

sepsis diagnostic); and Asahi Kesai Pharmaceuticals of America (AKPA, Waltham, Massachusetts; developing recombinant thrombomodulin). Dr. Russell reports having received an investigator-initiated grant from Grifols that is provided to and administered by University of British Columbia.

**James A. Russell, A.B., M.D.,** University of British Columbia and St. Paul's Hospital, Vancouver, British Columbia, Canada. jim.russell@hli.ubc.ca

## References

- Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, Rhodes A, Landoni G, Osawa EA, Melo RR, Sundin MR, Grande SM, Gaiotto FA, Pomerantzeff PM, Dallan LO, Franco RA, Nakamura RE, Lisboa LA, de Almeida JP, Gerent AM, Souza DH, Gaiane MA, Fukushima JT, Park CL, Zambolim C, Rocha Ferreira GS, Strabelli TM, Fernandes FL, Camara L, Zeferino S, Santos VG, Piccioni MA, Jatene FB, Costa Auler JO Jr, Filho RK: Vasopressin *versus* norepinephrine in patients with vasoplegic shock after cardiac surgery: The VASST randomized controlled trial. *ANESTHESIOLOGY* 2017; 126:85–93
- Russell JA: Vasopressin, norepinephrine, and vasodilatory shock after cardiac surgery: Another “VASST” difference? *ANESTHESIOLOGY* 2017; 126:9–11
- O'Connor PM, Cowley AW Jr: Vasopressin-induced nitric oxide production in rat inner medullary collecting duct is dependent on V2 receptor activation of the phosphoinositide pathway. *Am J Physiol Renal Physiol* 2007; 293:F526–32
- Rudichenko VM, Beierwaltes WH: Arginine vasopressin-induced renal vasodilation mediated by nitric oxide. *J Vasc Res* 1995; 32:100–5
- Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D; VASST Investigators: Vasopressin *versus* norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–87
- Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, Smith CR Jr, Rose EA, Landry DW, Oz MC: Management of vasodilatory shock after cardiac surgery: Identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg* 1998; 116:973–80
- Morales D, Madigan J, Cullinane S, Chen J, Heath M, Oz M, Oliver JA, Landry DW: Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. *Circulation* 1999; 100:226–9
- Morales DL, Garrido MJ, Madigan JD, Helman DN, Faber J, Williams MR, Landry DW, Oz MC: A double-blind randomized trial: Prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. *Ann Thorac Surg* 2003; 75:926–30
- Morales DL, Gregg D, Helman DN, Williams MR, Naka Y, Landry DW, Oz MC: Arginine vasopressin in the treatment of 50 patients with postcardiotomy vasodilatory shock. *Ann Thorac Surg* 2000; 69:102–6
- Elgebaly AS, Sabry M: Infusion of low-dose vasopressin improves left ventricular function during separation from cardiopulmonary bypass: A double-blind randomized study. *Ann Card Anaesth* 2012; 15:128–33
- Russell JA VJ, Kjølbye A, Olsson H, Blemings A, Grundemar L: Selepressin, a novel selective V1a agonist, reduces norepinephrine requirements and shortens duration of organ dysfunction in septic shock patients. *Crit Care Med* 2012; 40:1
- He X, Su F, Taccone FS, Laporte R, Kjølbye AL, Zhang J, Xie K, Moussa MD, Reinheimer TM, Vincent JL: A selective V(1A) receptor agonist, selepressin, is superior to arginine vasopressin and to norepinephrine in ovine septic shock. *Crit Care Med* 2016; 44:23–31
- Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT, Boldt DW, Chock S, Young PJ, Krell K, Wunderink RG, Ostermann M, Murugan R, Gong MN, Panwar R, Hästbacka J, Favory R, Venkatesh B, Thompson BT, Bellomo R, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Deane AM; ATHOS-3 Investigators: Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377:419–30

(Accepted for publication September 27, 2017.)

## In Reply:

We appreciate the comments from Dr. Jha. According to the study protocol, all patients received a cardiac output monitor aiming to optimize fluid status and cardiac index. Therefore, as our data show, with norepinephrine or vasopressin, we did not observe either a reduction in the cardiac index or a worsening of tissue perfusion and oxygenation parameters as lactate and central venous oxygen saturation.<sup>1</sup> Furthermore, the incidence of low cardiac output and cardiogenic shock in the norepinephrine and vasopressin groups was not different. We attribute this to the fact that we assessed the fluid status and used inotropes regularly, in accordance with an established protocol of care. Dobutamine is our inotrope of choice in vasoplegic syndrome because both levosimendan and milrinone have inherent vasodilating properties that result in hypotension in these cases. In the Vasopressin and Septic Shock Trial (VASST) substudy, Gordon *et al.* showed similar effects of both vasopressin and norepinephrine in septic shock patients in hemodynamic and cardiovascular biomarkers.<sup>2</sup> We postulate that vasopressin is as safe as norepinephrine in terms of cardiovascular effects in this group of patients, because we correct hypotension early and adequately monitor these patients in anticipation of inotropes needing a correction in fluid deficit.

We also appreciate the comments from Drs. Fan and Faraday about our article. They raised concerns about the doses and efficiency of the study vasopressor. The drug concentration we used was a final blind solution of either 0.12 U/ml vasopressin or 120 µg/ml norepinephrine. The vasopressor infusion was titrated to maintain a mean arterial pressure of at least 65 mmHg. This does not mean that our patients used the highest dosage of drugs; however, if the arterial pressure targets were not reached, the trained physicians and nurses titrated the drugs according to protocol. All patients were monitored with a minimally invasive cardiac output monitor, a protocol of volume status analysis was done regularly, and a bolus of fluids was administered if there was prediction of fluid responsiveness. We do not believe that we should compare our patients with patients from the VASST and Ventricular Tachycardia Ablation *versus* Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease trials; these trials included patients with septic shock who were already resuscitated and the VASST included only patients after

norepinephrine infusion.<sup>2,3</sup> On the other hand, we included patients in the acute phase of vasoplegic shock after cardiac surgery. Most included patients did not reach the maximum dosage, but considering the severity of this syndrome and the need to target a mean arterial pressure, these doses were allowed by the protocol.

We report mortality rates in our study of 15.9% in the norepinephrine group and 15.4% in the vasopressin group. We agree that the expected mortality of cardiac patients with a baseline EuroSCORE of 5 is about 5%. However, this prediction does not address the outcomes of vasoplegic syndrome. Patients with vasoplegic syndrome have mortality rates of about 15 to 20%.<sup>4,5</sup>

We do not agree with Fan and Faraday that the clinical treatment of patients in our study was not protocolized. As already mentioned, intraoperative and postoperative fluid management, erythrocyte transfusion, and inotrope use were protocolized in both groups. There was no difference between groups in cardiac index and in the incidence of cardiac output and cardiogenic shock. Cardiac index and other hemodynamic data are described in eTable 5 of the Supplemental Digital Content of the original publication (<http://links.lww.com/ALN/B337>).<sup>1</sup> These data are similar to the data published by Gordon *et al.* in a substudy of VASST, which show the cardiac safety of vasopressin as compared to norepinephrine.<sup>6</sup>

In addition, we appreciate the comments from Drs. James and Amour about our article. They raised concerns about the modification of the primary outcome. In the design phase of the study, we selected Brussels criteria as the primary outcome because it was similar to a landmark trial that compared vasopressin added to noradrenaline *versus* noradrenaline alone in septic shock patients (VASST).<sup>3</sup> However, in February 2013, before any study analysis had been undertaken, trial leadership decided to modify the endpoint without knowledge of the endpoint or related trial data results. The reason for this change was that few outcome data on vasoplegic patients were available in the literature at that time; therefore, the trial leadership considered it appropriate to select the modified Society of Thoracic Surgeons Score, which had been recently demonstrated to better measure outcomes in the field of cardiac surgery.<sup>7</sup> When this change was made, 81 patients were included in the study and the database had not been analyzed. An amendment was added to the study protocol, the ethics committee approved it, and we registered the change in Clinicaltrials.gov. In addition, the original primary outcome data ("days alive and free of organ dysfunction during the first 28 days according to the Brussels criteria") were also analyzed and are reported in table 7 of our original article, confirming a statistically significant decrease in acute renal failure in the vasopressin group as compared to the norepinephrine group.<sup>1</sup>

Regarding the concern about the incidence of previous renal dysfunction in the study patients, we should emphasize that according to the recommendation of the Consolidated Standards of Reporting Trials, "significance testing of

baseline differences in randomized controlled trials should not be performed, because it is superfluous and can mislead investigators and their readers."<sup>8</sup> We report the statistical test here, comparing the incidence of chronic renal dysfunction and showing no difference between groups (29.1% in the norepinephrine group *vs.* 24.8% in the vasopressin group,  $P = 0.401$ ); therefore, we do not believe it has altered the results of acute renal failure in these patients.

Regarding the concern about the postrandomization exclusions, we did not include 30 patients in the analysis because they were not eligible for randomization according to the study's inclusion/exclusion criteria, they never received the masked trial drug, and they were equally distributed between groups and therefore did not bias outcome ascertainment. This is acceptable according to Fergusson *et al.*, who wrote that "data on patients who were prematurely randomized and so did not receive an intervention can be excluded, as long as allocation to treatment arm cannot influence the likelihood that patients receive the intervention."<sup>9</sup> In VASST, this criteria of postrandomization exclusion was also used without compromising the results.<sup>3</sup>

## Competing Interests

The authors declare no competing interests.

**Ludhmila A. Hajjar, M.D., Ph.D., Juliano P. Almeida, M.D., Ph.D., Filomena R. B. G. Galas, M.D., Ph.D.** InCor, Faculdade de Medicina da Universidade de São Paulo, Universidade de São Paulo (L.A.H.). ludhmila@usp.br

## References

- Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, Rhodes A, Landoni G, Osawa EA, Melo RR, Sundin MR, Grande SM, Gaiotto FA, Pomerantzeff PM, Dallan LO, Franco RA, Nakamura RE, Lisboa LA, de Almeida JP, Gerent AM, Souza DH, Gaiane MA, Fukushima JT, Park CL, Zambolim C, Rocha Ferreira GS, Strabelli TM, Fernandes FL, Camara L, Zeferino S, Santos VG, Piccioni MA, Jatene FB, Costa Auler JO Jr, Filho RK: Vasopressin *versus* norepinephrine in patients with vasoplegic shock after cardiac surgery: The VANCs randomized controlled trial. *ANESTHESIOLOGY* 2017; 126:85–93
- Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, Pogson DG, Aya HD, Anjum A, Frazier GJ, Santhakumaran S, Ashby D, Brett SJ; VANISH Investigators: Effect of early vasopressin *vs* norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. *JAMA* 2016; 316:509–18
- Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D; VASST Investigators: Vasopressin *versus* norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–87
- Weis F, Kilger E, Beiras-Fernandez A, Nassau K, Reuter D, Goetz A, Lamm P, Reindl L, Briegel J: Association between vasopressor dependence and early outcome in patients after cardiac surgery. *Anaesthesia* 2006; 61:938–42
- Luckner G, Dünser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Mayr AJ, Friesenecker B: Arginine vasopressin in 316 patients with advanced vasodilatory shock. *Crit Care Med* 2005; 33:2659–66

6. Gordon AC, Wang N, Walley KR, Ashby D, Russell JA: The cardiopulmonary effects of vasopressin compared with nor-epinephrine in septic shock. *Chest* 2012; 142:593–605
7. Shahian, DM, O'Brien, SM, Filardo, G, Ferraris, VA, Haan, CK, Rich, JB, Normand, SL, DeLong, ER, Shewan, CM, Dokholyan, RS, Peterson, ED, Edwards, FH, Anderson, RP: The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg* 2009; 88:S2–22
8. de Boer MR, Waterlander WE, Kuijper LD, Steenhuis IH, Twisk JW: Testing for baseline differences in randomized controlled trials: An unhealthy research behavior that is hard to eradicate. *Int J Behav Nutr Phys Act* 2015; 12:4
9. Fergusson D, Aaron SD, Guyatt G, Hébert P: Post-randomization exclusions: The intention to treat principle and excluding patients from analysis. *BMJ* 2002; 325:652–4

(Accepted for publication September 27, 2017.)

## Should the Dominant or Nondominant Hand Be Used for Applying Cricoid Pressure?

### To the Editor:

In their excellent review, Salem *et al.*<sup>1</sup> suggest that the dominant hand should be used to apply cricoid pressure (CP) because even though either hand can achieve adequate CP, the applied force may become inadequate if it needs to be sustained with the nondominant hand.<sup>2</sup> I suggest that if there is any possibility that the person applying CP may be asked to perform a task that can be done with one hand (*e.g.*, upper lip retraction, removal of stylet), the CP should be applied with the nondominant hand. I have noticed that if one ever asks that person to do something, they reflexively tend to use their dominant hand and thus may prematurely release CP, putting the patient at increased risk of aspiration. Ideally the person applying CP should not be asked to do anything else. However, sometimes one is in the situation where additional trained personnel are not available. Most airways are secured quickly enough that fatigue of the nondominant hand does not become an issue.

### Competing Interests

The author declares no competing interests.

**Jonathan V. Roth, M.D.**, Albert Einstein Medical Center, Philadelphia, Pennsylvania. Rothj@einstein.edu

### References

1. Salem MR, Khorasani A, Zeidan A, Crystal GJ: Cricoid pressure controversies: Narrative review. *ANESTHESIOLOGY* 2017; 126:738–52
2. Cook TM, Godfrey I, Rockett M, Vanner RG: Cricoid pressure: Which hand? *Anaesthesia* 2000; 55:648–53

(Accepted for publication September 29, 2017.)

## Cricoid Pressure: Effective Measure or Ritual?

### To the Editor:

I read with great interest the review on cricoid pressure (CP) by Salem *et al.*<sup>1</sup> The authors assure the reader that they have “used discretion in deciding which articles to finally include, favoring peer-reviewed articles from highly ranked journals written in English.” However, a couple of key references are missing, and a couple of publications require additional commenting to place the findings in the proper clinical perspective.

Although the authors cite those recent guidelines that indicate the common use of CP, they fail to cite those guidelines recently published by various national and international professional societies that no longer recommend routine application of CP. These include the 2010 Scandinavian Clinical Practice Guidelines on General Anesthesia for Emergency Situations,<sup>2</sup> the 2015 Guideline on Airway Management released by the Board of the German Society of Anesthesiology and Intensive Care Medicine,<sup>3</sup> and the 2015 European Resuscitation Council Guidelines for Resuscitation.<sup>4</sup> Obviously, these guidelines reflect the doubt of the respective professional societies that the benefits of this technique outweigh its disadvantages. This may have considerable medicolegal implications, because a physician would no longer be blamed *per se* for not having applied CP. Based on findings of nonrandomized controlled trials, a recent Cochrane review concluded that CP may not be necessary to safely perform rapid sequence induction.<sup>5</sup>

The authors interpret recently published findings of an *in vitro* investigation of a tactile, single-use cricoid cartilage compression device<sup>6</sup> as showing that by, “careful titration of the force, the operator can be assured that the cricoid force is between 30 and 35 N.” However, the actual findings do not support this generalized statement. During 114 attempts, the target force of 30 N was achieved in only 15 attempts (13%), and a range of forces of 25 to 35 N was achieved in only 35 attempts (31%). These less-than-optimal results occurred despite highly controlled experimental conditions (*i.e.*, application of cricoid force on a CP training simulator by practitioners familiar with both device and simulator). It is predictable that the results will be even less favorable when CP is applied under less controlled conditions in humans with highly variable neck anatomy.

At first glance, the authors’ recommendation for training of personnel performing CP seems reasonable. However, because such training would have to be provided for countless healthcare providers every 2 weeks to 3 months (the duration of retention of training-acquired respective skills), such a recommendation is entirely unrealistic. It would be interesting to know whether members of the authors’ departments are this often regularly retrained in the application of CP.

Why does the CP literature continue to focus so closely on the cricoid force to be applied rather than on