CORRESPONDENCE

Comparison of Dopamine and Norepinephrine in Shock

TO THE EDITOR: The Sepsis Occurrence in Acutely Ill Patients (SOAP) II study, reported by De Backer and colleagues (March 4 issue),[1] is a major multicenter effort to find the elusive answer to the question of whether one vasopressor is superior to another as first-line therapy for patients with circulatory shock. The use of dopamine was associated with a greater number of adverse events in the overall population and an unexpected increase in the rate of death in the subgroup of patients with cardiogenic shock. As is known, patients in various states of circulatory shock have in common the need for timely and appropriate fluid resuscitation and for vasopressor drugs as priority actions for recovery. However, among patients with septic shock — approximately two thirds of the study population — the early initiation of effective antibiotic therapy and complementary measures for control of the focus of the infection (e.g., percutaneous drainage, débridement of infected necrotic tissue, or surgery) are of great importance with respect to survival.[2-4] In this context, it would be interesting to know whether in the subgroup of patients with septic shock these measures were implemented similarly in both groups of the protocol. This information could be very relevant to the proper interpretation of the results in this subgroup of patients.

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No potential conflict of interest relevant to this letter was reported.

1. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-89.
2. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96.
3. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34:17-60 [Erratum, Intensive Care Med 2008;34:783-5.]
4. Barochia AV, Cui X, Vitberg D, et al. Bundled care for septic shock: an analysis of clinical trials. Crit Care Med 2010;38:668-78.

TO THE EDITOR: De Backer et al. report in the subgroup analysis that the rate of death at 28 days among patients with cardiogenic shock was significantly higher among those who were treated with dopamine than among those who were treated with norepinephrine. This finding strongly challenges the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which recommend dopamine as the vasopressor of choice to increase arterial pressure in patients who have hypotension due to an acute myocardial infarction.[1]

An important limitation is that the authors do not address whether the underlying cause was appropriately treated. The most common cause of cardiogenic shock is an acute myocardial infarction, in which case the treatment of choice is immediate coronary reperfusion therapy.[2] Prompt

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revascularization by means of percutaneous coronary intervention or coronary-artery bypass surgery has been shown to decrease the risk of death.[3,4] Vasopressors are transitory agents that are instituted until the underlying cause can be treated. Therefore, without addressing whether the underlying cause of cardiogenic shock was properly treated, one cannot confidently conclude that dopamine is associated with a higher rate of death than is norepinephrine.

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1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110(9):e82-e292. [Errata, Circulation 2005;111:2013-4, 2007;115(15):e411.]
2. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. Circulation 2009;119;1330-52. [Erratum, Circulation 2009;119(15):e488.]
3. Berger PB, Holmes DR, Jr, Stebbins AL, Bates ER, Califf RM, Topol EJ. Impact of an aggressive invasive catheterization and revascularization strategy on mortality in patients with cardiogenic shock in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial. Circulation 1997;96:122-7.
4. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.

TO THE EDITOR: De Backer et al. find no significant difference in the rate of death at 28 days between the two study groups. However a subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients in cardiogenic shock. This increase in the rate of death was ascribed to a higher incidence of arrhythmic events in the dopamine group.

The current guidelines for the treatment of cardiogenic shock[1] recommend the insertion of an intraaortic balloon pump if the inotropic agent fails to restore systolic blood pressure and signs of organ hypoperfusion persist (class of recommendation, I; level of evidence, C).

The authors should clarify whether a procedure to insert an intraaortic balloon pump was performed in the patients with cardiogenic shock. These data would be relevant to explaining the higher rate of death among patients in cardiogenic shock treated with dopamine, since an intraaortic balloon pump may be helpful in decreasing the inotropic dose and thus reducing the potential risk of arrhythmias.

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1. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Eur Heart J 2008;29:2388-442. [Erratum, Eur Heart J 2010;12:416.]

TO THE EDITOR: De Backer et al. report that dopamine, as compared with norepinephrine, was associated with more arrhythmias and an increased rate of death among patients in cardiogenic shock. Dopamine and norepinephrine, at the doses used in this study, have been shown to have similar effects on arterial blood pressure.[1,2] Actually, the increase in arterial pressure was similar in the dopamine and norepinephrine groups, but the increase in heart rate was significantly greater in the dopamine group than in the norepinephrine group (Fig. 3A and 3B in the Supplementary Appendix of the article, available at NEJM.org). The findings indicate that the doses were equipotent in terms of alpha-adrenergic effects, but beta-adrenergic effects were more potent with dopamine than with norepinephrine. This difference explains the fact that there were worse outcomes in the dopamine group than in the norepinephrine group. Because norepinephrine therapy is associated with a relatively stable heart rate, one might expect to find even more favorable outcomes than those seen in this article if the maximum dose of norepinephrine is increased. In the study by De Backer et al., open-label norepinephrine was add-

ed in some patients without inducing complications. In several other studies, higher doses of norepinephrine than those used in this study showed excellent outcomes.[3,4] The dose-range of norepinephrine in the treatment of patients with shock warrants further study.

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No potential conflict of interest relevant to this letter was reported.

1. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. JAMA 1994;272:1354-7.
2. De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med 2003;31:1659-67.
3. Albanèse J, Leone M, Garnier F, Bourgoin A, Antonini F, Martin C. Renal effects of norepinephrine in septic and nonseptic patients. Chest 2004;126:534-9.
4. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. Crit Care Med 2000; 28:2758-65.

TO THE EDITOR: In the article by De Backer et al., I was surprised to find that 15.7% of the cohort represented patients who were in hypovolemic shock (primarily hemorrhagic). Previous studies[1] and animal models[2] have shown a possible trend toward harm (or no benefit) in treating hemorrhagic shock with vasopressors. The primary treatment remains the cessation of hemorrhage and volume replacement with either crystalloids or blood products. De Backer et al. state that adequate fluids for resuscitation were defined as 1000 cc of crystalloid or 500 cc of colloid, but there is no mention of controlling for blood products or of interventions to manage hemorrhage. Since the study was powered to detect a 15% difference in the rate of death, the fact that 15.7% of the cohort comprised patients in hypovolemic shock raises the probability of a type II error. The wide confidence interval in the Forest plot for the subgroup in hypovolemic shock may represent treatment equivalence; however the possibility of equivalent harm in a subgroup for which vasopressors are not indicated is a potential confounder that may bias the overall results of the study erroneously toward the null hypothesis.

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No potential conflict of interest relevant to this letter was reported.

1. Sperry JL, Minei JP, Frankel HL, et al. Early use of vasopressors after injury: caution before constriction. J Trauma 2008;64: 9-14.
2. Chernow B, Lake CR, Barton M, et al. Sympathetic nervous system sensitivity to hemorrhagic hypotension in the subhuman primate. J Trauma 1984;24:229-32.

TO THE EDITOR: We believe that the results of SOAP II study, reported by De Backer et al., might be confounded by the use of open-label norepinephrine. According to the study design, open-label norepinephrine was administered if the patient remained hypotensive after the maximum dose of dopamine or norepinephrine had been used. The authors report that about 26% of patients in the dopamine group and 20% of patients in the norepinephrine group were treated with open-label norepinephrine, with the maximum dose of 0.7 and 0.8 μg per kilogram per minute, respectively. These doses were much higher than the maximum dose of norepinephrine (0.16 μg per kilogram per minute) in the norepinephrine group, which might confound the results of the comparison between dopamine and norepinephrine. Accordingly, an a priori analysis of the primary outcome (the rate of death at 28 days) comparing the subgroup of patients who took open-label norepinephrine with the subgroup of patients who did not may better explain the treatment effect of the trial agents and open-label vasopressors.

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THE AUTHORS REPLY: The therapy for shock includes not only the use of vasopressor agents but other supportive measures and the treatment of the underlying cause. In our study, we took great care to ensure that these measures were adequately provided.

Romero rightly emphasizes the importance of administering appropriate antibiotics in patients with septic shock. We did not collect data on the results of bacteriologic tests and on the type of antibiotic administered, but we did collect infor-

mation on any change in antibiotic therapy. The antibiotic therapy was changed within 48 hours after a patient's inclusion in the study in only 9 of 502 patients in the norepinephrine group (1.8%) and 12 of 542 patients in the dopamine group (2.2%) (nonsignificant difference), providing indirect evidence that the antibiotic therapy was adequate in the vast majority of patients. Lee emphasizes the importance of reperfusion therapy in patients with cardiogenic shock.[1] Percutaneous angioplasty was attempted in most of the 161 patients who were in shock as a result of acute myocardial infarction. However, in contrast to Lee's statement, the need for vasopressor agents in these patients was seldom transient, since in our trial, it lasted for a mean (±SD) duration of 3±5 days. As De Santis et al. mentioned, the use of intraaortic counterpulsation is often recommended, even though its effect on the outcome is still controversial,[2] but we did not collect information on the use of intraaortic balloon pumps. Altogether, the patients in the trial were treated according to international recommendations, and there is no evidence that there was an imbalance between the two groups with respect to other therapies.

As indicated in our discussion, we agree with Tomoda that the greater increase in heart rate in the dopamine group as compared with the norepinephrine group suggests that there was a stronger beta-adrenergic stimulation with dopamine than with norepinephrine, and this may have played a role in the increased rate of death among patients with cardiogenic shock receiving dopamine. In response to Paolo's comments about hypovolemic and especially traumatic shock: vasopressor agents were also administered according to international guidelines and were used only when fluids failed to maintain tissue perfusion while physicians were attempting to find and control the source of the hemorrhage. Of note, trauma was the cause of shock in only 15.2% of patients with hypovolemic shock and 2.4% of patients with shock from any cause. To increase the external validity of our results, we decided to include all types of shock, since it is not always feasible to discriminate the type of shock initially.

In response to Du et al.: the analysis of the data without the use of open-label norepinephrine did not show a significant difference in the outcome between the dopamine group and the norepinephrine group ($P=0.45$). We agree with Tomoda that norepinephrine may be safer than is sometimes considered.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
2. Prondzinsky R, Lemm H, Swyter M, et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. Crit Care Med 2010;38:152-60.

Management of Varices in Cirrhosis

TO THE EDITOR: The comprehensive review of management of variceal bleeding by Garcia-Tsao and Bosch (March 4 issue)[1] highlights the special difficulties in managing bleeding gastric varices, particularly with the limited availability of vasoactive agents and the lack of licensed tissue-adhesive "glue" (cyanoacrylate) in the United States. An important alternative to "gluing" gastric varices is to "clot" with an endoscopic thrombin or thrombin–fibrinogen complex injection[2]; the latter method was reported with bovine thrombin in the early 1990s.[3] The availability of human thrombin has reduced fears related to the transmission of variant Creutzfeldt–Jakob disease. Data from uncontrolled case series suggest that thrombin is effective and has an acceptable safety profile for acute hemostasis, with the hemostasis rate comparable to that of gluing (see Table 1 in