Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: We thank Gareth Davies (Freeman Hospital, Newcastle) for the collation, anonymization, and distribution of clinical data, and the renal services staff for provision of plasmapheresis and vascular access.

Timothy J. Wells, B.Biotech., Ph.D.
University of Birmingham
Birmingham, United Kingdom

John Davison, M.Res., M.Sc., R.G.N.
Freeman Hospital
Newcastle, United Kingdom

Emma Sheehan, B.Sc., M.Sc.
University of Birmingham
Birmingham, United Kingdom

Suren Kanagasundaram, M.B. Ch.B., M.D.
Gavin Spickett, M.A., B.M., B.Ch., L.L.M., D.Phil.
Freeman Hospital
Newcastle, United Kingdom

Calman A. MacLennan, B.A., B.M., B.Ch., D.Phil.
University of Oxford
Oxford, United Kingdom

Robert A. Stockley, M.B. Ch.B., M.D., D.Sc.
Queen Elizabeth Hospital
Birmingham, United Kingdom

Adam F. Cunningham, B.Sc., Ph.D.
Ian R. Henderson, B.Sc., Ph.D.
University of Birmingham
Birmingham, United Kingdom

Anthony De Soyza, M.B. Ch.B., M.D., Ph.D.
Freeman Hospital
Newcastle, United Kingdom
and
Newcastle University
Newcastle, United Kingdom

ORCID IDs: 0000-0001-9694-0846 (C.A.M.); 0000-0002-8566-0344 (A.D.S.).

References

1. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Non-CF Bronchiectasis Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;65:577.
2. Whitters D, Stockley R. Immunity and bacterial colonisation in bronchiectasis. *Thorax* 2012;67:1006–1013.
3. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ. Quality-of-life determinants in patients with clinically stable bronchiectasis. *Chest* 2005;128:739–745.
4. Bilton D. Update on non-cystic fibrosis bronchiectasis. *Curr Opin Pulm Med* 2008;14:595–599.
5. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, Poppelwell L, Salih W, Pesci A, Dupont LJ, *et al*. The bronchiectasis severity index: an international derivation and validation study. *Am J Respir Crit Care Med* 2014;189:576–585.
6. Wells TJ, Whitters D, Sevastsyanovich YR, Heath JN, Pravin J, Goodall M, Browning DF, O'Shea MK, Cranston A, De Soyza A, *et al*. Increased severity of respiratory infections associated with elevated anti-LPS IgG2 which inhibits serum bactericidal killing. *J Exp Med* 2014;211:1893–1904.
7. Mahr A, Chaigne-Delalande S, De Menthon M. Therapeutic plasma exchange in systemic vasculitis: an update on indications and results. *Curr Opin Rheumatol* 2012;24:261–266.
8. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol* 2003;120:574–596.
9. Geri G, Dadoun S, Bui T, Del Castillo Pinol N, Paternotte S, Dougados M, Gossec L. Risk of infections in bronchiectasis during disease-modifying treatment and biologics for rheumatic diseases. *BMC Infect Dis* 2011;11:304.

Copyright © 2017 by the American Thoracic Society

Prolonged Apnea Supported by High-Frequency Noninvasive Ventilation: A Pilot Study

To the Editor:

Respiratory movements cause motion artifacts during image acquisition of the thorax and upper abdomen, which limit the clinical use of magnetic resonance imaging in the visualization of lung parenchyma and thoracic vascular structures (1, 2), reduce the accuracy of positron emission tomography (3, 4), and increase the toxicity of radiation therapy, directly influencing the amount of normal tissue included in the irradiated volumes (5, 6).

Suppressing respiratory movements during imaging acquisition and radiation therapy may, therefore, improve image quality and reduce healthy tissue irradiation while maximizing radiation dose to the tumor. The suppression of thoracic movement has been previously obtained in invasively ventilated subjects under general anesthesia using high-frequency ventilation (HFV), which ensures oxygen delivery and carbon dioxide (CO_2) clearance (7–9).

We performed an interventional, crossover, randomized, open-label study, applying for the first time HFV using a noninvasive interface (HF-NIV) to obtain prolonged apnea (absence of thoracoabdominal respiratory movements) in 10 nonsedated healthy adults with normal spirometry and no known cardiopulmonary disease (median age, 30 yr; range, 26–56 yr; 6/10 men). The study was conducted in accordance with the Declaration of Helsinki and the local ethics committee (Protocol 225/14 CHUV-DO-PART).

HF-NIV was performed using a Monsoon III ventilator (Acutronic Medical Systems, Hirzel, Switzerland) and a noninvasive patient interface (Phasitron; Percussionaire, Sagle, ID). This setting allowed constant monitoring of airway pressures and the application of ventilation with an open airway, protecting against overpressure, and allowing the resumption of spontaneous breathing at any moment during HFV. Each participant performed three breath hold attempts after 1 minute of self-induced hyperventilation: a maximal spontaneous (unassisted) apnea and two HF-NIV–assisted attempts with respiratory rate (RR) of 250/min and 500/min, in a randomized sequence. The working pressure of the ventilator was set to obtain a lung volume between the end-inspiratory lung volume and the total lung capacity, and a mean airway pressure of 15 to 20 cm H_2O, adapted according to volunteers' comfort. To minimize the risk of barotraumas, the ventilator safety pressure relief valve was set at 40 cm H_2O. Inspired oxygen fraction was

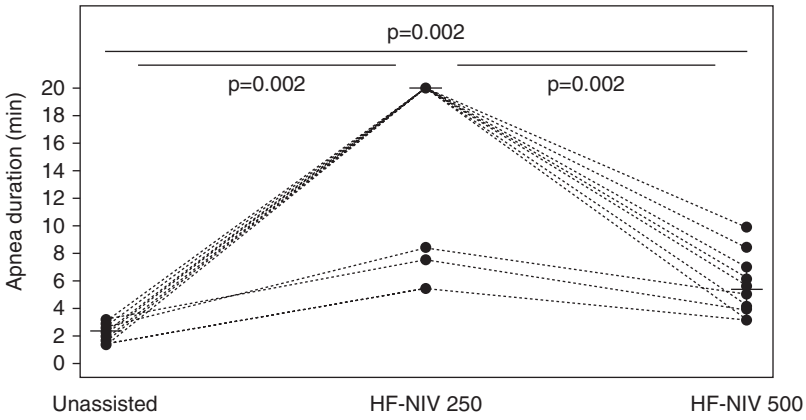

Figure 1. Apnea duration in the three test settings. Statistical analysis by paired Wilcoxon test; the *horizontal dashes* represent the median value. HF-NIV 250 = high-frequency noninvasive ventilation with respiratory rate at 250/min; HF-NIV 500 = high-frequency noninvasive ventilation with respiratory rate at 500/min; unassisted = maximal unassisted (spontaneous) apnea.

100%. The test was interrupted on resumption of spontaneous breathing or after 20 minutes of apnea. Chest and abdominal motion bands were applied to obtain respiratory inductive plethysmography, and a pneumotachograph and a pressure transducer were inserted in the ventilator circuit (Embla N7000; Embla Systems, Reykjavik, Iceland) to record ventilator's flow and pressure. Continuous transcutaneous capnography (Tc_{CO_2}) and oxygen saturation (Sp_{O_2}) were recorded using a Digital Monitoring System (SenTec, Therwil, Switzerland).

The duration of apnea was considered as the primary end point, defined as a reduction of the respiratory inductive plethysmography–derived flow (X flow) by 90% or more compared with spontaneous breathing. Artifacts secondary to swallowing movements, which briefly interrupt the ventilation delivery, were excluded from the analysis. We used paired Wilcoxon tests to compare measurements. The amplitude of the thoracic and abdominal movements during each test were assessed computing the coefficient of variation—defined as the ratio of the SD to the mean—of the values measured by the thoracoabdominal motion bands.

HF-NIV with an RR of 250/min resulted in a median apnea duration of 20:00 minutes (interquartile range [IQR], 11:16–20:00 min; in 7/10 participants the attempt was interrupted after 20:00 minutes according to the study protocol), which was significantly longer than the value obtained during unassisted apnea (median, 2:16 min; IQR, 1:41–2:45 min; $P = 0.002$) and using HF-NIV with RR 500/min (median, 5:16 min; IQR, 3:57–6:48 min; $P = 0.002$) (Figure 1). The efficacy of HF-NIV at 250/min was explained by an effective CO_2 clearance, with median Tc_{CO_2} at the end of the RR 250/min apnea trial being 0.8 mm Hg (IQR, −1.1 to 4.4 mm Hg) higher than the baseline value during spontaneous breathing ($P = 0.232$). In fact, the delivered tidal volume of HFV depends on the respiratory rate and was 54 ml (IQR, 52–57 ml) for the RR 250/min trial. Contrarily, the tidal volume was 26 ml (IQR, 26–27 ml) during the RR 500/min test, and Tc_{CO_2} increased by 6.2 mm Hg (IQR, 5.4–9.0 mm Hg; $P < 0.01$ compared with the baseline value during spontaneous breathing), leading to respiration resumption by the participant. Sp_{O_2} remained greater than or equal to 97% during all the HF-NIV tests. The very small tidal volumes resulted in a significant reduction of the thoracic and abdominal movements compared with spontaneous breathing (Figure 2).

In this pilot study, the application of HFV using a noninvasive interface allowed a significant prolongation of apnea time in

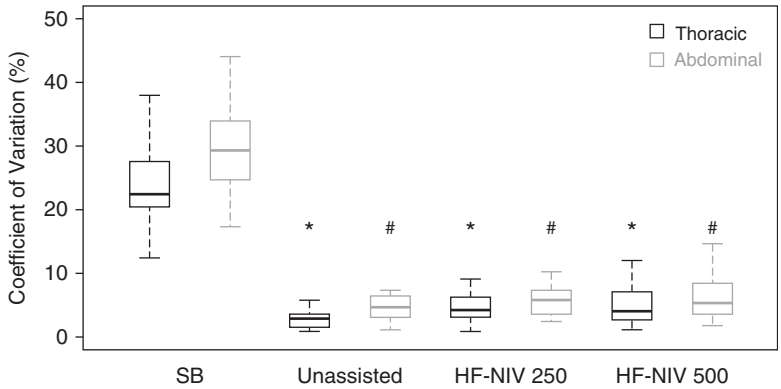

Figure 2. Thoracic and abdominal movements according to the test settings. *Boxes* represent the interquartile ranges, the *horizontal lines* inside the boxes represent the medians, and *whiskers* represent the 5th and 95th percentiles. $^{*}P < 0.01$ versus thoracic coefficient of variation during spontaneous breathing (SB) by paired Wilcoxon test; $^{\#}P < 0.01$ versus abdominal coefficient of variation during SB by paired Wilcoxon test. HF-NIV 250 = high-frequency noninvasive ventilation with respiratory rate at 250/min; HF-NIV 500 = high-frequency noninvasive ventilation with respiratory rate at 500/min; unassisted = maximal unassisted (spontaneous) apnea.

awake healthy subjects compared with spontaneous apnea, while preserving normal oxygen and carbon dioxide levels. The technique was safe and well tolerated by all the study participants, with dryness of the upper airways being the main reported discomfort.

This present work, a systematic efficacy and safety evaluation of the technique, enriches our group's experience showing some potential important clinical applications of HF-NIV in the fields of thoracic magnetic resonance imaging and radiotherapy (3, 5). The main finding is the relationship between P_{CO_2} control and apnea duration, both influenced by the set respiratory rate and the resulting tidal volume. According to the HFV characteristics, decreasing the RR resulted in an increase in tidal volume, which increased the efficiency of ventilation. In fact, HF-NIV with an RR of 250/min allowed us to obtain an apnea and a stable P_{CO_2} lasting 20 minutes in 7 of 10 participants, whereas the remaining 3 participants showed an increasing P_{CO_2} during the test and resumed spontaneous breathing after 5:26 to 8:22 minutes. We found no clinical characteristics allowing us to identify these subjects in advance. An individual titration of the RR would probably result in a better P_{CO_2} control, but this was not planned in our protocol.

Although very promising, our data should be considered as preliminary, because we selected healthy subjects in this pilot study. Furthermore, the use of HF-NIV is time consuming and needs a team experienced with the technique, although the participants did not require prior training to use the technique. The use of HF-NIV in patients suffering from lung diseases and its application during thoracic imaging and radiotherapy require further research.

In conclusion, we demonstrate the safety, feasibility, and good tolerability of HF-NIV to suppress respiratory motion in nonsedated subjects. This work represents the basis for subsequent studies, which should define its potential benefits in the different thoracic imaging and treatment application fields. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: We thank Jean-William Fitting and Kathleen Grant for their scientific support and constructive feedback.

Adam Ogna, M.D.
Maurizio Bernasconi, M.D.
Bastien Belmondo, Msc.P.T.
Olivier Long, Bs.P.T.
Julien Simons, Msc.P.T.
Nicolas Peguret, M.D.
Raphaël Heinzer, M.D.
Laurent P. Nicod, M.D.
Jean Bourhis, M.D.
Alban Lovis, M.D.
University Hospital of Lausanne (CHUV – Centre Hospitalier Universitaire Vaudois)
Lausanne, Switzerland

References

1. Ciet P, Serra G, Bertolo S, Spronk S, Ros M, Fraioli F, Quattrucci S, Assael MB, Catalano C, Pomerri F, *et al*. Assessment of CF lung disease using motion corrected PROPELLER MRI: a comparison with CT. *Eur Radiol* 2016;26:780–787.
2. Higano NS, Hahn AD, Tkach JA, Cao X, Walkup LL, Thomen RP, Merhar SL, Kingma PS, Fain SB, Woods JC. Retrospective respiratory self-gating and removal of bulk motion in pulmonary UTE MRI of neonates and adults. *Magn Reson Med* 2017;77:1284–1295.
3. Prior JO, Péguret N, Pomoni A, Pappon M, Zeverino M, Belmondo B, Lovis A, Ozsahin M, Vienne M, Bourhis J. Reduction of respiratory motion during PET/CT by pulsatile-flow ventilation: a first clinical evaluation. *J Nucl Med* 2016;57:416–419.
4. Dasari P, Johnson K, Dey J, Lindsay C, Shazeeb MS, Mukherjee JM, Zheng S, King MA. MRI investigation of the linkage between respiratory motion of the heart and markers on patient's abdomen and chest: implications for respiratory amplitude binning list-mode PET and SPECT studies. *IEEE Trans Nucl Sci* 2014;61:192–201.
5. Péguret N, Ozsahin M, Zeverino M, Belmondo B, Durham AD, Lovis A, Simons J, Long O, Duclos F, Prior J, *et al*. Apnea-like suppression of respiratory motion: first evaluation in radiotherapy. *Radiother Oncol* 2016;118:220–226.
6. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, Ewing M, Abdulrahman R, DesRosiers C, Williams M, *et al*. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24: 4833–4839.
7. Fritz P, Kraus HJ, Mühlnickel W, Sassmann V, Hering W, Strauch K. High-frequency jet ventilation for complete target immobilization and reduction of planning target volume in stereotactic high single-dose irradiation of stage I non-small cell lung cancer and lung metastases. *Int J Radiat Oncol Biol Phys* 2010;78:136–142.
8. Biro P, Spahn DR, Pfammatter T. High-frequency jet ventilation for minimizing breathing-related liver motion during percutaneous radiofrequency ablation of multiple hepatic tumours. *Br J Anaesth* 2009;102:650–653.
9. Denys A, Lachenal Y, Duran R, Chollet-Rivier M, Bize P. Use of high-frequency jet ventilation for percutaneous tumor ablation. *Cardiovasc Intervent Radiol* 2014;37:140–146.

Copyright © 2017 by the American Thoracic Society

Eucapnic Voluntary Hyperpnea Testing in Athletes

To the Editor:

The recent letter from Price and colleagues (1) reporting on their finding from a cross-sectional analysis of a cohort of asymptomatic athletes undergoing eucapnic voluntary hyperpnea (EVH) testing was of great interest. However, the authors' definition of their cohort as "healthy" may not be completely accurate. Despite acknowledging previous data on the lack of correlation between self-reported symptoms and objective testing, they chose to rely on symptoms as their gold standard for diagnosis of exercise-induced bronchoconstriction (EIB) to refute the positive EVH test (2). They provide no data on markers of inflammation or other mechanistic studies to support either the presence or absence of EIB in their population. Therefore, it is difficult to know if their cohort was in fact "healthy" or not (2). The study design also limits their interpretations, as there was no follow-up information after treatment of EVH-positive athletes who may underestimate their baseline symptoms or have other more subtle manifestations of EIB than classic cough and dyspnea. They claim a drop in EVH in athletes may be a "normative" airway response, which is not consistent with previously published cross-sectional data on negative EVH testing in athletes, which found only 4 of 144 positive EVH tests among a cohort of collegiate athletes, with many exhibiting bronchodilation (3). Their recommendation to interpret