike2 version 3.21, Cambridge Electronic Design, UK). In both systems, sleep/wake state was determined by using Electroencephalography (EEG) to monitor brain waves, electro-occulogram (EOG) to monitor eye movements and chin electromyography (EMG) to monitor muscle tone. Heart rate was monitored using electrocardiography (ECG), oxygen saturation (SaO$_2$) was monitored using pulse oximetry, snoring was monitored using a vibration sensor placed over the larynx, breathing effort was monitored using respiratory inductance plethysmography, and airflow at the nostrils was monitored using a thermistor and a pressure transducer referenced to ambient pressure.

**EEG, EOG and EMG Electrode Placement**

Electrodes for EEG were placed at locations on the scalp according to the international 10-20 system of electrode placement and according to the recommendations of the American Academy of Sleep Medicine guidelines (Iber et al., 2007). Anatomical landmarks were used as reference points for the placement of electrodes (inion, nasion, left and right pre-auricular points). The distance between pairs of anatomical landmarks was measured and subdivided into lengths of 10% and 20% of the total distance in order to locate electrode sites. Gold cup electrodes (Grass Technologies, USA) were filled with conducting paste (Ten20 EEG Paste, D.O. Weaver and Co., USA) and secured to the scalp using a conductive adhesive cream (EC2
Electrode Cream, Grass Technologies, USA) and a patch of gauze. Electrodes were placed at C3, C4, CZ, O1 and referenced contra-laterally to either A1 or A2. A grounding electrode was also placed on the forehead. Disposable skin surface electrodes (Neuroline 720, Ambu, Denmark) were used for EOG and chin EMG. EOG electrodes were placed 1cm below the left eye outer canthus and 1cm above the right eye outer canthus. Chin EMG electrodes were placed approximately 2cm below the inferior edge of the mandible and approximately 2cm to the left and right of the mid-line of the mandible.

**ECG, Pulse Oximetry, Breathing Effort and Airflow**

A 3-lead ECG was used to record heart rate continuously throughout all studies, with electrodes placed below the left and right clavicle notch and below the left rib cage to form an Einthoven's triangle. A transcutaneous infra-red pulse oximeter was placed on the finger to monitor blood oxygen saturation. Breathing effort was measured using uncalibrated respiratory inductance plethysmography bands placed around the chest and abdomen. Airflow was measured at the nostrils using a catheter coupled with a pressure transducer referenced to ambient pressure. A thermistor was also used to indirectly measure airflow at the nostrils and the mouth.

**Polysomnography Scoring**

Polysomnography data were analysed according to the AASM recommended scoring criteria (Iber et al., 2007). Sleep data were scored using standard visual rules to differentiate wake and different stages of sleep. Data were divided into 30 second epochs and classified as either wake, rapid eye movement (REM) sleep or non-REM sleep (further divided into stages N1, N2 and N3). Apnoeas were defined as a decrease in airflow of ≥90% lasting for ≥10 seconds accompanied by either ongoing respiratory efforts (obstructive); cessation of respiratory efforts (central); or cessation of respiratory effort in the first half of the apnoea with
resumption of respiratory efforts before resumption of airflow (mixed). Hypopnoeas were defined as a ≥30% reduction in airflow lasting for ≥10 seconds accompanied by a ≥4% decrease in oxygen saturation. No distinction was made between obstructive and central hypopnoeas.

2.2.2. Respiratory Polygraphy

A commercial polysomnography system (SOMNOscreen, Somnomedics GmbH, Germany) was adapted for respiratory polygraphy for screening studies in Chapter 5. Chapter 5 only included healthy volunteers with no signs or symptoms of OSA and had no comorbidities; thus they had low pre-test probability of OSA. In such a population respiratory polygraphy has been validated for screening for OSA, under the condition that studies are scored manually (Chesson et al., 2003). Respiratory polygraphy studies were unattended and performed either in the home of participants or in the Royal Brompton Hospital Research Sleep Laboratories. Data were recorded overnight onto an integral micro computer and flash card and downloaded the following morning onto a personal computer. A reduced number of signals were recorded compared to polysomnography; the parameters monitored were heart rate using electrocardiography (ECG), oxygen saturation (SaO₂) using pulse oximetry, snoring using a vibration sensor placed over the larynx, breathing effort using respiratory inductance plethysmography, and airflow at the nostrils using a pressure transducer referenced to ambient pressure. Sleep/wake state was not monitored using EEG, therefore participants were asked to complete a sleep diary recording the time that they turned their lights off to go to sleep, the time that they woke up in the morning, and any extended periods of wake during the night. The time between participants recording lights off and recording that they had woken in the morning on their sleep diary was designated as “sleep”. This period was then analysed to determine the AHI using standard AASM criteria for apnoeas and hypopnoeas (Iber et al., 2007). See section on polysomnography scoring above for a full description.
2.2.3. Respiratory Measurements

In Chapter 4 additional respiratory monitoring was required during the night in order to perform the Pcrit technique (see Chapter 1, Section 1.2.2 for a review of the literature; see Section 2.2.4 for the methods of the technique). Analogue respiratory signals were recorded in synchrony with sleep signals (described in Section 2.2.1 above) via an analogue to digital converter (Micro 1401, Cambridge Electronic Design, UK) and recorded using data acquisition software that allowed real-time viewing of signals (Spike2 version 3.21, Cambridge Electronic Design, UK).

Measurement of Airflow

In Chapter 4 respiratory airflow was measured using a non-heated pneumotachometer (model 4700A, Hans Rudolph, USA; linear flow range 0-160 l/min) attached to a nasal mask. The pneumotachometer contained 3 resistive mesh screens through which air was passed. It was assumed that airflow through the screens was laminar and that the pressure drop across the screens was proportional to airflow. The pressure drop across the screens was measured by coupling the pneumotachometer with a pressure transducer (DP45-14, Validyne, USA; range ± 2 cmH₂O) that produced a voltage signal proportional to airflow. This signal was amplified via a carrier demodulator (CD19A, Model MC1-3, Validyne, USA), passed through an analogue to digital converter (Micro 1401, Cambridge Electronic Design, UK) and recorded in real-time using data acquisition software (Spike2, version 3, Cambridge Electronic Design, UK).

Before each study a 5-point calibration was performed on the pneumotachometer to ensure the accuracy of airflow measurements. Five known airflows (0 L/min, ±10 L/min and ±20 L/min) were passed through the pneumotachometer in both directions to calibrate positive and negative airflow. Linear regression analysis of the relationship between known airflows and
voltage output from the pneumotachometer was used to determine the airflow value corresponding to 1 volt output from the pneumotachometer and this equation was entered as a correction factor in the data acquisition software.

**Measurement of Mask Pressure**

Mask pressure was measured using a differential pressure transducer (DP45-26, Validyne, USA; range ± 35 cmH\textsubscript{2}O) attached to a nasal mask. The pressure transducer was composed of 2 air-tight compartments with very low dead-space, each housing a magnetic inductance coil. The compartments were separated by a steel diaphragm which in the undeflected position was equidistant between the two magnetic coils. A pressure line was routed into each air-tight compartment and a change in pressure caused the steel diaphragm to be deflected towards the compartment with lower air pressure. This caused a change in magnetic inductance and generated a voltage that was proportional to the change in air pressure. This signal was amplified by a carrier demodulator (CD19A, Model MC1-3, Validyne, USA), passed through an analogue to digital converter (Micro 1401, Cambridge Electronic Design, UK) and recorded in real-time using data acquisition software (Spike2, version 3, Cambridge Electronic Design, UK).

Before each study a 5-point calibration was performed on the pressure transducer to ensure the accuracy of mask pressure measurements. Five known positive and negative pressures (0 cmH\textsubscript{2}O, ±10 cmH\textsubscript{2}O and ±20 cmH\textsubscript{2}O) were applied to the pressure transducer using a water manometer. Linear regression analysis of the relationship between known pressures and voltage outputs from the pressure transducer was used to determine the pressure value corresponding to 1 volt output from the pressure transducer and this equation was entered as a correction factor in the data acquisition software.
Measurement of Intrathoracic Pressure

Oesophageal pressure was measured using a solid tip pressure sensor (CTO-1, Gaeltec Ltd, UK) coupled with a pressure transducer (model S7b/2, Gaeltec Ltd, UK). The sensor was passed into the oesophagus via the nostril and positioned approximately 40 cm past the nares. Small adjustments were made to the positioning of the sensor in order to minimise cardiac artefacts. The sensor was secured externally by taping it below the nostrils and was held securely below the nasal mask during sleep studies. The pressure sensor contained a metal diaphragm in contact with the outside environment and was connected to an internal strain gauge. Changes in external pressure caused the diaphragm to deform which in turn deformed the strain gauge and caused a small alteration to its electrical resistance. This signal was amplified by the pressure transducer to produce a voltage proportional to pressure. The voltage signal was passed through an analogue to digital converter (Micro 1401, Cambridge Electronic Design, UK) and recorded in real-time using data acquisition software (Spike2, version 3, Cambridge Electronic Design, UK).

Before each study a 5-point calibration was performed on the pressure transducer to ensure the accuracy of oesophageal pressure measurements. Five known positive and negative pressures (0 cmH₂O, ±10 cmH₂O and ±20 cmH₂O) were applied to the pressure transducer using a water manometer. Linear regression analysis of the relationship and equation were calculated and entered into the data acquisition software as explained above.

2.2.4. Pharyngeal Critical Closing Pressure

Pharyngeal critical closing pressure (Pcrit) can be measured under conditions of active neuromuscular tone (active Pcrit) (Schwartz et al., 1988) or passive neuromuscular tone (passive Pcrit) (Schwartz et al., 1998). Both techniques have been used to demonstrate the increased upper airway collapsibility of patients with OSA (Patil et al., 2007). Active Pcrit is
thought to reflect the effect of the dynamic neuromuscular response to upper airway resistance on collapsibility, whereas passive $P_{crit}$ is thought to reflect the effect of mechanical loads on collapsibility (Patil et al., 2007). For my research I have chosen to perform measurements of passive $P_{crit}$. If fluid accumulation in the upper airway does influence upper airway collapsibility it would be expected to be via increased extraluminal pressure acting on the pharynx. This is a passive, mechanical force, and would not be expected to have a direct effect on neuromuscular tone.

Passive $P_{crit}$ is measured by inducing upper airway muscle hypotonia. This is achieved by applying continuous positive airway pressure (CPAP) via a nasal mask to a sleeping subject at the minimal effective pressure (holding pressure) sufficient to eliminate flow limitation (Schwartz et al., 1998). Hypotonia is assumed to prevail after approximately 3 minutes of stable sleep at holding pressure. After this, pressure at the mask ($P_{mask}$; taken as a surrogate of upper airway pressure) is rapidly reduced in order to induce upper airway narrowing and flow limitation (Figure 2.1). Following a rapid reduction in $P_{mask}$, hypotonia persists for up to 5 breaths, with the upper airway becoming most collapsible on the third inspiratory effort (Schwartz et al. 1998). Therefore measurement of $P_{crit}$ is made using the median of 5 breaths immediately after rapid reduction of $P_{mask}$. 
Patients were supplied with CPAP sufficient to eliminate flow limitation (holding pressure). Pressure was then reduced in a square wave fashion for runs of 5 breaths. Runs of reduced pressure were repeated at 60 second intervals at progressively more negative pressures until airflow ceased (defined as flow falling below 50 ml/s). This pressure was defined as Pcrit. A second and third series of runs were then performed to confirm the pressure at which Pcrit occurred. This protocol was performed at the start of the night and at the end of the night (Patil et al. 2004).

2.2.5. Protocol for Pcrit

Figure 2.2 is a diagram of the Pcrit breathing circuit. Patients were fitted with a tight-fitting nasal mask connected to a positive pressure source (Companion 318, Puritan Bennett, Colorado, USA) and a negative pressure source (Pegaso Cough, Dima Italia, Italy) via a 3-way tap. Airflow was measured using a pneumotachometer and Pmask was measured using a differential pressure transducer referenced to ambient pressure. A solid tipped pressure transducer was used to measure oesophageal pressure in participants that were able to tolerate the pressure transducer during sleep (see Section 2.2.3 for a full description of respiratory monitoring techniques). Sleep stage of the participants was monitored continuously.
throughout Pcrit measurements using the techniques described in Section 2.2.1.

Patients were allowed to fall asleep with a low pressure set on the CPAP machine. Once patients had entered stage I-III NREM sleep, CPAP was titrated to eliminate flow limitation (holding pressure). After at least 3 minutes at holding pressure, Pmask was rapidly reduced by 2 cmH\(_2\O\) from holding pressure for a run of 5 breaths in order to induce flow limitation; holding pressure was then re-established. After 60 seconds, Pmask was rapidly reduced by 4 cmH\(_2\O\) from holding pressure for another run of 5 flow-limited breaths. Pmask was progressively reduced for runs of 5 breaths in this manner in 1 or 2 cmH\(_2\O\) increments over at least 3 different mask pressures until criteria for Pcrit were met.

The criteria used to define Pcrit were dependent on whether participants were able to sleep with the oesophageal pressure transducer. In participants that were able to sleep with the oesophageal pressure transducer, Pcrit was defined as the pressure at which airflow at the nasal mask was absent accompanied by ongoing oesophageal pressure swings, indicating

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**Figure 2.2: Pcrit circuit diagram.**

Delivery of positive and negative pressure was controlled via a 3-way tap. This also allowed pressure to be rapidly reduced during measurements of Pcrit.
closure of the pharynx (Schwartz et al., 1998, 1988). In participants who were studied without the oesophageal pressure cannula, Pcrit was defined as the pressure at which airflow at the nasal mask was absent accompanied by ongoing thoracic and abdominal movements. In some participants, it was not possible to reach a mask pressure low enough to cause airflow to cease without causing an arousal from sleep. In these participants, linear regression of the relationship between airflow and mask pressure was performed in order to predict the mask pressure at which airflow would have ceased (Patil et al., 2004). Both of these methods have been validated and have been shown to produce similar results for Pcrit when used to analyse the same sets of data (Patil et al., 2004).

Once Pcrit was established, a second set of at least 3 runs encompassing holding pressure, flow limitation, and Pcrit were performed to confirm the Pmask at which Pcrit occurred. If the patient aroused during runs of reduced Pmask they were immediately returned to holding pressure and allowed at least 3 minutes of stable stage II-III NREM sleep before another run was attempted.

### 2.3. Validation of Pcrit Technique

Before recruiting any patients to my studies it was necessary to validate the Pcrit circuit. I constructed the Pcrit circuit using a CPAP machine (Companion 318, Puritan Bennett, Colorado, USA) to generate positive pressure and a cough assist machine (Pegaso Cough, Dima Italia, Italy) to generate negative pressure. It was necessary to test that the capabilities of the circuit were comparable to the system used in the seminal papers on the technique (Schwartz et al. 1988; Smith et al. 1988).

#### 2.3.1. Pharyngeal Pcrit Circuit

Key capabilities of the circuit were that it could rapidly alternate between positive and negative pressures of ±15 cmH₂O, and that it could deliver controlled increments in pressure
of $\leq 2$ cmH$_2$O. According to its built-in micro computer, the negative pressure source was capable of delivering negative pressures in increments of 1 cmH$_2$O. In order to achieve a mask pressure of -2 cmH$_2$O a controlled leak was introduced into the negative pressure limb of the Pcrit circuit. The micro computer of the positive pressure source was also capable of delivering increments of 1 cmH$_2$O and could deliver a minimum mask pressure of 1.5 cmH$_2$O. The aim of the validation was to quantify the sensitivity with which pressure at the mask could be controlled using the positive and negative pressure sources. Reproducibility of pressure delivery was not tested as part of the validation because the positive and negative pressure sources were both commercial products in routine clinical use and were assumed to deliver positive or negative air pressure reliably.

### 2.3.2. Methods

The Pcrit circuit was tested on an awake, healthy volunteer, who was set up as described in Section 2.2.5. The volunteer lay supine and was exposed to increments of mask pressure for up to 5 breaths, separated by 30 seconds of normal breathing on CPAP of 2.5 cmH$_2$O. Mask pressure was increased in increments of 2 cmH$_2$O up to 15 cmH$_2$O to test the positive pressure source. Mask pressure was then decreased in 2 cmH$_2$O increments down to -15 cmH$_2$O to test the negative pressure source. The Pearson correlation coefficient was calculated for the pressures measured at the mask and the pressures indicated by the micro computers of the positive and negative pressure sources.

### 2.3.3. Results

The measured pressures at the mask correlated strongly with the indicated pressures of the positive and negative pressure sources (positive source: $r^2 = 0.99$; negative source: $r^2 = 0.99$; Figure 2.3). There was also a strong correlation between the change in indicated pressures and the measured pressures for both the positive and negative pressure source (positive source: $r^2$...
= 0.99; negative source: $r^2 = 0.99$; Figure 2.4). A 1 cmH$_2$O increase in indicated pressure using the positive pressure source equated to an increase of 1 cmH$_2$O at the mask. A 1 cmH$_2$O decrease in indicated pressure using the negative pressure source equated to a decrease of 0.5 cmH$_2$O at the mask.

**Figure 2.3:** Correlation between indicated pressure from positive and negative pressure sources and nasal pressure measured at the mask. Squares represent positive pressures and diamonds represent negative pressures.
2.3.4. Summary of Pcrit Validation

The performance of the positive and negative pressure sources were comparable to the systems used in the seminal papers on the technique (Schwartz et al., 1998, 1988; Smith et al., 1988). Therefore the circuit as described in this Chapter was used for measurements of Pcrit in Chapter 4.

2.4. Acoustic Reflection

Acoustic reflection (AR) is the second technique that I developed for the measurements of upper airway calibre reported in this thesis. It is a non-invasive method for measuring the dimensions of any tube using sound waves. It was first used to measure airway geometry when Jackson et al. (1977) used the technique to make measurements of dog lungs in vitro. It was later used to make non-invasive measurements of human airways (Fredberg et al., 1980)

Figure 2.4: Correlation between change in display pressure at machine and change in measured pressure at mask. Squares represent positive pressures and diamonds represent negative pressures.
and has been developed in recent years for routine assessment of oral and nasal airway geometry (Brooks et al., 1989, 1984; Hilberg and Pedersen, 2000; Kamal, 2004, 2001). The advantages of AR over imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) are that it can be performed quickly and easily, with practically no discomfort to the subject. However, some skill is required of the subject in keeping relaxed but still during measurements and arranging their soft palate to occlude the nasal pharynx. Also, AR does not produce images, so although a 3-dimensional measurement of the upper airway can be obtained, only a limited number of specific anatomical landmarks can be reliably identified.

AR measurements can be made by subjects breathing a helium-oxygen gas mixture or by breathing air. Breathing a helium-oxygen mixture allows accurate and reproducible measurements to be made to the level of the trachea. Measurements made while breathing air are technically less challenging to perform, but are only accurate and reproducible to the level of the glottis (Brooks et al., 1984; Fredberg et al., 1980; Huang et al., 1998). I chose to make measurements during air breathing because the collapsible region of the upper airway encompasses the oropharynx and glottis, but does not extend to the trachea (Rama et al., 2002).

AR exploits the physical principle that sound waves travelling in tubes are reflected by a change in tube dimensions. A microphone is used to record the amplitude and wavelength of reflected waves, which can be analysed to construct serial measurements of cross-sectional area as a function of distance. The assumptions are that sound waves reflected from the airway have an amplitude proportional to the cross-sectional area of the airway, and a wavelength proportional to the airway length (Jackson et al., 1977). Figure 2.5 shows a typical trace, recorded during my experiments. Cross-sectional area on the y-axis is plotted against distance from the microphone on the x-axis. The region from 0-8 cm corresponds to
the wave tube and mouthpiece. The region from 8-18 cm encompasses the oral cavity, oropharynx, part of the laryngo-pharynx, and terminates at the glottis. In AR measurements this region (from the end of the mouthpiece to the glottis) is conventionally defined as the pharynx (Brown et al., 1986). Pharyngeal length can be measured between these two points. The peak pharyngeal area is assumed to inhabit the oral cavity but does not represent a specific anatomical feature. The glottis is identified as the minimum area distal to the peak pharyngeal area, and glottis area (AG) is measured at this point on the trace. Mean pharyngeal area (APmean) is obtained by calculating the mean cross-sectional area of serial measurements made between the end of the mouthpiece and the glottis. Pharyngeal volume (VP) can be obtained by integrating the area under the curve between the mouthpiece opening and the glottis.
The pharynx is designated as the region between the end of the mouthpiece and the glottis. Pharyngeal length is measured between the end of the mouthpiece and glottis. Mean pharyngeal area is obtained by calculating the mean cross-sectional area over the length of the pharynx. Pharyngeal volume is obtained by multiplying pharyngeal length by mean pharyngeal area. Glottis area is measured as the cross-sectional area at the glottis.

Figure 2.6 shows a diagram of the AR device used in my research (A1 Executive Acoustic Rhinometer, GM Instruments Ltd, Kilwinning, UK). It consists of a wave-tube sealed at the end distal to the mouth and open at the end proximal to the mouth. An acoustic pulse generator is positioned at the distal end of the wave-tube and a microphone for detection of acoustic pulse waves is positioned approximately 9cm from the proximal end.
In order to model the human airway as a continuous tube with no branching, it is necessary to make measurements with the soft palate elevated to occlude the nasopharynx (Fredberg et al., 1980). This can be achieved by asking subjects to breathe through their mouth only (Brooks et al., 1984). Allowing volunteers in my studies to breathe through their mouths during measurements presented a logistical problem because the wave-tube was sealed airtight at the end distal to the mouth. In other AR systems this problem is overcome by extending the wave-tube distal from the microphone by a distance that exceeds the length of the airway region to be measured (normally to the glottis; see Figure 2.7). In these systems, sound waves travel in both directions down the wave-tube, but because the distance to the open end of the wave-tube is greater than the distance to the glottis, reflected waves from the open end of the wave-tube arrive at the microphone later than reflected waves from the airway and so do not affect airway measurements. This is crucial because waves reflected from the open end of the wave-tube have amplitude that is proportional to the cross-sectional area of the surrounding room. If these waves arrived at the microphone at the same time or before reflected waves from the airway, they would saturate the signal recorded at the microphone and completely mask the smaller amplitude waves reflected from the upper airway.

Figure 2.6: Diagram of acoustic reflectometer used in these studies.
In order to overcome this problem for the AR device used in these studies, a different solution was required because it could not be simply extended at the distal end. Therefore a mouthpiece arrangement was designed with advice and guidance from Eric Grieg of GM Instruments that positioned a breathing tube parallel to the wave-tube. The breathing tube was longer than the distance from the microphone to the glottis, therefore, as with a conventionally extended wave-tube (as in Figure 2.7), sound waves reflected from the open end of the breathing tube could not interfere with sound waves reflected from the airway. However, with the breathing tube aligned parallel to the wave-tube a systematic offset was introduced to the signal recorded at the microphone equal to the cross-sectional area of the breathing tube ($1.8 \, \text{cm}^2$). Therefore it was necessary to apply a post-hoc correction during analysis to remove the effect of the breathing tube from the upper airway measurements (see Section 2.5 for validation study of AR device).
2.4.1. Protocol

AR measurements were made in both a seated and supine posture. For seated measurements, the same standard chair was used for all experiments. Participants sat in a comfortable upright posture with their arms either resting on the arms of the chair or on their lap. The height of the AR device was adjusted using a tripod to allow the head to rest in a neutral position, with the line of the chin parallel to the floor. This height was noted and used for all subsequent measurements of a given participant. For supine measurements, participants rested their head on a single pillow in a neutral position and the AR device was aligned perpendicular to the floor. Patients were instructed to breathe only through the mouth and were asked to remain still throughout the test and avoid moving the head, neck, jaw or tongue. Patients had at least 50 traces recorded at end tidal expiration, close to functional residual capacity. End expiration was estimated by careful observation of the patients abdominal and chest movements. This point in the respiratory cycle was chosen because it is relatively easy to identify by careful observation, and because acoustic reflection measurements of pharyngeal calibre are known to be relatively stable at end-tidal expiration (Brown et al., 1986; Huang et al., 1998).

Each end-expiratory trace was individually analysed to obtain the glottis cross-sectional area (AG), mean pharyngeal area (APmean), and pharyngeal volume (VP). These measurements from individual traces were then averaged in order to obtain mean values for each participant. Traces where the soft palate had not fully occluded the nasal cavity were identified by the cross-sectional area exceeding 15 cm² at any point on the airway trace. These traces were excluded from analysis. Traces where the participant had swallowed during data acquisition (resulting in a flat trace close to 0 cm²) were also excluded from analysis.

2.5. Validation of Acoustic Reflection Technique

The AR device was a commercial system that was designed for measuring the nasal cavity
and nasopharynx. It had not previously been validated for oral measurements. However acoustic reflection technology can be readily adapted to measure any tube, therefore a mouthpiece was fashioned to couple with the AR device to allow measurements to be made orally. The acoustic reflectometer was tested using this novel interface for accuracy and reproducibility.

The mouthpiece featured a breathing tube that allowed patients to breathe orally during measurements. This is an important requirement for making accurate measurements of the oropharynx as it allows patients to breathe while elevating their soft palate to occlude the nasopharynx. Occluding the nasopharynx allows the oropharynx to be modelled as a single tube, with no branching, which is a prerequisite for accurate AR measurements.

The aims of the validation tests were:

1. Establish the accuracy and repeatability of the AR device and compare its performance to established international standards.
2. Establish the effect of installing the novel mouthpiece onto the AR device on the accuracy and repeatability of measurements.
3. Establish the within-test repeatability and between-test reproducibility of the AR device when used in conjunction with the novel mouthpiece to measure human airway dimensions via the oral cavity.

2.5.1. Methods

Accuracy and Repeatability of Acoustic Reflection Device

The AR device was tested for accuracy and within-test repeatability using a tube with a known constant internal cross-sectional area (straight tube) and a tube designed to replicate the human nose that had a variable internal cross-sectional area (model nose). The straight tube was 18.5 cm long and had a constant internal cross-sectional area of 1.3 cm² (see Figure
The model nose was 15 cm long and had an internal cross-sectional area that varied along its length across a physiological range from 0.5 cm$^2$ to 7.6 cm$^2$ (see Figure 2.8, bottom right panel for area-distance trace). The model nose is a standard model that is used widely for standardisation of AR devices (Hilberg and Pedersen, 2000). It is constructed to replicate the internal cross-sectional area of a normal human nose based on known geometric dimensions.

The protocol used to test the accuracy and repeatability of the AR device was adapted from standard validation procedures designed for nasal measurements, described by the International Standardization Committee for Rhinomanometry (Hilberg & Pedersen 2000). The straight tube was measured geometrically to obtain its internal cross-sectional area. The geometric dimensions of the model nose had been measured previously, therefore a copy of these dimensions was obtained from the supplier of the model nose (GM Instruments, UK). The geometric dimensions of the two tubes were designated as the “known” dimensions. The known dimensions were used for comparison to the measured dimensions.

The straight tube and model nose were then measured under two sets of conditions. In the first condition the tubes were attached directly to the AR device. This condition was used to establish the accuracy and repeatability of the device itself and to act as a control for comparison against the installation of the mouthpiece onto the AR device. In the second condition the mouthpiece was connected to the AR device and the straight tube and model nose were attached in line to the mouthpiece. A total of 90 acoustic traces were recorded for each tube under each condition. This allowed the mean cross-sectional area to be calculated for the entire length of each tube.

The accuracy and repeatability of the AR measurements under each condition were tested by comparing the measured dimensions to the known dimensions of each tube. In acoustic measurements, accuracy tends to decrease as distance from the microphone increases.
Therefore the accuracy and repeatability of the AR device were calculated as a mean over the entire distance of each tube. Measurement error was calculated as the measured dimensions minus the known dimensions. The percentage error was calculated as the measurement error divided by the known dimensions, multiplied by 100. Accuracy was calculated as 100 minus percentage error. Repeatability of the device was expressed as the standard deviation of the mean measured dimensions. Coefficient of variation was calculated as the standard deviation divided by the mean measurement, multiplied by 100.

Repeatability and Reproducibility of Acoustic Reflection Measurements in Humans

Within-test repeatability and between-test reproducibility in human subjects was assessed by measuring the upper airway of 17 healthy volunteers. Each volunteer attended the laboratory on two separate occasions at least 24 hours apart and at the same time of day (±2 hours). On each occasion volunteers underwent AR measurements in a seated and supine posture according to the standard protocol described in Section 2.4.1.

Each individual trace was analysed to locate the junction where the mouthpiece ended and the oral cavity began, and to locate the glottis. The region between these two landmarks was designated as the pharynx. Further analysis of each trace was then performed to obtain the mean pharyngeal area. The mean pharyngeal area was then tested for its within-test repeatability and between-test reproducibility.

Within-test repeatability was assessed in each volunteer by calculating the coefficient of variation (CV). A CV of 10% or less has been suggested as an acceptable level of variance for AR measurements (Brooks et al., 1989, 1984; Hilberg and Pedersen, 2000). Between-test reproducibility was tested using the Bland-Altman method for assessing limits of agreement (Bland and Altman, 1999).
2.5.2. Results

Accuracy and Repeatability of Acoustic Reflection Device

Plots comparing measured dimensions to the known dimensions of the straight tube and model nose when directly connected to the acoustic device, and when connected via the mouthpiece, are presented in Figure 2.8. The accuracy and repeatability of measurements made of the straight tube and model nose when connected directly to the acoustic device are presented in Table 2.1. Measurements of the straight tube and the model nose had a very low measurement error and CV, meaning that they had high accuracy and repeatability.

Table 2.1: Accuracy and repeatability of measurements made while the straight tube and model nose were connected directly to the acoustic reflection device.

<table>
<thead>
<tr>
<th>Mean over length of tube</th>
<th>Straight Tube (mean ± SD of 90 traces)</th>
<th>Model Nose (mean ± SD of 90 traces)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known Dimensions (cm$^2$)</td>
<td>1.30</td>
<td>1.84 ± 1.6</td>
</tr>
<tr>
<td>Measured Dimensions (cm$^2$)</td>
<td>1.27 ± 0.03</td>
<td>1.84 ± 1.4</td>
</tr>
<tr>
<td>Measurement Error (cm$^2$)</td>
<td>-0.03 ± 0.03</td>
<td>0.003 ± 0.2</td>
</tr>
<tr>
<td>Repeatability</td>
<td>0.01 ± 0.01</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>Coefficient of Variation (%)</td>
<td>1.2 ± 0.4</td>
<td>4.3 ± 3.7</td>
</tr>
</tbody>
</table>

The accuracy and repeatability of measurements made of the straight tube and model nose when connected to the AR device via the mouthpiece are presented in Table 2.2. Measurements of both tubes again had a low measurement error, meaning that they had high accuracy. The CV was slightly increased for each tube, meaning that the repeatability of measurements made with the mouthpiece installed were reduced.
Table 2.2: Accuracy and repeatability of measurements made while the straight tube and model nose were connected to the acoustic reflection device via the mouthpiece.

<table>
<thead>
<tr>
<th></th>
<th>Mouthpiece+Straight Tube</th>
<th>Mouthpiece+Model Nose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known Dimensions (cm$^2$)</td>
<td>1.30</td>
<td>1.84 ± 1.6</td>
</tr>
<tr>
<td>Measured Dimensions (cm$^2$)</td>
<td>1.29 ± 0.2</td>
<td>1.85 ± 1.4</td>
</tr>
<tr>
<td>Measurement Error (cm$^2$)</td>
<td>-0.01 ± 0.2</td>
<td>0.01 ± 0.6</td>
</tr>
<tr>
<td>Repeatability</td>
<td>0.06 ± 0.02</td>
<td>0.1 ± 0.03</td>
</tr>
<tr>
<td>Coefficient of Variation (%)</td>
<td>4.9 ± 1.0</td>
<td>8.7 ± 7.2</td>
</tr>
</tbody>
</table>

Bottom left, straight tube connected directly to AR device; bottom right, model nose connected directly to AR device; top left, straight tube connected to AR device via mouthpiece; top right, model nose connected to AR device via mouthpiece.

Figure Key: Known dimensions: ——; Measured dimensions: ------.
Each individual subject's AR measurements of APmean made in a seated and supine posture on Day 1 and Day 2 are presented in Table 2.3. The mean CV for each posture on each day were calculated for the whole group of subjects. The mean CV was consistently below 10%.

The mean difference between measurements made on Day 1 and 2 in a seated posture was 0.08 ± 0.52cm², suggesting there was minimal day to day variation. This was also the case in supine measurements, where the mean difference between Day 1 and 2 was 0.15 ± 0.55cm². There were no significant differences between measurements made on Day 1 and 2 in the seated posture (p=0.5) or the supine posture (p=0.3). This was confirmed by measuring limits of agreement of measurements made in the same posture on Day 1 and 2 using Bland-Altman plots.
Table 2.3: Mean of 90 APmean measurements in 17 individual healthy volunteers (3 female).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Seated Day 1</th>
<th>Seated Day 2</th>
<th>Supine Day 1</th>
<th>Supine Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD (cm²)</td>
<td>CV (%)</td>
<td>Mean ± SD (cm²)</td>
<td>CV (%)</td>
</tr>
<tr>
<td>1</td>
<td>7.7 ± 0.3</td>
<td>4</td>
<td>8.1 ± 0.3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5.7 ± 0.3</td>
<td>5</td>
<td>5.1 ± 0.3</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>5.6 ± 0.5</td>
<td>9</td>
<td>6.3 ± 0.5</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>5.9 ± 0.7</td>
<td>12</td>
<td>6.2 ± 0.7</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>5.8 ± 0.2</td>
<td>3</td>
<td>5.9 ± 0.3</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>6.0 ± 0.3</td>
<td>5</td>
<td>5.6 ± 0.3</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>5.3 ± 0.2</td>
<td>4</td>
<td>5.5 ± 0.3</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>5.1 ± 0.2</td>
<td>4</td>
<td>5.6 ± 0.4</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>6.1 ± 0.6</td>
<td>3</td>
<td>5.9 ± 0.8</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>5.1 ± 0.8</td>
<td>13</td>
<td>5.1 ± 0.9</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>7.1 ± 0.3</td>
<td>4</td>
<td>6.5 ± 0.3</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>5.6 ± 0.4</td>
<td>7</td>
<td>6.1 ± 0.2</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>8.7 ± 0.3</td>
<td>3</td>
<td>8.0 ± 0.4</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>6.9 ± 0.5</td>
<td>7</td>
<td>6.4 ± 0.5</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>5.1 ± 0.3</td>
<td>6</td>
<td>4.5 ± 0.2</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>6.6 ± 0.4</td>
<td>6</td>
<td>5.6 ± 0.3</td>
<td>5</td>
</tr>
<tr>
<td>17</td>
<td>4.6 ± 0.3</td>
<td>7</td>
<td>5.1 ± 0.4</td>
<td>8</td>
</tr>
</tbody>
</table>

Mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD (cm²)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.1 ± 1.1</td>
<td>7 ± 3</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. See Bland-Altman plots for limits of agreement between Day 1 and Day 2.
The plot shows the mean of APmean measurements made on Day 1 and Day 2 (x-axis) plotted against the difference between APmean measurements made on Day 1 and Day 2 (y-axis). Each data point represents an individual subject. The mean difference between days (indicated by horizontal line) was close to zero, and all individuals had a difference between Day 1 and Day 2 of less than 2 SD from the mean (dashed lines). Therefore the agreement was high between Day 1 and Day 2.

Figure 2.9: Bland-Altman plot showing agreement between Day 1 and Day 2 for seated measurements. The plot shows the mean of APmean measurements made on Day 1 and Day 2 (x-axis) plotted against the difference between APmean measurements made on Day 1 and Day 2 (y-axis). Each data point represents an individual subject. The mean difference between days (indicated by horizontal line) was close to zero, and all individuals had a difference between Day 1 and Day 2 of less than 2 SD from the mean (dashed lines). Therefore the agreement was high between Day 1 and Day 2.
The plot shows the mean of APmean measurements made on Day 1 and Day 2 (x-axis) plotted against the difference between APmean measurements made on Day 1 and Day 2 (y-axis). Each data point represents an individual subject. The mean difference between days (indicated by horizontal line) was close to zero, and all but one individual had a difference between Day 1 and Day 2 of less than 2 SD from the mean (dashed lines). Therefore the agreement was high between Day 1 and Day 2.

2.5.3. Summary of Acoustic Reflection Validation

Accuracy and Repeatability of Acoustic Reflection Device

A threshold CV of approximately 10% has been suggested by other researchers as a standard for reasonable within-test variability for AR measurements of the upper airway via the oral cavity (Brooks et al., 1989, 1984; Hilberg and Pedersen, 2000). By this standard, the AR equipment and methods used in this study were within acceptable operating limits and comparable to other validated commercial and bespoke systems used by other laboratories.
It has been demonstrated that the use of the novel mouthpiece in the AR circuit introduced greater variability in measurements, as CV was approximately doubled. However, CV was still below 10%, which is within acceptable limits for device repeatability. The accuracy of the device did not seem to be significantly affected by introduction of the mouthpiece into the AR circuit.

**Repeatability and Reproducibility of Acoustic Reflection Measurements in Humans**

The within-test CV was also within acceptable limits in measurements of the human airway. Although there was individual variation, the mean CV across the group was below 10% in both the seated and supine posture on Day 1 and Day 2.

There were no significant differences in APmean between Day 1 and Day 2. The reproducibility of AR measurements in humans was confirmed using Bland-Altman limits of agreement plots. The agreement between two measurements can be said to have good agreement if ≥95% of measurements fall between 2 standard deviations of the mean (Bland and Altman, 1999). By this standard, the measurements between Day 1 and Day 2 fell within the limits of agreement in the seated and supine posture.
Chapter 3: Pharyngeal Calibre in Heart Failure Patients with Obstructive Sleep Apnoea
3.1. Introduction

The prevalence of SDB in CHF is estimated to be up to 50% with approximately 25% OSA (Bitter et al., 2009; Ferrier et al., 2005; Javaheri, 2006; Javaheri et al., 1998; Lanfranchi et al., 2003; MacDonald et al., 2008; Oldenburg et al., 2007; Schulz et al., 2007; Vazir et al., 2007). This contrasts with the general population where the prevalence of OSA in older subjects (50-60 yrs) is up to 15% (Young et al., 1993). The higher prevalence of OSA in CHF cannot be readily explained by mechanisms that most often contribute to OSA in the general population. For example, OSA is strongly associated with obesity, however the prevalence of obesity in the CHF population is similar to that in the general population when matched for age (Johansson et al., 2001; The NHS Information Centre, 2004). This finding would appear to support the theory that external extraluminal pharyngeal pressure, associated with obesity, may have different relative contributions to OSA in CHF, compared to OSA only. It is also possible that there may be mechanisms that contribute to OSA in CHF that are not present in the general population.

One such feature of CHF that may predispose patients to OSA is fluid retention during the day and subsequent rostral fluid shift during the night (see Chapter 1, Section 1.2.4). A series of studies have shown that application of 40 mmHg positive pressure to the legs using anti-shock trousers resulted in decreased leg fluid volume and increased neck circumference. After 5 minutes of positive pressure being applied to the legs it was found that pharyngeal resistance increased (Chiu et al., 2006), pharyngeal calibre decreased (Shiota et al., 2007) and pharyngeal critical closing pressure increased (Su et al., 2008). These studies were performed on a small number of healthy volunteers but support the notion that rostral fluid shift (albeit actively-induced fluid shift) may contribute to OSA by promoting pharyngeal narrowing and collapse. Passive overnight rostral fluid shift has subsequently been shown to negatively
correlate with AHI in OSA patients (Redolfi et al., 2009), although this finding was not replicated in a similar more recent study (Jafari and Mohsenin, 2011). Both studies were uncontrolled observational investigations and so it is not clear whether passive overnight rostral fluid shift is a normal physiological phenomenon or whether it is a feature of patients with OSA and/or CHF.

Rostral fluid shift could be more common and more severe in fluid-overloaded states such as CHF. The only study to date to investigate fluid shift in CHF studied 35 CHF patients with OSA and 22 CHF patients with CSA (Yumino et al., 2010). It was found that both groups experienced an overnight decrease in leg fluid volume (measured using bioelectrical impedance) and an increase in neck circumference (measured using a tape measure); both of these factors correlated with the AHI. However, as with previous studies, this study also lacked a healthy control group, therefore it remains unclear whether passive overnight rostral fluid shift is a special mechanism of OSA in CHF or whether passive nocturnal rostral fluid shift is a normal physiological phenomenon.

Changing from an upright posture to a supine posture is a normal event that frees fluid that has accumulated in dependent veins due to gravity and allows it to rejoin the vascular circulation. There has been only one study, published very recently, comparing overnight rostral fluid shift with posture-related fluid shift. Fischer et al. (2012) studied 9 males without OSA and 36 males with OSA (using an AHI cut-off of 5 events/hr); half of the whole group were obese. It was found that there was a significant immediate increase in neck circumference when changing posture from upright to supine and an additional significant increase in neck circumference overnight. Furthermore, the magnitude of the change in neck circumference from upright to supine was correlated with the AHI, whereas there was no such correlation with overnight change in neck circumference. The postural changes in neck circumference happened immediately, leading the authors to suggest that they were due to
rostral displacement of soft tissue in and around the neck.

The aims of this study were: 1) to determine any relative effects of postural change on neck circumference and pharyngeal calibre in CHF patients; and 2) to determine whether any passive overnight changes in neck circumference and pharyngeal calibre are greater in CHF patients with OSA (CHF-OSA) compared to CHF patients without OSA (CHF-only) and healthy age-matched controls. I tested the hypotheses that CHF-OSA patients have a larger neck circumference and smaller pharyngeal calibre during resting wakefulness than CHF-only patients and age-matched healthy controls. I also tested the hypothesis that CHF-OSA patients experience a greater posture-related increase in neck circumference and decrease in pharyngeal calibre when moving from a seated to supine posture and that CHF-OSA patients experience a greater increase in neck circumference and decrease in pharyngeal calibre overnight than CHF-only and healthy controls. The primary outcomes were the neck circumference and APmean measured overnight and in a seated and supine posture. The secondary outcomes were VP and AG. Pharyngeal dimensions were measured non-invasively using acoustic reflection.

3.2. Methods

3.2.1. Ethical Review

This study was reviewed by the local Research Ethics Committee (Brompton Harefield and NHLI Research Ethics Committee) and given a favourable opinion (REC number: 09/H0708/24). All volunteers gave written informed consent prior to participating in this study.

3.2.2. Subjects

CHF-OSA patients, CHF-only patients, and age-matched healthy controls were recruited to
participate in two studies investigating pharyngeal calibre (the present study) and pharyngeal collapsibility (see Chapter 4) in CHF patients with OSA. CHF-OSA patients and CHF-only patients were recruited from heart failure clinics at the Royal Brompton Hospital. Age-matched healthy controls were recruited from the general population. Possible CHF patients were identified by screening clinics in collaboration with the Royal Brompton Hospital Cardiology Department and CHF specialist team. Patients with systolic and diastolic CHF were eligible for this study, and were identified by clinical assessment and functional signs and symptoms of CHF by their clinical team. Patients who met the inclusion/exclusion criteria (Table 3.1) were approached by a member of their clinical care team and invited to participate in this study.

Healthy volunteers were recruited by advertising in local newspapers and by contacting local sports clubs, social clubs and charitable groups. Potential participants were matched to the CHF groups for age. This was done by targeting recruitment at healthy volunteers over 60 years old. Potential participants were contacted by telephone and asked for a brief medical history in order to determine their eligibility prior to being invited to join the study.

All CHF patients and healthy volunteers that agreed to participate in the study underwent nocturnal polysomnography to determine the presence or absence of OSA (see below for full description of techniques). CHF patients with an AHI ≥10 events/hr with >50% of apnoeas classified as obstructive were allocated to the CHF-OSA group. CHF patients with an AHI <10 events/hr were allocated to the CHF-only group. Healthy controls were admitted to the study if they had an AHI <10 events/hr and had no clinical history of CHF. Participants who did not meet inclusion/exclusion criteria after the polysomnography were excluded from analysis. Participants that were excluded on the basis of a previously undiagnosed sleep-disorder were informed immediately and a letter was sent to their GP explaining the findings. Inclusion/exclusion criteria for the 3 groups are presented in Table 3.1.
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF-OSA and CHF-only</td>
<td>- 18-85 years old</td>
</tr>
<tr>
<td></td>
<td>- NYHA class II-III</td>
</tr>
<tr>
<td></td>
<td>- Systolic or diastolic heart failure, in a stable condition (no hospital admissions or medication changes in the 3 months prior to recruitment)</td>
</tr>
<tr>
<td></td>
<td>- Any sleep-disorder other than OSA</td>
</tr>
<tr>
<td></td>
<td>- Previous upper airway surgery or any current treatment for sleep apnoea (including CPAP)</td>
</tr>
<tr>
<td></td>
<td>- Unstable angina or arrhythmia</td>
</tr>
<tr>
<td></td>
<td>- Myocardial infarction in the 3 months prior to recruitment</td>
</tr>
<tr>
<td></td>
<td>- Primary pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>- Any significant neurological condition or respiratory disease</td>
</tr>
<tr>
<td></td>
<td>- Unable to give written informed consent</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>- 18-85 years old</td>
</tr>
<tr>
<td></td>
<td>- AHI &lt;10 events/hr</td>
</tr>
<tr>
<td></td>
<td>- Any previous diagnosis of OSA</td>
</tr>
<tr>
<td></td>
<td>- Upper airway surgery</td>
</tr>
<tr>
<td></td>
<td>- Any other sleep-disorder</td>
</tr>
<tr>
<td></td>
<td>- Any history of significant cardiac disease</td>
</tr>
<tr>
<td></td>
<td>- Any significant neurological condition or respiratory disease</td>
</tr>
<tr>
<td></td>
<td>- Unable to give written informed consent</td>
</tr>
</tbody>
</table>
3.2.3. Protocol

CHF patients and healthy volunteers were invited to attend the Royal Brompton research sleep laboratory on two occasions, no longer than 1 month apart, as part of a pair of studies measuring pharyngeal calibre (visit 1; the current study) and pharyngeal critical closing pressure (visit 2; see Chapter 4). On their first visit, participants had their height, weight, blood pressure and lung function recorded and a detailed medical history was taken including current medications, sleep habits and subjective sleepiness according to the Epworth Sleepiness Score.

Participants were set up for nocturnal polysomnography using a multi-channel commercial polysomnography system. For full details of the polysomnography equipment and methods, see Chapter 2, Section 2.2.1. Before going to sleep participants underwent measurements of their weight and neck circumference. Weight was measured immediately before going to bed, however participants were allowed to drink during the night if desired and urine excretion was not measured.

Measurements of neck circumference and pharyngeal calibre were performed first in a seated posture, then in a supine posture. Neck circumference was measured below the level of the crico-thyroid cartilage. Marks were made on the skin around the neck after the first measurement in the evening to ensure that subsequent measurements were made at the same level. A spring-tensioned tape measure was used for all measurements in order to limit the variability in measurements due to human error.

Pharyngeal calibre was measured before and after sleep using the acoustic reflection (AR) technique. The general protocol for all AR measurements is given in the General Methods (Chapter 2, Section 2.4.1). In brief, evening measurements of neck circumference and pharyngeal calibre were first made in the seated posture, after 5 minutes of sitting quietly.
Measurements were then made in the supine posture, after 5 minutes of laying quietly. All seated measurements were performed in a standardised chair with participants sitting in a comfortable upright posture. All supine measurements were performed with participants lying on a bed with their heads supported by a single pillow. AR traces of the pharynx were recorded at a rate of 1 per breath for 50 breaths at end-tidal expiration. In the morning measurements were repeated. Neck circumference and pharyngeal calibre were measured in the supine posture before participants had sat up from bed, and then in the seated posture after sitting upright in a chair for 5 minutes. Weight was measured within 10 minutes of completing pharyngeal measurements and before participants had urinated or consumed any food or drink.

3.2.4. Data Analysis

Polysomnography data were analysed according to the AASM recommended scoring criteria (Iber et al., 2007). See Chapter 2, Section 2.2.1 for full details of sleep stage and apnoea-hypopnoea classifications. All participant's sleep studies were analysed to determine their total sleep time, posture during the night, sleep architecture and AHI.

Neck circumference measurements were compared between groups and within groups for each experimental condition (evening-seated, evening-supine, morning-supine, morning-seated). The magnitude of change from seated to supine in the evening, overnight, and from supine to seated in the morning were also compared between groups.

Acoustic reflection traces were analysed as described in the General Methods (Chapter 2, Section 2.4.1). Each individual AR trace (approximately 50 per experimental condition per participant) was analysed to find 3 measures of pharyngeal calibre: 1) mean pharyngeal area (APmean); 2) pharyngeal volume (VP); 3) glottis cross-sectional area (AG). Data for each measure of pharyngeal calibre was then averaged according to the experimental condition and
compared within and between groups. The magnitude of change from seated to supine in the evening, overnight, and from supine to seated in the morning were also compared between groups. Percentage changes within groups were also analysed for NC, APmean, VP and AG. The evening-seated measurement was taken as the baseline measurement and all measurements were expressed as a percentage of baseline.

3.2.5. Statistical Analysis

The required sample size was calculated based on detecting a within-group change in APmean overnight. Rostral fluid shift in healthy volunteers has been demonstrated to result in a significant within-group decrease in APmean from $2.68 \pm 0.13 \text{ cm}^2$ to $2.40 \pm 0.12 \text{ cm}^2$ (Shiota et al., 2007). The APmean data of Shiota et al. (2007) had a coefficient of variation (CV) of 5%. The acoustic reflection device used in the present study produced measurements with a CV of 10% (see validation study, Chapter 2, Section 2.5). Therefore my sample size calculation was performed assuming similar within-group differences in APmean overnight ($0.28 \text{ cm}^2$) but with twice the variance. The sample size was calculated assuming within-group comparisons of APmean would be made using paired-sample t-tests with a two-tailed hypothesis. Based on these assumptions it was calculated that a sample size of 11 participants per group (33 in total) would be required to achieve statistical power of 0.9 with a p-value of 0.05. This power calculation was verified by our statistician (Mr Winston Banya, Clinical Trials and Evaluation Unit, Royal Brompton Hospital and Imperial College London).

Data from most of the measurements violated one or more assumptions of normality, therefore all data were analysed using non-parametric methods and are presented as median and interquartile range (IQR). Within-group differences in pharyngeal dimensions and neck circumference associated with posture and overnight change were analysed using Friedman Rank Sum tests. When a difference was detected, pair-wise analysis of conditions was
performed using paired-sample Wilcoxon tests with a Bonferroni correction for multiple comparisons. Between-group differences in pharyngeal dimensions and neck circumference were analysed using Kruskal-Wallis tests. When a difference was detected, pair-wise analysis of groups was performed using two-sample Wilcoxon tests with a Bonferroni correction for multiple comparisons. All data were analysed using R-Project statistical packages (R Foundation for Statistical Computing, Austria) and R Commander (version 1.8-3).

3.3. Results

3.3.1. Subjects

35 CHF patients agreed to participate in this study. Seven were excluded due to previously undiagnosed sleep disorders (CSA, 4; periodic limb movements (PLMs), 3) being discovered on their polysomnography. Two CHF patients were excluded from final analyses because they did not yield complete or usable AR data due to being unable to voluntarily elevate their soft palate to occlude the nasal cavity. A total of 14 CHF patients were found to have OSA and met all other inclusion/exclusion criteria, and 14 CHF patients had no OSA and met all other inclusion/exclusion criteria (see Figure 3.1 for consort diagram). Twenty-one healthy controls agreed to participate. Six were excluded from the study due to previously undiagnosed sleep disorders (OSA/CSA, 3; PLMs, 3) being discovered on their polysomnography. Two healthy controls were excluded from final analyses because they did not yield complete or usable AR data due to being unable to voluntarily elevate their soft palate to occlude the nasal cavity. A total of 15 healthy controls had no OSA and met all other inclusion/exclusion criteria (see Figure 3.1 for consort diagram).
All three groups were matched for age and neck circumference, however healthy controls had a significantly lower BMI than CHF-OSA. Participant characteristics are given in Table 3.2.

Figure 3.1: Consort diagram for recruitment of CHF patients and healthy controls.
### Table 3.2: Participant Demographics.

<table>
<thead>
<tr>
<th></th>
<th>CHF-OSA (n=14)</th>
<th>CHF-only (n=14)</th>
<th>Controls (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>70 (65, 71)</td>
<td>70 (62, 77)</td>
<td>65 (59, 70)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 (29, 31)*</td>
<td>27 (25, 30)</td>
<td>26 (25, 28)</td>
</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>41 (40, 43)</td>
<td>39 (38, 42)</td>
<td>39 (38, 40)</td>
</tr>
<tr>
<td>Epworth (/24)</td>
<td>8 (4, 11)*</td>
<td>9 (7, 13)†</td>
<td>5 (2, 6)</td>
</tr>
<tr>
<td>NYHA (class I-IV)</td>
<td>2 (2, 2)</td>
<td>2 (2, 3)</td>
<td>N/A</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>46 (30, 55)</td>
<td>35 (30, 45)</td>
<td>N/A</td>
</tr>
<tr>
<td>BNP (pmol/L)</td>
<td>39 (35, 48)</td>
<td>47 (37, 61)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Medications:**

- Diuretics (%): 100 | 57 | N/A
- B-blockers (%): 73 | 86 | N/A
- Ace-inhibitors (%): 55 | 86 | N/A

*Data are expressed as median (interquartile range) unless otherwise stated. Although females were not excluded from this study, groups were all males. * CHF-OSA significantly different to healthy controls (p<0.05). † CHF-only significantly different to healthy controls (p<0.05).*

### 3.3.2. Sleep Studies

The CHF-OSA group included patients with moderate severity of OSA, defined using AHI (see Table 3.3). By design, the CHF-only patients and healthy controls had AHIs <10 events/hr.

Sleep architecture was similar in all 3 groups with no significant differences in total sleep time (TST) or sleep efficiency. Sleep stages were distributed similarly in all 3 groups with the exception of Stage N1, which was a significantly higher fraction of TST in CHF-OSA patients than healthy controls (p=0.04). Healthy controls also had a significantly higher arousal index than CHF-only patients (p=0.001) (Table 3.3).

All three groups spent the majority of the night (60-70% TST) in a lateral posture. CHF-OSA
patients appeared to spend a greater fraction of TST in the supine posture than CHF-only and healthy controls, however this difference was not significant due to the wide variability of sleeping posture in all three groups (Table 3.3).

Table 3.3. Sleep parameters.

<table>
<thead>
<tr>
<th></th>
<th>CHF-OSA (n=14)</th>
<th>CHF-only (n=14)</th>
<th>Controls (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Parameters:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (/hr)</td>
<td>13 (12, 32)</td>
<td>5 (3, 5)</td>
<td>1 (1, 4)</td>
</tr>
<tr>
<td>Obstructive apnoea Index (/hr)</td>
<td>2 (0.5, 9)</td>
<td>0 (0, 1)</td>
<td>0 (0, 0.5)</td>
</tr>
<tr>
<td>Central apnoea Index (/hr)</td>
<td>1 (0.2, 3)</td>
<td>0.2 (0, 0.3)</td>
<td>0.3 (0, 1)</td>
</tr>
<tr>
<td>Mixed apnoea Index (/hr)</td>
<td>0 (0, 0.3)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Hypopnoea Index (/hr)</td>
<td>12 (9, 14)</td>
<td>3 (2, 4)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>ODI, 4% desaturations (/hr)</td>
<td>16 (13, 28)</td>
<td>6 (3, 7)</td>
<td>2 (1, 2)</td>
</tr>
<tr>
<td><strong>Sleep Architecture:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Sleep Time (mins)</td>
<td>367 (330, 415)</td>
<td>351 (289, 380)</td>
<td>379 (277, 417)</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>73 (66, 81)</td>
<td>73 (66, 80)</td>
<td>77 (53, 82)</td>
</tr>
<tr>
<td>Arousal Index (/hr)</td>
<td>22 (11, 28)</td>
<td>8 (4, 19)†</td>
<td>32 (27, 37)</td>
</tr>
<tr>
<td>Stage REM (%TST)</td>
<td>16 (11, 21)</td>
<td>23 (21, 27)</td>
<td>21 (17, 26)</td>
</tr>
<tr>
<td>Stage N1 (%TST)</td>
<td>36 (27, 51)*</td>
<td>26 (17, 32)</td>
<td>22 (16, 27)</td>
</tr>
<tr>
<td>Stage N2 (%TST)</td>
<td>32 (20, 42)</td>
<td>42 (26, 46)</td>
<td>40 (34, 51)</td>
</tr>
<tr>
<td>Stage N3 (%TST)</td>
<td>10 (6, 20)</td>
<td>9 (6, 17)</td>
<td>7 (5, 23)</td>
</tr>
<tr>
<td>PLM Index (/hr)</td>
<td>22 (4, 47)</td>
<td>7 (0, 35)</td>
<td>7 (2, 19)</td>
</tr>
<tr>
<td><strong>Sleep Posture:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (%TST)</td>
<td>39 (27, 61)</td>
<td>28 (13, 47)</td>
<td>28 (13, 48)</td>
</tr>
<tr>
<td>Left (%TST)</td>
<td>22 (0, 37)</td>
<td>19 (15, 31)</td>
<td>20 (15, 42)</td>
</tr>
<tr>
<td>Right (%TST)</td>
<td>31 (12, 51)</td>
<td>41 (20, 62)</td>
<td>29 (15, 43)</td>
</tr>
<tr>
<td>Total Lateral (%TST)</td>
<td>56 (38, 71)</td>
<td>77 (49, 94)</td>
<td>64 (38. 87)</td>
</tr>
</tbody>
</table>

All data are expressed as median (interquartile range). Due to rounding of figures and data not being normally distributed, not all percentages add up to 100. *CHF-OSA significantly different to healthy controls (p<0.05). † CHF-only significantly different to healthy controls (p<0.05)
3.3.3. Posture-Related Changes in Neck Circumference

There were no significant differences between groups in NC. This was the case in every experimental condition (evening-seated, evening-supine, morning-supine, morning-seated). Within groups, NC increased significantly when changing from a seated to a supine posture in the evening in CHF-OSA patients (seated: 41.4; IQR 39.9, 42.6 cm; supine: 42.0; IQR 40.5, 43.9 cm), CHF-only patients (seated: 38.6; IQR 38.0, 43.0 cm; supine: 41.2; IQR 38.9, 43.0 cm) and healthy controls (seated: 38.6; IQR 38.2, 40.3 cm; supine: 39.6; IQR 39.1, 41.4 cm). In the morning the reverse occurred; NC decreased significantly when changing from a supine to seated posture in CHF-OSA patients (supine: 43.3; IQR 40.8, 45.2 cm; seated: 41.4; IQR 40.2, 42.9 cm), CHF-only patients (supine: 41.3; IQR 39.3, 42.3 cm; seated: 39.4; 38.4, 41.3 cm) and healthy controls (supine: 39.8; IQR 39.4, 41.4 cm; seated: 39.0; IQR 38.7, 40.9 cm) (see Figure 3.2, upper panel). There were no significant differences between groups in the magnitude of change in NC between the seated and supine posture, in the evening before sleep (p=0.3) or in the morning after sleep (p=0.7). Similar results were found when comparing percentage changes from baseline within groups (see Table 3.5). There were significant increases in NC from evening-seated to evening-supine in all 3 groups (CHF-OSA p=0.01; CHF-only p=0.04; healthy controls p=0.02). NC decreased significantly in the morning when moving from a supine to seated posture in CHF-OSA patients (p=0.03), healthy volunteers (p=0.002) but not CHF-only (p=0.06). NC did not change significantly overnight in any of the groups in the supine posture (CHF-OSA p=0.9; CHF-only p=1.0; healthy controls p=0.2) or the seated posture (CHF-OSA p=1.0; CHF-only p=0.9; healthy controls p=1.0).

3.3.4. Posture-Related Changes in Pharyngeal Calibre

There were no significant differences between groups in APmean, VP or AG. This was the
case in every experimental condition (evening-seated, evening-supine, morning-supine, morning-seated). Within groups, APmean decreased significantly when changing from a seated to a supine posture in the evening in all groups: CHF-OSA patients (seated: 6.0; IQR 3.6, 6.2 cm$^2$; supine: 4.0; IQR 2.6, 5.7 cm$^2$), CHF-only patients (seated: 6.6; IQR 5.3, 7.3 cm$^2$; supine: 4.2; IQR 3.5, 5.5 cm$^2$) and healthy controls (seated: 6.6; IQR 5.4, 7.3 cm$^2$; supine: 4.8; IQR 3.9, 6.0 cm$^2$). In the morning the reverse occurred; APmean increased significantly when changing from a supine to seated posture in all 3 groups: CHF-OSA patients (supine: 4.0; IQR 2.1, 4.4 cm$^2$; seated: 4.7; IQR 3.4, 6.2 cm$^2$), CHF-only patients (supine: 4.5; IQR 3.6, 5.0 cm$^2$; seated: 5.3; IQR 3.8, 6.4 cm$^2$) and healthy controls (supine: 4.1; IQR 3.4, 4.9 cm$^2$; seated: 6.0; IQR 4.8, 6.8 cm$^2$) (see Figure 3.2, lower panel). There were no significant differences between groups in the magnitude of change in APmean between the seated and supine posture, in the evening before sleep (p=0.2) or in the morning after sleep (p=0.5).

Similar results were found when comparing percentage changes from baseline within groups (see Table 3.5). APmean decreased significantly in the evening when moving from a seated to supine posture in all 3 groups (CHF-OSA p=0.005; CHF-only p=0.0005; healthy controls p=0.0002). In the morning APmean increased significantly when moving from a supine to seated posture in CHF-OSA patients (p=0.001) and healthy controls (p=0.0005) but not CHF-only patients (p=0.05).

VP underwent similar changes to APmean; in the evening it decreased significantly in the supine compared to seated posture in all 3 groups: CHF-OSA (seated: 51.8; IQR 27.2, 60.1 cm$^3$; supine: 37.1; IQR 18.6, 44.8 cm$^3$), CHF-only (seated: 57.6; IQR 48.9, 66.3 cm$^3$; supine: 39.1; IQR 28.5, 49.9 cm$^3$), and healthy controls (seated: 53.0; IQR 48.9, 61.6 cm$^3$; supine: 35.1; IQR 31.0, 55.1 cm$^3$). In the morning the reverse occurred; VP increased significantly in the seated compared to supine posture in all 3 groups: CHF-OSA (supine: 33.7; IQR 15.5, 39.6 cm$^3$; seated: 39.7; IQR 29.3, 56.0 cm$^3$), CHF-only (supine: 42.5; IQR 29.3, 46.7 cm$^3$;
seated: 50.9; IQR 31.6, 58.7 cm$^3$), and healthy controls (supine: 35.0; IQR 25.8, 46.2 cm$^3$; seated: 51.0; IQR 42.6, 58.9 cm$^3$) (see Figure 3.3, upper panel). There were no significant differences between groups in the magnitude of change in VP between the seated and supine posture, in the evening before sleep (p=0.3) or in the morning after sleep (p=0.2).

Similar results were found when comparing percentage changes from baseline within groups (see Table 3.5). VP decreased significantly in the evening when moving from a seated to supine posture in all 3 groups (CHF-OSA p=0.005; CHF-only p=0.0005; healthy controls p=0.0005). In the morning VP increased significantly when moving from a supine to seated posture in CHF-OSA patients (p=0.002) and healthy controls (p=0.0005) but not CHF-only patients (p=0.3).

AG also underwent similar changes to APmean as it was decreased significantly in the supine compared to seated posture in all 3 groups: CHF-OSA (seated: 3.1; IQR 1.8, 4.0 cm$^2$; supine: 2.2; IQR 1.2, 2.7 cm$^2$), CHF-only (seated: 4.0; IQR 3.1, 4.9 cm$^2$; supine: 1.7; IQR 1.2, 2.4 cm$^2$), and healthy controls (seated: 4.1; IQR 3.3, 5.3 cm$^2$; supine: 2.8; IQR 2.2, 3.6 cm$^2$). In the morning the reverse occurred; AG increased significantly in the seated compared to supine posture in all 3 groups: CHF-OSA (supine: 1.8; IQR 0.8, 2.3 cm$^2$; seated: 3.1; IQR 1.8, 3.7 cm$^2$), CHF-only (supine: 1.7; IQR 1.1, 2.6 cm$^2$; seated: 2.5; IQR 1.5, 3.7 cm$^2$), and healthy controls (supine: 2.3; IQR 1.3, 2.9 cm$^2$; seated: 3.4; IQR 2.8, 4.2 cm$^2$) (see Figure 3.3, lower panel). There were no significant differences between groups in the magnitude of change in AG between the seated and supine posture, in the evening before sleep (p=0.2) or in the morning after sleep (p=0.5).

Similar results were found when comparing percentage changes from baseline within groups (see Table 3.5). AG decreased significantly in the evening when moving from a seated to supine posture in CHF-only (p=0.003) and healthy controls (p=0.008) but not in CHF-OSA patients (p=0.05). In the morning AG increased significantly when moving from a supine to
seated posture in all 3 groups (CHF-OSA p=0.001; CHF-only p=0.003; healthy controls p=0.002).

### 3.3.5. Overnight Changes in Neck Circumference and Pharyngeal Calibre

There were no significant differences in weight at baseline between the 3 groups. Weight decreased significantly overnight within CHF-OSA patients (p=0.004), and CHF-only patients (p=0.006). Weight also appeared to decrease overnight in healthy controls, however this just failed to reach statistical significance (p=0.06) (Table 3.4).

**Table 3.4: Differences in weight between evening and morning.**

<table>
<thead>
<tr>
<th></th>
<th>CHF-OSA (n=14)</th>
<th>CHF-only (n=14)</th>
<th>Controls (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening Weight (kg)</td>
<td>88.7 (82.5, 98.5)</td>
<td>84.6 (78.5, 95.5)</td>
<td>78.8 (76.5, 82.8)</td>
</tr>
<tr>
<td>Morning Weight (kg)</td>
<td>86.9 (81.3, 98.4)</td>
<td>81.8 (77.5, 94.5)</td>
<td>77.8 (76.2, 88.1)</td>
</tr>
<tr>
<td>p-value (evening vs. morning)</td>
<td>0.004</td>
<td>0.006</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Data expressed and median (interquartile range). All 3 groups appeared to have a decrease in weight overnight. This difference was statistically significant in CHF-OSA and CHF-only but not in healthy controls.*

There were no significant changes in NC overnight in the supine or seated posture in CHF-OSA, CHF-only, or healthy controls (Figure 3.2, upper panel). APmean decreased significantly overnight in the supine posture in the healthy controls (4.8; IQR 3.9, 6.0 cm² to 4.1; IQR 3.4, 4.9 cm²) but was unchanged in the CHF-OSA patients (4.0; IQR 2.6, 5.7 cm² to 4.0; IQR 2.1, 4.4 cm²) and CHF-only patients (4.2; IQR 3.5, 5.5 cm² to 4.5; IQR 3.6, 5.0 cm²) (Figure 3.2, lower panel). In the seated posture, there was no overnight change in APmean in CHF-OSA patients (6.0; IQR 3.6, 6.2 cm² to 4.7; IQR 3.4, 6.2 cm²), however there was a significant decrease in CHF-only patients (6.5; IQR 5.3, 7.2 cm² to 5.3; IQR 3.8, 6.4 cm²) and healthy controls (6.6; IQR 5.4, 7.3 cm² to 6.0; IQR 4.8, 6.8 cm²).
Similar results were found when comparing percentage changes from baseline within groups (see Table 3.5). APmean decreased significantly overnight in the supine posture in healthy controls (p=0.008) but not CHF-OSA patients (p=0.08) or CHF-only patients (p=1.0). It also decreased significantly in the seated posture in healthy controls (p=0.002) and CHF-only patients (p=0.002) but not CHF-OSA patients (p=1.0).

VP underwent similar changes to APmean. In the supine posture VP decreased significantly overnight in the healthy controls (35.1; IQR 31.0, 55.1 cm³ to 35.0; IQR 25.8, 46.2 cm³) but was unchanged in the CHF-OSA patients (37.1; IQR 18.6, 44.8 cm³ to 33.7; IQR 15.5, 39.6 cm³) and CHF-only patients (39.1; IQR 28.5, 49.9 cm³ to 42.5; IQR 29.3, 46.7 cm³) (Figure 3.3, upper panel). In the seated posture VP also decreased significantly in the CHF-only patients (57.6; IQR 48.9, 66.3 cm³ to 50.9; IQR 31.6, 58.7 cm³) but not in the CHF-OSA patients (51.8; IQR 27.1, 60.1 cm³ to 39.7; IQR 29.3, 56.0 cm³) or healthy controls (53.0; IQR 48.9, 61.6 cm³ to 51.0; IQR 42.6, 58.9 cm³).

Similar results were found when comparing percentage changes from baseline within groups (see Table 3.5). VP decreased significantly overnight in the supine posture in healthy controls (p=0.003) but not CHF-OSA patients (p=0.2) or CHF-only patients (p=1.0). VP decreased significantly in the seated posture in CHF-only patients (p=0.005) but not in CHF-OSA patients (p=1.0) or healthy controls (p=0.2).

AG also underwent similar changes overnight to APmean. In the supine posture AG decreased significantly overnight in the healthy controls (2.8; IQR 2.2, 3.6 cm² to 2.3; IQR 1.3, 2.9 cm²) but was unchanged in the CHF-OSA patients (2.2; IQR 1.2, 2.7 cm² to 1.8; IQR 0.8, 2.3 cm²) and CHF-only patients (1.7; IQR 1.2, 2.4 cm² to 1.7; IQR 1.1, 2.6 cm²) (Figure 3.3, lower panel). In the seated posture AG did not change significantly in CHF-OSA (3.1; IQR 1.8, 4.0 cm² to 3.1; IQR 1.8, 3.7 cm²), CHF-only (4.0; IQR 3.1, 4.9 cm² to 2.5; IQR 1.5, 3.7 cm²), or healthy controls (4.1; IQR 3.3, 5.3 cm² to 3.4; IQR 2.8, 4.2 cm²).
Similar results were found when comparing percentage changes from baseline within groups (see Table 3.5). AG decreased significantly overnight in the supine posture in healthy controls (p=0.008) but not CHF-OSA patients (p=0.2) or CHF-only patients (p=1.0). AG decreased significantly in the seated posture in CHF-only patients (p=0.03) but not in CHF-OSA patients (p=1.0) or healthy controls (p=0.08).
All 3 groups had significant posture-related changes in neck circumference and mean pharyngeal area in the evening and morning. Healthy controls also had significant overnight decreases in mean pharyngeal area.

Figure 3.2: Overnight and posture-related changes in neck circumference (upper panel) and mean pharyngeal area (lower panel). All 3 groups had significant posture-related changes in neck circumference and mean pharyngeal area in the evening and morning. Healthy controls also had significant overnight decreases in mean pharyngeal area.
All 3 groups had significant posture-related changes in pharyngeal volume and glottis area in the evening and morning. Healthy controls also had a significant overnight decreases in pharyngeal volume and glottis area.

Figure 3.3: Overnight and posture-related changes in pharyngeal volume (upper panel) glottis area (lower panel).

All 3 groups had significant posture-related changes in pharyngeal volume and glottis area in the evening and morning. Healthy controls also had a significant overnight decreases in pharyngeal volume and glottis area.
Table 3.5: Percentage changes overnight and in relation to posture.

<table>
<thead>
<tr>
<th></th>
<th>Evening-Seated</th>
<th>Evening-Supine</th>
<th>Morning-Supine</th>
<th>Morning-Seated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck Circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF-OSA</td>
<td>0^i</td>
<td>3.5 (2.3, 4.8)</td>
<td>4.0 (2.3, 5.6)^j</td>
<td>0.5 (-0.8, 1.5)</td>
</tr>
<tr>
<td>CHF-only</td>
<td>0^i</td>
<td>2.5 (0.8, 3.6)</td>
<td>2.4 (1.0, 5.0)</td>
<td>0.9 (-0.2, 1.2)</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0^i</td>
<td>1.7 (0.5, 3.8)</td>
<td>2.4 (1.2, 4.0)^j</td>
<td>0.3 (-1.0, 1.7)</td>
</tr>
<tr>
<td>Mean Pharyngeal Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF-OSA</td>
<td>0^i</td>
<td>-20.9 (-31.8, -7.3)</td>
<td>-29.3 (-40.6, -20.8)^j</td>
<td>-7.7 (-18.7, -1.5)</td>
</tr>
<tr>
<td>CHF-only</td>
<td>0^i</td>
<td>-26.7 (-37.0, -22.3)</td>
<td>-30.0 (-37.4, -22.6)</td>
<td>-11.3 (-32.0, -5.5)^4</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0^i</td>
<td>-18.1 (-32.8, -13.8)^2</td>
<td>-33.2 (-40.8, -24.0)^j</td>
<td>-6.9 (-19.0, -3.2)^4</td>
</tr>
<tr>
<td>Pharyngeal Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF-OSA</td>
<td>0^i</td>
<td>-21.7 (-38.1, -13.0)</td>
<td>-32.8 (-43.2, -21.6)^j</td>
<td>-5.0 (-13.3, 4.0)</td>
</tr>
<tr>
<td>CHF-only</td>
<td>0^i</td>
<td>-31.0 (-37.7, -18.9)</td>
<td>-26.9 (-40.6, -16.8)</td>
<td>-14.6 (-32.8, -5.9)^4</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0^i</td>
<td>-23.3 (-34.7, -13.2)^2</td>
<td>-34.2 (-46.1, -21.6)^j</td>
<td>-12.3 (-17.1, 1.2)</td>
</tr>
<tr>
<td>Glottis Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF-OSA</td>
<td>0</td>
<td>-34.5 (-48.6, -18.1)</td>
<td>-52.8 (-65.1, -27.7)^j</td>
<td>2.2 (-20.9, 13.0)</td>
</tr>
<tr>
<td>CHF-only</td>
<td>0^i</td>
<td>-47.4 (-61.3, -37.9)</td>
<td>-47.8 (-64.0, -32.4)^j</td>
<td>-17.3 (-51.1, -11.3)^4</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0^i</td>
<td>-34.7 (-51.7, -12.2)^2</td>
<td>-51.1 (-69.8, -30.1)^j</td>
<td>-15.4 (-26.2, -5.6)</td>
</tr>
</tbody>
</table>

Data are expressed as percentage change from Evening-Seated. All data are presented as median (interquartile range). 1: Evening-seated significantly different to Evening-supine (p<0.05); 2: Evening-supine significantly different to Morning-supine (p<0.05); 3: Morning-supine significantly different to Morning-seated (p<0.05); 4: Morning-seated significantly different to Evening-seated (p<0.05).

3.3.6. Predictors of Neck Circumference and Pharyngeal Calibre

In order to determine the factors that predicted NC and pharyngeal calibre, a series of univariate linear regression models were constructed using evening-supine NC and evening-supine APmean as the respective outcome variables. The factors that were tested as predictors of evening-supine NC are shown in Table 3.6. The significant predictors were evening-supine APmean, BMI, evening weight and AHI. In a multivariate linear regression model the
associations with evening-supine NC remained independently significant for AHI (p=0.01) and evening weight (p=0.03) but not for evening-supine APmean (p=0.8) or BMI (p=0.5) (Table 3.6).

Table 3.6: Univariate linear regression models with evening-supine neck circumference as the response variable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>R²</th>
<th>Univariate p-value</th>
<th>Multivariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening-supine APmean</td>
<td>0.1</td>
<td>0.04</td>
<td>0.8</td>
</tr>
<tr>
<td>BMI</td>
<td>0.2</td>
<td>0.003</td>
<td>0.5</td>
</tr>
<tr>
<td>Evening Weight</td>
<td>0.3</td>
<td>0.0003</td>
<td>0.03</td>
</tr>
<tr>
<td>AHI</td>
<td>0.1</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The factors that were tested as predictors of evening-supine APmean are shown in Table 3.7. The only significant predictors were evening supine NC and evening weight. In a multivariate linear regression model the associations with evening-supine APmean were not independently significant for evening-supine NC (p=0.5) or evening weight (p=0.2) (Table 3.7).

Table 3.7: Univariate linear regression model 2: evening-supine mean pharyngeal area.

<table>
<thead>
<tr>
<th>Variable</th>
<th>R²</th>
<th>Univariate p-value</th>
<th>Multivariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening-supine NC</td>
<td>0.1</td>
<td>0.04</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI</td>
<td>0.06</td>
<td>0.1</td>
<td>-</td>
</tr>
<tr>
<td>Evening Weight</td>
<td>0.1</td>
<td>0.03</td>
<td>0.2</td>
</tr>
<tr>
<td>AHI</td>
<td>0.03</td>
<td>0.3</td>
<td>-</td>
</tr>
</tbody>
</table>

### 3.4. Discussion

The main findings of this study were that there were no significant differences in NC, APmean, VP, and AG in any posture in the evening or morning between groups. All 3 groups
experienced significant increases in NC and significant decreases in AP\text{mean}, VP and AG when changing from a seated to supine posture in the evening; this was reversed in the morning when sitting up from supine to seated. Weight significantly decreased overnight in CHF-OSA and CHF-only; this was associated with neither group experiencing any overnight change in NC, AP\text{mean}, VP or AG. Conversely, there was no significant overnight change in weight in healthy controls; this was associated with a significant overnight decrease in AP\text{mean}, VP and AG but no significant overnight change in NC.

3.4.1. Limitations

The main limitation of this study was that AR was used for indirect measurement of pharyngeal dimensions. This technique requires subjects to be awake during measurements. Neuromuscular activation of pharyngeal muscles is reduced in sleep compared to wake (Fogel et al., 2005) and this may have an impact on the observed differences in pharyngeal calibre overnight. Neuromuscular tone can compensate for an anatomically narrow airway during wake, but during sleep this compensation may be lost in OSA patients (Mezzanotte et al., 1992). It is possible that overnight rostral fluid shift results in accumulation of fluid that is sufficient to cause narrowing of the pharynx during sleep, but that is insufficient to cause narrowing of the pharynx during wake, when the neuromuscular tone of the pharynx is higher. I believe that this was unlikely in the present study because measurements of neck circumference suggest that there was not a significant overnight rostral fluid shift in any group.

Despite its limitations, the acoustic reflection technique offered a number of advantages over other imaging techniques. The system is portable and could be used in the bedroom of the sleep laboratory immediately before going to sleep and immediately after waking up. It was also easy to make measurements in different postures in quick succession which would not
have been possible with some other techniques such as magnetic resonance imaging and computed tomography.

3.4.2. Posture-Related Changes in Neck Circumference and Pharyngeal Calibre

A number of studies have demonstrated that pharyngeal calibre is decreased in the supine compared to seated posture (Fouke and Strohl, 1987; Huang et al., 1998; Jan et al., 1994; Martin et al., 1997). The mechanism for the posture-related decrease in pharyngeal calibre is not certain, but it is likely to involve narrowing at the level of the retro-palatal and retro-glossal pharynx (Neill et al., 1997; Pevernagie et al., 1995; Schwab et al., 1995; Yildirim et al., 1991). Decreased lung volumes in a supine posture may also contribute to reduced pharyngeal calibre by decreasing caudal traction on the pharynx, although this effect seems to be small (Fouke and Strohl, 1987; Jan et al., 1994). It has been speculated that the volume of blood in pharyngeal dilator muscles and other soft tissues surrounding the pharynx is affected by gravity and that this may also influence pharyngeal calibre (Beaumont et al., 1998).

The concept that fluid could affect pharyngeal calibre has been developed in recent years. Application of lower body positive pressure in healthy volunteers results in decreased leg fluid volume and increased neck circumference, suggesting that some fluid may shift rostrally under certain conditions. Decreased leg fluid volume and increased neck circumference correlate with increased pharyngeal resistance (Chiu et al., 2006), decreased pharyngeal calibre (Shiota et al., 2007), and increased pharyngeal collapsibility (Su et al., 2008) (see Chapter 4 for a study on pharyngeal collapsibility in CHF patients). These studies provide evidence that rostral fluid shift may be an important mechanism for OSA in CHF, because CHF patients retain more fluid in dependent veins during the day, meaning there is potentially more fluid able to shift rostrally during the night when a supine posture is adopted by these
patients (Yumino et al., 2010). However, the effects of passive rostral fluid shift, that occurs overnight as a result of adopting a supine posture, are more modest. Redolfi et al. (2009) found a significant correlation between overnight decreased leg fluid volume, increased neck circumference and AHI in OSA patients; however Jafari and Mohsenin (2011) did not. Redolfi et al. (2011b) also found that treating patients with venous insufficiency with compression stockings reduced daytime leg fluid volume and decreased AHI, however Elias et al. (2012) found no correlation between leg fluid volume and AHI in patients with end-stage renal disease. The only study to investigate overnight changes of fluid load in CHF patients found a correlation between leg fluid volume, neck circumference and AHI in CHF patients with OSA (Yumino et al., 2010). The reason for the variable results between different studies is not clear, however there may be a number of factors that could modify the effects of fluid shift on the upper airway.

First, the time-course of the fluid shift has not been measured directly. Berg et al. (1993) report that it takes approximately 40 minutes for a decrease in leg fluid volume to plateau after a change in posture from upright to supine. No comparable data exists for neck tissue fluid volumes, however (Shiota et al., 2007) report that a decrease in pharyngeal calibre plateaued after 5 minutes of lower body positive pressure. These differing times may be due to Berg et al. (1993) measuring passive fluid shift due to posture change, whereas Shiota et al. (2007) actively induced fluid shift by lower body positive pressure. This suggests that the effects of actively-induced fluid shift via lower body positive pressure are not comparable to the effects of passive fluid shift via postural change. It is possible that passive fluid shift takes longer than actively-induced fluid shift, allowing more time for normal fluid volume regulation to occur, thus mitigating any effects on pharyngeal calibre.

Second, in conditions where normal fluid regulation is impaired, such as CHF, the effects of fluid shift on pharyngeal calibre may be influenced by diuretics. Bucca et al. (2007) showed
that intravenous diuresis of obese CHF patients with OSA resulted in an increase in pharyngeal calibre and a decrease in AHI. This suggests that adequate diuresis has the potential to mitigate the effects of fluid-overload and rostral fluid shift on pharyngeal calibre.

My data confirm previous research showing that pharyngeal calibre is influenced by posture as this was evident in all 3 groups. It is not evident from my data that rostral fluid shift was the mechanism for this effect. My measurements of pharyngeal calibre were performed after 5 minutes of quiet breathing in either the seated or supine posture. Given that the time elapsed between a change in posture and measurements of pharyngeal calibre was substantially less than 40 minutes, I believe that the observed decrease in pharyngeal calibre in the supine compared to seated posture in this study was due to gravity acting on the pharynx. The observed increase in neck circumference in the supine compared to seated posture was likely due to redistribution of the muscles, fat and soft tissues of the neck, not due to passive rostral fluid shift. This view is supported by a recent study comparing neck circumference in the upright and supine posture, and overnight in obese and non-obese males, with and without OSA (Fischer et al., 2012). This study also found a significant posture-related change in neck circumference. The authors also concluded that changes in neck circumference were due to soft tissue redistribution, rather than rostral fluid shift.

### 3.4.3. Overnight Changes in Neck Circumference and Pharyngeal Calibre

The finding that pharyngeal calibre decreased overnight in healthy volunteers suggests that there may be a normal physiological nocturnal rostral fluid shift that occurs in the healthy population that is not sufficient to independently cause OSA. The fact that pharyngeal calibre did not decrease overnight in CHF-OSA or CHF-only may have been due to diuresis, as both groups lost more weight overnight than the healthy controls. Future studies would benefit from overnight monitoring of fluid intake and fluid loss.
3.4.4. Conclusions

In summary, this study shows that CHF-OSA and CHF-only patients experience an increase in NC and decrease in pharyngeal calibre in the supine compared to seated posture but that NC and pharyngeal calibre do not change overnight. Furthermore, the absolute NC and pharyngeal calibre of CHF-OSA patients is similar to CHF-only patients and healthy controls. Healthy controls experienced a significant overnight decrease in pharyngeal calibre, suggesting that nocturnal rostral fluid shift may be a normal physiological feature that is not unique to fluid-loaded states such as CHF. Optimal diuresis may be sufficient to attenuate fluid shift in CHF patients. Taken together, these data suggest that rostral fluid shift does not substantially contribute to pharyngeal calibre in a cohort of optimally treated CHF-OSA patients.
Chapter 4: Pharyngeal Critical Closing Pressure in Heart Failure Patients with Obstructive Sleep Apnoea
4.1. Introduction

In chapter 3 it was demonstrated that the pharyngeal calibre of CHF patients with OSA is similar to that in CHF patients who do not have OSA and healthy age matched controls. This suggests that factors other than pharyngeal calibre are related to the increased prevalence of OSA in the CHF population; an alternative mechanism could be increased pharyngeal collapsibility.

Su et al. (2008) observed that fluid shift from the legs to the neck can be induced in healthy volunteers, and that this could result in increased pharyngeal collapsibility during wake. It has also been observed that passive rostral fluid shift occurs during the night in non-obese OSA patients and that the volume of fluid leaving the legs during the night is correlated with OSA severity (Redolfi et al., 2009). However, a similar study investigating rostral fluid shift in OSA patients failed to replicate these findings (Jafari and Mohsenin, 2011).

CHF patients can retain increased fluid volume in the legs during the day, which may make them even more susceptible to nocturnal rostral fluid shift than OSA patients. This has led to rostral fluid shift being proposed as a mechanism for OSA in CHF. This hypothesis was supported by Yumino et al. (2010), who found that leg fluid volume correlated with OSA severity in CHF patients with OSA.

No studies to date have measured the pharyngeal collapsibility of CHF patients with OSA. If nocturnal rostral fluid shift has an effect on pharyngeal collapsibility it may also be predicted to have a greater effect at the end of the night compared to the start of the night, as greater quantities of fluid are displaced from the legs and into tissues of the upper airway overnight. Therefore the aim of this study was to measure the pharyngeal collapsibility of CHF patients with OSA (CHF-OSA), compared to CHF patients without OSA (CHF-only), and healthy age matched controls. The secondary aim was to measure overnight changes in pharyngeal
collapsibility to determine the effects of nocturnal rostral fluid shift on the pharynx in CHF patients.

The primary hypothesis was that the pharynx of CHF-OSA patients would be more collapsible than CHF-only patients, who in turn would have a more collapsible pharynx than healthy age matched controls. The secondary hypothesis was that the pharynx would be more collapsible at the end of the night compared to the start of the night in CHF patients with and without OSA but would remain unchanged in healthy age matched controls. Pharyngeal collapsibility was measured by the passive Pcrit technique (Schwartz et al., 1998).

4.2. Methods

4.2.1. Ethical Review

This study was reviewed by the local Research Ethics Committee (Brompton Harefield and NHLI Research Ethics Committee) and given a favourable opinion (REC number: 09/H0708/24). All volunteers gave written informed consent prior to participating in this study.

4.2.2. Subjects

CHF-OSA patients, CHF-only patients, and healthy age-matched controls were recruited to participate in a pair of studies investigating pharyngeal calibre (see Chapter 3) and pharyngeal collapsibility (the present study) in CHF patients with OSA. Full details of subject identification and recruitment are described in Chapter 3, Section 3.2.2 In brief, all CHF patients were recruited from heart failure clinics at the Royal Brompton Hospital and healthy age-matched controls were recruited from the general population using public advertising. Inclusion criteria for CHF patients included a diagnosis of systolic or diastolic heart failure, NYHA class II-III, and being in a stable condition, having had no unscheduled hospital
admissions in the 3 months preceding recruitment. Exclusion criteria included having any sleep-disorder other than OSA, any current treatment for OSA, and previous upper airway surgery. Inclusion criteria for healthy controls included having an AHI <10 events/hour. Exclusion criteria included a history of any sleep-disorder, and a history of any significant cardiac disease. A full description of inclusion and exclusion criteria can be found in Chapter 3, Table 3.1.

All CHF patients and healthy volunteers that agreed to participate in the study underwent nocturnal polysomnography to determine the presence or absence of OSA (sleep study described in Chapter 3). CHF patients with an AHI ≥10 events/hr with >50% of apnoeas classified as obstructive were allocated to the CHF-OSA group. CHF patients with an AHI <10 events/hr were allocated to the CHF-only group. Healthy controls were admitted to the study if they had an AHI <10 events/hr and had no history of CHF. Participants who did not meet inclusion/exclusion criteria after the polysomnography were excluded from analysis. Participants that were excluded on the basis of a previously undiagnosed sleep-disorder were informed immediately and a letter was sent to their GP explaining the findings.

4.2.3. Protocol

All CHF patients and healthy volunteers that agreed to participate in the study were invited to attend the Royal Brompton research sleep laboratory on two occasions no longer than 1 month apart as part of a pair of studies measuring pharyngeal calibre (visit 1; see Chapter 3) and pharyngeal critical closing pressure (visit 2; the current study).

On their first visit, participants had their height, weight, blood pressure and lung function recorded and a detailed medical history was taken including current medications, sleep habits and subjective sleepiness according to the Epworth Sleepiness Score. Participants then underwent a polysomnography to determine their AHI and had their pharyngeal calibre measured in the evening and morning using acoustic reflection. For full details of the first
visit, see Chapter 3.

On their second visit, participants underwent measurement of their pharyngeal collapsibility using the pharyngeal passive Pcrit technique (Schwartz et al., 1998, 1988). For full details of the technique, see Chapter 2, Section 2.2.4 In brief, the Pcrit technique was performed during sleep by applying a negative pressure to the pharynx via a nasal mask at increments of progressively greater negative pressure. The point at which airflow ceased was assumed to be the Pcrit, at which the pharynx had collapsed.

Prior to sleep, participants were instrumented for nocturnal polysomnography using a multi-channel data collection and signal amplifier system (Model 12 Neurodata acquisition system, Grass Instruments, USA). Signals were acquired via an analogue to digital converter (Micro 1401, Cambridge Electronic Design, UK) and recorded using data acquisition software that allowed real-time viewing of signals (Spike2 version 3.21, Cambridge Electronic Design, UK). Brain waves were monitored using electroencephalography (EEG), eye movements were monitored using electro-occulargrams (EOG), chin muscle tone was monitored using electro-myogram (EMG). Airflow was measured using a pneumotachometer attached in-line to a nasal mask and respiratory effort was monitored using respiratory inductance plethysmography. Respiratory effort was also monitored using an oesophageal pressure cannula (CTO-1, Gaeltec Ltd, UK) coupled with a pressure transducer (model S7b/2, Gaeltec Ltd, UK), positioned approximately 40cm past the nares and adjusted to minimise cardiac artefact. In participants that were unable to tolerate the oesophageal pressure cannula or in whom it could not be passed successfully the study was conducted without it. For full details of the Pcrit instrumentation and technique, see General Methods (Chapter 2, Section 2.2).

Participants slept with a tight-fitting nasal mask attached to a CPAP machine that acted as positive pressure source and a cough assist machine that acted as a negative pressure source. Participants were asked to sleep on their back, however those who could not sleep in this
posture were permitted to sleep in a lateral posture. Participants were allowed to fall asleep with a low pressure of CPAP being supplied to the mask, sufficient only to allow clearance of expired CO\textsubscript{2} from the nasal mask dead-space. After participants had fallen asleep CPAP pressure was titrated to the minimum pressure that was sufficient to eliminate flow limitation. This pressure was defined as the holding pressure and varied among individuals. Pcrit measurements were performed twice, early and late in the night. The early measurements were made during the first sleep cycle, after participants had entered stage N2 or N3 sleep. The late measurements were made approximately 4 hours later in stage N2 or N3 sleep. All Pcrit measurements were initiated after participants had maintained stable sleep for at least 3 minutes. After 3 minutes of stable sleep mask pressure was rapidly reduced from holding pressure for 3-5 breaths, then returned to holding pressure. After at least one minute the pressure was reduced further for 3-5 breaths. This was repeated, reducing the mask pressure in 1 or 2 cmH\textsubscript{2}O increments until airflow ceased. This point was defined as the Pcrit. The entire sequence was then repeated twice more to confirm the Pcrit measurement. Where repeated cycles of pressure reductions resulted in different Pcrit values, the median value was calculated and taken as the Pcrit.

4.2.4. Data Analysis

Apnoeas were defined as previously described in Chapter 2, Section 2.2.1 Pcrit measurements were analysed as described in the General Methods (Section 2.2.5). In participants that were able to sleep with the oesophageal pressure cannula, Pcrit was defined as the pressure at which airflow at the nasal mask was absent accompanied by ongoing oesophageal pressure swings, indicating closure of the pharynx (Schwartz et al., 1998). In participants who were studied without the oesophageal pressure cannula, Pcrit was defined as the pressure at which airflow at the nasal mask was absent accompanied by ongoing thoracic and abdominal movements. In some participants, it was not possible to reach a mask pressure low enough to
cause airflow to cease without causing an arousal from sleep. In these participants, linear regression of the relationship between airflow and mask pressure was performed in order to predict the mask pressure at which airflow would have ceased (Patil et al., 2004).

Pcrit measurements at the start of the night were used for comparisons between groups. Pcrit measurements made at the start of the night and at the end of the night were compared within groups in order to determine whether there was any overnight change in Pcrit due to fluid shift. Percentage changes within groups were also analysed for Pcrit. The measurement of Pcrit taken in the early part of the night was taken as the baseline measurement and all measurements were expressed as a percentage of baseline.

4.2.5. Statistical Analysis

The sample size was calculated based on a recent study comparing pharyngeal Pcrit in healthy participants and OSA patients (Patil et al., 2007). It showed that the mean difference between groups was -4.45 cmH$_2$O and the standard deviation of the mean difference was 2.7 cmH$_2$O. For the current study it was assumed that the difference in Pcrit between CHF-OSA and CHF-only would be smaller because pharyngeal collapsibility is thought to increase with age (Eikermann et al., 2007). It was also assumed that there would be a similar difference in Pcrit between CHF-only and healthy age-matched volunteers. Therefore, the sample size was calculated with the aim of detecting a mean difference of 3 cmH$_2$O and standard deviation of the mean difference of 2.7 cmH$_2$O. At 80% power with 5% confidence interval, 14 participants in each group (42 in total) would be required.

Data from most of the parameters measured violated one or more assumptions of normality, therefore all data were analysed using non-parametric methods and are presented as median and interquartile range (IQR). Differences between groups were analysed using Kruskal-Wallis tests. When a difference was detected, pair-wise analysis of groups was performed using two-sample Wilcoxon tests with a Bonferroni correction for multiple comparisons.
Overnight differences in Pcrit within groups were analysed using paired-sample Wilcoxon tests. All data were analysed using R-Project statistical packages (R Foundation for Statistical Computing, Austria) and R Commander (version 1.8-3).

4.3. Results

4.3.1. Subjects

As in Chapter 3, 35 CHF patients agreed to participate in this study; 7 were subsequently excluded from the study due to previously undiagnosed sleep-disorders (CSA, 4; PLMs, 3) being found on the polysomnography. Fourteen CHF patients were found to have OSA and met all other inclusion/exclusion criteria, and 14 had no OSA and met all other inclusion/exclusion criteria. After undergoing the Pcrit study, 5 CHF patients were excluded from final analysis because it was not possible to obtain Pcrit data in them as they were unable to sleep in the lab and they aroused during Pcrit measurements (see Figure 4.1 for consort diagram).

Twenty-one healthy controls agreed to participate in this study; 6 were subsequently excluded from the study due to previously undiagnosed sleep-disorders (OSA/CSA, 3; PLMs, 3) being discovered on the polysomnography. Fifteen healthy controls met all inclusion/exclusion criteria. After undergoing the Pcrit study, 7 healthy volunteers were excluded from final analysis because it was not possible to obtain Pcrit data in them as they were unable to sleep in the lab and arousing during Pcrit measurements (see Figure 4.1 for consort diagram).
All three groups were matched for age, BMI and neck circumference. Healthy controls had a significantly lower Epworth score than CHF-OSA and CHF-only patients (p<0.05). The characteristics of the 3 groups are given in Table 4.1.

Figure 4.1: Consort diagram for recruitment of CHF patients and healthy controls.
Table 4.1: Group characteristics.

<table>
<thead>
<tr>
<th></th>
<th>CHF-OSA (n=13)</th>
<th>CHF-only (n=10)</th>
<th>Controls (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (rs)</td>
<td>68 (63, 70)</td>
<td>70 (64, 77)</td>
<td>63 (59, 65)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 (29, 31)*</td>
<td>27 (26, 31)</td>
<td>27 (25, 29)</td>
</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>43 (40, 44)</td>
<td>41 (38, 43)</td>
<td>39 (39, 40)</td>
</tr>
<tr>
<td>Epworth (/24)</td>
<td>9 (5, 12)*</td>
<td>8 (5, 11)†</td>
<td>4 (1, 5)</td>
</tr>
<tr>
<td>NYHA (I-IV)</td>
<td>2 (2, 2)</td>
<td>2 (2, 3)</td>
<td>N/A</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>42 (29, 52)</td>
<td>38 (26, 57)</td>
<td>N/A</td>
</tr>
<tr>
<td>BNP (pmol/L)</td>
<td>39 (35, 58)</td>
<td>43 (27, 59)</td>
<td>N/A</td>
</tr>
<tr>
<td>Medications:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>69</td>
<td>70</td>
<td>N/A</td>
</tr>
<tr>
<td>B-blockers (%)</td>
<td>62</td>
<td>80</td>
<td>N/A</td>
</tr>
<tr>
<td>Ace-inhibitors (%)</td>
<td>46</td>
<td>80</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). * CHF-OSA significantly different to healthy controls (p<0.05). † CHF-only significantly different to healthy controls (p<0.05).

4.3.2. Sleep Studies

The CHF-OSA group had an AHI greater than 10 events/hr, and the CHF-only and healthy controls had an AHI below 10 events/hr by design. The CHF-OSA group included individuals whose OSA was predominantly in the moderate range of severity (10-30 events/hr) (see Table 4.2).
Table 4.2: Respiratory and sleep parameters.

<table>
<thead>
<tr>
<th></th>
<th>CHF-OSA (n=13)</th>
<th>CHF-only (n=10)</th>
<th>Controls (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Parameters:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (events/hr)</td>
<td>13 (12, 28)</td>
<td>5 (4, 6)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>Obstructive apnoeas Index (events/hr)</td>
<td>1 (0.5, 9)</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Central apnoeas Index (events/hr)</td>
<td>1 (0, 3)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Mixed apnoeas Index (events/hr)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Hypopnoeas Index (events/hr)</td>
<td>12 (9, 13)</td>
<td>3 (2, 5)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>ODI (4% desaturations/hr)</td>
<td>16 (13, 23)</td>
<td>6 (5, 8)</td>
<td>2 (1, 2)</td>
</tr>
<tr>
<td><strong>Pcrit Parameters:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration between Early and Late (hrs)</td>
<td>3.5 (3.0, 3.75)</td>
<td>2.25 (1.25, 4.25)</td>
<td>3.5 (1.75, 4.0)</td>
</tr>
<tr>
<td>Position (%Supine vs. %Lateral)</td>
<td>46/54</td>
<td>50/50</td>
<td>50/50</td>
</tr>
</tbody>
</table>

*Data expressed and median (interquartile range) unless otherwise stated.*

4.3.3. Pcrit Between Groups

The median Pcrit of CHF-OSA patients (-1.2; IQR -4.4, -0.5 cmH$_2$O) had a tendency to be higher than CHF-only (-5.9; IQR -6.8, -3.7 cmH$_2$O) and healthy controls (-2.7; IQR -4.3, -1.5 cmH$_2$O), however this trend failed to reach significance (Figure 4.2). There was also no significant difference between CHF-only and healthy controls (Figure 4.2).
Each data point represents an individual, p-values are for group statistics. There was no significant difference in $P_{crit}$ between any of the groups, although CHF-OSA patients had a tendency to have a higher $P_{crit}$ than CHF-only and controls.

4.3.4. Overnight Changes in $P_{crit}$

Approximately half of all participants had $P_{crit}$ measurements made while lying in a lateral posture due to being unable to sleep in a supine posture (CHF-OSA=46%; CHF-only=50%; controls=50%), with the remainder of $P_{crit}$ measurements being performed in the supine posture. In all participants, $P_{crit}$ was measured in the early and late parts of night in the same posture. The time elapsed between early and late measurements of $P_{crit}$ were similar in all three groups (see Table 4.2).

Figure 4.3 Shows the overnight changes in $P_{crit}$ for each group. There was individual variation, with some participants showing an increase in $P_{crit}$, some a decrease, and some remained the same. Overall there were no significant changes in median $P_{crit}$ between the early and late part of the night in CHF-OSA patients (-1.2; IQR -4.4, -0.5 cmH$_2$O vs. -1.2;
IQR -3.1, 0.3 cmH\textsubscript{2}O), CHF-only patients (-5.9; IQR -6.8, -3.7 cmH\textsubscript{2}O vs. -3.4; IQR -5.2, -3.0 cmH\textsubscript{2}O), or healthy controls (-2.7; IQR -4.3, -1.5 cmH\textsubscript{2}O vs. -2.0; IQR -3.4, -1.3 cmH\textsubscript{2}O).

When Perit measurements were analysed as a percentage of baseline, there were also no significant differences in any groups (Table 4.3).

### Table 4.3: Percentage difference in Pcrit from early to late part of night.

<table>
<thead>
<tr>
<th></th>
<th>CHF-OSA (n=13)</th>
<th>CHF-only (n=10)</th>
<th>Controls (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Pcrit (%baseline)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Late Pcrit (%baseline)</td>
<td>0 (-45, 21)</td>
<td>-27 (-40, -13)</td>
<td>0 (-40, 0)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.9</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). There were no significant differences between early and late Pcrit measurements when data were expressed as % baseline (where early measurements were taken as baseline).

#### 4.3.5. Predictors of Pcrit

Given that there were no significant differences between groups in Pcrit, the groups were pooled for further analysis of predictors of Pcrit. Linear regression models were computed with Pcrit as the response variable. The univariate factors that were tested for correlation with Pcrit were AHI, BMI, neck circumference and the various measures of pharyngeal calibre that were measured in Chapter 3. There were no significant univariate relationships between Pcrit and BMI, neck circumference or pharyngeal dimensions (mean pharyngeal area, pharyngeal volume, glottis cross-sectional area, pharyngeal length), as measured in Chapter 3. The only univariate correlation found was between Pcrit and AHI (see Table 4.4 for summary of univariate models).
### Table 4.4. Univariate predictors of Pcrit.

<table>
<thead>
<tr>
<th>Univariate Predictor</th>
<th>$R^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>0.02</td>
<td>0.4</td>
</tr>
<tr>
<td>Neck Circumference</td>
<td>0.01</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean Pharyngeal Area</td>
<td>0.01</td>
<td>0.7</td>
</tr>
<tr>
<td>Pharyngeal Volume</td>
<td>0.02</td>
<td>0.4</td>
</tr>
<tr>
<td>Glottis Area</td>
<td>0.02</td>
<td>0.4</td>
</tr>
<tr>
<td>Pharyngeal Length</td>
<td>0.1</td>
<td>0.07</td>
</tr>
</tbody>
</table>

When all groups were pooled, the only significant univariate predictor of Pcrit was AHI. Pharyngeal length was also close, but did not reach significance.
Each data point represents an individual participant and lines between data points indicate the change in $P_{crit}$ between the early and late part of the night; $p$-values are group statistics. The time between “Early” and “Late” measurements was approximately 2-4 hours in each group (see Table 4.2). Overall, there were no significant overnight changes in $P_{crit}$ in any group.

Figure 4.3: Overnight changes in $P_{crit}$. Each data point represents an individual participant and lines between data points indicate the change in $P_{crit}$ between the early and late part of the night; $p$-values are group statistics. The time between “Early” and “Late” measurements was approximately 2-4 hours in each group (see Table 4.2). Overall, there were no significant overnight changes in $P_{crit}$ in any group.
4.4. Discussion

The Pcrit of CHF-OSA patients had a tendency to be higher than CHF-only and healthy controls, however this did not reach statistical significance. There was also no significant difference in Pcrit between CHF-only and healthy controls. Moreover, there was no significant overnight change in Pcrit in CHF-OSA patients, CHF-only or healthy controls. When the data from all 3 groups were pooled, the only significant univariate predictor of Pcrit was AHI.

4.4.1. Limitations

There were some limitations that should be considered when interpreting the results of this study. The small sample size may have resulted in the study being underpowered, increasing the chance of a type II error. Care was taken during the planning of this study to ensure that sufficient numbers of participants were recruited, and a statistical power calculation was performed in collaboration with a statistician. The power calculation was conservative in its estimation of the difference to be detected between CHF-OSA patients and CHF-only and healthy age-matched controls. This is because pharyngeal collapsibility has a tendency to increase due to ageing (Eikermann et al., 2007; Kirkness et al., 2008), therefore the pharynx of all participants was likely to be more collapsible than would be expected in a younger population, irrespective of CHF and OSA (for a discussion of this topic see Chapter 1, Section 1.2.2). Therefore this study was powered to detect a smaller difference in Pcrit than is typically seen between middle-aged OSA patients and healthy controls. The target sample size was also calculated assuming a failure rate of Pcrit studies of approximately 10-20%. This was based on reports in the literature, however there have been no studies that attempted to measure Pcrit in the early and late part of the night. This led to a higher failure rate and a smaller sample size than had been anticipated.
The second potential limitation in this study was the decision to allow participants to choose their own sleeping posture. Pcrit is significantly higher in the supine posture compared to the lateral posture (Penzel et al., 2001), therefore many studies control for this by asking participants to sleep in a supine posture only. During early sleep studies for this investigation a number of CHF patients reported difficulty sleeping in the supine posture due to discomfort and breathlessness. Therefore to obtain as long a period of sleep as possible, participants were allowed to choose their sleep posture. In all 3 groups, approximately 50% of participants chose to sleep in the supine posture and approximately 50% in the lateral posture. Care was taken to ensure that all participants had their Pcrit measured in the same posture in the early and late parts of the night. Therefore, despite the posture of participants being a limitation in this study, I believe that comparisons between groups, and comparisons in Pcrit overnight were valid.

### 4.4.2. Pcrit in CHF-OSA, CHF-only and Healthy Controls

The finding that Pcrit was similar between all 3 groups was surprising, given that in the general population, OSA patients have a higher Pcrit than controls (Patil et al., 2007). It could be argued that due to the small sample size of the current study, the healthy age-matched controls were not representative of their population and that the true Pcrit of healthy controls should be lower in comparison to CHF-OSA patients. However, Kirkness et al. (2008) reported findings from a much larger cohort of subjects with and without OSA that appear to corroborate the data from the present study. Kirkness et al. (2008) showed that the Pcrit of participants aged 50-70 years old (with and without OSA) was between -5 and 5 cmH\textsubscript{2}O. The Pcrit values of healthy participants in the present study were similar but generally lower than those reported by Kirkness et al. (2008) and ranged from -7 to -1 cmH\textsubscript{2}O. Although data is limited in older populations, this demonstrates that the Pcrit values for the healthy volunteers of this study have external validity.
The majority of all participants from all 3 groups (21/31) had a Pcrit greater than -5 cmH₂O, placing them at a high risk of OSA (Kirkness et al., 2008). It is not clear from this study what differentiated the CHF patients with OSA from the CHF patients without OSA and healthy controls, given that all 3 groups were relatively well matched in demographics. Three of the CHF-OSA patients had Pcrit values equal to or greater than 0 cmH₂O, meaning that their airway was prone to collapse at atmospheric pressures. Pharyngeal collapse at or above atmospheric pressure is thought to be a consequence of high extra-luminal pressure, as opposed to being a consequence of negative intra-luminal pressure. This can be demonstrated using a Starling resistor model of the human airway (see Chapter 1, Section 1.2.2). This may hint that there was some additional extra-luminal pressure being exerted on the pharynges of these patients. However, regression analysis revealed that there was no relationship between neck circumference and Pcrit in the entire sample of patients and healthy controls as a whole (r²=0.01).

4.4.3. Overnight Changes in Pcrit

The finding that there was no overnight change in Pcrit for any group is contrary to what would be predicted from the rostral fluid shift hypothesis of OSA in CHF. This is the first study to measure the Pcrit of CHF-OSA patients in the early and late part of the night to try to ascertain the effects of rostral fluid shift on pharyngeal collapsibility. I found that there was no evidence that rostral fluid shift affected pharyngeal collapsibility of CHF-OSA, CHF-only, or healthy controls. One possible reason for finding no change overnight in Pcrit could be that rostral fluid shift is fast acting and the Pcrit tests did not have sufficient time resolution to detect the changes. The measurements of Pcrit certainly were time consuming and often took 1-2 hours at the start and end of the night respectively. Fluid shift may occur quickly, soon after assuming a recumbent posture and then remain stable for the rest of the night. If this is the pattern and time course of nocturnal rostral fluid shift then the Pcrit measurements would
not be expected to detect any change in the late part of the night compared to the early part of the night. These questions warrant further investigation, as the true impact of rostral fluid shift cannot be accurately determined if its time-course is not better understood.

This is not the first study to investigate overnight changes in sleep parameters in relation to overnight rostral fluid shift. Jafari and Mohsenin (2011) compared the AHI in the first half of the night to the AHI in the second half of the night in OSA patients. It was found that although there was evidence of rostral fluid shift during the night (neck circumference increased), there was no difference in AHI between the first and second half of the night. They concluded that rostral fluid shift may not be a significant risk factor in OSA patients.

4.4.4. Conclusions

This study reports for the first time, the Pcrit of CHF-OSA patients compared to CHF-only and healthy controls. Remarkably, the Pcrit was similar between all 3 groups, and all 3 groups had Pcrit values in a range normally associated with OSA. It is not clear why the Pcrit was similar between groups, given that the groups were well matched in all physical respects. This study demonstrates that Pcrit is not a sensitive predictor of OSA in CHF.
Chapter 5: The Effect of Age on Pharyngeal Calibre
5.1. Introduction

Pharyngeal calibre and pharyngeal critical closing pressure are similar in CHF patients with OSA, CHF patients without OSA, and age-matched healthy controls (Chapters 3 and 4). Given that all 3 groups were a similar age and that their Pcrit values were in a range normally associated with a higher risk of OSA (see discussion in Chapter 4), I speculate that ageing per se may result in anatomical and physiological changes to the upper airway that predispose it to narrowing and/or collapse.

There is growing evidence to suggest that the prevalence of OSA increases with age. In a seminal paper based on the Wisconsin Sleep Cohort (Young et al., 1993) it was observed that the prevalence of OSA (AHI >5 events/hr, with or without daytime somnolence) increased in males from 17% (95% CI: 9.6-25%) in 30-39 year olds to 31% (95% CI: 21-40%) in 50-60 year olds. In females OSA had a lower baseline prevalence at all ages but also increased with age, from 6.5% (95% CI: 1.4-11%) in 30-39 year olds to 16% (95% CI: 5.2-26%) in 50-60 year olds. These findings have been replicated in other large studies of cohorts drawn from different populations (Bixler et al., 2001, 1998; Durán et al., 2001). There is also limited prospective data suggesting that the severity of OSA increases over time (Young et al., 2002). Over the age of 65 years the prevalence and severity of OSA may plateau (Ancoli-Israel et al., 2001).

As in the general population, the mechanisms of OSA in older age are likely to be multifactorial and the relative contributions of certain factors within individuals are likely to vary. These factors include BMI (which has a tendency to increase with age; see Chapter 1, Section 1.2.6), pharyngeal collapsibility (which may increase with age; see Chapter 4), pharyngeal dilator muscle tone and responses to negative pressure challenge (which may deteriorate with age; Malhotra et al., 2006), and pharyngeal dilator muscle composition (which have been
shown to transition to fast twitch, fatigable muscle fibres with age in a rat model; Oliven et al., 2001; Skelly et al., 2011).

There is no clear consensus in the literature regarding the effects of ageing on pharyngeal calibre, despite a number of studies attempting to address this question, and despite data suggesting that surrounding bone and soft tissue structures are altered with age (see Chapter 1, Section 1.2.3). Some studies suggest that pharyngeal calibre is reduced with age (Brown et al., 1986; Huang et al., 1998; Kollias and Krogstad, 1999b; Martin et al., 1997; Shigeta et al., 2008b), some suggest that it is increased with age (Brooks and Strohl, 1992; Burger et al., 1992; Mayer et al., 1996; Tagaya et al., 2011), and others suggest there is no change (Malhotra et al., 2006). When the methodologies of these studies are examined, it is apparent that the studies reporting a decrease in pharyngeal calibre with age failed to screen their cohorts adequately to eliminate people with undiagnosed OSA. This could have led to false findings as the prevalence of OSA would be expected to increase with age (Bixler et al., 2001, 1998; Durán et al., 2001; Young et al., 1993), and the pharyngeal calibre of OSA patients is known to be smaller than non-OSA patients (Bradley et al., 1986; Ciscar et al., 2001). Therefore these studies may not accurately represent the effect of ageing per se on pharyngeal calibre. The majority of studies that report an increase or no change in pharyngeal calibre with age used polysomnography to screen for undiagnosed OSA in their cohorts, therefore there is currently stronger evidence to suggest that the effect of age on pharyngeal calibre is for it to increase (for a full discussion of these studies, see Chapter 1, Section 1.2.3).

A relatively new alternative hypothesis to explain the increase in OSA with age is that the pharynx may be longer in the older population (see Chapter 1, Section 1.2.5 for discussion of the mechanisms). This hypothesis is supported by findings suggesting that pharyngeal length is associated with OSA severity (Segal et al., 2008), and that older age is associated with increased facial length (Kollias and Krogstad, 1999a), a caudal shift of the hyoid bone
position (Pae et al., 2008), and increased pharyngeal length (Malhotra et al., 2006).

The aims of this study were to determine the effects of age per se on pharyngeal calibre and pharyngeal length, independent of confounding factors related to OSA, such as BMI and neck circumference. This was done by comparing a group of healthy older males with a group of healthy younger males, matched for BMI and neck circumference. The null hypothesis was that pharyngeal calibre and length would be similar in healthy older males and healthy younger males.

5.2. Methods

5.2.1. Ethical Review

This study was reviewed by the local Research Ethics Committee (London-Chelsea; formerly Brompton Harefield and NHLI Research Ethics Committee) and given a favourable opinion (REC number: 09/H0708/24). All volunteers gave written informed consent prior to participating in this study.

5.2.2. Subjects

Healthy younger males and healthy older males were recruited from the general population. Advertising was placed in local newspapers and local sports clubs, social clubs and charitable groups were contacted. Inclusion criteria for the study were that participants were male, aged between 18 and 40 years (younger group) or over 60 years (older group), and had no history of sleep, respiratory or cardiovascular disorders. Exclusion criteria included any previous diagnosis of a sleep disorder or an AHI >5 events/hr. The older group was recruited and studied first, thus providing a set of target demographics for the younger group to be matched to. The key demographics that groups were matched on at recruitment were BMI and neck circumference.
All potential participants were contacted by telephone prior to enrolment and asked for a medical history including self-reported height, weight, and subjective sleepiness according to the Epworth Sleepiness Score. Participants were then screened for sleep-disordered breathing using respiratory polygraphy performed in their home or in the sleep laboratory (see Protocol below for full description of techniques). Volunteers that met all inclusion/exclusion criteria were invited to undergo measurement of their upper airway calibre using acoustic reflection and magnetic resonance imaging (MRI).

5.2.3. Protocol

All volunteers that met the inclusion criteria after telephone interview underwent respiratory polygraphy either in their home or at the Royal Brompton Hospital research sleep laboratory, according to their preference. Prior to sleep, participants had their height, weight, blood pressure and lung function recorded. Participants were then instrumented for respiratory polygraphy using a commercial multi-channel polygraphy system (SOMNOscreen, Somnomedics GmbH, Germany). See Chapter 2, Section 2.2.2 for a full description of the polygraphy equipment and methods. In brief, airflow, respiratory effort, oxygen saturation and heart rate were monitored. Participants were asked to keep a written record of the time they turned their lights out in order to go to sleep, and the time that they woke up in the morning. Participants were also asked to record any periods when they woke during the night.

Participants whose AHI was <5 events/hr after respiratory polygraphy were invited to attend the Royal Brompton Hospital to undergo acoustic reflection and MRI scans of the upper airway. Pharyngeal dimensions were measured using the acoustic reflection technique. The same general protocol was followed for all acoustic reflection measurements (see Chapter 2, Section 2.4.1). Measurements were made in the supine posture only, after participants had lay quietly for 5 minutes. All participants also underwent measurement of their pharynx using
MRI. This was performed on the same day as acoustic reflection measurements. Due to the volume of data this produced and time constraints for the submission of this thesis, MRI data were not analysed in time to be included in this chapter.

5.2.4. Data Analysis

Respiratory polygraphy data were analysed according to AASM recommended scoring criteria (Iber et al., 2007). Time in bed was defined as the period between turning lights off, and waking in the morning, as reported by the participants. For the purposes of respiratory analysis, this period was defined as “sleep”. Apnoeas and hypopnoeas were scored using the methods described in Chapter 2, Section 2.2.1.

Acoustic reflection traces were analysed as described in the General Methods (Chapter 2, Section 2.4.1). Each individual acoustic reflection trace (up to 50 per participant) was analysed to find 3 measures of pharyngeal calibre: 1) mean pharyngeal area (APmean); 2) pharyngeal volume (VP); 3) glottis area (AG). Furthermore, pharyngeal length was obtained by measuring the distance between the end of the mouthpiece (positioned inside the oral cavity, between the incisors) and the glottis (defined as the minimal cross-sectional area on the acoustic trace, distal of the local maxima in the oral cavity; see Error: Reference source not found).

5.2.5. Statistical Analysis

This study was treated as a pilot study, to precede a larger cross-sectional study investigating pharyngeal calibre in older and younger males, females, and OSA patients. Therefore no sample size was calculated for the two pilot groups presented in this chapter.

Data from most of the measurements violated one or more assumptions of normality, therefore all data were analysed using non-parametric methods and are presented as median.
and interquartile range (IQR). Differences between groups were analysed using two-sample Wilcoxon tests. All data were analysed using R-Project statistical packages (R Foundation for Statistical Computing, Austria) and R Commander (version 1.8-3).

5.3. Results

5.3.1. Subjects

A total of 12 older males (>60 years old) underwent measurement of their upper airway by acoustic reflection and MRI (see consort diagram, Figure 5.1). Three older males (>60 years old) that had participated in previous research (see studies described in Chapter 3 and Chapter 4) agreed to participate in this study. All had received full nocturnal polysomnography studies within 6 months prior to entry into this study, therefore respiratory polygraphy testing was not performed. A further 11 older males that met all inclusion criteria were recruited after answering public advertising and canvassing of local sports clubs, social clubs and charity groups. Following respiratory polygraphy tests, two older males were found to have undiagnosed OSA (AHI ≥ 5 events/hr) and were excluded from further testing.

Sixteen younger males that met all inclusion criteria were recruited after answering public advertising and canvassing of local sports clubs, social clubs and charity groups. Following respiratory polygraphy tests, two younger males were found to have undiagnosed OSA (AHI ≥ 5 events/hr) and were excluded from further testing. A total of 14 younger males (18-40 years old) underwent measurement of their upper airway by acoustic reflection and MRI (see consort diagram, Figure 5.1).
Three older males from previous research had received full polysomnography studies within 6 months of participating in the present study, therefore they did not undergo respiratory polygraphy testing.

The baseline characteristics for the two groups are presented in Table 5.1. By design there was a significant difference between the groups' ages. The groups were well matched for all other characteristics.
Table 5.1: Participant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Younger Males (n=14)</th>
<th>Older Males (n=12)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28 (26, 32)</td>
<td>65 (63, 70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.8 (1.7, 1.8)</td>
<td>1.8 (1.7, 1.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 (79, 87)</td>
<td>76 (72, 93)</td>
<td>0.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 (24, 27)</td>
<td>26 (25, 29)</td>
<td>0.9</td>
</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>39 (38, 41)</td>
<td>40 (39, 41)</td>
<td>0.6</td>
</tr>
<tr>
<td>Epworth (/24)</td>
<td>6 (3, 8)</td>
<td>5 (3, 6)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range). There were no significant differences between groups in baseline characteristics, except for age by design.

5.3.2. Respiratory Polygraphy

Both groups reported spending a similar time in bed (younger males: 383, IQR 380, 509 mins; older males: 391, IQR 272, 413 mins). Older males had a tendency to spend more time in the lateral posture and less time in the supine posture than younger males, however this did not reach statistical significance (supine p=0.5; lateral p=0.3). The younger and older group had similar AHIs and ODIs and neither group had any significant sleep disordered breathing (Table 5.2).
Table 5.2. Sleep parameters.

<table>
<thead>
<tr>
<th></th>
<th>Younger Males (n=14)</th>
<th>Older Males (n=12)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Bed (mins)</td>
<td>383 (380, 509)</td>
<td>391 (272, 413)</td>
<td>0.2</td>
</tr>
<tr>
<td>AHI (/hr)</td>
<td>0.8 (0.6, 1.4)</td>
<td>2.4 (1.4, 4.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Obstructive apnoea Index (/hr)</td>
<td>0.2 (0.1, 0.3)</td>
<td>0.0 (0.0, 0.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Central apnoea Index (/hr)</td>
<td>0.2 (0.0, 0.2)</td>
<td>0.3 (0.0, 1.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>Mixed apnoea Index (/hr)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypopnoea Index (/hr)</td>
<td>0.7 (0.3, 1.2)</td>
<td>0.8 (0.1, 1.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>ODI (4% desaturations/hr)</td>
<td>0.8 (0.3, 1.9)</td>
<td>2.0 (0.7, 2.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Supine (%Time in bed)</td>
<td>42 (19, 71)</td>
<td>15 (12, 71)</td>
<td>0.5</td>
</tr>
<tr>
<td>Left (%Time in bed)</td>
<td>21 (3, 36)</td>
<td>25 (15, 54)</td>
<td>0.6</td>
</tr>
<tr>
<td>Right (%Time in bed)</td>
<td>27 (23, 35)</td>
<td>25 (13, 34)</td>
<td>0.8</td>
</tr>
<tr>
<td>Total Lateral (%Time in bed)</td>
<td>57 (29, 75)</td>
<td>85 (29, 88)</td>
<td>0.3</td>
</tr>
<tr>
<td>Prone (%Time in bed)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

All data are expressed as median (interquartile range). There were no significant differences between groups in any sleep parameter.

5.3.3. Pharyngeal Calibre and Length

Figure 5.2 shows original traces of the pharynx from a representative older and younger male.

The trace of the pharynx of the older male has a greater cross-sectional area than the younger male along most of its length, suggesting a larger APmean and VP. The lowest distal point on the traces represent the glottis and it can be seen that the AG is greater in the older male than the younger male, and that the location of the glottis as a function of distance along the airway is similar in the older and younger males, suggesting pharyngeal length is similar.
Figure 5.2: Original acoustic traces of the pharynx from an older and younger male. See Figure 2.5 for full description of acoustic trace. The older male had larger APmean, VP and AG than the younger male, but pharyngeal length was similar. See text for further description.

Overall, the pharyngeal calibre of older males was significantly greater than younger males according to the APmean (older: 4.7, IQR 3.8, 6.5 cm²; younger: 3.4, IQR 2.8, 4.6 cm²; p=0.03) (Figure 5.3, upper panel). Older males also had a significantly greater AG than younger males (older: 2.9, IQR 2.1, 4.0 cm²; younger: 1.2, IQR 1.1, 1.9 cm²; p=0.003) which by definition is the narrowest point on the pharyngeal acoustic reflection trace (Figure 5.3, lower panel). There was a tendency for VP to be greater in older males than younger males, however this just failed to reach statistical significance (older: 34.9, IQR 30.9, 54.1 cm³; younger: 27.2, IQR 22.7, 44.2 cm³; p=0.053) (Figure 5.4, upper panel). Pharyngeal length was similar in older males and younger males (older: 8.4, IQR 7.4, 9.6 cm; younger: 8.1, IQR 7.6, 8.7 cm; p=0.9) (Figure 5.4, lower panel).
Each data point represents one subject. The mean pharyngeal area was significantly greater in older males, suggesting that they had a larger pharyngeal calibre overall. The glottis area was also greater in the older males; the glottis area is the narrowest point in the airway that can be measured by acoustic reflection.

Figure 5.3: Mean pharyngeal area (upper panel) and glottis area (lower panel) in younger and older males.

Each data point represents one subject. The mean pharyngeal area was significantly greater in older males, suggesting that they had a larger pharyngeal calibre overall. The glottis area was also greater in the older males; the glottis area is the narrowest point in the airway that can be measured by acoustic reflection.
There was a tendency for pharyngeal volume to be greater in older males, however this failed to reach statistical significance. There was no significant difference in pharyngeal length.

Figure 5.4: Pharyngeal volume (upper panel) and pharyngeal length (lower panel) in older and younger males. There was a tendency for pharyngeal volume to be greater in older males, however this failed to reach statistical significance. There was no significant difference in pharyngeal length.
5.4. Discussion

The main findings of this study were that the pharyngeal calibre of healthy older males was significantly greater than the pharyngeal calibre of healthy younger males when groups were matched for BMI, neck circumference, subjective daytime sleepiness, AHI and ODI. However, pharyngeal length was not significantly different in older males compared to younger males.

5.4.1. Limitations

As in Chapter 3, the main limitation of this study was the use of AR to make measurements of pharyngeal calibre. The AR device requires subjects to be awake during measurements, meaning potentially important differences between the pharynx of older and younger males that occur during sleep may have been missed. Another limitation of the acoustic reflection technique is that it requires subjects to elevate their soft palate in order to occlude the nasopharynx. This allows the oropharynx to be modelled as a continuous tube. The result of this is that measurements of pharyngeal calibre exclude the retro-palatal region of the pharynx, and measurements of pharyngeal length are made between the incisors and the glottis and include measurement of the oral cavity. Other studies utilising imaging techniques such as CT and MRI measure the pharyngeal length from the hard or soft palate to the glottis. Therefore measurements of pharyngeal length reported in this study are not directly comparable to imaging studies. This limitation was overcome by also performing measurements of the pharynx using MRI. This data will be analysed at a later time.

5.4.2. Differences in Pharyngeal Calibre Between Older and Younger Males

The finding that pharyngeal calibre is greater in older males than younger males is consistent with some studies (Brooks and Strohl, 1992; Burger et al., 1992; Mayer et al., 1996; Tagaya et
al., 2011), however it contradicts others (Brown et al., 1986; Huang et al., 1998; Kollias and Krogstad, 1999b; Martin et al., 1997; Shigeta et al., 2008b). The reasons for these differing results are not clear, however a range of techniques, populations and methodologies have been used and may have contributed to some of the variability in the observations. A consistent methodological limitation in many studies is that study populations included OSA patients by design, or participants were not robustly screened for the presence of OSA. Given that OSA prevalence (irrespective of daytime somnolence) is known to increase with age (Bixler et al., 2001, 1998; Durán et al., 2001; Young et al., 1993), it is possible that many of these studies investigating the effects of age on pharyngeal calibre included participants with undiagnosed OSA. Table 5.3 has been constructed to further detail the methodological differences between studies.
Table 5.3: Characteristics of studies reporting age-related changes in pharyngeal calibre.

<table>
<thead>
<tr>
<th>Study</th>
<th>Pharyngeal Measurement</th>
<th>Study Design/ Target Population</th>
<th>Subjects (n)</th>
<th>Age (Old vs. Young)</th>
<th>AHI (/hr)</th>
<th>Screening Method</th>
<th>Effect of age on pharyngeal calibre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 10</td>
<td>F: 33±7</td>
<td>F: NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 54</td>
<td>F: 45±16</td>
<td>F: NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang et al. (1998)</td>
<td>Acoustic Reflection</td>
<td>Cross-sectional/ Healthy and OSA</td>
<td>M: 77</td>
<td>M: 45±2</td>
<td>M: NA</td>
<td>Medical history</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 78</td>
<td>F: 33±1</td>
<td>F: NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 24</td>
<td>Follow up: 43±2 (M); 43±2 (F)</td>
<td>F: NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigeta et al. (2008)</td>
<td>CT</td>
<td>Cross-sectional/ Healthy and OSA</td>
<td>M: 19</td>
<td>M: 57±16</td>
<td>M: NA</td>
<td>Medical history</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 19</td>
<td>F: 51±17</td>
<td>F: NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 98</td>
<td>F: 33±10</td>
<td>F: NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burger et al. (1992)</td>
<td>CT</td>
<td>Cross-sectional/ Healthy</td>
<td>Younger: 10</td>
<td>Younger: 28±1</td>
<td>Younger: 3±1</td>
<td>Polysomnography</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Older: 10</td>
<td>Older: 66±2</td>
<td>Older: 5±1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayer et al. (1996)</td>
<td>CT</td>
<td>Cross-sectional/ Snorers and OSA</td>
<td>Younger: 45</td>
<td>Younger: 42±7</td>
<td>Younger: 32±31</td>
<td>Polysomnography</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Older: 47</td>
<td>Older: 69±6</td>
<td>Older: 38±24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Older: 81</td>
<td>Older: 67±3</td>
<td>Older: 32±19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malhotra et al. (2006)</td>
<td>MRI</td>
<td>Cross-sectional/ Healthy</td>
<td>Younger: 8</td>
<td>Younger: 35±10</td>
<td>Younger: 3±2</td>
<td>Polysomnography</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Older: 10</td>
<td>Older: 65±9</td>
<td>Older: 5±3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In studies that screened for OSA using sleep studies, findings were consistent with the present study. As in the present study, Burger et al. (1992) and Mayer et al. (1996) both found that pharyngeal calibre was greater in older age. Malhotra et al. (2006) found a tendency for pharyngeal volume to be greater in older subjects that just failed to reach statistical significance (p=0.08). In the present study the groups were screened for OSA using respiratory polygraphy. Therefore it appears that when participants are adequately screened for OSA, older participants tend to have a greater pharyngeal calibre than younger participants.

The present study (and the studies cited above) had a cross-sectional design and did not include long term follow up of participants. The only longitudinal study of pharyngeal dimensions that I am aware of involved a 20 year follow up of students whose mean age was 22.3 ± 1.8 at baseline. After 20 years (at a mean follow up age of 42.7 ± 1.9 years) participants had a significant decrease in oropharyngeal calibre (Kollias and Krogstad, 1999b). Data from the Wisconsin Sleep Cohort suggest that over an 8 year follow up period, the progression of OSA (measured as the increase in AHI over time) is significantly greater in people aged 45-60 years at baseline compared to people aged 30-45 years at baseline (Young et al., 2002). Therefore it seems that (Kollias and Krogstad, 1999b) may have ended their follow up at a crucial age for the progression of OSA, missing potentially important changes to the pharynx for OSA progression.

5.4.3. Differences in Pharyngeal Length Between Older and Younger Males

The finding that pharyngeal length was similar in older and younger males was contrary to previous studies (Malhotra et al., 2006; Shigeta et al., 2008b) and contradicts the hypothesis that pharyngeal length may be a mechanism for increased OSA prevalence in older age. Some researchers have suggested that a longer pharynx may be more collapsible than a shorter pharynx (Pae et al., 1997; Segal et al., 2008; see Section 1.2.5 for a full discussion). Some
studies have used x-ray to image the bony structures of the upper airway and have observed that the hyoid bone is positioned more caudally in older subjects (Pae et al., 2008). Due to the hyoid bone having a number of superior attachments to muscles of the tongue and pharynx it is possible that a more descended hyoid bone is indicative of a longer pharynx. Direct measurement of pharyngeal length using MRI and CT scans would appear to support this; (Shigeta et al., 2008b) and Malhotra et al. (2006) measured the length of the pharynx from the level of the hard palate to the level of the epiglottis and observed a significant relationship between increased age and pharyngeal length.

In the current study pharyngeal length was measured using acoustic reflection which has a number of important differences to direct imaging techniques such as x-ray and MRI. In imaging studies it is common to obtain a sagittal image of the airway (or bony structures) and mark the bounds of the pharynx using easily identifiable anatomical landmarks such as the hard palate and epiglottis. Using these methods, the portion of the pharynx that is measured encompasses part of the nasopharynx, the oropharynx and part of the laryngopharynx. In contrast, the acoustic reflection technique measures the length of the pharynx between the incisors (where the mouthpiece terminates) and glottis. This measure encompasses the oral cavity, the oropharynx and part of the laryngopharynx. The contrasting findings between previous studies (Malhotra et al., 2006; Shigeta et al., 2008b) and the current study may be due to these differences in the segments of the pharynx that are measured using CT and MRI vs. acoustic reflection. Analysis of the MRI data collected for this study will resolve this issue in the future.

5.4.4. Conclusions

This study has investigated the differences in pharyngeal calibre between a group of older and younger males that were confirmed by sleep study to be free of OSA and that were carefully
matched for BMI, neck circumference, daytime sleepiness, AHI and ODI. I have shown in these very well matched healthy groups that older age is associated with increased pharyngeal calibre but no difference was found in pharyngeal length. Based on the results of this study I speculate that pharyngeal calibre may be an important factor in the pathogenesis of OSA in older age and that a large pharyngeal calibre may be protective against OSA in older age. Studies in older patients will be needed to investigate this suggestion.
Chapter 6: Changes in Pharyngeal Calibre and Neck Circumference Measured During Sleep Using Endoscopy in Patients with Heart Failure
6.1. Introduction

Obstructive sleep apnoea is defined as cessation of airflow despite ongoing respiratory efforts, indicating that the pharynx has closed. Central sleep apnoea is defined as cessation of airflow with cessation of respiratory efforts, indicating that ventilatory drive to the respiratory pump muscles has decreased or is absent (see Chapter 1, Section 1.2.7). The passive airway may be predicted to close during central apnoea; as neuromuscular tone to the pharyngeal dilator muscles is reduced the transmural pressure would decrease. If intra-luminal pressure were to fall to equal or lower than extra-luminal pressure, the pharynx would collapse passively (Gold and Schwartz, 1996; Schwartz et al., 1998, 1988). This phenomenon has been observed in patients with central sleep apnoea (Badr et al., 1995; see Chapter 1, Figure 1.1) and airway narrowing has been observed during induced hypocapnic hypopnoea in healthy volunteers (Sankri-Tarbichi et al., 2009). Passive narrowing of the airway has also been observed during expiration, the period of the respiratory cycle thought to be associated with low phasic respiratory and upper airway muscle tone (Morrell et al., 1998; Sankri-Tarbichi et al., 2009).

CHF patients have a high prevalence of both CSA and OSA (Bitter et al., 2009; Ferrier et al., 2005; Javaheri, 2006; Javaheri et al., 1998; Lanfranchi et al., 2003; MacDonald et al., 2008; Oldenburg et al., 2007; Schulz et al., 2007; Vazir et al., 2007).

CHF patients may be predisposed to CSA by being chronically hypocapnic with an arterial PCO$_2$ close to their hypocapnic apnoeic threshold (Xie et al., 2002). Moreover, patients with CHF are known to have an increased hypercapnic ventilatory response which may contribute to breathing instability during sleep (Javaheri et al., 1998). Taken together, a predisposition to breathing instability may be associated with passive upper airway collapse during central apnoeic events in patients with CHF.

Passive pharyngeal narrowing and collapse has not been directly measured in CHF patients.
before, however the rostral fluid shift hypothesis predicts that this phenomenon is likely to occur. Displacement of fluid from the legs to the neck may increase extra-luminal tissue pressure, resulting in decreased pharyngeal calibre (Shiota et al., 2007), increased pharyngeal resistance (Chiu et al., 2006) and increased pharyngeal collapsibility (Su et al., 2008).

The aims of this study were twofold; the first aim was to investigate whether CHF patients with CSA (CHF-CSA) experience any passive pharyngeal collapse during central sleep apnoea. The second aim was to determine any effects of rostral fluid shift on pharyngeal calibre across the night and during sleep in CHF-CSA patients. I tested two hypotheses: 1) that CSA is associated with passive pharyngeal collapse in CHF-CSA patients. 2) that overnight rostral fluid shift was associated with pharyngeal narrowing across the night and during sleep. In order to test both of these hypotheses, the pharyngeal lumen of CHF-CSA patients was directly visualised using a fibre-optic bronchoscope during sleep.

6.2. Methods

6.2.1. Ethical Review

This study was carried out while on sabbatical in Detroit, USA. The study was reviewed by the local Research Ethics Committee (John D. Dingell Veterans Affairs Medical Center and the Wayne State University Institutional Review Board; IRB number 081596MP4F) and given a favourable opinion. All volunteers gave written informed consent prior to participating in this study.

6.2.2. Subjects

CHF patients with predominantly CSA (CHF-CSA) were recruited from the John D. Dingell Veterans Affairs Medical Center, Detroit, USA over 6 months between February and August 2010. I identified potential participants by retrospective review of the hospital's electronic
database of clinical records and by screening of heart failure and sleep apnoea outpatient clinics.

The CHF status and diagnosis and severity of CSA of potential participants was determined by review of their clinical notes and clinical assessment by their clinical care team. To be included in the study, participants were required to be 18-85 years old, have an AHI ≥10 events per hour with >50% of events classified as central, have a left ventricular ejection fraction <40% and be in a clinically stable condition, having had no heart failure-related hospital admission in the 3 months prior to recruitment. Potential participants were excluded from the study if they had previously undergone upper airway surgery, had uncontrolled or treatment-resistant hypertension or were known to have recent or current problems with opioid abuse. Patients that met the inclusion/exclusion criteria were approached by a member of their clinical care team and invited to participate in this study. Following informed consent, patients were asked to attend the research sleep laboratory at the John D. Dingell Veterans Affairs Medical Center for one night. Patients were asked to restrict their sleep to approximately 4 hours on the night before the study and to abstain from caffeine or alcohol on the day of the study.

6.2.3. Materials and Data Acquisition

Prior to sleep, anthropometric measurements were performed including height, weight, neck circumference and routine lung function. Patients were then set up for the sleep study. Sleep/wake state was measured using standard polysomnography techniques. A commercial polysomnography system (Comet-PLUS, Grass Technologies, USA) was used to record brain waves (EEG), eye movements (EOG), chin muscle activity (EMG), heart rate (ECG), breathing movements (using respiratory inductance plethysmography) and arterial oxygen saturation (using a pulse oximeter attached to the ear).
Patients were attached to a bi-level positive air pressure (BiPAP) ventilator via a nasal mask prior to sleep. Attached to the mask was a pneumotachometer (range 0-160 L/min, Series 3700, Hans Rudolph Inc, USA) coupled with a pressure transducer (Series 1110 PA-1, Hans Rudolph Inc, USA) for recording of airflow. End-tidal carbon dioxide was sampled at the nose and measured using an infra-red carbon dioxide analyser (Model CD-3A, AEI Technologies, USA). Pressure at the mask was measured using a pressure transducer (Series 1110 PA-1, Hans Rudolph Inc, USA). Oesophageal pressure was measured using a solid-tip pressure manometer (Mikro-Tip pressure catheter, Millar Instruments, USA) passed trans-nasally and positioned just below the palatal rim. A paediatric fibre-optic bronchoscope was positioned at the approximate level of the palatal rim, allowing visualisation of the retro-palatal and retro-glossal pharyngeal lumen. The tip of the oesophageal pressure manometer was used to assist with locating the bronchoscope at the correct level of the airway. This procedure was carried out by a trained physician (Dr Sankri-Tarbichi; see Sankri-Tarbichi et al., 2009). All signals were amplified via an analogue to digital converter (Powerlab, ADInstruments, USA) and data was recorded via data acquisition software (LabChart Pro, ADInstruments, USA) that was synchronised with the video images of the airway from the bronchoscope and the polysomnography data.

6.2.4. Protocol

After monitoring equipment had been attached, patients were allowed to fall asleep in a supine posture. The BiPAP ventilator was set to deliver the lowest continuous pressure possible (baseline pressure of 2 cmH₂O). The bronchoscope was adjusted when necessary throughout the night in order to maintain a clear image of the pharyngeal lumen. Measurements of pharyngeal cross-sectional area were made during stage I-III non-REM (NREM) sleep and during central apnoeic events. Apnoeaic events were identified according to the criteria of the AASM; central apnoeas were identified by cessation of airflow associated
with cessation of respiratory efforts and oesophageal pressure swings.

Patients were allowed to breathe spontaneously for at least 30 minutes of NREM sleep at the start of the night and at the end of the night. If central apnoeas occurred spontaneously within these times then no further intervention was performed. If central apnoea did not occur after 30 minutes then patients were mechanically hyperventilated using the BiPAP ventilator in order to reduce $P_{ET}CO_2$ and induce central apnoea. Mechanical ventilation was applied for 3 minute periods and then abruptly returned to baseline pressure (2 cmH$_2$O). Hyperventilation was induced by increasing inspiratory pressure by 1-2 cmH$_2$O, while keeping expiratory pressure constant at 2 cmH$_2$O. Inspiratory pressure was increased by greater increments above baseline in subsequent periods of mechanical ventilation until termination of ventilation resulted in central apnoea.

6.2.5. Data Analysis

Polysomnography data were used for real-time sleep staging and classification of apnoeas as central, obstructive or mixed. Apnoeic events were later checked offline for accuracy of classification and to confirm the sleep stage. Scoring of sleep stages and classification of apnoeas was performed according to standard AASM definitions (Iber et al., 2007). See Chapter 3, Section 3.2.4 for definitions of apnoeas and hypopnoeas.

Image Analysis

Images of the pharyngeal lumen were sampled from periods of interest throughout the night (see Central Apnoea Analysis and Dynamic Pharyngeal Compliance Analysis below). The cross-sectional area of the pharynx was measured by manually outlining the pharyngeal lumen in each video frame using image analysis software (ImageJ, National Institutes of Health, USA). The measurements of pharyngeal cross-sectional area were calibrated in each frame using the tip of the oesophageal pressure manometer as a reference point with a known
cross-sectional area. Image frames where the tip of the pressure manometer could not be seen were excluded from analysis.

**Central Apnoea Analysis**

The start of a central apnoea was defined as the point of peak expiratory flow immediately preceding cessation of airflow. The end of central apnoeas was defined as the point at which a positive inspiratory airflow was detectable, which preceded resumption of ventilatory deflections in airflow. Images of the pharyngeal lumen recorded by video were inspected frame by frame between the start and end of central apnoeas to determine whether the airway occluded. If airway occlusion did occur, the time to occlusion was measured.

**Dynamic Pharyngeal Compliance Analysis**

In order to quantify the extent to which the pharyngeal calibre varies over the respiratory cycle, and to determine whether this variation changes overnight, a novel measure of within-breath dynamic pharyngeal compliance was conceived.

Pharyngeal cross-sectional area, airflow and mask pressure were measured simultaneously at 5 points in the respiratory cycle: 1) beginning inspiration (BI), defined as the point at which airflow crossed from positive to negative; 2) peak inspiration (PI), defined as the peak inspiratory airflow; 3) beginning expiration (BE), defined as the point at which airflow crossed from negative to positive; 4) peak expiration (PE), defined as the peak expiratory airflow; 5) end expiration (EE), defined as the point at which airflow crossed from positive to negative to begin a new respiratory cycle. Breaths were sampled from periods of stable breathing, during stage I-III NREM sleep. The within-breath dynamic compliance of the pharynx was then calculated during the inspiratory and expiratory phases of respiration.

Inspiratory dynamic compliance was calculated as the change in pharyngeal cross-sectional area between BI and EI. Expiratory dynamic compliance was calculated as the change in
pharyngeal cross-sectional area between BE and EE. Changes in pharyngeal cross-sectional area were divided by the change in mask pressure (Pmask) between BI and EI or BE and EE respectively in order to control for the confounding effect of ventilator pressure on pharyngeal cross-sectional area. The formula for inspiratory dynamic compliance (I-DC) and expiratory dynamic compliance (E-DC) are given in equations 1 and 2 below:

\[
I-DC = \frac{EI\text{ cross-sectional area} - BI\text{ cross-sectional area}}{EI\text{ Pmask} - BI\text{ Pmask}}
\]

Equation 1: Inspiratory dynamic pharyngeal compliance.

\[
E-DC = \frac{EE\text{ cross-sectional area} - BE\text{ cross-sectional area}}{EE\text{ Pmask} - BE\text{ Pmask}}
\]

Equation 2: Expiratory dynamic pharyngeal compliance.

6.3. Results

6.3.1. Subjects

From a population of approximately 1700 patients who had undergone polysomnography at the John D. Dingell Medical Center in the 5 years preceding this study (February 2005 to August 2010), 38 potential participants were identified on the basis of having both CHF and some form of sleep apnoea (AHI >10 events/hr; see Figure 6.1). After further review of clinical notes and sleep studies, 34 patients were excluded from participation in the study (10 had predominant OSA, 17 opioid abuse, 5 could not be contacted, 2 declined). Four patients were recruited for this study, however it was not possible to complete data collection and analysis in the fourth patient within the time limits of the collaboration, therefore the data
from 3 patients are presented in this chapter (see consort diagram, Figure 6.1). The characteristics of the 3 patients are given in Table 6.1.

**Figure 6.1: Consort diagram for the recruitment of CHF patients with predominant CSA. See text for further description.**
Table 6.1. Patient characteristics and sleep parameters for 3 patients studied.

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4</td>
<td>47.8</td>
<td>39.9</td>
</tr>
<tr>
<td>ESS</td>
<td>15</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>79</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>74</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>86</td>
<td>120</td>
<td>79</td>
</tr>
<tr>
<td>Resting CO₂ (mmHg)</td>
<td>36.5</td>
<td>39.2</td>
<td>40.5</td>
</tr>
<tr>
<td>Resting SpO₂ (%)</td>
<td>96</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>125</td>
<td>120</td>
<td>164</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Resting HR (beats/min)</td>
<td>70</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (%)</td>
<td>20</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>AHI (events/hr)</td>
<td>16</td>
<td>46.4</td>
<td>31.8</td>
</tr>
<tr>
<td>Central Apnoea Index (events/hr)</td>
<td>1.3</td>
<td>9</td>
<td>11.5</td>
</tr>
<tr>
<td>Obstructive Apnoea Index (events/hr)</td>
<td>0</td>
<td>5.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypopnoea index (events/hr)</td>
<td>14.7</td>
<td>32.1</td>
<td>20</td>
</tr>
<tr>
<td>Arousal Index (arousals/hr)</td>
<td>8.4</td>
<td>29.7</td>
<td>25.3</td>
</tr>
<tr>
<td>Oxygen Desaturation Index (≥4% desats/hr)</td>
<td>5.5</td>
<td>52.9</td>
<td>36.8</td>
</tr>
</tbody>
</table>

6.3.2. Spontaneous and Induced Central Apnoeas

All three patients experienced spontaneous central apnoeas during their sleep study, and all three patients were also mechanically ventilated for periods of the night in order to induce further hyperventilation and central apnoeas. Not all periods of mechanical ventilation resulted in central apnoeas, and not all central apnoeas were analysed due to movement of the bronchoscope rendering the images of the pharynx unusable. Table 6.2 summarises the number of spontaneous central apnoeas and induced central apnoeas for each patient.
Table 6.2. Number of spontaneous central apnoeas and induced central apnoeas yielding usable images for analysis in 3 patients.

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous Central Apnoeas:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Spontaneous Central Apnoeas (n)</td>
<td>2</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Spontaneous apnoeas yielding usable images (n)</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Induced Central Apnoeas:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation Periods (n)</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mechanical ventilation resulting in central apnoea (n)</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Induced apnoeas yielding usable images (n)</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total Central Apnoeas Analysed</strong></td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

**Patient A**

Patient A yielded 3 central apnoeas that were suitable for analysis, all of which were induced using mechanical ventilation. All three apnoeas resulted in narrowing of the pharynx and the pharynx completely occluded during two of the apnoeas. Table 6.3 summarises the results from the three apnoeas.

Table 6.3. Results of apnoea analysis for Patient A.

<table>
<thead>
<tr>
<th></th>
<th>Induced 1</th>
<th>Induced 2</th>
<th>Induced 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep stage during apnoea</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mask pressure during apnoea (cmH₂O)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Apnoea duration (s)</td>
<td>13.7</td>
<td>16.1</td>
<td>9.8</td>
</tr>
<tr>
<td>Pharyngeal occlusion (Y/N)</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Pre-apnoea EE lumen area (mm²)</td>
<td>2.6</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Min. lumen area (mm²)</td>
<td>0</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Min. lumen area (% pre-apnoea EE lumen area)</td>
<td>0%</td>
<td>45%</td>
<td>0%</td>
</tr>
<tr>
<td>Time to min. lumen area (s)</td>
<td>3.3</td>
<td>1.9</td>
<td>4.5</td>
</tr>
<tr>
<td>Time to min. lumen area (% apnoea duration)</td>
<td>24%</td>
<td>12%</td>
<td>46%</td>
</tr>
</tbody>
</table>
**Patient B**

Patient B yielded 3 central apnoeas that were suitable for analysis, all of which were spontaneous central apnoeas. All three apnoeas resulted in narrowing of the pharynx and the pharynx completely occluded during one of the apnoeas. Table 6.4 summarises the results of the three apnoeas.

*Scope moved, image unusable.*

**Table 6.4. Results of apnoea analysis for Patient B.**

<table>
<thead>
<tr>
<th></th>
<th>Spon. 1</th>
<th>Spon. 2</th>
<th>Spon. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep stage during apnoea</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mask pressure during apnoea (cmH(_2)O)</td>
<td>1.4</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Apnoea duration (s)</td>
<td>10.6</td>
<td>10.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Pharyngeal occlusion (Y/N)</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Pre-apnoea EE lumen area (mm(^2))</td>
<td>6.4</td>
<td>NA*</td>
<td>9.6</td>
</tr>
<tr>
<td>Min. lumen area (mm(^2))</td>
<td>2.6</td>
<td>0.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Min. lumen area (% pre-apnoea EE lumen area)</td>
<td>41%</td>
<td>0%</td>
<td>64%</td>
</tr>
<tr>
<td>Time to min. lumen area (s)</td>
<td>7.2</td>
<td>1.8</td>
<td>9.9</td>
</tr>
<tr>
<td>Time to min. lumen area (s, % apnoea duration)</td>
<td>68%</td>
<td>18%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Scope moved, image unusable.*

**Patient C**

Patient C yielded 5 central apnoeas that were suitable for analysis, 4 of which were spontaneous central apnoeas and 1 of which was induced by mechanical ventilation. Three of the spontaneous apnoeas resulted in narrowing of the pharynx, however in the fourth the pharyngeal cross-sectional area increased. The apnoea induced by mechanical ventilation resulted in complete occlusion of the pharynx. Table 6.5 summarises the results of the apnoeas.
Table 6.5. Results of apnoea analysis for Patient C

<table>
<thead>
<tr>
<th></th>
<th>Spon. 1</th>
<th>Spon. 2</th>
<th>Spon. 3</th>
<th>Spon. 4</th>
<th>Ind. 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep stage during apnoea</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mask pressure during apnoea (cmH₂O)</td>
<td>1.6</td>
<td>1.5</td>
<td>1.7</td>
<td>1.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Apnoea duration (s)</td>
<td>11.2</td>
<td>9.6</td>
<td>12.9</td>
<td>11.6</td>
<td>13.9</td>
</tr>
<tr>
<td>Pharyngeal occlusion (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Pre-apnoea EE lumen area (mm²)</td>
<td>30.8</td>
<td>10.2</td>
<td>12.7</td>
<td>18.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Min. lumen area (mm²)</td>
<td>15.1</td>
<td>3.9</td>
<td>10.5</td>
<td>21.4</td>
<td>0</td>
</tr>
<tr>
<td>Min. lumen area (% pre-apnoea EE lumen area)</td>
<td>49%</td>
<td>38%</td>
<td>83%</td>
<td>119%</td>
<td>0</td>
</tr>
<tr>
<td>Time to min. lumen area (s)</td>
<td>4.2</td>
<td>9.6</td>
<td>12.9</td>
<td>11.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Time to min. lumen area (% apnoea duration)</td>
<td>38%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>69%</td>
</tr>
</tbody>
</table>

6.3.3. Pharyngeal Cross-Sectional Area Across the Night During Sleep

A breakdown of pharyngeal cross-sectional area over the respiratory cycle at the start, middle and end of the night is presented for each patient in Figure 6.2. Patient A showed the most dramatic change in pharyngeal cross-sectional area of the 3 patients. The bronchoscope was maintained in a relatively stable position for 3 periods throughout the night, allowing images of the pharyngeal lumen to be measured from near the start of the night (00:59 hrs), middle of the night (01:39 hrs) and end of the night (04:37 hrs). The pharyngeal lumen was most patent at the start of the night, then narrowed in the middle of the night across all phases of respiration, and narrowed further by the end of the night in all phases of respiration. Patient A experienced an increase in neck circumference between the evening and morning, from 34.5 cm to 35.5 cm, respectively.

Patient B also yielded usable bronchoscope images near the start of the night (01:33 hrs), middle of the night (02:20 hrs) and end of the night (03:26 hrs). Pharyngeal cross-sectional area increased slightly during all phases of respiration from the start of the night to the middle of the night. It then decreased in all phases of respiration at the end of the night. Overall, there was not a large decrease in pharyngeal cross-sectional area between the start and end of the
night, however pharyngeal cross-sectional area was decreased at end inspiration/beginning expiration at the end of the night compared to the start of the night. Patient B experienced a decrease in neck circumference between the evening and morning, from 46 cm to 44.5 cm, respectively.

Patient C had the smallest pharyngeal lumen of the 3 patients and yielded usable bronchoscope images from near the start of the night (01:57 hrs) and end of the night (03:30 hrs). Pharyngeal cross-sectional area decreased across all phases of the respiratory cycle between the start and end of the night (Figure 6.2). Patient C experienced a slight increase in neck circumference between the evening and morning, from 37.5 cm to 38.0 cm, respectively.
Figure 6.2: Changes in pharyngeal cross-sectional area related to respiratory phase. Each line represents the mean of 5 breaths sampled during stable breathing during the start, middle and end of night; error bars represent SD. Patient C had no data available from the middle of the night. BI, Beginning Inspiration; PI, Peak Inspiration; EI/BE, End Inspiration/Beginning Expiration; PE, Peak Expiration; EE, End Expiration.

Figure Key: Solid line: start of night; dotted line: middle of night; dashed line: end of night.
6.3.4. Dynamic Pharyngeal Compliance Across the Night During Sleep

Following the analysis of pharyngeal cross-sectional area across the night during sleep, it was apparent that the pharyngeal lumen varied throughout the respiratory cycle, and that pharyngeal lumen had a tendency to decrease between the start and end of the night. Furthermore, it appeared that the normal variation in the cross-sectional area of the pharyngeal lumen within the respiratory cycle was attenuated at the end of the night compared to the start of the night. This phenomenon appeared to occur in all 3 patients but was most apparent in Patient A, where there is a clear “flattening” of the pharyngeal cross-sectional area graph at the end of the night compared to the start and middle of the night (Figure 6.2). Therefore we attempted to quantify this observation by calculating the inspiratory dynamic pharyngeal compliance (I-DC) and the expiratory dynamic pharyngeal compliance (E-DC). Figure 6.3 shows changes in dynamic pharyngeal compliance across the night for Patient A, B and C.

Patient A had a progressive decrease in I-DC between the start of the night (10.8 IQR 4.7, 10.9 mm$^2$/cmH$_2$O), middle of the night (5.1 IQR 4.4, 6.3 mm$^2$/cmH$_2$O), and end of the night (0.4 IQR -0.3, 0.9 mm$^2$/cmH$_2$O). The E-DC was similar at the start of the night (6.2 IQR 4.5, 7.6 mm$^2$/cmH$_2$O) and the middle of the night (5.6 IQR 5.6, 6.4 mm$^2$/cmH$_2$O), but was decreased at the end of night (0.5 IQR 0.4, 0.8 mm$^2$/cmH$_2$O).

Patient B had a progressive decrease in I-DC between the start of the night (4.2 IQR 3.3, 4.9 mm$^2$/cmH$_2$O), middle of the night (2.6 IQR 2.0, 3.4 mm$^2$/cmH$_2$O), and end of the night (1.5 IQR 0.8, 1.6 mm$^2$/cmH$_2$O). The E-DC also progressively decreased from the start of the night (4.8 IQR 4.3, 5.7 mm$^2$/cmH$_2$O), middle of the night (2.9 IQR 1.9, 4.6 mm$^2$/cmH$_2$O), and end of night (1.8 IQR 0.8, 2.3 mm$^2$/cmH$_2$O).

Patient C did not have usable data during the middle of the night therefore only data from the
start and end of the night are reported. In contrast to the other 2 patients, I-DC and E-DC were both low at the start of the night. There was also very little change between the start and end of the night in I-DC (-0.5 IQR -0.7, -0.1 mm$^2$/cmH$_2$O vs. -0.02 IQR -0.2, 0.2 mm$^2$/cmH$_2$O) or E-DC (0.4 IQR -0.1, 0.5 mm$^2$/cmH$_2$O vs. 0.3 IQR -0.3, 0.6 mm$^2$/cmH$_2$O).
Figure 6.3: Inspiratory and expiratory dynamic pharyngeal compliance. Patient C had no data available during the middle of the night. Box and whisker plots represent the median and interquartile range of 5 breaths sampled during stable breathing at the start, middle and end of night.
6.4. Discussion

The main findings of this study were that progressive pharyngeal narrowing or collapse occurred for all CHF-CSA patients and in all but one apnoea. Neck circumference increased and pharyngeal cross-sectional area decreased overnight in 2 out of 3 CHF-CSA patients, and a new method for quantifying the within-breath dynamic compliance of the pharynx showed that dynamic pharyngeal compliance was decreased between the start and end of the night in 2 out of 3 CHF-CSA patients.

6.4.1. Limitations

The main limitation of this study was the small number of participants. The population from which the study sample was drawn had a high prevalence of obesity and opioid abuse which made it difficult to recruit CHF patients with predominant primary CSA. However, the small numbers also allowed a more explorative approach to data analysis, which led to a new method to be conceived for quantifying the dynamic compliance of the pharynx within the respiratory cycle, which may be of use in future studies with further validation.

6.4.2. Pharyngeal Narrowing and Collapse During Central Sleep Apnoea

The pharynx passively narrowed during all central apnoeas in all 3 heart failure patients (except one apnoea where the pharyngeal cross-sectional area appeared to increase) and the pharynx completely occluded during central apnoea at least once in all 3 patients and in 5 out of a total of 11 apnoeas observed in all patients.

Passive pharyngeal collapse during central apnoea was first observed by Badr et al. (1995). These researchers (some of whom were part of the team that I collaborated with on this study) demonstrated that in patients with predominantly central- or mixed- sleep apnoea, the majority of central apnoeas resulted in progressive passive narrowing and occlusion of the
pharynx. This finding led them to suggest that the mechanisms of central and obstructive sleep apnoea are linked. They postulated that one of the causes for pharyngeal collapse during central apnoea could be increased extra-luminal pressure and that passive expiratory narrowing of the pharynx could also be a mechanism for obstructive sleep apnoea. This view was supported by Morrell et al. (1998) when they found that the pharyngeal lumen became progressively narrower at end-expiration in the 4 breaths preceding an obstructive apnoea in patients with OSA. This occurred at positive intra-luminal pressure, suggesting that extra-luminal positive pressure was greater than intra-luminal pressure and was sufficient to cause expiratory pharyngeal narrowing. The findings from the present study support the findings of Badr et al. (1995) and are the first data to measure progressive pharyngeal narrowing during central apnoea in CHF patients. Similarly to Morrell et al. (1998), passive pharyngeal narrowing occurred at positive pressure, suggesting that positive extra-luminal pressure may have caused passive pharyngeal narrowing and/or collapse in the CHF patients of this study.

6.4.3. Pharyngeal Cross-Sectional Area Across the Night During Sleep

Pharyngeal cross-sectional area decreased between the start and end of the night in 2 out of 3 patients and this was reflected in an overnight increase in neck circumference in the same 2 CHF-CSA patients. This is the first study that I am aware of that has attempted to quantify the overnight change in pharyngeal calibre during sleep in any population. In chapter 3, pharyngeal calibre was measured during wake in CHF patients and no difference was found between the evening and morning. The data from the current study suggest that overnight narrowing may occur in some heart failure patients during sleep. Taken together, these data are consistent with research suggesting that neuromuscular tone may compensate for a narrow pharynx during wake, but during sleep this compensation is reduced or absent (Fogel et al., 2005).
6.4.4. Dynamic Pharyngeal Compliance Across the Night During Sleep

Another interesting finding from this study with respect to overnight changes in pharyngeal calibre was that the dynamic behaviour of the pharynx within a respiratory cycle appeared to be altered overnight. All 3 patients had a tendency for the normal variation in pharyngeal calibre over the respiratory cycle to be attenuated at the end of the night. To explore this, a new measure was conceived to quantify the magnitude of the change in pharyngeal calibre during inspiration and expiration which we have called within-breath dynamic pharyngeal compliance. Two out of three patients in this study had a tendency for both I-DC and E-DC to decrease progressively from the start of the night to the end of the night. In the case of Patient B, dynamic pharyngeal compliance decreased between the start of the night and the middle of the night, despite the absolute pharyngeal calibre increasing. This suggests that a fixed measurement alone of pharyngeal calibre may not be sufficient to describe the dynamic behaviour of the pharyngeal lumen during sleep.

A similar pattern of decreased dynamic pharyngeal compliance can be observed in the data of Sankri-Tarbichi et al. (2009). They induced hypocapnic hypopnoea using mechanical ventilation in healthy volunteers and found that expiratory pharyngeal calibre was decreased during hypopnoea. Dynamic pharyngeal compliance was not quantified in their paper, however, a similar pattern of “flattening” of the pharyngeal lumen trace can be observed in their hypopnoeas compared to eupnoeic breaths. In the present study the same pattern was observed to occur between the start and end of the night during eupnoea. Given that neck circumference increased overnight in 2 out of 3 patients, and given that dynamic pharyngeal compliance was measured during eupnoea at the start and end of the night, the present study suggests that dynamic pharyngeal compliance may have been affected by passive mechanical forces acting on the pharyngeal lumen. This observation is consistent with the physiological model proposed by Shepard et al. (1996) whereby extra-luminal fluid may attenuate
inspiratory pharyngeal dilation (see Chapter 1, Figure 1.3).

6.4.5. Implications for the Pathogenesis of Sleep Apnoea in Heart Failure

This study has confirmed that passive pharyngeal narrowing occurs in CHF-CSA patients. Given that passive pharyngeal narrowing has been observed in CSA and OSA patients without heart failure, it is reasonable to suggest that passive pharyngeal narrowing may also contribute to the pathogenesis of SDB in CHF, particularly given the tendency for CHF patients to present with a mixture of central and obstructive respiratory events during a single night (Tkacova et al., 2001) and across several nights (Vazir et al., 2007). The data from this study showing an overnight increase in neck circumference associated with an overnight decrease in pharyngeal calibre during sleep suggests that rostral fluid shift could be a mechanism of increased extra-luminal pressure leading to pharyngeal narrowing and collapse during sleep. However, these data are not supported by the studies in Chapter 3. One possible reason for this could be that measurements of the pharynx were made during wake in Chapter 3, whereas they were made during sleep in this study. Taken together, the data from Chapter 3 and this study suggest that the pharynx may undergo overnight narrowing during sleep in CHF patients, but that this is compensated for during wake, perhaps by increased neuromuscular tone (Fogel et al., 2005, 2003).

The progressive overnight decrease in dynamic pharyngeal compliance in 2 out of 3 patients may have important repercussions for the pathogenesis of OSA in CHF. This supports the theory that rostral fluid shift may attenuate normal pharyngeal dilation during inspiration. A decreased pharyngeal cross-sectional area could increase the risk of pharyngeal occlusion due to negative intra-luminal pressure and/or positive extra-luminal pressure.

In summary, it has been shown that the pharyngeal lumen of CHF-CSA patients is subject to passive narrowing and closure during central apnoea. Furthermore, it has been shown that an
increase in neck circumference is associated with overnight pharyngeal narrowing during sleep; these may also be associated with decreased inspiratory expiratory dynamic pharyngeal compliance. Therefore this study supports the theory that rostral fluid shift may result in increased extra-luminal pressure being exerted on the pharynx during sleep, sufficient to increase the propensity for airway narrowing.
Chapter 7: General Discussion
7.1. Summary of Aims

OSA is prevalent in CHF but the reasons for this are are not clear. CHF patients with OSA are typically older, do not present with daytime somnolence, and have a BMI similar to the general population. This contrasts with OSA patients without CHF who present in clinic as being typically middle-aged, with daytime somnolence and are overweight or obese. A recently proposed mechanism to explain the high prevalence of OSA in CHF is retention of fluid during the day, and rostral fluid shift during the night, increasing extra-luminal pressure on the pharynx. The aim of this thesis was to investigate whether this mechanism contributed to the development of OSA in CHF. The studies in this thesis have also investigated the properties of the pharynx of CHF patients by measuring pharyngeal anatomical dimensions via indirect and direct techniques, and pharyngeal collapsibility during sleep.

7.2. Summary and Discussion of Main Findings

To investigate the role of pharyngeal calibre in the pathophysiology of OSA in CHF, measurements were made non-invasively using acoustic reflection in 14 CHF-OSA patients, 14 CHF-only patients and 15 healthy age-matched controls. Neck circumference and pharyngeal calibre were also measured in the seated and supine posture, in the evening and morning, in order to determine any differential effects of posture change and overnight rostral fluid shift on pharyngeal calibre. The results of this study showed that the pharyngeal calibre of CHF-OSA patients was similar to CHF-only patients and healthy controls. It was also shown that neck circumference increased and pharyngeal calibre decreased in all groups when assuming a supine posture. Finally it was shown that pharyngeal calibre decreased overnight in the healthy controls but not in the CHF-OSA or CHF-only patients. Based on these findings I have argued that rostral fluid shift may be a normal physiological phenomenon, but that it is
not a major mechanism for OSA in CHF. Measurements of pharyngeal calibre were made
during wake in this experiment. Therefore this argument assumes that the overnight
differences observed in the healthy controls would be similar if made during sleep. It is
known that there is a decrease in pharyngeal dilator muscle tone in sleep compared to wake
(Lo et al., 2007; Mezzanotte et al., 1992). It could be argued that a fluid shift-related effect
great enough to be detectable during wake, while pharyngeal dilator muscle tone is higher,
would also be likely to be detectable during sleep, when pharyngeal muscle tone is lower.
This would need to be confirmed by further controlled experiments.

To further investigate the possible mechanisms by which rostral fluid shift may contribute to
OSA in CHF, 13 CHF-OSA, 10 CHF-only and 8 healthy controls underwent measurement of
their pharyngeal collapsibility using the Pcrit technique. Pharyngeal collapsibility was
measured in the early and late part of the night in order to determine whether it was
influenced by fluid shift. As with pharyngeal calibre, it was found that the pharyngeal
collapsibility of CHF-OSA patients was similar to CHF-only patients and healthy controls.
Furthermore, there was no significant change in pharyngeal collapsibility overnight in any

group. These findings combined with the previous findings regarding pharyngeal calibre led
me to speculate that fluid shift does not have a substantial impact on pharyngeal calibre or
collapsibility in the a CHF population.

In order to investigate any impact of age on the pharyngeal calibre, 12 healthy older males
(age >60 years) and 14 healthy younger males (age 18-40 years) underwent measurements of
pharyngeal calibre using AR. The groups were closely matched for BMI, neck circumference,
AHI and ODI. It was found that the pharyngeal calibre of the older males was significantly
greater than that of younger males. This finding is supported by other studies utilising
different methods of pharyngeal measurement, that have also found that older subjects
without SDB have a larger pharyngeal calibre than younger subjects without SDB (see
Chapter 5, Table 5.3). This finding could be explained by two possible phenomena. First, it could be possible that the younger group represented a “normal” range of pharyngeal calibres. Thus the older group may have reflected a survivor effect whereby older people who survive to >60 years old without developing OSA may possess protective phenotypes such as a large pharynx. Alternatively, the older group may have been composed of people with a “normal” range of pharyngeal calibres. Thus the younger group may have contained participants with a smaller airway. This would reflect a phenotype that placed them at greater risk of developing OSA. This notion is illustrated graphically in Figure 7.1.

Figure 7.1: Theoretical diagram illustrating the incidence of SDB as a function of age.

In Figure 7.1 the typical onset of SDB, and particularly OSA, in middle-age is represented by the left-most hatched area and is characterised as an age-related disorder. This is because SDB
is associated with middle-age, but middle-age is not likely to be causative of SDB in itself (Bliwise, 2009). SDB that develops in middle-age may be associated with increased mortality therefore such a cohort may be predicted to decline in numbers as age advances and the number of survivors decrease. However, as age increases, the risk of developing SDB also increases, secondary to increased body mass, increased pharyngeal collapsibility, decreased sleeping pharyngeal muscle tone and decreased pharyngeal muscle fatigue resistance (see General Introduction for a discussion of all these factors). Therefore such cases of SDB could be argued to be age-dependent as the SDB is a consequence of the age-related changes to physiological systems (Bliwise, 2009). Such cases of SDB would have a later onset and are represented by the right-most hatched area in Figure 7.1.

The younger group of participants in Chapter 5 were free of any SDB at the time of being studied and so would not be placed in a group of age-related SDB patients (Figure 7.1, left-most hatched area). However, I would speculate that some may go on to develop age-dependent SDB in older age due to physiological changes associated with age, coupled with a pre-existing smaller airway (Figure 7.1, right-most hatched area). The older group of participants in Chapter 5 were free of any SDB at the time of being studied and so cannot be placed anywhere in the model illustrated in Figure 7.1. I would speculate that this is because they either possessed “normal” pharyngeal dimensions that did not place them at any particular risk of developing OSA in later life; or some may have been particularly resistant to age-dependent SDB due to possessing a larger pharyngeal calibre. In order to test these speculations, a larger study would be required in order to determine the range of pharyngeal calibre's across health and disease in younger and older populations.

Finally, in Chapter 6 the effects of rostral fluid shift on pharyngeal calibre during sleep were assessed by directly visualising the airway of 3 CHF-CSA patients using a fibre-optic bronchoscope. It was found that pharyngeal calibre was reduced during sleep. Additionally, a
novel method for quantifying the within-breath dynamic compliance of the pharynx was developed and was used to demonstrate that the within-breath dynamic pharyngeal compliance is also decreased overnight during sleep in CHF-CSA patients.

7.3. Future Directions

There were a number of novel findings in this thesis that warrant further investigation. The data in Chapter 5 could be used as a basis for a larger study including groups of older and younger females, and older and younger OSA patients. This study would address the effect of ageing per se on pharyngeal calibre in patients with OSA, and also the effect of gender, as the majority of patients studied in this thesis were male.

One of the difficulties in comparing the findings of the studies investigating rostral fluid shift to research in this field, is that previous studies have been uncontrolled observational studies. These studies have firmly established a correlation between rostral fluid shift and various risk factors and markers of OSA. However, in this thesis two studies were presented where a control group of healthy age-matched volunteers displayed similar or greater evidence of fluid shift than CHF patients. I speculated that optimal treatment on diuretics attenuated fluid shift in CHF patients, and so fluid shift may not be a significant mechanism of OSA in such a group of CHF patients. Further investigation of the effect of diuretics and other fluid control therapies would be very useful in evaluating the clinical merits of targeting fluid control therapies at CHF patients with OSA.

Finally, a novel method for measuring within-breath dynamic pharyngeal compliance was conceived in collaboration with our colleagues in Detroit. The preliminary findings presented in Chapter 6 suggest that it may have utility in investigating the effect of extra-luminal pressure on the pharynx, independent of changes in pharyngeal calibre. Before this measure is used further, it should be validated against conventional measures of pharyngeal compliance.
7.4. Conclusion

Overall, the findings from the studies presented in this thesis suggest that the mechanism of OSA in CHF is not a compromised pharyngeal calibre or increased pharyngeal collapsibility; although the possibility cannot be ruled out because changes in pharyngeal calibre were measured during wakefulness, not sleep. As age increases, the risk of developing OSA may also increase; therefore OSA in CHF may reflect the fact that CHF patients are older, and an age-related increase in OSA coincides with an age-related onset of CHF.
Chapter 8: References


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