Predictors of 1-year compliance with adaptive servoventilation in patients with heart failure and sleep disordered breathing: preliminary data from the ADVENT-HF trial

To the Editor:

Despite its effectiveness in suppressing sleep disordered breathing (SDB), positive airway pressure therapy (PAP) is not always well tolerated by patients and long-term adherence can be problematic. Recently, two multicentre, randomised clinical trials (RCTs) tested the effects of PAP for patients with cardiovascular disease and co-existing SDB on morbidity and mortality with negative outcomes [1, 2]. Relatively poor adherence to PAP therapy (mean 3.7 and 3.3 $h \cdot day^{-1}$, respectively) in these two trials might have contributed to their poor results. Indeed, higher PAP use per day is associated with better clinical outcomes than lower use [3].

The Effect of Adaptive Servo-ventilation on Survival and Cardiovascular Hospital Admissions in Patients with Heart Failure and Sleep Apnoea (ADVENT-HF) trial is a multinational RCT assessing the effects of treating SDB with peak flow targeted adaptive servoventilation (ASVpf) on morbidity and mortality in patients with heart failure and reduced ejection fraction (HFrEF) [4]. The purpose of this study was to determine the short- and long-term predictors of ASVpf adherence in an inception cohort of the ADVENT-HF trial. The trial has been registered (www.clinicaltrials.gov; NCT01128816), and its design, inclusion and exclusion criteria, and methods have been previously described [4].

The analysis included all patients from 38 sites randomised into the ASVpf treatment arm of the ADVENT-HF study before March 31, 2016, and for whom ASVpf adherence data were available at 1 and 12 months post-randomisation.

ASVpf compliance, defined as the average hours of use per day, was calculated for all patients and separately for the obstructive (OSA) and central sleep apnoea (CSA) groups. At 1 and 12 months, the percentage of patients compliant with ASVpf treatment, defined as use of >50% of the baseline total sleep time per day [4], and the percentage with good compliance, defined as use of $\geqslant 4$ $h \cdot day^{-1}$ were assessed. For patients who withdrew from the study or who discontinued using the device, hours of use were evaluated over the time during which the device was used and were imputed to be 0 h per night after discontinuation.

To define predictors of daily 1-month ASVpf use, univariable logistic regression was performed with the following as independent variables: age, body mass index, sex, presence of coronary artery disease, atrial fibrillation or flutter, country of site, baseline values of apnoea–hypopnoea index (AHI), Epworth Sleepiness Scale (ESS) score, sleep efficiency, arousal index, New York Heart Association class, N-terminal pro-B-type natriuretic peptide, left ventricular ejection fraction, Minnesota Living With Heart Failure Questionnaire scores, type of mask used, and leak at 1 month post-randomisation. A similar analysis was performed for daily 12-month ASVpf with the addition of the independent variables, daily hours of ASVpf use at 1 month, as well as AHI, ESS, type of mask and leak at 12 months post-randomisation. To define predictors of daily 12-month ASVpf use, a stepwise multiple regression analysis was performed.

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Adherence to sleep apnoea treatment is essential to evaluate trials involving cardiovascular end-points. In patients with heart failure and obstructive or central sleep apnoea in the ADVENT-HF trial, adherence to adaptive servoventilation was very good. http://ow.ly/5sNz30mDj2W

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Of 177 subjects randomised to ASVpf, compliance data were available in 136 (91 with OSA and 45 with CSA). Of the remainder, 27 did not attend the scheduled clinic visit and 14 either refused to participate or withdrew consent after randomisation. Characteristics of those with OSA and CSA were similar, except for a higher AHI among CSA patients (median (interquartile range) 37.4 (29.7) *versus* 50.8 (24.2) events per h, p=0.050).

ASVpf was effective in controlling both OSA and CSA. In those with predominantly OSA, while on ASVpf, the AHI decreased from mean±SD 42.7±19.8 at baseline to 3.9±2.7 events per h 1 month later and to 3.3±2.8 events per h 12 months later (p<0.01 for both). In those with predominantly CSA, while on ASVpf, the AHI decreased from 50.4±16.7 at baseline to 5.3±3.7 events per h 1 month later and to 3.9±2.5 events per h 12 months later (p<0.01 for both). This compares to a residual AHI of 6.6 events per h (mainly obstructive) 12 months post-randomisation on minute ventilation targeted adaptive servoventilation (ASVmv) in the SERVE-HF trial.

At 1 month, a nasal mask was used by 93 (68%) of patients: 60 (66%) with OSA and 33 (73%) with CSA. At 12 months, the use of a nasal mask did not change: 86 (63%) of patients, 57 (63%) with OSA and 29 (64%) with CSA. The remainder used a full-face mask.

By 1 month, of the 91 patients with OSA, only three (3%) had discontinued ASVpf, while among the 45 with CSA, only one (2%) patient had discontinued it. At 12 months, they increased to 18 (20%) and five (11%), respectively, or 23 (17%) for all patients. The percentage of patients compliant [4] at 1 month was 86% among OSA and 87% among CSA patients, and 12 months it was 67% and 80%, respectively. The median (interquartile range) daily use for all 136 subjects at 1 month was 4.7 (3.2) h and declined to 4.4 (4.3) h at 12 months (p<0.01). As shown in figure 1, daily ASVpf use declined from 4.6 to 4.1 h·day^{-1} in the OSA group, but remained stable at 5.2 h·day^{-1} in the CSA group.

Among patients with OSA, 56 (62%) and 48 (53%) used ASVpf ⩾4 h·day^{-1} at 1 and 12 months, respectively, while among patients with CSA, there were 30 (67%) and 27 (60%) at 1 and 12 months. No variable was a significant predictor of good compliance at 1 month. Hours of ASVpf use at 1 month was the only independent predictor of good ASVpf compliance at 12 months in the multivariate analysis of all patients (OR 2.02, 95% CI 1.58–2.60 (p<0.01)) and in the subgroups separately (for OSA: OR 1.94, 95% CI 1.27–2.78 (p<0.01); for CSA; OR 2.12, 95% CI 1.50–2.98 (p<0.01)).

Both short- and long-term ASVpf compliance were good in these patients with HFrEF and SDB enrolled in the ADVENT-HF trial.

The Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF) trial showed that ASVmv had no effect on the primary end-point, possibly due, in part, to low ASVmv compliance of 3.4 h·day^{-1} at 12 months and 3.7 h·day^{-1} over the entire 5-year trial period [5, 6]. Only 48% of patients used ASVmv ⩾4 h·day^{-1} over the trial period [2]. By contrast, ASVpf use in patients with CSA in the present study was higher in terms of hours of daily use and the proportion using it ⩾4 h·day^{-1}

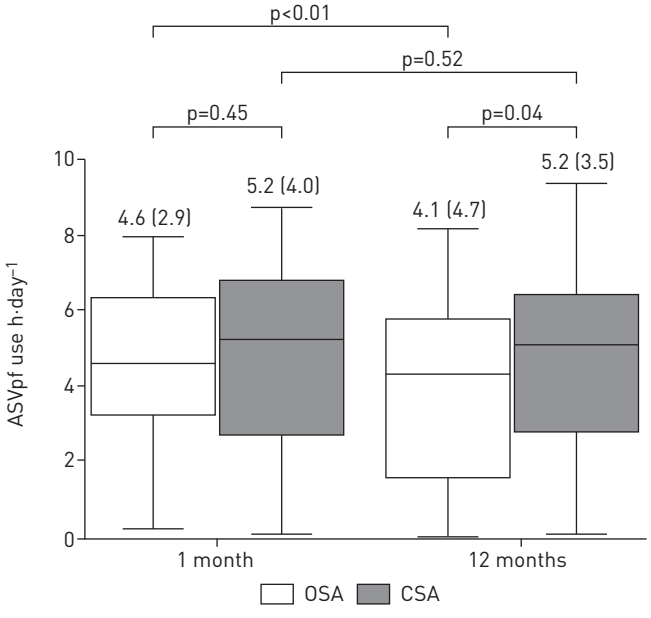

FIGURE 1 Daily hours of peak flow targeted adaptive servoventilation (ASVpf) use at 1 and 12 months among obstructive (OSA) and central sleep apnoea (CSA) groups. Data are presented as median (interquartile range). Hours of use remained unchanged from 1 to 12 months in the CSA group at 5.2 h, but hours of use declined significantly by 0.5 h from 1 to 12 months in the OSA group.

after 12 months, although the proportion of patients who discontinued ASVpf increased from 2% at 1 month to 11% at 12 months. Factors that might have contributed to better ASVpf compliance in the ADVENT-HF study include the technical characteristics of the ASVpf *versus* the ASVmv device used in SERVE-HF. ASVmv used relatively high default pressures with a minimum end-expiratory positive airway pressure (EPAP) of 5 cmH_2O and minimum inspiratory pressure support of 3 cmH_2O, whereas ASVpf in the present study used lower default pressures with a minimum EPAP of 4 cmH_2O and a minimum pressure support of 0 cmH_2O. These lower pressures might be better tolerated. In addition, unlike ASVmv that did not titrate EPAP to control obstructive events, ASVpf automatically titrates EPAP to control such events. This probably accounts for the lower residual AHI in patients on ASVpf, whether OSA or CSA, in the ADVENT-HF than in the SERVE-HF trial, where residual events were mainly obstructive. Centralised *versus* local interpretation of ASVpf titrations and prescription of ASVpf settings in ADVENT-HF *versus* SERVE-HF as well as more frequent interaction with patients due to semiannual *versus* annual follow-up visits in ADVENT-HF *versus* SERVE-HF may also have contributed to better ASVpf compliance. ASVpf compliance was also better in ADVENT-HF than ASVmv compliance in another recent RCT, in which daily use at 6 months was only 2.7 h [7].

Daily ASVpf use among patients with OSA in ADVENT-HF was also higher than continuous positive airway pressure (CPAP) use in the Sleep Apnea Cardiovascular Endpoints (SAVE) trial (3.5 $h \cdot day^{-1}$ 12 months post-randomisation) [1]. However, in contrast to patients with CSA, daily hours of ASVpf use among those with OSA declined at 12 months, in association with an increase in patients discontinuing ASVpf. The reason for the reduction in use over time was not clear. Once the trial is complete, it will be possible to assess outcomes data to determine if any of them are related to ASVpf compliance.

Recent RCTs testing CPAP therapy in nonsleepy OSA patients have demonstrated an absence of any effect on cardiovascular endpoints [1, 8, 9]. However, use of CPAP for >4 $h \cdot day^{-1}$ was associated with a reduction in the incidence of the primary end-point [8, 9]. Thus, there is a general tendency for PAP use of $\geqslant$4 $h \cdot day^{-1}$ to be associated with better outcomes. ASVpf has been shown to be more effective in suppressing OSA and CSA in patients with HFrEF than CPAP [5, 10, 11].

The only factor that independently predicted daily hours of good ASVpf compliance 12 months post-randomisation was hours of ASVpf use at 1 month. These findings are compatible with previous evidence, indicating that patients' initial experience with the treatment may influence their long-term compliance [12, 13].

Whether better adherence to ASVpf therapy in the present study than in previous studies of patients with cardiovascular diseases and SDB [1, 2, 7, 8] will be associated with better clinical outcomes will not be known until completion of the trial.

Elisa Perger[1,2], Owen D. Lyons[1,2,3], Toru Inami[1,2], Stephanie Smith[1], John S. Floras[4], Alexander G. Logan[4] and T. Douglas Bradley[1,2,4] for the ADVENT-HF Investigators[5]
[1]Sleep Research Laboratory of the University Health Network Toronto Rehabilitation Institute, Toronto, ON, Canada. [2]Centre for Sleep Medicine and Circadian Biology, Toronto, ON, Canada. [3]Dept of Medicine Women's College Hospital, Toronto, ON, Canada. [4]The University Health Network and Sinai Health System Dept of Medicine, Toronto, ON, Canada. [5]A complete list of trial personnel, trial sites and investigators can be found at the end of this article.

Correspondence: T. Douglas Bradley, University Health Network Toronto General Hospital, 9N-943, 200 Elizabeth Street, Toronto, ON, M5G 2C4, Canada. E-mail: douglas.bradley@utoronto.ca

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ADVENT-HF Trial Executive Committee: T.D. Bradley (Chair; Sleep Research Laboratory of the University Health Network Toronto Rehabilitation Institute, Centre for Sleep Medicine and Circadian Biology, and The University Health Network and Sinai Health System Dept of Medicine, Toronto, ON, Canada); J.S. Floras (Vice Chair; The University Health Network and Sinai Health System Dept of Medicine, Toronto, ON, Canada); A.G. Logan (Vice Chair; The University Health Network and Sinai Health System Dept of Medicine, Toronto, ON, Canada).

ADVENT-HF Steering Committee: T.D. Bradley (Chair); J.S. Floras (Member); A.G. Logan (Member); D.H. Delgado (Member; The University Health Network and Sinai Health System Dept of Medicine, Toronto, ON, Canada); R.J. Kimoff (Member; McGill University Health Center, Montreal, QC, Canada); M. Dunlap (Member; MetroHealth Medical Center, Cleveland, OH); G. Lorenzi-Filho (Member; Instituto do Coração do Hospital das Clínicas da FMUSP, Sao Paulo, Brazil); S. Redolfi (Member; AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Paris, France); G. Parati (Member; Istituto Auxologico Italiano - Ospedale San Luca, Milan, Italy); M. Arzt (Member; Universitätsklinikum Regensburg, Regensburg, Germany); J. Durán Cantolla (Member; Hospital Universitario Txagorritxu, Vitoria, Spain); T. Kasai (Member; Juntendo University School of Medicine, Tokyo, Japan).

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ADVENT-HF Investigators: T.D. Bradley, J.S. Floras, A.G. Logan, C.M. Ryan, D.H. Delgado, S. Mak and G. Tomlinson (University Health Network and Sinai Health System Dept of Medicine, Toronto, ON, Canada); R.S. Leung (St Michael's Hospital, Toronto, ON, Canada); D. Morrison (Capital District Health Authority, Halifax, NS, Canada); M. Fitzpatrick (Queen's University, Kingston, ON, Canada); P. Mayer (Hôpital Hôtel-Dieu du CHUM, Universite de Montreal, Montreal, QC, Canada); R.J. Kimoff (McGill University Health Center, Montreal, Canada); L. Mielniczuk and R. Beanlands (University of Ottawa Heart Institute, Ottawa, ON, Canada); F. Series (Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada); J.A. Fleetham and N. Ayas (Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada); C. Demers (Hamilton General Hospital, Hamilton, ON, Canda); A.C.P. Powles (St Joseph's Healthcare, McMaster University, Hamilton, ON, Canada); C. Rinne (St Mary's General Hospital, Kitchener, ON, Canada); E. Giannouli (St Boniface General Hospital, Winnipeg, MB, Canada); M. Povitz (London Health Sciences Centre, Victoria Hospital, London, ON, Canda); A. Dal Nogare (Glacier View Research Institute, Kalispell, MT, USA); M. Dunlap (MetroHealth Medical Center, Cleveland, OH, USA); M. Shanmugasundaram (Southern Arizona VA Health Care System, Tucson, AZ, USA); G. Lorenzi-Filho and L. Drager (Instituto do Coração do Hospital das Clínicas da FMUSP, Sao Paulo, Brazil); L.R. Bittencourt (Centro de Desenvolvimento em Estudos Clínicos Brasil, Sao Paulo, Brazil); C. Amodeo and A. Bertolami (Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil); R. P. Pedrosa (Pronto Socorro Cardiologico de Pernambuco, Recife, Brazil); M. Mayos Pérez (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); P. Lloberes Canadell (Hospital Universitari Vall d'Hebron, Barcelona, Spain); J.F. Masa Jimenez (Hospital San Pedro de Alcántara, Cáceres, Spain); F. Barbé (Hospital Arnau de Vilanova, Lleida, Spain); N.P. González Mangado (Fundación Jiménez Diaz-CAPIO, Madrid, Spain); F. Del Campo (Hospital Universitario Rio Hortega, Valladolid, Spain); J. Durán Cantolla (Hospital Universitario Txagorritxu, Vitoria, Spain); J.M. Marin Trigo (Hospital Universitario Miguel Servet, Zaragoza, Spain); M. González Martinez (Hospital Universitario Marqués de Valdecilla, Santander, Spain); M. Arzt (Universitätsklinikum Regensburg, Regensburg, Germany); W. Randerath (Wissenschaftliches Institut Bethanien e.V., Solingen, Spain); M.T. La Rovere (Istituti Clinici Scientifici Maugeri (ICS Maugeri), Istituto Scientifico di Montescano, Pavia, Italy); G. Parati (Istituto Auxologico Italiano, Ospedale San Luca, Milan, Italy); C. Tantucci (Ospedale "Spedali Civili" Di Brescia, Brescia, Italy); A. Braghiroli (ICS Maugeri, Istituto Scientifico di Veruno, Veruno, Italy); D. Raccagni (U.O. Cardiologia, ASST Franciacorta, Chiari, Italy); S. Redolfi (AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Paris, France); F. de Roquefeuil (AP-HP, Groupe Hospitalier Ambroise Paré, Boulogne-Billancourt, France); F. Goutorbe (Centre Hospitalier de Béziers, Béziers, France); P. Escourrou (AP-HP, Hôpital Antoine Béclère, Clamart, France); M-P. d'Ortho (AP-HP, Hôpital Bichat Claude Bernard, Paris, France); V. Puel (Nouvelle Clinique Bel Air, Bordeaux, France); R. Tamisier (Centre Hospitalier Universitaire de Grenoble, Grenoble, France); A. Williams (The Sleep Disorders Centre, Nuffield House, Guy's Hospital, London, UK); T. Kasai (Juntendo University School of Medicine, Tokyo, Japan); Y. Takata (Tokyo Medical University Hospital, Tokyo, Japan); K. Chin and K. Murase (Kyoto University Hospital, Kyoto, Japan); K. Narui and Y. Tomita (Toranomon Hospital, Tokyo, Japan).

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