resuscitation, which could impact patient outcome. Moreover, NUF rates are dynamic and vary depending on the clinical context. Thus, these results should be interpreted with caution. Attending physicians diagnosed fluid overload and also prescribed NUF rates, which were not protocol based. However, this reflects real-world practice. Finally, we calculated NUF rates as an average of total daily NUF, which normally has variation during therapy.

Conclusions. In patients undergoing CRRT, high NUF rates were associated with increased mortality compared with moderate NUF rates. This association appeared attenuated but not removed by the more negative DFB typically associated with higher NUF rate, especially in the setting of baseline fluid overload. These findings are hypothesis generating and provide preliminary support for the hypothesis that a negative mean DFB during CRRT might be safe when achieved with moderate rates of NUF. However, future randomized interventional trials are required to confirm these findings. ■

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

Thummaporn Naorungroj, M.D.
Mahidol University
Bangkok, Thailand
and
Austin Hospital
Melbourne, Victoria, Australia

Ary Serpa Neto, M.D., M.Sc., Ph.D.
Hospital Israelita Albert Einstein
São Paulo, Brazil
Amsterdam University Medical Center
Amsterdam, the Netherlands
Universidade de Sao Paulo
Sao Paulo, Brazil
and
Monash University
Melbourne, Victoria, Australia

Raghavan Murugan, M.D., M.S., F.R.C.P.
John A. Kellum, M.D.
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Rinaldo Bellomo, M.D., Ph.D.*
Austin Hospital
Melbourne, Victoria, Australia
and
The University of Melbourne
Melbourne, Victoria, Australia

*Corresponding author (e-mail: rinaldo.bellomo@austin.org.au).

References

1. Murugan R, Balakumar V, Kerti SJ, Priyanka P, Chang CH, Clermont G, *et al*. Net ultrafiltration intensity and mortality in critically ill patients with fluid overload. *Crit Care* 2018;22:223.
2. Murugan R, Kerti SJ, Chang CH, Gallagher M, Clermont G, Palevsky PM, *et al*. Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: a secondary analysis of the Randomized Evaluation of Normal vs Augmented Level (RENAL) of Renal Replacement Therapy trial. *JAMA Netw Open* 2019;2:e195418.
3. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, *et al*.; RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; 361:1627–1638.
4. Naorungroj T, Neto AS, Zwakman-Hessels L, Fumitaka Y, Eastwood G, Murugan R, *et al*. Mediators of the impact of hourly net ultrafiltration rate on mortality in critically ill patients receiving continuous renal replacement therapy. *Crit Care Med* 2020;48:e934–e942.
5. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009;4:914–920.
6. Slessarev M, Salerno F, Ball IM, McIntyre CW. Continuous renal replacement therapy is associated with acute cardiac stunning in critically ill patients. *Hemodial Int* 2019;23:325–332.
7. Roberts DM, Liu X, Roberts JA, Nair P, Cole L, Roberts MS, *et al*.; RENAL Replacement Therapy Study Investigators. A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics. *Crit Care* 2015;19:84.
8. Bellomo R, Ernest D, Parkin G, Boyce N. Clearance of vancomycin during continuous arteriovenous hemodiafiltration. *Crit Care Med* 1990;18:181–183.
9. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, *et al*.; RENAL Replacement Therapy Study Investigators. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. *Crit Care Med* 2012;40:1753–1760.

Does Heart Rate Play a Role in Cardiovascular Outcome in Patients with Obstructive Sleep Apnea?

To the Editor:

The effect of obstructive sleep apnea (OSA) on cardiovascular events in different acute coronary syndrome (ACS) subgroups were investigated by Zapater and colleagues (1) in a *post hoc* analysis of the ISAACC (Continuous Positive Airway Pressure in Patients with ACS and OSA) study, including 1,701 patients admitted for ACS. The cardiovascular risk subgroups were explored via the analysis of different cardiovascular (CV) risk phenotypes. In their study, the authors used unsupervised class analysis on categorized groups of 12 clinical factors commonly associated with CV risk (such as age, sex, lifestyle habits, comorbidities, and lipid levels). They identified two distinct CV risk phenotypes: "no-previous CV disease (CVD)" and "previous CVD." These distinct subgroups of patients with ACS differed mostly based on the prevalence of previous CVDs; hence, they are not necessarily distinct phenotypes, as there are not specific endotypes for such predisposition but rather the general risk of CVD. The word "phenotype" is the expression used in genetics for the composite recognizable characteristics or traits of an organism. The different clinical and pathophysiological backgrounds explain the apparent different effects of OSA in the two conditions of risk-stratified CV groups. The main findings of the study indicate a significant effect of moderate–severe OSA on the risk of

Supported by the U.S. Department of Veterans Affairs Office of Research and Development RX002885, Department of Defense SC150201, NIH/National Institute of Neurological Disorders and Stroke Award HL130552, and Blue Cross Blue Shield Foundation (to A.S.).

Originally Published in Press as DOI: 10.1164/rccm.202012-4536LE on February 19, 2021

recurrent CV events observed only in patients in the "no-previous CVD" subgroup with an adjusted hazard ratio (HR) of 1.54 (95% confidence interval [CI], 1.06–2.24). On the contrary, this effect was not observed in patients in the "previous CVD" subgroup (adjusted HR, 0.69; 95% CI, 0.46–1.04). The study reported data on medications that were taken by the two subgroups, namely, lipid-lowering agent, oral antidiabetic medication, insulin, and antiplatelet agents. However, there was no data reported on chronotropic medications (e.g., β-blocker or calcium channel blocker) (2), which may not only affect resting heart rate during wake and sleep but also dampen the autonomic response to respiratory events (3). A secondary analysis from the WSCS (Wisconsin Sleep Cohort Study), consisting of 569 participants with no previous CVD at baseline, were followed up to 15 years (4). Nocturnal total R-R interval dips index (RRDI) was associated with the composite CVD events (HR, 1.24 per 10-unit increment in RRDI [95% CI, 1.10–1.39]; $P < 0.001$). After adjusting for demographic factors (age, sex, and body mass index) and apnea–hypopnea index (4%), individuals with the highest total nocturnal RRDI category (≥28 vs. <15 dips/h) had a significant HR for the increased incidence of CVD and mortality of 7.4 (95% CI, 1.97–27.7; $P = 0.003$). Sleep RRDI was significantly associated with new-onset CVD events, which remained significant after adjusting for demographic factors, apnea–hypopnea index 4%, hypoxemia, and other comorbidities. The mechanism of increased incidence of CVD and association with RRDI can be explained by an increased sympathetic tone and associated endothelial dysfunction from the augmented shear forces (5). Such pathophysiologic changes in patients with OSA have been linked to nocturnal angina, myocyte necrosis leading to cardiomyopathy, and cardiac remodeling (6).

In conclusion, the authors should be praised for their efforts because their results surely expand our understanding of the effect of OSA on CVD. Nonetheless, careful use of predictors for adverse cardiovascular outcomes between subgroups of patients with OSA and the heart rate effect should be considered in future reports. ■

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

Abdulghani Sankari, M.D., Ph.D.,*
Wayne State University
Detroit, Michigan
John D Dingell VA Medical Center
Detroit, Michigan
and
Ascension Providence Hospital
Southfield, Michigan

ORCID ID: 0000-0002-2400-3375 (A.S.).

*Corresponding author (e-mail: asankari@wayne.edu).

References

1. Zapater A, Sánchez-de-la-Torre M, Benítez ID, Targa A, Bertran S, Torres G, *et al*.; Spanish Sleep Network. The effect of sleep apnea on cardiovascular events in different acute coronary syndrome phenotypes. *Am J Respir Crit Care Med* 2020;202: 1698–1706.
2. Wolf J, Drozdowski J, Czechowicz K, Winklewski PJ, Jassem E, Kara T, *et al*. Effect of beta-blocker therapy on heart rate response in patients with hypertension and newly diagnosed untreated obstructive sleep apnea syndrome. *Int J Cardiol* 2016;202: 67–72.
3. Sankari A, Pranathiageswaran S, Maresh S, Hosni AM, Badr MS. Characteristics and consequences of non-apneic respiratory events during sleep. *Sleep* 2017;4:zsw024.
4. Sankari A, Ravelo LA, Maresh S, Aljundi N, Alsabri B, Fawaz S, *et al*. Longitudinal effect of nocturnal R-R intervals changes on cardiovascular outcome in a community-based cohort. *BMJ Open* 2019;9:e030559.
5. Fisher AB, Chien S, Barakat AI, Nerem RM. Endothelial cellular response to altered shear stress. *Am J Physiol Lung Cell Mol Physiol* 2001;281: L529–L533.
6. Dincer HE, O'Neill W. Deleterious effects of sleep-disordered breathing on the heart and vascular system. *Respiration* 2006;73: 124–130.

Reply to Sankari

From the Authors:

We would like to thank Dr. Sankari for his interest in our article (1). In response to his comment on our study, we would like to present detailed information about the medications in the two groups of patients based on the phenotypes analyzed, which included some specific chronotropic drugs. As expected, the percentage of patients treated in the no previous cardiovascular disease (CVD) group was reduced compared with that in the previous CVD group (Table 1). This difference could at least partially justify the finding that in the group of previous patients with CVD, we were not able to observe an increase in the recurrence of cardiovascular events in those patients with obstructive sleep apnea (OSA).

From the initial observation of this ancillary study (1) from the Impact of Sleep Apnea Syndrome on the ISAACC (Continuous Positive Airway Pressure in Patients with Acute Coronary Syndrome [ACS] and OSA) trial (2), future studies should be performed to explore not only the mechanism associated with an increased risk in the recurrence of cardiovascular events and the role of OSA but also the potential therapeutic effect of OSA treatment in this specific profile of patients with no previous CVD in whom OSA would induce a deleterious cardiovascular effect. ■

Supported by ISCIII grants 10/02763, 10/02745, and 18/00449; FEDER "Una manera de hacer Europa"; SEPAR, Catalonian Cardiology Society; ResMed Ltd., Australia; Esteve-Teijin, Spain; Oxigen Salud, Spain; and ALLER, Centro de Investigación Biomédica en Red de Enfermedades Respiratorias.

Originally Published in Press as DOI: 10.1164/rccm.202101-0188LE on February 19, 2021