A pilot study on the stability of the human nasal cycle

Submitted to Cardiff University
for the degree
of Master of Philosophy

Mark Robert Williams
MB ChB MRCS (ENT)

Cardiff School of Biosciences
Cardiff University
Wales, United Kingdom

July 2016

DECLARATION

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

Signed ……(Mark R Williams) Date ……

STATEMENT 1

This thesis is being submitted in partial fulfilment of the requirements for the degree of MPhil

Signed ……(Mark R Williams) Date ……

STATEMENT 2

This thesis is the result of my own independent work/investigation, except where otherwise stated.
Other sources are acknowledged by explicit references. The views expressed are my own.

Signed ……(Mark R Williams) Date ……

STATEMENT 3

I hereby give consent for my thesis, if accepted, to be available online in the University's Open Access repository and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed ……(Mark R Williams) Date ……

STATEMENT 4: PREVIOUSLY APPROVED BAR ON ACCESS

I hereby give consent for my thesis, if accepted, to be available online in the University's Open Access repository and for inter-library loans **after expiry of a bar on access previously approved by the Academic Standards & Quality Committee.**

Signed ……(Mark R Williams) Date ……

Dedication and Acknowledgements

I dedicate this work to my parents Kathleen and Stephen who have always supported me throughout my studies.

My greatest thanks must go to my supervisor Prof. R Eccles, whose expertise, cheery disposition and enthusiasm for research have been an invaluable resource.

I thank my sister Sarah for her artistic help and advice on putting together some of my diagrams.

I thank Ben for your help and advice on equipment, orders and organization.

I thank Susu for your constant cheer, supplies of coffee and help with all the paperwork.

A final thanks to Edyta, Muhammad, Matt and Fiona for your help with the advertisement and recruitment.

“The outcome of any serious research can only be to make two questions grow where only one grew before” – Thorsten Veblen, The Place of Science in Modern Civilisation

Contents

Summary

It is well recognised that nasal airflow (secondary to patency) is not constant and can be influenced factors such as exercise and disease. There are also periodic fluctuations, which occur termed the nasal cycle. The term “classical” nasal cycle has been applied to the periodic and reciprocal changes in nasal airflow and has been defined by Flanagan and Eccles numerically [1].

Nasal airflow data was collected using anterior rhinomanometry for 30 subjects over an eight hour period on two study days at an approximately 1 week interval. Subjects also used the Subjective Ordinal Scale to self assess prior to each set of nasal airflow measurements. All data was analysed using the r-value (correlation coefficient comparing left and right nasal airflow) and the Airflow Distribution Ratio, the Nasal Partitioning Ratio was also used for the comparison of objective and subjective data.

The frequency of a “classical” nasal cycle within the subject group was comparable with that reported by Flanagan and Eccles at the first study day. The nasal cycle was demonstrated to be unstable for most subjects with only 37.5% of the subjects with a “classical” nasal cycle at study day 1 continuing in this group at study day 2. However a tendency towards reciprocity was demonstrated as overall r-values were seen to become more negative from study day 1 to study day 2 this was demonstrated by a correlation coefficient of -0.73 ($p < 0.001$).

The r-value was not found to be useful in conjunction with the Subjective Ordinal Scale as no correlation was found between subjective and objective values. A good correlation was found for the Airflow Distribution Ratio and the Nasal Partitioning Ratio (NPR) since the NPR can be used independently it may be useful as a tool in the subjective assessment of the nasal cycle.

Chapter 1: Introduction

1.1 Normal nasal airflow and factors influencing airflow

Normal nasal airflow

At rest and low levels of exertion inspired and exhaled air passes through the nasal passages. The nose when considered as an organ is responsible for Olfaction, filtration of the air and the provision of humidification and heating of the air flowing through it [2].

The cost of airflow through the nose is the resistance that is applied; this has been estimated to be around 30-50% of the total resistance to airflow during inspiration [2]. There is of course a great degree of variability due to structural and physiological variance, however one study has demonstrated that on average nasal airflow is responsible for over half the work of breathing [3]. There are three main areas of the nose that may be considered as contributing to the resistance to airflow. The nasal vestibule which accounts for around one third, the nasal valve which is the main area of resistance and the lateral nasal wall and structures which contribute little [4].

The nasal valve is the narrowest point of the nasal passage; it is made up of the cartilage at the end of the nasal vestibule and the start of the bony cavum and the erectile tissues of the inferior turbinates and septum [5]. Work by Haight and Cole (1983) [6] has shown the site of greatest resistance to lie at the level of the end of the inferior turbinate in the first few millimetres of the bony cavum, whilst noting that the tip of the inferior turbinate can extend by around five millimetres when engorged [6]. As air enters the narrowing of the nasal valve it accelerates and once it enters the larger cavity of the nose decelerates again disturbing the airstream in a phenomenon called orifice flow [5].

The nasal cavity has a rich arterial blood supply. The nasal septum and inferior turbinates of the nose both contain venous erectile tissue made up of venous sinusoids [4]. The drainage of blood from the venous sinusoids is controlled by longitudinal muscle fibres in distal veins. This allows for shunting of blood through the system as well as pooling of blood and therefore venous congestion [7]. Both the nasal septum and inferior turbinates are components of the nasal valve so filling of these vascular structures will increase the resistance to airflow at the nasal valve. It is worth noting that the venous sinusoids are particularly well developed in these areas to the point where they may be able to obstruct the nasal airway [8].

Control by the autonomic nervous system

The filling of the venous sinusoids is under the control of the autonomic nervous system and predominantly the sympathetic component. Sympathetic activity causes vasoconstriction and drainage of the venous sinusoids. This will be discussed in detail later in section 1.2.

The influence of the autonomic nervous system is traditionally seen as causing an alternating reciprocal pattern of congestion and decongestion of the venous tissues of the nasal cavity referred to as the nasal cycle.

Defining the nasal cycle

The first reported description of the nasal cycle is attributed to Kayser [9] despite the fact that he did not use the term “nasal cycle”. There is some disagreement in the published literature about who first used the term “nasal cycle”, but the earliest reference found on a Pubmed search is that of Stoksted’s 1953 paper “Rhinometric measurements for determination of the nasal cycle” [10]. Using this term Stoksted referenced Kaysers original observations that “the nasal cavities are subject to continuous alternating changes in the lumen and this cycle had no effect on the total nasal passage” [10]. This is clearly an idealised description of what occurs within the nasal

cavity and significant variation from this is seen in reality. Since Kayser's and Stoksted's descriptions the term nasal cycle has been used to describe changes in the nasal tissues which do not conform to this idealised description. In order to differentiate the type of activity Stoksted referred to, the term "classical" nasal cycle is used in this paper to refer to nasal airflow patterns, which resemble Kayser's original description. Some definitions of what can be considered a "classical" nasal cycle are listed in table 1.1. Flanagan and Eccles' [1] description applied quantifiable terms to a definition for a "classical" nasal cycle. The correlation coefficient and Airflow Distribution Ratio will be discussed in detail later in section 1.4. However it is clear that combining the two measures means that nasal airflow patterns fitting these criteria will have equal distribution of airflow between the two sides of the nose and thus fit well with Kayser's original description of the nasal cycle.

Paper	Definition
Stoksted 1952 [11]	"under ideal conditions, uniform nasal septa and uniformly developed turbinates will show symmetrical curves (nasal airflow)"
Hasegawa and Kern 1977 [12]	"Alternating congestion and decongestion of the nasal turbinates sufficient to produce a change in resistance of 20% or more in two consecutive calculations"
Fisher et al 1993[13]	"alternating, bilateral reciprocal rhythm"
Fisher et al 1994 [14]	"Reciprocal and alternating congestion/decongestion"
Fisher et al 1995 [15]	"Alternating reciprocal changes in nasal patency"
Mirza et al 1997 [16]	Alternating reciprocal changes in nasal airflow
Flanagan and Eccles 1997 [1]	Correlation coefficient more negative than -0.6 and Airflow Distribution Ratio greater than 0.7

Table 1.1 – Definitions of a "Classical" nasal cycle

Function of the nasal cycle

The function of the nasal cycle remains an area of discussion [17]. Certain possibilities have been excluded, such as an effect on the humidification of inhaled air, as no relationship between nasal patency and humidification of

nasally inhaled air is seen [18]. It has been suggested that the nasal cycle may allow a side to “rest” whilst the other predominates in function [19] and a possible beneficial effect on olfactory acuity [17]. There is evidence that there is increased plasma production in the decongested nostril, likely related to vasoconstriction of the venous sinusoids. This leakage of plasma fluid rich in immunoglobulins is likely to have an immune function as well as providing a physical flushing mechanism to remove pathogens [20]. An MRI based study has shown that the more patent nostril dehydrates in comparison to the congested nostril, where hydration is maintained in the congested nostril efficient mucociliary clearance can take place [21]. The physiological vasoconstriction and resultant decongestion of a nasal passage which is seen in the nasal cycle is maintained in upper respiratory tract infections to the point where there is only a 30% increase in total nasal resistance seen, so maintenance of the nasal airway in disease may be a key function of the nasal cycle [17]. Studies have shown variation in mucocillary clearance times, with this being slightly increased in the more congested nostril, but it remains uncertain as to whether this is clinically significant [19].

Exercise

There is of course a generalised increase in sympathetic activity with the initiation of exercise [8]. It logically follows that there would be bilateral vasoconstriction within the nasal cavity abolishing the nasal cycle to allow improved airflow and decrease the work of breathing. However this is only likely to be significant in low to moderate exercise before mouth breathing predominates [8]. The vasoconstriction induced by exercise is also able to overcome the congestion caused by exposure to freezing temperatures [22].

A decrease in nasal resistance is seen in proportion to the intensity of exercise with recovery to pre exercise levels taking up to 15 minutes [23]. Exercise has been proven useful as a method of decongesting the nose for assessment of septal abnormalities, in Brom’s 1982 rhinomanometric study it was shown that exercise provided greater decongestion than Oxymetazoline

nasal drops [24]. The effect of exercise is believed to be mediated by the sympathetic nervous system [25].

Posture

Adopting a supine posture has an amplification effect on the nasal cycle, but this is a filling effect related to changes in the Jugular venous pressure and not down to any neural response [8, 26].

Haight and Cole in 1986 [27] showed that in response to adopting a lateral recumbent position for a prolonged period (over 12 minutes) the nasal cycle was reversed with congestion of the nostril on the dependent side and decongestion contra laterally. He theorised that this occurred in response to stimulus from pressure receptors in the thorax and pectoral and pelvic girdles, which can be termed the corporo-nasal reflex and he demonstrated that the response could be eliminated by an intercostal nerve block [27]. This corporo-nasal reflex can of course also be observed during sleep, with changes in dominant nasal airflow triggered by repositioning [28]. However after time the cycle will continue resulting in decongestion of the nostril on the dependent side and congestion contra laterally [29]. In 1970 Rao [30] and in 1985 Davies [31], excluded other explanations for this response such as gravitational diversion of blood by comparing nasal airflow in subjects in a lateral recumbent position to the placement of a crutch under the arm to simulate pressure with comparable results [30] [31]. This gave scientific backing to a technique, which had been practiced in Yoga for hundreds of years [8]. Such effects of pressure stimulus whilst triggering changes in nasal blood flow are also recognised to influence sweating with an ipsilateral inhibition and contralateral increase further emphasising that this is indeed an autonomic response [8].

Sleep

In normal sleep where a recumbent posture is seen, the aforementioned changes to nasal airflow relating to posture are of course seen. Studies of the nasal cycle during sleep using a portable rhinoflowmeter suggest that in addition to the postural changes, the duration of cycle length increases [28, 32] and the amplitude of changes in nasal congestion increase [28] the latter probably remains an effect of posture rather than sleep itself. There also appears to be a tendency for changes in the cycle to occur during REM sleep [32], which may relate to higher levels of sympathetic activation at this time [28]. One study also suggested that the nasal cycle is synchronised with the sleep cycle and changes in the nasal cycle occur after multiples of the sleep cycle have passed [33].

Eating and the Nasal Cycle

Only one study seems to have considered the effect eating may have on the nasal cycle. It is weakened by its method of self-reporting of relative nostril patency for one subject and the observation of nasal misting of a mirror for a second. Funk and Clarke in 1980 [34] reported that right nostril predominance for one subject and left nostril predominance for a second during the main meals of breakfast and lunch which both fell on a regular schedule, based on observations over a month [34]. Regular cyclic patterns are expected in observations of the nasal cycle and therefore may occur independently of eating, with a possibility that sleeping patterns may apply a coordinating influence [33].

Temperature and nasal airflow

Exposure to the cold particularly where an acute temperature change occurs can cause an overall increase in nasal resistance to airflow, due to increased

venous congestion [35]. For instance exposure to a cold environment (15 degrees centigrade) during the summer is more likely to have a greater effect on nasal resistance than cold exposure in the winter months [36]. Where an increased temperature is concerned studies on the effects of temperature on nasal resistance in 50 healthy subjects have concluded that environmental changes in the tropics between 18-22°C and 30-33°C have no significant effect on nasal resistance [37].

Humidity and nasal airflow

Increased humidity may increase nasal cavity volume and therefore airflow, as suggested by an acoustic rhinometry study using nasal nebulisers to simulate humidity changes [38]. However a smaller study using humid room temperature air does not confirm these findings [39].

Disease and nasal airflow

Both structural and mucosal disease can affect nasal airflow detrimentally. The two main structural problems are nasal septal deviation and alar collapse due to weakened lateral cartilages. Both occur frequently, secondary to trauma.

Significant nasal septal deviation is difficult to define and there is a wide range in the reported prevalence within the literature (1-80%) [40]. The location of a septal deviation is key to its impact on airflow and it has long been recognised that the nasal valve region is the most significant area [6]. A significant septal deviation posterior to the nasal valve may have little effect on nasal airway resistance, whereas a septal deviation in the nasal valve region may more than double resistance [41]. The nasal cycle has been observed to be present in subjects with anterior septal deviations, in a similar proportion to a control population, when measured by acoustic rhinometery. It also appeared that there was a greater amplitude of change in minimum

cross-sectional area in the nostril from which the septum deviated away from [42].

Mucosal disease can occur acutely e.g. upper respiratory tract infection (URTI) or chronically e.g. allergic rhinitis. Both result in the release of a mix of inflammatory mediators and the predominating result is vasodilation and nasal congestion. For allergic rhinitis histamine is the main mediator, whereas bradykinin is the main mediator for infectious rhinitis [8].

Rhinitis of any form will tend to result in a symmetrical vasodilation, but this will be superimposed on any asymmetry already present, be that structural or physiological. Rhinitis has little impact on sympathetic vasoconstriction and therefore little impact on nasal airflow will be seen where there are high levels of sympathetic activity. This means that sympathomimetic drugs such as decongestants or the decongestive effects of exercise remain at least in part. Where the inflammatory process is unopposed by sympathetic activity, high levels of congestion and resistance to nasal airflow can be expected [8]. Hence subjective nasal obstruction is frequently reported in URTI [43].

Drugs and their effect on nasal airflow

Alcohol

Alcohol is known to significantly increase upper airway resistance in both the pharynx and nasal cavity and therefore consumption is linked to exacerbation of obstructive sleep apnoea [44]. Alcohol is known to cause peripheral vasodilation and have central depressant action, which may affect the sympathetic nervous system, both factors are thought to be involved in the observed increase in nasal resistance seen with alcohol [45].

Medications

Many different medications can influence nasal airflow via effects on the vascular smooth muscle or the sympathetic nervous system [8].

Sympathomimetics and sympatholytics

Ephedrine, pseudoephedrine, phenylpropanolamine and phenylephrine all have direct and indirect sympathetic actions causing release of neurotransmitters and working as alpha and beta-receptor agonists. Their side effects and duration of action vary, but the mechanism by which they affect airflow is similar and will override the nasal cycle for their duration of action [46]. Oxymetazoline and xylometazoline are used topically and have predominantly alpha2-agonist activity, with oxymetazoline having weak partial alpha1-agonist activity [47]. In prolonged use topical decongestants can lead to rhinitis medicamentosa where rebound congestion is seen and a cycle of chronic use may develop [46]. Decongestion caused by these medications is equivalent to that which occurs physiologically e.g with exercise [48].

Menthol

Menthol does not cause any objective decongestive effect only a subjective sensation of decongestion, in fact inhaled menthol may increase nasal congestion [46].

Anti-histamines

H1 receptor antagonists do not appear to have any positive effect on the relief of nasal congestion, Chlorpheniramine maleate has been shown to have a small effect on nasal airway resistance after histamine challenge, whilst a H2 receptor antagonist Ranitidine was not shown to have any significant effect on nasal airway resistance. Combined use of H1 and H2

receptor antagonists at a relatively high dose did however produce a significant reduction in nasal airway resistance [49].

Corticosteroids

Topical corticosteroids when used consistently are effective at improving nasal airflow following allergen provocation. This has been proven with ciclesonide where anterior rhinomanometry measurements showed improvement at day 5 of use [50].

Anti-hypertensives

ACE-Inhibitors are known to infrequently cause symptomatic nasal congestion as a side effect but exact prevalence is not known [51] and objective measurement is lacking. Beta-blockers may also cause nasal congestion with associated “Rhinitis” as a side effect being reported [52].

Effects of hormones on nasal airflow

The main hormone to affect the nasal mucosa is adrenaline and its analogues. However both male and female sex hormones are seen to affect the nasal mucosa with increased levels of nasal secretion and congestion seen in puberty, pregnancy and with menstruation [8]. Early oestrogen rich oral contraceptive pills were seen to cause nasal congestion and squamous metaplasia was seen in the nasal mucosa [53].

Menstrual cycle

Histological evidence shows that there are no structural changes that occur in the nasal mucosa during the menstrual cycle that may be caused by changes in levels of oestrogen and progesterone [54]. Later cytological evidence has shown higher levels of young epithelial cells in the nasal cavity during menstruation, but whether this relates to any increase in physiological

congestion is uncertain [55]. Work by Ellegard and Karlsson (1994) [53] using home measured nasal peak inspiratory flow showed higher levels of resistance during the menstrual phase, when oestrogen levels would be at their lowest [53]. However detailed multi-method work by Philpott et al (2004) [56] showed nasal congestion mid cycle, consistent with a change caused by raised oestrogen, this was accompanied by an increased mucocilary clearance time [56]. Haeggstrom et al's study (2000) [57] using acoustic rhinometry and rhinostereometry demonstrated that the nasal mucosa was more sensitive to the effects of histamine during the oestrogen peak levels of ovulation [57].

Pregnancy

Subjective reporting of nasal obstruction is frequent in pregnancy. Histological studies have demonstrated differences in the ultrastructure of the nasal mucosa of both asymptomatic and symptomatic pregnant females. Asymptomatic individuals were found to have glandular hyperactivity, increased phagocytic activity, and an increased amount of acid mucopolysaccharides with symptomatic individuals also showing features of allergic rhinitis [58]. Ellegard and Karlsson's 1999 [59] study did not show any objective decrease in nasal airflow in pregnancy, only a subjective increase in nasal obstruction associated with "pregnancy rhinitis" [59]. Later work by Philpott et al (2004) [60] showed a decrease in nasal resistance, as assessed by anterior rhinomanometry, as pregnancy progressed but failed to show any significant changes with peak inspiratory nasal flow rate or acoustic rhinometry. This suggests that there is not a simple positive effect of congestion by oestrogen and progesterone on the nasal mucosa as levels of both rise as pregnancy progresses. Inflammatory mediators and other hormones such as placental growth hormone may also be involved [60].

1.2 Autonomic control of the nasal mucosa

The autonomic nervous system is responsible for homeostasis within the core of the body and allows adaptation to environmental stressors [61]. It is divided into the sympathetic and parasympathetic components. The sympathetic component's functions are mostly focused on the flight and fight response, where it acts upon blood vessels it generally causes vasoconstriction (with the exception of cardiac vessels) and in most glands it acts to decrease secretion (with the exception of sweat glands). In its component nerves preganglionic axons release acetylcholine at their synapses, and noradrenaline is the transmitter released by postganglionic axons (except in sweat glands, where it is acetylcholine). The parasympathetic systems functions include secretory functions as well as those contributing to feeding and sexual function. Acetylcholine is the main neurotransmitter for parasympathetic synapses [62]. The autonomic nervous system generally acts with symmetrical effects on paired organs despite anatomical division into the left and right, the bilateral constriction of the pupil in response to a stimulus of light in one eye is a physiological example of this [63]. Within the human nasal mucosa sympathetic innervation is seen for arteries, veins and arteriovenous shunts [64]. Sympathetic stimulation of the nasal mucosa causes a constriction of resistance vessels and a redistribution of blood flow away from shunt vessels, which feed the venous sinusoids [65]. Parasympathetic stimulation has a mainly secretory function within the nasal mucosa.

Sympathetic control

Sympathetic nerves supplying the soft tissues of the nasal airways have a vasoconstrictive effect as in other areas of the body. Such an effect allows drainage of the venous sinuses located within the turbinates and on the nasal septum, which increases nasal patency and airflow. Often this occurs in an alternating regular pattern between the two nasal cavities known as the nasal cycle. Noradrenaline is the primary neurotransmitter involved in sympathetic control, which acts upon alpha-adrenoceptors along with a lesser input from

neuropeptide Y, both have a strong vasoconstrictive effect [66]. The nasal mucosa is very sensitive to this adrenergic effect and has been shown to be five times as sensitive to adrenaline compared to the cardiac tissues [67]. This effect of sympathomimetic substances is frequently used by the ENT surgeon to facilitate examination and surgical access within the nasal cavity and is utilised in the pharmacological relief of nasal congestion [68]. Work by Malm in 1975 [69] evidenced that both resistance vessels (pre and post capillary vessels determining regional blood flow) and capacitance vessels (encompassing the whole venous component) are both constricted by adrenaline or noradrenaline [69]. Anggard and Densert's 1974 [70] functional and histological study showed that the majority of sympathetic neurons were acting on blood vessels with a sparse innervation of the acini of the mucosal glands [70].

The sympathetic innervation to the nasal mucosa is supplied from the cervical plexus via branches of the trigeminal nerve and the nerve of the pterygoid canal (the Vidian nerve); these are innervated by the superior cervical ganglion, which takes preganglionic fibres from the thoracolumbar region of the spinal cord, specifically the first and second thoracic segments in the lateral horn cells [2] [8].

Animal experimental models have been the main basis for establishing the innervating nerves and areas of control relevant to the venous sinuses of the nasal cavity. In 1913 Tschalussow stimulated the cervical sympathetic nerve in dogs eliciting a vasoconstrictive response within the nasal cavity. Sternberg expanded on this in 1915 by sectioning the vagosympathetic trunk to show a vasodilatory response. Together implying that alternation of sympathetic drive could cause expansion and relaxation of the venous nasal tissues to alter airflow [8]. Stoksted in 1953 [71] demonstrated that inhibition of the sympathetic system through stellate ganglion blockade in humans resulted in a predominantly ipsilateral nasal congestion [71]. These findings were replicated by Malcomson in 1959 with the addition of demonstrating the Vidian nerve as a pathway by its excision [67]. Malm in 1973 [72] proved that although the Vidian nerve provided a significant route for sympathetic fibres

that a second pathway exists by sectioning the nerve in cats and stimulating the cervical sympathetic chain. The same study also demonstrated crossover of fibres into the contralateral nostril where an instantaneous response was seen to sympathetic stimulation [72]. In 1974 Eccles and Wilson [73] confirmed the Vidian nerve as part of the pathway by stimulation in a cat model, where a relatively high voltage showed vasoconstriction [73]. Wilson and Yates in 1975 [74] confirmed earlier findings that there is a small amount of crossover by sympathetic fibres to the contralateral nasal cavity. They observed limited vasoconstriction in the contralateral nostril on sympathetic stimulation [74]. Anatomical variations in this crossover could potentially explain deviation from the “classical” nasal cycle.

Later experimental models on cats have shown that both the hypothalamus and brainstem have influence over these sympathetic fibres. Where stimulation of the hypothalamus causes a bilateral and profound vasoconstrictor response in the nasal mucosa, without any reciprocal changes [75]. Stimulation of the brainstem resulted in a transient ipsilateral vasodilation during active stimulation followed by vasoconstriction with contralateral vasodilation [76]. This suggests that central control for the nasal cycle is most likely to originate in the brainstem, where oscillations may occur to manifest as a rhythmic cycle [77].

Parasympathetic control

Parasympathetic innervation plays a different role within the nasal cavity; it is mainly responsible for stimulation of nasal secretion.

Parasympathetic innervation originates from the superior salivatory nuclei of the brainstem. Fibres are joined with those of the facial nerve, travelling via the geniculate ganglion to join post ganglionic sympathetic fibres in the superior cervical ganglion, from here they are relayed to the greater superficial petrosal nerve and the nerve of the pterygoid canal (Vidian nerve) to the sphenopalatine ganglion where they synapse and are distributed within

the nasal cavity [2] [8]. Stimulation of both the brainstem and Vidian nerve in cats is shown to produce a watery nasal secretion [78]. It is the general consensus that parasympathetic fibres contribute little if at all to the control of nasal venous sinuses and mainly influence glandular blood flow and secretions [68]. However some animal studies have shown a small vasodilator effect [67, 79], Eccles and Wilson in 1974 [73] showed that low voltage stimulation of the Vidian nerve had a vasodilator effect, suspected to be due to stimulation of the parasympathetic component [73]. Anggard in 1974 [80] isolated the parasympathetic component of the Vidian nerve by prior superior cervical ganglionectomy to demonstrate production of nasal secretions with a small increase in blood flow through the nasal tissues but concluded it was not large enough to significantly affect nasal patency [80].

1.3 Control of the nasal cycle

Stoksted in 1953 was the first to theorise about an area of central control for the nasal cycle, he pointed towards the hypothalamus as the originating centre of control [8], whilst the hypothalamus certainly can influence the nasal mucosa it is thought to be an area of the brainstem between the level of the trigeminal motor nucleus to the level of the genu of the facial nerve, which holds the key to control of the nasal cycle [76].

Using the cat as an animal model Eccles and Lee in 1981 [81] expanded on Malcomson's earlier 1959 experiment to show the influence of the hypothalamus on the nasal mucosa with exclusion of the influence of catecholamines by bilateral adrenalectomy. Their results showed that electrical stimulation of the hypothalamus, on either side, lead to bilateral vasoconstriction within the nasal mucosa with the addition of an effect on the nictitating membrane. This suggests a generalised sympathetic output from the hypothalamus not consistent with the reciprocal changes seen in the nasal mucosa of the nasal cycle [81]. Later work on the cat model by Bamford and Eccles (1982) [76] with unilateral stimulation of the brainstem, between the level of the trigeminal motor nucleus to the level of the genu of the facial nerve was however more conclusive. It was found that an electrical stimulus in the brainstem produced ipsilateral vasoconstriction with a reciprocal contralateral vasodilation, which could be reversed by stimulating the opposite side of the brainstem. A conclusion was therefore drawn that the area of control for the nasal cycle is likely to lie in these areas [76]. Work using an Electroencephalogram (EEG) by Werntz in 1983 [82] suggested a link to predominance in cerebral hemispheric activity. A close correlation was seen between predominant nasal airflow and levels of contralateral cerebral hemispheric activity, as has been seen with other autonomic functions [82]. How this may link to the brainstem and its sympathetic outflow to the nasal mucosa remains uncertain. There remains little evidence for any peripheral or nasal input into the nasal cycle, however Eccles in 1978 [83] observed in a porcine model that unilateral section of the cervical sympathetic nerve resulted in a bilateral loss of cyclical activity within the nasal cavity,

suggesting some sensory input from both nostrils may be required [83], figure 1.3 summarises our current knowledge of the control of the nasal cycle.

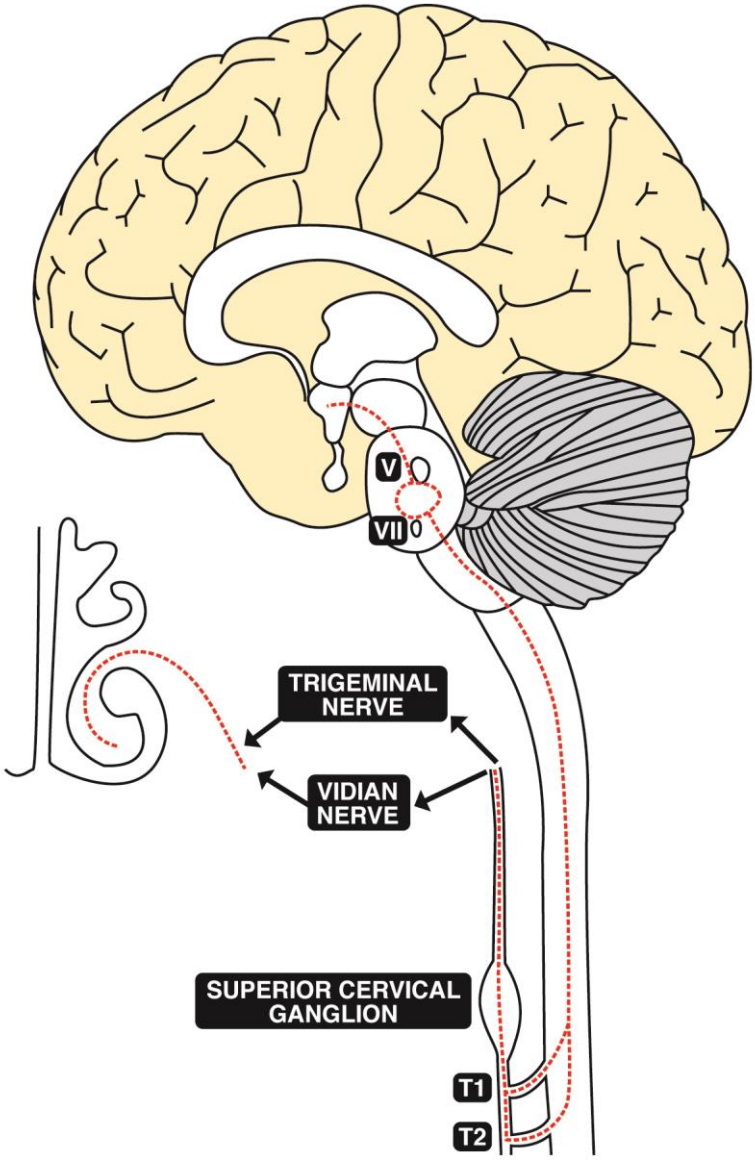


Figure 1.3 – A diagram to show our current knowledge of the control of the nasal cycle. Both the hypothalamus and an area of the brainstem (between the trigeminal motor nucleus and the level of first genu of the facial nerve) influence the nasal cycle. The input of sympathetic nerves to the nasal mucosa is then derived from the trigeminal and vidian nerves via the superior cervical ganglion.

Because of the obvious ethical issues involved there have been few human experimental studies in this area apart from those, which are non invasive. A study by Haight and Cole in 1983 [84] failed to show any change in the contralateral side of the nose in response to changes brought about by histamine, Xylometazoline or physical obstruction of the nostril, which suggests there does not appear to be any afferent input from the nasal cavity that influences the central control of the nasal cycle [84]. There is however afferent input to the nasal mucosa received from postural factors, which have been discussed earlier in section 1.2. The presence of a regular cycle involving reciprocal changes as classically seen in the nasal cycle, implies that there is an area of control. The lack of an afferent input to the cycle in the region of the nasal cavity points towards control within the central nervous system.

There are however more observational studies which have endeavoured to add to our knowledge. Ishii et al in 1993 [85] observed the retention of the nasal cycle in 4 out of 5 patients with Horner's syndrome, where it would be expected to be lost with interruption of the sympathetic drive [85]. This could possibly be explained by the small crossover of sympathetic fibres between the two nasal cavities. Saroha et al in 2003 [86] looked at patients following cervical spinal cord trauma, using acoustic rhinometry to monitor nasal patency and concluded that trauma may initially disrupt the cervical sympathetic nerves supplying the nasal cavities and therefore the nasal cycle, with recovery of the cycle seen around 1-4 years later [86]. Fisher et al in 1994 [14] observed using acoustic rhinometry the presence of the nasal cycle in patients who had undergone laryngectomy, although this was seen less frequently than in control patients, finding the presence of a "classical" cycle in 25% of patients. This proved that a lack of airflow through the nose did not result in loss of the cycle [14]. Galioto et al's 1991 [87] small study on patients with Kallmann's syndrome (a disorder of development of the hypothalamus, resulting in hypogonadotrophic hypogonadism) found an absence of the nasal cycle in such patients compared to a control group (non-Kallmann hypogonadotrophic hypogonadism) suggesting a circadian

rhythm maintained by the hypothalamus may influence the control centre of the nasal cycle [87].

1.4 Methods used in the study of nasal airflow and patency

Active Rhinomanometry

Active rhinomanometry is a functional test, measuring nasal airflow and resistance. Air moving through the nose, does so down a pressure gradient, as is the case with the movement of all fluids. Rhinomanometry measures the difference in pressure between anterior and posterior parts of the nose during inspiration and expiration as well as the airflow through the nose. The key formula used in rhinomanometry is; Nasal resistance = pressure difference across the nose / nasal airflow [88] Rhinomanometry can either be performed by an anterior or posterior technique. The first person to demonstrate the technique of rhinomanometry was Courtade in 1903 [89].

Anterior Rhinomanometry

In anterior rhinomanometry a test nostril remains patent, whilst the non-test nostril is occluded usually with surgical tape through which a nasal pressure hose is applied (2mm internal diameter). As the nostril is otherwise sealed this measures the pressure in the posterior nasopharanx, whilst air flows freely through the test nostril, airflow is measured by a flowhead through a facemask. This is illustrated in the figure 1.41. Issues with anterior rhinomanometry may arise due to air leaks around the surgical tape for the occluded nostril, air leaks around the face mask, due to a septal perforation or due complete occlusion of one nostril [88].

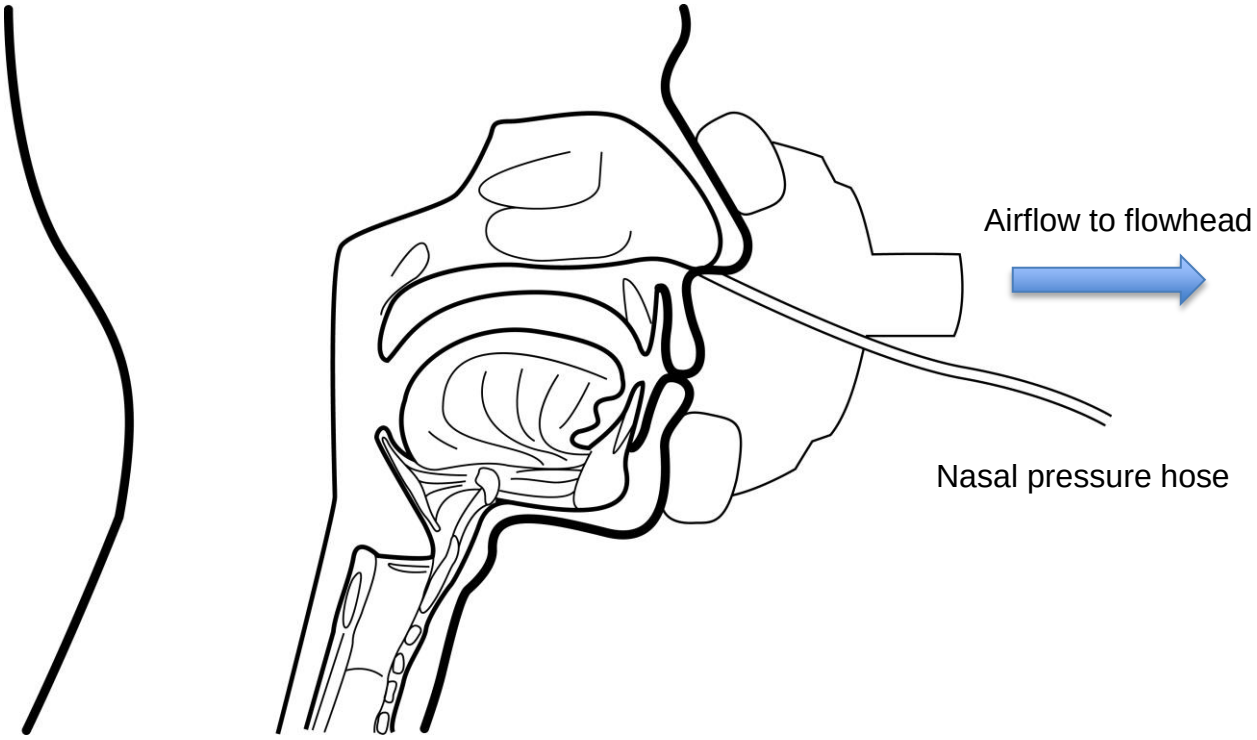


Figure 1.41 – A diagram showing the set up for anterior rhinomanometry

Posterior Rhinomanometry

Posterior rhinomanometry measures total nasal airflow and resistance, but can be adapted for single nostril measurements by occluding a nostril with surgical tape. In posterior rhinomanometry a large bore cannula (3mm internal diameter) is inserted into the mouth and the lips sealed around it, to allow the pressure within the posterior nasopharanx to be measured. This is illustrated in the figure 1.42. Training is required to keep the tongue and soft palate from blocking airflow and around 10% of test subjects are unable to manage this. Because of the path of airflow any constriction added by the soft palate or adenoidal tissue will raise the measured resistance, which may be an important consideration when choosing an experimental technique [88].

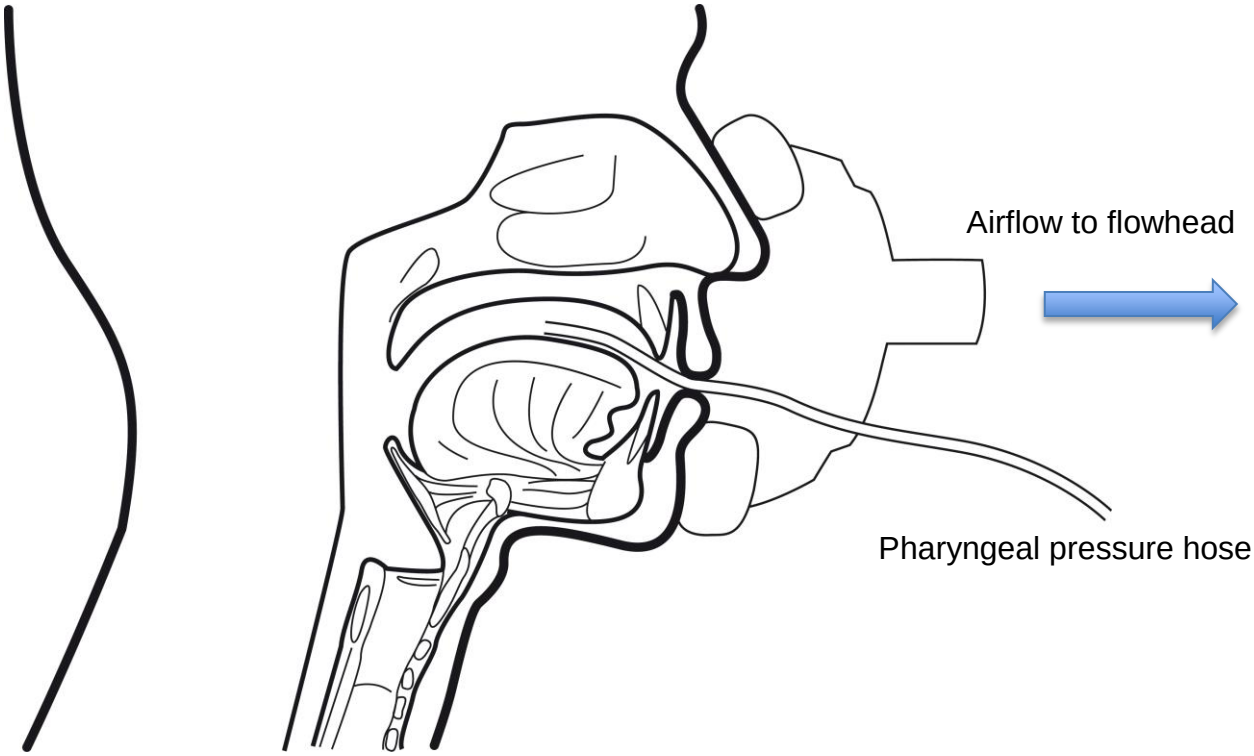


Figure 1.42 – A diagram showing the set up for posterior rhinomanometry

Rhinospirometry

Rhinospirometry is purely a measure of expired nasal airflow, with no pressure measurements recorded. It has been performed using a spirometer adapted to the purpose by the use of a nasal piece [90] and with custom made equipment where simultaneous measurements of airflow through both nostrils are taken [91]. Airflow data are usually presented as a Nasal partitioning ratio using the formula vol L – vol R / vol L + vol R (volumes of expired air), the ratio has a range of +1 (complete right sided obstruction) to -1 (complete left sided obstruction) [90].

Acoustic Rhinometry

Acoustic rhinometry uses the reflection of sound waves within the nasal cavity to calculate the cross sectional area at any given point. As such it can be used to assess the relative patency of the two nasal cavities, be that as a pre-operative tool or for physiological studies of the nasal cycle [92]. Strictly

speaking it is an anatomical rather than a functional measurement as there is no active recording of nasal airflow [88].

Long-term rhinoflowmetry

Long-term rhinoflowmetry is a relatively new technique, with only three papers published detailing its use [28, 93, 94]. The system takes the form of a wearable data collection unit with attached nasal speculae adapted to measure relative airflows. It has the advantage of continuous data capture, so short lived changes are not missed and it can also be worn during sleep, whereas with rhinomanometry and other methods this would not be possible [28]. Little critique is as yet available, but possible issues would include the dislodging of equipment during movement (particularly sleep) and error introduced into readings due to the lack of a sealed system.

The hygrometric method (mirror technique)

Zwaardemaker was the first in 1889 to measure nasal airflow using a mirror, by observing the size of resultant condensation spots [68], a technique still used as a simple and quick assessment tool in the ENT clinic today. This only provides a relative measure of airflow as it is clearly difficult to quantify precisely [95]. It may be made more precise by the use of specially designed polished metal plate, with concentric semi-circles at 1cm distance to aid in the estimation of misting [89]. The area of elliptical misting patterns produced can be calculated using the formula area = (π x width x length)/4 [15]. When compared to acoustic rhinometry there is only a 47% agreement between the two methods [15].

Subjective Self Assessement

Visual Analogue Scale (VAS)

A visual analogue scale is a commonly used tool for patient self assessment in many situations. In this case it is adapted as a means for subjects to indicate relative airflow between two nostrils. It is printed as a 100mm scale and has been used to aid assessment of septal deviation [96] and in the assessment of nasal airflow. Such scales can either be used to rate the patency of each nostril individually [97] or to indicate to which side nasal airflow predominates as shown in figure 1.43 from Boyce and Eccles 2006 [96].

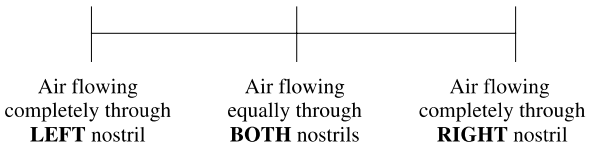


Figure 1.43 – The visual analogue scale for assessment of relative nasal airflow from Boyce Eccles 2006 [96]

Subjective ordinal scale for asymmetry of airflow

The Subjective ordinal scale is a self assessment tool for nasal patency, whereby the subject assigns a numerical value for how freely they feel air flows through each nostril. It was created by Boyce and Eccles in 2006, A copy of the scale taken from their 2006 paper is presented in figure 1.44. The scale has a high sensitivity of 81% and specificity of 60% for detecting an abnormal Nasal Partitioning Ratio [96].

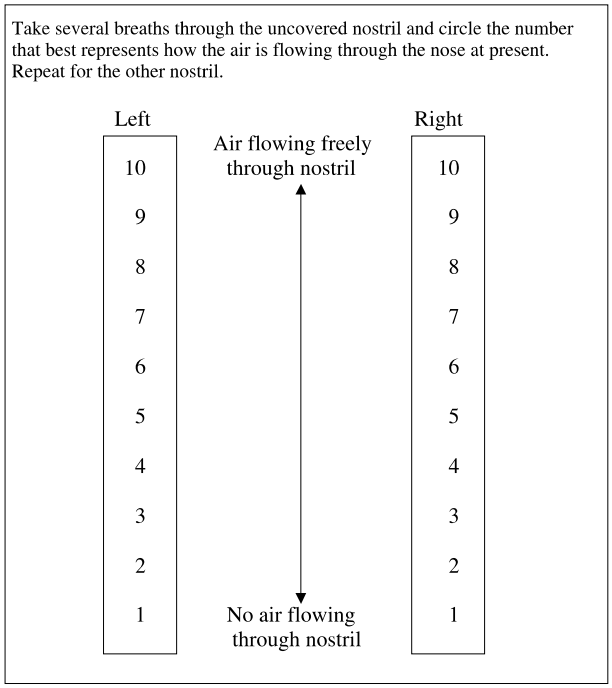


Figure 1.44 - The Subjective ordinal scale for assessment of nasal patency from Boyce and Eccles 2006 [96]

Qualitative subjective assessment of nostril dominance

Funk and Clarke in 1980 [34] found that subjective assessments of nostril dominance i.e. self assessment of which nostril felt more patent, were concordant with rhinomanometric assessment in 114 out of 123 measurements (93%), however they were not able to use this to demonstrate a “classical” nasal cycle [34].

Measurements of asymmetry and reciprocity

Nasal Partitioning Ratio

The nasal partitioning ratio (NPR) represents relative airflow between the left and right nasal passages. Hanif first described this measure in 2001 [90]. A value of -1 indicates complete obstruction of the left and a value of +1 indicates complete obstruction of the right [98]. The NPR can be calculated using rhinospirometery or rhinomanometry and is comparable for both [90]. A

weakness of the NPR is that in representing asymmetry of airflow it does not represent any obstruction that is shared in both nostrils, as may be seen with an S-shaped nasal septum [99].

The nasal partitioning ratio can be calculated using the formula:

NPR = Left vol - Right vol / Right vol + Left vol

Correlation coefficient

The correlation coefficient represents the correlation of the two airflows of the left and right nasal passages, describing the relationship of their changes, with a value r. The value ranges from -1 to +1, where -1 represents a strict reciprocal relationship and +1 represents changes in airflow that are strictly in phase [1]. A value of 0 indicates that there is no linear relationship within the data. For normally distributed data, the correlation coefficient is best calculated using Pearson's method, for non-parametric data Spearman's rank correlation can be used. The significance of an r value can be demonstrated with hypothesis testing. A simple way of doing this is to look at the two-tailed P value, a value of less than 0.05 is commonly used to demonstrate statistical significance. A table has been reproduced (table 1.41 from Altman 1991 [100]) to provide relevant examples, where the r exceeds the tabulated value for the relevant sample size, the Two-tailed probability (P) is less than the value for the relevant column, which gives a statistical measure of the significance of r [100]. So for a sample size of 8 sets of data an r value over 0.7067 could be said to represent significant reprocity as its two-tailed probability will be less than 0.05.

Sample size	Two-tailed probability (P)	
	P<0.05	P<0.01
6	0.8114	0.9172
7	0.7545	0.8745
8	0.7067	0.8343
9	0.6664	0.7977

Table 1.41 – Showing the correlation coefficient required to achieve statistical significance in different sample sizes - reproduced from Altman 1991 [100]

Airflow distribution ratio

The airflow distribution ratio represents the distribution of airflow between the left and right nasal passages over a fixed period of time. It is calculated as a percentage of the total volume of nasal airflow (formula below). It is recorded as a value of 0 to 1, where 1 indicates equal airflow in both nostrils and 0 would indicate complete obstruction of one nostril, the value itself does not indicate which nostril has the greater amount of airflow [1].

ADR = (airflow A / total airflow) / (airflow B / total airflow)

Where A is the lower value of airflow

Combination of correlation coefficient and ADR in graph

The combination of a correlation coefficient and airflow distribution ratio can be used to create a numerical assessment of the classical aspects of the nasal cycle. For a group of cycles this can be displayed in scatter graph form, with sections to indicate which cycles fulfil set criteria. An example of this from Flanagan and Eccles 1997 [1] is shown in figure 1.45. In this case nasal cycles that have a high ADR and highly negative r value are highlighted as being “classical” in nature (marked out by the box in the lower right corner). The distribution of other cycles not fitting these criteria is also shown [1].

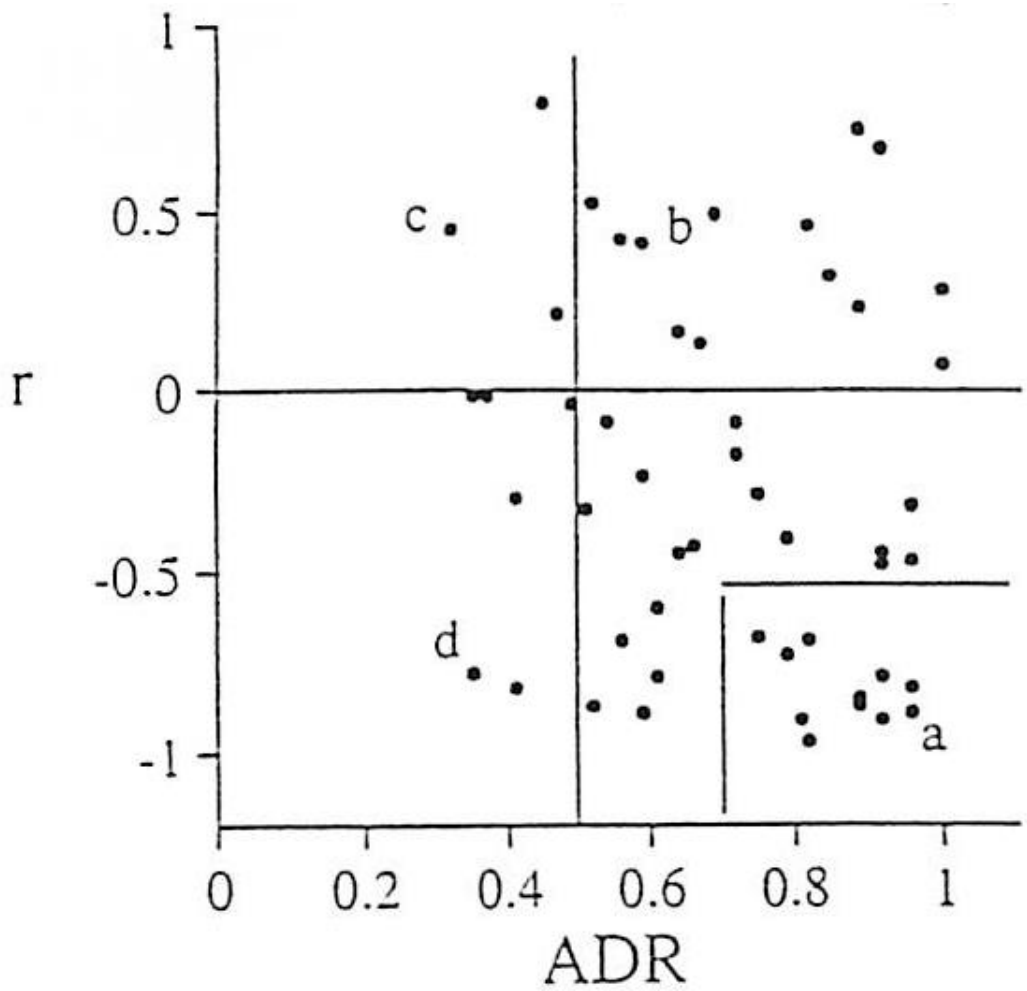


Figure 1.45 – A graph from Flanagan and Eccles 1997 [1] showing the distribution of r and ADR values for his subjects, those fitting the “classical” criteria are marked out separately in the bottom right corner

1.5 Studies on the nasal cycle – a description

Establishing the presence and frequency of the nasal cycle

The discovery of the nasal cycle through a physiological study is attributed to Kayser in 1895, although he did not put the name “nasal cycle” to his observations [9], Stoksted in 1953 appears to be the first to use the term “nasal cycle”[10]. Kayser’s study involved timing the flow of air through the nasal passages into a set of bellows controlled by a fixed weight. He noted that there was variation in the rate of airflow over time and that there appeared to be a pattern to this. He correctly attributed these observations to changes in blood volume within the nasal tissues[9]. Following on from Kayser’s work others sought to confirm his findings and establish the frequency of the nasal cycle’s occurrence within the normal population.

Heetderks in 1927 [101] performed visual observations of the nasal turbinate mucosa at 10 minute intervals over 2 hours, in 60 subjects across a range of ages. Heetderks observed fluctuation in the size of the turbinates in all observed subjects and classified 80% as being cyclical and 20% as non-cyclical i.e without reciprocal changes, the length of the cycle varying between 50 minutes to 4 hours [101]. Unfortunately there was little to quantify Heetderks observations, with no reported quantifiable measurements beyond the time periods described in his paper.

Beickert in 1951 [102] studied the nasal cycle using bulb shaped probes to measure the nasal cavity volume directly at 30 minute intervals. He also performed stimulation of the nasal cavity through histamine application and unilateral stellate ganglion block. Beickert concluded that there was rhythmical oscillation of the vascular innervation with compensatory contralaterality. He demonstrated that blockade of the stellate ganglion had an effect of vasoconstriction on the nasal cavity and proposed that this implicated a central origin for the control of the nasal cycle [102].

Stoksted's 1953 study [71] is unique in its level of intervention on human subjects. Stoksted applied a stellate ganglion block and studied the effects of this on the nasal cycle using a rhinomanometric technique. He observed a significant increase in ipsilateral nasal resistance after application of the stellate ganglion block, as well as a much smaller contralateral increase in nasal resistance simultaneously. His observations show us that blockade of the sympathetic input causes an increase in nasal tissue volume and therefore nasal resistance. They also suggest a small crossover of sympathetic fibres to the contralateral side within the nasal cavity [71].

Hasegawa in 1977 [12] used a rhinomanometric technique to look at a group of 50 subjects looking for an alternating congestion and decongestion of the nasal turbinates sufficient to produce a change in resistance of 20% or more in two consecutive calculations and established a frequency of 72% within the subject group [12].

Mirza's 1997 study [16] using liquid crystal thermography exhalation monitor to measure relative airflow between the two nostrils demonstrated a lower frequency of the nasal cycle in older subjects, compared to younger subjects, using the definition of an alternating reciprocal pattern [16].

Flanagan and Eccles in 1997 [1] used rhinomanometry to observe nasal airflow and a numerical definition to establish a frequency for the nasal cycle of 21% in a normal population [1]. This study will be discussed in more detail later in this section.

Abolmaali et al in 2013 [103] looked at a group of 28 subjects over periods of up to 14 hours using MRI imaging at 30 minute intervals. They were able to demonstrate detectable changes in mucosal thickness and nasal airway volume. Using a definition of inverse correlation between the left and right nasal cavity they described a frequency of 50% for the presence of the nasal cycle in the subject group [103].

Studies of the nasal cycle in pathological states

Stoksted in 1952 [11] performed a small study on 8 subjects using an early form of rhinomanometry based on work by Heetderks. Stoksted looked at subjects he considered healthy as well as those with rhinitis and nasal septal deviation. With small numbers of subjects he concluded that subjects with nasal septal deviation were likely to have asymmetrical nasal airflow patterns. He also found the absence of a regular cycle in a subject with vasomotor rhinitis and minimal activity in a subject with atrophic rhinitis [11]. These being observations of single subjects it is not satisfactory to draw any conclusions from this study in regards to rhinitis and the nasal cycle.

Ishii et al in 1993 [85] looked at subjects with autonomic disturbance, including 20 with a facial palsy, to represent loss of parasympathetic function and 5 with Horner's syndrome to represent loss of sympathetic function. Nasal airflow was recorded by the use of anterior rhinomanometry. They observed the presence of a reciprocating nasal cycle in 65% of the subjects with facial palsy and 80% of those with Horner's syndrome, concluding that the parasympathetic pathway has little to do with control of the nasal cycle and concluded there may be compensation by a secondary neural pathway for sympathetic stimulation of the nasal mucosa [85].

Fisher et al in 1994 [14] looked at 20 subjects (with an age matched control group of 10) who had undergone total laryngectomy on average 4 years prior to the study (range 2 weeks to 10 years) using acoustic rhinometry. The patterns of nasal patency were assigned to four groups; "classical", in concert, irregular and nil. Fisher found that only 25% of the laryngectomy subjects had a "classical" nasal cycle compared to 50% of the control group, with 40% of the laryngectomy subjects having and irregular nasal cycle compared to 20% of the control group. This study proves that a lack of airflow through the nose does not stop the nasal cycle occurring; proving that peripheral stimulus within the nose is not required for the nasal cycle to occur. That there is a lesser frequency of the "classical" nasal cycle present in post laryngectomy subjects is not surprising as the cervical sympathetic

nerves would be disrupted during neck dissection [14], however the numbers for the control group in this study were small and therefore may be subject to type 1 error.

Sung et al in 2000 [42] demonstrated that the presence of a nasal septal deviation did not influence the presence of the nasal cycle. They looked at 24 subjects (control group 26) with an anterior nasal septal deviation using acoustic rhinometry. They found a nasal cycle in 83% of the subjects with a nasal septal deviation and 77% of the control group [42].

Animal studies looking at the nasal cycle

Malcolmson in 1959 [67] studied the nasal tissues of cats using a direct rhinomanometry in animals that had been tracheotomised. He found that stimulation of the superior cervical ganglion or sympathetic chain, caused vasoconstriction within the nasal cavity without any systemic effects, whilst section resulted in vasodilation. He also demonstrated vasoconstriction secondary to hypothalamic stimulation but also noted a generalised sympathetic response. [67] Although there were no cyclical effects demonstrated, this work helped identify the neural pathways involved in control of the nasal cycle.

Bojsen-Moller and Faherenberg in 1971 [104] were able to demonstrate the presence of a spontaneously alternating nasal cycle in rabbits and rats. They used hygroscopy (the measurement of the area of condensation on a cold mirror) over an 8 to 10 hour period. They demonstrated such a pattern of airflow changes in 19 out of 20 rats and 13 out of 15 rabbits, proving that such changes in airflow patterns are not confined to humans but are present in other animals. The length of the nasal cycle varied from 30-85 minutes in rats and from 80 to 150 minutes in rabbits [104].

Eccles and Maynard (1975) [105] were the first to study the nasal cycle itself in animals; previous animal studies were based on nasal secretions and the

nervous supply of the nose. Their study on nine pigs used nasal spirometry to demonstrate cyclical changes in airflow [105]. A later porcine study by Eccles [83] used a fixed forced airflow through the nasal cavity in the anaesthetised pig and measurement of air pressure proximally and distally to the nasal cavity to measure resistance. The reciprocal activity of the nasal cycle was demonstrated in this way in 10 out of 13 animals, which was eliminated by section of the cervical sympathetic nerve [83].

Bamford and Eccles in 1982 [76] performed a feline study, using nasal plethysmography to monitor the effects of brain stimulation. Without stimulation changes in the nasal tissues representative of the nasal cycle were demonstrable. It was possible to create a reciprocal change in the side of the nose in which vasoconstriction occurred through stimulation of the reticular formation of the brainstem, with ipsilateral vasosconstriction and contralateral vasodilation seen in response to such stimulus [76]. This study suggests the origin of stimulus for the nasal cycle lies in the region of the reticular formation.

Studies using analytical techniques

Gilbert and Rosenwasser in 1987 [106] appear to have been the first to try to apply numerical standards to the nasal cycle and did so on a sample of 16 subjects. They used the correlation coefficient as a measure of reciprocity and autocorrelation analysis to assess for rhythmicity. Their study had a very high sampling density and produced 49 paired measurements for each subject, allowing them to perform the autocorrelation analysis with some accuracy. Despite this they were unable to produce statistically significant periodicities but regularly repeated autocorrelation peaks were seen in 7 subjects with only 2 of these being bilateral. For this study a statistically significant level of reciprocity was used for the correlation coefficient ($p<0.05$), which in this case meant a r value of less than -0.29, meaning that 43.8% of subjects were considered to have a statistically significantly reciprocal nasal cycle [106].

A later small study of nine subjects by Gilbert in 1989 [107] repeated his 1987 work with the observation density doubled to a frequency of one every 5 minutes, with a range of 88 to 97 paired measurements taken for each subject. 44% of subjects in this study were considered to have reciprocal airflow patterns, as with the previous study a statistical level of significance ($p<0.05$) was used to judge whether a correlation coefficient represented a reciprocal nasal cycle. Bilateral rhythmicity as assessed by autocorrelation analysis was seen in 22% of subjects, with periods of 3.5 to 6 hours estimated [107].

Mirza in 1997 [16] used both the correlation coefficient and autocorrelation analysis, to look at different types of nasal cycle in 4 age groups. The technique for studying airflow was liquid crystal thermography, where colour change on a heat sensitive material is measured to quantify airflow. A statistical level of significance was used with the correlation coefficient to identify “classical” and parallel nasal cycles. Where these were not seen autocorrelation analysis was used to identify “hemi-cyclical” airflow patterns. A decrease in the frequency of a “classical” nasal cycle and an increase of non-cyclical activity was reported with increasing age [16].

Work by Flanagan and Eccles in 1997 [1], analysed the nasal cycle according to numerical features. The Correlation coefficient (r value) and Airflow Distribution Ratio (ADR) were utilised to define a “classical” nasal cycle. The correlation coefficient is a statistical test to describe the relationship of two sets of data. The number it gives ranges from -1 to +1, where -1 shows a strictly reciprocal relationship and +1 a relationship that can be considered strictly in phase. The ADR measured from 0 to 1 describes whether there is equality of airflow throughout all measurements made for a nasal cycle. Where 1 indicates equal volumes overall and 0 indicates all airflow is on a single side. Criteria of an r value of less than -0.6 and an ADR of over 0.7 were set to define a “classical” nasal cycle. Their study reported a “classical” cycle according to these numerical features in

21% of test subjects (sample size 52), with 34.6% of subjects having a correlation coefficient of less than -0.6 and 51.9% having a ADR over 0.7 [1].

Studies using objective and subjective methods

Gungor in 1999 [108] combined the technique of acoustic rhinometry with a visual analogue scale (VAS) to monitor the nasal cycle. Gungor looked for a correlation between CSA2 measurements taken using acoustic rhinometry and the VAS but was unable to find any correlation, indicating that the VAS is a poor tool for monitoring the nasal cycle [108].

1.6 Rationale of this thesis

The concept of the nasal cycle has long been established along with the idealised “classical” nasal cycle where alternating reciprocal changes in nasal patency and airflow are seen [14, 15]. It is widely acknowledged that the “classical” nasal cycle is often only seen in a small proportion of subjects with a figure of 21% reported by Flanagan and Eccles in their 1997 study [1]. Mirza et al in 1997 showed that the reciprocity within nasal airflow patterns was seen less frequently in older compared to younger subjects [16], however there has yet to be any work to show how reciprocity as a measure of the “classical” nasal cycle changes over short periods of time.

The subjective assessment of nasal airflow is complicated due to the indirect way in which the sensation of airflow is detected by the nervous system, which is primarily due to a cold sensation [95]. Previous work has found a good correlation between subjective and objective data when looking at subjects assessed for nasal septal deviation [96, 109] and artificially induced nasal obstruction [110]. But when such scales have been used to monitor the nasal cycle there have been mixed results, with Gungor et al (1999) reporting no correlation between the Visual Analogue Scale and acoustic rhinometry [108] but Clarke et al (2005) found a good correlation between unilateral airflow and the Visual Analogue Scale in patients with upper respiratory tract infections [111]. No study has looked at the use of the Subjective Ordinal Scale developed by Boyce and Eccles [96] in assessment of the nasal cycle.

This thesis presents a pilot study into the stability of nasal airflow over time. It looks objectively (using data from anterior rhinomanometry) at the concept of the “classical” nasal cycle by measuring reciprocity using the r-value (correlation coefficient of left and right nasal airflow) and the equality of airflow using the Airflow Distribution Ratio. Secondarily a comparison is made between the objective measurement of nasal airflow and subjective assessment using the Subjective Ordinal Scale. A potential relationship between change in nostril dominance and meal times was also explored.

Chapter 2: Methodology

Ethical Approval

The study has been reviewed and approved by The School of Biosciences Research Ethics Committee, Cardiff University. It has been conducted in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice [112]. All subjects provided informed consent and signed a study consent form prior to screening.

Study design

The study was a prospective pilot study involving normal healthy volunteers. Subjects were recruited by email and poster advertisements and those responding were invited to a screening visit. This consisted of a medical interview and examination of the anterior nasal cavity to determine suitability for enrolment according to the inclusion and exclusion criteria (as listed below). Subjects who were included were invited back to two study days, one week apart (allowed window of six to nine days). On the study days the inclusion/exclusion criteria were revisited to ensure the subjects remained suitable. The subjects were given a 30 minute rest period to acclimatise to the environment of the lab and anterior rhinomanometry readings were taken every hour (allowed window of 15 minutes either side).

Inclusion criteria

1. Aged 18 or over
2. Have given written informed consent

Exclusion criteria

1. Any history of chronic nasal conditions
2. Active nasal disease e.g. current upper respiratory tract infection

3. Any history of trauma to nose or sinuses
4. Any significant septal abnormality
5. Presence of upper lip facial hair that may interfere with use of the rhinomanometer
6. Known allergy to surgical tape
7. Any disease or medical or surgical history that the investigator deems may affect nasal physiology and influence the results of the study e.g. chronic respiratory disease or intake of medicines known to affect the nose such as topical corticosteroids.
8. Member of study staff or partner or relative of study staff (except for Prof R Eccles)
9. Intake of more than 4 units of alcohol within 12 hours of measurement of nasal airflow
10. A current smoker, defined by a daily use of any tobacco product

Study Population

39 subjects were recruited to the study, with 30 completing. Of those who did not complete, 1 was excluded at screening due to significant nasal septal deviation, 1 was excluded on the first study day due to complete nasal obstruction preventing measurement and the remainder were lost due to non-attendance. Of those who completed the study 13 were male and 17 female, with a mean age of 22.7 (range 19-66 years). Measures of the nasal index and height and weight were omitted in one subject. For the remaining 29 subjects the mean nasal index was 68.78 with a range 58.42-96.74, mean BMI was 23.2 with a range 19.84-32.03 (the measures from which these are derived are summarised in table 2.1). 5 subjects reported a medical history; 2 seasonal allergic rhinitis, 1 essential hypertension, 1 iron deficiency anaemia, 1 Crohn’s disease. None of these conditions were felt to impact upon nasal

airflow during the study period. For those with a history of seasonal allergic rhinitis this was not an issue as the study was conducted in a pollen free environment in the winter time. 20 of the subjects recruited reported current medication usage, 15 were taking a herbal medicine (pelagonium) for a concurrent study, 8 were on an oral contraceptive, 1 had the contraceptive implant, 1 lisniopril, 1 ferrous sulphate, 1 Humira. None of these medications are known to impact on nasal airflow.

	Nasal height (mm)	Nasal width (mm)	Nasal Index	Height (cm)	Weight (kg)	BMI
Mean	49.74	33.98	68.78	172.46	69.48	23.20
Minimum	43.00	29.50	58.42	150.00	48.00	19.84
Maximum	61.50	44.50	96.74	190.50	106.10	32.03

Table 2.1 – A summary of the physical characteristics of the subject group

Study environment

The study was conducted in the Common Cold Centre of Cardiff University, subjects were acclimatised to room temperature conditions over a period of 30 minutes. Exposure to stimulants such as caffeine and nicotine was prohibited. Subjects were also instructed to refrain from sleep, lying down or exercise

Choice of method and equipment

Rhinomanometry is considered the gold standard for assessment of nasal obstruction [113], as the nasal cycle causes obstruction of the nostrils through venous engorgement of the turbinates and septum, a rhinomanometry based study was considered to provide the most accurate results. Posterior rhinomanometry is noted to have measurement benefits over the anterior method, such that total or near total unilateral nasal obstruction is not problematic. However posterior rhinomanometry requires training in its use and as such 10-20% of subjects are unable to perform a

measurement with this method. It was therefore decided to use anterior rhinomanometry for this study. The Happersberger Otopront RHINO-SYS system (manufactured by Happersberger Otopront in Germany, D-65329 Hohenstein) provides a user-friendly interface and guides test subjects with a traffic light system during use. This provides useful feedback for test subjects and it was felt that it would therefore facilitate data collection from subjects.

Anterior rhinomanometry technique

Measurements were recorded using an Otopront RHINO-SYS rhinomanometer according to SOP No. 24 - Procedure for measurement of nasal airflow using the otopront RHINO-SYS Rhinomanometer. The anterior rhinomanometry technique works on the basis of the measurement of nasal pressure via the non test nostril as this is equal throughout the nasal cavity and the measurement of airflow via a flowhead in the test nostril. From these readings nasal resistance is calculated by the rhinomanometer software. Each resistance measurement is recorded at a fixed reference pressure, commonly either 75 Pa or 150 Pa is used. In this case a reference pressure of 75 Pa was chosen as the higher pressure of 150 Pa may not be achieved in a physiological study such as this [114]. To ensure the reliability of results two readings were recorded for each nostril and a coefficient of variation was calculated, readings were only accepted if this was 15% or less.

Recording the nasal cycle - Airflow vs resistance measurements

Recording nasal resistance to airflow has a disadvantage statistically when a totally (or near totally) obstructed nose is encountered, as in this situation no value for resistance could be recorded. However if nasal airflow is recorded instead a value of zero can be recorded allowing statistical analysis [88]. It is for this reason that the resistance values initially obtained were converted to airflow for presentation and analysis.

The subjective ordinal scale

The subjective ordinal scale created by Boyce and Eccles in 2006 [96] has been described in the introduction (section 1.4). It has been shown to have greater specificity than a Visual Analogue Scale (VAS) when assessing differences in nasal airflow [96]. However previous use was limited to assessment of nasal septal deviation and its inclusion in this study is explorative, to give an indication of the scale's usefulness in studies of the nasal cycle. The scale was completed by the subject prior to each set of anterior rhinomanometry measurements.

Subject expenses

Subjects for the trial were paid a total of £80 by cheque at completion of the study, a smaller sum of £5 was given if they failed screening. Subjects also received a standardised lunch during the study days, this consisted of a cold sandwich, packet of crisps, a chocolate bar and bottled water.

Calculation of airflow

In order to calculate the airflow distribution ratio and for the plotting of data, resistance measurements were converted to flow velocities, using the formula below where the pressure is fixed at the reference pressure:

Resistance = pressure (75 Pa ref pressure) / flow (v)

This is reversed to:

V= 75/r

Statistical analysis

The correlation coefficient is used both as a measure of reciprocity within the nasal cycle and for calculation of relationships. In both cases Pearson's method is used. Differences between subjects at study day 1 and study day 2 were tested by the use of a paired Student's t-test.

Calculation of the correlation coefficient

The correlation coefficient was calculated using Pearson's coefficient of variance as using this method the values for left and right nasal airflow are compared at each data point. Whereas the alternative method of Spearman's rank correlation reorganises the values as part of the calculation and uses an assigned rank number instead of the original data inputted for the calculation.

Calculation of the Airflow Distribution Ratio

The Airflow Distribution Ratio (ADR) was calculated using the formula:

ADR = (airflow A / total airflow) / (airflow B / total airflow)

Where A is the lower value of airflow

Calculation of the Nasal Partitioning Ratio

The Nasal Partitioning Ratio (NPR) was calculated using the formula:

NPR = vol L – vol R / vol L + vol R (total rate of airflow)

Chapter 3: The characteristics of the nasal cycle in the study population at the first day of examination by anterior rhinomanometry

The characteristics of the nasal cycle in the study population at the first day of examination by anterior rhinomanometry

Aim – To establish, numerically, what characteristics the nasal cycles of the study population have at the start of the study.

Introduction

Types of nasal cycle

The nasal cycle can be defined as “the spontaneous and often reciprocal changes in unilateral nasal airflow associated with congestion and decongestion of the nasal venous sinuses” [95]. When reciprocal changes in the congestion of the nasal mucosa are seen in observations of the nasal cycle, such cycles are often referred to as “classical”. Other types of cycle that have been described include “in phase” (“in concert”) and “irregular”. Where cycles are said to be “in phase” parallel changes occur in the congestion and decongestion of the nasal mucosa, an “irregular” cycle may have a mixture of features of the “in phase” and “classical” groups or no discernible pattern at all [15].

Numerical descriptors used in studying the nasal cycle

Both the correlation coefficient (r value) and Airflow Distribution Ratio (ADR) can be used to describe the nasal cycle numerically. The correlation coefficient as a measure of reciprocity has been used in studies of the nasal cycle examining nasal airflow, those using acoustic rhinometry [115] and in those using Magnetic resonance imaging techniques [103].

Flanagan and Eccles [1] defined a “classical” nasal cycle numerically as having a correlation coefficient more negative than -0.6 and an ADR (as defined in section 1.4) greater than 0.7. Their study was based on eight sets of airflow recordings taken at hourly intervals from 52 healthy volunteers; of

this group 21% had a “classical” nasal cycle according to these criteria [1], however these criteria were chosen arbitrarily. Gilbert and Rosenwasser in 1987 [106] had previously used a statistical level of significance for the correlation coefficient (where the p value is 0.05) to help define a “classical” or reciprocal nasal cycle, in this case 49 sets of airflow measurement were obtained for each nasal cycle. So a correlation coefficient more negative than -0.29 was considered significantly reciprocal [106].

Method

Anterior rhinomanometry was performed over a seven-hour period with subjects at rest in lab conditions. The subjects were given a 30 minute rest period prior to measurements to allow for acclimatisation. Measurements were taken every hour, as per the study protocol. Airflow measurements were obtained by conversion from resistance measurements, with measurements being taken at a reference pressure of 75 Pa.

The correlation coefficient was calculated for each subject’s nasal cycle using Pearson’s method. This method was chosen as it meant that the airflow values were paired, whereas Spearman’s method ranks values.

The period in which a set lunch was taken was recorded as being the time after a set of nasal airflow measurements were taken. For an assessment of any potential relationship to meals and a change in nostril dominance the time of the last data entry was recorded and the point of changeover on the nasal airflow graph was read.

Results

The correlation coefficient for all 30 subjects at study day 1 ranged between -0.89 to 0.97 with a mean value of -0.39. The airflow distribution ratio ranged between 0.26 to 1 with a mean value of 0.72. The combination of these data

and their distribution is represented in figure 3.1, where a clear grouping is seen in the top left hand corner, representing subjects with correlation coefficients close to -1 and an airflow distribution ratio close to 1.

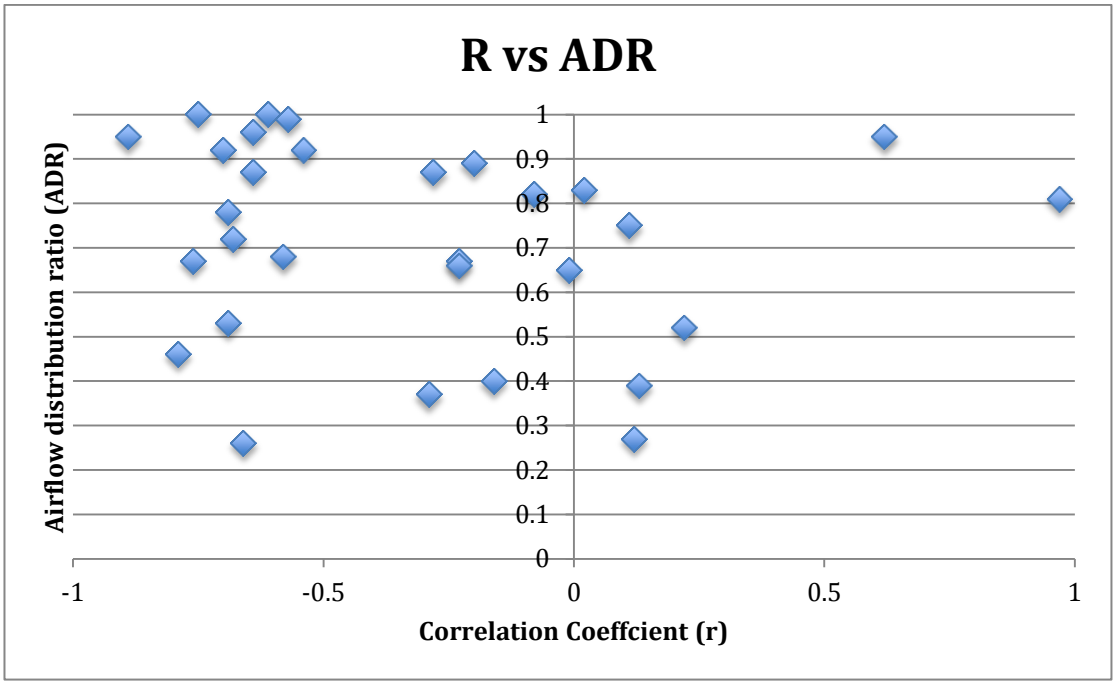


Figure 3.1 – A graph showing the distribution of values for r and ADR for each subject at study day 1

Using Flanagan's criteria for a "classical" nasal cycle (r -0.6 to -1 and ADR 0.7 to 1) eight of the group of 30 subjects (26.7%) can be defined as having a "classical" nasal cycle. Overall 23 subjects (76.7%) were seen to have a negative correlation coefficient and 12 subjects (40%) were seen to have a correlation coefficient of less than -0.6. 17 subjects (56.7%) overall had an ADR of greater than 0.7.

Subjects 15, 17, 18, 21 and 24 meet Flanagan's criteria for the "classical" nasal cycle. In addition subjects 33, 35 and 36 all conform to a higher level of the "classical" criteria having a statistically significant correlation coefficient of less than -0.7 and an ADR of over 0.7. An example of this group subject 35 (see figure 3.2) could be said to have a very long cycle, from a critical point of view the highly negative correlation coefficient and high ADR could be explained by the high peaks in right-sided airflow for the final two data points.

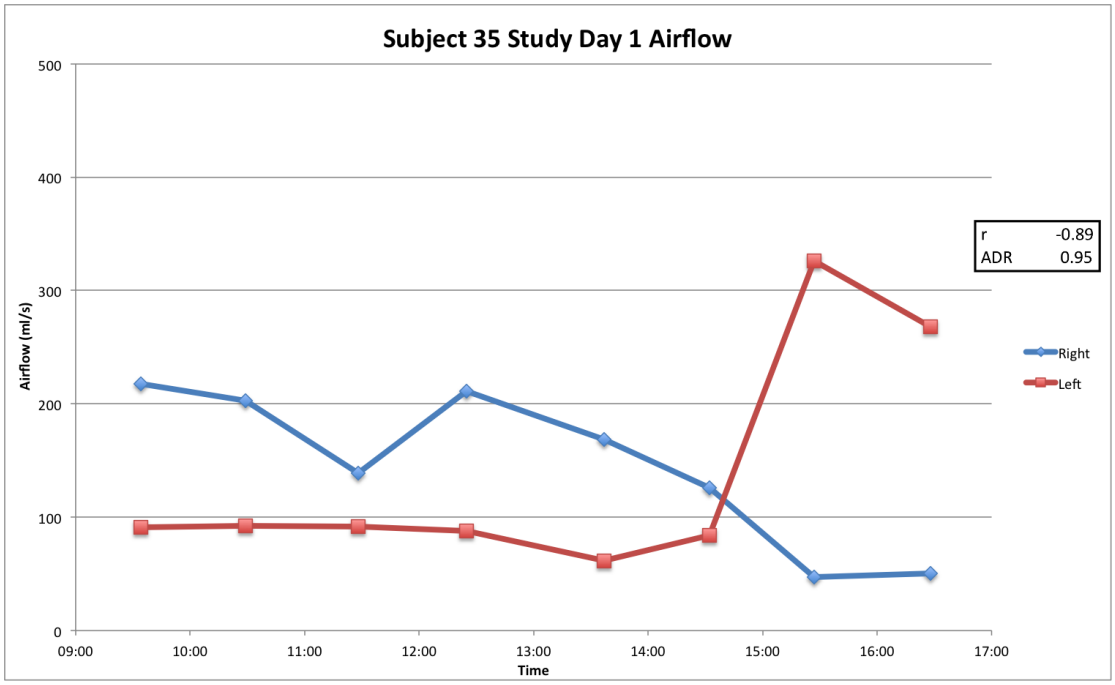


Figure 3.2 – A graph showing airflow for the left and right nasal passages for subject 35 on study day 1

From this group subject 021 (see figure 3.3) makes the best visual example of what is expected from a “classical” nasal cycle, with generally clear reciprocal changes taking place and even distribution of airflow. It also appears to display periodicity within the cycle, although the sampling rate for this study is unlikely to be high enough to detect the peaks required for measurement of this.

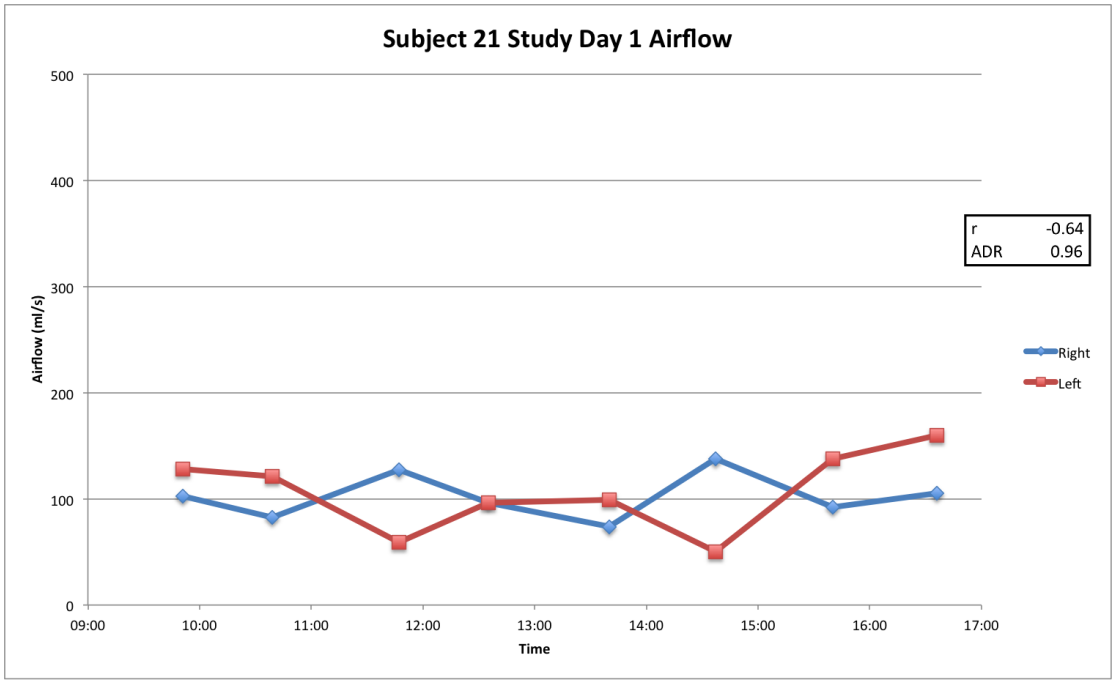


Figure 3.3 – A graph showing airflow for the left and right nasal passages for subject 21 on study day 1

On the converse side if a high correlation coefficient (>0.6) can be considered to represent subjects who are “in phase” two subjects fit this criterion. Below are graphs demonstrating the airflow patterns of the two subjects with a correlation coefficient greater than 0.6. As the correlation coefficient increases from 0.62 to 0.97 from subject 011 (see figure 3.4) to subject 019 (see figure 3.5) visually an “in phase” nasal cycle is more obvious, with no cross over points seen in 019’s cycle.

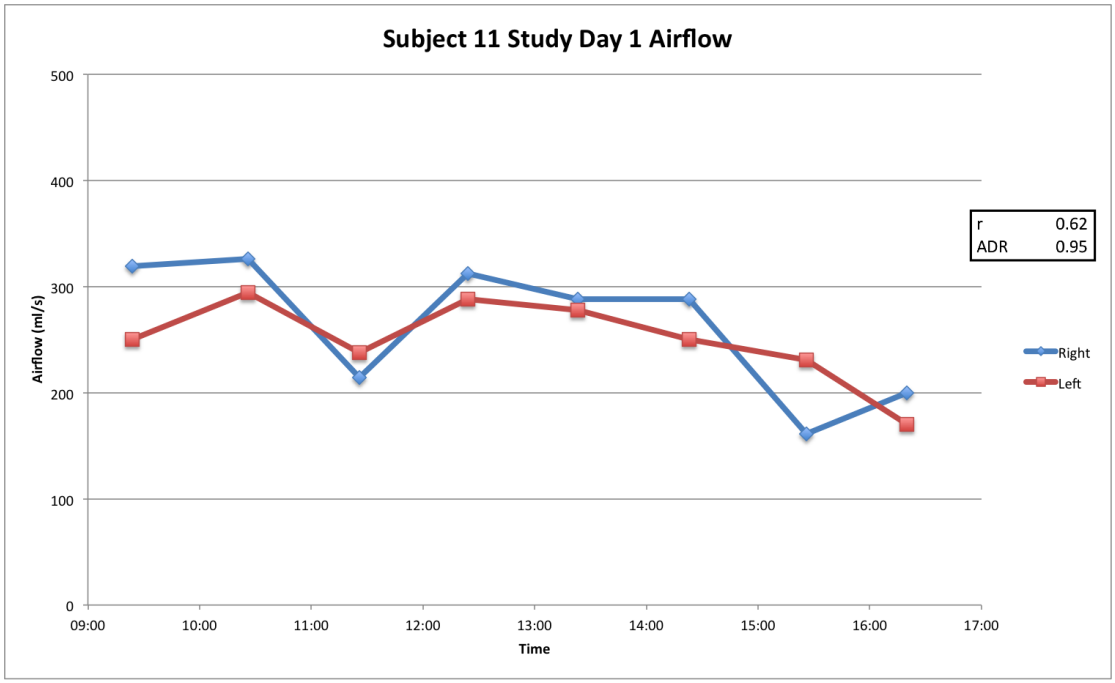


Figure 3.4 – A graph showing airflow for the left and right nasal passages for subject 11 on study day 1

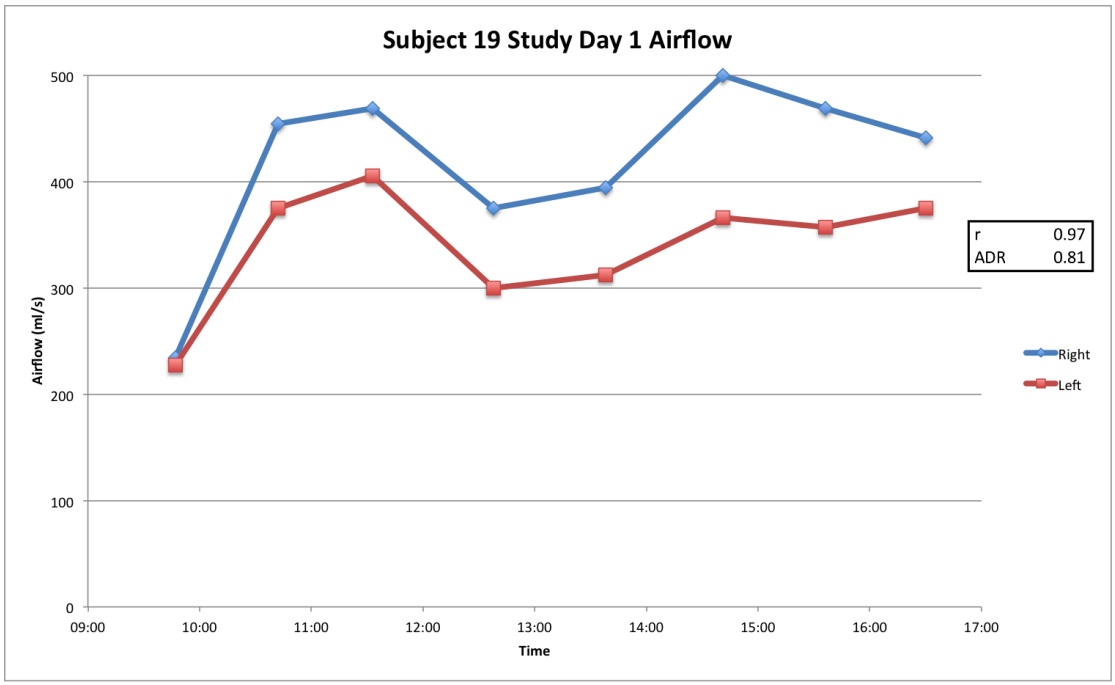


Figure 3.5 – A graph showing airflow for the left and right nasal passages for subject 19 on study day 1

This leaves 20 out of 30 subjects (66.7%) who fit neither the criteria for a "classical" nasal cycle nor the criteria for an "in phase" nasal cycle. These

subjects can be termed to have non-significant nasal airflow patterns, this term is used since the criteria for both the “classical” nasal cycle and “in phase” nasal cycle are determined using a statistical test (the correlation coefficient).

Of the 30 subjects in the study the period of the meal time was omitted from the data in two cases. In six cases there was no cross-over point following on from the meal period. This meant that 8 subjects in total were omitted from this analysis. For the remaining 22 subjects the mean time from the start of the meal period to cross over was 1 hour 41 minutes with a range of 7 minutes to 4 hours 52 minutes (data detailed in table 3.1). A correlation coefficient calculated for the relationship of the start of the meal period to the subsequent cross over point was non-significant with a value of -0.24 ($p > 0.2$).

Subject no	Meal Period	Meal period start	Cross-over time	Time lag
1	3	11:35 am	1:00 pm	01:25
2	4	12:41 pm	12:48 pm	00:07
8	3	11:34 am	3:33 pm	03:59
11	3	11:26 am	2:45 pm	03:19
16	3	11:43 am	2:12 pm	02:29
17	4	12:21 pm	2:20 pm	01:59
18	4	12:29 pm	12:36 pm	00:07
21	4	12:35 pm	1:54 pm	01:19
22	4	12:31 pm	3:42 pm	03:11
24	4	12:36 pm	12:54 pm	00:18
25	4	12:27 pm	2:03 pm	01:36
27	3	11:33 am	12:09 pm	00:36
28	4	12:30 pm	1:30 pm	01:00
29	3	11:38 am	4:30 pm	04:52
31	4	12:29 pm	1:30 pm	01:01
32	4	12:24 pm	12:48 pm	00:24
33	4	12:29 pm	3:54 pm	03:25
34	4	12:20 pm	2:45 pm	02:25
35	4	12:25 pm	2:39 pm	02:14
36	4	12:30 pm	1:00 pm	00:30
37	4	12:25 pm	12:39 pm	00:14
38	4	12:36 pm	1:24 pm	00:48

Table 3.1 – A table showing meal times for subjects on study day 1 who subsequently had a change in nostril dominance and the time lag from meal start time to the change in nostril dominance.

Discussion

Not all subjects with what would appear at visual inspection to be a “classical” nasal cycle were represented in this way numerically. An example of this is subject 027 (see figure 3.6) who has a highly negative r value, but the ADR is just under 0.7. Whilst initial inspection of the chart for subject 027 suggests a “classical” nasal cycle, it is clear that in the sample period right sided airflow does predominate as the left sided points never peak as highly and drop to lower levels that the right side, which results in an uneven distribution of airflow.

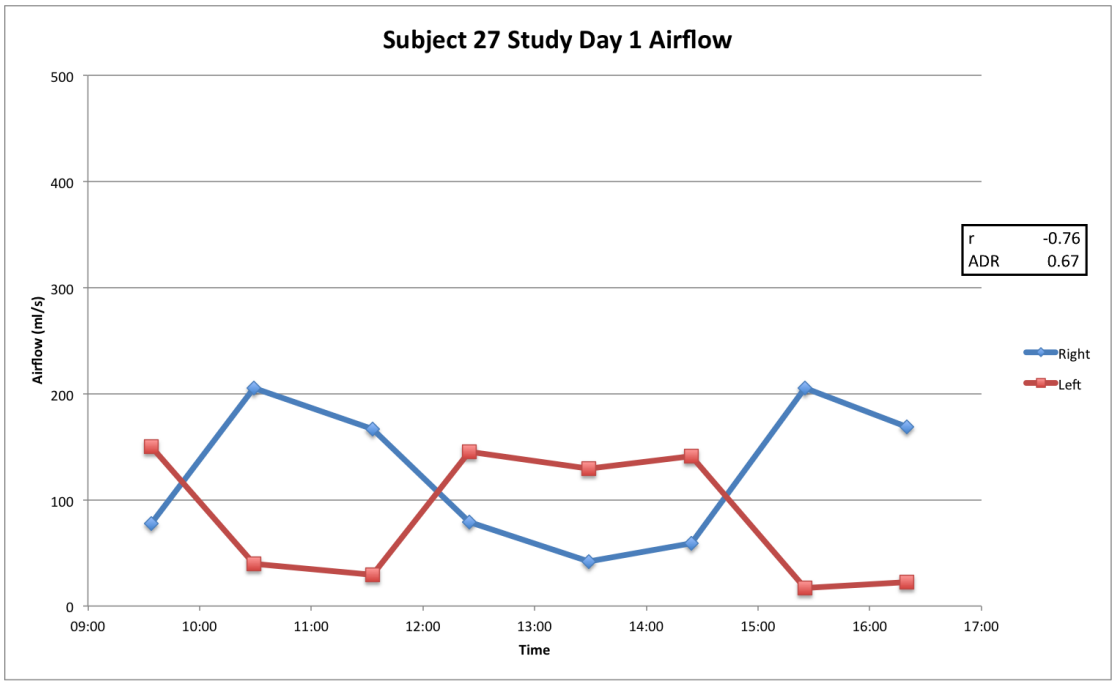


Figure 3.6 – A graph showing airflow for the left and right nasal passages for subject 27 on study day 1

Subject 36's chart (see figure 3.7) shows a negative r value and a significant ADR and therefore is numerically "classical" but visual inspection would suggest this is not the case. The changes in airflow do not appear to occur in a reciprocal fashion to visual inspection at points 2 and 7. However it is clear that right and left sided peaks and troughs for airflow occur at similar levels allowing for an even distribution of airflow and a highly negative correlation coefficient.

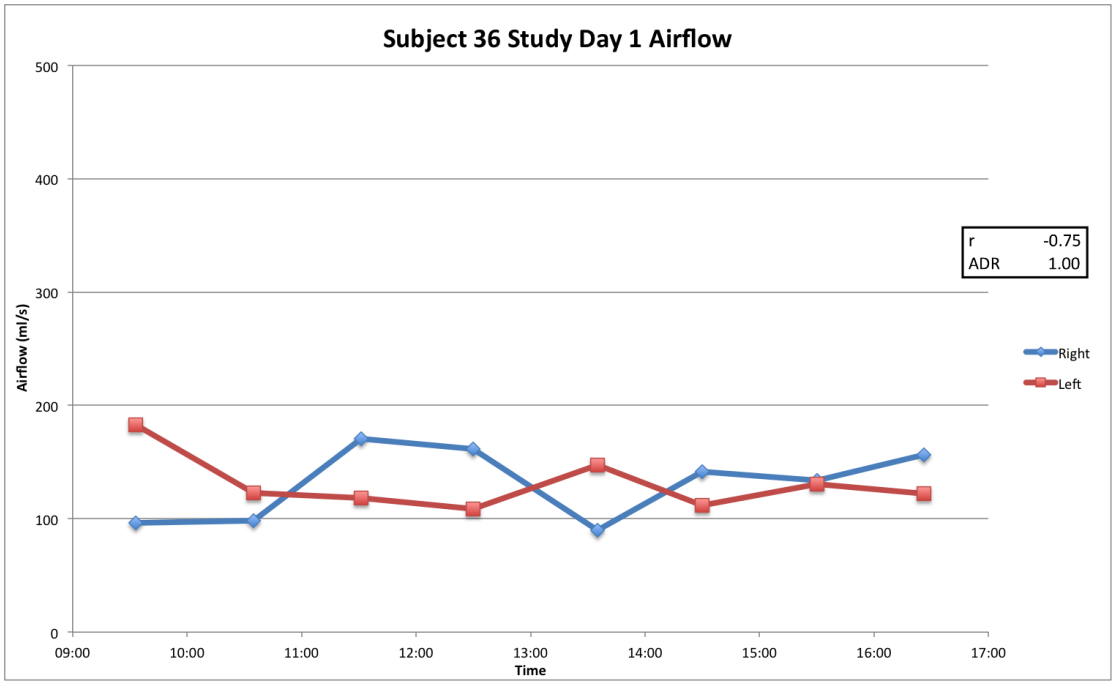


Figure 3.7 – A graph showing airflow for the left and right nasal passages for subject 36 on study day 1

Conclusions

Using Flanagan's criteria for a "classical" nasal cycle 8/30 (26.7%) subjects in this study can be classified as such at study day 1. This is slightly higher than the 21% value obtained by Flanagan and Eccles' original study [1]. Other reported rates for the presence of a nasal cycle are higher, but often less stringent criteria are used. For example a study by Abolmaali et al using MRI imaging to assess the nasal cycle only used a correlation coefficient more negative than -0.5 to define the presence of a nasal cycle, thus reporting a frequency of 46% in their study of 28 healthy subjects [103]. Gilbert and Rossenwaser's earlier study [106] again used the correlation coefficient as one of their criteria for assessment of the nasal cycle (autocorrelation analysis was also used to assess rhythmicity). In their sample seven of 16 subjects were shown to have significant reciprocity however a statistical definition of significance was applied ($p<0.05$) meaning a correlation coefficient of less than -0.29 was seen as significant due to a large sample of airflow measurements [106].

Using a criterion of r >0.6 two subjects were considered to have an “in phase” cycle and this is demonstrated graphically.

There is no proven relationship between the start of the meal period time and the subsequent crossover in dominance of nasal airflow.

Chapter 4: How the characteristics of the nasal cycle in the study population change over time

How the characteristics of the nasal cycle in the study population change over time

Aim - To study the stability of the nasal cycle over a period of 6-9 days

Introduction

There has been little work on the stability of the nasal cycle over time and no studies to date have assessed this objectively using numerical values such as the correlation coefficient and Airflow Distribution Ratio (ADR). A single study of 18 healthy subjects used anterior rhinomanometry to monitor changes in the nasal cycle over a 3 month period with nasal airflow measurements performed at the start and end of this period. Subjects were classified subjectively as cyclical, irregular and noncyclical according to their airflow patterns at the start and the end of the study. Of the 18 subjects 7 were classified in a different group at the end of the study compared to the beginning. Unfortunately this study is weakened significantly by its use of subjective assessment as the examples presented do not clearly represent a “classical” nasal cycle although they are reported as such [116].

The changes in nasal airflow patterns seen in the subject group will be described and assessed numerically.

Method

Nasal airflow measurements for the two study days were recorded using anterior rhinomanometry as described previously in chapter 2. The correlation coefficient (r value) and Airflow Distribution Ratio were calculated for each nasal cycle (as previously described in Chapter 2). Comparative statistics are used as well as the correlation coefficient to assess how these variables change over time.

Results

There was a 100% return rate for study day 2, two subjects had a delay in return, one due to illness and one due to a family bereavement. One subject did not complete study day 2 needing to leave early, so only 6 of 8 measurements were obtained for subject 29 on study day 2.

The mean r value became more negative from study day 1 to study day 2 moving from -0.32 (range -0.89 to 0.97) to -0.47 (range -0.9 to 0.5). The mean ADR also showed a slight decrease from study day 1 to study day 2 from 0.72 (range 0.26 to 1) to 0.68 (range of 0.19 to 1) (as summarised in table 4.1). The distribution of r values and ADR values is shown in figure 4.1.

	r study day 1	ADR study day 1	r study day 2	ADR study 2
Mean	-0.32	0.72	-0.47	0.68
Min	-0.89	0.26	-0.9	0.19
Max	0.97	1	0.5	1

Table 4.1 – A summary of r values and ADR values at study day 1 and study day 2

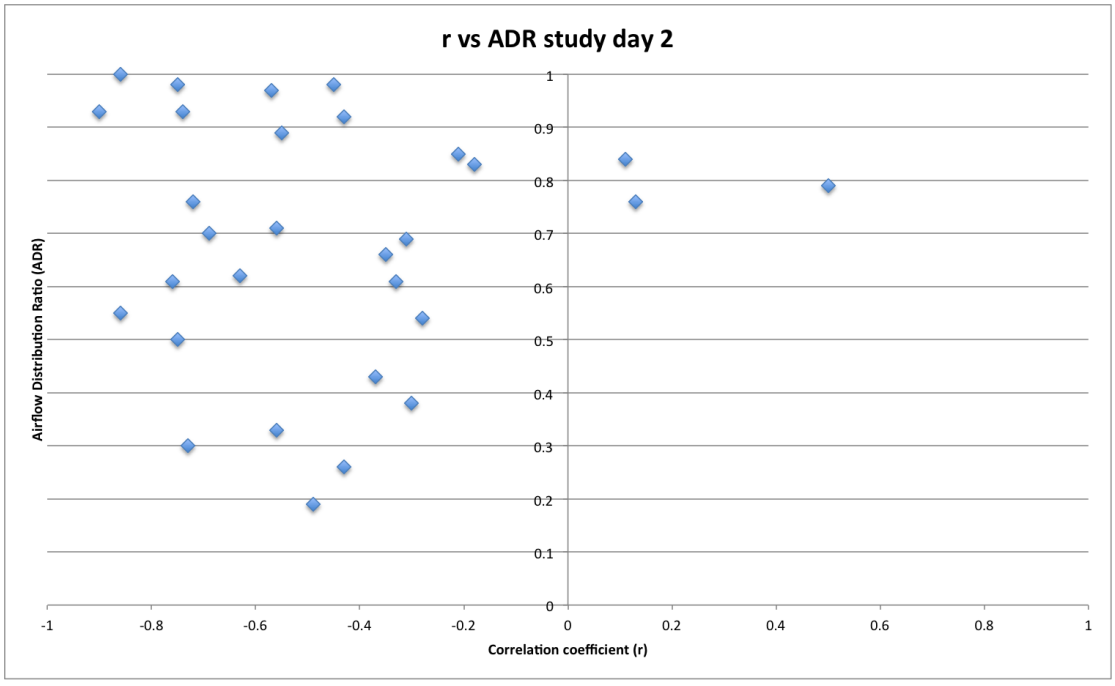


Figure 4.1 – A graph showing the distribution of values for r and ADR for each subject at study day 2

The number of subjects with a “classical” nasal cycle according to Flanagan’s criteria [1] decreased slightly from study day 1 to study day 2 with a decrease from 26.7% to 16.7% of subjects meeting both criteria. However when a statistical level of significance for the r value ($p < 0.05$) is used, i.e r less than -0.7, there is an increase in the number of subjects meeting the two criteria. This is summarised in table 4.2. A graphical representation of how the r value and ADR have changed from study day 1 to study day 2 is shown in figure 4.2. Overall the correlation coefficient has become more negative and the ADR has reduced in the subject group.

	Study day 1	**Percentage**	**Study day 2**	**Percentage**
r <-0.6	12	40	11	36.7
ADR > 0.7	17	56.7	15	50
r <-0.6 and ADR > 0.7	8	26.7	5	16.7
r <0	23	76.7	27	90
r>0.6	2	6.7	0	0.00
r <-0.7	5	16.7	9	30
r <-0.7 and ADR > 0.7	3	10	5	16.7

Table 4.2 – A summary of the change in classification of r values and ADR values, with the numbers and percentages for each group listed.

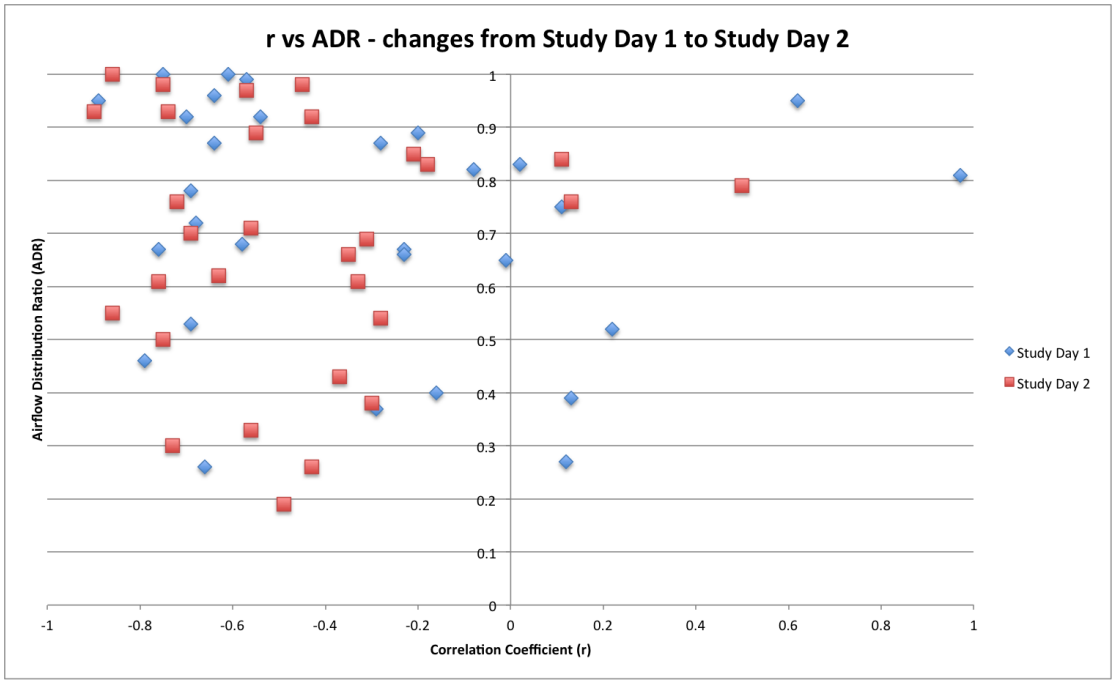


Figure 4.2 - A graph showing the distribution of values for r and ADR for each subject at study days 1 and 2.

Overall there was a tendency for the correlation coefficient to be more negative at study day 2 compared to study day 1. In total most of the correlation coefficient values obtained over both days are negative. This is illustrated in figure 4.3 which shows that where there was an initially high r value this decreased often becoming negative at study day 2.

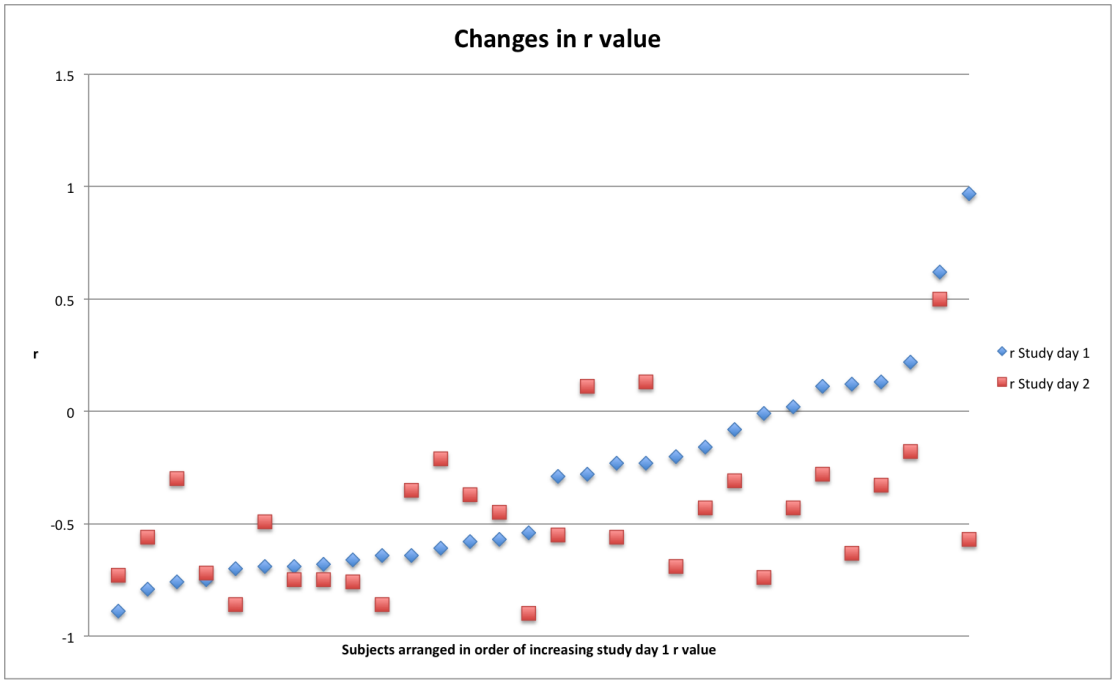


Figure 4.3 – A graph showing the change in r value for individual subjects from study day 1 to study day 2.

Furthermore there is a relationship between the r value at study day 1 and the change in r value. Where the r value was more negative the change tended to be small, as the r value increases and becomes positive there are larger changes in the r value from study day 1 to study day 2. All subjects with a positive r value at study day 1 and those with an r value close to 0 showed a negative change in r value from study day 1 to study day 2. This is illustrated in figure 4.4, where there is a strong negative correlation of -0.73 for the relationship between study day 1 r value and the change in r value from study day 1 to study day 2. This relationship is significant with a p value of less than 0.001.

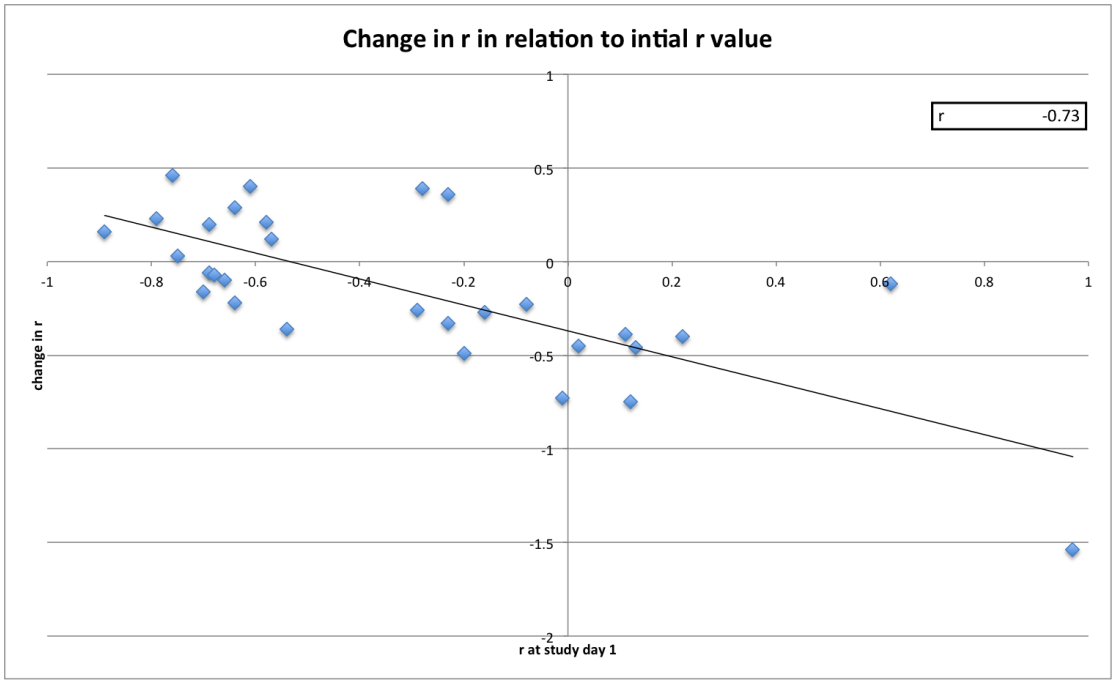


Figure 4.4 – A graph showing the relationship between study day 1 r value and the change in r value.

Subjects in "classical" group at study day 1

Of the eight subjects at study day 1 who met Flanagan's criteria for a "classical" nasal cycle only three subjects (37.5%) continued to meet these criteria at study day 2 (subjects 17, 21 and 36), although all continued to have a negative r value at study day 2. The changes in the r-values and ADR values are shown in table 4.3. Of those three subjects only subject 36 met the higher statistical level of significance for the r-value at both study days.

Subject	r study day 1	ADR study day 1	r study day 2	ADR study day 2
15	-0.61	1	-0.21	0.85
17	-0.69	0.78	-0.75	0.98
18	-0.68	0.72	-0.75	0.5
21	-0.64	0.96	-0.86	1
24	-0.64	0.87	-0.35	0.66
33	-0.7	0.92	-0.86	0.55
35	-0.89	0.95	-0.73	0.3
36	-0.75	1	-0.72	0.76

Table 4.3 – A summary of the r-values and ADR values of those subjects in the “classical” group at study day 1

Subjects in “in phase” group at study day 1

Subjects 11 and 19 were considered to have nasal cycles that were “in phase” on study day 1 due to r-values of 0.62 and 0.97 respectively. Their nasal airflow patterns are shown as figures 3.4 and 3.5. At study day 2 subject 11’s r-value decreased to 0.5 and subject 19’s decreased to -0.57. Therefore neither remained within the “in phase” group, nor did they enter the “classical” group.

Subjects in non-significant group at study day 1

The majority of subjects (20 out of 30) were deemed to have non-cyclical patterns on study day 1, not fitting with Flanagan’s criteria for a “classical” nasal cycle nor having a high r-value to indicate an “in phase” cycle. At study day 2 three (15%) of these subjects (subjects 2, 12, 15) met Flanagan’s criteria for a “classical” nasal cycle. None moved into the “in phase” group. The data for this group are shown in table 4.4.

Subject	r study day 1	ADR study day 1	r study day 2	ADR study day 2
1	0.02	0.83	-0.43	0.92
2	-0.54	0.92	-0.9	0.93
3	0.12	0.27	-0.63	0.62
8	0.11	0.75	-0.28	0.54
10	-0.69	0.53	-0.49	0.19
12	0.22	0.52	-0.18	0.83
14	-0.29	0.37	-0.55	0.89
16	-0.28	0.87	0.11	0.84
22	-0.58	0.68	-0.37	0.43
23	0.13	0.39	-0.33	0.61
25	-0.2	0.89	-0.69	0.7
27	-0.76	0.67	-0.3	0.38
28	-0.66	0.26	-0.76	0.61
29	-0.01	0.65	-0.74	0.93
31	-0.16	0.4	-0.43	0.26
32	-0.23	0.67	-0.56	0.71
34	-0.57	0.99	-0.45	0.98
37	-0.23	0.66	0.13	0.76
38	-0.08	0.82	-0.31	0.69
39	-0.79	0.46	-0.56	0.33

Table 4.4 - A summary of the r-values and ADR values of those subjects in the non-significant group at study day 1

Discussion

It has previously been suggested by Gilbert and Rosenwasser in 1987 that the nasal cycle as concept should be considered as an unstable and episodic phenomenon [106]. By studying the subjects in groups according to Flanagan's classification [1] using the correlation coefficient and ADR, it has been demonstrated that the nasal cycle is not a stable phenomenon when viewed over a period of approximately one week. Of those in the "classical" group on study day 1 only 37.5% remained in the "classical" group at study day 2 and none of those in the in phase group at study day 1 remained in this group at study day 2. Of those in the non-significant group at study day 1 15% entered the "classical" group at study day 2. This demonstrates that

large proportions of the study groups moved from one type of nasal cycle to another.

In all subjects over the two study days the r value mostly was negative, demonstrating some level of reciprocity within the nasal airflow patterns. This implies that there is inherent reciprocal input for the control of the nasal venous tissues, which influence nasal airflow. That the nasal cycle is generally reciprocal in nature has been reported previously [1, 106] and thus supports the data obtained for this study. There was a tendency for those with a reciprocal nasal cycle to maintain this from study day 1 to study day 2. As shown in figure 4.3 none of the 15 subjects who at study day 1 had an r value more negative than -0.5 had a positive r value at study day 2. In contrast of the 15 subjects whose r value at study day 1 was more positive than -0.5, 12 (80%) had a more negative r value at study day 2. This is a significant shift towards reciprocity.

The most significant finding is of the trend for the r value to become more negative from study day 1 to study day 2. This is demonstrated by a significant correlation coefficient of -0.73 ($p < 0.001$), which shows a trend of higher study day 1 r values to have a larger negative change over the observation period. Again this reinforces the suggestion of an inherent reciprocal nature to the nasal cycle, which is likely to originate from a central source of control.

Chapter 5: What are the characteristics of the nasal cycle within the study population when assessed using subjective ordinal scale?

What are the characteristics of the nasal cycle within the study population when assessed using subjective ordinal scale?

Introduction

The subjective ordinal scale (SOS) as a tool for the assessment of nasal patency was introduced in 2006 by Boyce [96] and has previously been discussed in chapter 1.4. It was designed to detect an abnormal Nasal Partitioning Ratio (NPR) (as discussed in chapter 1.4) which would then be used as a simple tool in the screening of patients for consideration of nasal septal surgery. Results from Boyce's paper showed that the subjective ordinal scale had a sensitivity of 81% for detecting an abnormal NPR [96]. The use of this tool was included within this study to establish whether it may be used as a simple tool for future studies on the nasal cycle, where subjects may be able to self monitor their nasal patency. Previous studies trying to relate subjective assessment tools to rhinomanometric measurements of nasal airflow have failed to show any consistent correlation. This is suspected to be due to the complex way in which the sensation of nasal congestion and airflow is picked up indirectly by different receptors within the nasal cavity [97].

The Nasal Partitioning Ratio and Airflow Distribution Ratio are both measures which give an indication of the equality of airflow distribution between the two sides of the nose. They differ in that the Nasal Partitioning Ratio is able to indicate which side the majority of airflow goes through by giving a positive or negative value e.g -1 indicates that all airflow is through the right side of the nose and +1 indicates all airflow is through the left side of the nose [99]. Whereas the Airflow Distribution Ratio gives a value of 0 to 1 where 1 indicates equal distribution of airflow between the two sides of the nose and 0 indicates that all airflow is through one side of the nose without indicating which side is dominant [1]. Both measures have previously been described along with their calculation in chapter 1.4.

The focus of this thesis so far has been monitoring the nasal cycle over time using an r-value (correlation coefficient), which compares left and right nasal airflow and the Airflow Distribution Ratio (ADR). This chapter seeks to establish whether monitoring of the nasal cycle is possible using the subjective ordinal scale. Therefore the previously collected objective data (i.e. obtained from rhinomanometry) are compared with subjective data (i.e. obtained from the subject's self assessment using the subjective ordinal scale) and analysed accordingly.

Method

Prior to each set of measurements made in the study using anterior rhinomanometry each subject was asked to self assess their nasal patency using the subjective ordinal scale and the indicated values recorded. All subjects were educated in the use of the subjective ordinal scale prior to the start of the study by the investigator.

An r-value (correlation coefficient) comparing the left and right nasal passages, an Airflow Distribution Ratio and a Nasal Partitioning Ratio were all calculated for each subject on each study day for both the objective (rhinomanometric) data and the subjective data (using the subjective ordinal scale). Correlation coefficients were calculated using Pearsons method to examine for any relationship between the objective (rhinomanometric) data and the subjective data (subjective ordinal scale).

Section 1 - r-values (correlation coefficients)

Results

An initial comparison is made between the r-value (correlation coefficients comparing left and right sided nasal airflow) for the subject's objective data and the r-value for the subjective data on each study day. This is summarised by plots of the two different r-values in figures 5.11 (study day 1)

and 5.12 (study day 2). The spread of data on these plots is clearly wide and the applied trend line is therefore affected by many outlying points on both plots. The correlation coefficients derived from the relationships between the r-value for objective data and the r-value for subjective data are low being 0.1 for study day 1 and 0.16 for study day 2. These are both not statistically significant with p-values of over 0.2 (see table 5.11). When calculating the r-value (correlation coefficient) for the subjective data, the calculation is not possible to perform for certain number sequences e.g where the test subject had indicated a single value for all eight measurments on one side of the nose, hence there are four gaps in the data which can be seen in table 5.12 (subjects 08, 25 and 34). This meant that when the r-values for the objective data and subjective data were compared using the correlation coefficient, these subjects were removed from the calculation. The correlation coefficients shown in table 5.11 and figures 5.11 and 5.12 therefore only represent 28 subjects for each study day. There was no relationship demonstrated between the r-values for objective data and subjective data on either study day.

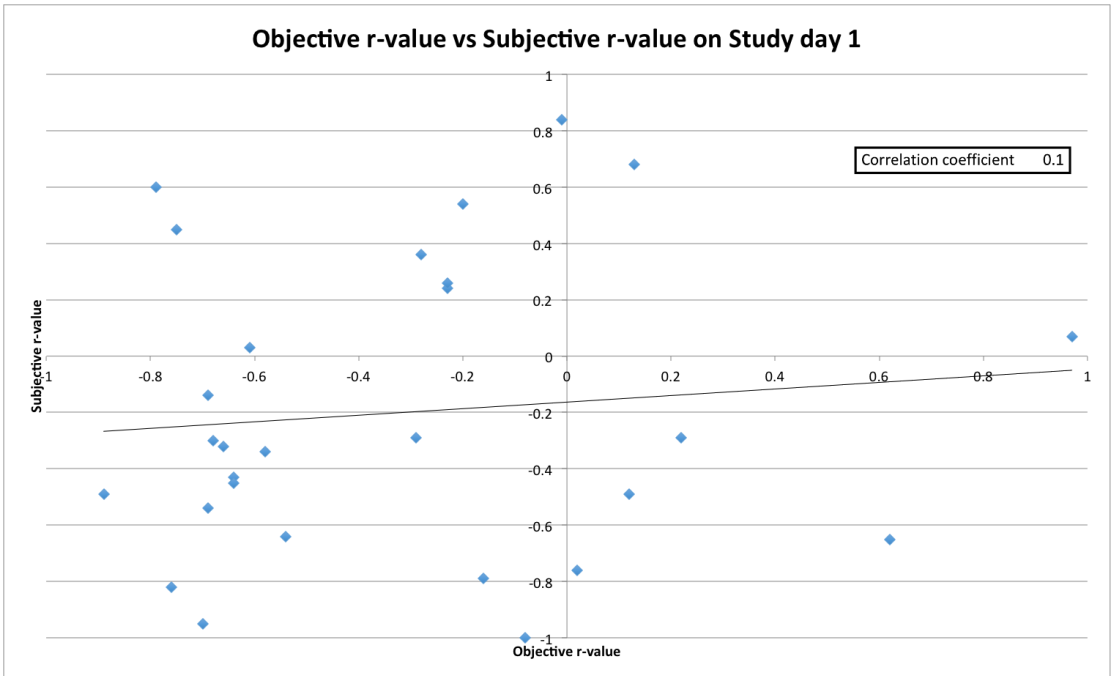


Figure 5.11 – A scatter graph of the r-value for objective data vs the r-value for subjective data on study day 1

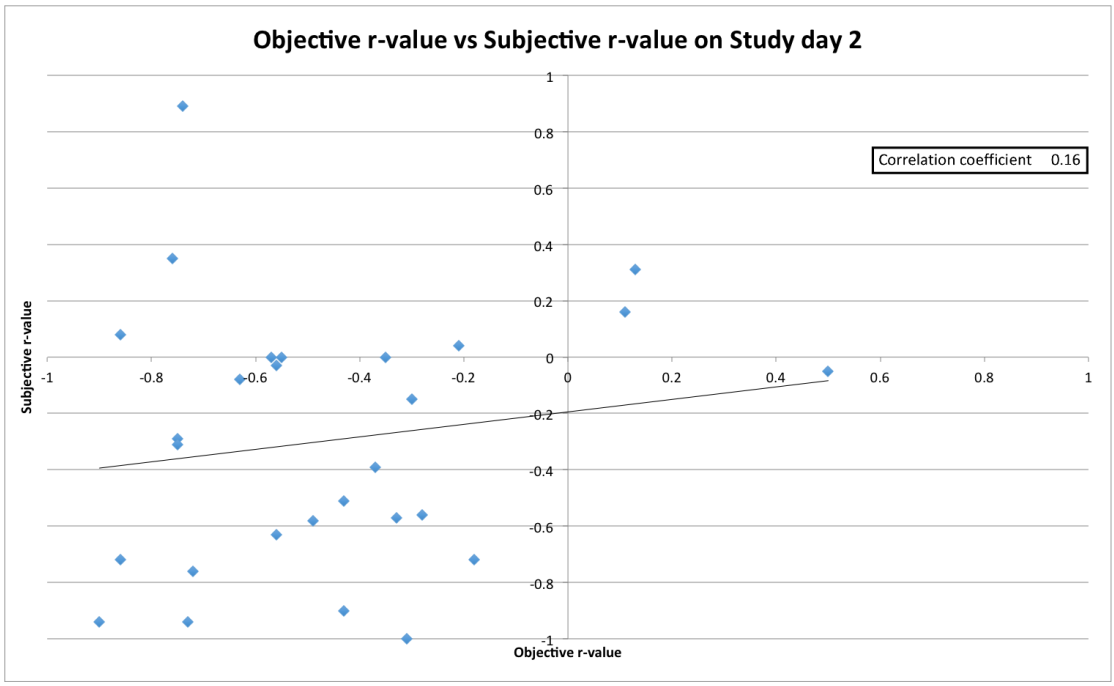


Figure 5.12 - A scatter graph of the r-value for objective data vs the r-value for subjective data on study day 2

	Correlation coefficient	p-value
Study day 1	0.1	>0.2
Study day 2	0.16	>0.2

Table 5.11 – A table showing the correlation coefficients for the relationship between r-value for rhinomanometric data and r-value for subjective ordinal scale – two subjects removed due to incomplete data.

	Study day 1		Study Day 2	
Subject	r -obj	r -sub	r - obj	r -sub
01	0.02	-0.76	-0.43	-0.9
02	-0.54	-0.64	-0.9	-0.94
03	0.12	-0.49	-0.63	-0.08
08	0.11		-0.28	-0.56
10	-0.69	-0.54	-0.49	-0.58
11	0.62	-0.65	0.5	-0.05
12	0.22	-0.29	-0.18	-0.72
14	-0.29	-0.29	-0.55	0
15	-0.61	0.03	-0.21	0.04
16	-0.28	0.36	0.11	0.16
17	-0.69	-0.14	-0.75	-0.29
18	-0.68	-0.3	-0.75	-0.31
19	0.97	0.07	-0.57	0
21	-0.64	-0.43	-0.86	0.08
22	-0.58	-0.34	-0.37	-0.39
23	0.13	0.68	-0.33	-0.57
24	-0.64	-0.45	-0.35	0
25	-0.2	0.54	-0.69	
27	-0.76	-0.82	-0.3	-0.15
28	-0.66	-0.32	-0.76	0.35
29	-0.01	0.84	-0.74	0.89
31	-0.16	-0.79	-0.43	-0.51
32	-0.23	0.24	-0.56	-0.63
33	-0.7	-0.95	-0.86	-0.72
34	-0.57		-0.45	
35	-0.89	-0.49	-0.73	-0.94
36	-0.75	0.45	-0.72	-0.76
37	-0.23	0.26	0.13	0.31
38	-0.08	-1	-0.31	-1
39	-0.79	0.6	-0.56	-0.03

Table 5.12 – A table comparing r-values (correlation coefficients) derived from objective data with corresponding values derived from the subjective data.

Discussion

When considering the r-values (correlation coefficients for left and right nasal airflow) the agreement between objective (rhinomanometric) and subjective (subjective ordinal scale) data is very limited with only nine out of 56 calculated r-values for the subjective data being within 0.1 of the r-value calculated from the objective data (all values are presented in table 5.12).

An example of where the r-values for the objective and subjective data are dissimilar is subject 01 for the first study day. This is represented graphically in Figures 5.13 and 5.14 showing the airflow data and subjective ordinal scale data respectively.

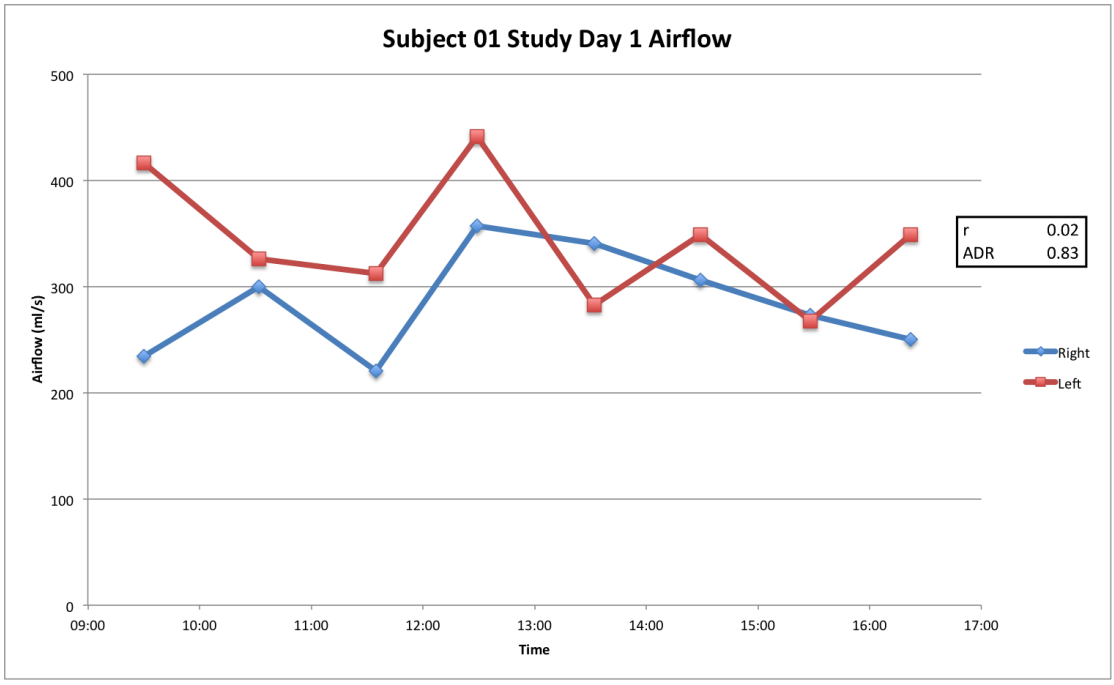


Figure 5.13 – A graph showing the left and right nasal airflow of subject 01 on study day 1 (objective data)

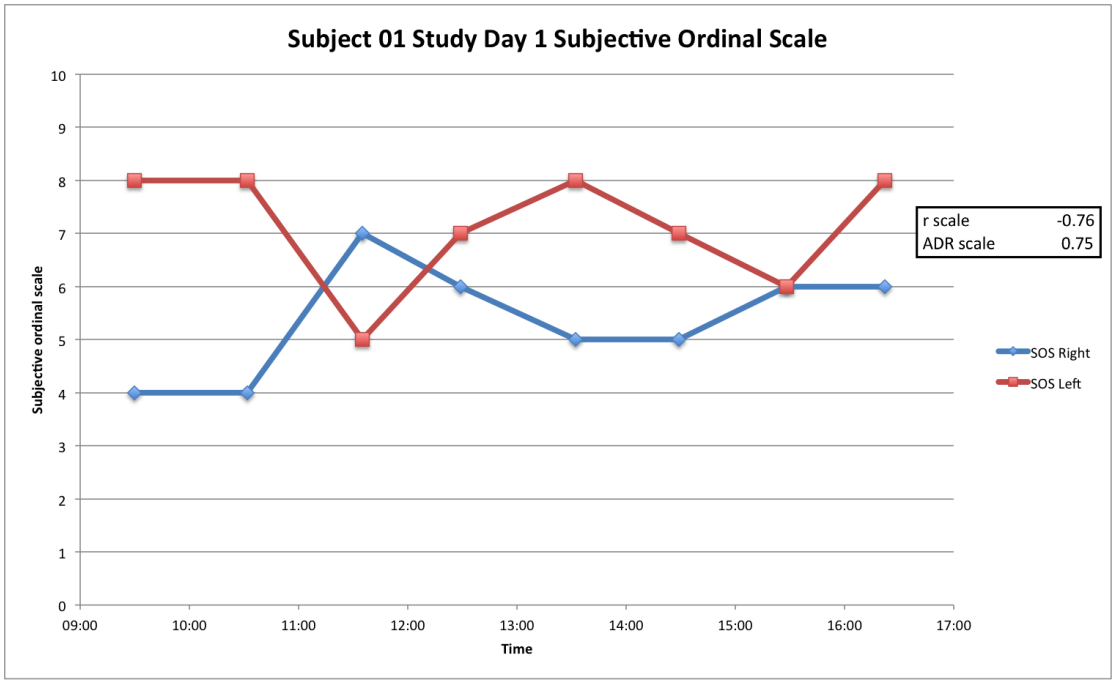


Figure 5.14 – A graph showing the left and right subjective ordinal scale of subject 01 on study day 1 (subjective data)

An example of where the r-values for objective and subjective data match closely is subject 02 on the first study day. This is represented in figure 5.15 and 5.16 which show the airflow data and subjective ordinal scale data respectively.

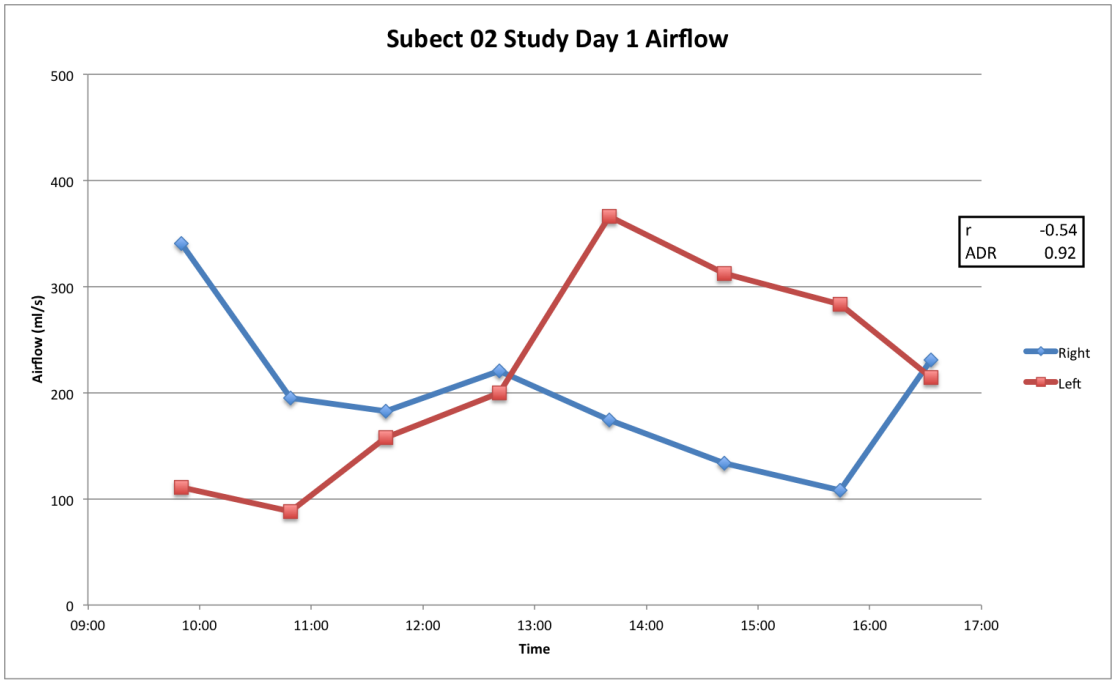


Figure 5.15 - A graph showing the left and right nasal airflow of subject 02 on study day 1 (objective data)

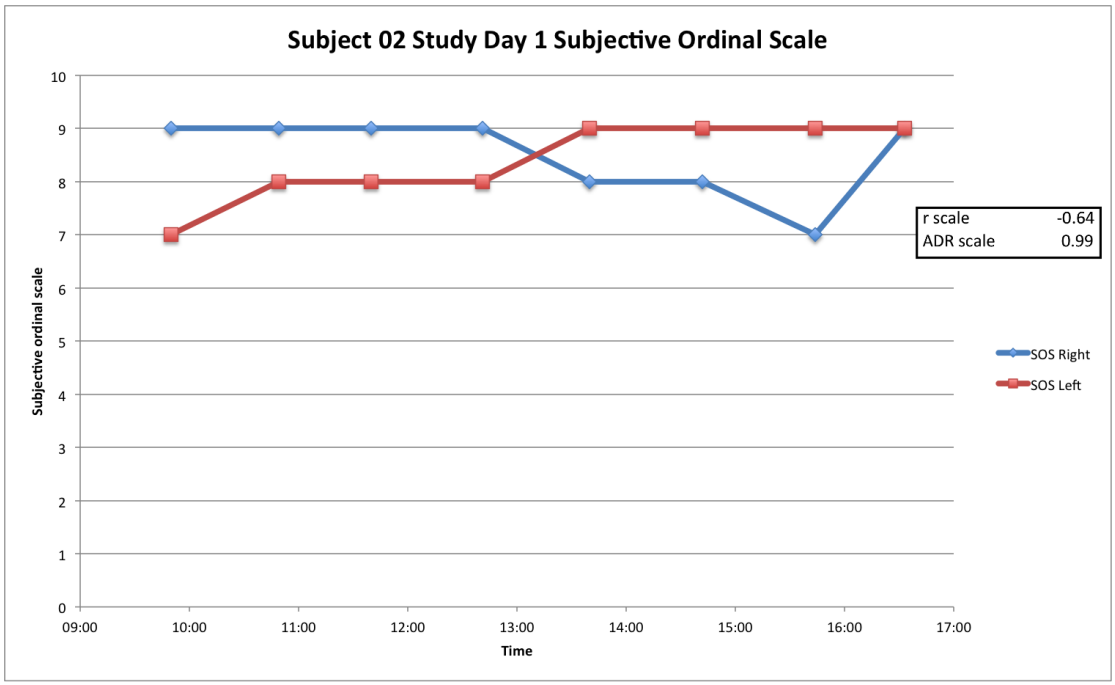


Figure 5.16 - A graph showing the left and right subjective ordinal scale of subject 02 on study day 1 (subjective data)

Such variation between subjects raises the question as to whether some may be more “in tune” with their sensation of nasal patency than others. Table

5.13 shows data for the 17 subjects who had a difference of less than 0.3 between their r-values for their objective data (rhinomanometric) and subjective data (subjective ordinal scale) on either study day. Colour coding has been used to highlight how close the values are (red for less than 0.1, yellow 0.1 to 0.2, green 0.2 to 0.3). Only six out of 17 subjects had a difference of less than 0.3 between the r-values for their objective and subjective data on both study days (subjects 02, 08, 10, 22, 27, and 33). This suggests that if the ability to accurately detect changes in nasal airflow is possible then it is an uncommon ability. It is also possible that the use of an r-value (correlation coefficient for left and right nasal airflow) in combination with the ADR as used previously in chapters 3 and 4 strives for a level of accuracy, which is beyond that achievable through monitoring of the nasal cycle using subjective measures.

Subject	Study day 1 r diff	Study day 2 r diff
02	0.1	0.04
08	0.11	0.28
10	0.15	0.09
14	0	0.55
15	0.64	0.25
16	0.64	0.05
21	0.21	0.94
22	0.24	0.02
23	0.55	0.24
24	0.19	0.35
27	0.06	0.15
31	0.63	0.08
32	0.47	0.07
33	0.25	0.14
35	0.4	0.21
36	1.2	0.04
37	0.49	0.18

Table 5.13 – A table displaying the differences between r-values (correlation coefficients) for objective and subjective assessment of nasal airflow. Colour

coding has been used to highlight how close the values are (red for less than 0.1, yellow 0.1 to 0.2, green 0.2 to 0.3.

No prior studies have looked at the use of an r-value (correlation coefficient for left and right nasal airflow) in combination with a subjective form of assessment of airflow. Therefore there are not any studies which are directly comparable with the results presented here. There have however been several studies which have attempted to correlate the subjective assessment of nasal airflow with objective findings including some specific to the nasal cycle.

Sipila et al in 1994 [109] first looked at a group of 102 subjects referred for septoplasty finding that where there was significant septal deviation as detected by rhinomanometry, there was good correlation between this data and subjective identification of the more obstructed nostril, with 46 out of 62 subjects in this group correctly identifying the more obstructed nostril. However in subjects with a normal airway resistance only half were able to correctly identify the more obstructed nostril [109]. Such results suggest that subjective assessment of the nasal sensation of airflow is difficult when the contrast between nostrils is small.

Sipila et al in 1995 [110] looked at varying levels of nasal obstruction (it was divided into four levels), both physiological and artificially introduced, using the Visual Analogue Scale (VAS) and rhinomanometry. For unilateral airflow there was good agreement between rhinomanometry and subjective data, however it was found that agreement with total airway resistance was poor. Sipila also stated that there was a better correlation between the VAS and unilateral rhinomanometry data when there was a high resistance on one side of the nose to produce obstructive symptoms [110]. This supports Siplia's previous study in the suggestion that contrast is needed in order for the nose to subjectively assess airflow correctly.

Gungor et al in 1999 [108] looked at the nasal cycle using a Visual Analogue Scale (VAS) whilst simultaneously monitoring the nasal cycle using acoustic

rhinometry. He observed that nasal volume measurements and CSA2 measurements in the study recorded using acoustic rhinometry were unstable and found no correlation between nasal volume and CSA2 measurements and the VAS which was observed to be more stable, giving the impression that the nose was insensitive to most changes in nasal volume [108].

Clark et al in 2005 [111] in a study of subjects with upper respiratory tract infections found a good correlation between unilateral conductance and the Visual Analogue Scale with a spearman rank coefficient of 0.5 ($p < 0.001$), but failed to find any correlation with overall nasal conductance [111]. It seems with more extreme states of nasal congestion that changes in nasal volume are easier to detect using a subjective scale. It could be argued that the r-value as a measure, which looks at bilateral nasal airflow, is similar to total nasal conductance and therefore unlikely to correlate with a subjective measure of nasal airflow.

Conclusions

There was no significant correlation between the r-values (correlation coefficients for left and right nasal airflow) calculated from objective data (rhinomanometric) and those calculated from subjective data (subjective ordinal scale) on either study day. When this is combined with the fact that calculation of an r-value from data obtained from the subjective ordinal scale is not always possible (two subjects had to be excluded from the analysis for this reason) it seems clear that the subjective ordinal scale cannot be used in combination with an r-value for monitoring of the nasal cycle.

Section 2 – Airflow Distribution Ratio

Results

In a comparison of the Airflow Distribution Ratios calculated from the objective data (from rhinomanometry) and subjective data (from subjective ordinal scale) as presented in the two scatter graphs figures 5.21 and 5.22 a positive relationship is shown between the subjective and objective data on both study days. This is demonstrated by correlation coefficients between the objective and subjective data on each study day of 0.38 for study day 1 and 0.46 for study day 2. The full data for the Airflow Distribution Ratios calculated from the objective and subjective data are presented in table 5.21 along with the corresponding r-values (correlation coefficients for nasal airflow).

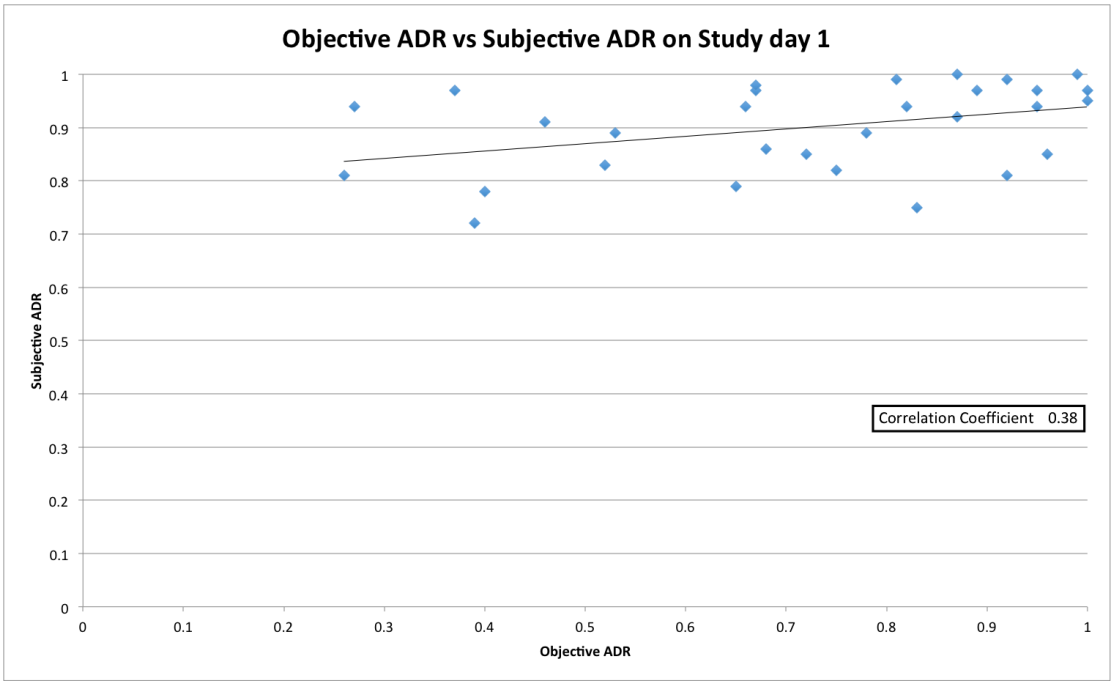


Figure 5.21 – A scatter graph of the ADR for objective data vs the ADR for subjective data on study day 1

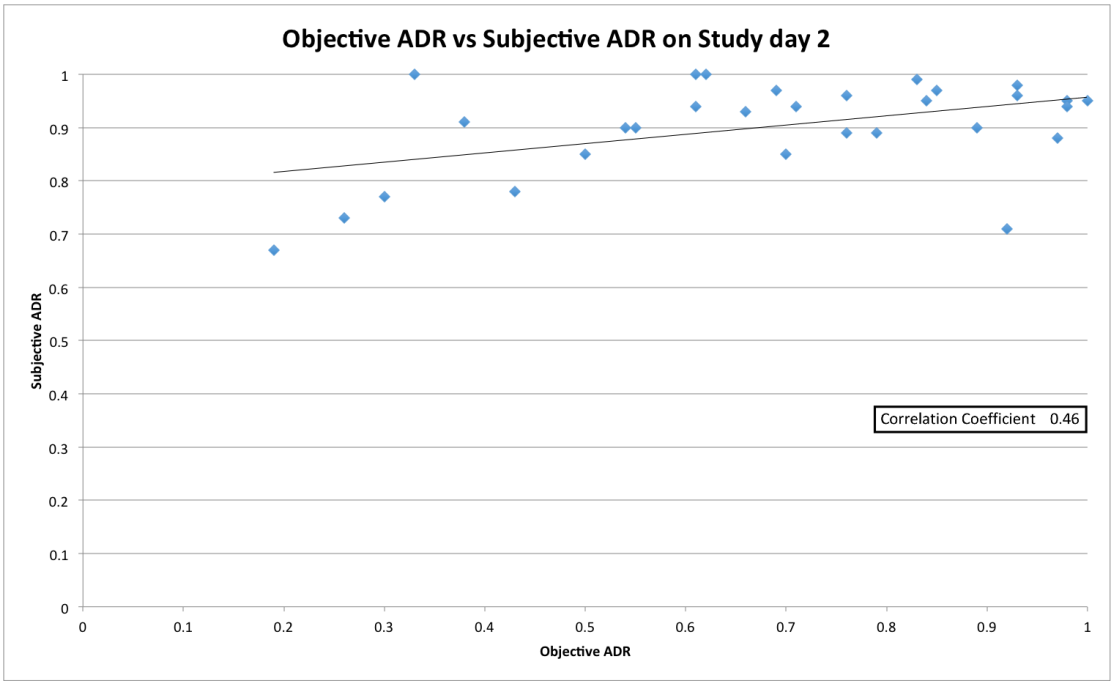


Figure 5.22 – A scatter graph of the ADR for objective data vs the ADR for subjective data on study day 2

	Study day 1				Study Day 2			
Subject	r - obj	r - sub	ADR – obj	ADR - sub	R - obj	r - sub	ADR - obj	ADR - sub
01	0.02	-0.76	0.83	0.75	-0.43	-0.9	0.92	0.71
02	-0.54	-0.64	0.92	0.99	-0.9	-0.94	0.93	0.96
03	0.12	-0.49	0.27	0.94	-0.63	-0.08	0.62	1
08	0.11		0.75	0.82	-0.28	-0.56	0.54	0.9
10	-0.69	-0.54	0.53	0.89	-0.49	-0.58	0.19	0.67
11	0.62	-0.65	0.95	0.94	0.5	-0.05	0.79	0.89
12	0.22	-0.29	0.52	0.83	-0.18	-0.72	0.83	0.99
14	-0.29	-0.29	0.37	0.97	-0.55	0	0.89	0.9
15	-0.61	0.03	1	0.97	-0.21	0.04	0.85	0.97
16	-0.28	0.36	0.87	1	0.11	0.16	0.84	0.95
17	-0.69	-0.14	0.78	0.89	-0.75	-0.29	0.98	0.95
18	-0.68	-0.3	0.72	0.85	-0.75	-0.31	0.5	0.85
19	0.97	0.07	0.81	0.99	-0.57	0	0.97	0.88
21	-0.64	-0.43	0.96	0.85	-0.86	0.08	1	0.95
22	-0.58	-0.34	0.68	0.86	-0.37	-0.39	0.43	0.78
23	0.13	0.68	0.39	0.72	-0.33	-0.57	0.61	1
24	-0.64	-0.45	0.87	0.92	-0.35	0	0.66	0.93
25	-0.2	0.54	0.89	0.97	-0.69		0.7	0.85
27	-0.76	-0.82	0.67	0.97	-0.3	-0.15	0.38	0.91
28	-0.66	-0.32	0.26	0.81	-0.76	0.35	0.61	0.94
29	-0.01	0.84	0.65	0.79	-0.74	0.89	0.93	0.98
31	-0.16	-0.79	0.4	0.78	-0.43	-0.51	0.26	0.73
32	-0.23	0.24	0.67	0.98	-0.56	-0.63	0.71	0.94
33	-0.7	-0.95	0.92	0.81	-0.86	-0.72	0.55	0.9
34	-0.57		0.99	1	-0.45		0.98	0.94
35	-0.89	-0.49	0.95	0.97	-0.73	-0.94	0.3	0.77
36	-0.75	0.45	1	0.95	-0.72	-0.76	0.76	0.96
37	-0.23	0.26	0.66	0.94	0.13	0.31	0.76	0.89
38	-0.08	-1	0.82	0.94	-0.31	-1	0.69	0.97
39	-0.79	0.6	0.46	0.91	-0.56	-0.03	0.33	1

Table 5.21 - A table comparing r (correlation coefficient) and ADR derived from objective data with corresponding values derived from the subjective data

Full data were obtainable for the Airflow Distribution Ratio calculations. The calculated correlation coefficients comparing the objective data and the subjective data are listed in table 5.22. The calculated correlation coefficients demonstrated significant relationships for the relationship between the subjective and objective ADR on both study days.

	Correlation coefficient	**p-value**
ADR study day 1	0.38	<0.05
ADR study day 2	0.46	<0.02

Table 5.22 – A table showing the correlation coefficients for the relationship between the ADR for objective data and subjective data

Discussion

Whilst the correlation between subjective and objective data for the Airflow Distribution Ratio is clear (as seen in figures 5.21 and 5.22) and statistically significant (p-value for study day 1 <0.05 and p-value for study day 2 <0.02), the data does not appear to completely conform with a strict direct relationship. On both study days it can be seen in figures 5.21 and 5.22 that the objective ADR has been calculated to be less than 0.3 for some subjects, however the lowest calculated subjective ADR is around 0.7. This represents a clear discrepancy where an ADR calculated from subjective data cannot be expected to be equal to one calculated from objective data. This problem is particularly emphasised by the presence of outlying data points.

As mentioned previously it has been found that there is a poor correlation between subjective measurements and total nasal conductance, but a good correlation can be found for unilateral conductance [111]. The ADR considers the equality of airflow based on two unilateral conductance measures. It is in line with the expectation then that we see a significant correlation between

objective and subjective measures for the ADR. This is the first study to look at nasal airflow using a combination of subjective measurement and the ADR.

Conclusions

There is a statistically significant relationship between the objective data and subjective data for the airflow distribution ratio. However this measure in isolation without the use of an r-value is unlikely to be useful in monitoring the nasal cycle.

Section 3 – Nasal Partitioning Ratio

Results

The data obtained for objective (rhinomanometric) and subjective (subjective ordinal scale) assessment of nasal airflow by the Nasal Partitioning Ratio (NPR) are presented in figures 5.31 and 5.32. These figures demonstrate the correlation between objective and subjective data on study days 1 and 2 respectively. There is a strong positive correlation between objective and subjective data on both study days proven by correlation coefficients of 0.67 for study day 1 and 0.72 for study day 2. These correlation coefficients are statistically significant with p-values of less than 0.001 (see table 5.31).

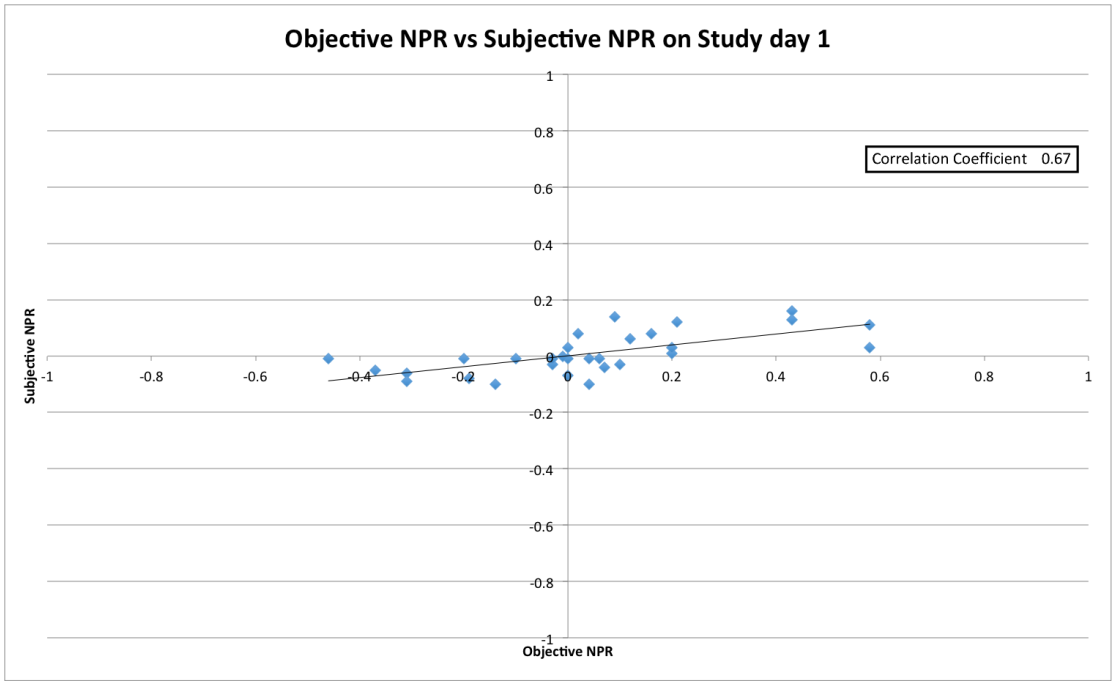


Figure 5.31 - A scatter graph of the NPR for objective data vs the NPR for subjective data on study day 1

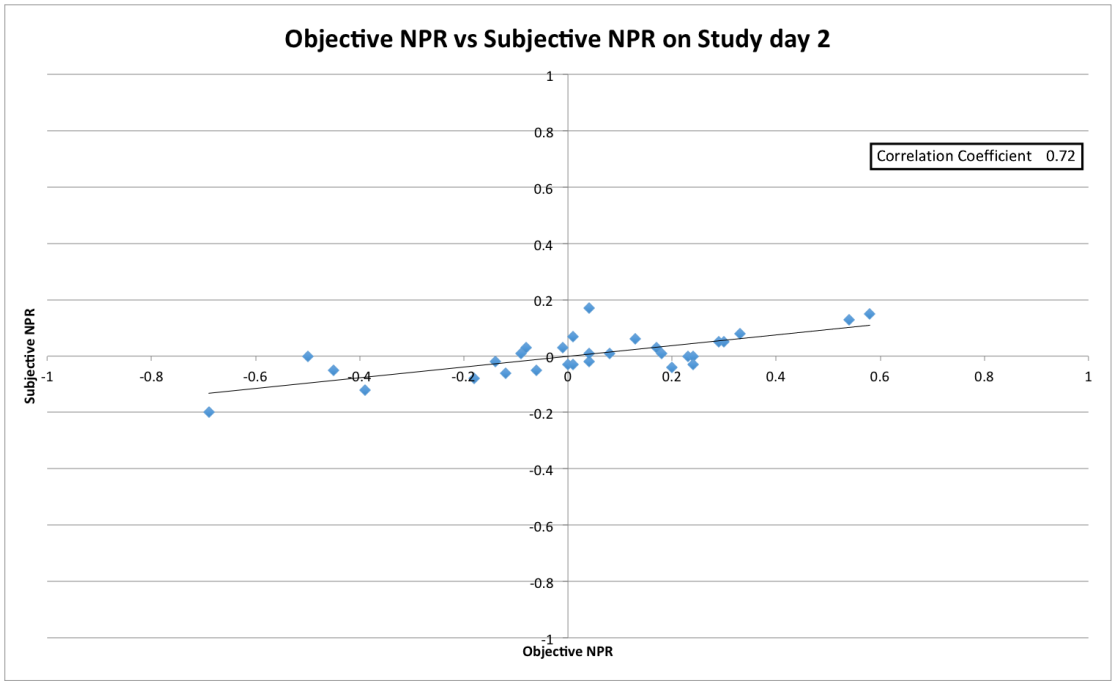


Figure 5.32 - A scatter graph of the NPR for objective data vs the NPR for subjective data on study day 2

	Correlation coefficient	p-value
NPR study day 1	0.67	<0.001
NPR study day 2	0.72	<0.001

Table 5.31 - A table showing the correlation coefficients for the relationship between the NPR for objective data and subjective data

	Study day 1		Study Day 2	
Subject	NPR - obj	NPR - sub	NPR - obj	NPR - sub
01	0.09	0.14	0.04	0.17
02	0.04	-0.01	0.04	-0.02
03	0.58	0.03	0.23	0
08	-0.14	-0.1	0.3	0.05
10	-0.31	-0.06	-0.69	-0.2
11	-0.03	-0.03	-0.12	-0.06
12	-0.31	-0.09	-0.09	0.01
14	-0.46	-0.01	-0.06	-0.05
15	0	-0.01	0.08	0.01
16	0	-0.07	-0.08	0.03
17	0.12	0.06	-0.01	0.03
18	0.16	0.08	0.33	0.08
19	-0.1	-0.01	0.01	0.07
21	0.02	0.08	0	-0.03
22	-0.19	-0.08	-0.39	-0.12
23	0.43	0.16	0.24	0
24	0.07	-0.04	0.2	-0.04
25	0.06	-0.01	-0.18	-0.08
27	-0.2	-0.01	-0.45	-0.05
28	0.58	0.11	0.24	-0.03
29	0.21	0.12	0.04	0.01
31	0.43	0.13	0.58	0.15
32	0.2	0.01	0.17	0.03
33	0.04	-0.1	0.29	0.05
34	-0.01	0	0.01	-0.03
35	-0.03	-0.01	0.54	0.13
36	0	0.03	-0.14	-0.02
37	0.2	0.03	0.13	0.06
38	0.1	-0.03	0.18	0.01
39	-0.37	-0.05	-0.5	0

Table 5.32 - A table comparing the Nasal Partitioning Ratio derived from objective data with corresponding values derived from the subjective data

Full data were obtainable for the calculation of the Nasal Partitioning Ratio on both study days and are presented in table 5.32.

Discussion

Whilst the relationship between subjective and objective data for the Nasal Partitioning Ratio (NPR) is proportional, it is clear that the two sets of data are not equivalent. As seen in table 5.32 and represented graphically in figure 5.31 and figure 5.32 the subjective NPR values range between -0.2 and 0.17, whereas the objective values range between -0.9 and 0.58. So the subjective value for NPR is much lower than the objective NPR value it is matched to. By combining the NPR data from both study days as seen in figure 5.33 a formula showing the relationship between the objective and subjective NPR is demonstrable, this formula is y = 0.1917x + 0.0002, where y is the subjective NPR and x is the objective NPR. Such a formula may be potentially useful when using the subjective ordinal scale for monitoring the nasal cycle.

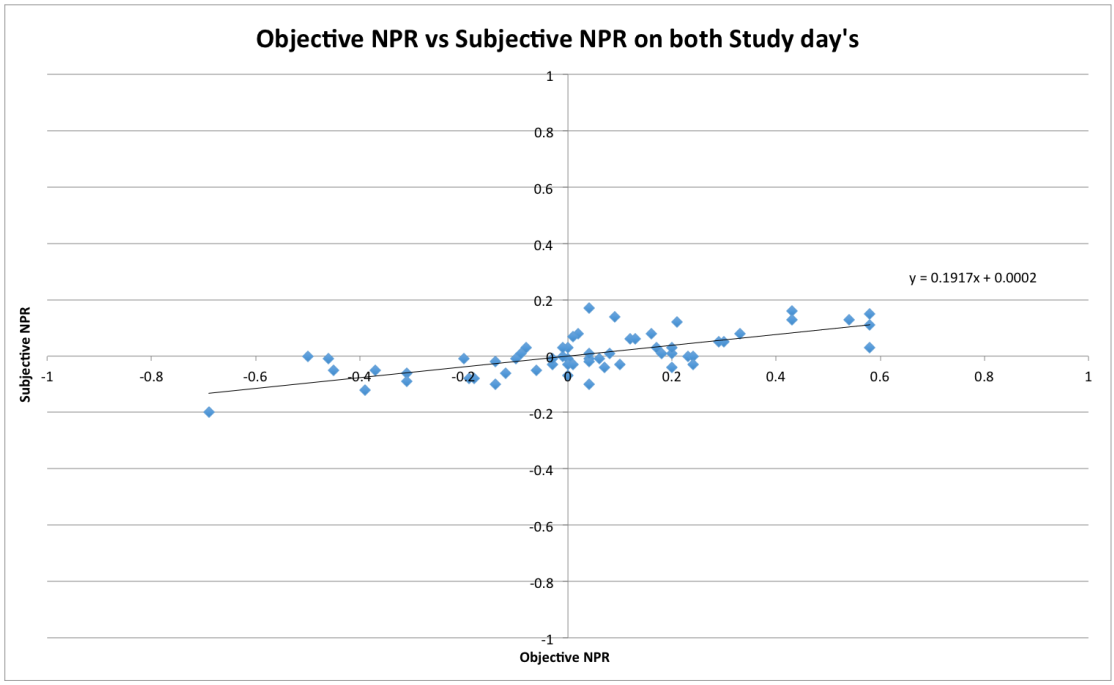


Figure 5.33 – A scatter graph showing the relationship between objective and subjective data for the Nasal Partitioning Ratio on both study days with formula for the trend line given.

It is useful to make a comparison with the results of Boyce and Eccles' 2006 study [96], which developed the Subjective Ordinal Scale and demonstrated its use in combination with the Nasal Partitioning Ratio (NPR). Boyce's study differed slightly in the use of rhinospirometry rather than rhinomanometry to measure nasal airflow. However the Nasal Partitioning Ratio is applicable to both methods of nasal airflow measurement. Boyce reported a correlation coefficient of 0.8 ($p=0.001$) for the correlation between his objective and subjective data (collected from use of the subjective ordinal scale) [96]. There is a difference however in comparison to the data reported by Boyce in that the calculated NPR values for subjective and objective data are more equivalent as shown in figure 5.34, e.g. an objective value of 0.5 is likely to correspond to subjective value of around 0.5. Whereas for the data reported in this study there is low corresponding subjective value compared to the objective value as previously demonstrated in figures 5.31 and 5.32, e.g a subjective value of 0.2 may correspond to objective value of around 0.7. The subject groups, which were recruited, may explain this as Boyce's study recruited subjects who were awaiting septoplasty for nasal septal deviation [96] and so aware of their asymmetric airflow, whereas this study recruited normal subjects in who such deviation was excluded and were therefore less aware of any asymmetry in their nasal airflow.

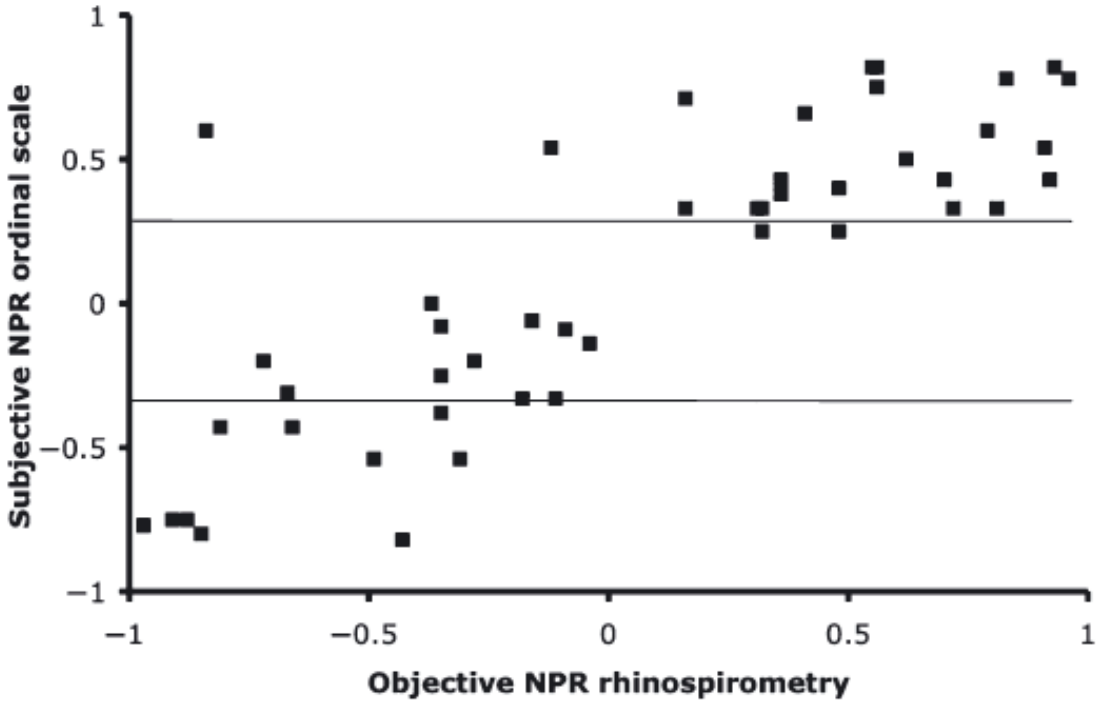


Figure 5.34 – A scatter diagram comparing the Nasal Partitioning Ratio calculated from subjective and objective data in Boyce's study – taken from Boyce and Eccles 2006 [96]

Conclusions

The relationship between objective (rhinomanometric) and subjective (subjective ordinal scale) data for the Nasal Partitioning Ratio (NPR) is statistically very significant ($p < 0.001$). Using the NPR in combination with subjective ordinal scale is likely to be a reliable method for observing the nasal cycle without the use of rhinomanometry. The limitation of this method being that the NPR indicates a single point on a graph where airflow predominates rather than giving two individual points for left and right nasal airflow.

Chapter 6: Final Discussion and Conclusions

Final Discussion and Conclusions

The aims of this study were:

1. To study the nasal cycle in healthy subjects over a period of 7 hours
2. To study the stability of the nasal cycle over a period of 6-9 days
3. To assess the use of a subjective ordinal scale as a tool for measurement of the nasal cycle

This study uses a numerical definition set out for the “classical” nasal cycle by Flanagan and Eccles of having a correlation coefficient more negative than -0.6 and an Airflow Distribution Ratio of more than 0.7 [1].

According to the criteria set out by Flanagan and Eccles 26.7% of the subjects in this study had a “classical” nasal cycle at study day 1. This is comparable with the figure of 21% reported by Flanagan and Eccles themselves [1]. This figure did however decrease at study day 2 with only 16.7% of subjects fitting with the Flanagan and Eccles’ criteria for a “classical” nasal cycle.

The nasal cycle was shown to be unstable within the study group, only 37.5% of those defined as having a “classical” nasal cycle at study day 1 continued to meet the definition at study day 2, 15% of those previously defined as having non-significant airflow patterns moved into the “classical” group at study day 2.

There was an overall trend seen within the data for r-values (a correlation coefficient for left and right nasal airflow), with a tendency for the r-value at study day 2 to be more negative than the corresponding r-value at study day 1. This is demonstrated by a significant correlation coefficient of -0.73 ($p < 0.001$). Such a trend suggests that there is an inherent reciprocal input to the nasal cycle. Previous work by Bamford and Eccles using a feline model in 1985 has shown the reticular formation of the brainstem is an area capable of reciprocal input to the nasal cycle, although non-reciprocal input was also

demonstrated in the hypothalamus [76]. Based on these observations a model for control of the nasal cycle can be proposed, whereby a hypothalamus oscillator gives input to the nasal cycle, which is modified by two brainstem oscillators. This is illustrated in figure 6.1. This model is proposed because of the variation seen in the types of nasal cycle recorded. For example on study day 1 subject 21 (see figure 3.3) and subject 19 (see figure 3.5) both display cyclical changes in airflow such as may be generated by an oscillator. However where subject 21's airflow pattern is reciprocal in nature, subject 19's is seen to be in phase. It is therefore proposed that when the left and right brainstem oscillators are in equal opposition that an "in phase" type of nasal cycle would occur, but this may change to a state where the left and right brainstem oscillators predominate in an alternating fashion giving negative feedback to one another, which would produce a "classical" nasal cycle. This is likely to be an imperfect mechanism, hence airflow patterns, which are not easy to classify, may occur e.g subject 8 on study day 2 (see figure 6.2). The proof for this model may be difficult to obtain, but could potentially lie in the field of imaging with the use of functional Magnetic Resonance Imaging and so could be the focus of future research.

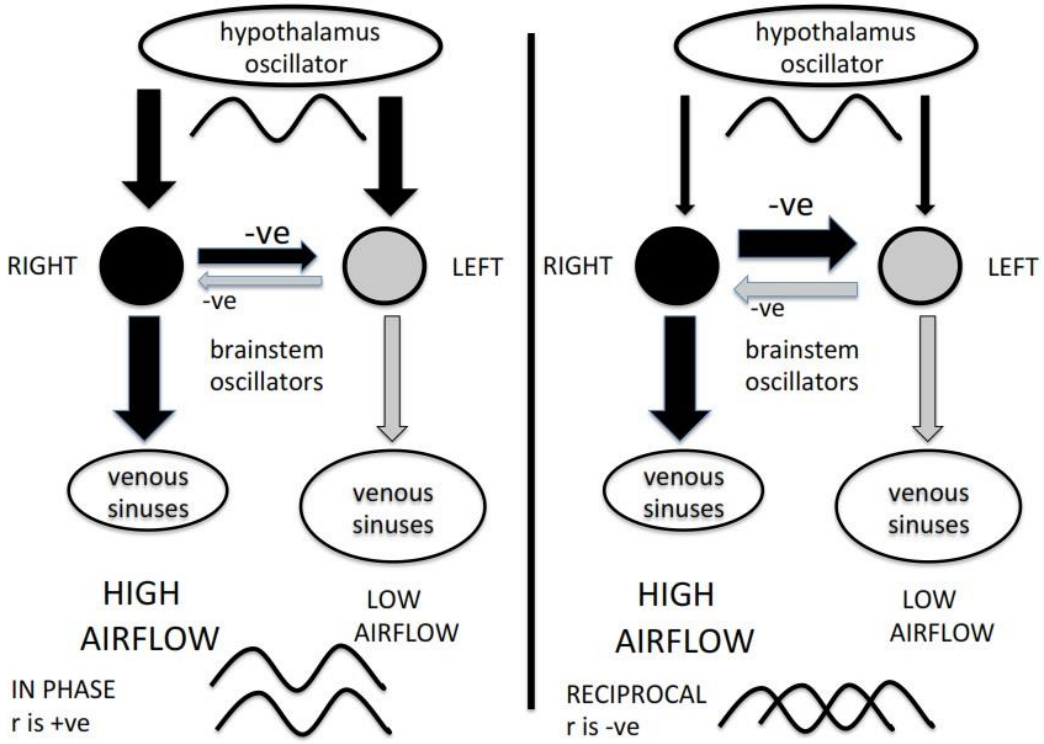


Figure 6.1 – A diagram illustrating a proposed model for the control of the nasal cycle by a hypothalamus oscillator and two brainstem oscillators.

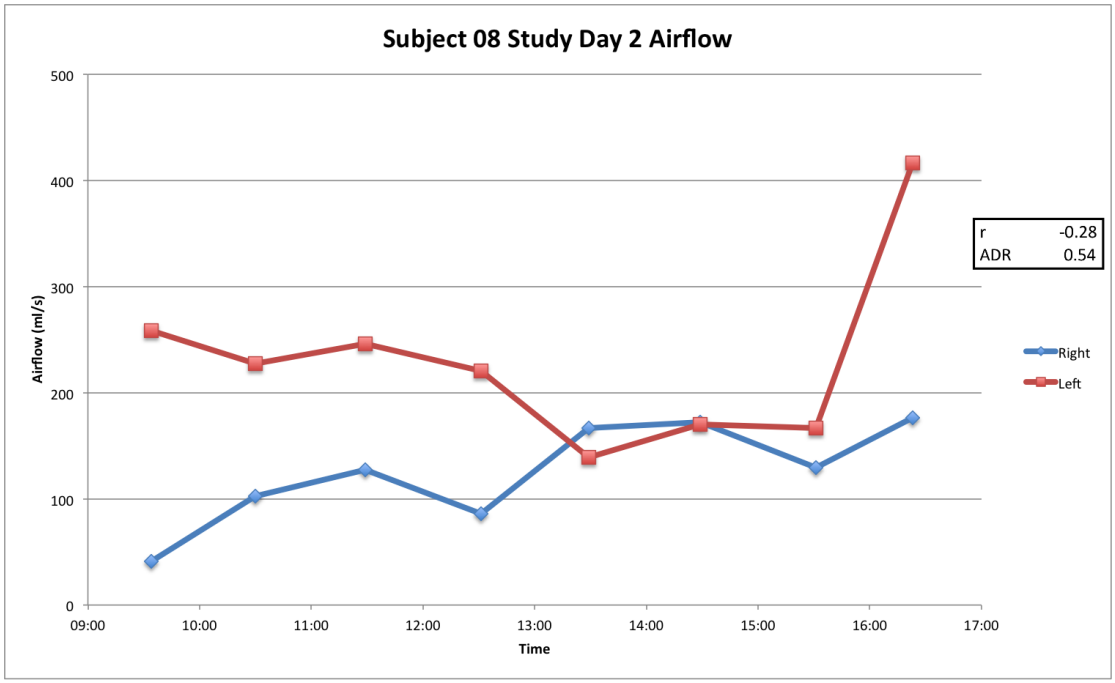


Figure 6.2 – A graph showing airflow for the left and right nasal passages for subject 08 on study day 2

The use of the Subjective Ordinal Scale as a self-assessment tool for monitoring the nasal cycle was investigated in this thesis. As with the objective assessment of nasal airflow the measures of an r-value and Airflow Distribution Ratio (ADR) were applied to the collected subjective data. In addition the Nasal Partitioning Ratio (NPR) was also used for comparison of the objective and subjective data.

There was no significant correlation between the objective and subjective data for the r-value, but significant correlations were found between the objective and subjective data for the ADR and NPR. The relationship for the NPR was particularly strong with a p-value of <0.001 on both study days, suggesting that the Subjective Ordinal Scale could be used in combination with the NPR for monitoring the nasal cycle subjectively.

References:

1. Flanagan, P and Eccles, R, *Spontaneous changes of unilateral nasal airflow in man. A re- examination of the 'nasal cycle'.* Acta Oto-laryngol (Stockholm), 1997. **117**(4): p. 590-595.
2. Geurkink, N, *Nasal anatomy, physiology, and function.* The Journal of allergy and clinical immunology, 1983. **72**(2): p. 123-8.
3. Butler, J, *The work of breathing through the nose.* Clinical Sciences, 1960. **19**: p. 55-62.
4. Lund, VJ, *Nasal physiology: neurochemical receptors, nasal cycle, and ciliary action.* Allergy and asthma proceedings : the official journal of regional and state allergy societies, 1996. **17**(4): p. 179-84.
5. Cole, P, *The four components of the nasal valve.* Am. J. Rhinol., 2003. **17**(2): p. 107-10.
6. Haight, JS and Cole, P, *The site and function of the nasal valve.* The Laryngoscope, 1983. **93**(1): p. 49-55.
7. Jones, N, *The nose and paranasal sinuses physiology and anatomy.* Advanced drug delivery reviews, 2001. **51**(1-3): p. 5-19.
8. Eccles, R, *Nasal airflow in health and disease.* Acta Otolaryngol., 2000. **120**(5): p. 580-95.
9. Kayser, R, *Die exacte messung der luftdurchgangigkeit der nase.* Archiv fur Laryngol Rhinol, 1895. **3**: p. 101-120.
10. Stoksted, P, *Rhinometric measurements for determination of the nasal cycle.* Acta Otolaryngol. Suppl., 1953. **109**: p. 159-75.
11. Stoksted, P, *The physiologic cycle of the nose under normal and pathologic conditions.* Acta Otolaryngol., 1952. **42**(1-2): p. 175-9.
12. Hasegawa, M and Kern, EB, *The human nasal cycle.* Mayo Clin. Proc., 1977. **52**(1): p. 28-34.
13. Fisher, EW, Scadding, GK, and Lund, VJ, *The role of acoustic rhinometry in studying the nasal cycle.* Rhinology, 1993. **31**(2): p. 57-61.
14. Fisher, EW, Liu, M, and Lund, VJ, *The nasal cycle after deprivation of airflow: a study of laryngectomy patients using acoustic rhinometry.* Acta Otolaryngol., 1994. **114**(4): p. 443-6.
15. Fisher, EW, Palmer, CR, and Lund, VJ, *Monitoring fluctuations in nasal patency in children: acoustic rhinometry versus rhinohygrometry.* J. Laryngol. Otol., 1995. **109**(6): p. 503-8.
16. Mirza, N, Kroger, H, and Doty, RL, *Influence of age on the 'nasal cycle'.* The Laryngoscope, 1997. **107**(1): p. 62-6.
17. Eccles, R, *The nasal cycle in respiratory defence.* Acta oto-rhino-laryngologica (Belgica), 2000. **54**: p. 281-286.
18. Lindemann, J, Leiacker, R, Rettinger, G, and Keck, T, *The relationship between water vapour saturation of inhaled air and nasal patency.* Eur. Respir. J., 2003. **21**(2): p. 313-6.
19. Littlejohn, MC, Stiernberg, CM, Hokanson, JA, Quinn, FB, Jr., and Bailey, BJ, *The relationship between the nasal cycle and mucociliary clearance.* The Laryngoscope, 1992. **102**(2): p. 117-20.

20. Eccles, R, *A Role For the Nasal Cycle In Respiratory Defense.* Eur. Respir. J., 1996. **9**(2): p. 371-376.
21. White, DE, Bartley, J, and Nates, RJ, *Model demonstrates functional purpose of the nasal cycle.* Biomedical engineering online, 2015. **14**(1): p. 38.
22. Cole, P, Forsyth, R, and Haight, JS, *Effects of cold air and exercise on nasal patency.* The Annals of otology, rhinology, and laryngology, 1983. **92**(2 Pt 1): p. 196-8.
23. Forsyth, RD, Cole, P, and Shephard, RJ, *Exercise and nasal patency.* Journal of applied physiology: respiratory, environmental and exercise physiology, 1983. **55**(3): p. 860-5.
24. Broms, P, *Rhinomanometry. III Procedures and criteria for distinction between skeletal stenosis and mucosal swelling.* Acta Oto-laryngol (Stockholm), 1982. **94**(3-4): p. 361-370.
25. Dallimore, NS and Eccles, R, *Changes in human nasal resistance associated with exercise, hyperventilation and rebreathing.* Acta Otolaryngol., 1977. **84**(5-6): p. 416-21.
26. Stroud, RH, Wright, ST, and Calhoun, KH, *Nocturnal nasal congestion and nasal resistance.* The Laryngoscope, 1999. **109**(9): p. 1450-3.
27. Haight, JS and Cole, P, *Unilateral nasal resistance and asymmetrical body pressure.* The Journal of otolaryngology. Supplement, 1986. **16**: p. 1-31.
28. Rohrmeier, C, Schittek, S, Ettl, T, Herzog, M, and Kuehnel, TS, *The nasal cycle during wakefulness and sleep and its relation to body position.* The Laryngoscope, 2014. **124**(6): p. 1492-7.
29. Cole, P and Haight, JS, *Posture and the nasal cycle.* The Annals of otology, rhinology, and laryngology, 1986. **95**(3 Pt 1): p. 233-7.
30. Rao, S and Potdar, A, *Nasal airflow with body in various positions.* J. Appl. Physiol., 1970. **28**(2): p. 162-5.
31. Davies, AM and Eccles, R, *Reciprocal changes in nasal resistance to airflow caused by pressure applied to the axilla.* Acta Otolaryngol., 1985. **99**(1-2): p. 154-9.
32. Kimura, A, et al., *Phase of nasal cycle during sleep tends to be associated with sleep stage.* The Laryngoscope, 2013. **123**(8): p. 2050-5.
33. Atanasov, AT and Dimov, PD, *Nasal and sleep cycle--possible synchronization during night sleep.* Med. Hypotheses, 2003. **61**(2): p. 275-7.
34. Funk, E and Clarke, J, *The nasal cycle. Observations over prolonged periods of time.* Reseach Bulletin of the Himalaya International Institute, 1980. **Winter**: p. 1-3.
35. Olsson, P and Bende, M, *Influence of environmental temperature on human nasal mucosa.* Ann. Otol. Rhinol. Laryngol., 1985. **94**(2 Pt 1): p. 153-5.
36. Sano, H, *[Influence of environmental temperature (cold exposure) on nasal resistance].* Nihon Jibiinkoka Gakkai Kaiho, 1992. **95**(11): p. 1785-99.
37. Yogeetha, R, Raman, R, and Quek, KF, *Effects of temperature changes on nasal patency.* Singapore Med. J., 2007. **48**(4): p. 304-6.
38. Lal, D, Gorges, ML, Ungkhara, G, Reidy, PM, and Corey, JP, *Physiological change in nasal patency in response to changes in posture, temperature,*

and humidity measured by acoustic rhinometry. Am. J. Rhinol., 2006. **20**(5): p. 456-62.
39. Salman, SD, Proctor, DF, Swift, DL, and Eveering, SA, *Nasal resistance: description of a method and effect of temperature and humidity changes.* Ann. Otol. Rhinol. Laryngol., 1971. **80**(5): p. 736-43.
40. Roblin, D and Eccles, R, *What, if any is the value of septal surgery ?* Clin. Otolaryngol., 2002. **27**: p. 77-80.
41. Garcia, GJ, Rhee, JS, Senior, BA, and Kimbell, JS, *Septal deviation and nasal resistance: an investigation using virtual surgery and computational fluid dynamics.* Am J Rhinol Allergy, 2010. **24**(1): p. e46-53.
42. Sung, YW, Lee, MH, Kim, IJ, Lim, DW, Rha, KS, and Park, CI, *Nasal cycle in patients with septal deviation: evaluation by acoustic rhinometry.* Am. J. Rhinol., 2000. **14**(3): p. 171-4.
43. Hanif, J, Jawad, SS, and Eccles, R, *The nasal cycle in health and disease.* Clin. Otolaryngol. Allied Sci., 2000. **25**(6): p. 461-7.
44. Robinson, RW, White, DP, and Zwillich, CW, *Moderate alcohol ingestion increases upper airway resistance in normal subjects.* Am. Rev. Respir. Dis., 1985. **132**(6): p. 1238-41.
45. Eccles, R and Tolley, NS, *The effect of alcohol ingestion upon nasal airway resistance.* Rhinology, 1987. **25**: p. 245-248.
46. Eccles, R, *Nasal airflow and decongestants*, in *Rhinitis Mechanisms and management*, Naclerio, RM, Durham, SR, and Mygind, N, Editors. 1999, Marcel Dekker: New York. p. 291-312.
47. Haenisch, B, et al., *Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline.* Fundam. Clin. Pharmacol., 2010. **24**(6): p. 729-39.
48. Flanagan, P and Eccles, R, *Physiological versus pharmacological decongestion of the nose in healthy human subjects.* Acta Oto-laryngol (Stockholm), 1998. **118**(1): p. 110-113.
49. Secher, C, Kirkegaard, J, Borum, P, Maanssom, A, Osterhammel, P, and Mygind, N, *Signifigance of H1 and H2 receptors in the human nose: rationale for topical use of combined antihistamine preparations.* J. Allergy Clin. Immunol., 1982. **70**(3): p. 211-218.
50. Schmidt, BMW, et al., *The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis.* J. Clin. Pharmacol., 1999. **39**(10): p. 1062-1069.
51. Pinargote, P, Guillen, D, and Guarderas, JC, *ACE inhibitors: upper respiratory symptoms.* BMJ Case Rep., 2014. **2014**.
52. Cheng, JW, *Nebivolol: a third-generation beta-blocker for hypertension.* Clin. Ther., 2009. **31**(3): p. 447-62.
53. Ellegard, E and Karlsson, G, *Nasal congestion during the menstrual cycle.* Clin. Otolaryngol. Allied Sci., 1994. **19**(5): p. 400-3.
54. Toppozada, H, Michaels, L, Toppozada, M, El-Ghazzawi, E, Talaat, A, and Elwany, S, *The human nasal mucosa in the menstrual cycle. A histochemical and electron microscopic study.* The Journal of laryngology and otology, 1981. **95**(12): p. 1237-47.
55. Navarrete-Palacios, E, Hudson, R, Reyes-Guerrero, G, and Guevara-Guzman, R, *Correlation between cytological characteristics of the nasal epithelium and the menstrual cycle.* Archives of otolaryngology--head & neck surgery, 2003. **129**(4): p. 460-3.

56. Philpott, CM, El-Alami, M, and Murty, GE, *The effect of the steroid sex hormones on the nasal airway during the normal menstrual cycle.* Clin. Otolaryngol. Allied Sci., 2004. **29**(2): p. 138-42.
57. Haeggstrom, A, Ostberg, B, Stjerna, P, Graf, P, and Hallen, H, *Nasal mucosal swelling and reactivity during a menstrual cycle.* ORL; journal for oto-rhino-laryngology and its related specialties, 2000. **62**(1): p. 39-42.
58. Toppozada, H, Michaels, L, Toppozada, M, El-Ghazzawi, I, Talaat, M, and Elwany, S, *The human respiratory nasal mucosa in pregnancy. An electron microscopic and histochemical study.* J. Laryngol. Otol., 1982. **96**(7): p. 613-26.
59. Ellegard, E and Karlsson, G, *Nasal congestion during pregnancy.* Clin. Otolaryngol., 1999. **24**(4): p. 307-311.
60. Philpott, CM, Conboy, P, Al-Azzawi, F, and Murty, G, *Nasal physiological changes during pregnancy.* Clin. Otolaryngol. Allied Sci., 2004. **29**(4): p. 343-51.
61. Barrett, K, Brooks, H, Boitano, S, Barman, S, *The Autonomic Nervous System*, in *Ganong's Review of Medical Physiology*. 2010, McGraw-Hill Medical. p. 261-272.
62. Hansen, JT, *Introduction to the Human Body*, in *Netter's Clinical Anatomy*. 2010, Saunders Elservier: Philadelphia. p. 1-40.
63. Eccles, R and Eccles, KSJ, *Asymmetry in the autonomic nervous system with reference to the nasal cycle, migraine, anisocoria and Meniere's syndrome.* Rhinology, 1981. **19**: p. 121-125.
64. Olsson, P and Bende, M, *Sympathetic neurogenic control of blood flow in human nasal mucosa.* Acta Otolaryngol., 1986. **102**(5-6): p. 482-7.
65. Olsson, P, *Studies of bloodflow in human nasal mucosa with Xe133 washout technique and laser doppler flowmetry (thesis).* Department of Oto-Rhino-Laryngology, 1986. **102**.
66. Lacroix, JS, Stjarne, P, Anggard, A, and Lundberg, JM, *Sympathetic vascular control of the pig nasal mucosa: (I). Increased resistance and capacitance vessel responses upon stimulation with irregular bursts compared to continuous impulses.* Acta Physiol. Scand., 1988. **132**(1): p. 83-90.
67. Malcomson, KG, *The vasomotor activities of the nasal mucous membrane.* The Journal of laryngology and otology, 1959. **73**(2): p. 73-98.
68. Davis, SS and Eccles, R, *Nasal congestion: mechanisms, measurement and medications. Core information for the clinician.* Clin. Otolaryngol. Allied Sci., 2004. **29**(6): p. 659-66.
69. Malm, L, *Resistance and capacitance vessels in the nasal mucosa.* Rhinology, 1975. **13**: p. 85-89.
70. Anggard, A and Densert, O, *Adrenergic innervation of the nasal mucosa in cat.* Acta Otolaryngologica, 1974. **78**: p. 232-241.
71. Stoksted, P and Thomsen, KA, *Changes in the nasal cycle under stellate ganglion block.* Acta Otolaryngol. Suppl., 1953. **109**: p. 176-81.
72. Malm, L, *Stimulation of sympathetic nerve fibres to the nose in cats.* Acta Otolaryngologica (Stockholm), 1973. **75**: p. 519 - 526.
73. Eccles, R and Wilson, H, *The autonomic innervation of the nasal blood vessels of the cat.* J. Physiol., 1974. **238**: p. 549-560.

74. Wilson, H and Yates, MS, *Proceedings: Crossed sympathetic innervation of the cat nasal vasculature.* The Journal of physiology, 1975. **247**(1): p. 4P-5P.
75. Eccles, R and Lee, RL, *The Influence of the Hypothalamus on the Sympathetic Innervation of the Nasal Vasculature of the Cat.* Acta Otolaryngol., 1981. **91**(1-2): p. 127-134.
76. Bamford, OS and Eccles, R, *The Central Reciprocal Control of Nasal Vasomotor Oscillations.* Pflug Arch Eur J Phy, 1982. **394**(2): p. 139-143.
77. Eccles, R, *Sympathetic control of nasal erectile tissue.* Eur J Respir Dis Suppl, 1983. **128 (Pt 1)**: p. 150-4.
78. Eccles, R and Wilson, H, *The parasympathetic secretory nerves of the nose of the cat.* The Journal of physiology, 1973. **230**(1): p. 213-23.
79. Blier, Z, *Physiology of the sphenopalatine ganglion.* Am. J. Physiol., 1930. **93**(2): p. 398-406.
80. Anggard, A, *The effects of parasympathetic nerve stimulation on the microcirculation and secretion in the nasal mucosa of the cat.* Acta Otolaryngologica (Stockholm), 1974. **78**: p. 98-105.
81. Eccles, R and Lee, RL, *The influence of the hypothalamus on the sympathetic innervation of the nasal vasculature of the cat.* Acta Otolaryngologica (Stockholm), 1981. **91**: p. 127-134.
82. Werntz, DA, Bickford, RG, Bloom, FE, and Shannahoff-Khalsa, DS, *Alternating cerebral hemispheric activity and the lateralization of autonomic nervous function.* Hum. Neurobiol., 1983. **2**(1): p. 39-43.
83. Eccles, R, *The domestic pig as an experimental animal for studies on the nasal cycle.* Acta Otolaryngologica (Stockholm), 1978. **85**: p. 431-436.
84. Haight, JS and Cole, P, *Nasal responses to local unilateral stimuli in man.* Rhinology, 1983. **21**(1): p. 67-72.
85. Ishii, J, Ishii, T, and Ito, M, *The nasal cycle in patients with autonomic nervous disturbance.* Acta Otolaryngol. Suppl., 1993. **506**: p. 51-6.
86. Saroha, D, Bottrill, I, Saif, M, and Gardner, B, *Is the nasal cycle ablated in patients with high spinal cord trauma?* Clin. Otolaryngol. Allied Sci., 2003. **28**(2): p. 142-5.
87. Galioto, G, Mevio, E, Galioto, P, Fornasari, G, Cisternino, M, and Fraietta, L, *Modifications of the nasal cycle in patients with hypothalamic disorders: Kallmann's syndrome.* The Annals of otology, rhinology, and laryngology, 1991. **100**(7): p. 559-62.
88. Eccles, R, *A guide to practical aspects of measurement of human nasal airflow by rhinomanometry.* Rhinology, 2011. **49**(1): p. 2-10.
89. Gertner, R, Podoshin, L, and Fradis, M, *A simple method of measuring the nasal airway in clinical work.* J. Laryngol. Otol., 1984. **98**(4): p. 351-5.
90. Hanif, J, Eccles, R, and Jawad, S, *The use of a portable spirometer for studies on the nasal cycle.* Am. J. Rhinol., 2001. **15**: p. 303-306.
91. Owens, D, Moore, M, Craven, C, Magurean, C, Backhouse, S, and Whittet, H, *'Valve-stabilised' rhinospirometry can predict the benefit of septal surgery: a pre- and post-operative correlation study.* European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies, 2012. **269**(1): p. 113-9.

92. Roithmann, R, Cole, P, Chapnik, J, Shpirer, I, Hoffstein, V, and Zamel, N, *Acoustic rhinometry in the evaluation of nasal obstruction.* The Laryngoscope, 1995. **105**(3 Pt 1): p. 275-81.
93. Ohki, M, Ogoshi, T, Yuasa, T, Kawano, K, and Kawano, M, *Extended observation of the nasal cycle using a portable rhinoflowmeter.* The Journal of otolaryngology, 2005. **34**(5): p. 346-9.
94. Kimura, A, et al., *Phase of nasal cycle during sleep tends to be associated with sleep stage.* Laryngoscope, 2013. **123**(8): p. 2050-5.
95. Eccles, R, *Nasal airflow in health and disease.* Acta Oto-laryngol (Stockholm), 2000. **120**(5): p. 580-595.
96. Boyce, JM and Eccles, R, *Assessment of subjective scales for selection of patients for nasal septal surgery.* Clin. Otolaryngol., 2006. **31**(4): p. 297-302.
97. Tomkinson, A and Eccles, R, *Comparison of the relative abilities of acoustic rhinometry, rhinomanometry, and the visual analog scale in detecting change in the nasal cavity in a healthy adult-population.* Am. J. Rhinol., 1996. **10**(3): p. 161-165.
98. Roblin, DG and Eccles, R, *Normal range for nasal partitioning of airflow determined by nasal spirometry in 100 healthy subjects.* Am. J. Rhinol., 2003. **17**(4): p. 179-83.
99. Hanif, J, Jawad, SS, and Eccles, R, *A study to assess the usefulness of a portable spirometer to quantify the severity of nasal septal deviation.* Rhinology, 2003. **41**(1): p. 11-5.
100. Altman, D, *Practical statistics for medical research*. Vol. Chapman abd Hall. 1991, London. pg 410.
101. Heetderks, DL, *Observations on the reaction of normal nasal mucous membrane.* American Journal of Medical Science, 1927. **174**: p. 231-244.
102. Beickert, P, *Halbseitenrhythmus der vegetativen innervation.* Archiv fur Ohren-Nasen-und Kehlkopifheikonde, 1951. **157**: p. 404-411.
103. Abolmaali, N, Kantchew, A, and Hummel, T, *The Nasal Cycle: Assessment Using MR Imaging.* Chemosensory Perception, 2013. **6**(3): p. 148-153.
104. Bojsen-Moller, F and Fahrenkrug, J, *Nasal swell bodies and cyclic changes in the air passages of the rat and rabbit nose.* J. Anat., 1971. **110**: p. 25-37.
105. Eccles, R and Maynard, RL, *Proceedings: Studies on the nasal cycle in the immobilized pig.* J Physiol, 1975. **247**(1): p. 1P.
106. Gilbert, AN and Rosenwasser, AM, *Biological rhythmicity of nasal airway patency: a re-examination of the 'nasal cycle'.* Acta Otolaryngol., 1987. **104**(1-2): p. 180-6.
107. Gilbert, AN, *Reciprocity versus rhythmicity in spontaneous alternations of nasal airflow.* Chronobiol. Int., 1989. **6**(3): p. 251-7.
108. Gungor, A, Moinuddin, R, Nelson, RH, and Corey, JP, *Detection of the nasal cycle with acoustic rhinometry: techniques and applications.* Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery, 1999. **120**(2): p. 238-47.
109. Sipila, J, Suonpaa, J, and Laippala, P, *Sensation of nasal obstruction compared to rhinomanometric results in patients referred for septoplasty.* Rhinology, 1994. **32**(3): p. 141-4.

110. Sipila, J, Suonpaa, J, Silvoniemi, P, and Laippala, P, *Correlations between subjective sensation of nasal patency and rhinomanometry in both unilateral and total nasal assessment.* ORL J. Otorhinolaryngol. Relat. Spec., 1995. **57**(5): p. 260-3.
111. Clarke, JD, Hopkins, ML, and Eccles, R, *Evidence for correlation of objective and subjective measures of nasal airflow in patients with common cold.* Clin. Otolaryngol., 2005. **30**(1): p. 35-8.
112. *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice.* J. Postgrad. Med., 2001. **47**(3): p. 199-203.
113. Schumacher, MJ, *Nasal dyspnea: the place of rhinomanometry in its objective assessment.* Am. J. Rhinol., 2004. **18**(1): p. 41-6.
114. Clement, PAR, *Committee report on standardisation of rhinomanometry.* Rhinology, 1984. **22**: p. 151-155.
115. Baczek, M, Hassmann, E, Alifier, M, and Iwaszko-Krawczuk, W, *Acoustic rhinometry assessment of the nasal cycle in neonates.* Acta Otolaryngol., 2001. **121**(2): p. 301-4.
116. Tatar, A, Altas, E, *Nasal Cycle Pattern Can Transform Into Another Form Over Time.* European Journal of General Medicine, 2014. **11**(1): p. 1-5.

Appendix 1: calibration of the RHINO-SYS Rhinomamometer against GM systems using artificial nose's

As a system designed for clinical use the RHINO-SYS rhinomanometer has a simple in built "system test" function, which gives a positive or negative outcome to indicate if the system is working correctly. This is not sufficient for the research purposes as it lacks a quantifiable output. So a measurement of resistance values for the supplied artificial nose was performed for the purposes of calibration. The setup for measuring in this way is shown in figure A1.1.

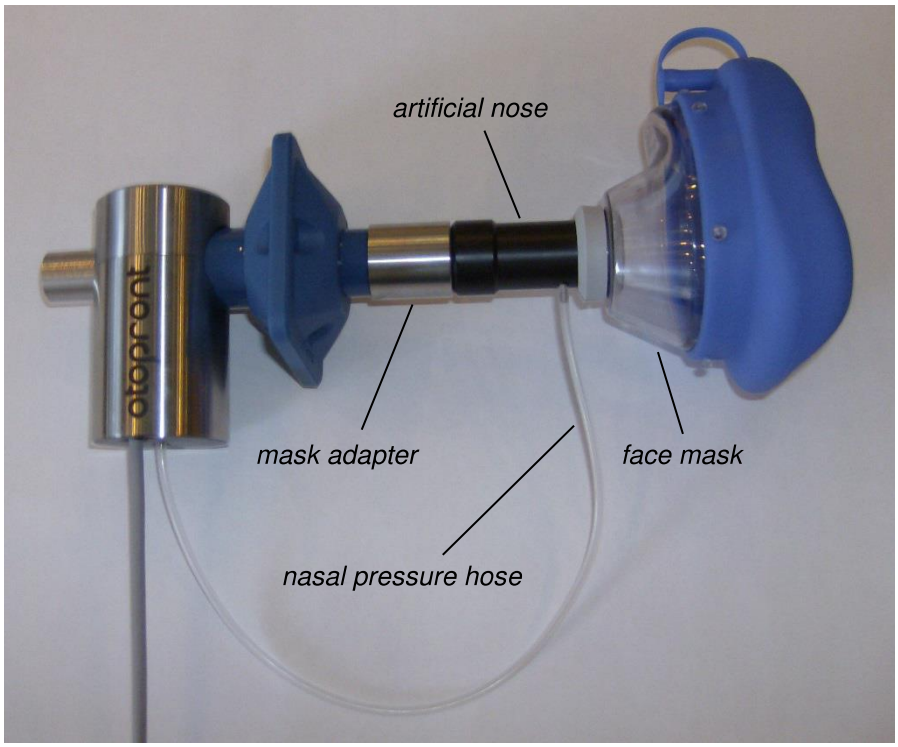


Figure A1.1 – A graphical representation of the set up for the RHINO-SYS rhinomanometer for a system check.

Using a standard measurement procedure resistance values were obtained for the supplied calibration artificial nose and a RHINOCAL artificial nose

(GM instruments). The values obtained for the RHINOCAL artificial nose did not match those specified by the manufacturer so both were also checked using a GM instruments rhinomanometer which was calibrated using a flowmeter for calibration of airflow and a sloping paraffin manometer for calibration of pressure. Sets of resistance measurements were obtained (without the use of a filter to avoid this as a confounding factor) and are presented in table A1.1. The resistance values obtained for the RHINOCAL nose did not match those specified by the manufacturer when tested on either machine. However for both artificial noses when a coefficient of variance was applied to the mean readings values of less than 10% were obtained for all with the exception of the inspiratory resistances for the OTOPRONT nose.

Having proven the consistency of resistance measurements obtained by the RHINO-SYS Rhinomamometer and that its resistance measurements are comparable with those obtained from the calibrated GM instruments machine, it was decided that the supplied OTOPRONT nose could be used for a daily calibration check. The target would be for the resistance values obtained of 0.18 (sPa/cm^3 at 75 Pa) (including a viral filter, the resistance of which is confirmed elsewhere) with a tolerance of 10% i.e. +/- 0.02. The results of the daily calibration check were documented in a calibration book.

	OTOPRONT nose	RHINOCAL nose
Specified resistances	Unknown	0.31 inspiratory 0.29 expiratory
RHINO-SYS inspiratory resistance	0.16, 0.16 (0.16)	0.38, 0.38 (0.38)
GM instruments inspiratory resistance	0.185, 0.185 (0.185)	0.387, 0.386, 0.387, 0.390 (0.388)
CV of mean of inspiratory resistances	10.2	1.47
RHINO-SYS expiratory resistance	0.15, 0.15 (0.15)	0.40, 0.40 (0.40)
GM instruments expiratory resistance	0.149, 0.147 (0.148)	0.388, 0.408, 0.404, 0.406 (0.402)
CV of mean of expiratory resistances	0.95	0.35

Table A1.1 – A table demonstrating resistance values (in sPa/cm^3 at 75 Pa) obtained when testing artificial noses on both the RHINO-SYS and GM instruments rhinomanometers for comparison (a mean value is shown in brackets)

Appendix 2: Testing the resistance values of viral filters used with the RHINO-SYS rhinomanometer

The RHINO-SYS rhinomanometer is designed to be used with a single patient use viral filter in series with the flowhead, both to protect the flowhead and prevent transfer of infection between patients. The resistance to airflow that this creates is however unspecified and it was therefore uncertain whether there may be any significant variability between resistance added by the viral filters.

A baseline resistance was established for a viral filter of 0.02 (measured in sPA/cm^3 at a reference pressure of 75Pa) by removing it from the circuit when used with the OTOPRONT artificial nose, (resistance value of artificial nose and filter 0.18 at reference pressure of 75Pa, resistance value of artificial nose without filter 0.16, values of inspiratory resistance) we sought to see if any variability could be found by testing 5 different viral filters.

Method

Five unused and packaged viral filters were selected randomly for use in the experiment. The viral filters were connected in series with the OTOPRONT artificial nose as per set up for system test and calibration and 4 resistance values obtained for each (measured in sPA/cm^3 at a reference pressure of 75Pa). A Coefficient of variance check was performed and a mean value calculated for each filter.

Results

The individual results are displayed in table A2.1, the overall mean value for all readings was 0.176 with a coefficient of variance of 1.6% for the 5 mean

values obtained, showing that there is not significant variance between the viral filters used in the study.

Filter	Resistance value 1	Resistance value 2	Resistance value 3	Resistance value 4	Coefficient of variance	Mean resistance value
1	0.18	0.17	0.18	0.17	3.3%	0.175
2	0.17	0.18	0.18	0.18	2.8%	0.178
3	0.17	0.18	0.17	0.17	2.9%	0.173
4	0.18	0.18	0.18	0.18	0%	0.18
5	0.17	0.17	0.18	0.18	3.3%	0.175

Table A2.1 – A table showing the resistance values obtained for 5 test viral filters.

Discussion

The resistance values obtained in this test are similar to those recorded in daily calibration checks for the RHINO-SYS rhinomanometer. It therefore seems conclusive that the resistance added by viral filters is consistent, as there is no significant difference between the five individual viral filters in this experimental group.

A resistance of approximately 0.02 sPA/cm^3 is added by the viral filter and is included in all experimental recordings within the research study. Since it is consistent, there will be no effect on trends in resistance or airflow patterns.

Appendix 3: Testing for error using artificial noses

In order to establish the amount of error that may be introduced by the test equipment and thus the accuracy of airflow measurements recorded, a test of the Rhino-sys system was undertaken using artificial noses. In this test resistance measurements for two artificial noses were recorded over two seven hour periods at a seven day interval. An artificial nose gives a fixed stable resistance to airflow. In this case the two used were the Otopront artificial nose (Otopront, Germany) supplied for system checks and a Rhinocal artificial nose (GM instruments, UK).

The methodology for testing mirrored the protocol for test subjects. In brief four resistance measurements were made every hour for seven hours (a total of 8 sets of measurements). The first two were assigned to be group A measurements (normally taken for the right side) and the second as group B measurements (normally taken for the left side), as the procedure for measurements taken with test subjects prescribes that they are taken in this order. All measurements were recorded and a coefficient of variation calculated. No repeat measurements were required. The setup for measuring airflow through an artificial nose is shown in figure A3.1.

For display graphically and comparison, two resistance measurements for each group are combined by creating a mean value and converted to an airflow measurement using the formula airflow (v) = pressure / resistance (the pressure is set at 75Pa as the reference pressure).

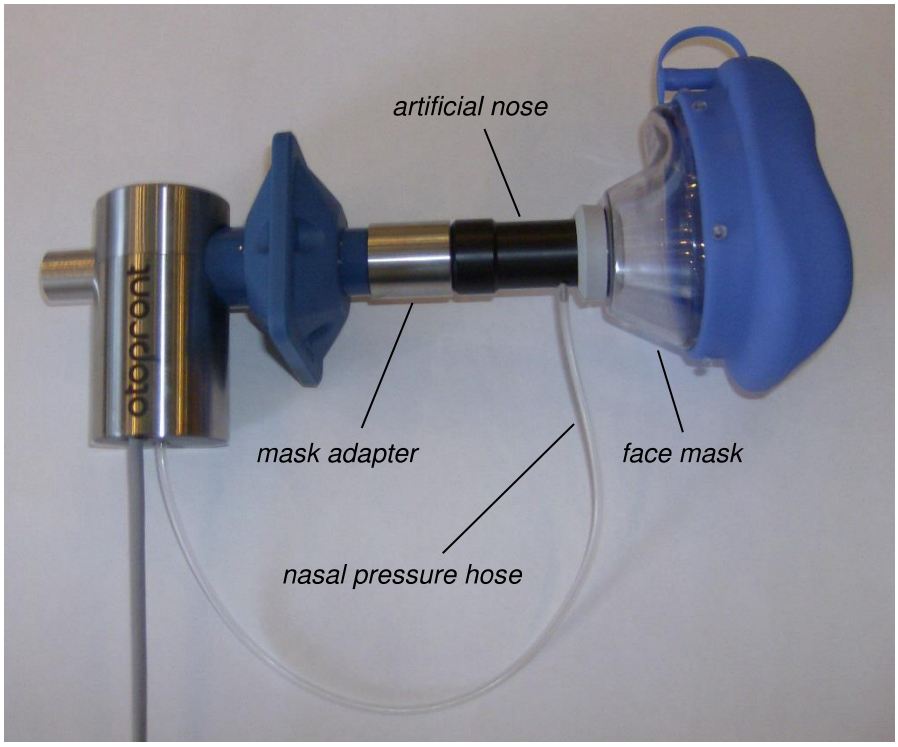


Figure A3.1 - A graphical representation of the set up for the RHINO-SYS rhinomanometer for the measurement of airflow through an artificial nose.

The resistance values for the two artificial noses were established in the previous appendix on calibration as being 0.16 sPa/cm^3 for the Otopront nose and 0.38 sPa/cm^3 for the Rhinocal nose, when using the Otopront Rhinosys rhinomamometer with a 75pa reference pressure. Added onto these is the resistance for the viral filter established in the previous appendix as being 0.02 sPa/cm^3. Therefore the expected resistance values for this experiment were 0.18 sPa/cm^3 for the Otopront nose and 0.40 sPa/cm^3 for the Rhinocal nose.

Results

Data from both artificial noses displayed little variance, with resistance measurements staying within +/-0.02 of the expected resistance values, this remains within tolerances specified for calibration. All recorded data is shown in tables A3.1, A3.2, A3.3 and A3.4.

Reading	Time	A 1	A 2	CV	B 1	B 2	CV	Right Mean	Left Mean
1	09:35	0.18	0.18	0	0.18	0.18	0	0.18	0.18
2	10:37	0.17	0.18	4	0.18	0.18	0	0.175	0.18
3	11:41	0.17	0.17	0	0.18	0.18	0	0.17	0.18
4	12:31	0.17	0.18	4	0.18	0.18	0	0.175	0.18
5	13:36	0.17	0.18	4	0.17	0.18	4	0.175	0.175
6	14:32	0.18	0.18	0	0.18	0.18	0	0.18	0.18
7	15:39	0.17	0.18	4	0.18	0.18	0	0.175	0.18
8	16:34	0.18	0.18	0	0.18	0.18	0	0.18	0.18

Table A3.1 – A table showing the resistance values obtained for the Otopront artificial nose on week 1

Reading	Time	A 1	A 2	CV	B 1	B 2	CV	Right Mean	Left Mean
1	09:47	0.18	0.18	0	0.18	0.18	0	0.18	0.18
2	10:45	0.18	0.18	0	0.18	0.18	0	0.18	0.18
3	11:39	0.18	0.18	0	0.18	0.18	0	0.18	0.18
4	12:39	0.18	0.18	0	0.18	0.18	0	0.18	0.18
5	13:42	0.18	0.18	0	0.18	0.18	0	0.18	0.18
6	14:40	0.18	0.18	0	0.18	0.18	0	0.18	0.18
7	15:40	0.18	0.18	0	0.18	0.18	0	0.18	0.18
8	16:36	0.18	0.18	0	0.18	0.19	3.8	0.18	0.185

Table A3.2 – A table showing the resistance values obtained for the Otopront artificial nose on week 2

Reading	Time	A 1	A 2	CV	B 1	B 2	CV	Right Mean	Left Mean
1	09:48	0.4	0.39	1.8	0.4	0.4	0	0.395	0.4
2	10:44	0.39	0.39	0	0.39	0.4	1.8	0.39	0.395
3	11:48	0.39	0.38	1.8	0.4	0.4	0	0.385	0.4
4	12:39	0.39	0.39	0	0.39	0.39	0	0.39	0.39
5	13:38	0.39	0.4	1.8	0.4	0.4	0	0.395	0.4
6	14:43	0.39	0.39	0	0.38	0.39	1.8	0.39	0.385
7	15:42	0.39	0.4	1.8	0.4	0.39	1.8	0.395	0.395
8	16:37	0.39	0.39	0	0.39	0.39	0	0.39	0.39

Table A3.3 – A table showing the resistance values obtained for the Rhinocal artificial nose on week 1

Reading	Time	A 1	A 2	CV	B 1	B 2	CV	Right Mean	Left Mean
1	09:43	0.4	0.4	0	0.41	0.39	3.5	0.4	0.4
2	10:38	0.39	0.4	1.8	0.4	0.4	0	0.395	0.4
3	11:47	0.4	0.39	1.8	0.4	0.4	0	0.395	0.4
4	12:40	0.39	0.39	0	0.39	0.4	1.8	0.39	0.395
5	13:41	0.39	0.4	1.8	0.39	0.4	1.8	0.395	0.395
6	14:40	0.39	0.39	0	0.4	0.4	0	0.39	0.4
7	15:39	0.39	0.4	1.8	0.39	0.4	1.8	0.395	0.395
8	16:34	0.39	0.4	1.8	0.39	0.4	1.8	0.395	0.395

Table A3.4 – A table showing the resistance values obtained for the Rhinocal artificial nose on week 2

For the Otopront nose as expected the majority of measurements gave a resistance of 0.18 sPa/cm^3, for the Rhinocal nose the distribution is skewed to a resistance of 0.39 sPa/cm^3, with a mean value of 0.394 sPa/cm^3 overall. The four graphs below (figures A3.2, A3.3, A3.4 and A3.5) show the stability of the hourly airflow readings taken, all have high Airflow distribution ratios (ADR) and low non-significant correlation coefficients (r).

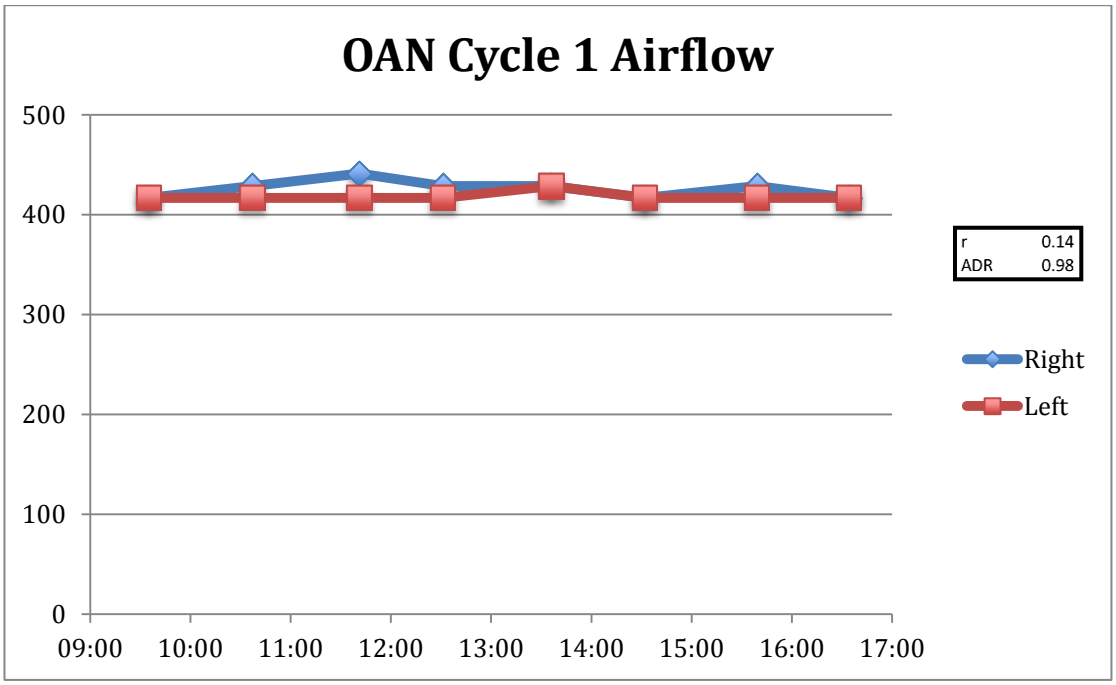


Figure A3.2 - A graph showing airflow for the “right” (group A) and “left” (group B) measurements for the Otopront artificial nose on study day 1

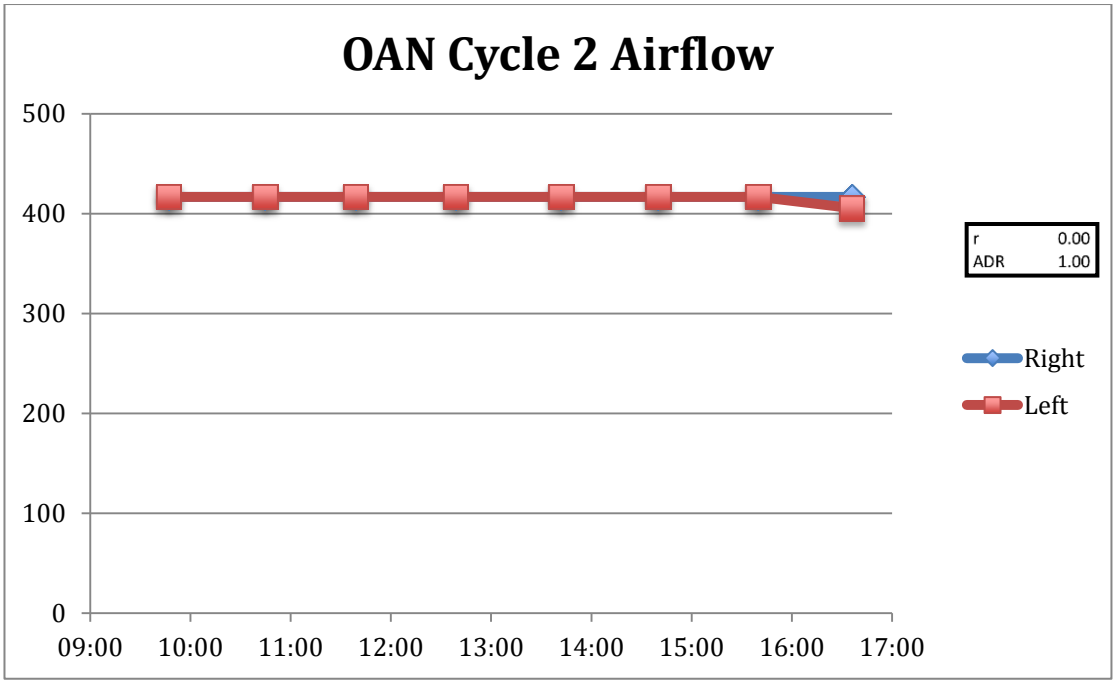


Figure A3.3 - A graph showing airflow for the “right” (group A) and “left” (group B) measurements for the Otopront artificial nose on study day 2

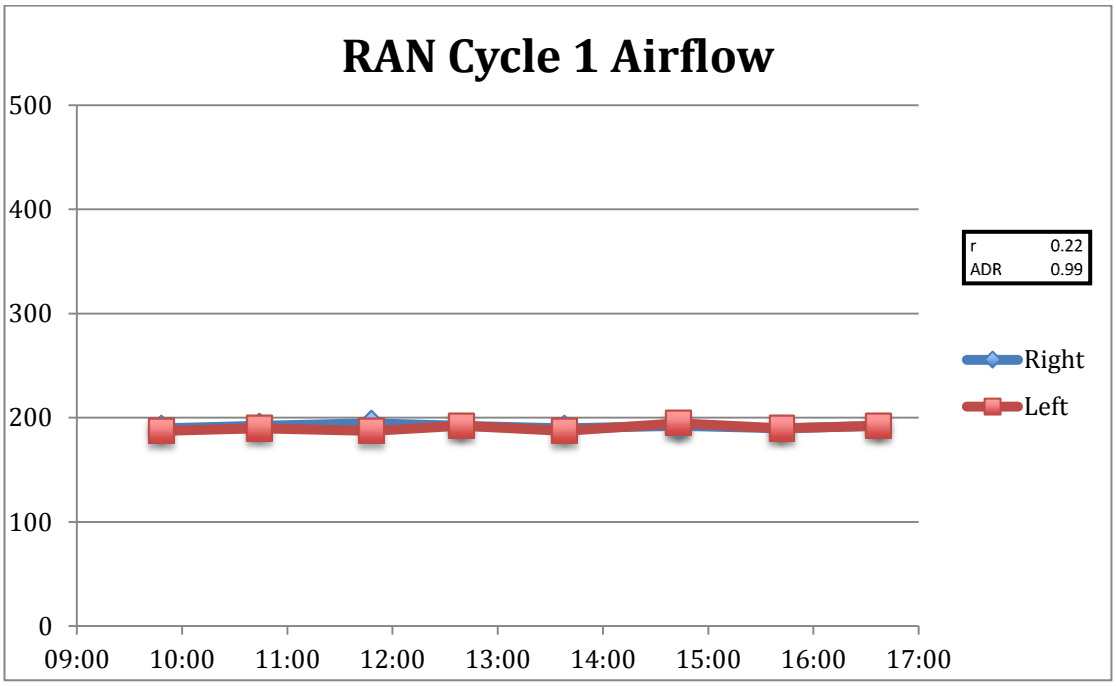


Figure A3.4 - A graph showing airflow for the “right” (group A) and “left” (group B) measurements for the Rhinocal artificial nose on study day 1

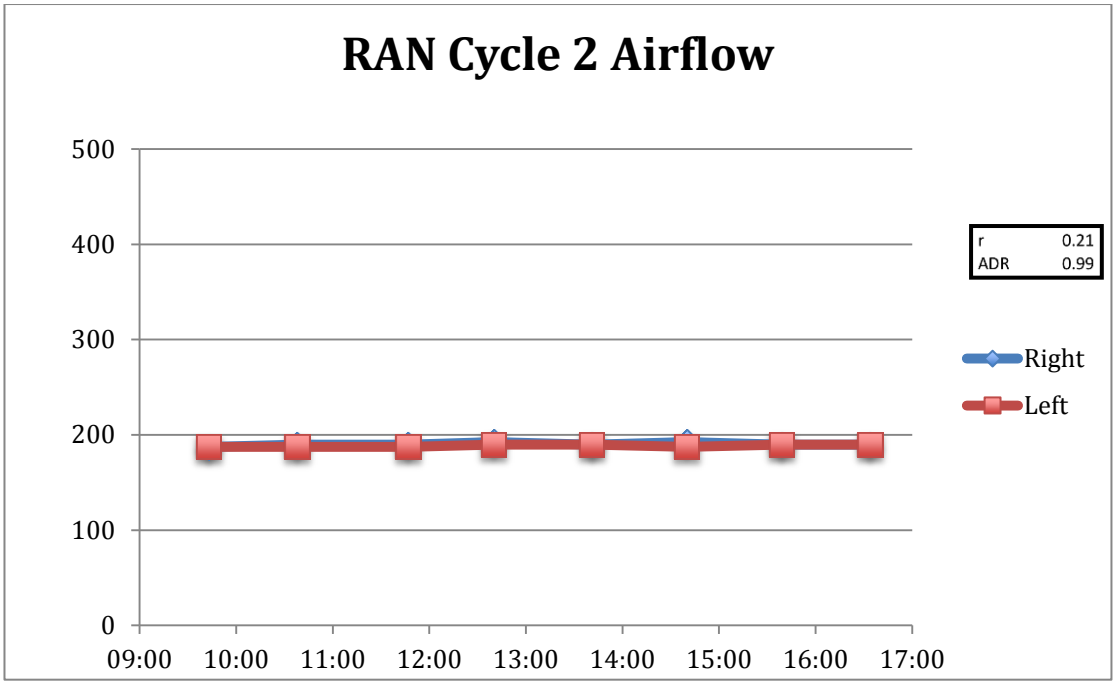


Figure A3.5 - A graph showing airflow for the “right” (group A) and “left” (group B) measurements for the Rhinocal artificial nose on study day 1

As with the presentation of the study data, hourly resistance values were converted into hourly airflow for graphical presentation and minimum, maximum and mean airflow values calculated for each side and week. As demonstrated in tables A3.5 and A3.6 there is minimal variation between sides or the weeks as assessed using the coefficient of variation.

Group A			
Airflow	Week 1	Week 2	CV
Min	416.67	416.67	0
Max	441.18	416.67	0.04
Mean	425.68	416.67	1.1
Group B			
Airflow	Week 1	Week 2	CV
Min	416.67	405.41	0.02
Max	428.57	416.67	0.02
Mean	418.15	415.26	1.1

Table A3.5 – A table showing the weekly airflow values for the Otopront artificial nose

Group A			
Airflow	Week 1	Week 2	CV
Min	189.87	187.50	0.01
Max	194.81	192.31	0.01
Mean	191.71	190.19	0.01
Group B			
Airflow	Week 1	Week 2	CV
Min	187.50	187.50	0
Max	194.81	189.87	0.02
Mean	190.21	188.69	0.01

Table A3.6 - A table showing the weekly airflow values for the Rhinocal artificial nose

Comparing the data using a paired t-test there does appear to be a difference between Group A and Group B total airflow (over the seven hour period) for week 1 using the Otopront artificial nose and week 2 using the Rhinocal artificial nose as demonstrated by the two tailed p value (see table 3.7). When comparing Group A mean airflow between week 1 and 2 for both

artificial noses, there are also significant two tailed p values for both (see table 3.8).

	Mean A	Mean B	Percentage difference	Standard deviation Right	Standard deviation Left	Paired t-test	Two tailed P
OAN Week 1 airflow	425.68	418.15	1.78	8.6	4.2	2.38	0.05
OAN Week 2 airflow	416.67	415.26	0.34	0	3.98	1	0.35
RAN Week 1 airflow	191.71	190.21	0.78	1.74	2.73	1.49	0.18
RAN Week 2 airflow	190.19	188.69	0.79	1.54	1.27	2.38	0.05

Table A3.7 – A table showing the differences between group A and group B airflow for the two artificial noses over weeks 1 and 2.

	Mean week 1	Mean week 2	Percentage difference	Standard deviation week 1	Standard deviation week 2	Paired t-test	Two tailed P
OAN Group A airflow	425.68	416.67	2.14	8.6	0	3	0.02
OAN Group B airflow	418.15	415.26	0.69	4.2	3.98	1.53	0.17
RAN Group A airflow	191.71	190.19	0.8	1.74	1.54	2.36	0.05
RAN Group B airflow	190.21	188.69	0.8	2.73	1.27	1.5	0.18

Table A3.8 - A table showing the differences between week 1 and week 2 airflow for groups A and B for the two artificial noses.

Discussion

The designation of Group A and Group B to airflow values in this experiment was arbitrary, with Group A being the values recorded first by the Otopront

machine. As such differences between the values of the two groups were expected to be minimal.

Analysis of the minimum, maximum and mean airflow values using the coefficient of variation demonstrated very little variation between airflow for weeks 1 and 2 in either group or for either artificial nose. The percentage difference between means was 2.14% or below for all analyses of the data, with the maximum value obtained comparing Group A airflow from week 1 to week 2 on the Otopront artificial nose.

Analysis using a paired t-test does suggest some significant variation between Group A and Group B mean airflow for the Otopront artificial nose in week 1 and the Rhinocal artificial nose in week 2. In comparing mean airflow at week 1 to week 2 for a single group again significant differences appear to be seen in group A for both artificial noses. The highest level of significance obtained here was for the analysis of group A mean airflow from week 1 to week 2 for the Otopront artificial nose, the p-value being 0.02, conferring a 1 in 50 chance of this result occurring by chance.

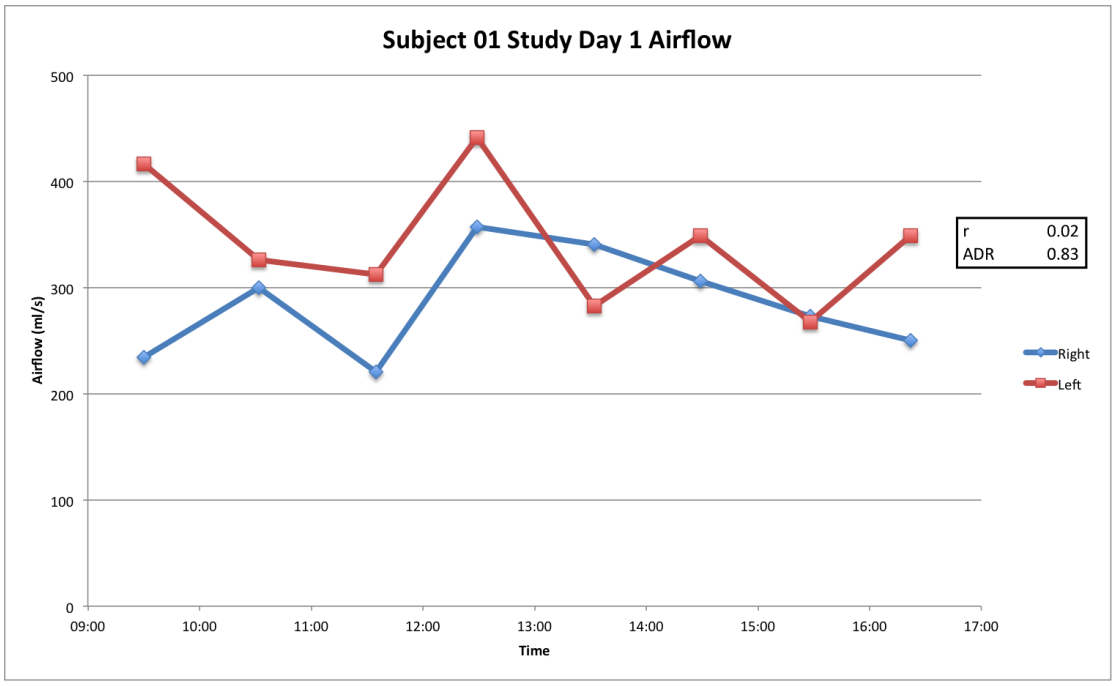
In this test model the facemask was used but no seal to the nostril was needed due to the use of the artificial nose. It is more likely that a good seal was achieved with the facemask in this model as the investigator was applying the mask as apposed to a test subject. Therefore a greater measurement error may been seen with test subjects due to possible air leaks around the mask or nasal seal, although every effort was taken to eliminate this.

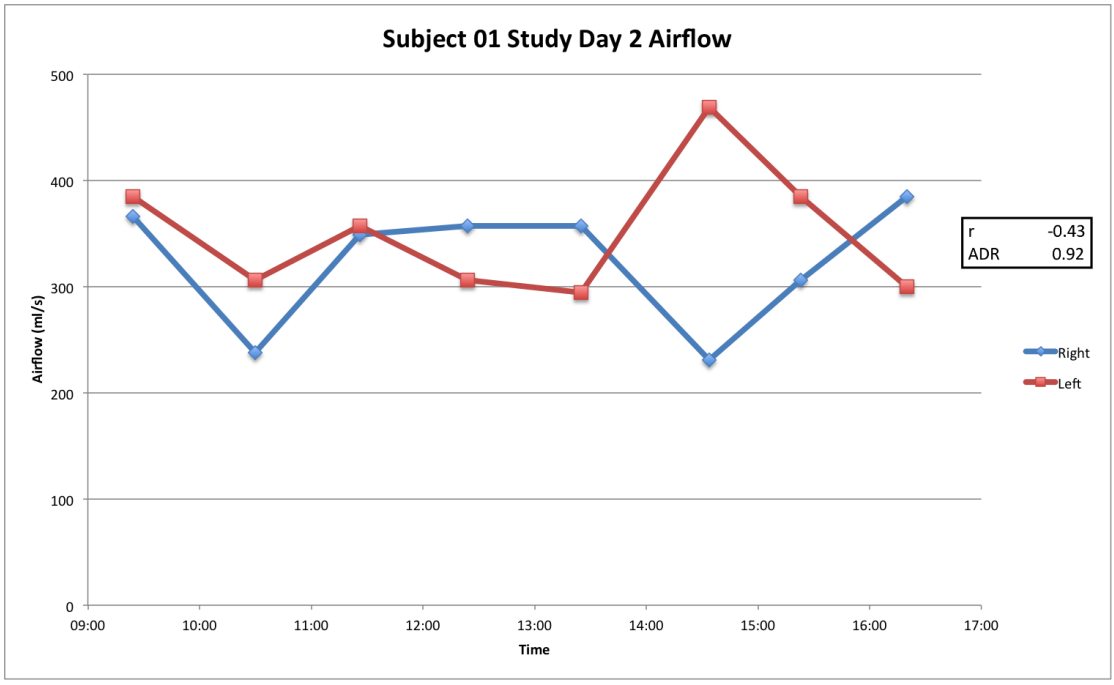
Conclusions

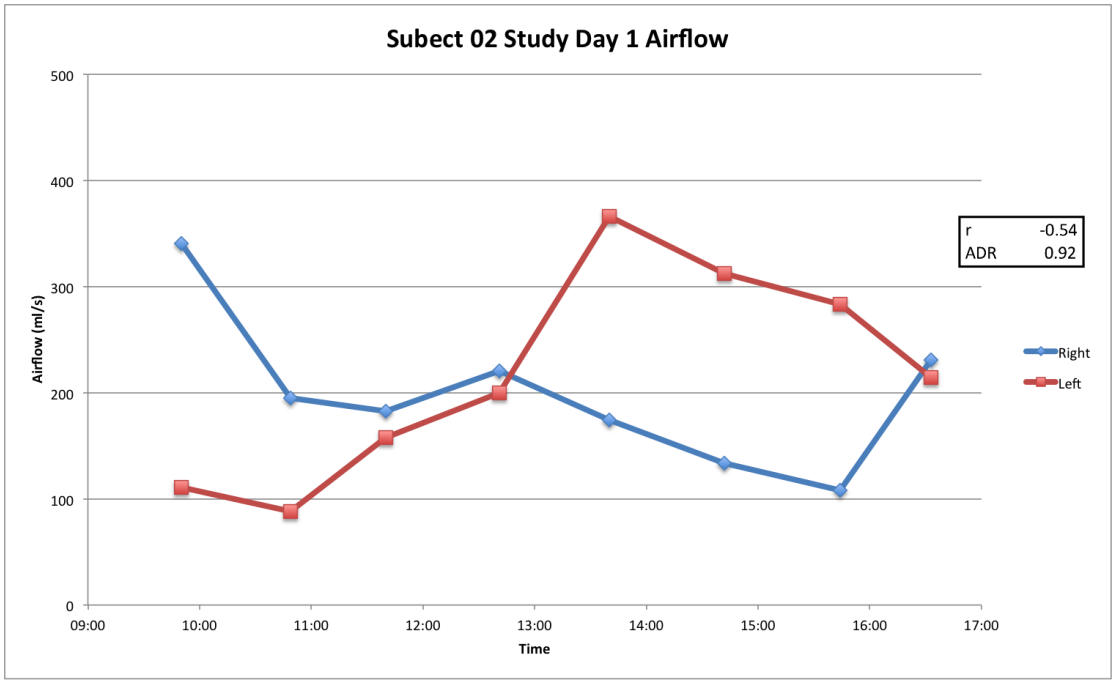
The largest percentage change between mean values for data groups seen in this analysis was 2.14%. This implies that any percentage change greater than this can be considered due to changes in the nasal cavity affecting airflow or air leaks and not due to measurement artefact accounted for by the rhinomanometer. That differences between the arbitrary groups were found

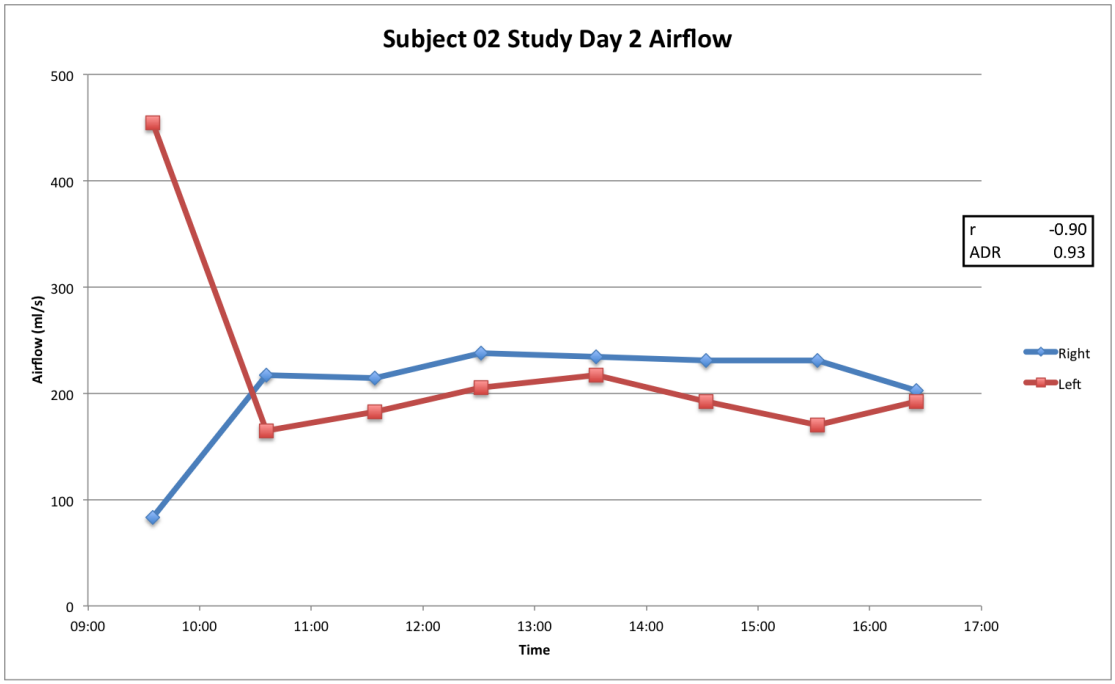
with a statistical level of significance (p value 0.05 for 3 out of 4 of these) was unexpected, however the percentage differences between these groups and standard deviations within them remain very low. Since the Groups A and B were assigned arbitrarily to measurements, the differences seen can be interpreted as the level of measurement error expected within this study.

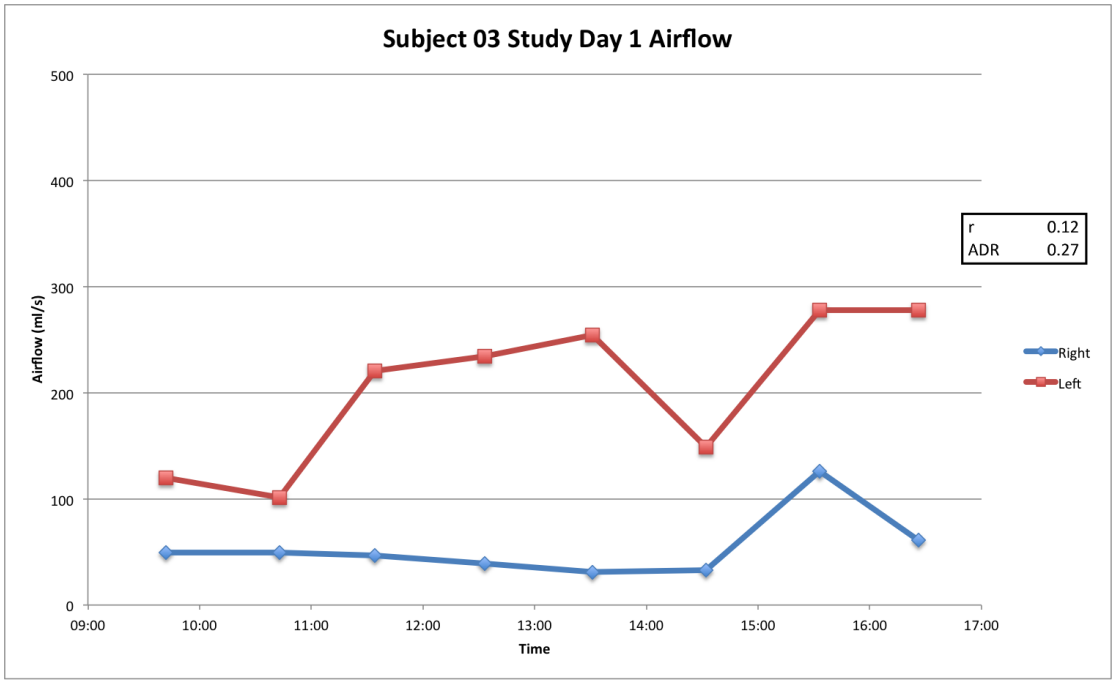
Appendix 4: Airflow Graphs

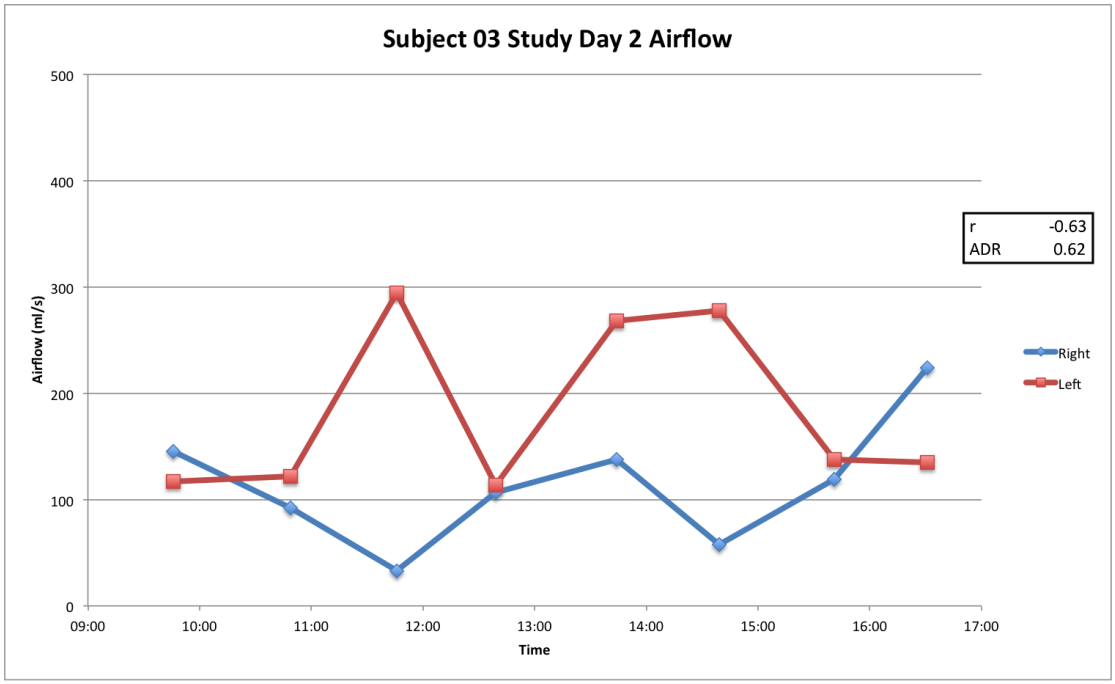


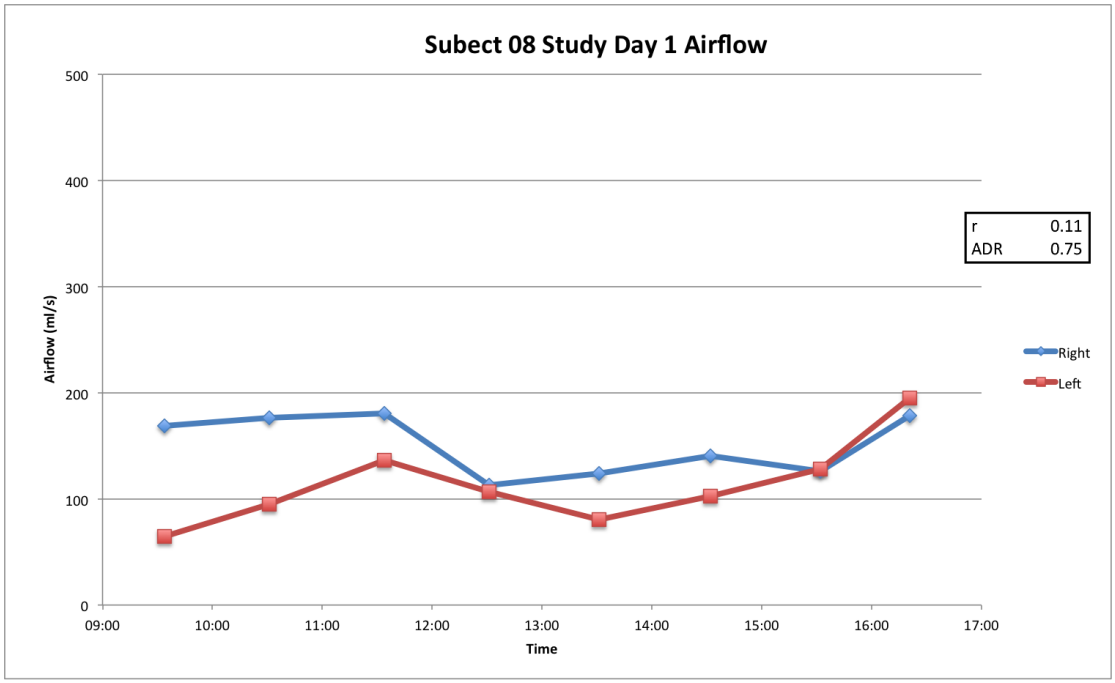


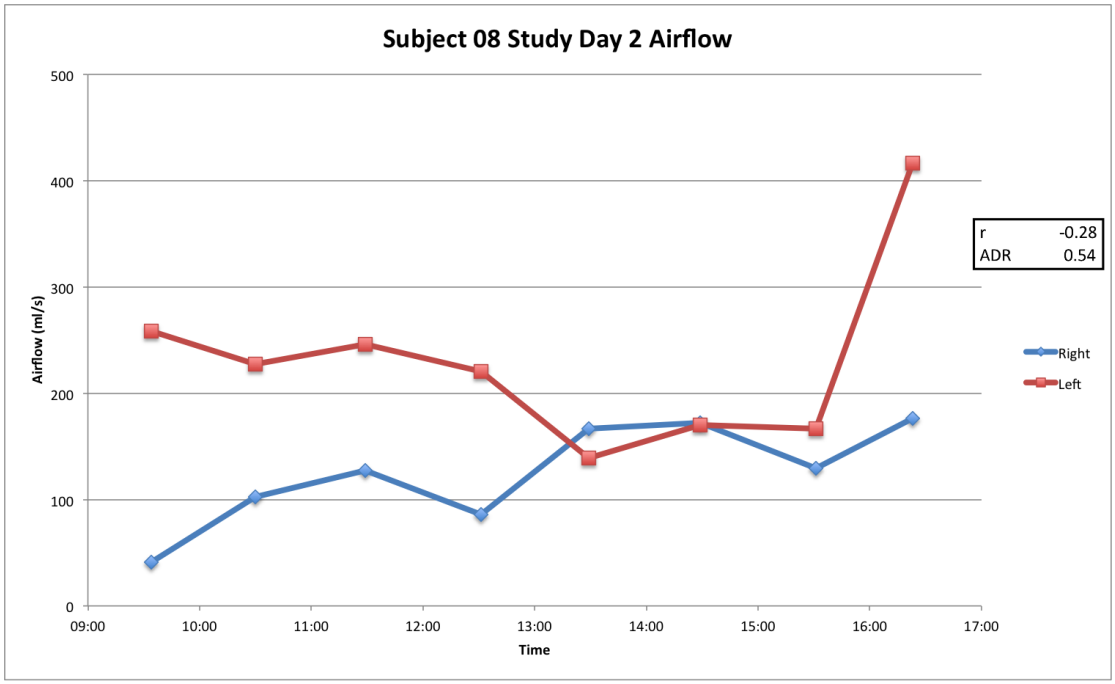

Subect 02 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.54
ADR 0.92
Right
Left

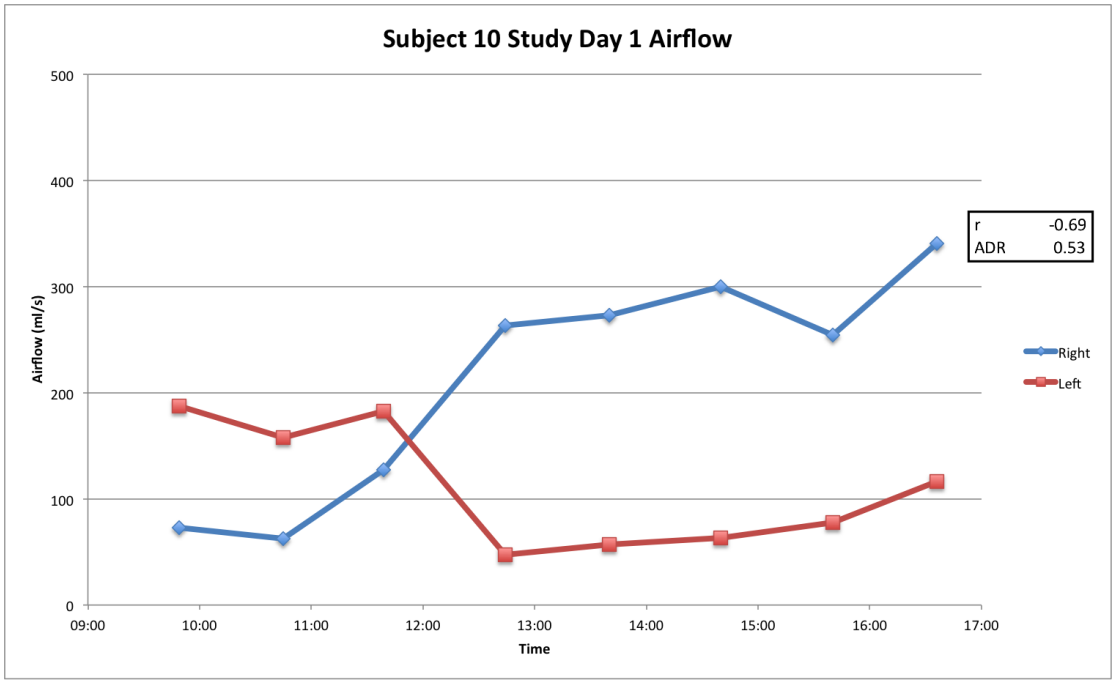

Subject 02 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.90
ADR 0.93
Right
Left

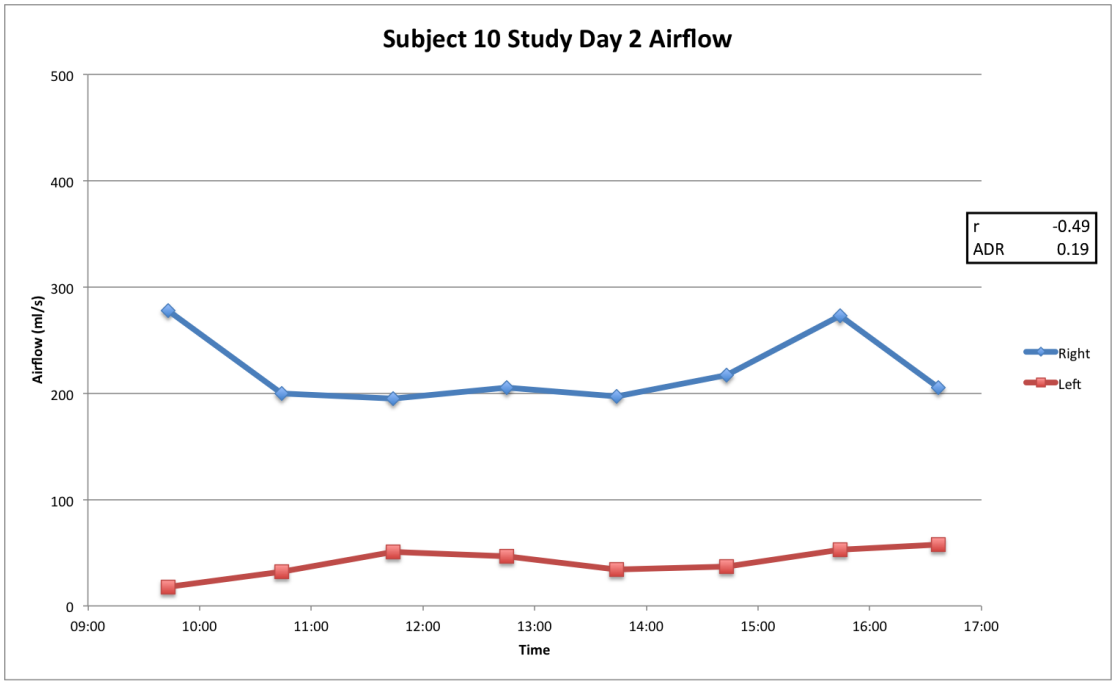

Subject 03 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.12
ADR 0.27
Right
Left

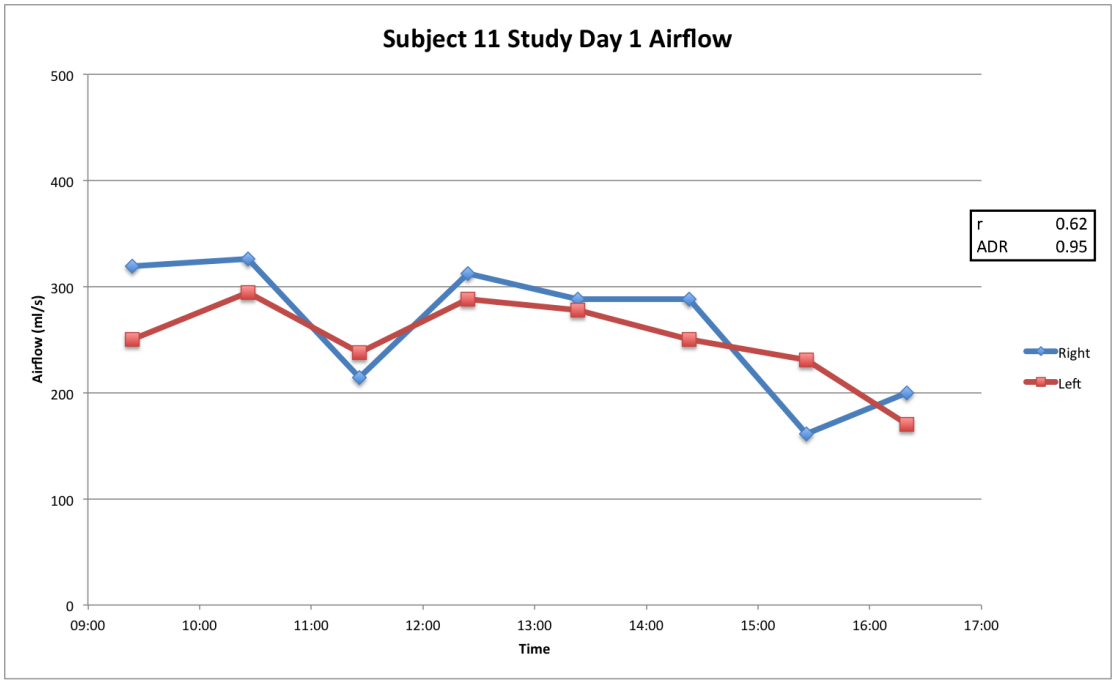

Subject 03 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.63
ADR 0.62
Right
Left

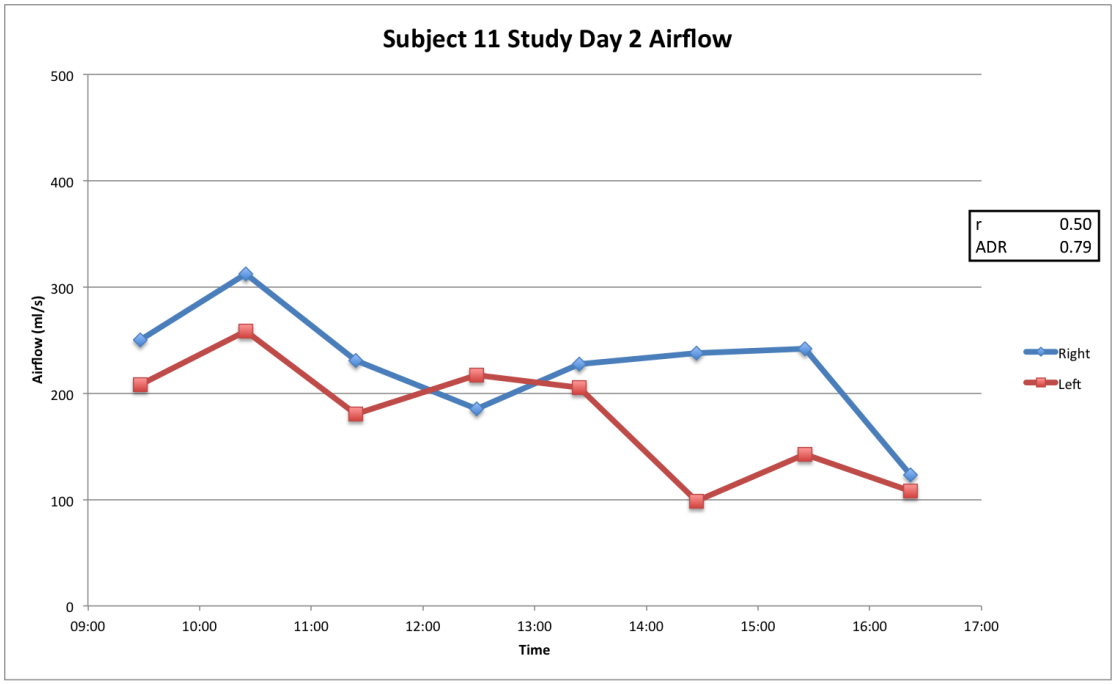

Subect 08 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.11
ADR 0.75
Right
Left

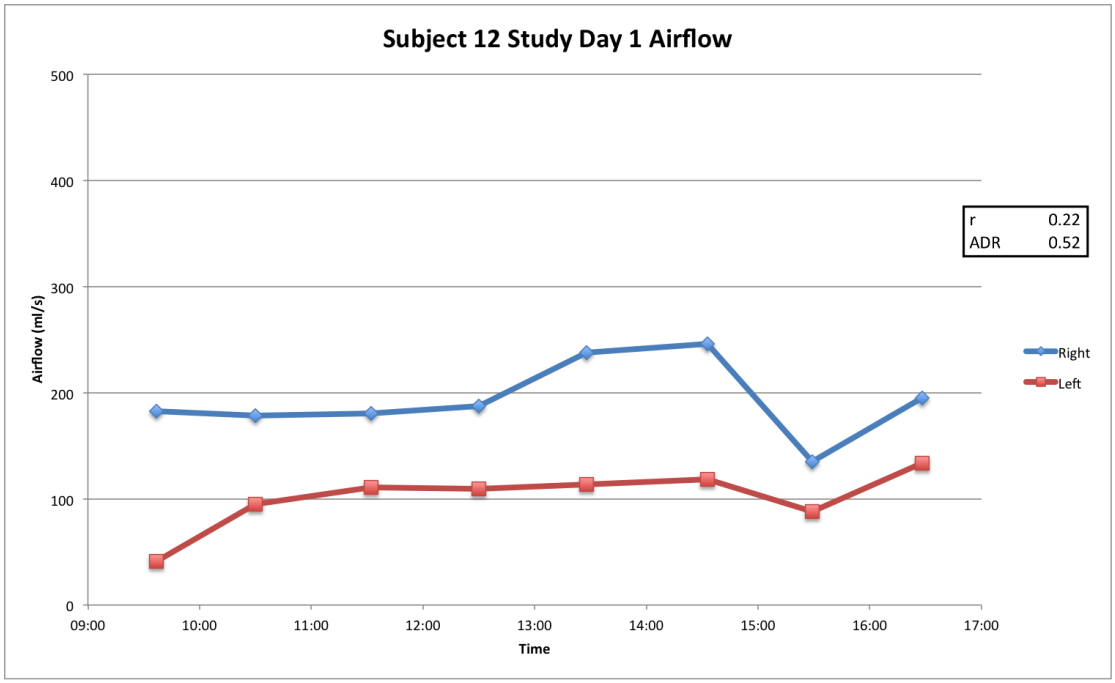

Subject 08 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.28
ADR 0.54
Right
Left

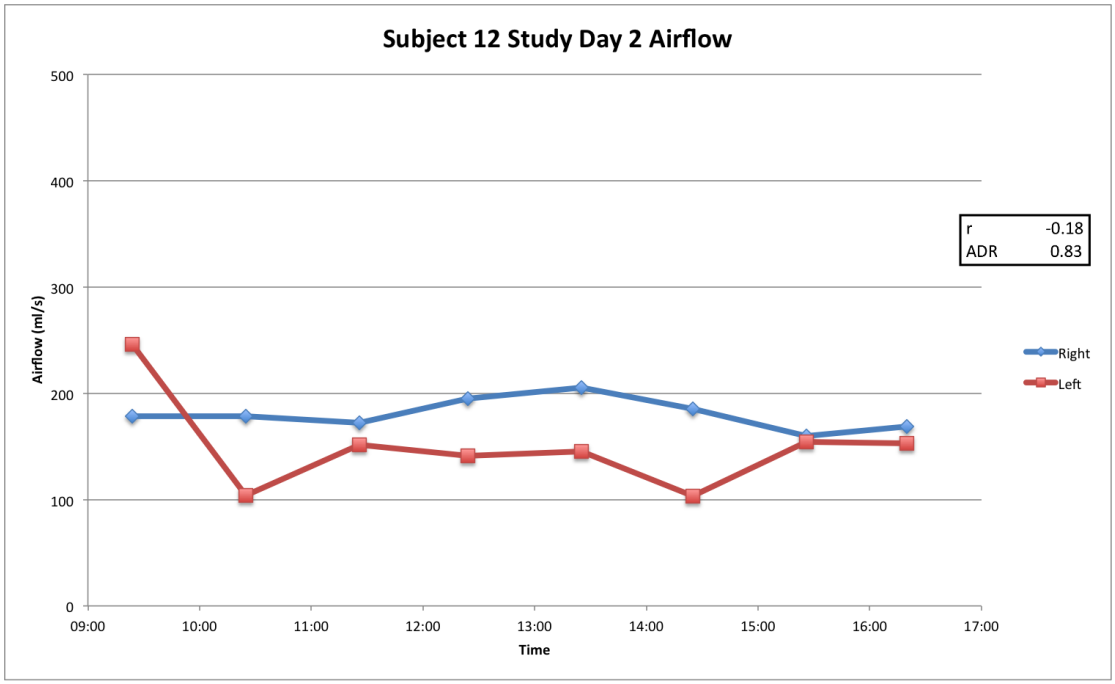

Subject 10 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.69
ADR 0.53
Right
Left

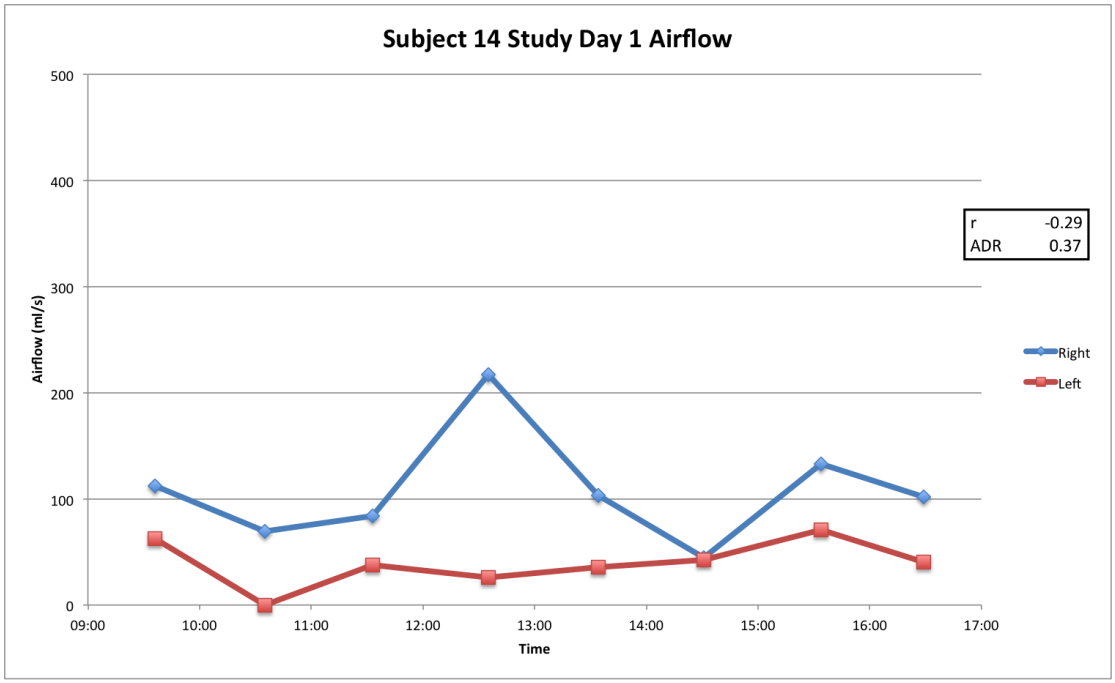

Subject 10 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.49
ADR 0.19
Right
Left

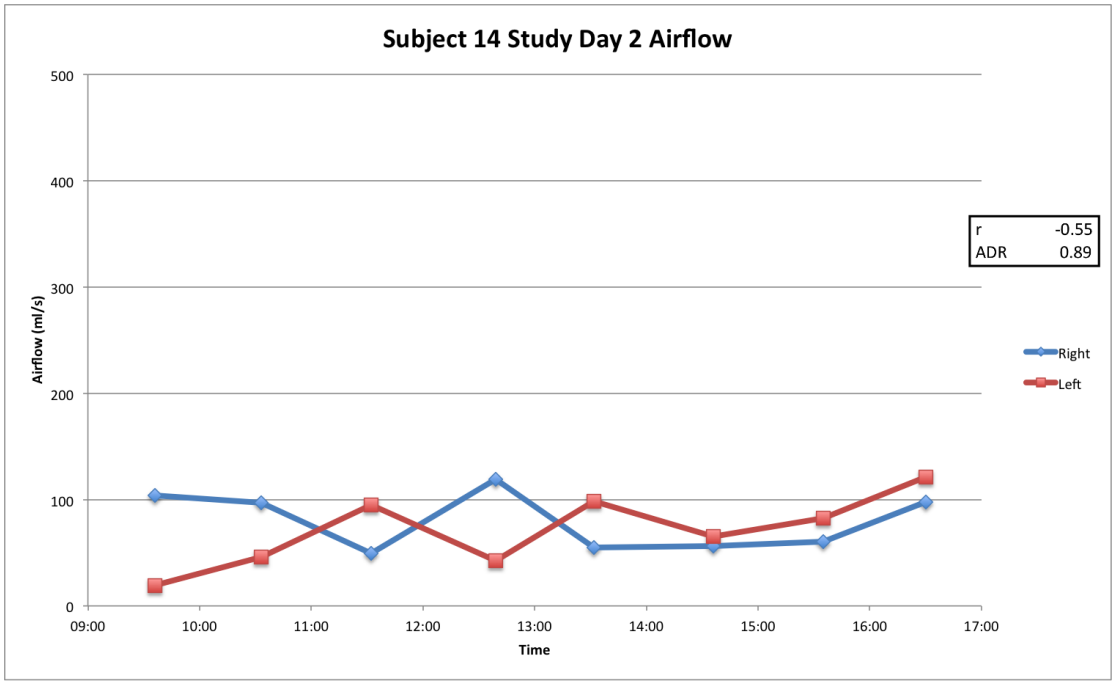

Subject 11 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.62
ADR 0.95
Right
Left

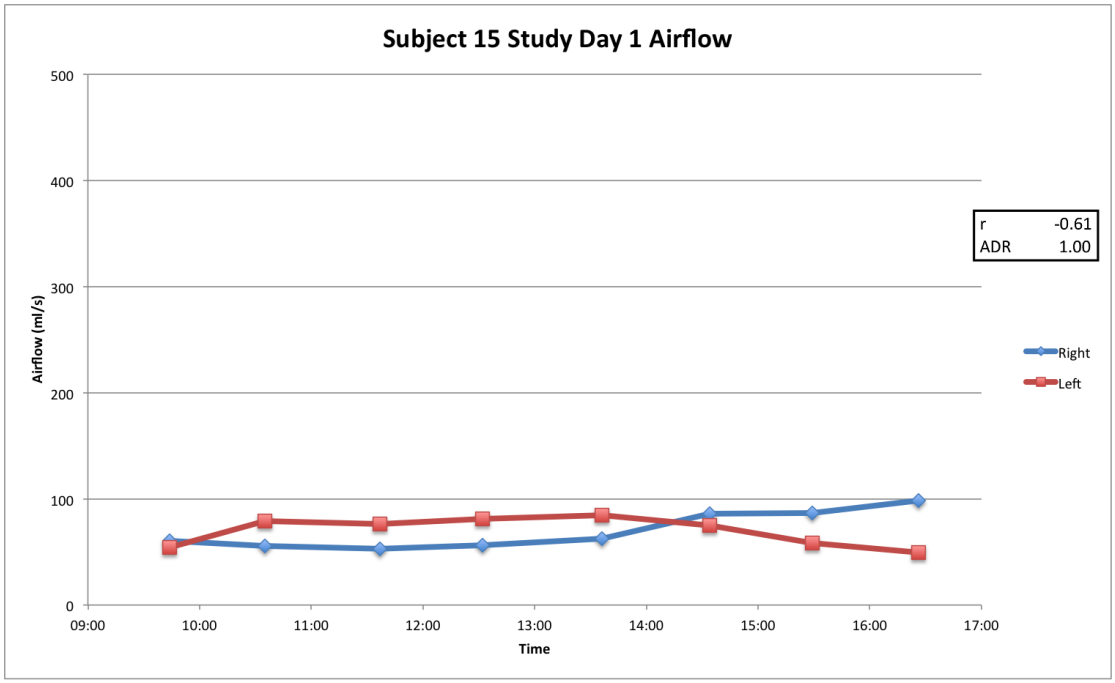

Subject 11 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.50
ADR 0.79
Right
Left

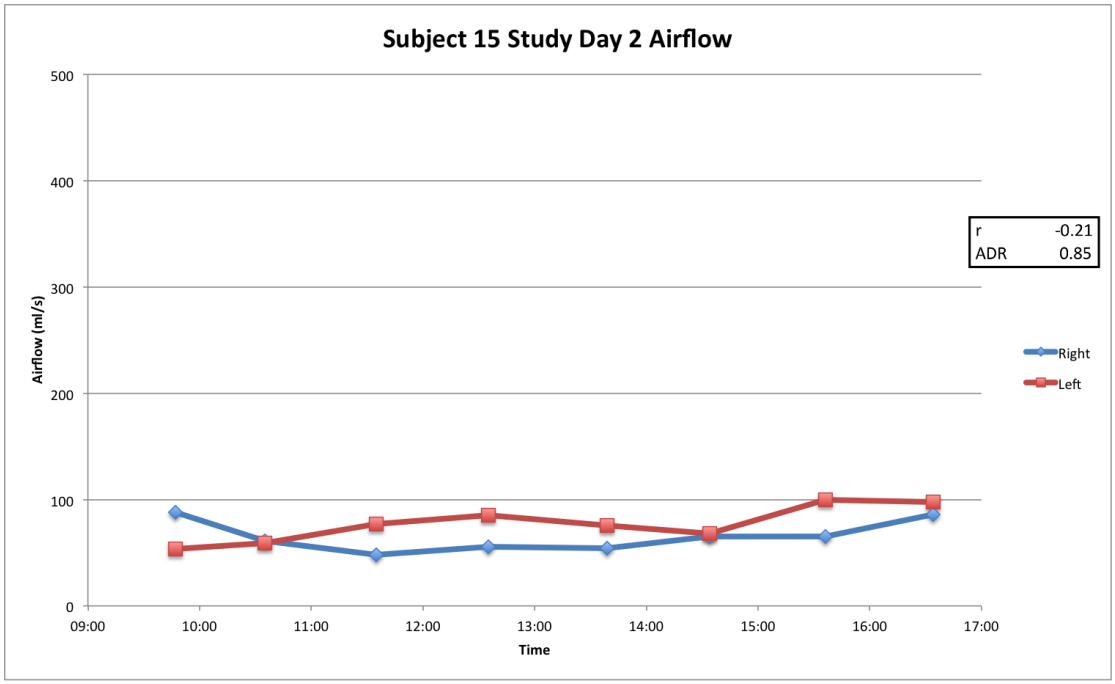

Subject 12 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.22
ADR 0.52
Right
Left

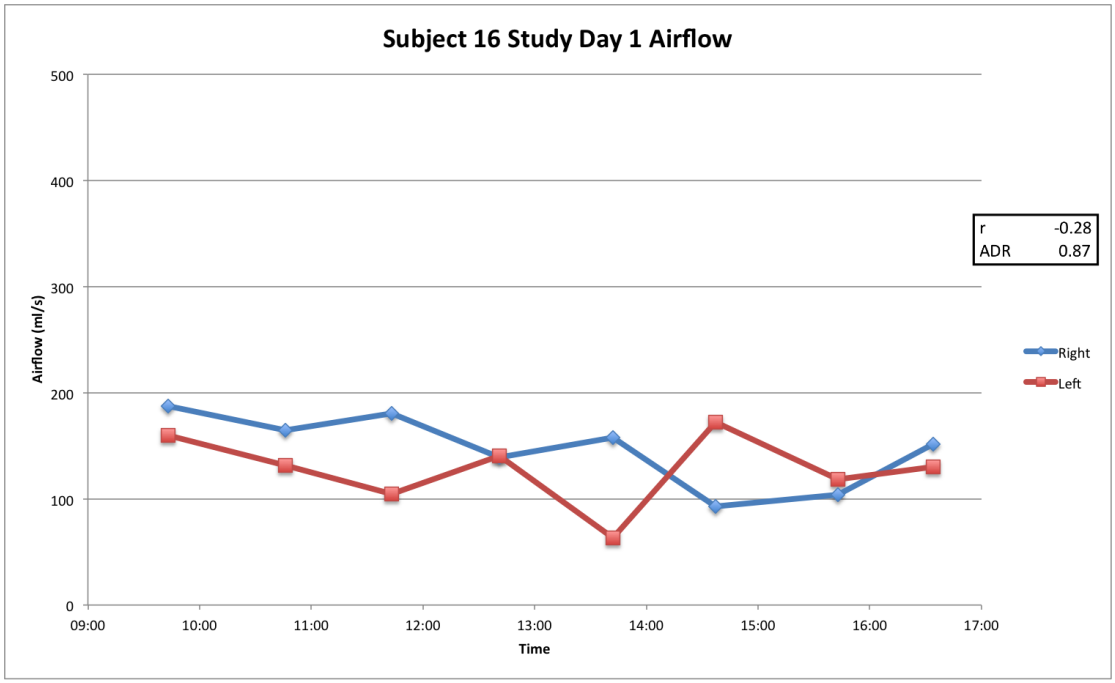

Subject 12 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.18
ADR 0.83
Right
Left

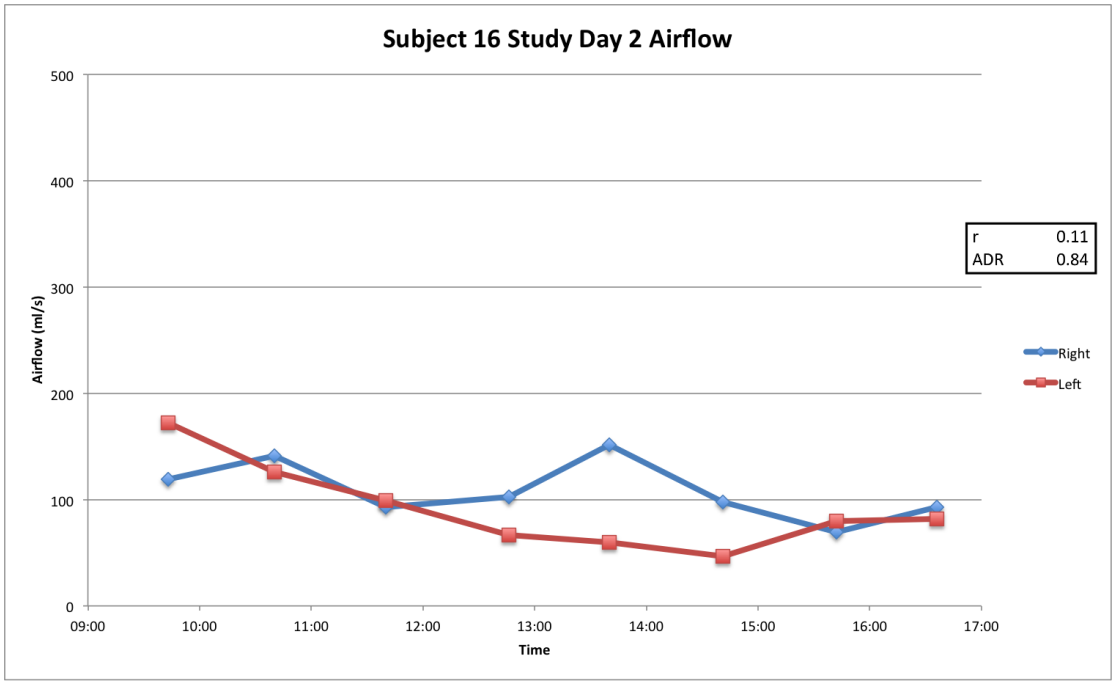

Subject 14 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.29
ADR 0.37
Right
Left

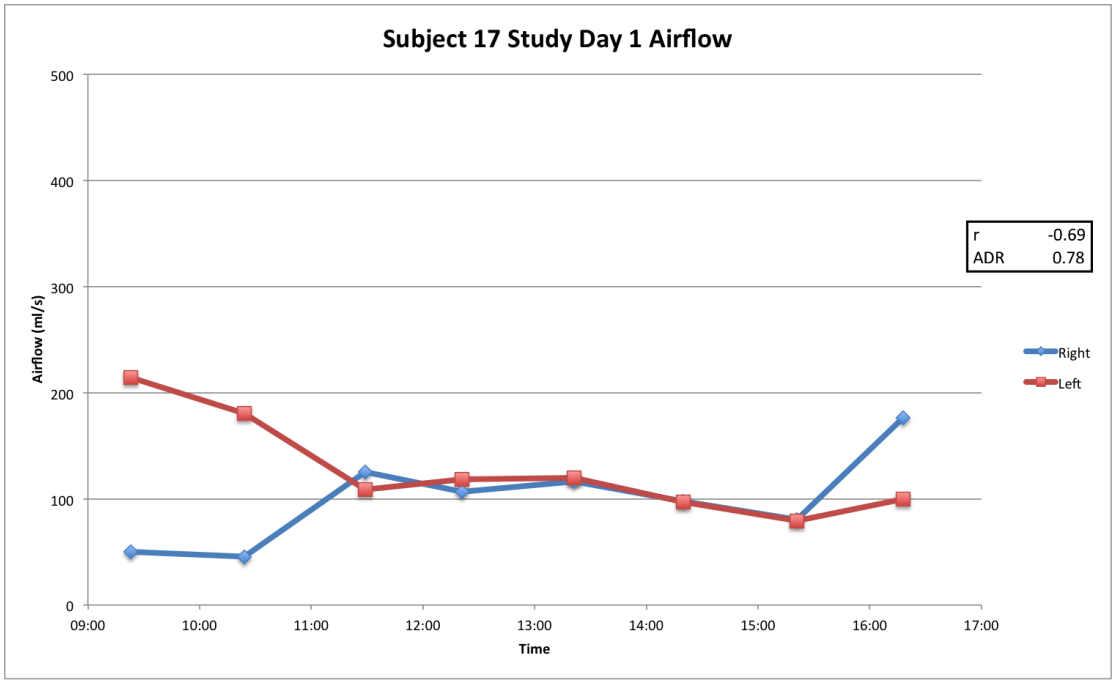

Subject 14 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.55
ADR 0.89
Right
Left

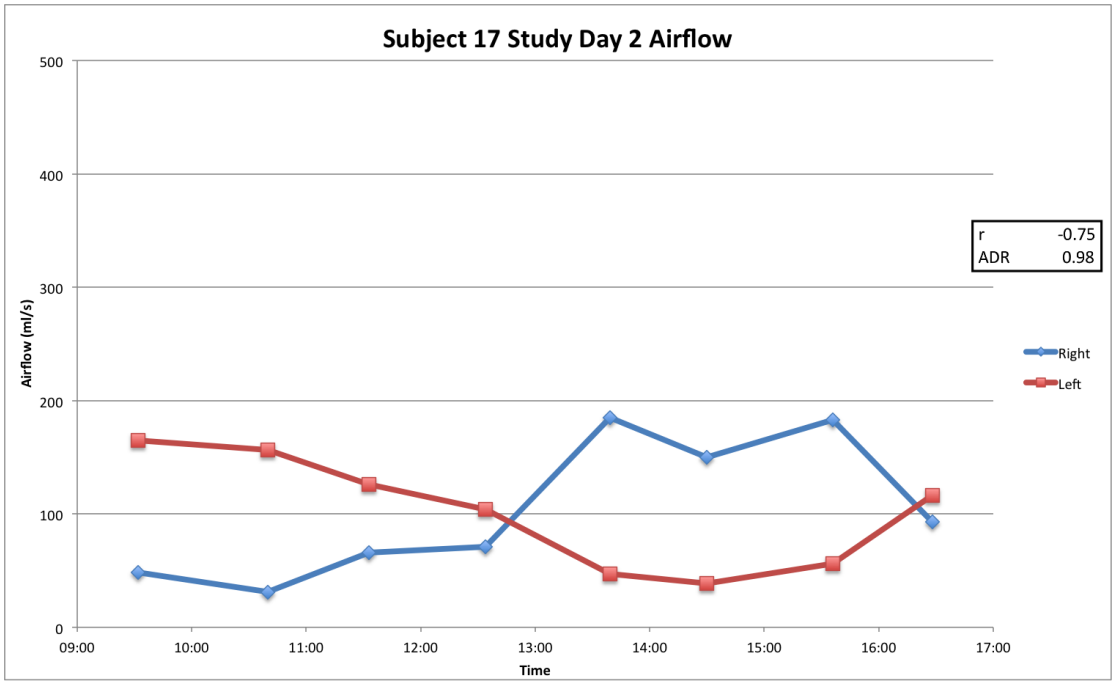

Subject 15 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.61
ADR 1.00
Right
Left

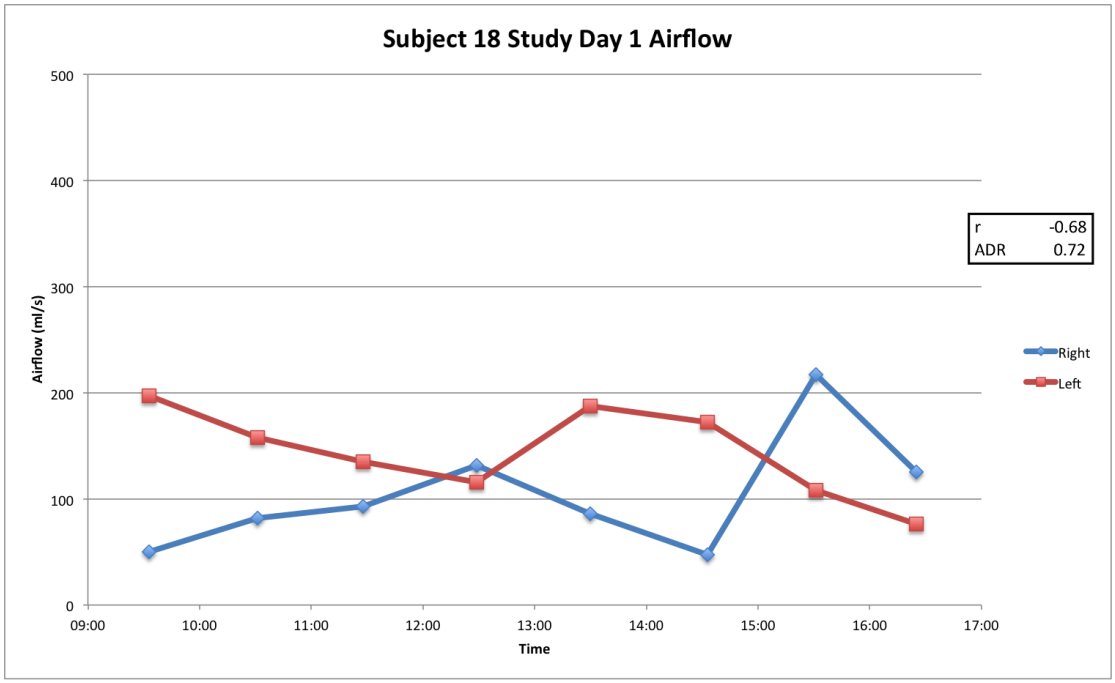

Subject 15 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.21
ADR 0.85
Right
Left

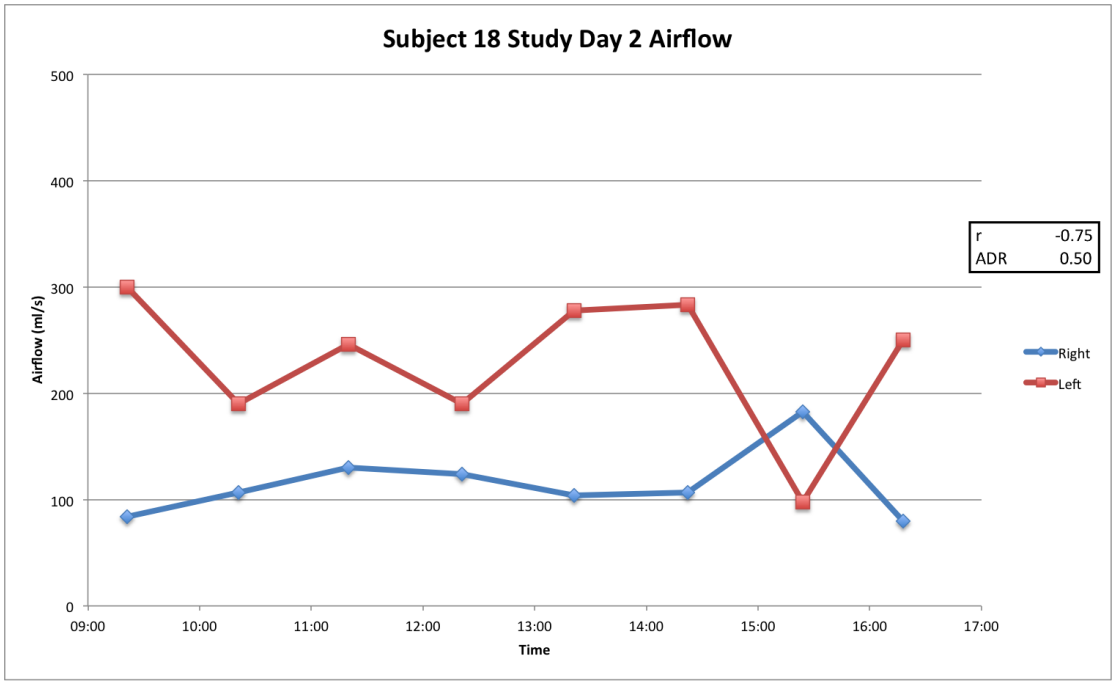

Subject 16 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.28
ADR 0.87
Right
Left

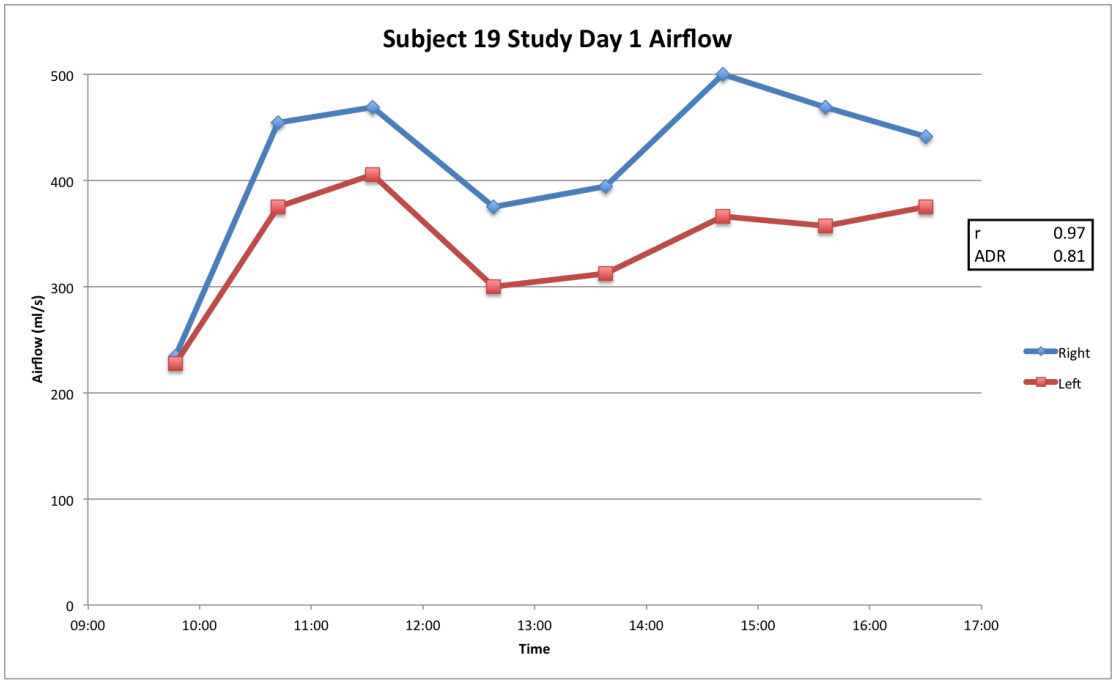

Subject 16 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.11
ADR 0.84
Right
Left

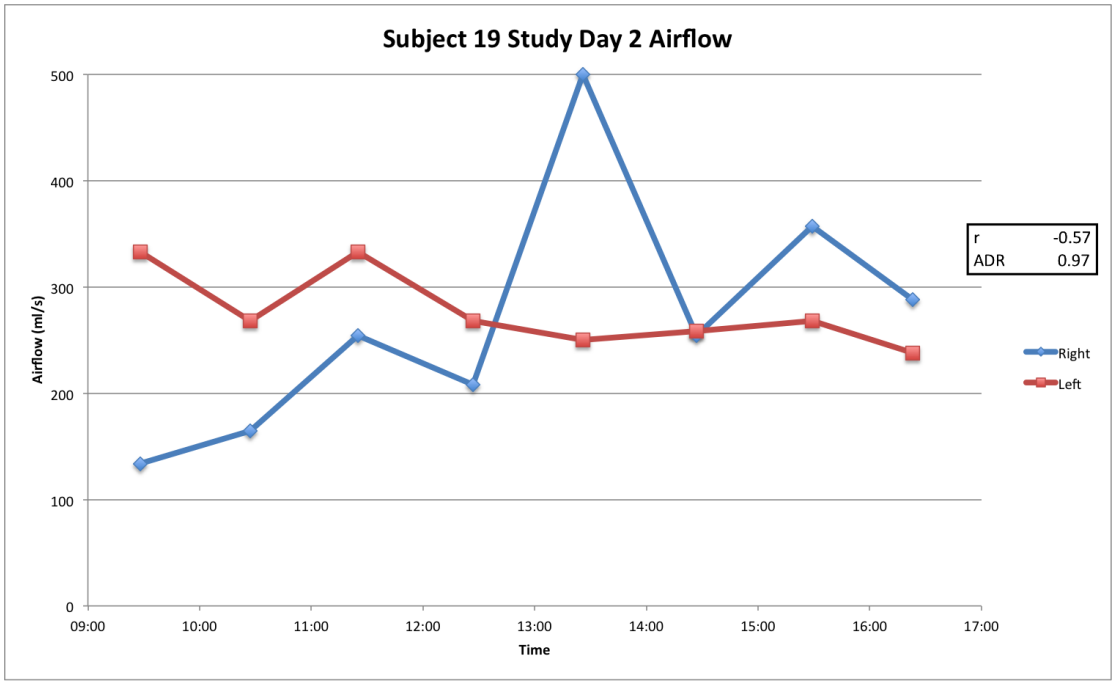

Subject 17 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.69
ADR 0.78
Right
Left

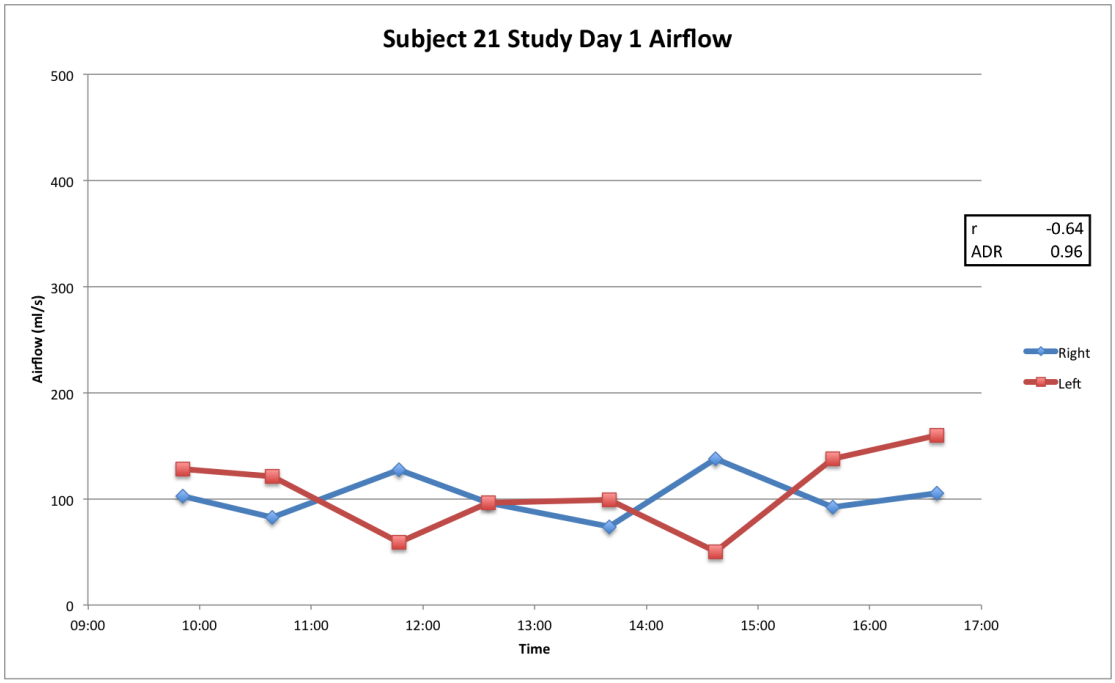

Subject 17 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.75
ADR 0.98
Right
Left

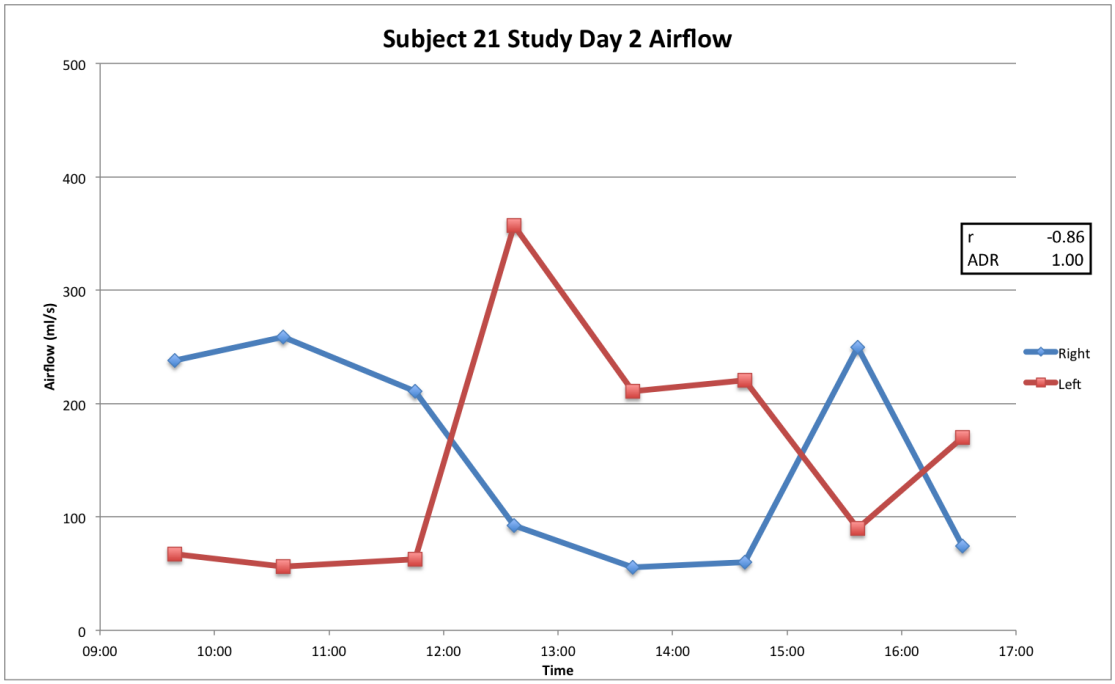

Subject 18 Study Day 1 Airflow
Airflow (ml/s)
500
400
300
200
100
0
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.68
ADR 0.72
Right
Left

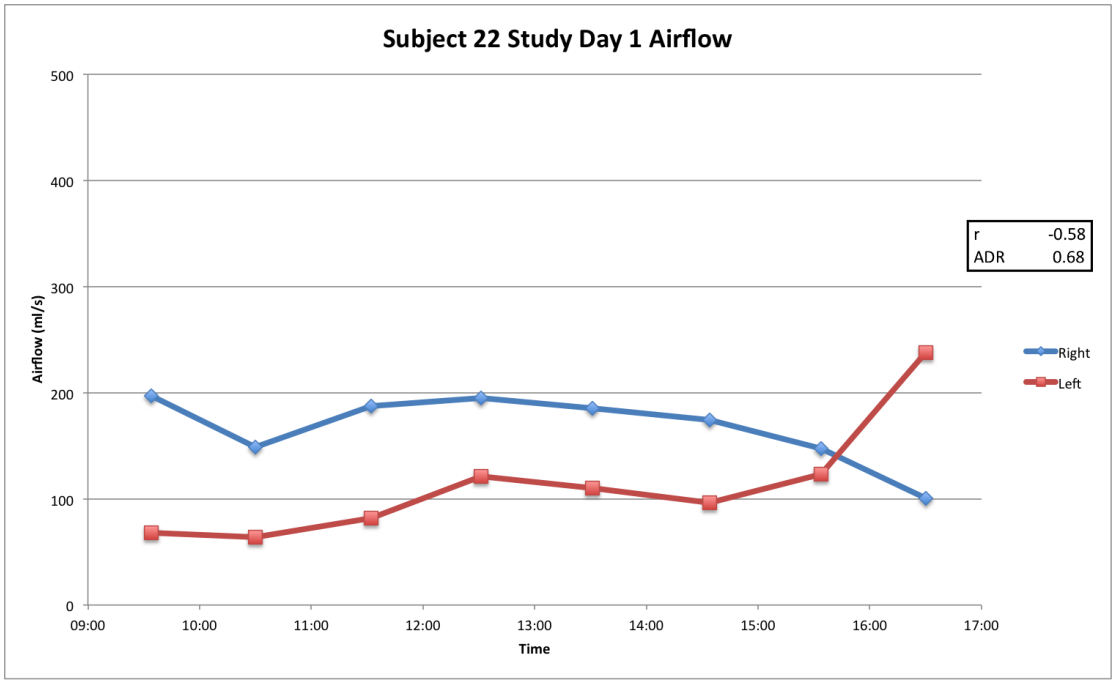

Subject 18 Study Day 2 Airflow
Airflow (ml/s)
500
400
300
200
100
0
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.75
ADR 0.50
Right
Left

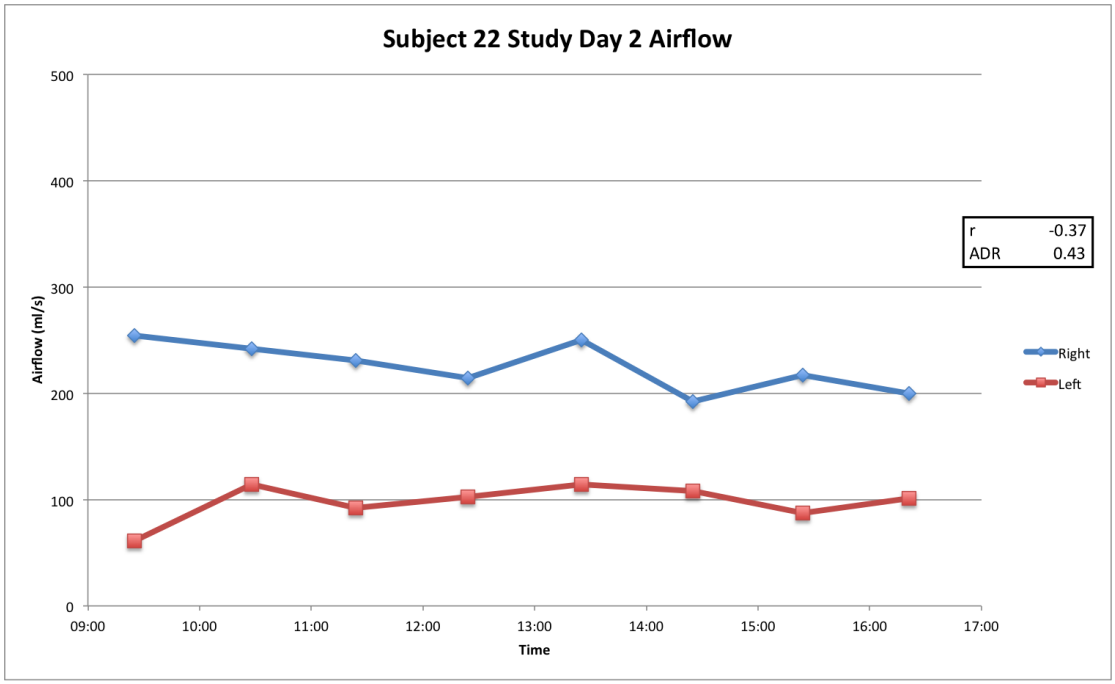

Subject 19 Study Day 1 Airflow
Airflow (ml/s)
500
400
300
200
100
0
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.97
ADR 0.81
Right
Left

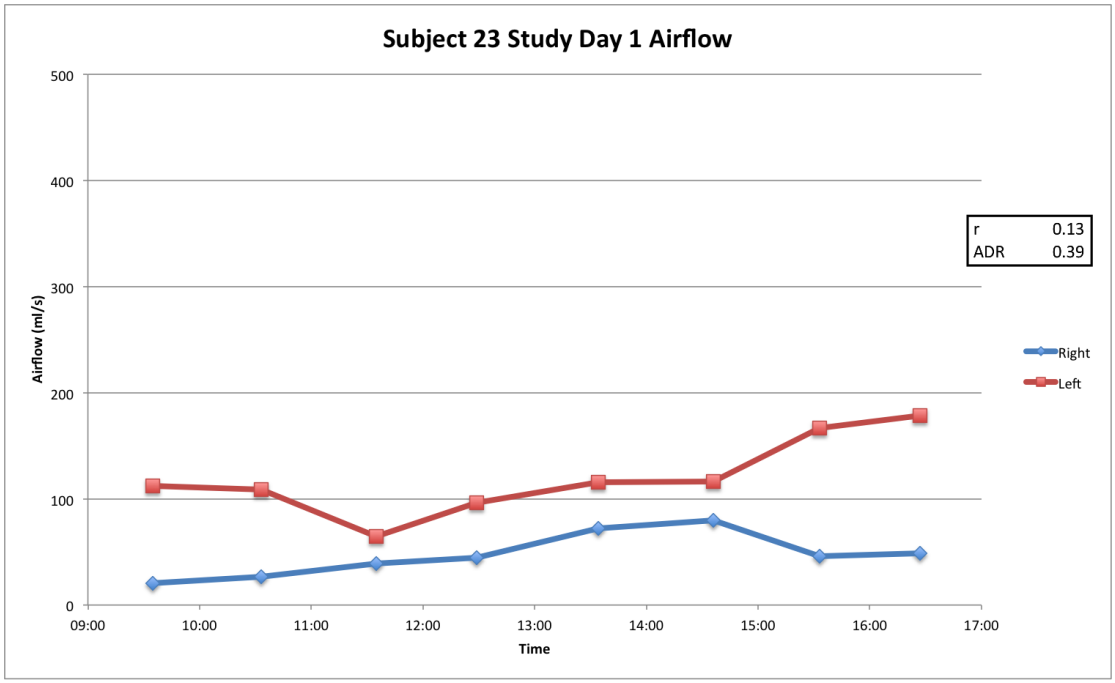

Subject 19 Study Day 2 Airflow
Airflow (ml/s)
500
400
300
200
100
0
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.57
ADR 0.97
Right
Left

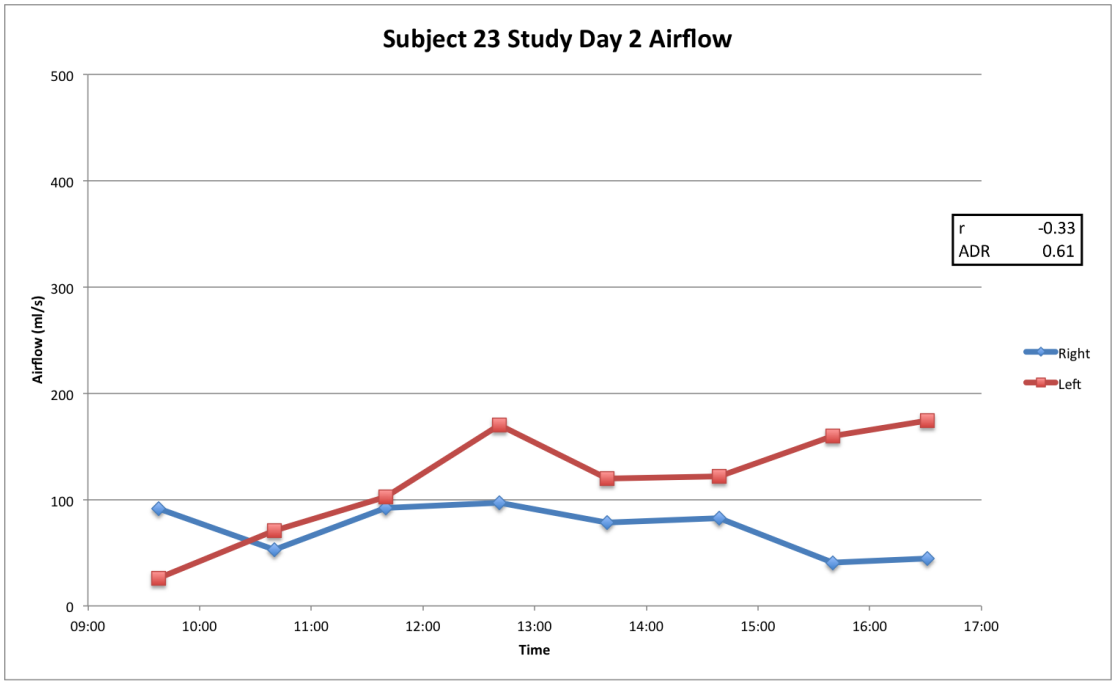

Subject 21 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.64
ADR 0.96
Right
Left

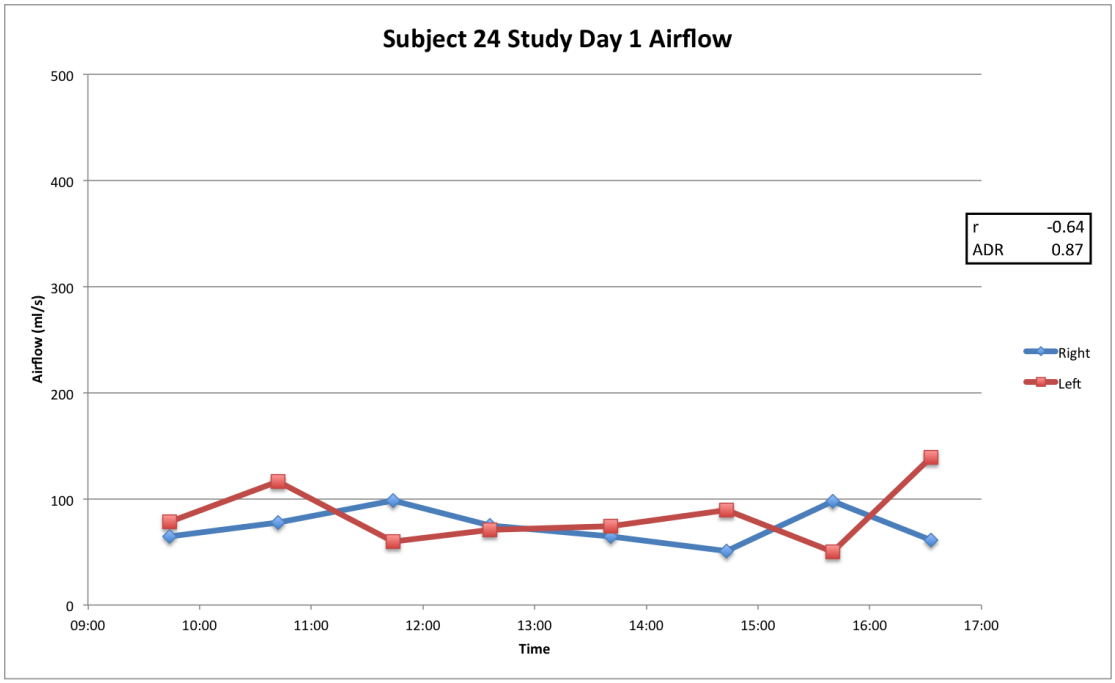

Subject 21 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.86
ADR 1.00
Right
Left

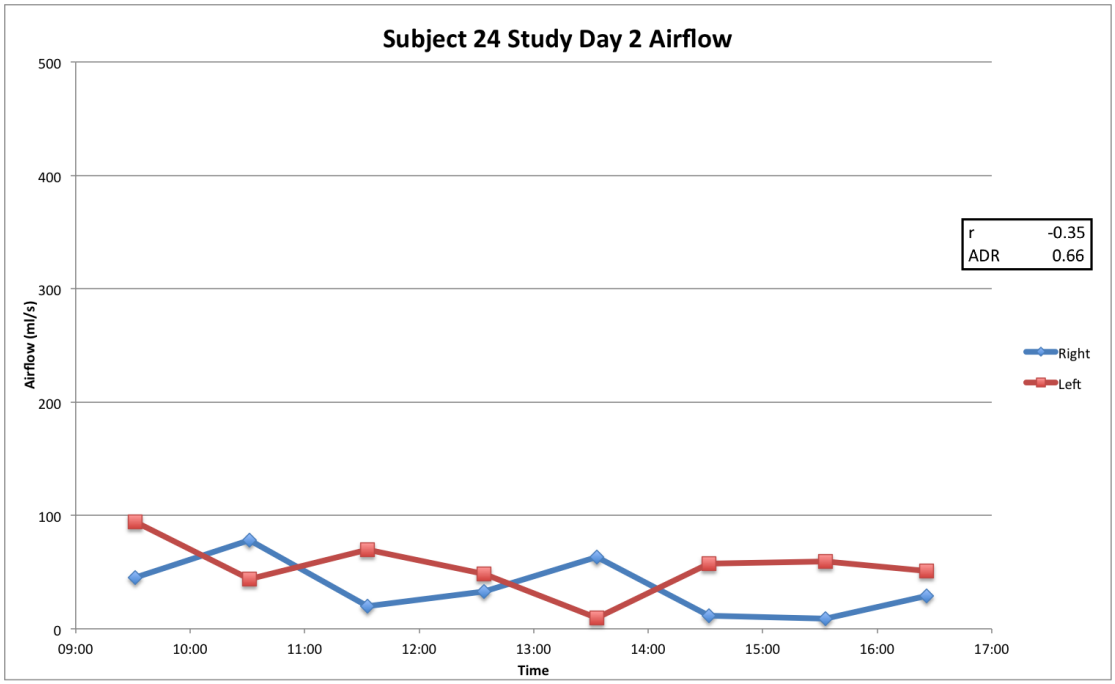

Subject 22 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.58
ADR 0.68
Right
Left

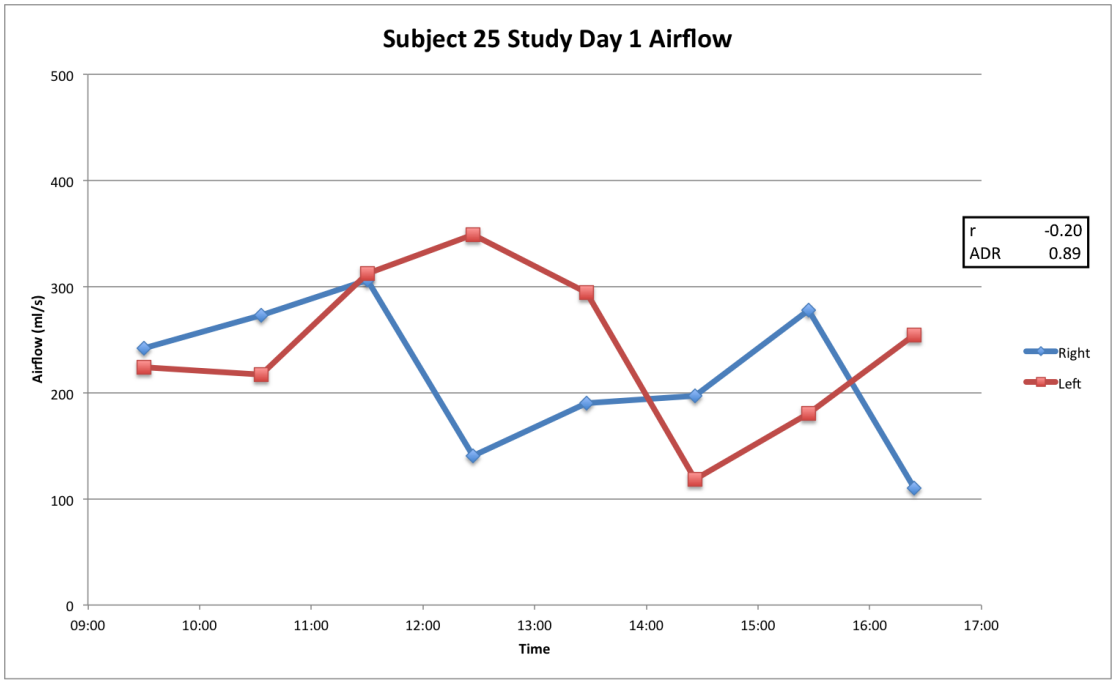

Subject 22 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.37
ADR 0.43
Right
Left

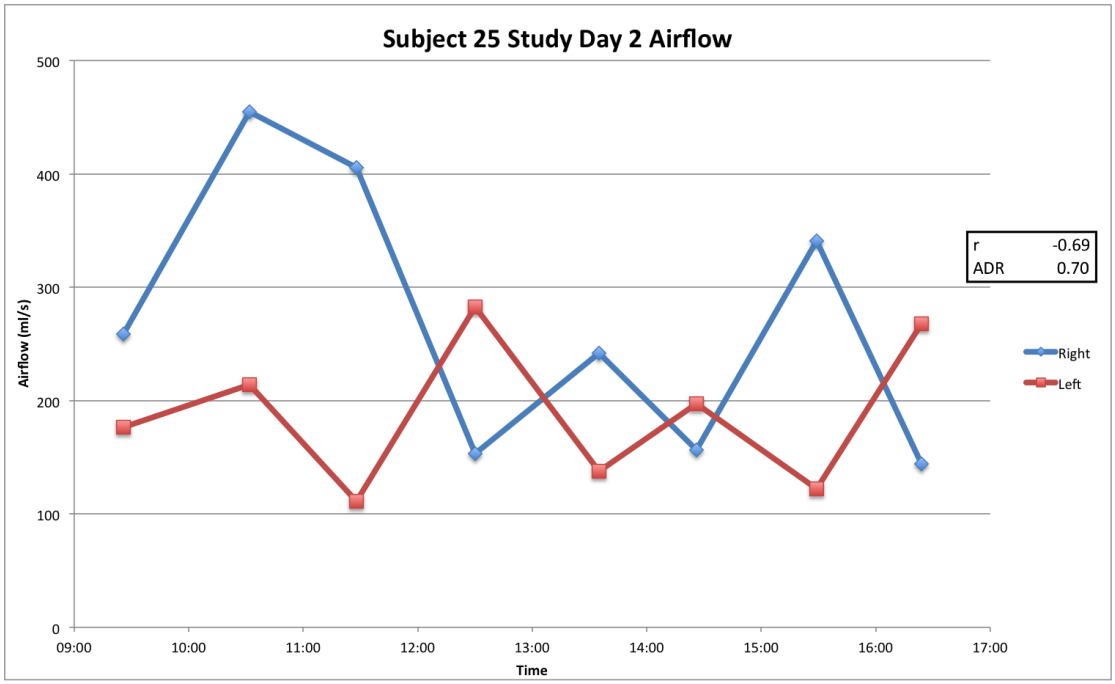

Subject 23 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.13
ADR 0.39
Right
Left

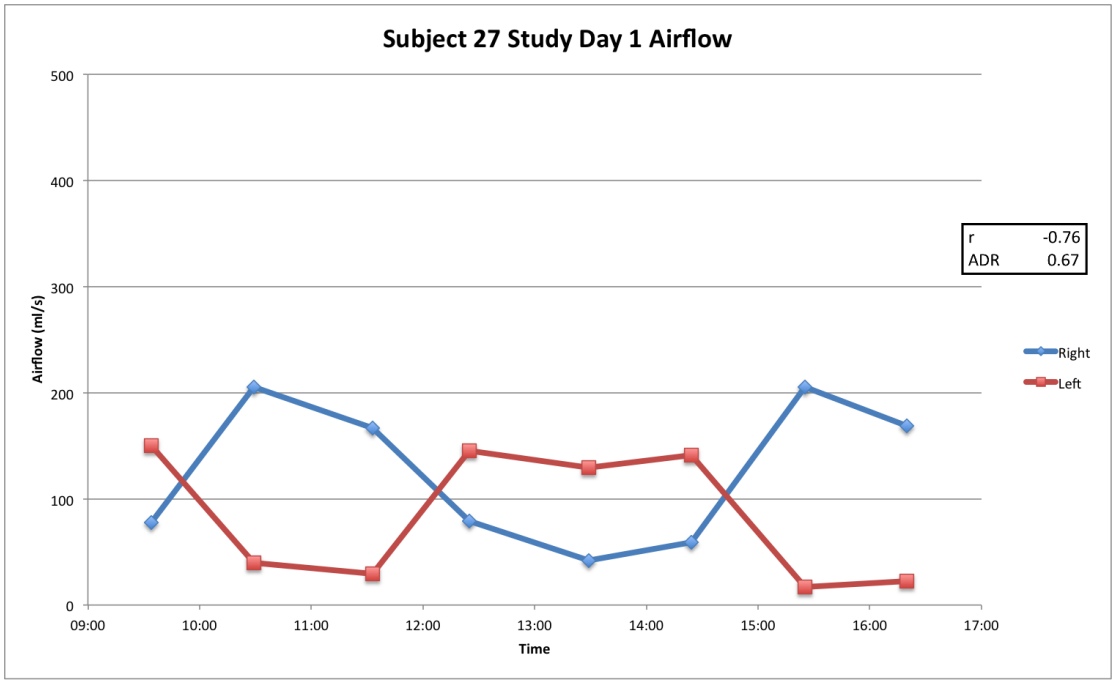

Subject 23 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.33
ADR 0.61
Right
Left

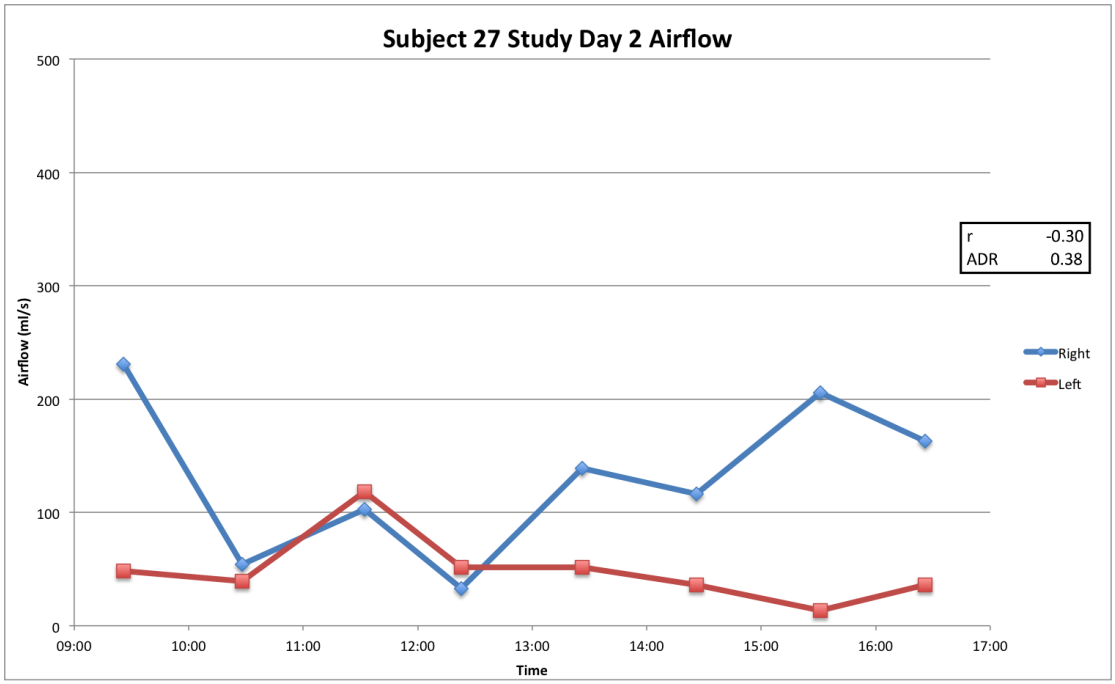

Subject 24 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.64
ADR 0.87
Right
Left

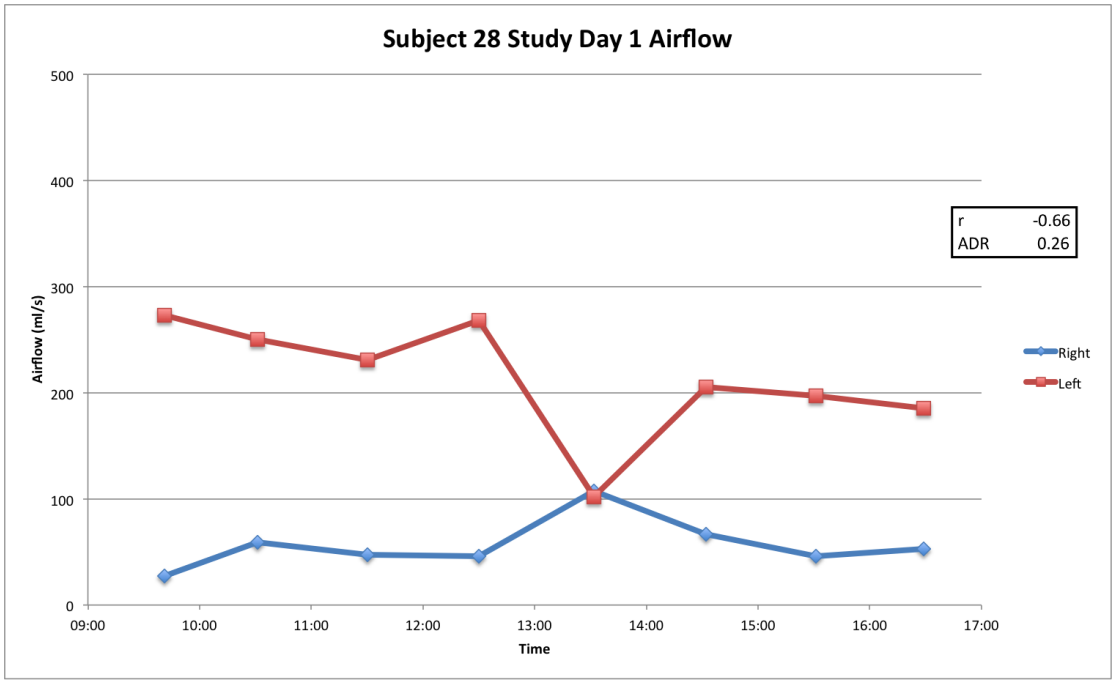

Subject 24 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.35
ADR 0.66
Right
Left

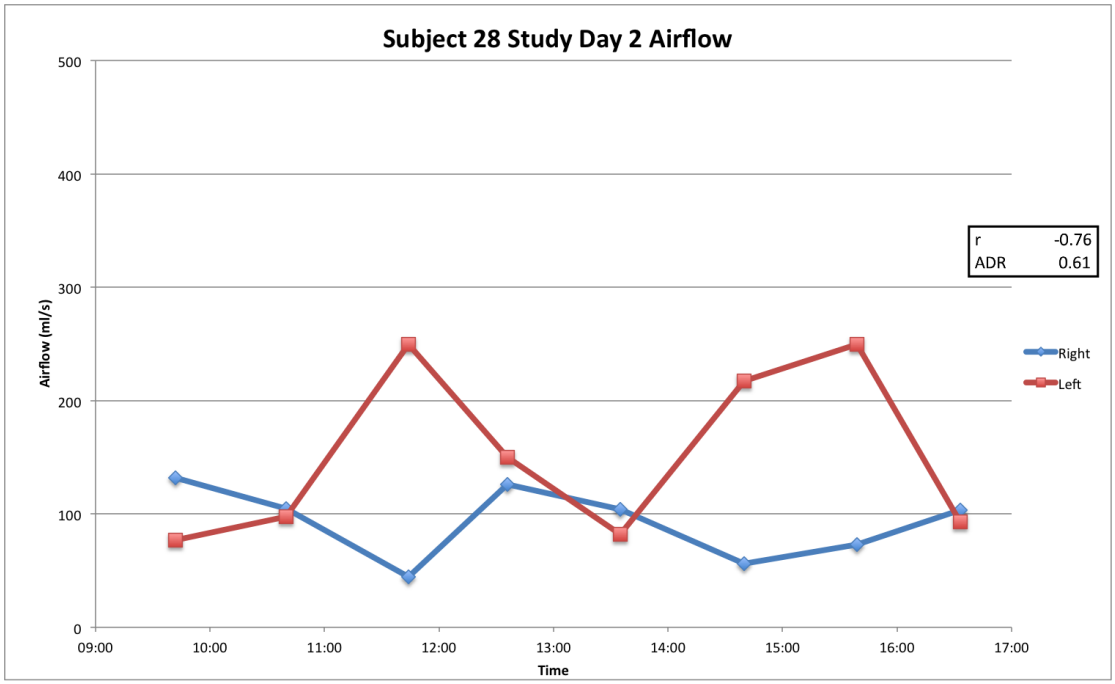

Subject 25 Study Day 1 Airflow
Airflow (ml/s)
500
400
300
200
100
0
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.20
ADR 0.89
Right
Left

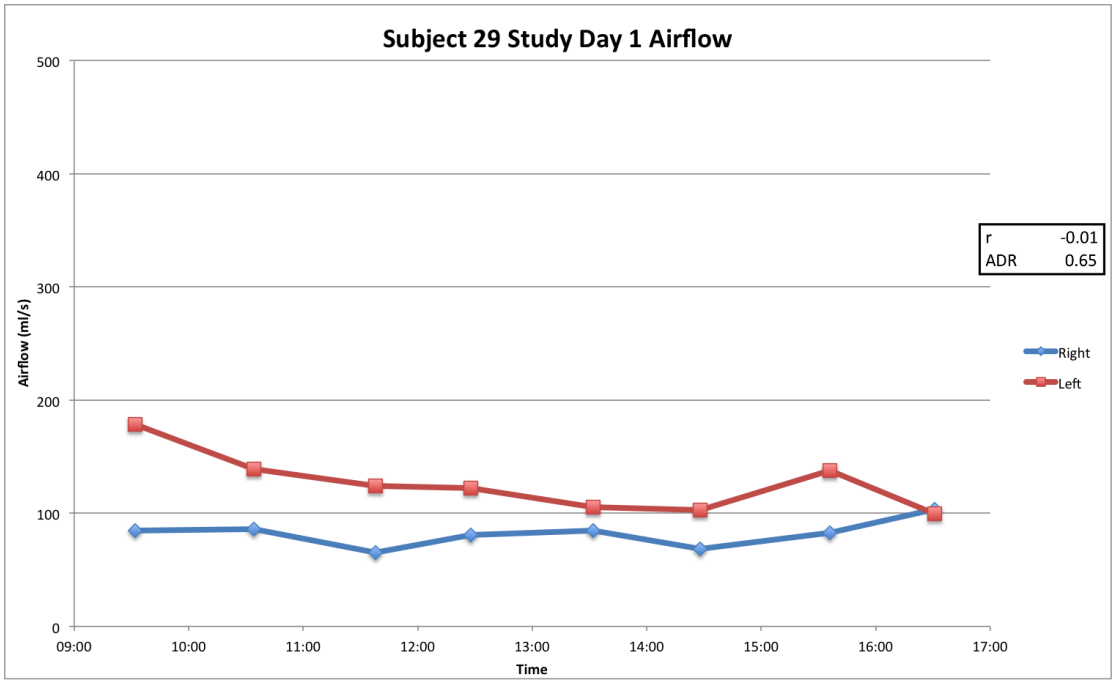

Subject 25 Study Day 2 Airflow
Airflow (ml/s)
500
400
300
200
100
0
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.69
ADR 0.70
Right
Left

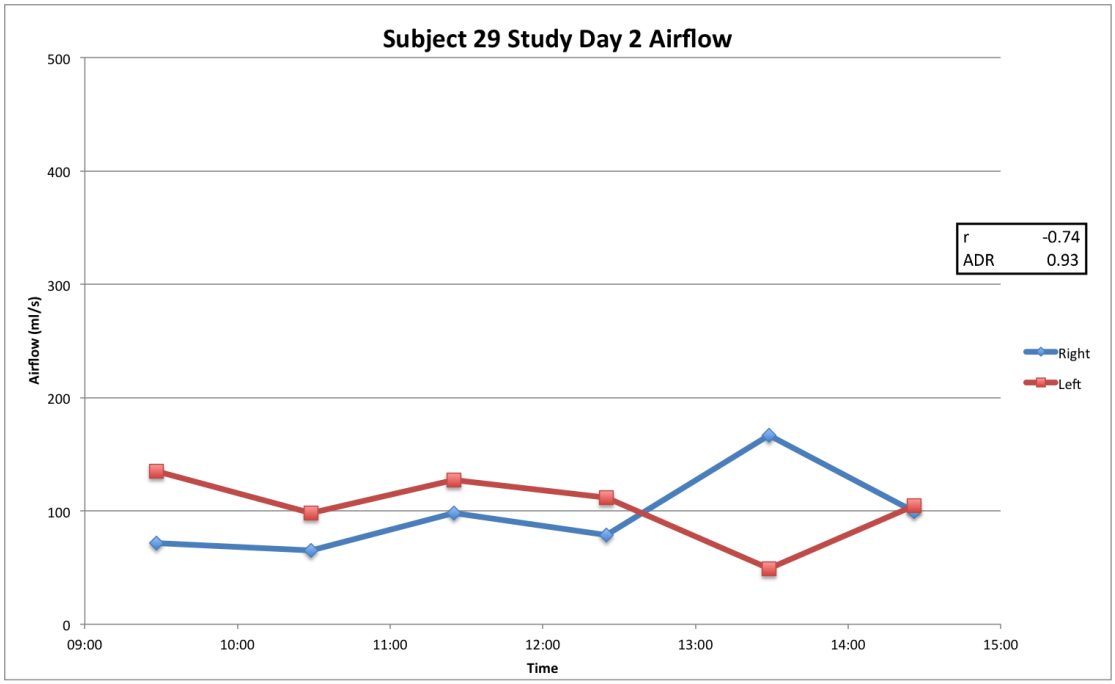

Subject 27 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.76
ADR 0.67
Right
Left

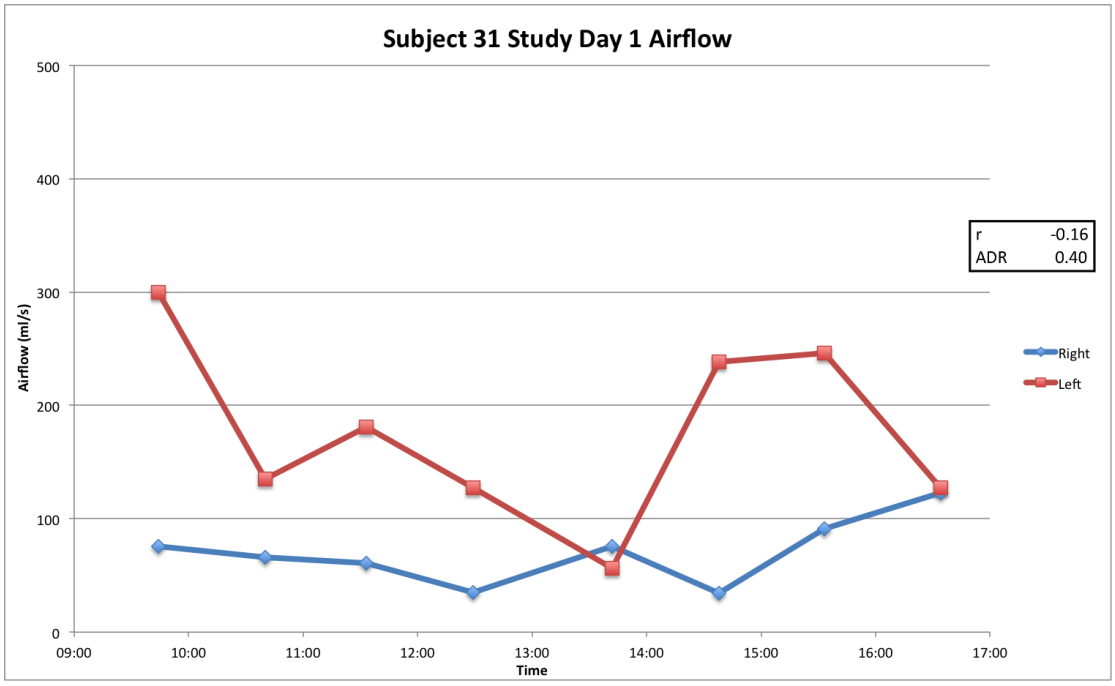

Subject 27 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.30
ADR 0.38
Right
Left

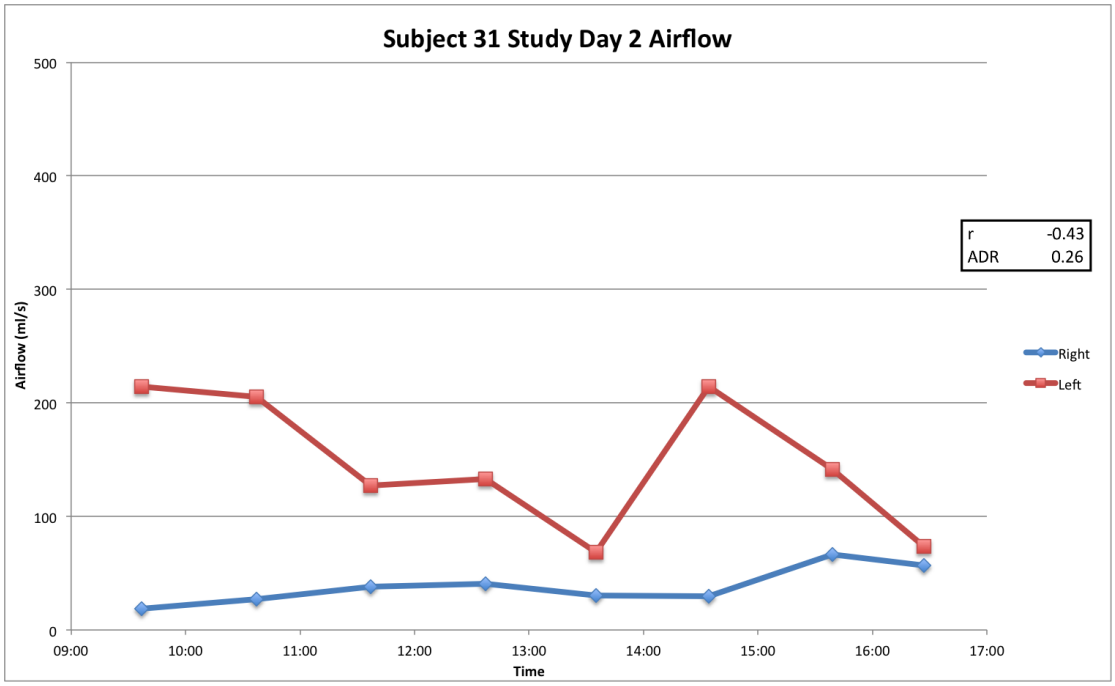

Subject 28 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.66
ADR 0.26
Right
Left

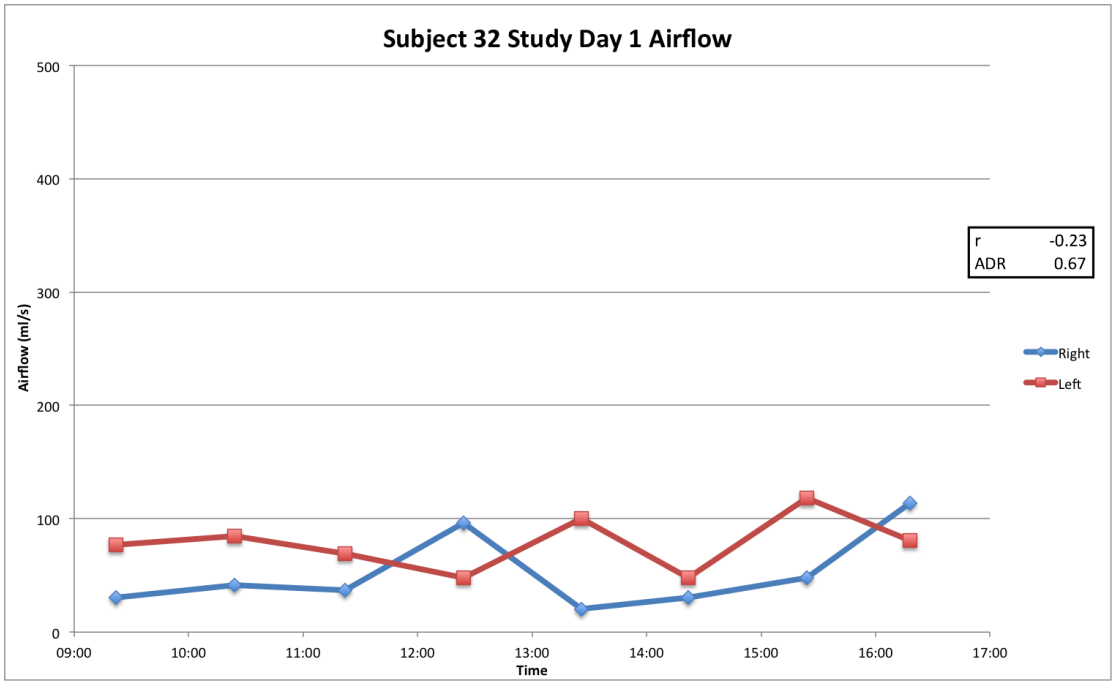

Subject 28 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.76
ADR 0.61
Right
Left

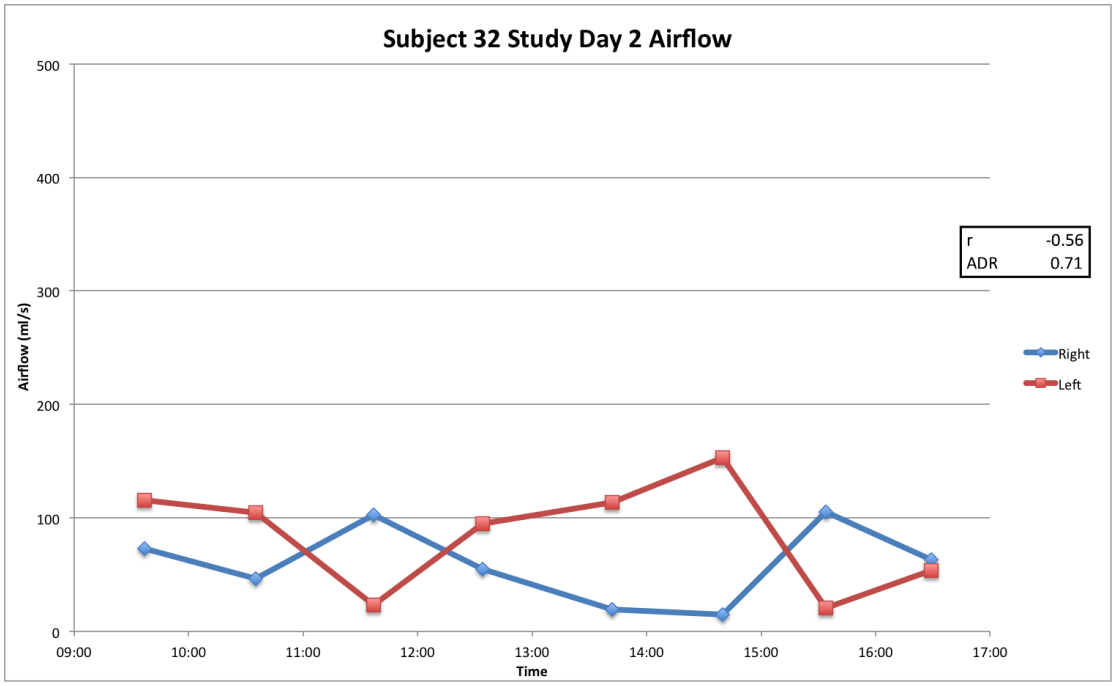

Subject 29 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.01
ADR 0.65
Right
Left

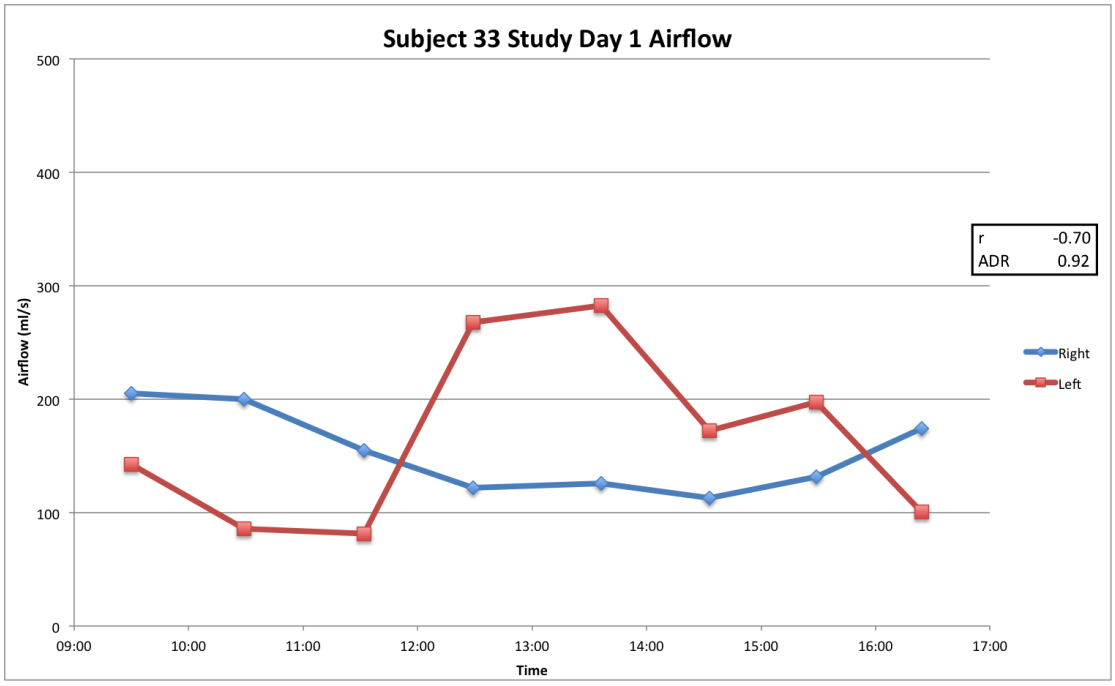

Subject 29 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
Time
r -0.74
ADR 0.93
Right
Left

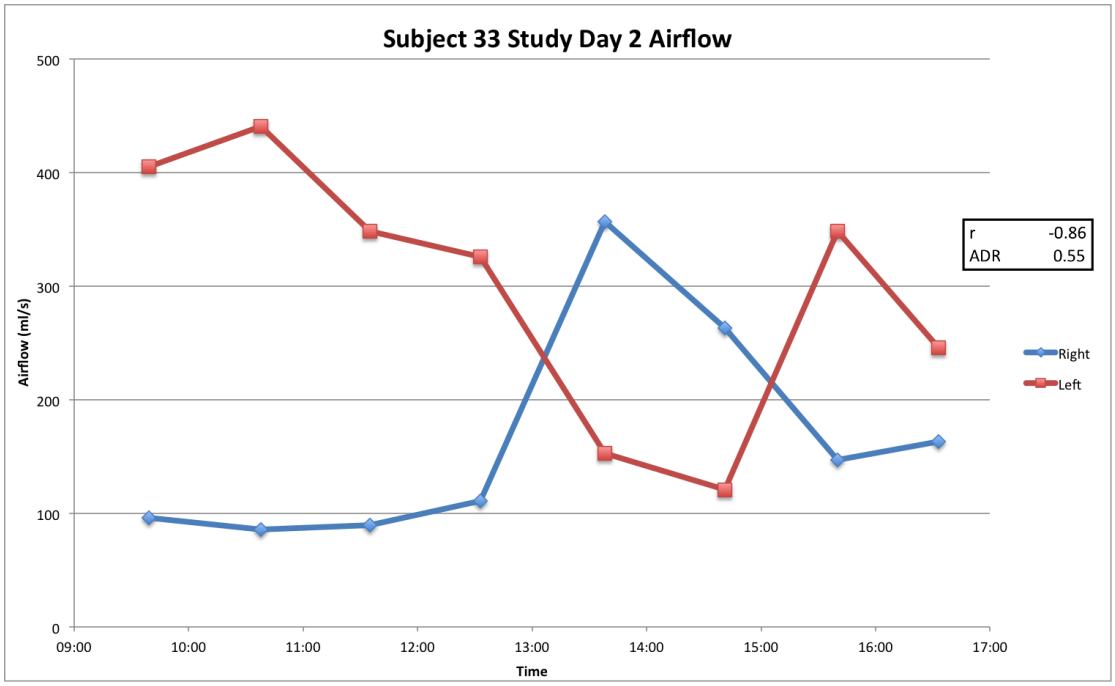

Subject 31 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.16
ADR 0.40
Right
Left

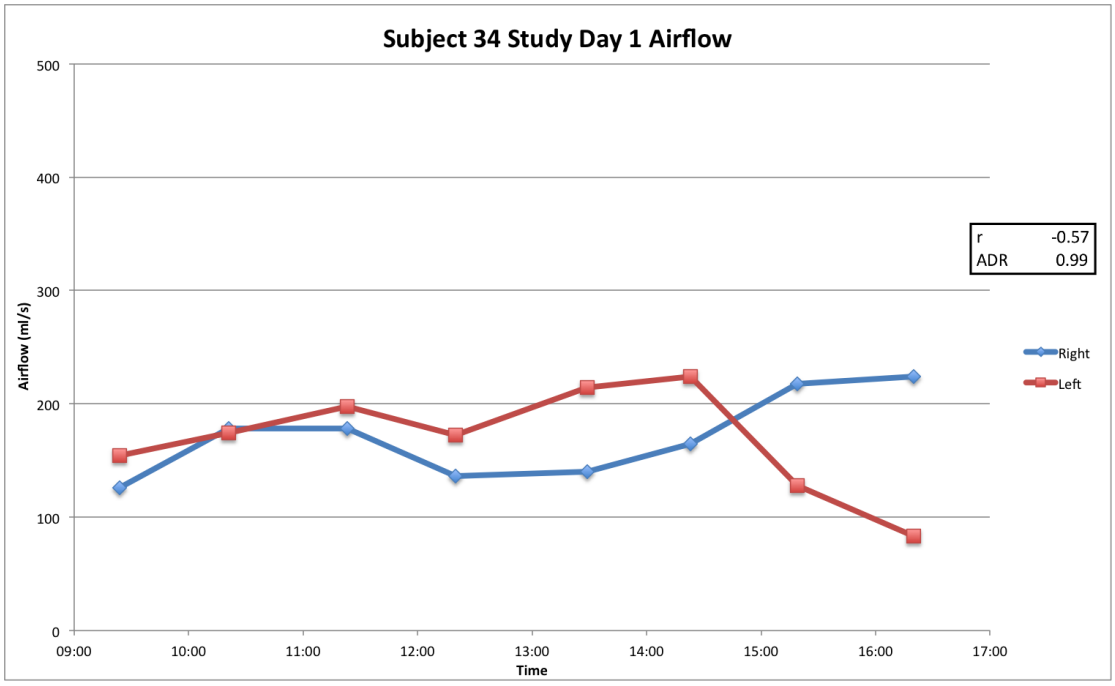

Subject 31 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.43
ADR 0.26
Right
Left

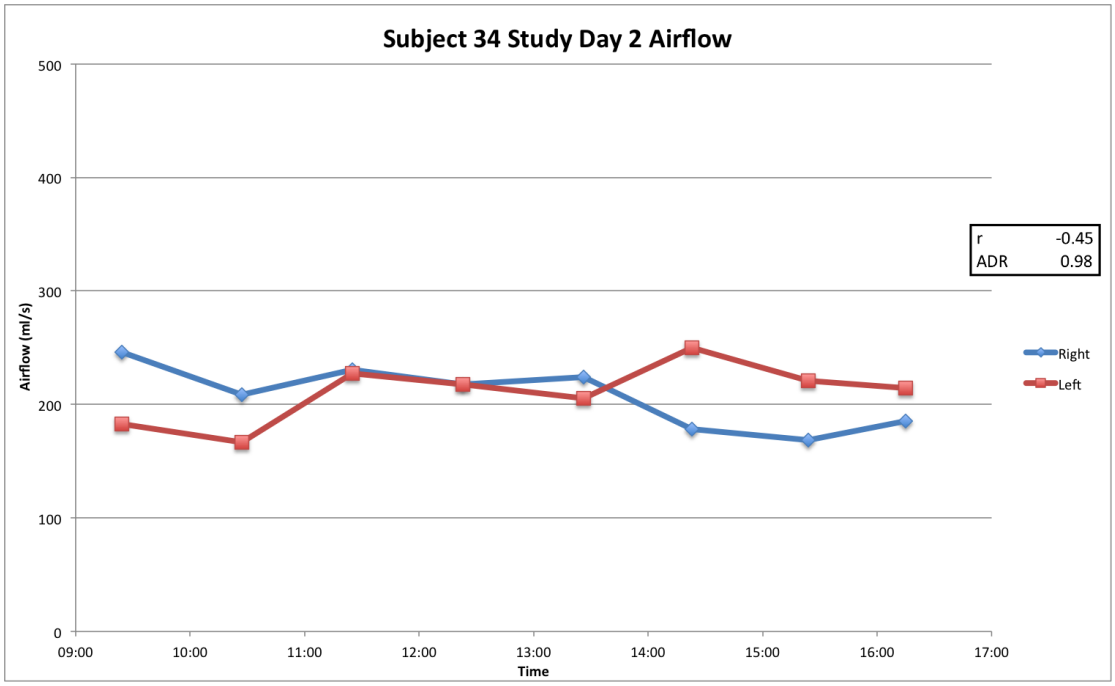

Subject 32 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.23
ADR 0.67
Right
Left

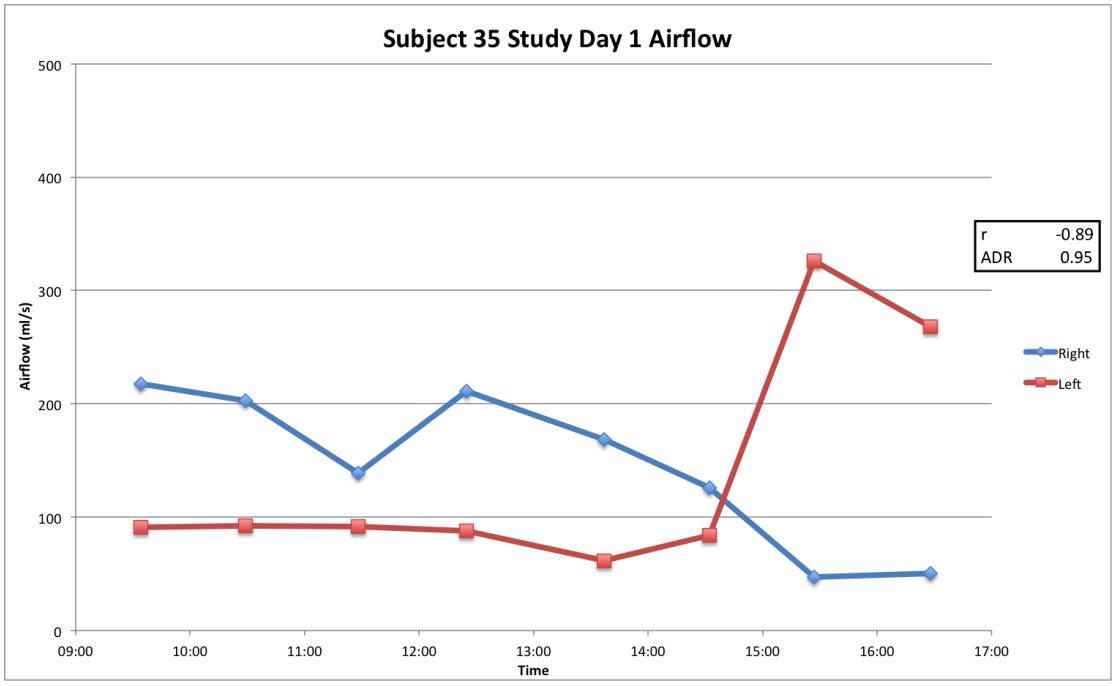

Subject 32 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.56
ADR 0.71
Right
Left

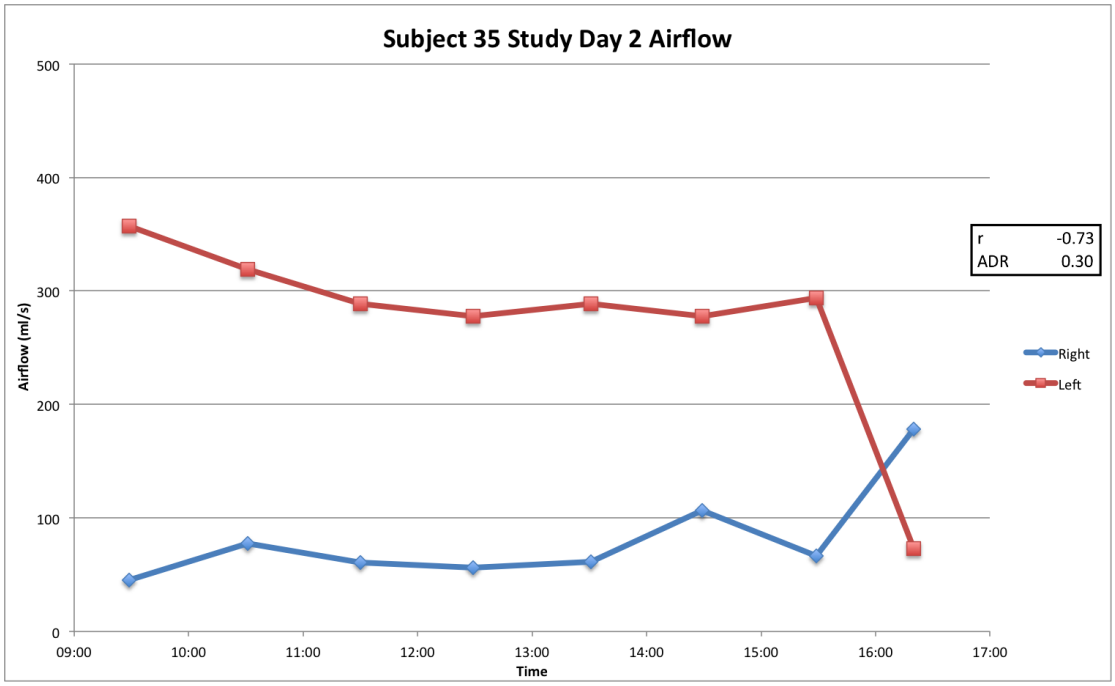

Subject 33 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.70
ADR 0.92
Right
Left

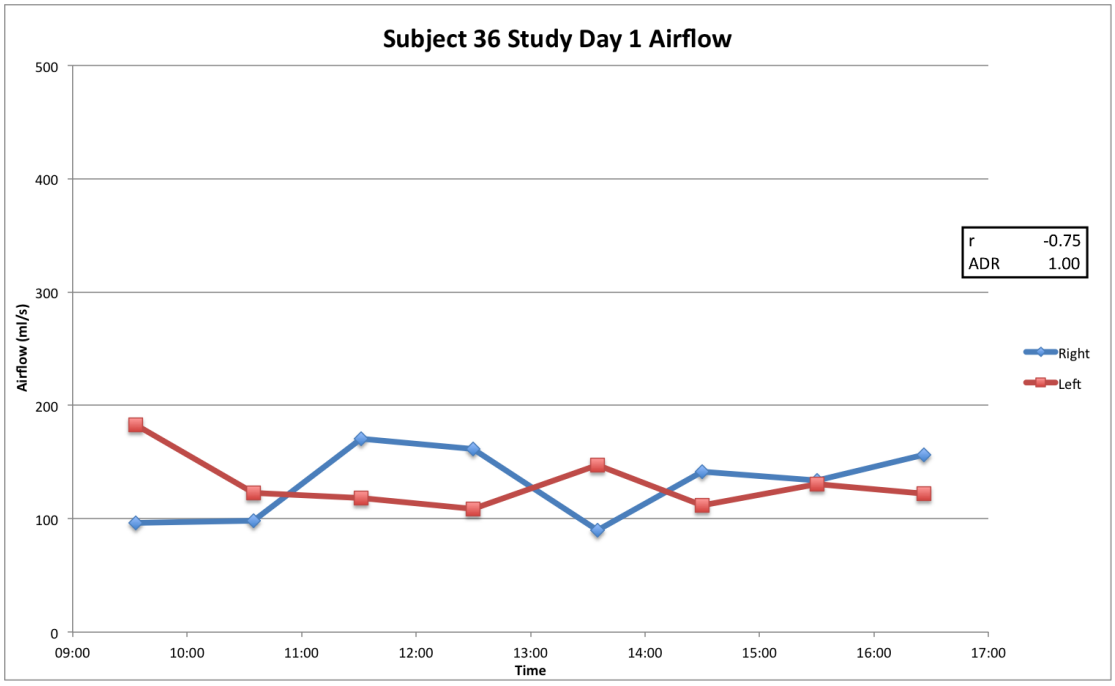

Subject 33 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.86
ADR 0.55
Right
Left

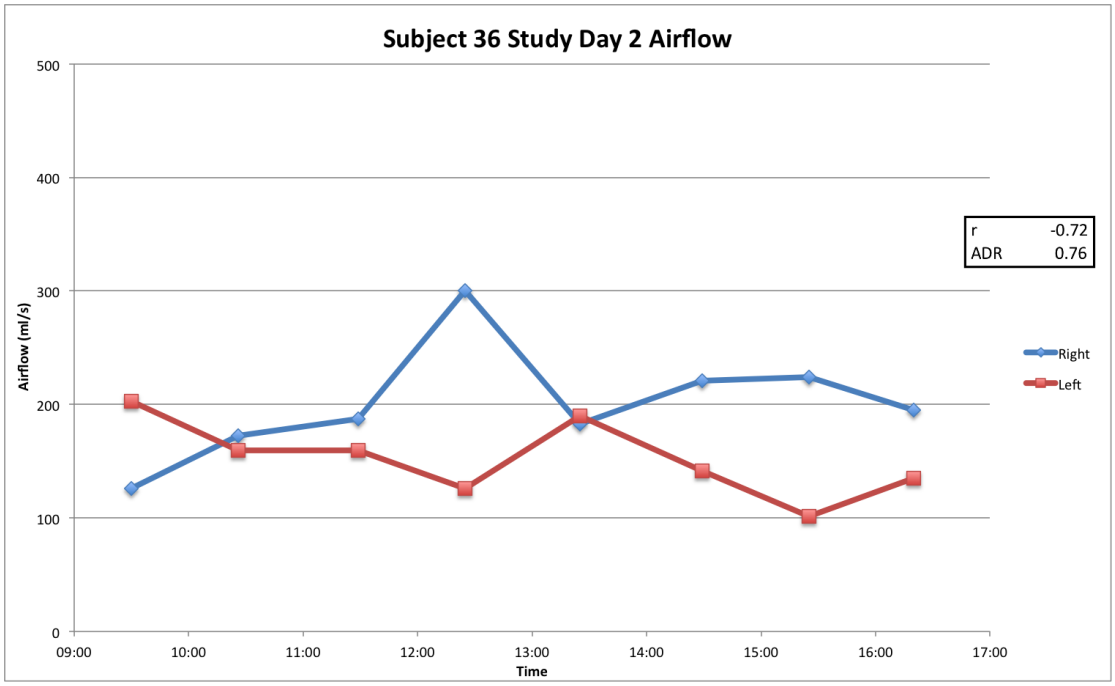

Subject 34 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.57
ADR 0.99
Right
Left

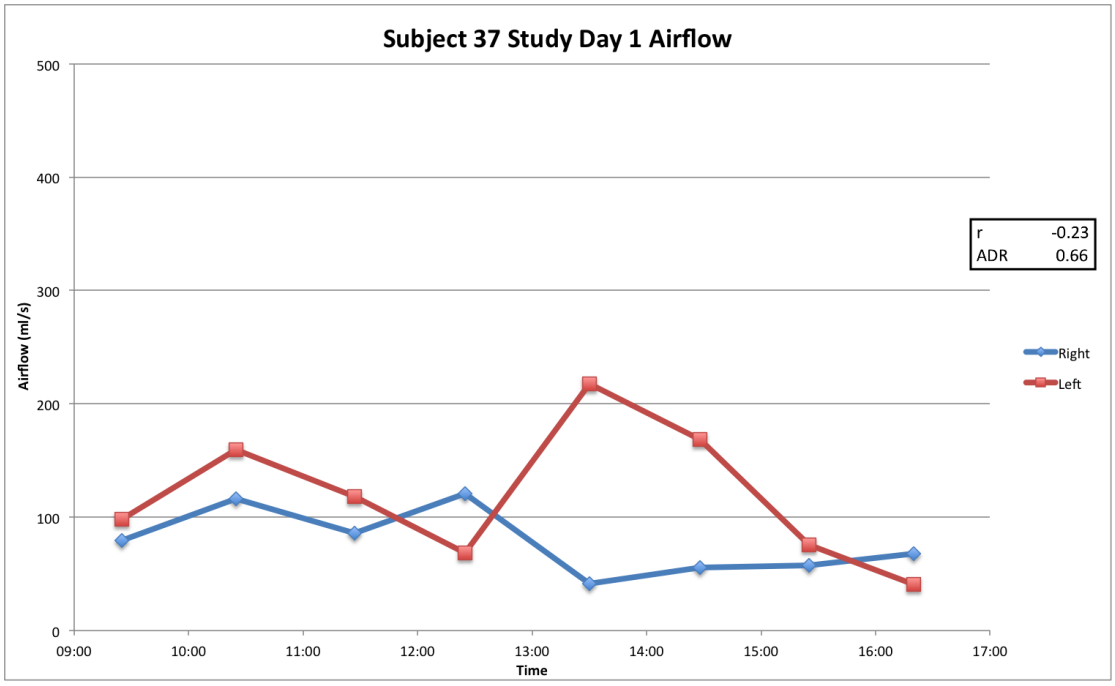

Subject 34 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.45
ADR 0.98
Right
Left

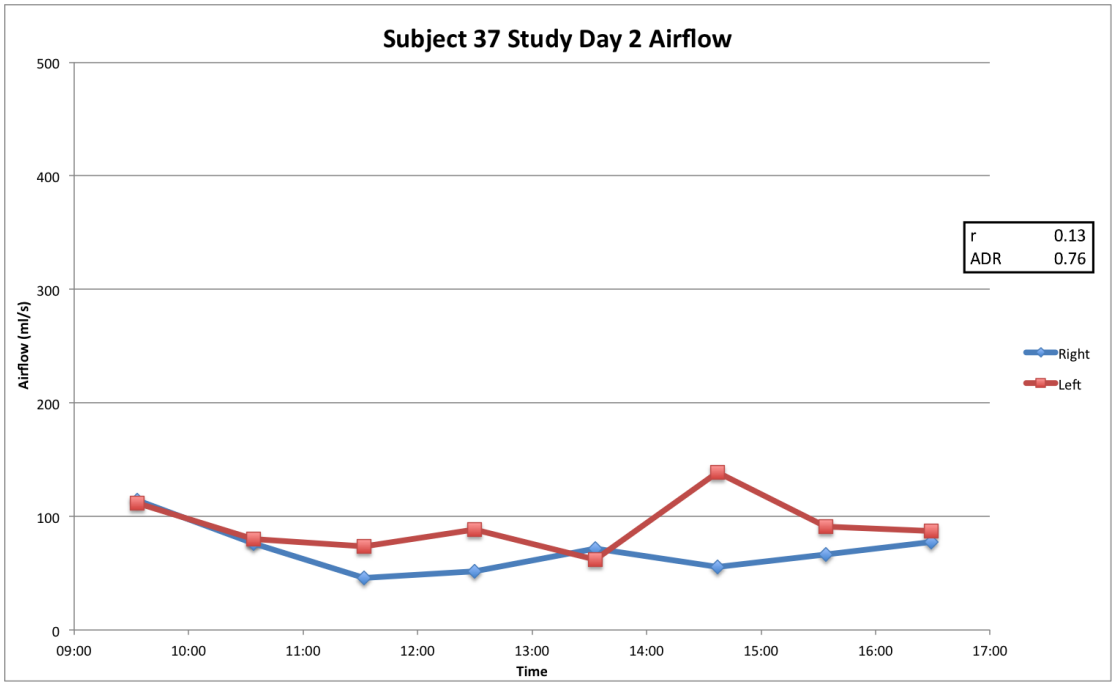

Subject 35 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.89
ADR 0.95
Right
Left

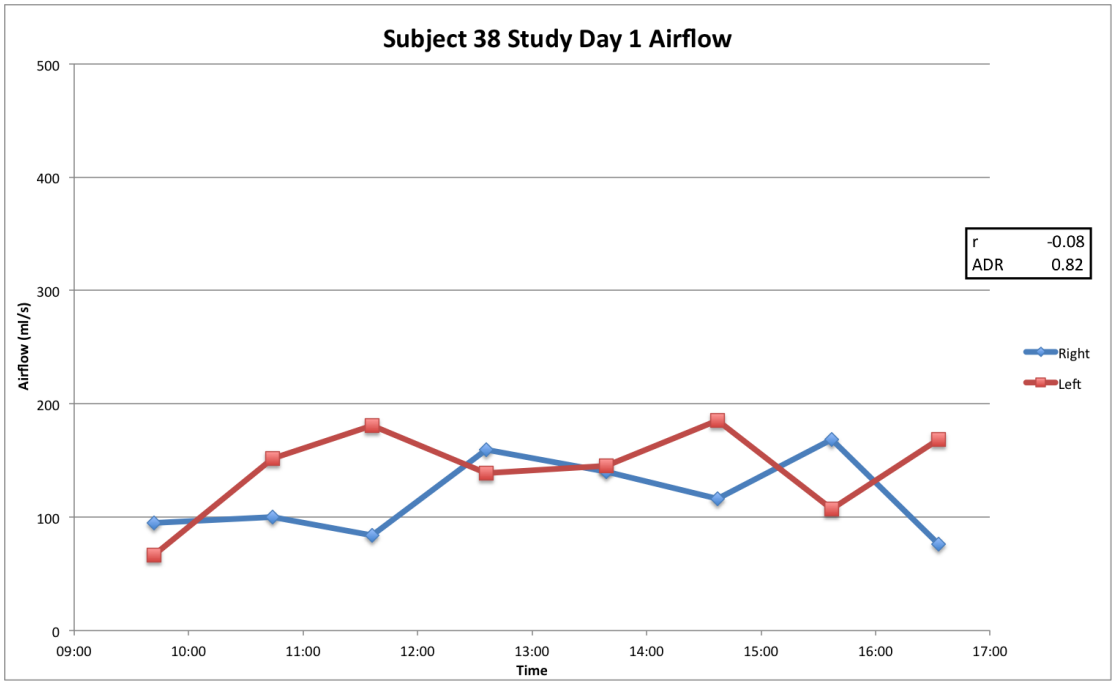

Subject 35 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.73
ADR 0.30
Right
Left

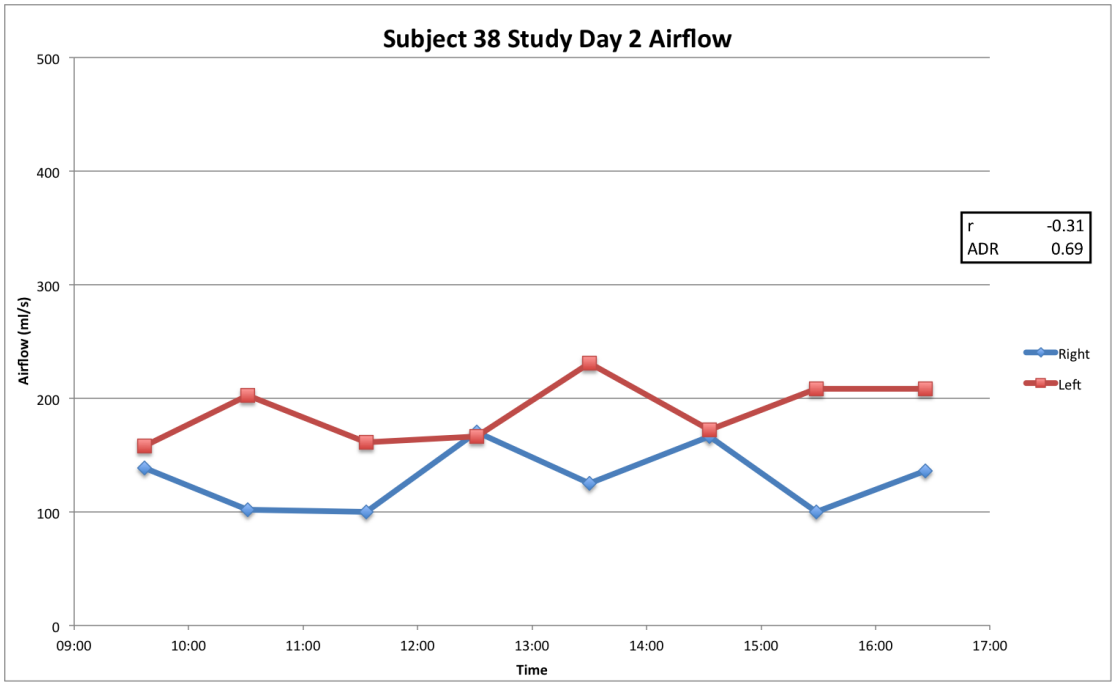

Subject 36 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.75
ADR 1.00
Right
Left

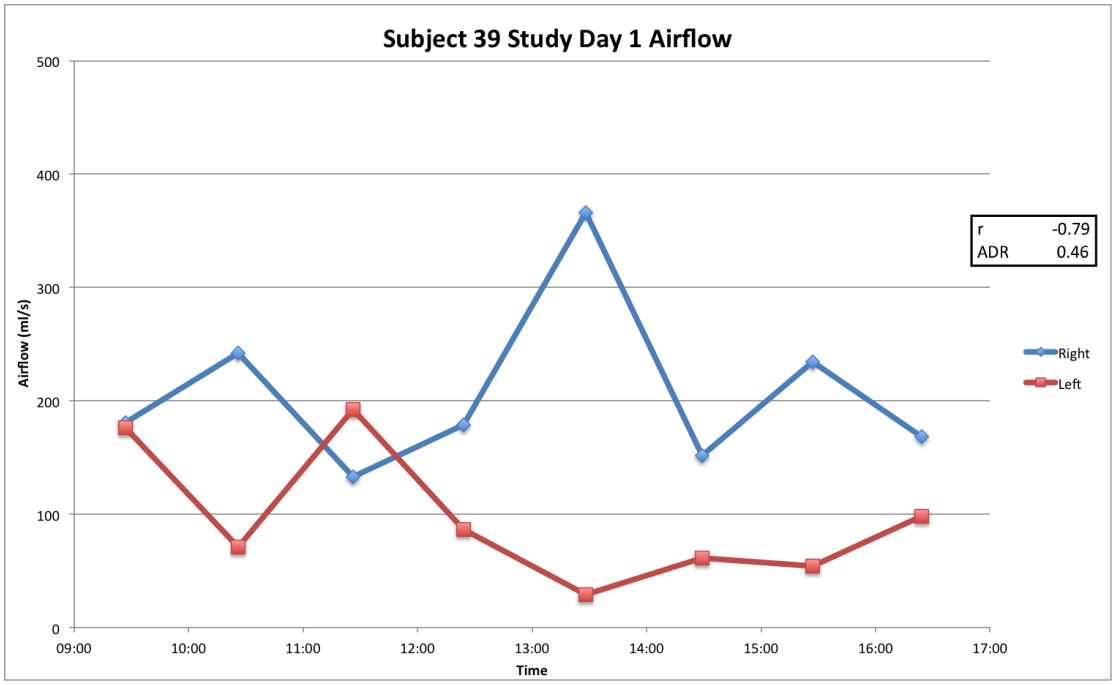

Subject 36 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.72
ADR 0.76
Right
Left

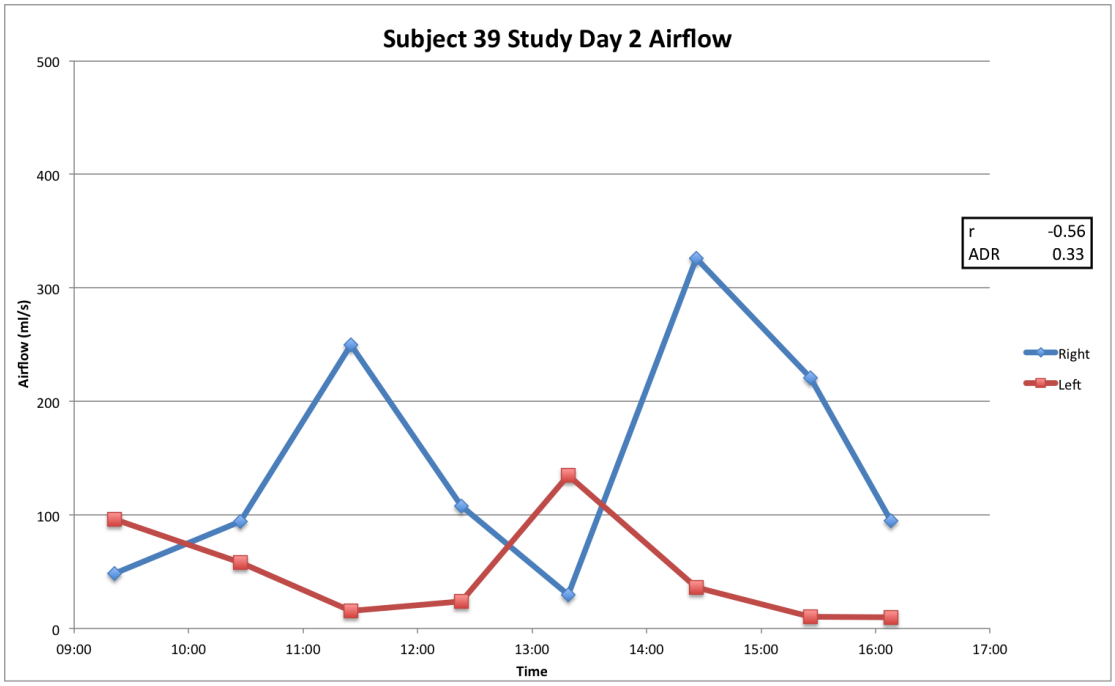

Subject 37 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.23
ADR 0.66
Right
Left


Subject 37 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r 0.13
ADR 0.76
Right
Left


Subject 38 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.08
ADR 0.82
Right
Left


Subject 38 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.31
ADR 0.69
Right
Left


Subject 39 Study Day 1 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.79
ADR 0.46
Right
Left


Subject 39 Study Day 2 Airflow
500
400
300
200
100
0
Airflow (ml/s)
09:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
Time
r -0.56
ADR 0.33
Right
Left