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# THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

- ❖ Risks Associated with Long-Term Use of Proton Pump Inhibitors
- ❖ Chronic Lung Disease in Adults and Air Travel
- ❖ Meeting Anna Formosa

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# EDUCATIONAL FAILURE? THINK DEMENTIA...

In a recent publication<sup>1</sup> in *The Lancet*, Livingston et al. identified nine factors which contribute to the risk of dementia. These are:

- Mid-life hearing loss - responsible for 9% of the risk
- Failing to complete secondary education - 8%
- Smoking - 5%
- Failing to seek early treatment for depression - 4%
- Physical inactivity - 3%
- Social isolation - 2%
- Hypertension - 2%
- Obesity - 1%
- Diabetes - 1%

These risk factors, adding to 35%, are potentially modifiable. The other 65% is thought to be largely related to non-modifiable risks. At this stage it is relevant to highlight the limitations of the study, including the exclusion of other important potential risk factors - diet, alcohol consumption, living near major roads and lack of sleep. This means that the potentially preventable fraction of dementia might actually be underestimated in the study.

Although the link between obesity, diabetes and hypertension, and dementia can be considered to be of a logical manner, the relationship between dementia and the other risk factors may not be so obvious. Take for example the failure to complete secondary education, which is considered a major risk factor [25% of the modifiable risk factors in the above study]. Why is this so? This is thought to occur because individuals who do not continue to study/learn throughout life are less likely to build additional 'cognitive brain reserves'. These cognitive reserves are built during one's lifetime, strengthening the brain's networks so it can continue to function in later life despite damage. Another risk

factor is hearing loss in middle age. Researchers have concluded that denying people a cognitively rich environment leads to social exclusion and depression, which are in turn also listed as potentially modifiable risk factors for dementia.

In Malta there are an estimated 6,000 individuals with dementia. This represents 1.5% of the general population and is envisaged to increase to 10,000 individuals by 2030.<sup>2</sup> The cost is also striking. Taking 2009 as an example [which is the latest data available], the average cost for Malta was estimated to be €80 million, which includes both informal care as well as direct medical and social care costs.<sup>3</sup>

In keeping with the above, adopting a healthy lifestyle such as avoiding smoking, treating hypertension and diabetes can all reduce the risk of dementia [as well as reduce the risk for cardiovascular disease and cancer]. Doing exercise and having a healthy weight also helps. So stop reading and go out running! 🏃

*Pan Ellul*

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Cover: During the 1837 cholera epidemic Vilhena Palace in Mdina served as a temporary hospital. In 1860 it was used as a sanatorium for British troops. Early in the 20th century the palace was passed to the Maltese government and was converted into a hospital for tuberculosis patients and was formally inaugurated by King Edward VII on 22 April 1909 and was referred to as the Connaught Hospital. On 10 January 1956 the hospital closed down. Today the building houses the National Museum of Natural History. - *Heritage Malta*

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# RISKS ASSOCIATED WITH LONG-TERM USE OF PROTON PUMP INHIBITORS

ANTHEA BRINCAT & NEVILLE AZZOPARDI

## ABSTRACT

Proton pump inhibitors (PPIs) are widely used in the management of upper gastrointestinal disorders. In recent years, concerns have been raised on the potential adverse effects of long-term PPI use. This article reviews the published evidence of the effect of long-term PPI use on the absorption of minerals and vitamins, risk of infections, chronic kidney disease and dementia.

## INTRODUCTION

Proton pump inhibitors (PPIs) are amongst the most commonly prescribed drugs globally, widely used for the prevention and treatment of acid-related disorders such as gastroesophageal reflux disease and peptic ulcer disease. Studies have however, shown that PPIs are often overprescribed or used inappropriately, with 25% - 70% of patients taking these drugs without having an appropriate indication.<sup>1</sup> Although PPIs are well tolerated and have been approved for long-term use, concern and evidence on the potential long-term adverse effects are increasingly emerging. This article reviews published information on adverse effects associated with long-term PPI use.

## ABSORPTION OF VITAMINS AND MINERALS

PPIs block the hydrogen-potassium adenosine triphosphatase enzyme system of the gastric parietal cell, leading to inhibition of gastric acid secretion. This in turn, can lead to decreased absorption of minerals such as calcium, magnesium and iron as well as vitamins such as vitamin B12.

Gastric acid suppression by PPIs has been postulated to result in altered calcium metabolism, causing low bone density and an increased risk of fractures. The mechanism is related to both decreased absorption of calcium compounds in the presence of achlorhydria and primary hyperparathyroidism. The latter results from parathyroid hyperplasia secondary to the hypergastrinaemia caused by profound acid suppression.<sup>2</sup> Several studies have investigated the association of PPIs to fracture risk; however the results have been inconsistent. The latest meta-analysis of observational studies, published in 2016, has shown that PPI use modestly increased the risk of hip, spine, and any-site fracture, but with no evidence of duration effect in subgroup analysis.<sup>3</sup> Thus, in patients with increased risk of bone fractures, caution should be exercised

when prescribing long term PPIs. Adequate dietary calcium intake with vitamin D and calcium supplementation should be considered, ideally in forms that are not influenced by gastric acid for absorption, such as calcium citrate.<sup>2,4</sup>

Iron and vitamin B12 absorption can be hindered by the low gastric acid levels produced by PPIs. Dietary iron is present in food as non-haem (66%) or haem iron (32%). Gastric acid assists food sources containing non-haem iron to dissociate and to solubilize the iron salts. These salts can then form complexes with sugars and amines, facilitating absorption.<sup>5</sup> The data on the effect of PPIs on iron absorption is inconsistent. There are case reports showing iron deficiency anaemia which resolved when PPI therapy was stopped<sup>6</sup> and a retrospective cohort study showing a significant decrease in haemoglobin in PPI users.<sup>7</sup> Patients with hereditary haemochromatosis were shown to require less frequent phlebotomies when given PPIs.<sup>8</sup> On the other hand, two small studies did not show any significant change in iron levels in patients on short or long-term PPIs<sup>9,10</sup> whilst a cohort of patients with Zollinger-Ellison Syndrome who received treatment with PPIs for over 10 years did not demonstrate a clinically significant iron deficiency.<sup>11</sup> As yet, there are no recommendations to monitor patients on long-term PPI therapy for iron deficiency anaemia and patients shown to be anaemic should be investigated as per published guidelines.

Vitamin B12 is a protein-bound vitamin that requires the presence of gastric acid and pepsin for it to be released in the stomach.<sup>12</sup> Once again, studies have shown conflicting data with a recent, large, case-control study showing that the use of PPIs for two years or more was significantly associated with a new diagnosis of vitamin B12 deficiency.<sup>13</sup> On the other hand, a cross-sectional study failed to show a significant difference in serum B12 levels in patients on PPIs, compared to their partners who were not on PPIs<sup>14</sup>. In a systematic review, the authors concluded that PPI therapy does not statistically affect the absorption of vitamin B12.<sup>5</sup>

In 2011, the FDA released a warning that long-term PPI use may cause hypomagnesaemia, including clinically serious adverse events. In approximately one-quarter of the cases reviewed, magnesium supplementation did not improve the low magnesium level and the PPI had to be discontinued. Whilst the true incidence of PPI-induced hypomagnesaemia is unknown, FDA recommends checking magnesium levels periodically in patients expected to be on prolonged PPI treatment or who take PPIs with other medications that may cause hypomagnesaemia (such as diuretics) or digoxin.<sup>4</sup>

## INFECTIONS

Gastric acid secretion is part of the local defence system against orally ingested pathogens and its suppression could, theoretically, lead to an increased risk of enteric infections. In addition, a twin study has shown a significant impact of PPIs on the gut microbiome.<sup>15</sup>

Infection with *Clostridium difficile* is of particular importance due to its morbidity. A meta-analysis of 42 observational studies has shown a probable association between PPI use and incident and recurrent *Clostridium difficile* infection.<sup>16</sup> This resulted in the FDA issuing a safety announcement on the increased risk in PPI users of *Clostridium difficile*-associated diarrhoea, especially in elderly patients with chronic underlying medical conditions or on broad spectrum antibiotics.<sup>4</sup> A systematic review has also shown that PPI use increases patient susceptibility to other enteric infections such as Salmonella, *Campylobacter jejuni* and small intestinal bacterial overgrowth.<sup>17</sup>

Long-term PPI treatment has also been linked to pneumonia. The mechanism with this association may be due to upper gastrointestinal bacterial overgrowth, resulting in an increased susceptibility to respiratory infections by potential micro-aspiration or translocation into the lungs. Data is inconsistent, with some recent meta-analyses suggesting that PPI use is associated with an increased risk of both community and hospital-acquired pneumonia<sup>18</sup> and others failing to show an association.<sup>19</sup>

## RENAL DISEASE

Over the years, concerns have been raised about the adverse renal effects of PPIs, with acute interstitial nephritis being the most frequently observed acute kidney damage in PPI users. The proposed mechanism is thought to be secondary to deposition of PPIs or their metabolites in the kidney's tubulo-interstitium compartment and direct stimulation of an immune response.<sup>20</sup> Three large population-based studies in Canada, the United States and New Zealand have all shown a higher risk of acute interstitial nephritis in patients on PPIs compared to controls. In some cases, this acute injury goes unrecognized and therefore uncorrected. While most patients recover kidney function, many are left with some level of chronic kidney injury.<sup>12,20</sup> Several studies have shown an association of PPI use with chronic kidney disease.<sup>21</sup> Caution should therefore be exercised when prescribing PPIs to patients who have other risk factors for renal disease and patients on long-term treatment should have their renal function monitored.

... IN PATIENTS WITH INCREASED RISK OF BONE FRACTURES, CAUTION SHOULD BE EXERCISED WHEN PRESCRIBING LONG TERM PPIs... CALCIUM SUPPLEMENTATION SHOULD BE CONSIDERED, IDEALLY IN FORMS THAT ARE NOT INFLUENCED BY GASTRIC ACID FOR ABSORPTION, SUCH AS CALCIUM CITRATE

## DEMENTIA

PPIs were shown to lead to higher levels of amyloid-beta in the brains of mice in a manner similar to the extracellular deposition of amyloid-beta peptides seen in the pathogenesis of Alzheimer's disease. This led to the hypothesis that PPI use can be associated with an increased risk of dementia. A systematic review looking at 11 studies showed a positive association between PPI use and dementia (three out of four studies) or acute cognitive impairment; however, the authors pointed out several methodological problems and conflicting results.<sup>22</sup> Further longitudinal studies are needed to confirm this association.

## CONCLUSION

Although PPIs are safe and effective drugs, their long-term use carries potential risks. As with all medications, there should be a clear indication when prescribing PPIs, with the lowest effective dose being used. It is recommended to weigh the benefits of PPI therapy against the risks, especially in patients with multiple comorbidities and in the elderly. As clinical situations may change over time, patients should be regularly reviewed as to whether acid suppression is still required. ❄️



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## RESEARCH

# WASP (WRITE A SCIENTIFIC PAPER) AGAIN IN MALTA AND LONDON

VICTOR GRECH

The ability to write up research in a paper that can withstand peer-review is a crucial and critical requisite for all academics, not only to disseminate their work, but also to further their careers. The skills required are manifold and are usually acquired piecemeal. WASP (Write a Scientific Paper) is an intensive and comprehensive 3-day course that covers all requisite paper-writing skills.

Core subjects include: literature appraisal, proposals, ethics and data protection, seeking materials for publication, preparing a compelling abstract, an attractive poster and a captivating presentation, how to lay out a paper, which journals to target (and why), editors' viewpoints, tackling editors, the difference between a paper and a thesis, and statistics. Almost a third of WASP includes statistical analysis using the familiar Microsoft Excel environment. The WASP faculty comprises experienced researchers and journal editors. WASP's purpose is to impart the lecturers' collective experience to the delegates in this crucial aspect of career progress.

WASP courses include soft copies of all talks, all papers discussed as examples, all spreadsheets including actual data

used in published papers, as well as spreadsheets that extend Excel's native capabilities. WASP also has a half day of statistics exercises using Microsoft Excel. The author is well suited to impart the statistics lectures, having co-written the statistics chapter in *The Science of Paediatrics: MRCPCCH Mastercourse*.<sup>1</sup>

WASP has been held in Malta almost annually since 2010. After each iteration, feedback has been used for fine-tuning WASP. The course was held in London, for the first time, at the Royal College of Paediatrics and Child Health at the end of January 2017. This is a unique course worldwide and feedback has been excellent (table 1). The modus operandi for WASP has also been published.<sup>2</sup>

This event is suitable for all individuals in the sciences field who wish to enhance their paper writing skills by acquiring sound competences in academic writing. WASP will once again be held in Malta (2-4/10/2017) and in London (23-25/10/2017). The WASP faculty looks forward to meeting you. Registration is available at [www.ithams.com/wasp](http://www.ithams.com/wasp).

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# TELLING STORIES IN MORE WAYS THAN ONE

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**T**he Synapse meets pharmacist Anna Formosa who also happens to be an applied drama practitioner, and widely known for her creative community projects especially her latest intergenerational project 'Darba Wahda...'



## TS: HOW DO YOU RECONCILE YOUR WORK AS A PHARMACIST WITH DARBA WAHDA...?

I strongly believe that general well-being is a result of a healthy social, mental and physical well-being. The arts in fact are a key to well-being as creativity has been proven to provide meaningful creative expressions and connections. In keeping with this, various studies have proven that participation of the elderly in the arts contributes to better general health, less doctor visits, fewer medication usage and increased engagement in social activities. This, in turn, reduces the government's burden of healthcare costs. Engaging in a creative activity stimulates not only the mind but also the senses and provides a platform for social interaction and meaningful connections engendering a sense of self-esteem and meaning in life. To me, both pharmacy and my applied drama projects have the same aim, promoting health and well-being, one through giving access of medicines to patients, and the other through creativity. *Darba wahda...* is about using creativity to harness the strengths, potentials and achievements of elderly people, and the joy and youthfulness of children to provide a line of communication that transcends the generational divide.

## TS: HOW DID YOU DISCOVER THE WORLD OF APPLIED DRAMA PRACTICE?

I graduated in Malta as a pharmacist in 2002. Having always been interested in the theatre and having performed on stage

several times, I eventually decided to study for a Master's degree in Applied Drama at Exeter University, UK in 2004. I was most interested in the performance process which contributed to my personal development, hence my research revolved around the role of drama in education and as a social intervention tool, that is, how creative techniques can provide a positive learning experience in the context of education and personal development. The course was part theoretical and part practice-based, hence during that year, part of the fun was enjoying travelling extensively around the southern part of the UK to participate in projects, workshops, community theatre and youth festivals, and learning from different practitioners until I started my own projects.

## TS: WHAT SKILLS DOES THIS KIND OF EXPERIENCE REQUIRE, WHICH WILL EVENTUALLY HELP YOU DEVELOP ON A PERSONAL LEVEL?

I find that the greatest skills required are empathy and patience, skills which I find are also essential for healthcare professionals. Being creative and having the ability to involve others are another two important skills – as these will help you unleash the participants' creative potentials, see opportunities rather than problems and understand the group you work with. To be a good leader you also need to be well-organised, anticipating what could happen so you are well-prepared for any eventuality. One can develop these skills along the way and these are also transferrable skills.

You also learn to trust your intuition and the process itself, that by paying attention to little details and by being careful how to create the platform for this interaction, this will lead to a great outcome for participants, essentially a group of strangers, to create something constructive.

### TS: HOW DID *DARBA WAHDA...* COME TO BE?

Along the years I have been involved in many projects, in education, with people with disability and in care homes. *Darba wahda...* in fact evolved from previous work with the elderly. The project was from my own initiative but was made tangible thanks to the Valletta 2018 Foundation. *Darba wahda...* is a Valletta 2018 project as part of the cultural programme. The project brings together the young and the elderly in a joint experience that allows them to share memories and create new ones via varied creative and sometimes unconventional forms of story-telling and other creative techniques such as drama, improvisation, painting, puppet-making, etc. *Darba Wahda...* attracts children aged 9-12 years and elderly persons of varying ages. Every season there are three or four projects in different locations. I usually work with local councils, schools, day centres and other community groups to promote the project and enrol participants. I manage the project and also lead the workshops and other artists involved in the project. There is a lot of work behind the scenes but people who attend the workshops give us really positive feedback and benefit on different levels from the project so it is all worthwhile.



Photos credit: Carl Farrugia

## DARBA WAHDA... MANAGES TO BRING TO LIFE QUITE A VARIETY OF NARRATIVES TO PRODUCE A UNIQUE LEARNING EXPERIENCE TO BOTH YOUNG AND OLDER PARTICIPANTS IN A FUN AND SAFE ENVIRONMENT

### TS: WHAT SORT OF STORIES DO YOU WORK AROUND WITH YOUR GROUPS?

Old traditional stories, legends, popular verse and folk tales coming from participants and myself - Kuncett u Marinton, Fra Muđest or Ġaħan are perhaps the best known, but there are other less popular stories which the young would have never had the opportunity of listening to, if it were not for the elderly participants who still remember such stories from their own childhood days. We also work with stories from artefacts, such as old coins and petroleum lamps, and old traditional games, which always elicit a smile in the elderly as well as the children. Basically I create the platform and over the space of ten weeks, *Darba Wahda...* manages to bring to life quite a variety of narratives to produce a unique learning experience to both young and older participants in a fun and safe environment.

### TS: SO WHAT ABOUT YOUR WORK AS A PHARMACIST?

I love it. I feel I am both scientific and creative so this combination is perfect for me. Pharmacy keeps me grounded while my projects, like *Darba Wahda...* allow me to be creative and give me the healthy break to keep looking at pharmacy with interest. I used to work as a community pharmacist but am now working in regulatory affairs with a leading pharmaceutical company in Malta.

### TS: WILL DARBA WAHDA... LAST FOREVER?

With regards to intergenerational work, *Darba Wahda...* only touches the tip of the iceberg. There is so much work to be done. To begin with, *Darba wahda...* only caters for elderly and young people in the community, there are many more in care homes. So far we have had 13 projects in various localities around Malta and Gozo. The next season of workshops will kick off in October 2017. In 2018 *Darba Wahda...* will be celebrated in a surprising way and I hope that this work will continue the legacy started through Valletta 2018. ✂

## I READ THE SYNAPSE BECAUSE...

I keep abreast with developments in the healthcare scene.



# CHRONIC LUNG DISEASE IN ADULTS AND AIR TRAVEL

## ABSTRACT

The safety of travelling in patients suffering from chronic lung conditions is a frequently encountered problem amongst healthcare professionals. The objective of this paper is to review currently available literature, with the aim of clarifying such issues for doctors dealing with such concerns. The article will describe the effect of altitude on healthy and diseased lungs, assessment tools to be utilised when assessing patients with suspected or diagnosed chronic lung conditions and international guideline recommendations for chronic lung conditions.

## ABBREVIATIONS

**COPD** - Chronic obstructive pulmonary disease

**FEV<sub>1</sub>** - Forced expiratory volume in one second

**CPAP** - Continuous positive airway pressure

**CXR** - Chest X-ray

**SpO<sub>2</sub>** - Peripheral capillary oxygen saturation

**PaO<sub>2</sub>** - Arterial partial pressure of oxygen

**BTS** - British Thoracic Society

## INTRODUCTION

In recent years there has been a progressive rise in the number of people who travel by air.<sup>1</sup> The ease of travel as well as the increasing availability of lower cost travel makes journeys accessible to older or less financially advantaged travellers.<sup>2</sup> In addition, advances in the monitoring of many chronic respiratory diseases as well as the availability of medications have improved quality in the lifestyle of such patients, allowing chronically ill patients to consider the possibility of air travel. It has become common for people with lung disease to request to travel and in turn seek advice from their medical practitioners about related issues. Surprisingly, reports of serious incidents concerning travellers with lung disease are relatively rare. Since respiratory problems are estimated to make up about 11% of in-flight emergencies it is reasonable to assume that the burden of risk surrounding the flight itself, and later disruption of the journey, is significant.<sup>3</sup>

## FIGHT ENVIRONMENT AND ALTITUDE EFFECTS

Commercial aircraft are pressurised to cabin altitudes of up to 8000 feet (2438m) although this ceiling may be exceeded in

emergencies. Pressurization of the aircraft cabin is achieved using exterior air that is compressed and mixed with filtered and re-circulated cabin air. Up to 50% of the cabin air is not re-circulated and is expelled, to be replaced with exterior air, with 20–30 complete air exchanges occurring per hour.<sup>4</sup> At that altitude, the partial pressure of oxygen falls to the equivalent of breathing 15.1% oxygen at sea-level.

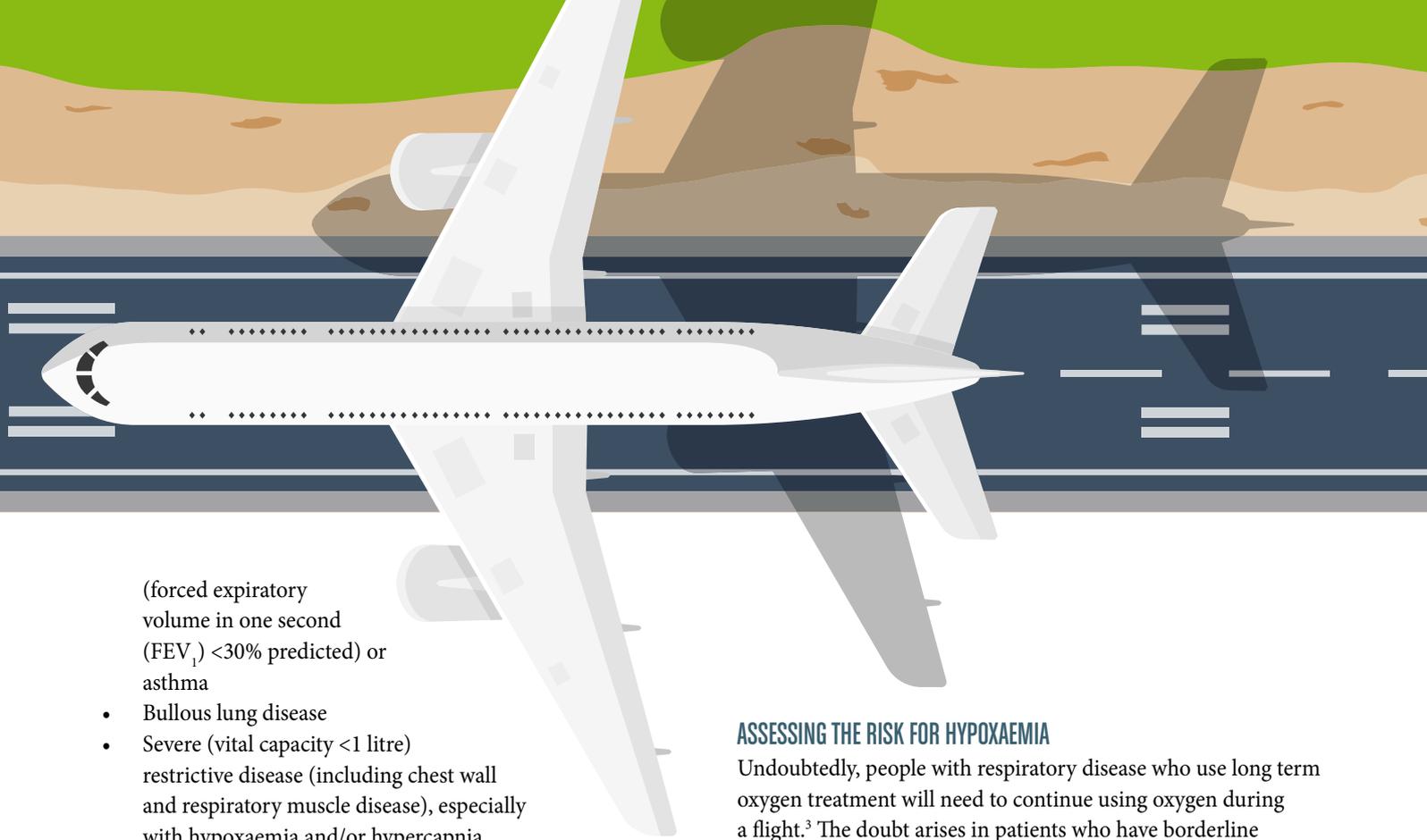
The rapid reduction in pressure associated with ascent is usually well tolerated by the healthy lung. At cabin altitude even normal people can occasionally desaturate but will generally compensate by increasing alveolar ventilation,<sup>3</sup> such that people with healthy lungs remain asymptomatic throughout the flight.

On the other hand, apart from the usual health risks of airline flight, the principal additional challenge for patients with chronic respiratory disease is exposure to hypobaric hypoxia. Patients suffering from chronic respiratory illness may have mild hypoxaemia, which may even go unrecognized at times. Altitude exposure may worsen hypoxaemia in pulmonary disease. Compensatory pulmonary mechanisms may be inadequate in patients with lung disease despite normal sea-level oxygen requirements. In addition, compensatory cardiovascular mechanisms may be less effective in some patients who are unable to increase cardiac output.<sup>4</sup> Such patients may be vulnerable to the relatively minor pressure changes, causing an enlargement of a pre-existing pneumothorax or rupture of an emphysematous bulla or other spaces containing air.<sup>3</sup> The physiological compensation for acute hypoxaemia is mild to moderate hyperventilation, limited by the fall in arterial carbon dioxide tension (PaCO<sub>2</sub>) together with a moderate tachycardia.<sup>2</sup>

## PRE-FLIGHT ASSESSMENT

If there is doubt about the patient's fitness to fly and if there are co-morbidities affecting fitness, assessment is advised. In general, the patient's respiratory condition should be stable and the patient must have recovered from any recent exacerbation before travel. It is recommended that those patients with the following conditions should be assessed with at least, a history and physical examination:

- Previous air travel intolerance with significant respiratory symptoms (dyspnoea, chest pain, confusion or syncope)
- Severe chronic obstructive pulmonary disease (COPD)



(forced expiratory volume in one second ( $FEV_1$ ) <30% predicted) or asthma

- Bullous lung disease
- Severe (vital capacity <1 litre) restrictive disease (including chest wall and respiratory muscle disease), especially with hypoxaemia and/or hypercapnia
- Cystic fibrosis
- Co-morbidity with conditions worsened by hypoxaemia (cerebrovascular disease, cardiac disease or pulmonary hypertension)
- Pulmonary tuberculosis
- Within six weeks of hospital discharge for acute respiratory illness
- Recent pneumothorax
- Risk of or previous venous thrombo-embolism
- Pre-existing requirement for oxygen, continuous positive airway pressure (CPAP) or ventilator support.<sup>2</sup>

During such an assessment patients should have their condition optimised, where possible, thus decreasing the risk of complications and potentially reducing the severity of hypoxaemia.

### PRE-FLIGHT SCREENING HISTORY, PHYSICAL EXAMINATION, AND SPIROMETRY

As part of a pre-flight screening evaluation, a detailed history and physical examination should be performed. Any previous flying history should therefore be explored, as this may yield important information on the symptoms or complications that may have occurred during or after previous air travel. Physicians should also consider the flight duration, destination, as well as the control of the disease.

In the absence of any contraindication, the American Thoracic Society recommends that spirometry should be performed on patients with a history of acute or chronic lung disease or with symptoms suggestive of lung disease. Pulse oximetry at rest should also be done, with arterial blood gas confirmation in addition to this, if hypercapnia is suspected.<sup>4</sup>

### ASSESSING THE RISK FOR HYPOXAEMIA

Undoubtedly, people with respiratory disease who use long term oxygen treatment will need to continue using oxygen during a flight.<sup>3</sup> The doubt arises in patients who have borderline hypoxaemia at sea level, in which case these patients need to be assessed thoroughly.

A number of methods of assessment for hypoxaemia risk during air travel are available. These include:

- Sea-level measurement of  $SpO_2$  and  $PaO_2$
- The use of equations to predict hypoxaemia at altitude
- Hypoxic challenge testing, performed under either normobaric or hypobaric conditions.

Measuring  $SpO_2$  at sea level to risk-stratify patients has become recognized as a less reliable predictor of in-flight  $SpO_2$  compared to other methods. In the 2002 British Thoracic Society (BTS) guidelines, an  $SpO_2$  of 92–95% without risk factors or  $SpO_2$  greater than 95% was used to indicate that no further testing was warranted.<sup>5</sup> However, in one study, 23% of patients having an  $SpO_2$  greater than 96%, tested by hypoxic challenge testing, experienced significant hypoxaemia warranting in-flight oxygen supplementation.<sup>6</sup> In another study of 100 COPD patients, stratified on the basis of  $SpO_2$  thresholds from the 2002 BTS algorithm, who underwent pulse oximetry and normobaric hypoxic challenge testing, the sensitivity and specificity for these  $SpO_2$  thresholds were only 59% and 72%, respectively.<sup>7</sup> Despite this method being readily available, cheap, and not laborious, this tool is not considered sufficiently robust to screen patients.

Predictive equations have also been used to estimate the risk of hypoxaemia at high altitude; they incorporate sea-level measurements of  $PaO_2$  and other parameters such as  $FEV_1$  or anticipated cabin altitude.<sup>8,9</sup> Many of the equations consistently overestimated the need for supplemental oxygen, thus incurring unnecessary additional cost.<sup>4</sup> The novel non-linear predictive models represent a low cost option for the prediction of



significant hypoxia during flight and perform better than SpO<sub>2</sub> in identifying those patients who require more formal assessment with hypoxic challenge testing.<sup>10</sup>

Hypoxic challenge testing, though costly and time-consuming, is now the preferred method to assess risk of hypoxaemia at altitude.<sup>4</sup> It uses a decreased (normobaric) fraction of inspired oxygen (FiO<sub>2</sub>) to simulate the hypoxic conditions at altitude.<sup>4</sup> It is performed in a specialist lung function unit after referral to a respiratory specialist.<sup>2</sup> However, it is not available locally, rendering it difficult to advise our local patients accordingly, even in a hospital setting. The hypoxic challenge test is not a 'fitness to fly' test but is used to determine whether a patient needs in-flight oxygen; most importantly, even with in-flight oxygen and/or ventilator support, safety cannot be guaranteed.<sup>2</sup> In fact, in one particular study, *in PaO<sub>2</sub> hypoxic altitude simulation testing*, no difference was identified between COPD patients with and without respiratory symptoms.<sup>11</sup>

FEV<sub>1</sub> is also a useful marker of clinical severity. However, neither resting sea-level oxygen saturations nor FEV<sub>1</sub> appear to predict hypoxaemia or complications accurately during or after air travel in patients with respiratory disease.<sup>2</sup>

Based on the current literature, it can be concluded that air travel is safe for most patients. However, those at risk of hypoxia can benefit from supplemental in-flight oxygen.<sup>12</sup>

Further research is required to determine whether a symptom-based approach, for instance the Medical Research Council dyspnoea scale or clinical exercise testing might be more reliable for screening.<sup>2</sup>

## CONTRAINDICATIONS TO COMMERCIAL AIR TRAVEL

Certain patients suffering from pulmonary disease should be advised to avoid flying, either because of high risk of deterioration of their pre-existing condition or else, because they pose a risk to others. These include:

- Ongoing pneumothorax with persistent air leak
- Major haemoptysis
- Infectious tuberculosis
- Usual oxygen requirement at sea level at a flow-rate exceeding 4L/min.<sup>2,4</sup>

## CHRONIC LUNG DISEASES

### OBSTRUCTIVE PULMONARY DISEASE (ASTHMA AND COPD)

Before travel, patients should have their condition optimised, with the least possible symptoms as well as minimal use of reliever medication. They should carry their inhalers, including spacer, at all times. A patient should also be treated and has recovered from an exacerbation before being advised to travel. A bronchodilator given via a spacer is as effective as a nebuliser. For acute exacerbations on board, the patient's own bronchodilator inhaler, ideally with a spacer, should be taken, and the dose repeated until symptomatic relief is obtained. According to BTS recommendations, it is advised that patients with severe or brittle asthma or severe COPD (FEV<sub>1</sub> <30% predicted) should consult their respiratory specialist beforehand for optimisation of their condition and the patient may consider carrying an emergency supply of prednisolone in addition

to their usual medication.<sup>2</sup> A recent study has suggested that hypoxic challenge testing should be performed for patients suffering from severe asthma.<sup>13</sup>

## BRONCHIECTASIS

Positive sputum cultures should ideally be treated so as to optimize the patients' condition. Bronchodilators should be prescribed as necessary. Nebulised antibiotics or nebulised bronchodilators are not generally required.<sup>2</sup>

## CANCER

Severe or symptomatic anaemia should be corrected beforehand, as should hyponatraemia, hypokalaemia and hypercalcaemia. Treatment (radiotherapy, chemotherapy and/or stenting) for major airway obstruction, including upper airways stridor, should be complete before travel and sufficient time passed to enable the physician/oncologist to confirm stability. Patients with lymphangitis carcinomatosa or superior vena cava obstruction should only fly if essential, and must have in-flight oxygen available. Pleural effusions should be drained as much as possible before travel. Patients with major haemoptysis should not fly.<sup>2</sup>

## AIRBORNE INFECTIONS

Pre-flight assessment is advised for those with acute and chronic respiratory infections. Patients with infectious tuberculosis must not travel by public air transportation. World Health Organization guidelines state that 'physicians should inform all infectious and potentially infectious tuberculosis patients that they must not travel by air on any commercial flight of any duration until they are sputum smear-negative on at least two occasions'.<sup>2</sup>

## INTERSTITIAL LUNG DISEASE

Patients should be carefully assessed. Supplemental oxygen should be considered if travelling at high altitude destinations. Carrying an emergency supply of antibiotics and prednisolone is recommended and medical advice on their usage should be given in the case of an exacerbation.<sup>2,4</sup>

## NEUROMUSCULAR DISEASE AND CHEST WALL DISEASE

International guidelines recommend that all patients with conditions causing severe extra-pulmonary restriction, including those needing home ventilation, should undergo hypoxic challenge testing before travel, if available. The decision to recommend in-flight oxygen and/or non-invasive ventilation must be made on an individual clinical basis.<sup>2,4</sup>

## CYSTIC LUNG DISEASE

In addition to hyperinflation within communicating airways, at an altitude of 8,000 feet, Boyle's law predicts there will be a 38% increase in the size of closed air-filled pockets within the body.<sup>14</sup> This gas expansion may be associated with an increased risk of pneumothorax in patients with bullous or cystic lung disease. In patients with chronic lung disease who are already at risk of hypoxaemia, the development of a pneumothorax in-flight could

be a significant challenge. A previous history of pneumothorax may be more relevant in patients with lung disease, as rapid changes in barometric pressure may precipitate recurrence.<sup>4</sup>

### OBSTRUCTIVE SLEEP APNOEA SYNDROME

A doctor's letter is required outlining the diagnosis and necessary equipment, and patients should keep their CPAP machine in the cabin. Alcohol and sedatives should be avoided before and during travel.<sup>2</sup>

### PNEUMOTHORAX

Patients with a closed pneumothorax should not travel on commercial flights (with the exception of the very rare case of a loculated or chronic localised air collection which has been very carefully evaluated). Patients who have had a pneumothorax must have a chest X-ray (CXR) to confirm resolution before a flight, and flying is not advised for at least seven days after confirmation of resolution. For patients who have suffered a traumatic pneumothorax, the delay after full radiographic resolution should ideally be two weeks. Prognosis is good for those who opt for surgical intervention as a treatment measure. The risk of recurrence is higher in those with coexisting lung disease and does not fall significantly for at least one year.<sup>2,4</sup> Alternative forms of transport might be considered for other patients.

### THORACIC SURGERY

In patients who underwent thoracic surgery with drain insertion, chest radiography is required after drain removal to ensure full expansion of the lung. Patients who have a pneumothorax after drain removal should not travel on commercial flights until full re-expansion has been confirmed on CXR. If chest radiography after drain removal confirms full re-expansion, it is prudent to wait for seven days before air travel. Any symptoms or signs suggesting the possibility of a pneumothorax should prompt a further CXR before air travel.<sup>2,4</sup>

### GENERAL ADVICE

Advance planning is of utmost importance. Our patients must be advised to seek medical attention before flying. Patients should be advised to carry around a list of their prescription medication, including oxygen, and to take an adequate supply to last the whole trip. For patients who make use of portable oxygen concentrators, they must check in advance to see if the airline allows this and notify them accordingly. If needed, one should book extra services with the airline in advance, such as in-flight oxygen or wheelchairs, and check with the airline regarding the carriage of nebuliser machines, ventilators or CPAP machines. Travellers must also ensure that proper arrangements are made for travel insurance. The physician might also consider prescribing an emergency supply of antibiotics, with or without prednisolone, to be used as required by the patient, in case of an exacerbation whilst abroad.

### ADDITIONAL CONSIDERATIONS

When evaluating patients for air travel, it is important to highlight the following points:

1. Even at 35,000 feet, different types of commercial aircraft can have widely differing cabin altitudes, ranging from an equivalent of approximately 5,400 feet to 8,000 feet.<sup>15</sup> In addition, commercial aircraft may also vary their cruising altitude a number of times during the flight, which in turn can alter cabin pressure.<sup>15,16</sup>
2. Respiratory symptoms may occur despite having a pre-flight assessment. One study found 18% of patients with COPD developed respiratory symptoms despite having a pre-flight evaluation.<sup>17</sup>
3. Flight duration is another important factor to consider. Longer flight durations are associated with increased symptoms,<sup>6</sup> particularly when lasting over three hours.<sup>18</sup>
4. The levels of activity of the patient during the flight should also be considered. Patients with COPD, restrictive lung disease, and cystic fibrosis demonstrate significant worsening of hypoxaemia at simulated altitude with a workload equivalent to that of walking around the aircraft cabin.<sup>19-21</sup>

### CONCLUSION

Being diagnosed with a chronic lung condition does not mean that the patient can no longer travel but there are a number of limitations and implications. Patients must be advised to carefully plan their travel and to seek medical advice accordingly.

International guidelines recommend that hypoxic challenge testing should be considered for patients with chronic lung diseases, since such patients are at risk of developing significant hypoxaemia and complications during air travel. In the absence of its availability locally, medical professionals must ensure that such patients have their respiratory status optimised, following a thorough assessment with the help of available tools, and that expert advice is sought when deemed necessary.

### CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest. ❖

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## CARDIAC ARRHYTHMIAS

The American Heart Association defines cardiac arrhythmias as any change from the normal sequence of electrical impulses. Cardiac arrhythmias can be the result of either an abnormality of impulse formation [which can lead to impulses that are too fast, too slow or irregular] or else an abnormality in impulse conduction [which can lead to heart block].

During a normal cardiac cycle the electric impulse originates in the sino-atrial node (SA node), it then passes through the atria where it reaches the atrio-ventricular node (AV node) and is then conducted through the ventricles.

When there is a change in the formation of the electrical impulse, impulses may be formed in the SA node at a very fast or slow rate (sinus tachycardia and sinus bradycardia, respectively). Sometimes the electrical impulses start to originate from areas in the heart outside the SA node. This may either occur occasionally (such as in supraventricular ectopic or ventricular ectopic) or else, all electrical impulses start to originate from outside the SA node (atrial fibrillation or ventricular fibrillation). The former type usually results in impulses which follow the baseline sinus rhythm but which are



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too fast or too slow. On the other hand, the latter usually result in electrical impulses which arise in a very fast and irregular manner. The exceptions to this are junctional rhythm, which involves electrical impulses arising from the AV node at a very slow and regular rate, and supraventricular tachycardia, which involves electrical impulses arising from a site in the atria outside the SA node at a fast but regular rate.

When there is a change in electrical impulse conduction the result is heart block. Heart block can be classified as 1<sup>st</sup>, 2<sup>nd</sup> or 3<sup>rd</sup> degree. In 1<sup>st</sup> degree heart block there is a delay in the conduction of electrical impulse at the AV node. In 2<sup>nd</sup> degree heart block there is intermittent non-conduction of the electrical impulses at the AV node. In 3<sup>rd</sup> degree heart block none of the electrical impulses arising in the SA node are conducted through the AV node to the ventricles. Cardiac arrhythmias can usually be successfully managed with medication, discontinuing any causative drugs or else by inserting a pacemaker in the case of heart block. ❌





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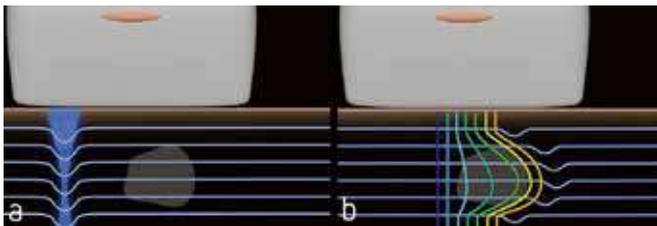
# ULTRASOUND SHEAR-WAVE ELASTOGRAPHY FOR MUSCULOSKELETAL INJURIES

PIERRE VASSALLO

**G**reyscale and Doppler Ultrasound (US) are well established as first line imaging methods for the evaluation of musculoskeletal (MSK) injuries, often providing information comparable with that of magnetic resonance imaging (MR). However, early or minor injuries are often not detected by US. Ultrasound Elastography is proving helpful for the detection of injuries that are not detected by greyscale US and for monitoring healing of MSK injuries.

US Elastography evaluates the elasticity of tissues, which changes in different tissue states. Inflammatory change, tears and even muscle contraction result in alterations of tissue elasticity that are detectable with US Elastography. There are several different US-related technologies that have been used to measure tissue elasticity. The two main methods that are found on many new ultrasound scanners are Compression Elastography and Shear-wave Elastography (SWE). However, the value of measuring tissue elasticity is hampered by its limited reproducibility. SWE has received most interest for the measurement of tissue elasticity because it appears to be the most reproducible technique.

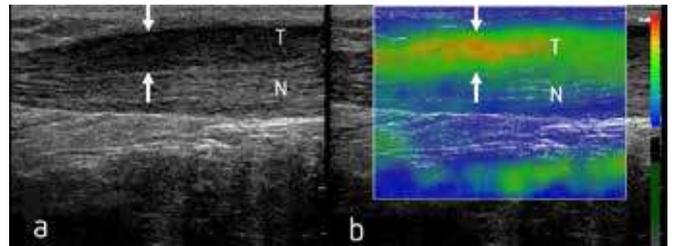
Review of recent scientific literature shows that SWE is useful for the assessment of many post-traumatic MSK conditions and to a lesser extent for inflammatory and neoplastic MSK lesions. It has been used to assess such conditions involving tendons, muscles, nerves and even ligaments. However, to date, SWE has been shown to be of greatest value in the assessment of tendons, followed by muscles and nerves.



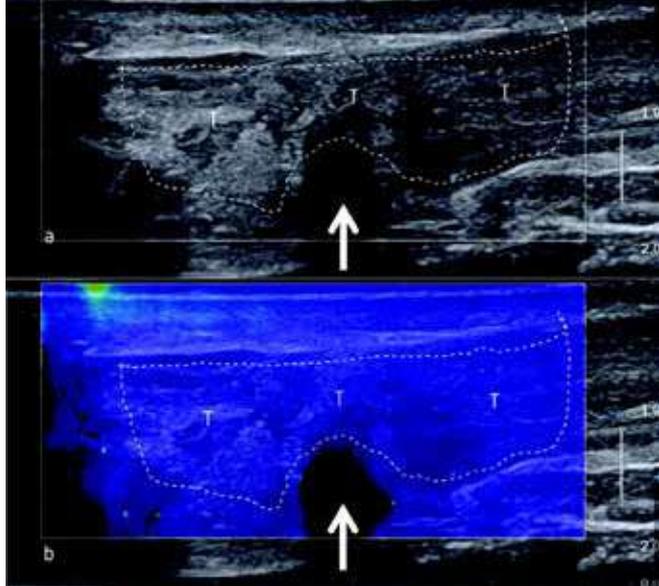
**Figure 1.** a. Diagram showing normal sound wave propagation as thin horizontal blue lines and shear wave generation as blue vertical band to the left. b. Note that shear wave travels horizontally through the tissues and causes shifts in the ultrasound waves that are dependent on tissue elasticity. These shifts are colour-coded to produce the elastographic image.

The physics behind US Elastography is complex and a detailed explanation of the physical principles is beyond the scope of this article. However, in oversimplified terms, it involves the generation of a compression or shear wave produced by manual compression or by the same crystals in the ultrasound probe that generate ultrasound waves. The compression or shear wave travels perpendicular to the ultrasound wave beam and generates tissue movements (Fig 1). In stiffer tissues, the compression/shear wave propagates faster, whereas in softer (more elastic) tissues the wave propagates more slowly. The speed of compression/shear wave transmission (or any other value derived from this variable) is displayed on a colour scale ranging from red through yellow and green to blue based on tissue stiffness measurements. Reference should always be made to the colour scale displayed at the side of the image display as different companies may code low tissue elasticity (stiff tissues) as blue and high elasticity as red, while others may code in a reversed manner.

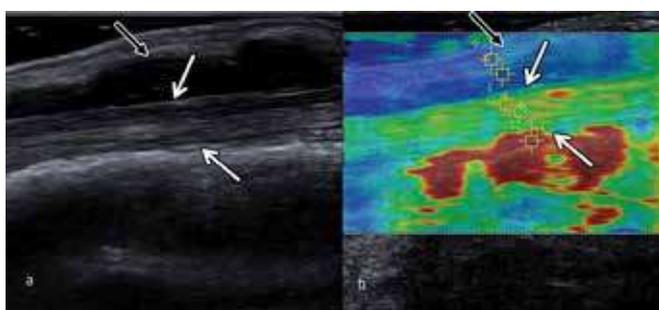
Tendons function as transmitters of tensile force from a muscle to its bony insertion during muscle contraction; they are therefore, by nature, stiff. Any increase in their elasticity would result in a decrease in the efficiency of muscle function. Healthy tendons therefore have high stiffness values on US Elastography. A decrease in elasticity seen in a damaged portion of the tendon will show a different colour on US Elastography (Fig 2). A complete tear in any portion of the tendon, where the gap is filled with fluid, would be depicted as showing no colour as there is no shear wave



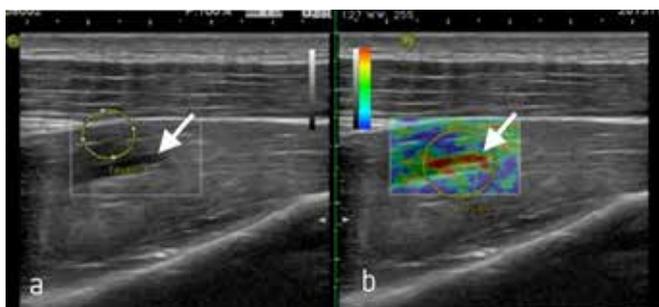
**Figure 2.** Grey scale (a) and compression elastographic (b) scans showing a longitudinal image of the Achilles' tendon. The intact deeper portion of the tendon shows a normal fibrillar more echogenic texture (N) and has coded blue on the compression elastographic scan (b). The partially torn superficial portion of the tendon (arrows) exhibits diminished echogenicity (T) compared with the intact deeper portion tendon with loss of the fibrillar pattern on grey scale US and shows evidence of increased elasticity coded as red and yellow on the compression elastographic scan.



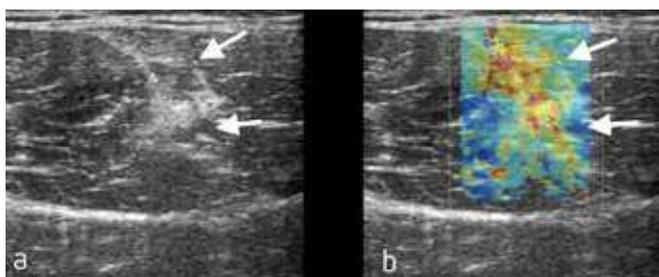
**Figure 3.** Grey scale (a) and SWE (b) scans depicting a longitudinal section through the Achilles' tendon. (a) The grey scale image shows a very heterogeneous echotexture in the Achilles' tendon (T) with loss of the fibrillar pattern indicating extensive tendon damage as well as an anechoic (fluid filled) area (arrow) that represents a complete tear at that site (arrow). (b) The SWE shows high elasticity throughout the damaged tendon coded blue with no colour in the complete tear (arrow).



**Figure 4.** Grey scale (a) and SWE (b) scans showing an extensor pollicis brevis tendon (between white arrows) that is thickened and demonstrates increased elasticity values (yellow and green) indicative of tendonitis and a thickened synovial sheath (black arrow) that exhibits higher elasticity values (blue).



**Figure 5.** Grey scale (a) and compression elastographic (b) images. a. demonstrates a tear at the musculo-tendonous junction in one of the forearm muscles (arrow). b. depicts increased elasticity at the site of the tear and in the surrounding muscle.



**Figure 6.** Grey scale (a) scan through a gastrocnemius muscle showing scar formation (arrows) at the site of an old tear. SWE scan (b) shows diminished tissue elasticity (red/yellow coding) within the scar, whilst normal adjacent muscle is blue.

transmission (Fig 3). Note that coding of elasticity in Figures 2 and 3 is reversed, with high elasticity shown as red in figure 2 and blue in figure 3; this is unfortunately due to lack of standardisation between machine vendors, but is also due to different coding methods between compression Elastography and SWE. It is important to refer to the colour scale displayed at the edge of the image to understand the significance of the colours displayed.

US Elastography is useful for assessing small tendon inflammation. Increased tendon elasticity and synovial hypertrophy with high elasticity values in the synovial sheath are features of tenosynovitis (Fig 4).

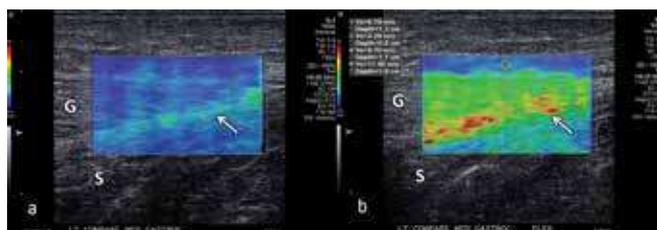
Muscle tears, which most commonly occur in the myo-tendonous and myofascial junctions, are readily seen on grey scale ultrasound; US Elastography adds information by depicting the size and severity of the damage since the degree of increased elasticity reflects the severity of the injury (Fig 5).

The age of a muscle tear can also be assessed with US Elastography. Fresh tears are soft and hence exhibit increased elasticity, whereas older tears (or scars) are harder than muscle and hence shows diminished elasticity (Fig 6).

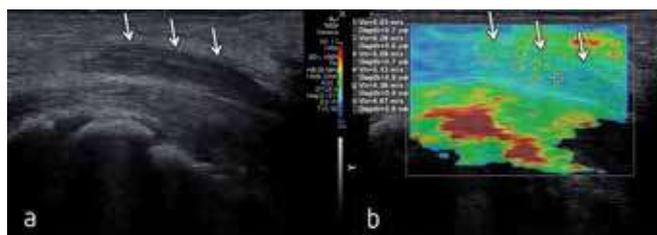
Contraction of muscles and tension in tendons results in a diminished elasticity and increased shear wave velocities (Fig 7).

US evaluation is useful in detecting peripheral neuropathy, however signs may be quite subtle and difficult to detect. Changes in cross-sectional shape (oval to round), thickening and altered echogenicity of the nerve are indicators of inflammatory disease. Normal nerves are of a relatively soft composition with high elasticity, while inflammatory disease results in decreased nerve elasticity (Fig 8).

US Elastography is a relatively recent additional tool that is showing promise for evaluation of the musculo-skeletal system. Further advances and standardisation of this technique as well as increasing scanning experience will contribute to its increased use for assessing musculo-skeletal trauma and inflammatory disease. ❄️



**Figure 7.** SWE scans of the gastrocnemius (G) and soleus (S) muscles with the intervening soleus fascia (arrow) displayed in longitudinal section in the relaxed (a) and contracted (b) states. Note that the elasticity is higher in the relaxed state of the muscles (blue) and fascia (blue/green) than in the contracted state with the muscles depicted green and the fascia shown in yellow/red.



**Figure 8.** Grey scale (a) and SWE (b) scans of an inflamed median nerve within the carpal tunnel. (a) The grey scale image shows focal thickening and diminished echogenicity (arrows) within a section of the nerve. (b) SWE evaluation demonstrates diminished elasticity (green/yellow) (arrows) within the thickened portion of the nerve.



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