evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999; 16:9–13

6. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT; Investigators of the Ischemia Research and Education Foundation; Multicenter Study of Perioperative Ischemia Research Group: A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004; 291:1720–9
7. Kaireviciute D, Aidietis A, Lip GY: Atrial fibrillation following cardiac surgery: Clinical features and preventative strategies. Eur Heart J 2009; 30:410–25

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In Reply:

Drs. Fan and Faraday write with concerns about the Vasopressin and Cardiac Surgery Trial[1] and my editorial[2]; I agree with some, but not all, of their points. My first point of agreement is the criticism that clinical treatment was not protocolized; however, in most randomized controlled trials, nonrandomized care is most often not protocolized for simple logistical reasons. The point is that nonprotocolized care was used in both masked arms of the Vasopressin and Cardiac Surgery Trial. Greater use of dobutamine in the norepinephrine group in the Vasopressin and Cardiac Surgery Trial could have been because vasopressin had less negative inotropic effects than norepinephrine, as vasopressin has some vasodilation action due to release of nitric oxide.[3,4]

Another point of agreement is Drs. Fan and Faraday's "caution against generalizing these results across centers and to bias against specific drugs classes." Indeed, I stated: "in settings such as the *study hospital* [my italics for emphasis herein], vasopressin infusion for treatment of vasodilatory shock after cardiac surgery may improve some clinically important outcomes."[2] I also stand by my recommendation that "this trial deserves replication in *other multicenter healthcare settings* [my italics for emphasis herein] to create confidence about generalizability."

Drs. Fan and Faraday state that in the Vasopressin and Cardiac Surgery Trial masked infusion doses of vasopressin and norepinephrine were not equivalent, and that norepinephrine doses (10 to 60 μg/min) were about five times higher than those used in their center (a citation or a table of their actual data would be helpful here). They state that in the Vasopressin and Septic Shock Trial[5] norepinephrine doses were 5 to 15 μg/min, but that is not correct. Supplemental Digital Content (http://links.lww.com/ALN/B337) shows mean doses of 15 to 17 and upper SD of 27 μg/min in the Vasopressin and Septic Shock Trial. The literature regarding norepinephrine doses in vasodilatory shock after cardiovascular surgery helps somewhat here[6–9]: norepinephrine doses were up to (upper SD) 40 μg/min,[6] 10 μg/min,[8] and 30 μg/min,[9] suggesting that norepinephrine doses may have been lower in previous studies of vasopressin *versus* norepinephrine in cardiovascular surgery than in the Vasopressin and Cardiac Surgery Trial.

My points of disagreement include unequal dosing regimens for vasopressin and norepinephrine having the potential to unmask the clinical care and that "differences between treatment groups in duration and alternative pressor/inotrope usage would also be noticeable to clinicians." I am not sure how one can ever prove that masked treatment arms were effectively unmasked in blinded, randomized controlled trials. Drs. Fan and Faraday assume that the vasoconstriction and increased blood pressure effects would have been greater in the norepinephrine arm; however, they do not mention that in both arms, patients are also randomly improving or deteriorating, so mean arterial pressure is changing independent of vasopressin or norepinephrine effects, therefore making efforts to unmask a risky business at best.

Another point of partial disagreement is in the assertion that "overall complication rates reported in this study are much higher than expected." I am not entirely sure this is true because one has to review such rates in the remarkably few reported cohorts and randomized controlled trials of patients with vasodilatory shock after cardiovascular surgery. The 60 to 80% incidence of atrial fibrillation in the Vasopressin and Cardiac Surgery Trial does seem high and may indicate that patients in the Vasopressin and Cardiac Surgery Trial were sicker than those in other vasodilatory cohorts and randomized controlled trials. I also previously stated that "mortality rates were high—16 and 15% at 28 days and 17 and 16% at 90 days (norepinephrine *vs.* vasopressin)—in the Vasopressin and Cardiac Surgery Trial; remarkably, mortality rates were not reported in previous smaller trials of vasopressin *versus* norepinephrine for vasodilatory shock after cardiac surgery."[6,8–10]

To conclude, I recommend that Drs. Fan, Faraday, and others: (1) create multicenter registries of vasodilatory shock after cardiovascular surgery to understand risks and outcomes of same; (2) do proof-of-principle randomized controlled trials of novel compounds, such as the selective V1a agonist selepressin[11,12] and angiotensin 2[13]; and (3) do large, pivotal, randomized controlled trials of vasopressin *versus* norepinephrine in North America to see whether the Vasopressin and Cardiac Surgery Trial results are applicable in this setting.

Competing Interests

Dr. Russell reports patents owned by the University of British Columbia (Vancouver, British Columbia, Canada) that are related to PCSK9 inhibitor(s) and sepsis, and related to the use of vasopressin in septic shock. He is an inventor on these patents. Dr. Russell is a founder, director, and shareholder in Cyon Therapeutics, Inc. (Vancouver, British Columbia, Canada; developing a sepsis therapy). He has share options in Leading Biosciences, Inc. (Carlsbad, California), and he is a shareholder in Molecular You Corp. (Vancouver, British Columbia, Canada). Dr. Russell also reports receiving consulting fees from: Cubist Pharmaceuticals (now owned by Merck, New York, New York; formerly was Trius Pharmaceuticals; developing antibiotics); Leading Biosciences (developing a sepsis therapeutic); Ferring Pharmaceuticals (Copenhagen, Denmark; manufactures vasopressin and is developing selepressin); Grifols (Barcelona, Spain; sells albumin); La Jolla Pharmaceuticals (San Diego, California; developing angiotensin II; Dr. Russell chairs the DSMB of a trial of angiotensin II); CytoVale, Inc. (San Francisco, California; developing a

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.

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References

1. 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
2. Russell JA: Vasopressin, norepinephrine, and vasodilatory shock after cardiac surgery: Another "VASST" difference? Anesthesiology 2017; 126:9–11
3. 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
4. Rudichenko VM, Beierwaltes WH: Arginine vasopressin-induced renal vasodilation mediated by nitric oxide. J Vasc Res 1995; 32:100–5
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
6. 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
7. 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
8. 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
9. 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
10. 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
11. Russell JA VJ, Kjolbye 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
12. 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
13. 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

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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.[1] 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.[2] 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