active asthma is a contraindication. Determining the need for ongoing treatment or prevention of asthma should be reassessed from time to time and the diagnosis of hyperresponsive airways (or bronchial hyperreactivity) needs to be remembered more often.

There are grey areas in the consideration for diving fitness. One active asthmatic has clearly not escaped injury, but continued (and thoroughly enjoyed) diving for years. Is there a case for allowing diving occasionally if one has excellent lung function tests but takes a prophylactic inhaled steroid? (Budesonide especially appears very effective.) If one only wheezes and gets asthma after a specific allergen challenge (such as riding horses) should this exclude the individual from ever scuba diving? Is exercise induced asthma the main diagnosis of exclusion? How many divers have asthma and ignore conventional wisdom? I believe we should be studying that group in much more depth.

A five year asthma free period seems unreasonable for adolescents who often outgrow the disease. Active asthma in the last month appears to be a useful marker. Those with significant asthma still fail the provocation test despite being on regular inhalational treatment. As the actual risks and consequences of pulmonary barotrauma in asthmatics are in fact not well described, perhaps they can be ignored in those who pass a saline challenge. The paucity of clinical data is notable, but ignoring the theoretical risks and consequences of pulmonary barotrauma seems unwise. Guidelines for examining doctors should perhaps urge dividing trivial from more serious asthma. A continuum of risk exists, and perhaps an informed consent approach could be adopted allowing some recreational diving to a wider public. Certainly this would be welcomed by many in the dive industry, but the safety of this advice is ill defined at present.

Questions

Mike Davis, Christchurch

I was not quite clear what your advice was to asthmatics, with a positive history and on medication, who had a negative challenge test with regard to their diving.

Chapman-Smith

The reason it is not clear is I did not mention it. I thought it would be interesting to discuss, rather than say what I had done. In fact I suggested to those who had a negative test that they could do a dive course, after adequate discussion of the risks of barotrauma, which is a dilemma because a number of those people I would never, before doing the test, have suggested they should dive. So I have changed my advice to patients on the basis of this test .

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LUNG FUNCTION AND BRONCHIAL PROVOCATION TESTS FOR INTENDING DIVERS WITH A HISTORY OF ASTHMA

Sandra D Anderson, John Brannan, Louise Trevillion and Iven H Young

(presented by Sandra Anderson)

Abstract

With our experience over 7-10 years in assessing intending divers with a past history of asthma we have concluded that full spirometric tests, bronchial provocation and response to bronchodilator should be performed, together with measurements of functional residual capacity and residual volume, if possible. This combination of tests to assess risk has arisen over time and in consultation with our referring medical practitioners. The choice of bronchial provocation test (pharmacological or physical) may present some difficulty. The use of dry air hyperpnea and hypertonic saline have the advantage of being familiar and relevant to the intending diver and having a high specificity for asthma. The use of pharmacological challenges, while well accepted by the medical community, are less acceptable for the intending diver as the stimulus is not relevant to diving. Further, the low specificity for identifying current asthma may lead to the unnecessary exclusion of some persons with otherwise normal lung function. Occasionally a response to a pharmacological agent is negative but the airway response to dry air challenge positive.

Asthma is an inflammatory disease of the airways that can vary widely in severity over a life-time. In assessing 180 adults with a past history of asthma we have found that 50% had no evidence of the disease and had normal lung function and no bronchial hyperresponsiveness. Others who had been symptom free for some years, had abnormal lung function and/or were hyperresponsive. We

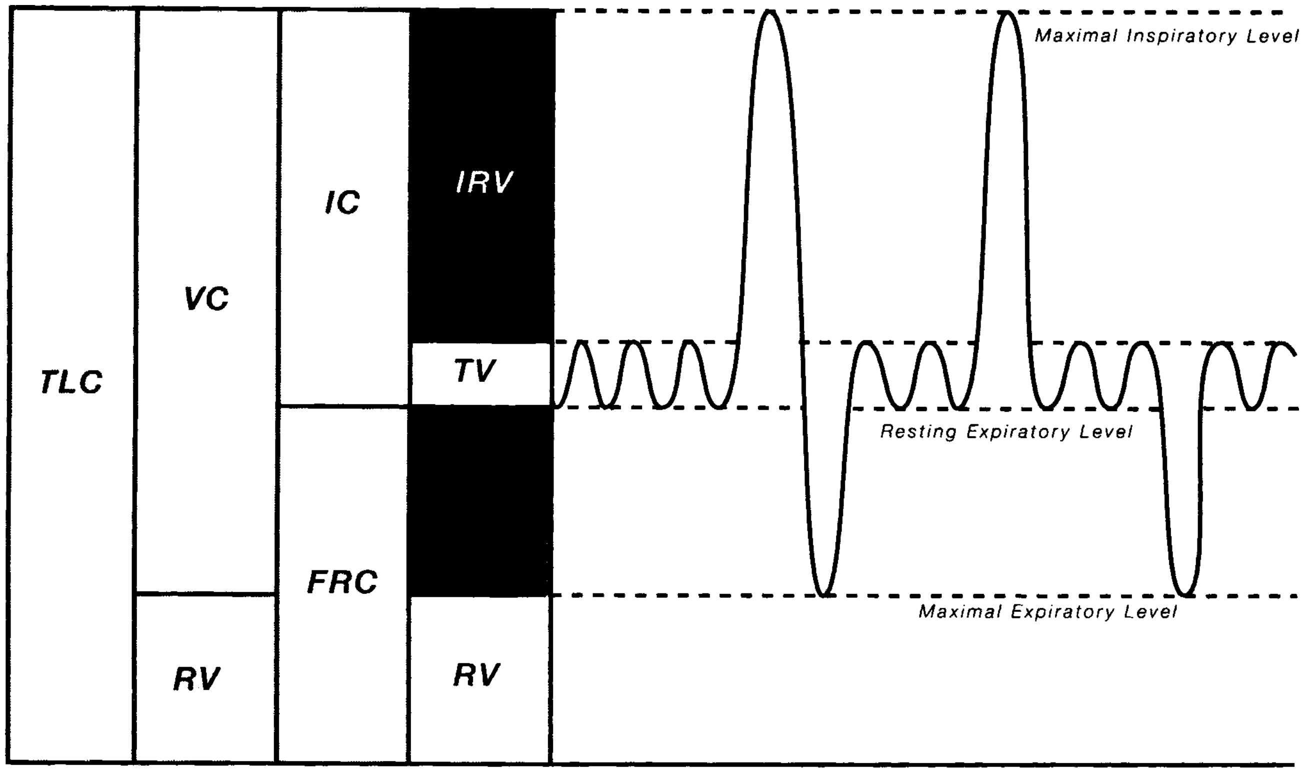

Figure 1. The lung volumes as they appear on a spirogram. After performing a maximum inspiratory capacity (IC) the total lung capacity (TLC) is reached. After a vital capacity manouvre (VC) the residual volume (RV) is left in the lung. When breathing with a normal tidal volume (TV) the functional residual capacity (FRC) is the volume in the lung just before the next breath in. The thoracic gas volume measured during plethysmography is approximately equal to the FRC and TV. The inspiratory reserve volume (IRV) and expiratory reserve volume (ERV) are both utilised to increase tidal volume during exercise but the IRV is used more than the ERV. Taken from Comroe.[5]

believe that persons with abnormal lung function and who are hyperresponsive to the effects of dry air or hypertonic saline are theoretically at an increased risk from pulmonary barotrauma. From our experience of a high rate of abnormality in the referred patients, it would seem cost effective and appropriate to conclude that lung function assessment and bronchial provocation tests serve a useful purpose in identifying people who may be at risk from diving and who may benefit from treatment for asthma.

Introduction

Many candidates presenting for a diving medical examination give a past history of asthma or childhood respiratory illness. This is not surprising given the high prevalence of asthma symptoms reported in the Australian community over the last twenty years.[1,2] For most, the diagnosis of asthma will have been made on history alone with no objective testing of lung function or bronchial hyperresponsiveness, a hallmark of asthma.

It is widely accepted by the diving medical community[3] and by respiratory physicians[4] that persons with a past history of asthma who wish to dive with underwater breathing apparatus, should have tests of lung function and a bronchial provocation test. Such tests usually include the measurement of lung volumes and forced expiratory flow and volume before and after a bronchoconstrictor stimulus or a bronchodilator. These tests have been readily available through most public hospital laboratories for many years. The development of electronic spirometers and easy techniques for bronchial provocation has resulted in some practitioners offering testing at the time of the diving medical examination. This approach has obvious advantages, particularly for the many tourists who wish to dive but have a history of respiratory illness, or, who are heavy smokers.

This paper describes some of the lung function tests and bronchial provocation tests available in major public teaching hospital laboratories in Australia. These tests are discussed for their usefulness in assessing persons with a past history of asthma who wish to dive. It is suggested that specific tests of lung function and bronchial provocation be considered in the assessment of risk of pulmonary complications from diving.

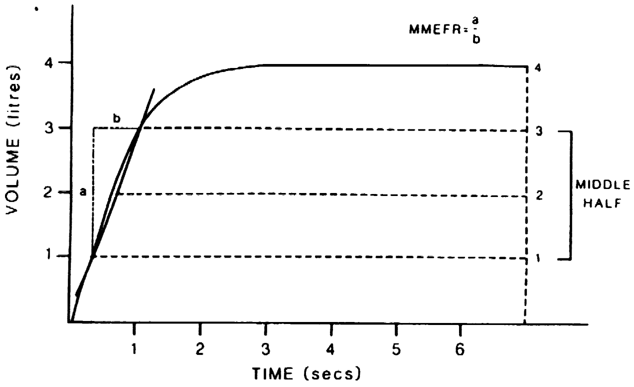

Figure 2. Forced expired vital capacity in relation to time. The maximum mid-expiratory flow rate (MMEFR) also known as the forced expiratory flow rate through the middle half of the vital capacity (FEF_{25-75}). It is calculated from a spirogram by measuring the time (b) taken to expire the middle portion of the vital capacity (a). It is expressed in litres per second. Taken from Alison.[6]

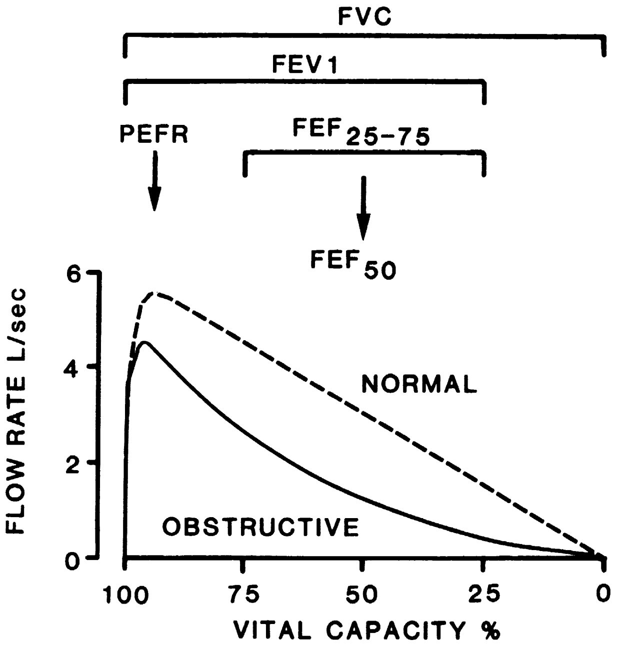

Figure 3. The forced expiratory flow in relation to volume during a forced vital capacity (FVC) manouvre as it would be seen before (normal) and after (obstructive) exercise in a person with exercise-induced asthma or before (obstructive) and after (normal) bronchodilator in a person with acutely reversible air flow limitation. The peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), and flow rates through the middle portion of the vital capacity (FEF_{25-75}) are shown in relation to volume. In this example the FVC remained the same but the FVC is normally reduced in exercise-induced asthma and is often increased after a bronchodilator. Taken from Anderson.[10]

Spirometry and flow rates

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are the two most common measurements made from a forced expiratory manoeuvre. Traditionally these measurements have been made recording time and volume simultaneously (e.g. bellows type Vitalograph, wet spirometer) and correcting the volume from ambient temperature and water vapour pressure (ATPS) to body temperature and water vapour pressure (BTPS).

Spirometric tests are effort dependent and are only accurate if the forced expiratory manoeuvre to residual volume follows maximal inspiration to total lung capacity and no leaks occur during expiration (Figure 1).[5] The flow rates through the middle portion of the forced vital capacity (FEF_{25-75}), also known as the maximum mid-expiratory flow rate (MMEFR), can also be obtained from an accurate volume-time tracing (Figure 2).[6] It is important that the person measuring spirometry is aware of the criteria used to determine acceptability of the results.[7]

For comparison with normal, a set of predicted values is required. Predicted normal values vary according to sex, age, height and ethnic origin. A value greater than 80% or more of predicted normal is usually considered as within the normal range if all other volume values are a similar percentage. The value of 80% usually represents the 95% confidence limit. Table 1 gives normal predicted values and standard deviations, to calculate the confidence intervals, for spirometry for Caucasion persons of European origin.[8] Non-Caucasians usually have smaller lungs[9] and 80-90% of the predicted Caucasian value is considered within normal limits by most laboratories.

Flow volume Curve

The introduction of electronic spirometers with sensitive flow measuring devices has facilitated the recording of expiratory flow in relation to expiratory volume. The electronic spirometers allow the flow signal to be "instantaneously" integrated to volume and a flow-volume curve is obtained (Figure 3).[10] This contrasts with the volume-time curve obtained in classic spirometry (Figure 2). Simultaneous plotting of expiratory flow against volume has permitted a better assessment of flow through the smaller airways and in the less effort dependent part of the flow-volume curve.

In addition to the FEV_1 and VC values, the flow-volume curve gives the forced expiratory flow rates through the middle portion of the vital capacity (FEF_{25-75}). Due to the increase in density of air with increasing depth these flow rates are markedly reduced with submersion. The changes in flow-volume characteristics have been measured in recompression chambers and an example is

TABLE 1

EQUATIONS FOR OBTAINING NORMAL VALUES OF SPIROMETRY RESULTS FOR CAUCASIAN ADULTS AGED 18-70§

The lower 5 or upper 95 percentiles are obtained by subtracting or adding the figure in the last column from the predicted mean.

Variable	**Gender**	**Measurement**	**Equation to obtain mean**	**RSD**	**1.64 RSD**
IVC	F	l	4.66H - 0.026A - 3.28	0.42	0.69
FVC	F	l	4.43H - 0.026A - 2.89	0.43	0.71
FEV_1	F	l	3.95H - 0.025A - 2.60	0.38	0.62
FEV_1/FVC	F	%	- 0.19A + 89.10	6.51	10.70
FEF_{25-75}	F	$l.s^{-1}$	1.25H - 0.034A + 2.92	0.85	1.40
PEF	F	$l.s^{-1}$	5.50H - 0.030A - 1.11	0.90	1.48
IVC	M	l	6.1 0H - 0.028A - 4.65	0.56	0.92
FVC	M	l	5.76H - 0.026A - 4.34	0.61	1.00
FEV_1	M	l	4.30H - 0.029A - 2.49	0.51	0.84
FEV_1/FVC	M	%	- 0.18A + 87.21	7.17	11.80
FEF_{25-75}	M	$l.s^{-1}$	1.94H - 0.043A + 2.70	1.04	1.71
PEF	M	$l.s^{-1}$	6.14H - 0.043A + 0.15	1.21	1.99

Abbreviations

IVC = inspiratory vital capacity. FVC = forced vital capacity. FEV_1 = forced expiratory volume in one second. FEV_1/FVC = ratio of FEV_1 to FVC. FEF_{25-75} = forced expiratory flow through the middle portion of the vital capacity. PEF = peak expiratory flow. l = litre. l s^{-1} = litres per second. H = standing height in m. A = age in years. RSD = residual standard deviation.

§: between 18 and 25 years, use thevalue of 25 in the equations.
Taken from Quanjer et al. *Eur Respir J* 1993; Suppl 16: 4-40.

illustrated in Figure 4.[11] The importance of these mid-expiratory flow rates may be appreciated better when it is understood that it is this part of the flow-volume curve that determines the maximum flow that can be reached during exercise. At rest the flow generated during a tidal breath is low but with increasing intensity of exercise the flow increases. The capacity of the flow to increase is determined by the maximum flow-volume characteristics of the lung. If the flow rates through the middle portion of the vital capacity are low, then the ability to increase flow is reduced. This problem is exacerbated with increased density of the inspired air at depth.

It is thought that breathlessness on exertion occurs when the flow reaches the limit of the flow volume curve. If this is the case, it may be predicted that persons with a compromised flow-volume curve may experience breathlessness earlier or for the first time whilst diving. This sense of breathlessness could lead to panic at depth with subsequent rapid ascent.

The normal values for FEF_{25-75} are more variable than FEV_1 or FVC. The lower end of the 95% confidence interval is about 65% rather than 80%. However, any reduction in these flow rates is likely to affect maximum exercise performance. An acceptable normal value for divers for this test may need to be more than 65%, if they need to exercise maximally at depth. Simpson and Meehan[12] have measured FEF_{25-75} in 49 current experienced divers and recorded a mean ± SD value of 99.4 ± 26.2 % of predicted normal for FEF_{25-75} (range 50-164 % predicted). Five of the 49 had a FEF_{25-75} below 65% of predicted, the lower limit of normal.

Significance of spirometry and flow-volume curves

Normal spirometry (FEV_1, FVC, and its ratio) and normal flow rates (FEF_{25-75}) excludes airway narrowing at rest. A normal peak flow does not exclude airway narrowing as it is only a measure of the peak of the flow and does not encompass airflow through the small airways (Figure 3). Normal spirometry does not preclude airway narrowing in response to a provoking stimulus. Many persons with a past history of asthma, but normal spirometry and flow rates, can have airway narrowing provoked by breathing dry air at high flow rates or by accidental aspiration of salt or fresh water. Figure 3 illustrates the

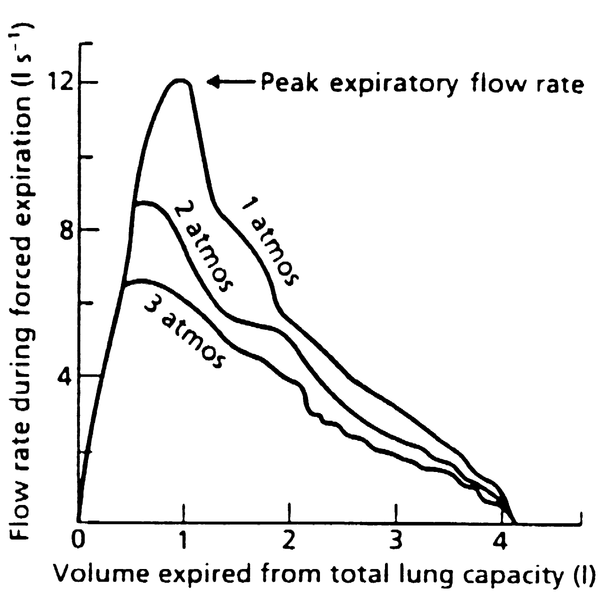

Figure 4. Forced expiratory flow volume curves measured during submersion at 1, 2 and 3 atmospheres (10, 20 and 30 m or 33, 66 and 99 feet of seawater). Note the reduction in peak flow rate and flow rate through the mid-portion of the vital capacity due to the increase in density of the inspired air with depth. It is possible that a person starting with a reduced mid-expiratory flow rate will be limited in their ability to increase expiratory flow rates during exercise at depth. The flow volume characteristics could be further affected by breathing dry air or the inhalation of an aerosol of salt water. In the situation where flow rates are reduced breathlessness and panic could occur. Taken from Cotes. [11]

type of flow-volume curve that would be obtained in a person with hyperresponsive airways. Before a bronchial provocation test the forced expired volumes and flow rates may be normal but after the test the flow-volume curve is concave which represents an obstructive pattern. Such an obstructive pattern may also be recorded in a patient with airflow limitation and this may often be acutely reversed after bronchodilator.

A FEV_1/FVC ratio of 75% or more is usually considered essential for intending divers. This may be unduly stringent as many persons, particularly swimmers and elite athletes, have large vital capacities (e.g.130% predicted) but a normal FEV_1 (e.g.100% predicted) resulting in a low FEV_1/FVC ratio. If the flow-volume curve has a normal shape, it would be inappropriate to suggest that these persons were unfit to dive.

Documentation of abnormal spirometry or flow rates may be all that is needed to decide that a person is medically unfit to dive. However, for the benefit of the person and with a view to treatment, it is advisable to complete the testing to determine if the airflow limitation is acutely reversible. An increase in FEV_1 of 15% or more is considered a significant response to a β_2 adrenoceptor agonist (e.g. terbutaline, salbutamol). It is more difficult to assess responsiveness on the basis of changes in FEF_{25-75}. If the vital capacity remains the same, an increase of 25% in FEF_{25-75} after bronchodilator is considered a significant response. Changes are less easy to interpret if the VC is different after a bronchodilator.

A person with airflow limitation, with or without acute reversibility, should be advised that theoretically, they have an increased risk of problems while diving and they should be alerted to the type of problem. They could also be offered treatment and reassessment to determine whether their airflow limitation is chronic. Chronic airflow limitation is more likely to occur in persons with a past history of asthma who smoke, but untreated asthma, in a non-smoker, can also result in premature and irreversible airflow limitation.

A person with no airflow limitation but values for FEV_1 and VC below normal and a high FEV_1/FVC ratio should be advised to have a more thorough pulmonary assessment to exclude lung disease. Lung volumes were shown to be smaller when a study of victims of pulmonary barotrauma were studied in retrospect[13] so that persons with low volumes may be at an increased risk.

Static lung volumes

In a Pulmonary Function Laboratory it would be usual for a person referred for a diving assessment to have a measurement of all lung volumes (Figure 1). The reason for this is to determine if there is any hyperinflation (abnormally high total lung capacity or functional residual capacity in relation to other volumes) or gas trapping (an abnormally high residual volume in relation to other volumes). The techniques used to make the measurements are most commonly helium dilution, body plethysmography, or nitrogen washout. Values are considered normal in the range of 80-120% of the predicted value. However it would be expected that all the volumes would be a similar percentage. Thus a total lung capacity of 90% and a residual volume of 120% is not normal.

Significance of static lung volumes

The documentation of either increased or decreased volumes, suggests that there would be an increased risk of barotrauma if rapid ascent is required. Demonstrating the presence of hyperinflation or gas trapping with mild airflow limitation would seem sufficient to advise the intending diver of an increased risk. The documentation of normal lung volumes at rest does not preclude the possibility that acute hyperinflation and gas trapping could

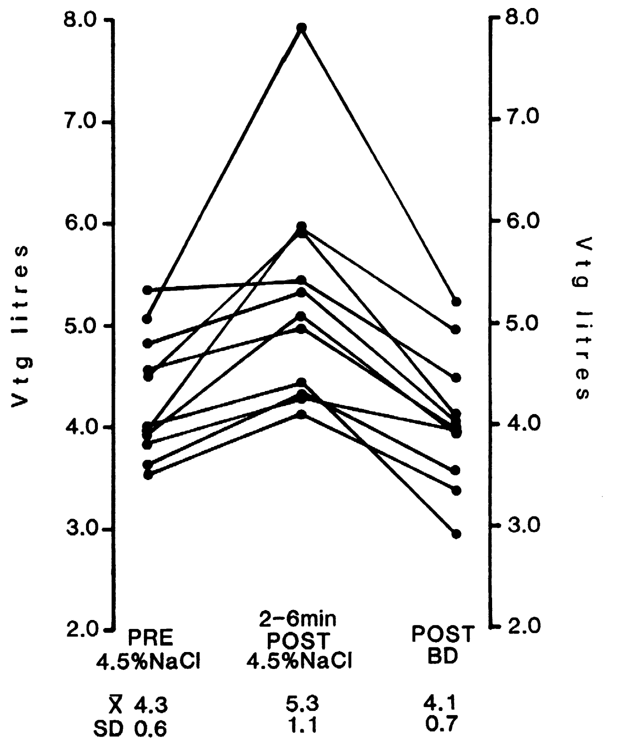

Figure 5. Thoracic gas volume (Vtg) measurements before and 2 to 6 minutes after inhaling an aerosol of 4.5% saline and 10 to 15 minutes after inhaling a bronchodilator in a group of 11 asthmatic subjects. Note the large increases in volume that occurred in some subjects. This hyperinflation occurred at the time the airways were narrowing as a result of inhaling the 4.5% saline. The hyperinflation was quickly reversed by inhaling terbutaline by aerosol (Bricanyl). The thoracic gas volume is equivalent to the functional residual capacity and tidal volume during panting.

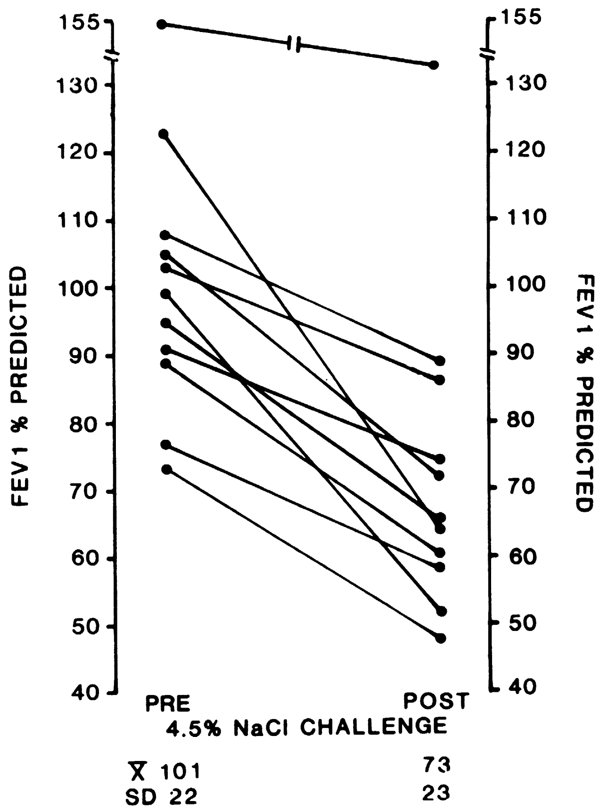

Figure 6. Forced expiratory volume in one second (FEV_1) expressed as a percentage of the predicted normal value in a group of 11 asthmatic subjects before and after inhaling an aerosol of 4.5% saline generated by an ultrasonic nebuliser. For most subjects the FEV_1 was within the normal range (greater than 80% predicted) before the challenge and their lung function at rest did not predict bronchial responsiveness to challenge with 4.5% saline aerosol. Lung hyperinflation occurred in association with airway narrowing to the aerosol and the change in volume

occur in response to bronchoconstricting stimuli such as dry air or hypertonic saline.

Acute airway narrowing associated with acute hyperinflation

The results of 11 asthmatic subjects aged 17-41years (7 M, 4 F) who had measurements of thoracic gas volume (a measurement close to functional residual capacity) in a whole body plethysmograph before and after inhaling an aerosol of 4.5% sodium chloride are illustrated in Figures 5 and 6. Although the reduction in FEV_1 in response to this hypertonic stimulus was abnormal (>15% of baseline) in all subjects (Mean ± SD 28.8% ± 11.7) it was less than 20% in 4 subjects (Mean ± SD, % Fall 17.% ± 1.7). For these 4 subjects there was an increase of 900ml ± 700ml SD in thoracic gas volume when the saline had induced narrowing of the airways. This shows that a relatively small reduction in FEV_1 can be associated with hyperinflation and gas trapping.

Acute airway narrowing provoked by exercise or other stimuli is frequently accompanied by hyperinflation and gas trapping (Figure 7).[14] Indeed hyperinflation acts as a distending force to open narrowed airways. The combination of airway narrowing, hyperinflation and gas trapping would, theoretically, provide a greater risk for pulmonary barotrauma than airway narrowing alone. For this reason, persons with mild narrowing of the airways may not necessarily be at a lesser risk of pulmonary barotrauma than a person who has a greater fall in FEV_1 but who did not become hyperinflated. Thus classification of bronchial responsiveness as mild/moderate/or severe may be misleading when assessing risk for divers.

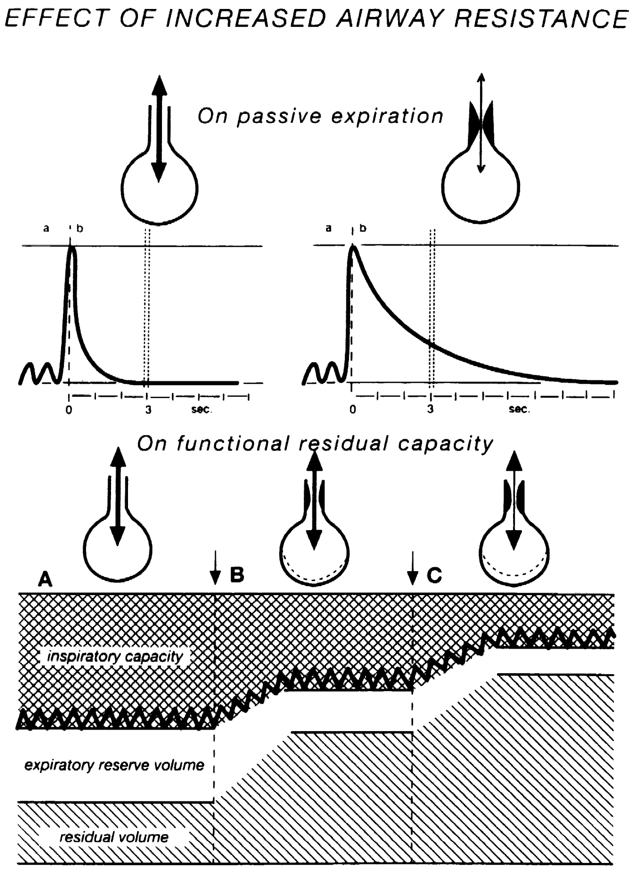

Figure 7. Spirometry and static lung volumes before and during an attack of asthma. Note the reduced inspiratory capacity, expiratory reserve volume, forced vital capacity and forced expiratory volume, and the increased functional residual capacity (hyperinflation) and residual volume (gas trapping). Taken from Comroe.[5]

An indirect method available to most diving doctors to determine the presence of gas trapping is the measurement of vital capacity. As the airways narrow in response to a provoking stimulus, a reduction in vital capacity indicates an increase in volume of trapped gas (increased residual volume). This, in itself, would theoretically put the person at greater risk from pulmonary barotrauma. It is suggested that vital capacity should be measured before and during a bronchial provocation test to determine if gas trapping has occurred or is reversed by a bronchodilator.

Bronchial provocation tests

The role of bronchial provocation tests is to identify persons who would be at risk from acute airway narrowing and hyperinflation when diving. Bronchial hyperresponsiveness (often referred to as bronchial hyperreactivity) can be measured to a wide variety of stimuli. These include pharmacological stimuli or physical stimuli.

Bronchial provocation tests using pharmacological agents such as methacholine and histamine are referred to as direct challenge tests because the administered substance acts directly on bronchial smooth muscle receptors to cause contraction. Thus these tests provide a good measure of bronchial smooth muscle responsiveness to the administered substance.

Bronchial provocation tests using physical stimuli such as airway drying or changes in airway osmolarity are referred to as indirect challenge tests. The reason being that airway drying or changes in airway osmolarity cause the endogenous release of substances that cause the airways to narrow. The presence of these contractile substances (e.g. histamine, leukotrienes, prostaglandins, neuropeptides) and the magnitude of the airway response to them is related to airway inflammation.[15] For this reason the indirect challenges are thought to provide a measure of the cellular and neural contribution to airway narrowing arising from inflammation, the underlying abnormality in asthma.

The range of provocation tests offered by laboratories varies but most offer at least one direct and one indirect challenge test. The diving doctor should ascertain which hospitals provide which challenge tests. It is also useful to know which laboratories use challenge tests with the stimuli relevent for the intending diver (e.g. dry air, hyperosmolar saline). Laboratories such as ours, with an active research interest in asthma, may provide four or more of the challenge tests, e.g. exercise, hyperventilation, hypertonic saline, distilled water, and methacholine. Nowadays, few laboratories offer challenge with histamine.

Advantages and disadvantages of tests

There are advantages and disadvantages in using both the pharmacological and physical challenge tests to identify bronchial hyperresponsiveness in an intending diver. The major arguments to support the use of pharmacological challenges include their high sensitivity to detect airway hyperresponsiveness and the cheapness and availability of equipment to administer the substance, (e.g. jet nebulizer). The major arguments against the use of pharmacological agents are their low specificity to identify asthma, the poor availability of the substances prepared in accordance with British, European or US Pharmacopoeas and the regular need to make up solutions of varying concentration. Perhaps an important argument is the lack of relevance of the stimulus for the intending diver. Further, there is an increasing number of reports of persons, in the random population, being found negative to histamine or methacholine, but positive to an exercise challenge. This raises the question as to whether the sensitivity of the pharmacological agents to predict bronchial hyperresponsiveness to other stimuli, is as high in the random population as it appears to be in a specialist referred population.

The major argument to support using physical challenge tests is that they represent the stimuli to which the intending diver is exposed. Further, they have a high specificity for identifying persons who have asthma that requires treatment.[16,17] It has been our experience that persons who have a positive response to hypertonic saline are likely to abstain voluntarily from diving and to refrain from seeking another medical opinion.

The major disadvantage associated with the physical challenge tests is that the equipment required to carry out the tests can be expensive and the sensitivity to detect asthma in a general community has been reported to be 50%.[17] This value however is not different to the 53% reported for histamine for a similar population of school children.[18] Persons with a history of asthma, but negative to the physical challenge tests may not have sufficient airway inflammation to have adequate levels of mediators to cause the airways to narrow at the time of testing. It is possible that, for some persons, increasing the strength of the stimulus may render them positive. However it is unlikely that a greater strength of stimulus would be encountered by the intending diver providing that hyperventilation with dry air was performed at maximum ventilation and the concentration of saline used was above that of sea water.

Many medical practitioners would consider a positive response to these challenge tests an increased risk for pulmonary complications from diving. However many persons with well treated asthma in the past, normal lung function and no responsiveness to the dry air hyperpnea or saline will have positive responses to histamine or methacholine. Because of better treatment for asthma it is likely that many persons with this lung function profile will seek to dive in the future.

Medication at the time of test

One would not expect that many intending divers being referred for testing to the laboratory would be taking medications on a regular basis. However, if they are, they should be advised to withhold medications that could affect their airway response to bronchial provocation tests. For short acting antihistamines (diphenhydramine hydrochloride, pheniramine) 48 hours, long-acting ones (terfenadine, astemizole, loratadine) one week; for ordinary preparations of oral bronchodilators, 12 hours and for sustained release oral bronchodilators, 24 hours; for the short-acting β_2 adrenoceptor agonists (salbutamol, terbutaline, fenoterol) and for sodium cromoglycate or nedocromil sodium a period of six hours; the longer-acting β_2 adrenoceptor agonists, such as salmeterol, 24 hours. Inhaled corticosteroids (budesonide, beclomethasone, fluticasone) should be avoided on the day of the study.

Response to bronchodilator

This can be performed using any of a rapidly acting β_2 adrenoceptor agonist such as salbutamol or terbutaline. These are the most commonly used bronchodilators in Australia. Spirometry is done before and after the bronchodilator. The interval between administering the bronchodilator and making the spirometry measurement is important and should be at least 15 minutes, and preferably longer. The response is best measured by FEV_1 and an increase of 15% or more in FEV_1 is regarded as abnormal and consistent with bronchial hyperresponsiveness. In order to ensure that an adequate dose of the drug deposits in the airways we often administer twice the clinically recommended dose by either a pressurised metered dose inhaler or a non-pressurised metered dose inhaler (e.g.Turbuhaler). For persons with a positive bronchial provocation test we usually administer a β_2 adrenocepter agonist in combinations with ipratropium bromide, by a jet nebuliser driven by compressed oxygen.

Methacholine and histamine test protocols

Both methacholine and histamine have been in use in Europe since the 1940s. The most common protocols used in Australia for these pharmacological challenges are those described by Yan et al,[19] and Cockcroft et al.[20] These and other protocols have been recently summarised by Sterk et al.[21] The Yan technique has the advantage of being faster than the others and the nebulizers used are activated by hand rather than by compressed air or electronic devices.

All these techniques require the preparation of a solution of the substance. As doses are low, this normally requires a balance capable of weighing to 0.01 of a gram and sterile containers, pipettes and solutions. The preparation of these solutions has mainly confined their use to public hospitals although some private laboratories do have facilities for preparation. The solutions for the Yan protocol are usually 0.6%, 2.5% and 5.0% and for the Cockcroft protocol 0.05-1.6%. The same strength of solution is prepared for both histamine and methacholine.

Bronchial provocation tests with these substances have been widely used both in the hospital and epidemiological setting to identify persons with bronchial hyperresponsiveness.[1,2,21] Their safety, efficacy and reproducibility have been well established over many years. Their usefulness in identifying asthma specifically has recently been questioned by the original proponents of the challenge.[22] In population studies between 30% and 60% of persons with positive challenges to histamine have no history of asthma.[1,22] Thus the positive predictive value for identifying asthma is low. It is the high percentage of positive responses to these challenges, without other evidence of current asthma, that makes them less attractive for assessing the intending diver. Further, it is hard to justify the use of pharmacological agents to tourists from countries less accepting of a this approach to measure bronchial responsiveness.

Significance of the results

A positive test result is if the provoking dose of methacholine required to induce a 20% fall in FEV_1 (PD_{20}) is < 3.6 micromols for the Yan protocol although some investigators use a cut-off point of < 8.0 micromols. For the Cockcroft protocol a positive response is recorded if the concentration to induce a 20% fall in FEV_1 (PC_{20}) is less than 16 mg/ml. 8 micromols of methacholine is approximately equivalent to 16 mg/ml. Edmonds[23] suggested that a fall in FEV_1 of 10% or more in response to the inhalation of histamine should exclude a person from diving. This seems to be unnecessarily stringent in that most people, asthmatics or not, will respond to histamine given a high enough dose! Further, as histamine can cause oedema, in addition to contraction of smooth muscle, the airway narrowing in response to challenge may be different in nature from challenges that do not provoke oedema, e.g. methacholine.

There are reports of persons with negative responses to pharmacological agents but positive responses to exercise testing.[24-26] This raises the important question as to whether the documentation of a negative response to a pharmacological agent is an assurance of low risk for airway responsiveness to dry air breathing in a hyperosmolar environment.

Exercise testing

Exercise testing was first used to identify children with asthma and assess asthma severity more than 30 years ago. Studies in the early 1970s identified intensity and duration of the exercise as important determinants of the airway response. By 1978-79 the importance of the water content of the air inspired during exercise was also recognised. This had been convincingly demonstrated by showing that inhaling warm humid air during exercise or hyperpnea completely prevented the airways of asthmatics from narrowing. Since that time it has been appreciated that the major determinants of exercise-induced asthma are the level of ventilation reached and sustained during exercise and the water content of the inspired air.[10] The loss of water, by evaporation from the lower respiratory tract, in bringing large volumes of air to alveolar conditions in a short time is recognised as the stimulus whereby exercise provokes the airways to narrow. The mechanism whereby this water loss acts is thought to relate to both the thermal and dehydrating effects of water loss. Evaporative water loss increases osmolarity of the fluid lining the surface of the airway and probably the submucosa/subepithelium. A hyperosmolar environment enhances release of bronchoconstricting substances from inflammatory cells[27,28] and nerves.[29]

Exercise induced asthma testing protocol

Most laboratories work to a standard protocol[10] that involves the subject exercising sufficiently hard to raise the ventilation rate to approximately 20 times the FEV_1 (50-60% of maximum voluntary ventilation or MVV) and sustaining this for 6 to 8 minutes. Compressed air is inspired via a demand valve and only mouth breathing is used. The FEV_1 is measured before and at regular intervals for 10-20 minutes after exercise.

Significance of the results

If a reduction of 10% or more in FEV_1 is recorded using a standardised laboratory protocol the person is considered to have exercise-induced asthma (EIA), also known as exercise-induced bronchoconstriction (EIB). A value of 15% or more is usually taken as positive for exercise performed in the field. If the test is negative the referring physician should be assured by the laboratory staff that the test was performed with the appropriate ventilation rate achieved and sustained and that the water content of the air was less than 10 mg per litre of air inspired (e.g. temperature less than 23°C and relative humidity less than 50%). Like all bronchial provocation tests, no medication should be taken for the required time before testing.

The temperature of the compressed air inhaled during diving is likely to be less than that inhaled in the laboratory. The cooler air is unlikely to increase the airway response greatly because the inspired air temperature has to be less than 0°C to cause significant enhancement of the airway response. Providing the air is dry there is no significant enhancement in response over the temperature range 9-65°C.[30,31] We use compressed air because it is always dry and it is the same as that inhaled by the intending diver.

Eucapnic or isocapnic hyperventilation testing

This test is a surrogate for exercise and was championed by the US Army to assess recruits.[32-34] The stimulus and mechanism whereby the airways narrow are thought to be the same for exercise and hyperventilation. Hyperventilation with dry air may be a more potent challenge compared with exercise as the inhibiting factors provided by the increased sympathetic drive are absent.

Hyperventilation testing protocol

The patient voluntarily increases the ventilation rate while breathing dry gas containing 4.9% CO_2, 21% O_2 and balance N_2. The expired CO_2 levels remain the same (isocapnia) and within normal limits (eucapnia) for ventilation rates between 30 and 110 litres per minute. The test can be performed at progressively increasing levels of ventilation (e.g. 30, 60 and 90% of MVV)[35] or at a single level for 6 minutes at a high ventilation rate (30 x FEV_1). We have found hyperventilation a very potent test for provoking airway narrowing in known asthmatics. For this reason we use and recommend a test that comprises progressively increasing levels of ventilation for 3 minutes rather than a single high ventilation rate for 6 minutes for known asthmatics.

Significance of the results

A fall in FEV_1 of 10% or more is taken as abnormal. As diving requires the inhalation of dry gas, sometimes at high ventilation rates, the hyperventilation test would seem an appropriate challenge. Further, asthmatics are known to hyperventilate during exercise and this hyperventilation may be exacerbated by fear or panic making this challenge particularly relevant.

Non-isotonic aerosol testing

In 1980 Allegra and Bianco[36] reported a bronchial provocation test to identify asthma using an aerosol of distilled water generated by an ultrasonic nebulizer. In 1981 Schoeffel and colleagues[37] confirmed the usefulness of this technique. Further they recognised the osmolarity of the solution as important and found hyperosmolarity was also a potent stimulus for provoking the airways of asthmatics to narrow. At the time the mechanism whereby exercise and hyperventilation provoked airway narrowing was thought to be a transient hyperosmolarity of the airway surface liquid. Thus studies were designed to compare responses to hyperpnea with dry air to inhaling aerosols of hyperosmolar saline.[38-40] The studies demonstrated that persons sensitive to the effects of dry air hyperpnea were also sensitive to aerosols of hypertonic saline. This led to a standardized challenge using an aerosol of 4.5% sodium chloride as a cheap surrogate for exercise.[41] As with exercise, there is a period following challenge with hyperosmolar saline, during which the airway response will not be reproduced in response to the same stimulus. This is known as the refractory period and can last for up to two hours.[42]

Non-isotonic aerosol testing protocol

As hyperosmolar challenge combined the natural stimuli of dry air and salt water confronting the diver this challenge has become the popular for assessing intending divers with a past history of asthma. The protocol requires the subject to inhale an aerosol of 4.5% sodium chloride.[43] This concentration of saline is close to sea water. The aerosol is generated by an ultrasonic nebuliser and the rate should exceed 1 ml/minute. If a two-way valve is used the rate should be 1.2 ml/minute, or more, delivered to the inspiratory port of the valve. The FEV_1 is measured before challenge and 60 seconds after exposure to the aerosol. The time of inhalation is doubled for each exposure, 30 seconds, 60 seconds, 2 minutes, 4 minutes, 8 minutes until a 15% reduction in FEV_1 occurs and at least 18.6 ml of 4.5% saline has been delivered to the subject. The dose of aerosol is measured by weighing the canister and tubing before and after challenge or determining the volume loss by subtraction (small nebulizers). If the total time of exposure and the total dose is known, the dose delivered per minute can be calculated and a dose response curve drawn. The dose of aerosol required for a 15% fall in FEV_1 is obtained by plotting the % fall in FEV_1 against the dose (Figure 8). Details of the protocol have been published[43,44] and are available on request. This technique is now widely used in Australia to assess intending divers. It has also been used for epidemiological studies.[18,44] Distilled water can be substituted for the 4.5% saline to study those intending to dive in fresh water.

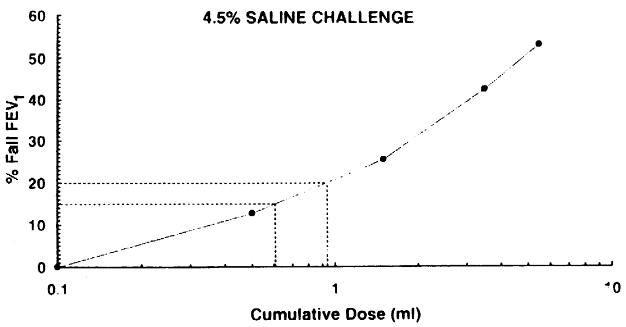

Figure 8. The fall in forced expiratory volume in one second FEV_1 ,expressed as a percentage of the pre-challenge value (% fall FEV_1), in relation to the cumulative dose of 4.5% saline. The broken lines represent the value for the dose of 4.5% saline required to provoke a 15% (PD_{15}) and 20% (PD_{20}) fall in FEV_1. Taken from Anderson et al.[43]

TABLE 2

RESULTS OF 4.5% SALINE CHALLENGE IN 180 PROSPECTIVE DIVERS

The table contains the changes in forced expiratory volume in one second (FEV_1) expressed as a percentage of the pre-challenge FEV_1 after saline challenge. The first column groups the results. The other columns give the mean ± 1 SD of the various groups. The second gives the % fall. The third the % rise in FEV_1 after bronchodilator, expressed as a percentage of the pre-challenge FEV_1. The fourth gives the lability index (% fall after saline + % rise after bronchodilator). The remaining columns give FEV_1 (fifth), FVC (sixth), and FEF_{25-75}(seventh, expressed as a percentage of the predicted normal, and the actual values for the FEV_1/FVC ratio (eighth).

% fall group	**% fall 4.5% saline**	**% rise b'dilator**	**Lability % change**	**FEV_1 % predicted**	**FVC % predicted**	**FEF_{25-75} % predicted**	**FEV_1/FVC actual**
<15% n=150	4.5 ± 3.7	2.9 ± 4.3 n=121	7.4 ± 6.5 n=121	106.3 ± 14.0	105.5 ± 10.9	81.7 ± 23.5 n = 108	79.8 ± 8.4
>15% n=30	22.3 ± 6.5	3.9 ± 6.5 n=29	26.2 ± 11.8 n=29	100.3 ± 13.7	105.1 ± 12.1	69.6 ± 20.4 n = 26	76.1 ± 8.8
10-14.9% n=21/150	11.5 ± 1.5	2.6 ± 6.3 n=17	14.1 ± 7.2 n=17	103.2 ± 14.4	104.6 ± 11.5	71.7 ± 12.6 n = 12	78.0 ±7.7
<15% FEF_{25-75} normal n=77/108	4.2 ± 3.5	1.9 ± 3.2 n=72	6.1 ± 4.4 n=72	111.8 ± 12.4	105.3 ± 11.5	91.6 ± 20.2 n = 77	84.0 ± 6.1
<15% FEF_{25-75} abnormal n=31/108	4.2 ± 3.7	4.5 ± 3.2 n=29	8.7 ± 4.3 n=29	95.8 ± 7.0	105.3 ± 8.3	57.1 ± 7.2 n = 31	72.1 ± 5.4

Significance of the results

A fall in FEV_1 of 15% or more is considered as abnormal. A person who has a positive test to hypertonic saline would be expected to be positive to challenge with dry air. They would usually, but not always, have a PD_{20} to histamine of less than 2 micromol and methacholine less that 4 micromol[40,43] However a person positive to a methacholine or histamine is not necessarily positive to a 4.5% saline or exercise challenge. Some investigators have found an increase in methacholine responsiveness after hypertonic saline[45] while others have not.[46] This effect may relate to refractoriness to the saline challenge.[47] It would seem advisable that if a pharmacological challenge and a physical challenge are both to be performed that they should be performed on separate days.

Mechanisms provoking airway narrowing.

The mechanism whereby dry air and hyperosmolar saline provoke airway narrowing is thought to involve release of mast cell mediators [28,48,49] and sensory neuropeptides.[29] The evidence for mast cell involvement comes from studies demonstrating the effectiveness of antihistamines given either orally or by aerosol in preventing the airway responses.[50-52] Prevention of the responses by this class of drug however, is impractical and not recommended due to unwanted side-effects, the high dose required with tablets, and inconvenient mode of administration as an aerosol.

In addition to the mast cell, we think that the sensory nerves are probably involved in responses to exercise, hyperventilation, and hyperosmolar aerosols. To date the evidence to support this comes only from work in animals.[29,53] However, it is thought that part of the effectiveness of drugs like sodium cromoglycate (Intal) and nedocromil sodium (Tilade) in blocking the responses to these stimuli comes from their action on nerves.[54] The effectiveness of these drugs on many cell types (mast cell, nerves, epithelial cells) and at many different sites in the body (lungs, nose, eye, stomach) probably relates to their ability to block chloride ion channels.[54-56]

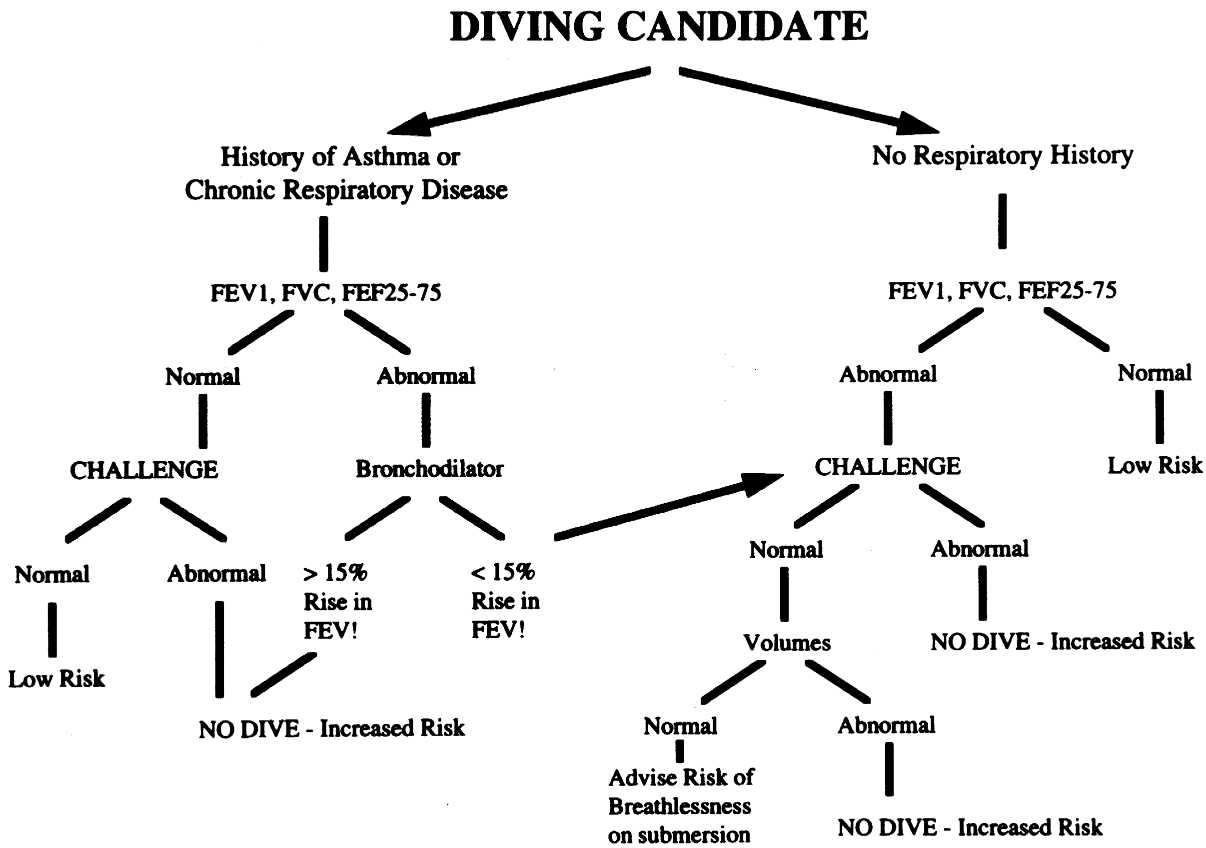

Figure 9. DECISION CHART TO AID IN RESPIRATORY ASSESSMENT OF INTENDING DIVERS

Treatment for those having a positive response

Because false positive responses are uncommon to dry air and hyperosmolar saline it is likely that a person having a positive response to these challenge tests will benefit from treatment for asthma. β_2 adrenoceptor agonists, terbutaline (Bricanyl) or salbutamol (Ventolin, Respolin) sodium cromoglycate (Intal Forte), or nedocromil sodium (Tilade) given immediately before the challenge will inhibit or prevent the airway responses to these stimuli in the majority of asthmatics. Drugs such as sodium cromoglycate and nedocromil sodium are only effective in persons with asthma. Demonstration of prevention of the airway response to hyperpnea or hyperosmolar challenge by these drugs should confirm the diagnosis of asthma. We have found that treatment with budesonide (Pulmicort) (1000 µg/day) for 8 weeks is very effective in inhibiting and even completely preventing airway responses to challenge with 4.5% saline. We found that 50% of our subjects were no longer responsive after this regimen.[56,57] Similar findings have been made in children suffering EIA, taking 400 µg budesonide daily.[58] We have not found beclomethasone as effective as budesonide in this regard.[59] In persons who are still responsive to exercise and to inhalation of 4.5% saline and who are taking aerosol corticosteroids we find the addition of 10 mg nedocromil sodium[60] or 20 mg of sodium cromoglycate[56] to be remarkably effective in blocking airway responses to 4.5% saline.

Laboratory findings

Since 1989 we have been referred 209 intending recreational scuba divers with a past history of asthma or asthma-like symptoms or with a borderline spirometry result suggestive of asthma. Of these, 180 were adults (mean age 27 years, range 18-51) who successfully completed a standardised challenge protocol using 4.5% sodium chloride aerosol.

Measurements of lung function for the groups of subjects separated on the basis of their airway response to 4.5% saline are given in Table 2. An abnormal test is regarded as :

1 Fall in FEV_1, in response to 4.5% NaCl, of 15% or more of baseline
2 Rise in FEV_1, in response to a bronchodilator, of 15% or more of baseline
3 A lability greater than 20% i.e. the % fall in FEV_1

from baseline after saline plus the % rise from baseline in FEV_1 after bronchodilator totals more than 20% (e.g. (9 % fall + 14% rise = 23% lability)

4 FEV_1 % <80% of predicted

5 FVC % <80% of predicted

6 FEF_{25-75} less than approximately 65 % predicted, based on lowest confidence interval.

A decision chart (Figure 9) is given to aid in the respiratory assessment of an intending diver.

Normal lung function

Ninety of the 180 subjects (50%) had normal lung function tests and no bronchial hyperresponsivess (were completely normal) and would be considered as low risk from pulmonary complications from diving with compressed gases.

Bronchial hyperresponsiveness

Thirty (16.6%) of the 180 subjects had a 15% or more fall in FEV_1 after inhaling 4.5% saline for up to 15.5 minutes or more and 28.3 % had a fall in FEV_1 of 10% or more. The mean % fall in $FEV_1 \pm 1$ SD for the entire group of 180 was 7.45% ± 7.9 and the distribution of this fall is given in Figure 10. This distribution is normal and the current asthmatics represent the tail of the normal curve in this population.

The thirty subjects who had a fall in FEV_1 greater than 15% or more to 4.5% saline were also the only subjects to have abnormal responses to a bronchodilator or an abnormal lability index. This finding was a little surprising but it gives confidence that the response to 4.5% saline identified those with bronchial hyperresponsiveness. It should be noted that a positive response to 4.5% saline also identifies persons hyperresponsive to hyperpnea with dry air.[18,38-40,43] As acute narrowing of the airways is associated with gas trapping and acute hyperinflation of the lungs (Figure 5-7) we would consider that persons who are hyperresponsive to 4.5% saline are at an increased risk from pulmonary complications from diving.

Abnormal lung function without bronchial hyperresponsiveness

One hundred and fifty people had a fall in FEV_1 less than 15% after 4.5% saline and no response to bronchodilator, of these 108 had measurements of FEF_{25-75} and 31 (29%) had a value for FEF_{25-75} that was below the lower limit of the predicted normal (Predicted minus 1.64 RSD, see Table 1). Of these all but 2 had an FEV_1/FVC ratio less than 79%. Only one of these subjects had hyper-

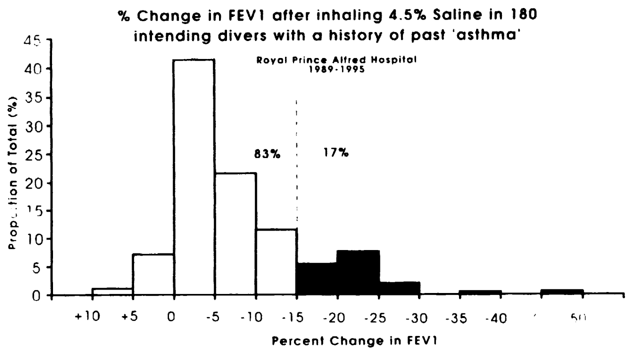

Figure 10. The percent reduction in FEV_1 in response to inhaling hyperosmolar (4.5%) saline in a group of 180 adults with a history of past asthma, or symptoms of asthma, who were referred to the laboratory as a consequence of a medical examination for diving.

inflation (an abnormally high functional residual capacity) measured before challenge and there was no gas trapping in any subject. These persons with a reduced FEF_{25-75} may be at an increased risk of feeling breathless at depth but may not necessarily be at an increased risk of pulmonary complications from diving. However they could be distressed as a result of heightened perception of breathing. They should be advised of this possibility. It may be more advisable to suggest that they do not dive.

Based on our findings, and those of others, in smaller numbers of persons without a history of asthma, we have previously suggested that an abnormal fall in FEV_1 to be taken as 15% or more. Of our group of 150 persons who had a fall less than 15% in response to saline, the mean fall in FEV_1 was 4.47% ± 3.7. Considering these persons had a past history of asthma, a value of 15%, which represents the mean + 3 SDs of this group representing 97% of the population would seem appropriate. For the 129 people who had a fall in FEV_1 of less than 10%, the mean % fall in FEV_1 was 3.3% ± 2.5. This value was exactly the same for the 70 persons who had normal values for FEF_{25-75} and a fall in FEV_1 to 4.5% saline less than 10%. Using these data the cut off point for mean plus 3 SDs is 10.8%.

Edmonds[23] has suggested that a fall of 10% or more in FEV_1 in response to saline should preclude a subject from diving. Of our 180, 51 had a fall in FEV_1 of 10% or more. A fall of 10-14.9% may be unnecessarily stringent if other parameters of lung function are all normal. These borderline cases, however, need to be assessed in terms of responses to bronchodilator and other indices of lung function to assess risk.

Discussion

We do not know the outcome for those referred to us. We do know that many who were positive to salt water thought it unwise to dive. Most stated they would not take part or complete their diving course given this finding.

Of those who did go on to complete their courses and to dive we do not know how many had adverse events that could be related to their past history of asthma. Some may have had asthma symptoms again and discontinued their diving. Others may still be diving.

While we consider that we provided a service to evaluate the subject for asthma at the time we would have provided a greater service if we had followed up. By doing so we may have gone further towards establishing what factors contribute to mortality and morbidity in diving persons with a past history of asthma. Perhaps an international effort between interested parties will help to give the additional data required "to define accurately risks of diving in subjects with different forms of asthma".[61]

Audience participation

Unidentified speaker

Why do we not use water?

Anderson

Because water does not necessarily identify persons with exercise induced asthma. We have found that water provokes too much cough. We used it until about 1986. Hyperosmolarity is more likely to be a common stimulus to the airways. However a diver going into fresh water should have a water challenge.

Bove

The test can be graded very nicely in a dose response relationship and I guess the question we have in diving is how does it relate to the outcome results, for example in an asthmatic in general. Is there good data relating to the outcome of the tests to the consequent morbidity, not for diving but for asthma in general.

Anderson

Yes, persons responsive to hyperosmolar saline also have exercised induced asthma. Furthermore treatment with steroids reduces responses to saline and reduces the severity of exercise induced asthma.

Bove

In the States of course we are recommending for athletes that have exercise induced asthma, but not necessarily for divers, that they go on a drug and that they use it on the days of their competition. It seems to work.

Anderson

I am not worried about exercise in air, but I am worried about breathing dry air under water.

Bove

I think that in the States it is agreed that the major problem is the lack of exercise capacity while swimming on the surface and the consequent panic and drowning. This is much more important than the potential for pulmonary barotrauma. Under these circumstances the requirement for athletic performance outweighs concern for pulmonary barotrauma.

Anderson

I agree with this. However we must be wary as we do not wish current asthmatics with exercise induced asthma to dive. I believe that asthma is more severe in Australia and New Zealand compared with the USA. Our vigilance may be the reason that asthmatics are not over represented in our statistics.

Veale

It is probably worth emphasising that the test correlates very well with clinical severity of asthma and allows one to establish a range of mild to severe asthmatics.

Anderson

It also correlates with the pathology but I did not have time to show that.

Acknowledgement

We would like to thank the many medical practitioners who referred the patients. In particular we would like to thank Drs Carl Edmonds and Douglas Walker for their long term interest and enthusiasm that led us to developing this range of tests for the intending diver.

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