Pulmonary dysanapsis and diving assessments

LIN MIN ONG¹, MICHAEL H. BENNETT³ and PAUL S. THOMAS ¹,²,⁴

¹Prince of Wales Clinical School, ²Centre for Infection and Inflammation Research, School of Medical Sciences, Faculty of Medicine, University of New South Wales and the Departments of ³Hyperbaric Medicine and ⁴Respiratory Medicine, Prince of Wales Hospital, Randwick, NSW 2031, Australia.

ABSTRACT
Airway obstruction is a relative contraindication to diving. Dive candidates are assessed clinically, and lung function tests evaluate variables such as forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and the FEV₁/FVC ratio. A small number of individuals have a normal FEV₁, but a disproportionately large lung capacity, or pulmonary dysanapsis. These individuals have a decreased FEV₁/FVC ratio, suggesting airway obstruction, which may affect their dive medical assessments.

Three cases of pulmonary dysanapsis presented for fitness-to-dive assessment.

- Case 1, a 29-year-old male had an FEV₁: 3.52L (85% predicted), FVC: 5.31L (108.5% predicted), giving a FEV₁/FVC of 66%.
- Case 2, a 25-year-old male with an FEV₁: 4.55L (95% predicted), FVC: 7.0L (121% predicted) and a FEV₁/FVC of 66%. Albuterol produced an FEV₁ increase of 11%, but his hypertonic saline challenge was negative.
- Case 3, a 61-year-old man had an FEV₁: 3.49L (126% predicted), FVC: 7.06L (216% predicted), and a FEV₁/FVC of 49%.

This report highlights pulmonary dysanapsis which may be confused with obstructive airway disease and applicants deemed unfit to dive. While pulmonary dysanapsis may increase the risk of airway hyper-responsiveness, there is no evidence of an association with diving-related pulmonary barotrauma.

INTRODUCTION
Airway obstruction is a relative contraindication to scuba diving. Therefore, lung function tests (LFTs) are used to assess dive candidates (1). LFTs evaluate expiratory flow variables such as forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and the FEV₁/FVC ratio (FEV₁%).

Small numbers of individuals have a normal FEV₁ but a disproportionately large lung capacity. This may result in a decreased FEV₁%, which can be confused with airway obstruction as seen in diseases such as asthma.

Airway obstruction is usually measured by an FEV₁/FVC ratio of less than 70% - 75% or an FEV₁ value of less than 80% predicted (1). The forced expiratory flow between 25% and 75% of the FVC (FEF₂₅-₇₅%) can also be derived from the expiratory flow volume curve and measures small airway obstruction in contrast to FEV₁, which represents large airway obstruction. Other measurements include the FEF₂₅-₇₅%/FVC ratio and the ratio of FEV₁/FEV₁%.

It is thought that differences in the ratio of airway flow to lung parenchyma size can be quantified by relationships such as FEF₂₅-₇₅%/FVC (3). Women and boys have lower airway flow to lung size ratios than adult males (4). The individual ratio of airway size to parenchyma size develops in early childhood (5,6,7) and could possibly have a genetic basis (8,9).

It has been proposed that disproportionate growth of the airway and lung parenchyma affects the proportion of FVC that is expired per unit time, and an apparent reduction in this flow has been termed “dysanapsis” (10).

Dysanapsis (as measured by the FEF₂₅-₇₅%/FVC ratio) has been found to be associated with airway hyper-responsiveness (AHR) (7,11) and atopy (12). By this association, it was proposed that dysanapsis could have a role in the pathogenesis of obstructive disease such as asthma and chronic obstructive pulmonary disease (10,12). Such a relation is inconsistent in the literature, and the reliability of the FEF₂₅-₇₅%/FVC ratio as an indicator of dysanapsis is not absolute (3,12).
This report reviews three asymptomatic cases of pulmonary dysanapsis who were presented regarding their fitness to dive. This report aims to highlight pulmonary dysanapsis in the context of dive medical assessments, as static airway obstruction alone may not be a contradiction to diving (13).

CASE REPORTS

CASE 1

A 29-year-old nonsmoking male was referred regarding a diagnosis of asthma and for review of his suitability for military diving. He gave no history indicative of asthma or any symptoms such as wheezing or nocturnal breathlessness; he had been diagnosed with asthma four years previously, based on his spirometry and lung function tests, including a whole-body plethysmography.

At that time, a test of bronchial hyper-responsiveness was not performed, and he was uncertain whether chest X-rays were performed. He was prescribed Seretide 250/50 (fluticasone 250mcg and salmeterol 50mcg/dose) via a dry powder inhaler (one inhalation, twice daily), which he ceased, as he had no symptoms.

Examination was normal. Spirometry was performed again; his initial values suggested mild airway obstruction with FEV1 3.52L and a FEV1/FVC ratio of 66%. This pattern was reproducible with

| TABLE 1 |
|---------------------------------|---------------------|---------------------|---------------------|
| Spirometry variables            | Vigorous expiratory | Slow expiratory     | Post-salbutamol     |
|                                 | manoeuvre           | manoeuvre           | (slow manoeuvre)    |
| Actual value                    | % Predicted         | Actual value        | % Predicted         |
| FEV1                            | 3.52L               | 85                  | 3.70L               | 90                  | 3.87L               | 94                  |
| FVC                             | 5.31L               | 108.5               | 5.17L               | 106                 | 5.10L               | 104                 |
| FEV1/%                          | 66                  | 78                  | 72                  | 85                  | 76                  | 90                  |
| FEV1/FVC%                       | 5.32%               | 106                 | 5.17%               | 106                 | 5.11%               | 104                 |
| FEF25-75/FVC                    | 43%                 | 44                  | 53%                 | 54                  | 60%                 | 60                  |

| TABLE 2 |
|---------------------------------|---------------------|---------------------|
| Spirometry variables            | Pre-salbutamol      | Post-salbutamol     |
|                                 | Actual value        | % Predicted         |
| FEV1                            | 4.55L               | 95                  |
| FVC                             | 7.10L               | 124                 |
| FEV1/%                          | 64%                 | 77                  |
| FEV1/FVC%                       | 7.11%               | 124                 |
| FEF25-75/FVC                    | 46%                 | 50                  |

| TABLE 3 |
|---------------------------------|---------------------|
| Spirometry variables            | Actual value        | % Predicted         |
| FEV1                            | 3.49L               | 126                 |
| FVC                             | 7.06L               | 216                 |
| FEV1/%                          | 49%                 | 58                  |
| FEV1/FVC%                       | 7.12%               | 219                 |
| FEF25-75/FVC                    | 10%                 | 10                  |

TABLES 1-3. Spirometry values of Cases 1-3.

Note the disproportionately large FVC, which creates the erroneous impression of airway obstruction when FEV1 is expressed as a function of FEV1/FVC. The normal FEV1/FVC is >70%.
vigorousexpiratory maneuvers. However, normal spirometry with a FEV\textsubscript{1} of 3.7L, FVC 5.17L and FEV\textsubscript{1}/FVC ratio of 72% was obtained with a less forceful expiration (Table 1, Page 376). Administration of albuterol 200mcg did not significantly improve these volumes (< 15% improvement in FEV\textsubscript{1}).

This subject had normal lung function, but vigorous expiratory maneuvers erroneously suggested obstructive lung disease. These features are compatible with pulmonary dysanapsis or possible mildly collapsible airways. As there was no evidence of asthma, he was passed fit for diving.

**CASE 2**
A 25-year-old male presented for review of his fitness to continue military diving. He was physically fit and did not have any symptoms of asthma, bronchitis or a history of previous chest infections. He had been diving for four years, during which he had experienced two incidents of ear barotrauma and an episode of dehydration that required military hospital consultation.

Spirometry performed five months previously indicated a FEV\textsubscript{1} of 4.54L (94% predicted), FVC of 7.04L (121% predicted) and a reduced FEV\textsubscript{1}/FVC ratio of 64% due to his large FVC (Figure 1, above). A hypertonic saline challenge at that time was normal. Although he lacked symptoms, there was a change in his FEV\textsubscript{1} of 16% after the administration of 200mcg salbutamol. Therefore, he was prescribed inhaled budesonide, which he used for approximately six months, possibly on an irregular basis.

On review, examination of his respiratory, cardiovascular system and upper abdomen was normal. Spirometry again showed a reduced FEV\textsubscript{1}/FVC ratio of 64% as a result of a large FVC (Table 2, Page 376). These values remained unchanged with slow vital capacity maneuvers. On this occasion, there was an 11% increase in FEV\textsubscript{1} post 200mcg of inhaled salbutamol.

In summary, this man had normal spirometry results but demonstrated an obstructive pattern due to his large FVC in comparison to a normal predicted FEV\textsubscript{1}. This was consistent with pulmonary dysanapsis, and it was unlikely that this man had asthma. However, the diagnosis was complicated by his partial response to salbutamol, which was not significant. His negative hypertonic saline challenge would not support the diagnosis of asthma, and a repeat challenge after three months off inhaled steroids was again normal. He was evaluated as fit to dive.

**CASE 3**
A 61-year-old man was referred for review of his fitness to dive recreationally. He had no history or symptoms of asthma or obstructive lung disease.

Spirometry was performed routinely, and his spirometry values demonstrated a pattern of obstructive lung disease due to his large FVC in comparison to his FEV\textsubscript{1}. This was consistent with pulmonary dysanapsis (Table 3, Page 376). He was passed fit to dive.

**DISCUSSION**
The matching of the airway growth with the lung parenchyma probably has an embryological or early developmental basis. The situation where growth of these two parts of the lung are not matched has been termed “dysanapsis” (from the Greek dys = unequal, and anaptixy = growth) and may have implications for the pathogenesis of airway disease (10,5).

Dysanapsis has been identified in both adults and children, and it remains contentious as to whether it is an abnormal state or whether it is an extreme of the normal range. There is no information on this condition and diving.
Martin et al. followed 47 healthy subjects between the ages of 6 and 27 years and demonstrated there were significant inter-individual differences in maximal expiratory flow (MEF) when compared to lung volumes (measures of airway function to parenchymal size) in early childhood. These differences persisted with lung growth, indicating the likelihood that dysanapsis stems from early childhood (5,6,7).

Dysanapsis may well have a genetic basis, as there were significant correlations in first-degree relatives for Vmax50:FVC, and there is evidence suggesting a single locus gene or cluster of genes may be responsible for this ratio (11). Genetic linkages have been suggested for FEF25-75% and FEF25-75%/FVC on chromosomes 2q and 12p and to a lesser significant extent on chromosomes 16, 20 and 22 (5).

A degree of correlation between MEF and lung volume has been described with resistance to flow being the major determinant; thus individual variability in airway caliber and function, independent of lung parenchymal size, accounts for the between-individual variability the MEF: lung volume relationship (10).

Green et al. graphically plotted lung recoil versus upstream conductance, diving subjects into four groups, each expressing a type of lung function and structure. Those with lower conductance and less lung recoil were postulated to be more likely to be at greater risk for cigarette smoking, predisposing them to the development of airway diseases (10).

The ratio of (Vmax50/VC x Pst[L]50)/VC was developed to quantify the relationship between airway function and parenchymal size, where Vmax50 is the maximal expiratory flow at 50% of vital capacity (VC), and Pst[L]50 is the static recoil pressure at 50% VC. A low ratio would indicate a lower airway flow in proportion to lung parenchyma. This ratio also indicates the expiratory flow (at 50% VC) at which the lungs are emptying, which is similar to the expression of FEV1/FVC (or FEV1%), with males having higher Vmax50 values (12).

Therefore, it was suggested that the ratio of FEV1/FVC should vary with lung size, and all three cases presented had FEV1/FVC % values larger than their percentage predicted of normal, suggestive of dysanapsis. Likewise, other measures of flow, e.g., the FEF25-75% and its relationship to FVC could also be an indicator of dysanapsis (4). In all three cases, the individuals had FEV1/FVC ratios of less than 70%, which was thought to reflect mild airway obstruction. All cases, particularly Cases 2 & 3, had large FVC volumes (121% and 216% predicted respectively) compared to their FEV1 volumes. Likewise, their FEF25-75%/FVC ratios were significantly less than the predicted of normal (44%, 50% and 10% predicted).

A reduced ratio between MEF, FEV1, or FEF25-75% and FVC is thought to reflect relative airway narrowing and thus, obstruction or airway-parenchymal dysanapsis; this has led to the suggestion that this reduction could be associated with airway hyper-responsiveness. AHR is defined as an excessive response to a bronchoconstrictor or other stimulus, such as methacholine, histamine, exercise or hypertonic saline.

This simplistic view of dysanapsis was complicated by a study where the FEF25-75%/FVC ratio and the tracheal cross-sectional area (X-SA)/FVC ratio were examined in 45 family members of individuals with atopic bronchial asthma; while no association between FEF25-75%/FVC, X-SA/FVC and inhaled methacholine AHR was established, an association between X-SA/FVC and atopy was identified. Individuals with relatively smaller airways may be more sensitive to inhaled bronchoconstrictors or antigens as a result of increased airway deposition (12).

A separate study of 764 subjects, aged 4 to 91 years, found that a low FEF25-75%/FVC ratio (small airway size to lung size ratio) correlates with greater airway responsiveness to methacholine in vulnerable individuals (14). Other possible factors that contribute to the association of a low FEF25-75%/FVC ratio and airway hyper-responsiveness include the degree of airway smooth muscle shortening and the amount of circumferential muscle compared to wall thickness (7).

Prospective long-term studies will be required to verify whether a low FEF25-75%/FVC ratio increases the risk of an individual developing AHR, but in cross-sectional studies, no significant correlation between this ratio and either cold air or methacholine AHR was found, even in individuals who recently experienced a respiratory illness (7).

The significance of AHR in otherwise normal individuals is unclear. It has been suggested that airway hyper-responsiveness can contribute to the pathogenesis of conditions such as asthma and chronic obstructive pulmonary disease (COPD)(7). Green, Mead and
others suggested a relationship between a vulnerability to COPD, which is defined by airway obstruction, and pulmonary dysanapsis, while a smaller airway size to lung size ratio may contribute to a greater susceptibility to the development of COPD (2,11).

AHR is used to evaluate a dive candidate’s airway responsiveness as a surrogate marker of asthma (1). Usually, a ≥15% reduction in FEV\textsubscript{1} following exposure to such a stimulus is accepted as significant AHR. Another method uses a ≥40% reduction in specific airway conductance (sGaw) to determine airway hyper-responsiveness. sGaw measurements indicate large central airway obstruction, whereas FEV\textsubscript{1} measurements are influenced by both large- and smaller airway constriction.

Individuals with a higher FEF\textsubscript{25-75%}/FVC ratio can respond to methacholine with a reduction in sGaw without a significant decrease in FEV\textsubscript{1}. This group of individuals may have larger airways and are less prone to experiencing a significant decrease in FEV\textsubscript{1} for a certain amount of bronchoconstriction, compared to individuals with smaller airways. Subjects with pulmonary dysanapsis referred for review of asthma might have negative methacholine airway hyper-responsiveness on spirometry alone (11).

Although Case 2 had a negative hypertonic saline challenge, his results could have been different with the use of sGaw measurements, but this is not a generally accepted method of evaluating AHR. Nonetheless, he has no symptoms or history suggestive of asthma, and AHR alone does not indicate asthma.

Other more advanced methods of diagnosing asthma have been proposed, such as sputum eosinophilia or exhaled nitric oxide, which are novel and perhaps more specific ways of distinguishing asthma from the simple physiological methods which have been used in the past (15).

This report highlights pulmonary dysanapsis in the context of dive medical assessments, to draw attention to the circumstances where dive candidates with pulmonary dysanapsis may be incorrectly diagnosed with obstructive airway disease and certified unfit to dive, although obstruction has not been proved to be a risk for gas-trapping or barotrauma (16). While pulmonary dysanapsis may increase the risk of AHR, there is no evidence to date, that such a condition is associated with diving related pulmonary barotrauma.

**SUGGESTED STEPS**

Thus, a diving candidate whose spirometry reveals a picture typical of pulmonary dysanapsis (i.e., a normal FEV\textsubscript{1} with disproportionately large FVC and consequently low FEV\textsubscript{1}%), the following steps are suggested.

First, a careful history should be taken to exclude symptoms of reactive airway disease, particularly relating to symptoms of asthma or COPD as well as a past history of childhood asthma.

Second, consideration could be given to formal testing for bronchial hyper-reactivity using a hypertonic or exercise challenge. The advantage of these types of challenge is the lower likelihood of a false positive response (1,17).

If there is no history to support a diagnosis of asthma, and if any tests for significant hyper-reactivity are negative, then the candidate can be cleared to dive after counseling about the theoretically increased risk of pulmonary barotrauma of ascent.

While spirometry remains a useful screening test in dive medicals, a reduction in FVC, rather than the FEV\textsubscript{1} or FEV\textsubscript{1}% is the only variable that has been identified as a risk factor for pulmonary barotrauma, suggesting that FVC is the better predictive measurement. Thus, it is becoming apparent that if active asthma is not present, a slightly reduced FEV\textsubscript{1} in isolation may not be significant (1,13).

**REFERENCES**


