Institution: University of South Wales

Unit of Assessment: C26

Title of case study:
Intermittent hypoxia and its impact on human health: on mountains, medals and medicine!

1. Summary of the impact

Brugniaux's applied research on intermittent hypoxia training (IHT) has been instrumental in informing the International Olympic Committee's (IOC) decision to endorse its use as a legal means of improving elite sports performance. From a clinical perspective, **Brugniaux** has developed a novel model of intermittent hypoxia that simulates the cycles of stop-start breathing observed in patients suffering from obstructive sleep apnoea (OSA) in whom vascular dysfunction and premature cardiovascular mortality occurs. Collectively, this research has improved our understanding of the mechanisms that underpin elite performance and provided unique insight into the link between breathing instability and pathophysiology of vascular disease.

2. Underpinning research

Exposure to hypoxia triggers a series of physiological responses, but can also result in maladaptation due to an intrinsic inability to cope with the stimulus. While (repeated) exposures to hypoxia have been used by athletes to improve sea-level aerobic performance for decades, emerging evidence suggests that it is a primary cause of the vascular dysfunction and premature mortality associated with clinical diseases including OSA.

One of the primary mechanisms underpinning adaptation to repeated exposures to hypoxia involves secretion of erythropoietin (Epo), which stimulates the production of new red blood cells eventually leading to an improvement in physical performance subsequent to improved oxygen delivery. However, despite this adaptation, exercise capacity is equally impaired in hypoxia, hindering the benefits of training carried out at altitude. As a consequence, more complex models of hypoxic training including the 'Live High–Train Low' (LHTL) paradigm have been developed. This consists of living in hypoxia in order to stimulate Epo, while training at sea level allows the athlete to maintain their "normal" training intensity. This model has grown in popularity amongst athletes though raised concerns with the IOC in terms of its legitimacy as an ergogenic aid. Grants awarded by the IOC and the French Ministry of Sport allowed **Brugniaux** to further optimise the efficacy and safety of the LHTL model (i) demonstrating for the first time in an elite population that it can improve aerobic, endurance-based performance (ii). More recently, **Brugniaux** has focused on the development of additional novel IHT paradigms that have been exploited by a number of World-Class endurance athletes optimising their preparation for the London 2012 Olympic Games and expeditionary members including Richard Parks (see 4).

OSA is a common sleep disorder characterised by recurrent episodes of complete or partial obstruction of the upper airway. These intermittent occlusions result in chronic intermittent hypoxia (CIH) that involves repeated episodes of arterial desaturation. Importantly, OSA patients are more prone to vascular disease. In an attempt to explore the independent role of hypoxia in the pathophysiology of this disease, **Brugniaux** developed a novel model of intermittent hypoxia that involved cycles of 2 minutes of hypoxia followed by 2 minutes of normoxia specifically designed to simulate the apnoeic phases associated with OSA. This study provided mechanistic insight into the ventilatory response to CIH highlighting the fundamental pathways that led to a systemic increase in Epo (iii) and free radical concentrations (iv) providing a metabolic basis to explain the increased ventilatory sensitivity and vascular impairment in hypoxia, supporting earlier research conducted by **Bailey** (v) . This model provided unique insight into the mechanisms underpinning the premature cardiovascular and cerebrovascular disease typically observed in OSA patients (vi).

3. References to the research

i. **Brugniaux, J.V.**, Schmitt, L., Robach, P., Jeanvoine, H., Zimmermann, H., Nicolet, G., Duvallet, A., Fouillot, J.P. and Richalet, J.P. (2006). Living high-training low: tolerance and acclimatization in

elite endurance athletes.
European Journal of Applied Physiology and Occupational Physiology 96:66-77.

ii. **Brugniaux, J.V.**, Schmitt, L., Robach, P., Nicolet, G., Fouillot, J.P., Moutereau, S., Lasne, F., Pialoux, V., Saas, P., Chorvot, M.C., Cornolo, J., Olsen, N.V. and Richalet, J.P. (2006). Eighteen days of "Living High - Training Low" stimulate erythropoiesis and enhance aerobic performance in elite middle-distance runners.
Journal of Applied Physiology 100:203-11.

iii. **Brugniaux, J.V.**, Pialoux, V., Foster, G.E., Duggan, C.T.C., Eliasziw, M., Hanly, P.J. and Poulin, M.J. (2011). Effects of intermittent hypoxia on erythropoietin, soluble erythropoietin receptor and ventilatory patterns in healthy humans.
European Respiratory Journal 37:880-887.

iv. Pialoux, V., Hanly, P.J., Foster, G.E., **Brugniaux, J.V.**, Beaudin, A.E., Hartmann, S.E., Pun, M., Duggan, C.T. and Poulin, M.J. (2009). Effects of exposure to intermittent hypoxia on oxidative stress and hypoxic ventilatory response in humans.
American Journal of Respiratory and Critical Care Medicine 180:1002-1009.

v. **Bailey, D.M.,** Davies, B. and Young, I.S. (2001). Intermittent hypoxic training: implications for lipid peroxidation induced by acute normoxic exercise in active men.
Clinical Science 101: 465-475.

vi. Foster, G.E., **Brugniaux, J.V.**, Pialoux, V., Duggan, D.T.D., Hanly, P.J., Ahmed, S.B. and Poulin, M.J. (2009). Cardiovascular and cerebrovascular responses to acute hypoxia following exposure to intermittent hypoxia in healthy humans.
Journal of Physiology 587:3287-3299.

4. Details of the impact

Sports performance impacts

The Sports Performance Group actively collaborate with the Welsh Institute of Sport in Cardiff and the London Altitude Centre (eg https://www.altitudecentre.com/about-us/partnerships/) and have been approached by elite sports teams including the GB Cycling Team (http://www.britishcycling.org.uk/gbcyclingteam) and individual elite athletes who have sought to improve sports performance by gaining a legal competitive age through improved vascular oxygen transport. These include one of Wales' most successful professional boxers, Nathan Cleverly (http://www.nathancleverly.co.uk/) ahead of his successful bid to become WBO Light Heavyweight Boxing World Champion. Endurance athletes that have also extensively taken advantage of the IHT facilities during their preparation for the London 2012 Olympic Games include Dame Sarah Storey DBE (http://www.teamstoreysport.com/sarah-storey.html), GB's most decorated female Paralympian in history having won 11 Gold, 8 Silver and 3 Bronze medals across an impressive 6 Paralympic Games and Helen Jenkins, Olympic triathlete and double world champion (http://helenjenkins.co.uk/). These athletes have confirmed that the Group's IHT programs informed by our scientific research, including work with hypoxic tents for home-based "sleep-high, train-low", was a critical component underpinning their successes in the Olympic Games.
IHT has also been employed by individuals engaged in high-profile mountaineering fund-raising expeditions to accelerate the acclimatisation process in an attempt to reduce altitude illness and improve summit success in the field. This has included the Brains SA Captains Climb that included retired captains of the Welsh Rugby Union and the Tenovus Kilimanjaro Challenge. The Group has also assisted with the British Explorer Richard Parks' preparations during his pioneering 7 month race that saw him summit the highest mountain on each of the world's continents and venture to The South and Geographical North Poles (737 Challenge; seven summits, three poles, seven months) for Marie Cure Cancer Care (http://www.737challenge.com/). Ongoing scientific support based on the Group's research expertise is also being provided to assist with his Project X Challenge which will see him attempt to record the fastest solo, unsupported and unassisted journey to the South Pole (http://www.richardparks.co.uk/).

Creativity impacts
Building on the research conducted by **Bailey** demonstrating that hypoxia causes free radical-mediated vascular dysfunction, **Brugniaux** has utilised intermittent hypoxia as a model to determine its functional impact in OSA. The impact of the development of this model is significant, inasmuch as providing a new tool to improve understanding of OSA to the scientific community. To assess the role of Epo and its specific soluble receptor (sEpoR) in the sensitivity to hypoxia, the Group further developed a novel enzyme-linked immunosorbent assay. In so doing, we were able to accurately detect circulating levels of sEpoR for the first time in healthy human plasma. This model and technique are now being utilised by several world-renowned groups.

Health and welfare impacts
Patients with OSA utilise almost double the healthcare resources compared with healthy controls and its prevalence is set to rise given the worldwide increase in obesity and ageing of the population. Despite a growing body of evidence linking OSA with cardiovascular morbidity and mortality, metabolic dysfunction and neurocognitive impairment, our understanding of the underlying pathophysiology remains unclear. The Group's research in this area has advanced understanding of the fundamental mechanisms involved in the development of cardiovascular and cerebrovascular disease in OSA patients. It has revealed two novel pathways involved in promoting breathing instability in OSA patients. Collectively, these findings have significant implications for the practitioner since they suggest that antioxidant therapy could reduce sensitivity to hypoxia and stabilise breathing. This approach could ultimately complement current therapy, ultimately improving a patient's quality of life.

Science communication impacts
Concerted attempts have been made to engage with the public to disseminate research findings and demonstrate how this has had a beneficial impact on sports performance. This has been particularly successful given the Group's specialist input into high-profile expeditions and work with Olympic athletes prior to the London 2012 Olympic games, reaching a global audience and raising awareness of the team's international expertise in high-altitude physiology and medicine.

5. Sources to corroborate the impact

i. Testimonial from an Olympic athlete
Testimonial (in the form of a signed letter) from an ex-Olympic triathlete and coach to a current World Champion triathlete, attesting to the performance-enhancing benefits of IHT (including the novel training paradigms based on the Group's research) during their preparation for the London 2012 Olympic Games (August 2013).

ii. Committee positions helping inform public policy and debate
Member of the French group for hypoxic training that informed the IOC decision not to place hypoxic training on the list of prohibited methods (2008-).

iii-ix. Dissemination activities
Reaching out to elite athletes:
Presentation to the US Olympic Training Center Colorado Springs, CO, USA entitled "Effect of living high–training low on aerobic performance in elite athletes" (June 2009).

Involved in the physiological preparation of Richard Parks' (past) 737 Challenge and (ongoing) "Project X" expedition (June 2010-).
http://www.737challenge.com/
http://www.richardparks.co.uk/

Reaching out to the lay public:
Presentation to Science Alliance Cymru entitled "It's all about oxygen!!! From air to the cell" (March 2012).
(http://www.britishscienceassociation.org/science-society/science-alliance-cymru)

Times Education Supplement: Finding gold in the grey matter (June 2012).
"Faster? Higher? Stronger? New research shows that 'exercise starts and ends in the brain'. Jo Knowsley investigates"
http://www.tes.co.uk/article.aspx?storycode=6257859

Swansea Science Café Public Science Communication ("Adventures with oxygen; a "radical" perspective"). October 2012.
http://www.swansea.ac.uk/science/swanseasciencecafe/
Learned Society of Wales and Royal Society of Chemistry invited Public Science Communication entitled "Life at the extremes; oxygen, the miracle molecule?" (March 2013)
http://learnedsocietywales.ac.uk/cy/node/450

Pushing the Olympic Limits (Summer Edition, June 2012)
"Glamorgan Professor Damian Bailey argues that the next generation of athletes will always be fitter and faster than the last".
http://profile.glam.ac.uk/media/files/documents/2012-07-11/TALENT_Spring_Summer_20121.pdf).

x. Broadcast citation
BBC Wales Tonight: Research helping World champion triathlete Helen Jenkins prepare for gold in the London 2012 Olympic Games (April 2012).
http://www.itv.com/wales/tri-athlete-helen-jenkins-2012-medal- hopes90777/