proliferative and calcified vascular lesions in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2016;194: 1273–1285.
4. Kristanto W, van Ooijen PMA, Groen JM, Vliegenthart R, Oudkerk M. Small calcified coronary atherosclerotic plaque simulation model: minimal size and attenuation detectable by 64-MDCT and microCT. *Int J Cardiovasc Imaging* 2012;28:843–853.
5. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832.
6. Tanguay VF, Ruffenach G, Chabot S, Montani D, Bonnet S, Boucherat O, *et al*. Calcified lesions on computed tomography and their clinical impact in pulmonary arterial hypertension [abstract]. *Am J Respir Crit Care Med* 2016;193:A7323.
7. Grams AE, Rehwald R, Schmittnägel C, Schmidt T, Tanislav C, Berghoff M, *et al*. Factors influencing intracranial vessel densities on unenhanced computed tomography: differences between hemispheres. *Clin Imaging* 2016;40:1081–1085.
8. Meloche J, Lampron MC, Nadeau V, Maltais M, Potus F, Lambert C, *et al*. Implication of inflammation and epigenetic readers in coronary artery remodeling in patients with pulmonary arterial hypertension. *Arterioscler Thromb Vasc Biol* 2017;37: 1513–1523.
9. Rajaram S, Swift AJ, Condliffe R, Johns C, Elliot CA, Hill C, *et al*. CT features of pulmonary arterial hypertension and its major subtypes: a systematic CT evaluation of 292 patients from the ASPIRE registry. *Thorax* 2015;70:382–387.
10. Abdul-Salam VB, Wharton J, Cupitt J, Berryman M, Edwards RJ, Wilkins MR. Proteomic analysis of lung tissues from patients with pulmonary arterial hypertension. *Circulation* 2010;122: 2058–2067.

Mediation Analysis of High Blood Pressure Targets, Arrhythmias, and Shock Mortality

To the Editor:

Associations between new arrhythmias and the risk of death during a critical illness are well described (1, 2). However, whether arrhythmias during a critical illness are markers of more severe disease or lie on pathways that mediate increased mortality risks is unclear. Results from two randomized trials suggested that the use of higher blood pressure targets during shock increased the risks for arrhythmias and, in patients requiring more than 6 hours of vasopressors before trial enrollment, mortality (3–5). We analyzed data from these randomized trials to evaluate the role of new arrhythmias in pathways linking higher blood pressure targets to poor outcomes during shock.

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Methods

We performed a secondary analysis of individual patient-level data from two randomized controlled trials: SEPSISPAM (Assessment of Two Levels of Arterial Pressure on Survival in Patients with Septic Shock) (5) and OVATION (Optimal Vasopressor Titration) (6). Details of the source trial methods can be found in the original publications (6, 7). Briefly, adult patients with vasodilatory shock (OVATION) or septic shock (SEPSISPAM) were randomized to vasopressors titrated to achieve either higher (mean arterial pressure 75–85 mm Hg) or lower (mean arterial pressure 60–70 mm Hg) blood pressure targets. Each trial recorded postrandomization ventricular and supraventricular arrhythmias as adverse events.

Pathways that link interventions with outcomes may be explored through mediation and moderation analyses. Mediation quantifies the extent to which hypothesized pathways may explain the effect of an intervention on an outcome. Moderation (i.e., interaction) analyses evaluate the extent to which a variable modifies the effect of an intervention on an outcome without representing an intermediate step on the causal pathway. We used Proc Causalmed in SAS 9.4 T1M5 (7) to quantify mediation and interaction by new tachyarrhythmias within previously described associations between higher (versus lower) blood pressure targets and the outcome of persistent organ dysfunction or death at Day 28 (4). Aspects of mediation and interaction that are most relevant for evaluating the potential benefits of a therapeutic intervention include *1*) the controlled direct effect (i.e., the component of the effect of higher blood pressure targets not due to mediation or interaction with arrhythmia) and *2*) the "portion eliminated"—a composite of mediation and interaction effects that represents the theoretical proportion of adverse outcomes that could be eliminated if the proposed mediator (new-onset tachyarrhythmias) were prevented (8). Models were adjusted for potential confounders between the mediator and outcome using a propensity score for arrhythmia onset calculated from age, sex, medical or surgical admission, predicted probability of mortality (from Simplified Acute Physiology Score II or Acute Physiology and Chronic Health Evaluation II), Day 1 total vasopressor dose, comorbid hypertension, heart failure, coronary artery disease, arrhythmia history, and trial, using a random effect for study center. The primary analysis was conducted among patients who were enrolled after 6 or more hours of shock, in whom higher blood pressure targets were associated with higher risks of death (4). Sensitivity analyses evaluated patients who were enrolled within 6 hours of shock, and supraventricular and ventricular arrhythmias were considered separately.

Results

Among 894 patients across two randomized trials of blood pressure targets during septic shock (5), 122 (14%) had more than 6 hours of shock before enrollment and were included in the primary analysis. Figure 1 shows the observed outcomes in the proposed pathways between high blood pressure targets (intervention), new tachyarrhythmias (proposed mediator), and persistent organ dysfunction or death by Day 28 (outcome). Compared with lower blood pressure targets, higher targets were associated with increased risk for persistent organ dysfunction or death (odds ratio [OR], 2.49 [95% confidence interval (CI), 1.17–5.31], $P = 0.02$), and a numerically higher risk of new arrhythmia (OR, 2.36 [95% CI,

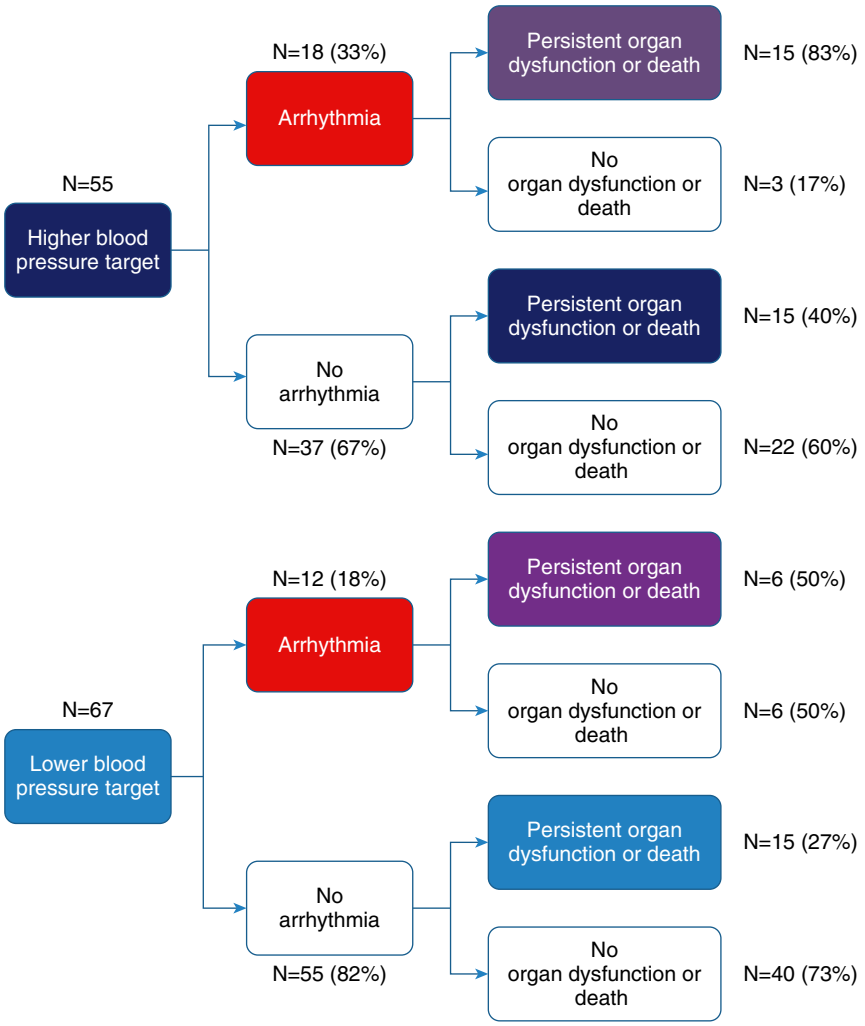

Figure 1. Outcome distributions in the proposed pathways among higher blood pressure targets, arrhythmia, and persistent organ dysfunction or death.

0.97–5.72], $P = 0.06$). New arrhythmias were also associated with increased risk of the primary outcome of persistent organ dysfunction or death at Day 28 (OR, 4.69 [95% CI, 1.83–12.0], $P = 0.001$). Analysis stratified by presence of arrhythmia suggested an interaction between arrhythmia onset and higher blood pressure targets for persistent organ dysfunction or death by Day 28 (OR, 1.75 [95% CI, 0.72–4.28] among patients without arrhythmia; OR, 4.5 [95% CI, 0.78–26] among patients with arrhythmia).

Results of the mediation analysis are shown in Figure 2. Approximately 79% (95% CI, 37–121%) of the observed effects of higher blood pressure targets on persistent organ dysfunction or death were due to either mediation by or interaction with arrhythmias (i.e., the "portion eliminated"), whereas controlled direct effects of higher blood pressure targets accounted for 21% (95% CI, −21% to 63%). Sensitivity analyses showed a "portion eliminated" for supraventricular arrhythmias of 68% (95% CI, 14–121%); however, ventricular arrhythmia models were not estimable because there were only four recorded ventricular events. Among patients who were randomized before 6 hours of shock, in whom higher blood pressure targets were not associated with primary outcome (OR, 0.90 [95% CI, 0.70–1.16]), the portion eliminated for arrhythmias was 5% (95% CI, −140% to 150%).

Discussion

We explored the potential role of arrhythmias in mediating associations between higher blood pressure targets and persistent organ dysfunction or mortality among patients with shock. Our findings suggest that arrhythmias have a complex role in pathways linking higher blood pressure targets to poor outcomes, acting to both mediate and potentiate the downstream effects of higher blood pressure targets. The mechanisms of mediation of poor outcomes by arrhythmias are mostly speculative. One possible mechanism that is supported by temporal associations between supraventricular arrhythmia onset and hemodynamic worsening is higher vasopressor doses triggering arrhythmias, which then lead to reduced diastolic filling, cardiac output, and perfusion (9). Mechanisms by which arrhythmias may interact with higher blood pressure targets are less clear and require further study, but potentially involve synergistic potentiation of diastolic dysfunction

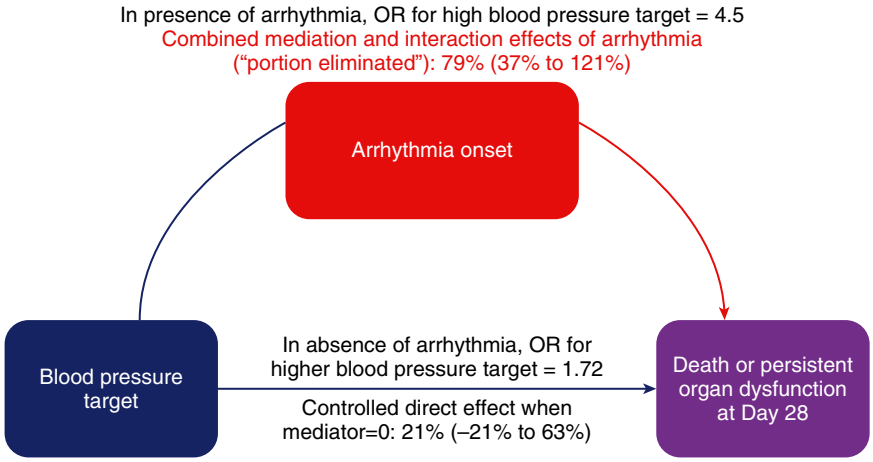

Figure 2. Results of analyses assessing proposed pathways between higher blood pressure targets and persistent organ dysfunction or death that account for effects of arrhythmia through mediation and interaction. Arrhythmias were estimated to account for 79% (95% confidence interval, 37–121%) of the observed effects of higher blood pressure targets on persistent organ dysfunction or death could be decomposed into *1*) controlled direct effects 21% (−21% to 63%)—the component not due to mediation by or interaction with arrhythmias, i.e., setting arrhythmia to 0; *2*) reference interaction 37% (0.92% to 74%)—the component due to interaction, but not mediation, with arrhythmias; *3*) mediated interaction 35% (−0.3% to 70%)—the component due to both mediation by and interaction with arrhythmias; and *4*) pure indirect effects 7% (−11% to 24%)—the component due to mediation through arrhythmia alone. OR = odds ratio.

or ventriculoarterial uncoupling (10). Our findings should be considered in light of the limitations of a small sample size, low statistical power, lack of differentiation between arrhythmias (e.g., atrial fibrillation vs. other supraventricular arrhythmias), and evaluation of secondary subgroup analyses of randomized trials. The validity of our results is based on assumptions that associations between higher blood pressure targets, arrhythmias, and persistent organ dysfunction or mortality are not affected by unmeasured confounders. Thus, our results should be considered exploratory and hypothesis generating, but they support the concept that new supraventricular arrhythmias may play both direct and indirect roles in pathways that lead to poor patient outcomes during shock. Future trials are needed to test the hypothesis that prevention or improved treatment of supraventricular arrhythmias during critical illness (e.g., through alternative vasopressor strategies or β blockade) may positively impact patient outcomes. ■

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References

1. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011;306:2248–2254.
2. Shaver CM, Chen W, Janz DR, May AK, Darbar D, Bernard GR, *et al*. Atrial fibrillation is an independent predictor of mortality in critically ill patients. *Crit Care Med* 2015;43:2104–2111.
3. McIntyre WF, Um KJ, Alhazzani W, Lengyel AP, Hajjar L, Gordon AC, *et al*. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: a systematic review and meta-analysis. *JAMA* 2018;319:1889–1900.
4. Lamontagne F, Day AG, Meade MO, Cook DJ, Guyatt GH, Hylands M, *et al*. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. *Intensive Care Med* 2018;44:12–21.

5. Asfar P, Meziani F, Hamel J-F, Grelon F, Megarbane B, Anguel N, *et al*.; SEPSISPAM Investigators. High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014;370:1583–1593.
6. Lamontagne F, Meade MO, Hébert PC, Asfar P, Lauzier F, Seely AJE, *et al*.; Canadian Critical Care Trials Group. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med* 2016;42:542–550.
7. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology* 2014;25:749–761.
8. VanderWeele TJ. Policy-relevant proportions for direct effects. *Epidemiology* 2013;24:175–176.
9. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L; Canadian Critical Care Trials Group. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. *J Crit Care* 2012;27:326.e1–326.e8.
10. Guarracino F, Ferro B, Morelli A, Bertini P, Baldassarri R, Pinsky MR. Ventriculoarterial decoupling in human septic shock. *Crit Care* 2014;18:R80.

Acute and Chronic Effects of Cigarette Smoking on sRAGE

To the Editor:

I read the article by Pouwels and colleagues with great interest (1). To the best of my knowledge, the authors for the first time have explored the acute effect of cigarette smoking on the serum levels of sRAGE (soluble receptor for advanced glycation end products). They elegantly showed a significant reduction of serum sRAGE levels in subjects who smoked three cigarettes within 1 hour. This effect was shown in patients with chronic obstructive pulmonary disease as well as in young and old healthy control subjects without airway obstruction. Based on a time-course study using three healthy subjects, the authors claimed that the maximum decline of serum sRAGE levels occurred after approximately 8 hours of cigarette smoking, which was not fully restored after 48 hours. In fact, the data presented in Figure 2B in Reference 1 demonstrate that the serum sRAGE values remained persistently low after 48 hours and were almost similar to the maximum decline values observed after 8 hours of cigarette smoking. The latter finding suggests that active smokers who regularly smoke several cigarettes per day should have lower serum levels of sRAGE than never smokers. However, Pouwels and colleagues did not observe any difference in sRAGE values between active smokers and never smokers (data not shown). To support this finding, the authors cited previous studies that also found no difference in sRAGE levels between smokers and nonsmokers, and stated that recent smoking within the smokers group may be the reason why some studies found decreased serum sRAGE levels in smokers (1). Unfortunately, Pouwels and colleagues did not cite our study in which we found elevated serum sRAGE levels in otherwise healthy, nondiabetic cigarette smokers (2).

Cigarette smoke is known to increase the formation of AGEs and the expression of RAGE (3, 4). However, the effect of cigarette smoking on sRAGE is inconsistent across the literature. Decreased, elevated, and unchanged levels of sRAGE were found in different studies, as reviewed by Prasad and colleagues (5). However, most of those studies, as I explained previously (6), were not specifically designed to explore the effect of smoking on sRAGE and thus were confounded by the presence of other diseases or conditions that affect sRAGE levels. Therefore, in our study, we specifically aimed to compare sRAGE levels between cigarette smokers and nonsmokers, controlling for the majority of confounding variables (2). In that study, we showed for the first time a significant elevation of sRAGE in cigarette smokers, a strong correlation between sRAGE and the number of cigarettes smoked per day, and an independent association of sRAGE with smoking habit (2). Although the exact mechanism of this apparently surprising finding is not yet known, we proposed a number of scientifically valid explanations (2, 6). Now, Pouwels and colleagues have identified the acute effect of cigarette smoking on sRAGE, which is the opposite of the chronic effect of smoking previously identified by our group (2). Therefore, further studies are required to explore the true effect of cigarette smoking on serum sRAGE levels and to explain the discrepancy among these studies. These issues need to be resolved before we can consider sRAGE as a biomarker for inflammatory conditions or as a protective factor against AGEs and other RAGE ligands. ■

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References

1. Pouwels SD, Klont F, Kwiatkowski M, Wiersma VR, Faiz A, van den Berge M, *et al*. Cigarette smoking acutely decreases serum levels of the chronic obstructive pulmonary disease biomarker sRAGE. *Am J Respir Crit Care Med* 2018;198:1456–1458.
2. Biswas SK, Mudi SR, Mollah FH, Bierhaus A, Arslan MI. Serum soluble receptor for advanced glycation end products (sRAGE) is independently associated with cigarette smoking in non-diabetic healthy subjects. *Diab Vasc Dis Res* 2013;10:380–382.
3. Cerami C, Founds H, Nicholl I, Mitsuhashi T, Giordano D, Vanpatten S, *et al*. Tobacco smoke is a source of toxic reactive glycation products. *Proc Natl Acad Sci USA* 1997;94:13915–13920.
4. Reynolds PR, Kasteler SD, Cosio MG, Sturrock A, Huecksteadt T, Hoidal JR Jr. RAGE: developmental expression and positive feedback regulation by Egr-1 during cigarette smoke exposure in pulmonary epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2008;294:L1094–L1101.
5. Prasad K, Dhar I, Caspar-Bell G. Role of advanced glycation end products and its receptors in the pathogenesis of cigarette smoke-induced cardiovascular disease. *Int J Angiol* 2015;24:75–80.
6. Biswas SK. What does cigarette smoking do to the circulating level of soluble receptor for advanced glycation end products? *Int J Angiol* 2016;25:137–138.

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