Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study*

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Objective: **The optimal adrenergic support in shock is controversial. We investigated whether dopamine administration influences the outcome from shock.**

Design: **Cohort, multiple-center, observational study.**

Setting: **One hundred and ninety-eight European intensive care units.**

Patients: **All adult patients admitted to a participating intensive care unit between May 1 and May 15, 2002.**

Interventions: **None.**

Measurements and Main Results: **Patients were followed up until death, until hospital discharge, or for 60 days. Shock was defined as hemodynamic compromise necessitating the administration of vasopressor catecholamines. Of 3,147 patients, 1,058 (33.6%) had shock at any time; 462 (14.7%) had septic shock. The intensive care unit mortality rate for shock was 38.3% and 47.4% for septic shock. Of patients in shock, 375 (35.4%) received dopamine (dopamine group) and 683 (64.6%) never received dopamine. Age, gender, Simplified Acute Physiology Score II, and Sequential Organ Failure Assessment score were comparable between the two groups. The dopamine group had higher intensive care unit (42.9% vs. 35.7%, $p = .02$) and hospital (49.9% vs. 41.7%, $p = .01$) mortality rates. A Kaplan-Meier survival curve showed diminished 30 day-survival in the dopamine group (log rank = 4.6, $p = .032$). In a multivariate analysis with intensive care unit outcome as the dependent factor, age, cancer, medical admissions, higher mean Sequential Organ Failure Assessment score, higher mean fluid balance, and dopamine administration were independent risk factors for intensive care unit mortality in patients with shock.**

Conclusions: **This observational study suggests that dopamine administration may be associated with increased mortality rates in shock. There is a need for a prospective study comparing dopamine with other catecholamines in the management of circulatory shock. (Crit Care Med 2006; 34:589–597)**

KEY WORDS: vasopressors; catecholamines; vasoactive agents; acute circulatory failure; survival; intensive care

The optimal adrenergic support in shock is controversial. Dopamine and norepinephrine are the most commonly used agents to restore tissue perfusion pressure in these conditions. Although dopamine is the natural precursor of norepinephrine, and both combine α- and β-adrenergic properties, they are different molecules and have different pharmacologic profiles. Dopamine has relatively stronger β_1-adrenergic properties, thus increasing myocardial contractility more than norepinephrine, which has relatively stronger α-adrenergic properties and thus increases arterial pressure and systemic vascular resistance more than dopamine.

Both have their advantages and potential disadvantages, although many of the suggested effects of vasopressors have not been demonstrated in humans, particularly in those with critical illness. Dopamine is more likely to increase cardiac output and may also preferentially distribute blood flow to the splanchnic and renal vasculature by its additional dopaminergic properties (1, 2). Dopamine may have beneficial effects on diaphragmatic function (3) and on the resorption of edema fluid (4, 5). However, it may increase heart rate and can produce tachyarrhythmias. Dopamine may also suppress pituitary function, particularly prolactin secretion (6).

Norepinephrine is a more potent vasoconstrictor, through its potent α_1 stimulation with moderate β_1 and minimal β_2 activity. Norepinephrine was found to be more effective than dopamine in restoring hemodynamic stability and even sometimes urine output in patients with sepsis (7). Concerns with the use of norepinephrine are the potential risks of excessive vasoconstriction and decreased

***See also p. 890.**

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Table 1. Catecholamine use in patients with shock (%)

	Any Shock (n = 1058)	Septic Shock (n = 462)	Nonseptic Shock (n = 596)	p Value
Alone or in combination				
Norepinephrine	848 (80.2)	386 (83.5)	462 (77.5)	.015
Dopamine	375 (35.4)	181 (39.2)	194 (32.6)	.025
Dobutamine	359 (33.9)	170 (36.8)	189 (31.7)	.083
Epinephrine	246 (23.3)	126 (27.3)	120 (20.1)	.006
Single agent[a]				
Norepinephrine	336 (31.8)	123 (26.6)	213 (35.7)	.002
Dopamine	93 (8.8)	31 (6.7)	62 (10.4)	.035
Epinephrine	48 (4.5)	16 (3.5)	32 (5.4)	.14
Norepinephrine + dobutamine	163 (15.4)	73 (15.8)	90 (15.1)	.754
Norepinephrine + dopamine	123 (11.6)	64 (13.9)	59 (9.9)	.047
Epinephrine + norepinephrine	68 (6.4)	45 (9.7)	23 (3.9)	<.001
Dopamine + dobutamine	29 (2.7)	14 (0.3)	15 (2.5)	.612
Epinephrine + dobutamine	14 (1.3)	2 (0.4)	12 (2.0)	.026
Epinephrine + dopamine	9 (0.9)	5 (1.1)	4 (0.7)	.47
Norepinephrine + dopamine + dobutamine	75 (7.1)	39 (8.4)	36 (6.0)	.131
Norepinephrine + epinephrine + dobutamine	49 (4.6)	22 (4.8)	27 (4.5)	.859
Norepinephrine + epinephrine + dopamine	18 (1.7)	8 (1.7)	10 (1.7)	.947
Four agents	28 (2.6)	20 (4.3)	8 (1.3)	.023

[a]Two patients received only vasopressin, and two received phenylephrine as a single agent.

organ perfusion. However, the combination of norepinephrine with dobutamine may counteract this effect (8).

In a large cohort of European intensive care unit (ICU) patients included in the Sepsis Occurrence in Critically Ill Patients (SOAP) study, we determined whether dopamine administration was associated with a poor outcome in patients with shock due to any cause and in a subgroup of septic shock patients, and we identified other factors associated with a poor outcome in these patients. Although the study was purely observational, multivariate analyses can help to identify important factors.

Table 2. Characteristics of patients with shock on admission

	All Patients (n = 1058)	No Dopamine (n = 683)	Dopamine (n = 375)	p Value
Age,[a] mean ± SD	63 ± 16	62 ± 17	64 ± 16	.194
Male[b] (%)	649 (61.9)	408 (60.2)	241 (65.0)	.144
Comorbid diseases (%)				
Cancer	133 (12.5)	90 (13.2)	43 (11.5)	.698
Hematologic cancer	36 (3.4)	22 (3.2)	14 (3.7)	.660
COPD	117 (11.1)	64 (9.4)	53 (14.1)	.018
Liver cirrhosis	54 (5.1)	32 (4.7)	22 (5.9)	.404
HIV infection	8 (0.8)	4 (0.6)	4 (1.1)	.294
Heart failure	140 (13.2)	68 (10.0)	72 (19.2)	<.001
Diabetes	81 (7.7)	52 (7.6)	29 (7.7)	.944
Medical admission (%)	504 (48.6)	338 (49.5)	176 (46.9)	.650
SAPS II score,[c] mean ± SD	47 ± 17	47 ± 17	47 ± 18	.975
SOFA score,[d] median (IQR)	8 (6–11)	8 (6–11)	8 (5–10)	.111
Infection (%)	397 (37.5)	256 (37.5)	141 (37.6)	.970

COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; IQR, interquartile range.

[a]One missing; [b]nine missing gender (valid percentage is presented after exclusion of missing data); [c]12 missing; [d]ten missing (11 missing variables were replaced).

METHODS

Study Design. This report is the result of a substudy from the SOAP database: a prospective, multiple-center, observational study that was designed to evaluate the epidemiology of sepsis in European countries and was initiated by a working group of the European Society of Intensive Care Medicine. Institutional recruitment for participation was by open invitation from the study steering committee to European ICUs. Since this epidemiologic, observational study did not require any deviation from routine medical practice, institutional review board approval was either waived or expedited in participating institutions and informed consent was not required. We included all adult patients (>15 yrs) admitted to the participating centers (see the Appendix for a list of participating countries and centers) between May 1 and May 15, 2002. Patients were followed up until death or hospital discharge or for 60 days. Those who stayed in the ICU for <24 hrs for routine postoperative observation, and patients with burns, were excluded.

Data Management. Data were collected prospectively using preprinted case report forms. Detailed instructions, explaining the aim of the study, instructions for data collection, and definitions for various important items were available for all participants through an Internet-based Web site before starting data collection and throughout the study period. The steering committee maintained continuous contact with the investigators and processed all queries during data collection.

Data were entered centrally by medical personnel using the SPSS version 11.0 for Windows (SPSS, Chicago, IL). A random sample of 5% of data was reentered by a different encoder and revised by a third; a consistency of >99.5% per variable and 98.5% per patient was observed during the whole process of data entry. In case of inconsistency, data were verified and corrected. Daily frequency tables were reviewed for all variables, and the investigators were queried when data values either were questionable or were missing for required fields. There was no data quality control at the data collection level. Data collection on admission included demographic data and comorbid diseases. Clinical and laboratory data for Simplified Acute Physiology Score (SAPS) II (9) were reported as the worst value within 24 hrs after admission. Microbiological and clinical infections were reported daily as

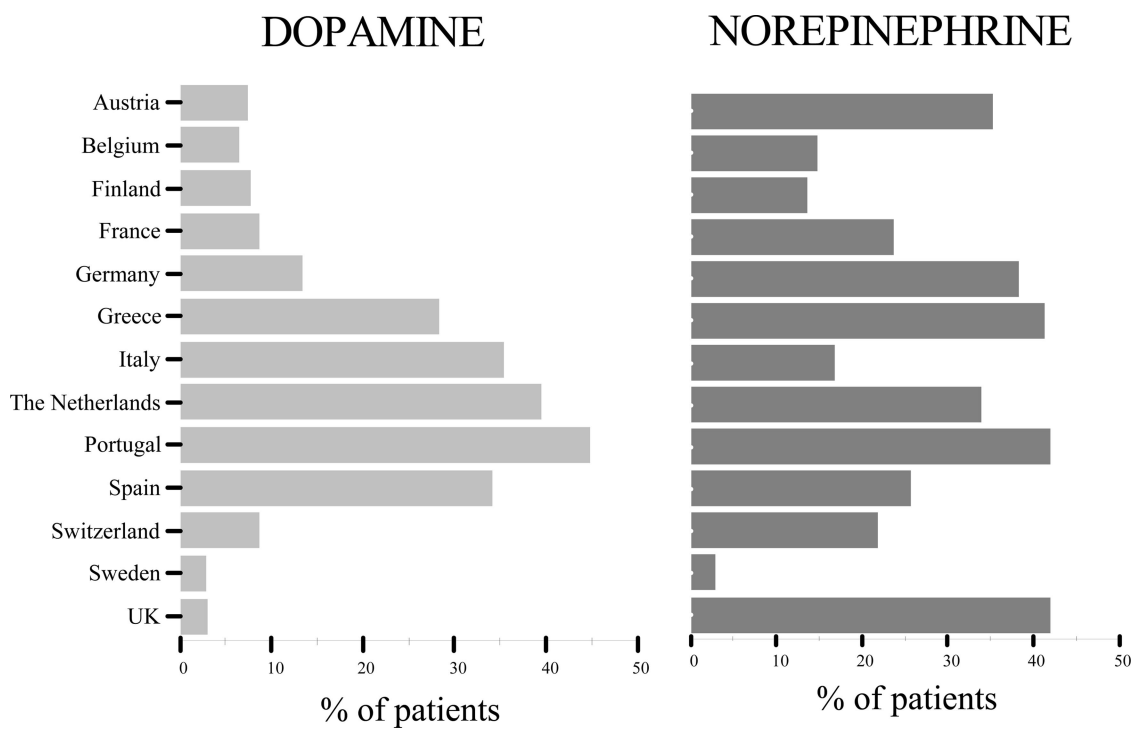

Figure 1. Use of dopamine and norepinephrine in the various European countries (only countries with >50 patients).

well as the antibiotics administered. A daily evaluation of organ function that was based on a set of laboratory and clinical variables according to the Sequential Organ Failure Assessment (SOFA) score (10) was performed, with the most abnormal value for each of the six organ systems (i.e., respiratory, renal, cardiovascular, hepatic, coagulation, and neurologic) being collected on admission and every 24 hrs thereafter. For a single missing value, a replacement was calculated using the mean value of the results on either side of the absent result. If the first or the last value was missing, the nearest value was carried backward or forward, respectively. When more than one consecutive result was missing, it was considered to be a missing value in the analysis. Missing data represented <6% of the total collected study data, of which only 2% were replaced. Missing data in the current analysis (patients with shock) represented <1% of the overall variables. Only 28 patients had one or more missing value. Infection was defined as the presence of a pathogenic microorganism and/or clinical infection necessitating antibiotic administration, and ICU-acquired infection was defined as infection occurring ≥48 hrs after ICU admission. Circulatory shock was defined as a cardiovascular SOFA score >2 (the need for vasopressor agents, i.e., dopamine >5 μg/kg/min, or epinephrine or norepinephrine any dose), and septic shock was defined as the association of shock and infection (11). Fluid balance was calculated during the shock episode: the cumulative fluid balance as the sum of daily fluid balance, and the mean fluid balance as the cumulative fluid balance in liters divided by the number of days in shock.

Statistical Methods. Data were analyzed using SPSS 11.0 for Windows. Descriptive statistics were computed for all study variables. Kolmogoroff-Smirnov test was used to verify the normality of distribution of continuous variables. Nonparametric measures of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using the two-tailed Student's *t*-test, Mann-Whitney U test, chi-square test, and Fisher's exact test as appropriate. We performed a multivariable, forward stepwise, logistic regression analysis with ICU outcome as the dependent variable in patients with shock due to any cause and in patients with septic shock. Variables considered for the multivariable analysis included age, gender, comorbid diseases and SAPS II score on admission, the extent of organ failure assessed by the SOFA score, the initial and maximum dose of vasopressors, and the mean fluid balance. Variables were introduced in the multivariate model if significantly associated with a higher risk of ICU mortality on a univariate basis at $p < 0.2$. Colinearity between variables was excluded before modeling by computing the correlation of estimates, with an $R^2 > .7$ considered to be significant. Interaction terms involving combinations between comorbid diseases on admission and between various catecholamines were tested. After adjustment for demographic variables, comorbidities on admission, severity scores, and fluid balance, the initial and the maximum doses of each agent were injected in the model in a stepwise fashion. Three countries were associated with higher and one with lower ICU mortalities in comparison with other countries and were adjusted for in the final model. The use of each catecholamine was introduced in the last step as a categorical variable. A Hosmer and Lemeshow goodness-of-fit test was performed; Nagelkerke pseudo R^2, classification tables, and odds ratios with 95% confidence interval were computed. Kaplan-Meier survival curves were plotted and compared using a signed log rank test. To minimize the effect of censored data in the survival analysis, we considered 30-day survival as a target. All statistics were two-tailed, and a $p < .05$ was considered to be significant.

RESULTS

Of the 3,147 patients included in the SOAP study, 1,058 (33.6%) had shock at any time; 462 (14.7%) had septic shock. Among 198 contributing centers, 101 (1,719 patients) were university, 64 (879 patients) city, and 33 (549 patients) community hospitals. The incidence of shock due to any cause (25.5%, 34.2%, and 35.9%, respectively, $p < .001$) and septic shock (10.6%, 14.9%, and 15.9%, respectively, $p = .004$) was lower in community compared with city and university hospitals.

Catecholamine Use. Norepinephrine was the most commonly used vasopressor agent (80.2%), used as a single agent in

31.8% of patients with shock. Dopamine was used in 35.4% of patients with shock, as a single agent in 8.8% of patients and combined most commonly with norepinephrine (11.6%). Epinephrine was used less commonly (23.3%) but rarely as a single agent (4.5%). Dobutamine was combined with other catecholamines in 33.9% of patients, mostly with norepinephrine (15.4%). All four catecholamines were administered simultaneously in 2.6% of patients (Table 1). Other, less commonly used vasoactive/inotropic drugs included dopexamine (n = 16), vasopressin (n = 11), isoproterenol (n = 9), milrinone (n = 9), and phenylephrine (n = 5).

Among patients with shock, 375 patients (35.4%) received dopamine (dopamine group) and 683 (64.6%) did not (Table 2). Age, gender, SAPS II score, SOFA score, and infection rates on admission were comparable between dopamine groups and other patients in shock. The dopamine group had a higher incidence of chronic obstructive pulmonary disease and heart failure. The maximum dose of dopamine administered per patient was 8.5 (5.5–13.3) μg/kg/min (median [interquartile range]). Of the 375 patients who received dopamine, 290 (77.3%) received doses of >5 μg/kg/min, 42 (11.2%) received 3–5 μg/kg/min, and 43 (11.5%) received <3 μg/kg/min (in conjunction with either epinephrine or norepinephrine). Dopamine was used more in community than in university or city hospitals (43.6%, 36.3%, and 29.9%, respectively, $p = .016$). There was substantial international variability in the use of vasopressors (Fig. 1).

Morbidity and Mortality. ICU and hospital mortality rates were higher in patients with shock due to any cause (38.3% vs. 8.5% and 44.6% vs. 13.6%, respectively, both $p < .01$) than in patients without shock, and higher in patients with septic than nonseptic shock (47.4% vs. 31.2% and 54.1% vs. 37.2%,

Table 3. Morbidity and mortality in patients with shock

	All Patients (n = 1058)	No Dopamine (n = 683)	Dopamine (n = 375)	p Value
SOFA score, median (IQR)				
Maximum SOFA score	10 (8–13)	10 (8–13)	10 (8–14)	.579
Mean SOFA score	7 (5–9)	7 (5–9)	7 (5–10)	.408
ICU-acquired infection	158 (14.9)	93 (13.6)	65 (17.3)	.105
Hemofiltration (%)	182 (17.2)	121 (17.7)	61 (16.3)	.550
Hemodialysis (%)	78 (7.4)	48 (7.0)	30 (8.0)	.563
ICU stay, days, median (IQR)	6 (3–14)	6 (3–13)	7 (3–15)	.165
Hospital stay,[a] days, median (IQR)	20 (8–43)	20 (8–46)	20 (8–38)	.102
ICU mortality (%)	405 (38.3)	244 (35.7)	161 (42.9)	.021
Mortality at 30 days (%)	419 (39.6)	252 (36.9)	167 (44.5)	.013
Hospital mortality[b] (%)	468 (44.6)	283 (41.7)	185 (49.9)	.011

SOFA, Sequential Organ Failure Assessment; IQR, interquartile range; ICU, intensive care unit.
[a]18 missing; [b]three missing.

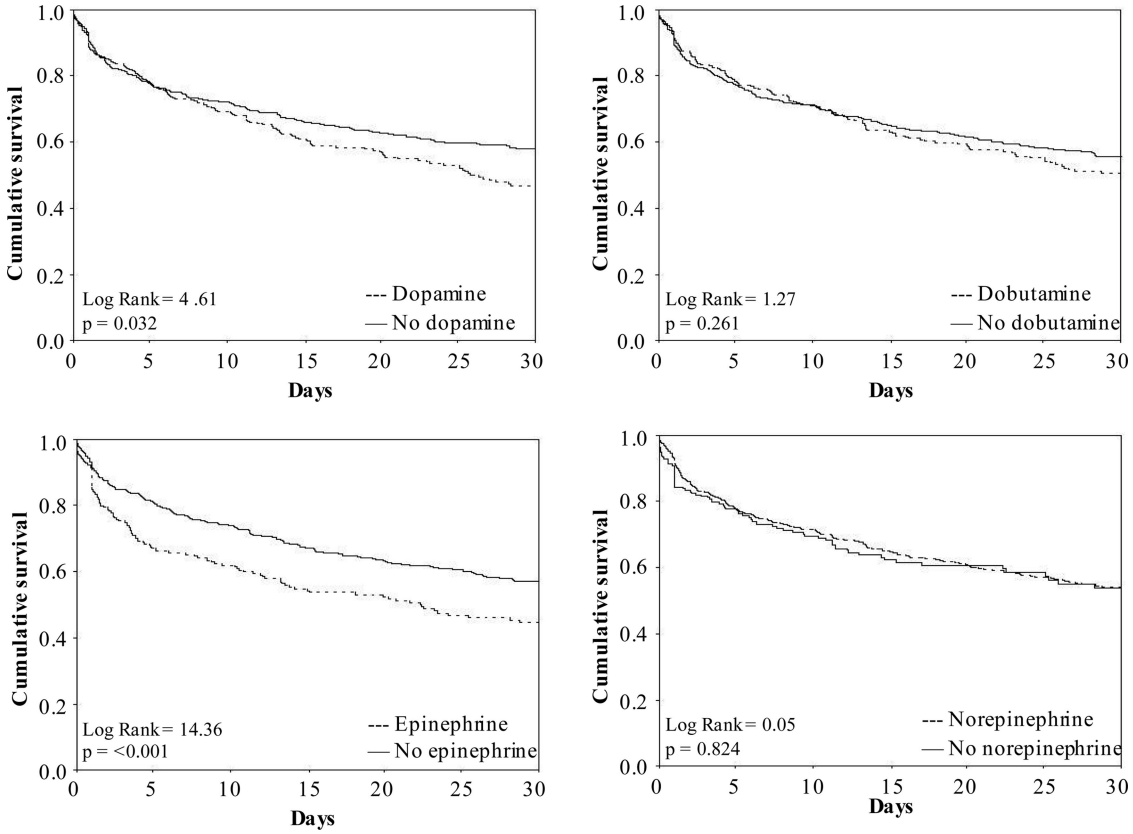

Figure 2. Kaplan-Meier survival curve at 30 days of ICU admission in patients with shock due to any cause (n = 1058) according to administration of dopamine (*upper left*), dobutamine (*upper right*), epinephrine (*lower left*), and norepinephrine (*lower right*). Survival was decreased in patients who received dopamine or epinephrine compared with those who did not.

Table 4. Characteristics of survivors and nonsurvivors of shock due to any cause (n = 1058)

	Nonsurvivors (n = 405)	Survivors (n = 653)	p Value
Age,[a] mean ± SD	65 ± 15	61 ± 17	.005
Female[b] (%)	174 (43.4)	226 (34.9)	.006
Comorbid diseases (%)			
Cancer	60 (14.8)	73 (11.2)	.023
Hematologic cancer	22 (5.4)	14 (2.1)	.004
COPD	53 (13.1)	64 (9.8)	.098
Liver cirrhosis	30 (7.4)	24 (3.7)	.007
HIV infection	5 (1.2)	3 (0.5)	.680
Heart failure	52 (12.8)	88 (13.5)	.776
Diabetes	31 (7.7)	50 (7.7)	.999
Medical admission (%)	254 (62.7)	260 (39.8)	<.001
SAPS II,[c] mean ± SD	54.9 ± 18.4	41.9 ± 14.8	<.001
SOFA score, median (IQR)			
Initial SOFA score[d]	9 (6–12)	8 (5–10)	<.001
Maximum SOFA score	13 (10–15)	9 (7–11)	<.001
Mean SOFA score	10 (7–13)	6 (4–7)	<.001
Infection on admission (%)	174 (43.0)	223 (34.2)	.004
ICU-acquired infection (%)	59 (14.6)	99 (15.2)	.793
Sepsis at any time (%)	243 (60.0)	339 (51.9)	.010
Mechanical ventilation (%)	391 (96.5)	591 (90.5)	<.001
Catecholamine use (%)			
Norepinephrine	332 (82.0)	516 (79.0)	.241
Dopamine	161 (39.8)	214 (32.8)	.021
Epinephrine	123 (30.4)	123 (18.8)	<.001
Dobutamine	151 (37.3)	208 (31.9)	.070
Maximum catecholamine dose,[e] mean ± SD			
Norepinephrine	0.7 ± 0.7	0.5 ± 0.7	<.001
Dopamine	13.4 ± 10.8	8.6 ± 5.5	<.001
Epinephrine	0.8 ± 0.8	0.6 ± 0.8	.001
Dobutamine	11.3 ± 8.0	7.5 ± 5.2	<.001
Cumulative fluid balance, L, mean ± SD	4.5 ± 18.1	−1.8 ± 17.2	<.001
Mean fluid balance, L, mean ± SD	1.0 ± 1.7	−0.1 ± 1.2	<.001
ICU stay in days, median (IQR)	4 (1–12)	7 (3–15)	<.001
Hospital stay in days, median (IQR)	9 (3–23)	29 (15–56)	<.001

COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; IQR, interquartile range; ICU, intensive care unit.

[a]One missing; [b]nine missing gender (valid percentage is presented after exclusion of missing values); [c]12 missing; [d]ten missing (11 missing variables were replaced); [e]doses in $\mu g/kg \cdot min^{-1}$.

Table 5. Summary of a multivariable forward stepwise logistic regression analysis with intensive care unit outcome as the dependent factor in patients with shock due to any cause and those with septic shock

	Shock Due to Any Cause[a] (n = 1058)		Septic Shock[b] (n = 462)	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Mean SOFA score	1.53 (1.44–1.62)[c]	<.001	1.52 (1.39–1.67)[c]	<.001
Mean fluid balance	1.42 (1.26–1.59)[d]	<.001	1.39 (1.19–1.63)[d]	<.001
Medical admission	2.36 (1.7–3.27)	<.001	1.83 (1.12–2.99)	.016
Age	1.02 (1.01–1.03)[e]	.001	1.03 (1.01–1.04)[e]	.001
Dopamine administration	1.67 (1.19–2.35)	.003	2.05 (1.25–3.37)	.005
Cancer	2.05 (1.27–3.3)	.003	3.54 (1.72–7.3)	.001

CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

[a]Hosmer and Lemeshow goodness-of-fit chi-square = 6.9 (p = .543). Nagelkerke R^2 = .494. This model has a 79.8% correct classification (88.8 for survivors and 65.4 for nonsurvivors); [b]Hosmer & Lemeshow chi square = 5.9 (p = .661), Nagelkerke R^2 = .501. This model has 76.4% correct classification (81.5% in survivors and 70.6% in nonsurvivors); [c]per point; [d]per liter; [e]per year. The country effect was not significant and was not retained in the final model.

respectively, both $p < .01$). ICU mortality rate in patients with shock was similar among university, city, and community hospitals (39.4%, 38.9%, and 32.1%, respectively, p = .273). Patients treated with dopamine had higher ICU, 30-day, and hospital mortality rates than other patients in shock (Table 3). No difference in ICU mortality rates in patients treated with dopamine was observed among university, city, and community hospitals (45.1%, 42.2%, and 36.1%, respectively, p = .445). The degree of organ dysfunction, as assessed by the maximum and mean SOFA scores during the ICU stay, was similar among patients treated with dopamine and those who received no dopamine, as was hospital and ICU length of stay (Table 3). Similar rates of renal support therapy were observed in both groups. A total of 284 (26.8%) patients stayed in the hospital for ≥30 days. The Kaplan-Meier survival curves are shown in Figure 2. The 30-day survival was decreased in the dopamine group (log rank = 4.6, p = .032) compared with the no-dopamine group. Epinephrine administration was also associated with a decreased 30 day-survival (log rank = 14.4, $p < .001$).

Of 244 patients who were treated with both dopamine and norepinephrine, 141 (57.8%) received both drugs on the same first day, another 73 (29.9%) received norepinephrine as the first vasopressor treatment, and 30 (12.3%) received dopamine first. Mortality rates were 47.3%, 54.8%, and 53.3%, respectively (p = not significant).

Predictors of ICU Outcome. Shock nonsurvivors (n = 405) were older (Table 4), were more commonly medical rather than surgical admissions, and were more likely to be female than the survivors. Comorbid diseases associated with a poor outcome included cancer, hematologic cancer, and liver cirrhosis. As expected, SAPS II and SOFA scores were higher in nonsurvivors. Although infection on admission was more common in nonsurvivors than survivors, ICU-acquired infection rates were similar in both groups. As expected, nonsurvivors required higher catecholamine doses. Dopamine and epinephrine were used more in nonsurvivors than in survivors. Cumulative and mean fluid balances were greater and ICU and hospital lengths of stay were longer in nonsurvivors than in survivors.

In a multivariate, logistic forward stepwise analysis with ICU outcome as the dependent factor, age, cancer, medical admission, higher mean SOFA score, greater mean fluid balance, and dopamine administration were independent risk factors for ICU mortality in patients with shock (Table 5). None of the tested interactions were significant and, there-

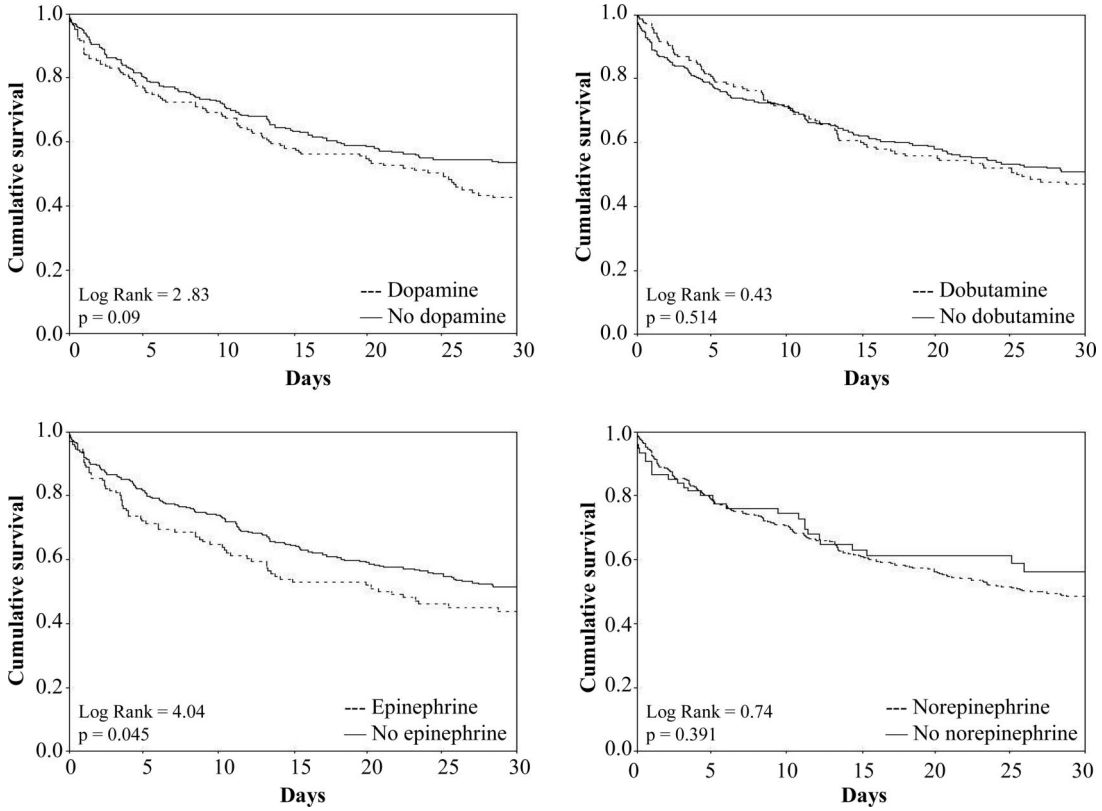

Figure 3. Kaplan-Meier survival curve at 30 days of ICU admission in patients with septic shock (n = 462) according to administration of dopamine (*upper left*), dobutamine (*upper right*), epinephrine (*lower left*), and norepinephrine (*lower right*). Survival was decreased in patients who received epinephrine compared with those who did not. There was a tendency for decreased survival in the dopamine compared with the no-dopamine group.

fore, were not considered in the final model.

Dopamine Use in Septic Shock. In the 462 patients with septic shock, dobutamine use was more common in nonsurvivors than in survivors (41.6% vs. 32.5%, $p < .05$). There was a tendency toward more epinephrine use (31.5% vs. 23.5%, $p = .052$) and dopamine (43.4% vs. 35.4%, $p = .079$) administration in nonsurvivors than in survivors. Also, there was a tendency toward lower 30-day survival (Fig. 3) in patients with septic shock treated with dopamine than others (log rank = 2.8, $p = .09$). Epinephrine administration was associated with decreased 30-day survival (log rank 4.04, $p = .045$). However, norepinephrine and dobutamine administration was not associated with altered 30-day survival. Other factors associated with ICU mortality from septic shock included older age, female gender, cancer, hematologic cancer, medical admission, higher SAPS II and SOFA scores, and higher fluid balance (Table 6). The ICU mortality rate in patients with septic shock was similar among patients admitted from a university, city, or community hospital (47.6%, 47.3%, 46.6%, respectively, $p = .989$) with a similar incidence of dopamine administration (41.4%, 32.1%, 44.6%, respectively, $p = .127$). In septic shock patients treated with dopamine, ICU mortality rates were also similar (52.2%, 54.8%, and 50%, respectively, $p = .925$).

In a multivariate logistic forward stepwise analysis (Table 5) with ICU mortality as the dependent factor, dopamine administration was independently associated with a higher risk of death from septic shock (odds ratio, 2.05; 95% confidence interval, 1.25 –3.37), in addition to higher SOFA score, greater mean fluid balance, cancer, older age, and medical admission.

In patients with nonseptic shock (n = 596), ICU (34% vs. 30%, $p = .303$) and hospital (42% vs. 35%, $p = .117$) mortality rates were higher, but statistically not significant, in patients who received dopamine compared with those who did not. In a multivariable logistic regression analysis with ICU mortality as the dependent variable, dopamine administration was not an independent risk factor for mortality in this group of patients (data not shown)

DISCUSSION

Our data suggest that dopamine administration may be associated with a worse outcome from shock due to any cause. Our study included almost 200 ICUs and >3,000 patients. One third of the patients had shock at some point during their ICU stay and 15% had septic-shock. Dopamine was used in 35% of the patients with shock in these European ICUs.

Dopamine administration was associated with ICU and hospital mortality rates 20% higher than in patients with shock who did not receive dopamine; survival rates were also lower at 30 days than for other patients in shock. These differences could not be explained by differences in severity of disease, as SAPS II and SOFA scores on admission were similar in the two groups. Despite the relatively higher incidence of treatment with dopamine in ICUs located in community hospitals and the lower incidence in those located in city hospitals, this factor could not explain the worse outcome associated with dopamine use in this study as mortality rates were similar across hospital types

Table 6. Characteristics of survivors and nonsurvivors of septic shock (n = 462)

	Septic Shock (n = 462)	Survivors (n = 243)	Nonsurvivors (n = 219)	p Value
Age, yrs, mean ± SD	63 ± 16	61 ± 17.2	66 ± 14.8	.002
Female[a] (%)	178 (38.6)	79 (32.5)	99 (45.4)	.004
Comorbid diseases (%)				
Cancer	61 (13.2)	23 (9.5)	38 (17.4)	.013
Hematologic cancer	23 (5.0)	5 (2.1)	18 (8.2)	.002
COPD	61 (13.2)	30 (12.3)	31 (14.2)	.566
Liver cirrhosis	25 (5.4)	11 (4.5)	14 (6.4)	.375
HIV infection	5 (1.1)	2 (0.8)	2 (0.9)	.917
Heart failure	57 (12.3)	30 (12.3)	27 (12.3)	.996
Diabetes	39 (8.4)	18 (7.4)	21 (9.6)	.400
Medical admissions (%)	246 (53.2)	116 (47.7)	130 (59.4)	.012
SAPS II,[b] mean ± SD	49.8 ± 17.1	45.6 ± 14.7	54.0 ± 18.3	<.001
SOFA score, median (IQR)				
Initial SOFA score[c]	8 (6–11)	8 (5–10)	9 (6–12)	.002
Maximum SOFA score	11 (9–14)	10 (8–12)	13 (11–16)	<.001
Mean SOFA score	7 (5–10)	6 (4–8)	9 (7–13)	<.001
Infection on admission (%)	335 (72.5)	179 (73.7)	156 (71.2)	.559
ICU-acquired infection (%)	88 (19.0)	41 (16.9)	47 (21.5)	.210
Catecholamine use (%)				
Norepinephrine	386 (83.5)	197 (81.1)	189 (86.3)	.134
Dopamine	174 (37.7)	86 (35.4)	95 (43.4)	.079
Epinephrine	126 (27.3)	57 (23.5)	69 (31.5)	.052
Dobutamine	170 (36.8)	79 (32.5)	91 (41.6)	.044
Cumulative fluid balance, L, mean ± SD	2.5 ± 23.1	−2.9 ± 23.0	5.6 ± 23.0	<.001
Mean fluid balance, L, mean ± SD	0.9 ± 1.7	−0.1 ± 1.3	1.0 ± 1.8	<.001
ICU stay, days, median (IQR)	10 (5–21)	12 (7–25)	7 (3–15)	<.001
Hospital stay,[d] days, median (IQR)	27 (11–29)	44 (23–60)	14 (5–31)	<.001

COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; IQR, interquartile range; ICU, intensive care unit.

[a]One missing gender (valid percentage is presented after exclusion of missing values); [b]five missing; [c]six missing (eight missing variables were replaced); [d]eight missing.

This observational study suggests that dopamine administration may be associated with increased mortality rates in shock.

not only in the whole population with shock but also in the subgroup with septic shock.

The use of norepinephrine did not show even a trend toward higher mortality in our patients. Patients treated with epinephrine had a worse outcome, but this agent is often given as a second-line agent in patients with more severe forms of cardiovascular failure. Also, dobutamine may be used more commonly for patients who have more severe myocardial depression (12). However, the multivariable analysis identified dopamine as an independent risk factor for death in patients with shock due to any cause.

Our data cannot identify the reason for the increased mortality in dopamine-treated patients, but several hypotheses can be raised. First, dopamine may induce tachyarrhythmias. However, the increase in heart rate may contribute to the increase in cardiac output, thereby improving organ perfusion. The administration of dobutamine together with norepinephrine can also increase heart rate. Second, some investigators have suggested that norepinephrine may have more beneficial effects on gut mucosal perfusion than dopamine (7). However, this statement is primarily based on a pilot study, suggesting a higher gastric intramucosal pH with norepinephrine than with dopamine, an observation that is debated (2, 13). Experimental studies on this have yielded controversial results. Ruokonen et al. (14) found no changes in splanchnic blood flow or oxygen consumption with norepinephrine, whereas dopamine consistently increased splanchnic blood flow. More recently, De Backer et al. (2) found no differences in splanchnic blood flow or P_{CO_2} gap between norepinephrine and dopamine in 20 patients with septic shock. If anything, dopamine was associated with a lower mixed venous-hepatic venous oxygen saturation gradient, indicating a better oxygen balance with dopamine than norepinephrine (2). Hence, it is unlikely that norepinephrine has more beneficial effects on gut mucosal perfusion than dopamine. Third, norepinephrine may have more beneficial effects on renal perfusion and more effectively restore urinary output (15). On the other hand, the use of renal dose dopamine has been challenged for its lack of efficacy (16) and can no longer be recommended, although, interestingly, 23% of patients who received dopamine received doses ≤5 μg/kg/min, suggesting that dopamine is still used in some ICUs for its supposed beneficial effects on renal function. We observed no difference in the need for renal support therapy in our study between dopamine-treated patients and other patients. Fourth, dopamine administration can reduce the release of a number of hormones from the anterior pituitary gland, including prolactin (17, 18), which can have important immunoprotective effects. The tendency toward a higher incidence of ICU-acquired infection in dopamine-treated patients in our study may favor this mechanism. However, one may argue that if dopamine is used only for limited periods of time (as in shock resuscitation), the deleterious effects of this action may be transient and may even be beneficial in septic shock if the host response is exaggerated.

One report showed improved outcomes for patients in septic shock treated with norepinephrine (19), but the nonrandomized, observational nature of that study means that the results must be interpreted with caution. No clinical study has definitely indicated that one catecholamine is superior to another, so that at present no agent should be preferred over the other (20, 21).

Observational studies such as the current one have their limitations. The inclusion period was very short (2 wks) and participation was voluntary, so the results may not be extrapolated to all ICU patients. Moreover, the multivariable analyses cannot take all possible confounding factors into account, including organizational issues and differences in clinical practice (22) at the level of individual ICUs; the use of novel therapies that have proven efficacy in certain subsets of ICU patients, such as activated protein C (23); and the adoption of early goal-directed therapy (24). Also, in cases

of nonseptic shock, we were not able to discriminate between the various etiologies (anaphylactic, cardiac failure, etc), their management, and potential differences in their outcomes. We cannot determine a cause-and-effect relationship based on the current analysis. Nevertheless, this study suggests that dopamine administration may be associated with worse outcomes from shock of any cause. This observation needs further evaluation by a prospective, randomized, controlled study.

REFERENCES

1. Ruokonen E, Takala J, Kari A, et al: Regional blood flow and oxygen transport in septic shock. *Crit Care Med* 1993; 21:1296–1303
2. De Backer D, Creteur J, Silva E, et al: Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? *Crit Care Med* 2003; 31:1659–1667
3. Aubier M, Murciano D, Menu Y, et al: Dopamine effects on diaphragmatic strength during acute respiratory failure in chronic obstructive pulmonary disease. *Ann Intern Med* 1989; 110:17–23
4. Saldias FJ, Comellas AP, Pesce L, et al: Dopamine increases lung liquid clearance during mechanical ventilation. *Am J Physiol Lung Cell Mol Physiol* 2002; 283:L136–L143
5. Adir Y, Azzam ZS, Lecuona E, et al: Augmentation of endogenous dopamine production increases lung liquid clearance. *Am J Respir Crit Care Med* 2004; 169:757–763
6. Van den Berghe G, de Zegher F, Lauwers P: Dopamine suppresses pituitary function in infants and children. *Crit Care Med* 1994; 22:1747–1753
7. Martin C, Papazian L, Perrin G, et al: Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103:1826–1831
8. Duranteau J, Sitbon P, Teboul JL, et al: Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. *Crit Care Med* 1999; 27:893–900
9. Le Gall J-R, Lemeshow S, Saulnier F: A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; 270:2957–2963
10. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996; 22:707–710
11. ACCP-SCCM Consensus Conference: Definitions of sepsis and multiple organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874
12. Vincent JL, Reuse C, Kahn RJ: Effects on right ventricular function of a change from dopamine to dobutamine in critically ill patients. *Crit Care Med* 1988; 16:659–662
13. Hasibeder W, Germann R, Wolf HJ, et al: The effects of short-term endotoxemia and dopamine on mucosal oxygenation in the porcine jejunum. *Am J Physiol* 1996; 270: G667–G675
14. Ruokonen E, Takala J, Kari A: Regional blood flow and oxygen transport in patients with the low cardiac output syndrome after cardiac surgery. *Crit Care Med* 1993; 21: 1304–1311
15. Bellomo R, Kellum JA, Wisniewski SR, et al: Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. *Am J Respir Crit Care Med* 1999; 159: 1186–1192
16. Bellomo R, Chapman M, Finfer S, et al: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356:2139–2143
17. Bailey AR, Burchett KR: Effect of low-dose dopamine on serum concentrations of prolactin in critically ill patients. *Br J Anaesth* 1997; 78:97–99
18. Devins SS, Miller A, Herndon BL, et al: Effects of dopamine on T-lymphocyte proliferative responses and serum prolactin concentrations in critically ill patients. *Crit Care Med* 1992; 20:1644–1649
19. Martin C, Viviand X, Leone M, et al: Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000; 28:2758–2765
20. Dellinger RP, Carlet JM, Masur H, et al: Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
21. Hollenberg SM, Ahrens TS, Annane D, et al: Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; 32:1928–1948
22. Pronovost PJ, Jenckes MW, Dorman T, et al: Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. *JAMA* 1999; 281:1310–1317
23. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
24. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377

Appendix: Participants by Country (Listed Alphabetically)

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Marx); Stirling Royal Infirmary (C. McCulloch); University Hospital of Wales, Cardiff (P. Morgan); St George's Hospital of London (A. Rhodes); Gloucestershire Royal Hospital (C. Roberts); St. Peters of Chertsey (M. Russell); James Paget Hospital of Great Yarmouth (D. Tupper-Carey, M. Wright); Kettering General Hospital (L. Twohey); Burnley DGH (J. Watts); Northampton General Hospital (R. Webster); Dumfries Royal Infirmary (D. Williams).

Pharmacologic support of the failing circulation: Practice, education, evidence, and future directions*

Following a physiologic stress, the organism initiates the so-called acute phase response, which involves inflammatory mediators, hormones (thyroid hormones, steroids, sexual hormones, insulin), and the autonomic nervous system. Pharmacologic support of the failing circulation has been debated for >40 yrs, and catecholamines have been used for near a century to support it (1, 2). These physiologic neurohumoral mediators are mandatory to be adapted to terrestrial life as, for example, the massive catecholamine surge necessary to adapt from an intrauterine to an extrauterine life in which umbilical cord catecholamine levels correlate with perinatal stress (3). Actually, several agents are available with different pharmacologic spectra. Among catecholamines, dopamine, dobutamine, epinephrine, and norepinephrine are the most used drugs.

The SOAP initiative is a "snapshot" of all patients admitted to 200 intensive care units (ICUs) across Europe during 2 wks, and has recently been published in the journal (3a). In the present issue of *Critical Care Medicine*, Dr. Sakr and colleagues (4) present a secondary analysis focusing on hemodynamic support using the database. They isolated patients receiving catecholamines and analyzed their survival according to the drug received. Other aspects from the SOAP survey were published as abstracts (5–8) or articles assessing specific points such as the pulmonary artery catheter (9).

Database Analysis

The SOAP database includes 3,197 patients (a mean number of 16 patients per ICU) of which 1,058 received catecholamines and 462 had an infection and received catecholamines. Despite concerns (10), more and more subgroup and sub-subgroup analyses occur in the recent literature. Multiplying numerous subgroup analysis (type of shock, type of catecholamine) with several outcomes (death, length of stay, length ventilation, acquired infections) leads to a plethora of statistical tests. This could lead to false-positive tests by chance alone and also reveal false-negative results due to chance or lack of power (11). In fact, when comparing by univariate analysis 20 x variables with ten outcomes, ten comparisons will be positive by chance only. This is nicely illustrated by the analysis in the ISIS-2 database showing that aspirin has a positive effect on myocardial infarction survival (12). In the subgroup analysis of patients with the Libra or Gemini astrological sign, aspirin increased cardiovascular mortality (9% ± 13%, not significant), whereas all other astrological signs showed protective effect of aspirin (12). The study by Dr. Sakr and coworkers (4) represents a tremendous amount of work, and the authors should be congratulated for this. This is a prospective cohort study of >3,000 ICU patients. However, the results should be read with caution: The translation from a statistically significant piece of information to a clinically relevant result is sometimes like finding a needle in a haystack.

A major methodological concern in cohort studies is the control for potential confounding factors, and statistical methods to adjust for them are well described in the literature (13) with their advantages and inconveniences. The major difficulty is to select potential variables to adjust for them: First, if confounders are not completely adjusted for, they may have some residual effects. For example, are all patients with an admission SOFA score in the third quartile (8–11) comparable? Second, several confounding variables may be interrelated and not independent. For example, in Table 5 of Dr. Sakr and colleagues' (4) article, one could suggest that patients with a higher SOFA score had a higher fluid balance. Third, the border between confounding variables to adjust and outcome variables is thin and sometimes hard to define. For example, prolonged length of stay may be a risk factor for nosocomial infection, but nosocomial infection may prolong length of stay.

Definition of Shock

There is a continuous spectrum between normal physiology and end-stage cellular failure leading to cell apoptosis or necrosis. The borders of shock lie somewhere in this gray area. Cardiogenic shock, for example, has been defined by a cardiac output value and septic shock by a hypotension "refractory" to fluid therapy. Dr. Sakr and colleagues (4) used a SOFA cardiovascular score ≥2, corresponding to the use of catecholamines. This is definitively not the standard definition of shock but has the advantage of been clear-cut. We must be cautious using this definition. With the same approach, Dr. Sakr and colleagues defined infection by "the presence of a pathogenic microorganism and/or clinical infection necessitating antibiotic." These definitions change the spotlight on this article: This is not a article on shock management but rather on catecholamine use. Does epinephrine/norepinephrine/dopamine/dobutamine have an effect?

This study focuses on four catecholamines, but other catecholamines and nonadrenergic hemodynamic drugs such as vasopressin receptor analogues or calcium sensitizers are used more and more frequently. However, they are used as second-line agents after conventional drugs fail, and when looking at the mortality rate in patients receiving these drugs vs. patients not receiving them, it is expected that they will "apparently" increase mortality rate. The role of these drugs may change when the results of the VASST study become available (14).

*See also p. 589.

Key Words: acute phase response; catecholamines; sepsis

This author has nothing to disclose.

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Cohort and Controlled Studies

Cohort studies are not randomized controlled trials. In cohort studies, a) patients are enrolled according to defined criteria—as admission to the ICU other than as a "simple" postoperative case in the present study; b) treatment allocation is not controlled but determined by practice pattern, personal choices, or policy; c) outcomes can be defined after intervention; and moreover d) the statistical analyses are more complicated and require complex multivariate analysis (15). It has been suggested that cohort studies should confirm the results of randomized controlled trials (16), but in the present cohort study the authors suggest that a randomized trial should be done. With the advent of large ICU database allowing number crunching and statistical exploration, the role of so-called cohort studies is changing: They allow the exploration of potential associations to be ultimately tested in prospective randomized trials.

Dopamine Pharmacology

Physiologically, dopamine is synthesized from the amino acid phenylalanine by two cytosolic enzymes, thyroxine hydroxylase and dopa decarboxylase. Dopamine is further converted by the granular enzyme dopamine-β-hydroxylase into norepinephrine, which is converted into epinephrine by phenylalanine-N-methyltransferase. Norepinephrine and epinephrine are catabolized by the catechol-O-methyl-transferase into normetanephrine and metanephrine and degraded into vanilmandelic acid by the monoaminoxydase. Dopamine infusions in the pharmacologic range yield plasma concentrations 100-fold above physiologic concentrations (17), but dopamine has a marked interindividual pharmacokinetic variability: Infusing 10 μg/kg/min dopamine in healthy volunteers yielded steady-state plasma concentration in the 12,000–200,000 ng/L range (18). Norepinephrine has been recently shown to have the same interindividual pharmacokinetic with a 70–10,000 mL/min range in plasma clearance (19). Perfusing dopamine increased the plasma concentration of its metabolite norepinephrine (20). This could add to the α-mediated effect. Therefore dopamine, norepinephrine, and epinephrine are related drugs, linked by pharmacokinetics and pharmacodynamics relations.

"One Size Fits All" Strategy and Hemodynamic Support

Leone et al. (21) in a French survey showed that in selected clinical situations, the choice of catecholamine is based on personal and cultural preferences: Dobutamine for cardiogenic shock and epinephrine for anaphylactic shock and cardiac arrest had an agreement >90%. On the other end, norepinephrine was used as first-line vasopressor for septic shock in only 52%, and there was a lack of consensus on the catecholamine to use for "regional flow optimization" or in "high-risk surgical patients." An important point shown by Dr. Sakr and colleagues (4) is that the pattern of catecholamine use is very different between community and teaching university hospitals and that the pattern is very different from one country to another: Community hospital physicians prescribe relatively more dopamine and less norepinephrine than teaching centers. There are different ICU settings and cultures from Portugal to Sweden, but it is surprising that >40% of Portuguese patients receive dopamine and >40% norepinephrine, whereas <6% of Swedish patients receive either dopamine or norepinephrine. The lower proportion of patients requiring catecholamine in community hospitals implies that physicians are exposed to fewer catecholamine-dependent patients and do not care for multiple catecholamine-dependent patients daily. There is no rational evidence to support this, but one may argue that among community hospital physicians, there is a certain "fear" of norepinephrine and the belief that dopamine, "a little bit β and a little bit α, as inotrope or vasopressor, may do the job." We could therefore extend Bailey's (22) editorial on dopamine pharmacokinetics titled "One Size Does Not Fit All" to "One Drug Does Not Fit All."

The blame on dopamine could be extended to epinephrine: from Dr. Sakr and colleagues' (4) Figure 2 one can conclude that epinephrine is associated with a lower survival rate. Epinephrine has several metabolic side effects limiting its use. Therefore, it has been mainly used as a second-line or rescue agent when the first line fails. It is obvious that patients receiving epinephrine have a higher mortality rate than patients not receiving epinephrine. We could do the same analysis showing that patients receiving vasopressin had a higher mortality rate than patients not receiving it. However, who will discard these drugs from the pharmacopeia based on the present article?

Low-Dose Dopamine Is Still Alive!

How long will it be before low-dose or so-called renal dose dopamine will be definitively abandoned (23, 24) ? More than 40 yrs have passed since McDonald et al. (25) showed that dopamine administration increased urine production in healthy volunteers. Acute renal failure is almost always the result of renal hypoperfusion, and magnetic resonances studies have confirmed the resultant renal hypoxia (26). There is evidence that dopamine may increase renal oxygen consumption and may therefore jeopardize renal oxygen supply/demand balance. There is also ample evidence that the so-called renal dopamine does not change mortality, risk of renal failure, or need for extracorporeal renal replacement therapy (24). The evidence-based guidelines published in 2004 in this journal do not support the use of dopamine as renal protection or renal salvage agent (27). The data from Dr. Sakr and colleagues (4) unveil the gap between the evidence-based data and bedside clinical practice.

As suggested by Dr. Sakr and colleagues (4), are we ready to begin a randomized trial comparing dopamine and norepinephrine for hemodynamic support? What type of monitoring should be applied (9, 28), how should information of this monitoring be read (29, 30) and interpreted (31) and what would be the end point of resuscitation? Who will apply in a trial where the active drug (dopamine) may kill more patients than the other group (no dopamine)? Is a randomized trial the top priority? The monitoring armamentarium is expanding toward continuous cardiac output, continuous stroke volume variation, pulse pressure variation, intrathoracic blood volume, global end-diastolic volume, echocardiography, and microcirculation. The therapeutic possibilities now include vasopressin and its analogues, phosphodiesterase inhibitors, and calcium channel sensitizers. The present article shows a potential association between certain catecholamines and an important outcome—mortality—but no causal relationship could be demonstrated. The lack of well-designed clinical trials contributes to the persistence of the biodiversity in catecholamine use. The article by Dr. Sakr and colleagues (4) raises

more questions than answers and has reopened the eternal dispute on which catecholamine to use in shock.

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REFERENCES

1. Fearon RE: Comparison of norepinephrine and isoproterenol in experimental coronary shock. Observations on the effects of dextran infusion. *Am Heart J* 1968; 75: 634–648
2. Shanbour LL, Hinshaw LB: Cardiac and peripheral effects of dopamine infusion in endotoxin shock in the dog. *J Pharmacol Exp Ther* 1969; 170:108–116
3. Herlenius E, Lagercrantz H: Development of neurotransmitter systems during critical periods. *Exp Neurol* 2004; 190(Suppl 1): S8–S21

3a. Vincent JL, Sakr Y, Spring CL, et al: Sepsis in European intensive care units: Results of the SOAP study. *Crit Care Med* 2006; 34: 344–353

4. Sakr Y, Reinhart K, Vincent J-L, et al: Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Crit Care Med* 2006; 34:589–597
5. Brunkhorst F, Sakr Y, Vincent JL, et al: On behalf of the SOAP investigators: Outcome of early, late and recurrent shock in the ICU: Results of the SOAP study. *Intensive Care Med* 2004; 30(Suppl):S47
6. Moreno R, Sakr Y, Vincent JL, et al: On behalf of the SOAP investigators: Predictors of poor outcome in various age groups: Results of the SOAP study. *Intensive Care Med* 2004; 30(Suppl):S53
7. Sakr Y, Vincent JL, Reinhart K, et al: On behalf of the SOAP investigators: Medical admission are associated with worse ICU outcome: Results of the SOAP study. *Intensive Care Med* 2004; 30(Suppl):S31
8. Sakr Y, Reinhart K, Payen D, et al: A SOFA score based index at ICU discharge predicts subsequent mortality on referral to general floors. *Crit Care Med* 2004; 33(Suppl 12):A83
9. Sakr Y, Vincent JL, Reinhart K, et al: Use of the pulmonary artery catheter is not associated with worse outcome in the ICU. *Chest* 2005; 128:2722–2731
10. Horton R: From star signs to trial guidelines. *Lancet* 2000; 355:1033–1034
11. Schulz KF, Grimes DA: Multiplicity in randomised trials II: Subgroup and interim analyses. *Lancet* 2005; 365:1657–1661
12. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2:349–360
13. Normand SL, Sykora K, Mamdani M, et al: Readers guide to critical appraisal of cohort studies: 3. Analytical strategies to reduce confounding. *BMJ* 2005; 330:1021–1023
14. Holmes C: VASST study. University of British Columbia 2005. Available at: http://www.icapture.ubc.ca/projects/trials/cihrshtml. Accessed October 25, 2005
15. Rochon PA, Gurwitz JH, Sykora K, et al: Reader's guide to critical appraisal of cohort studies: 1. Role and design. *BMJ* 2005; 330: 895–897
16. Black N: Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996; 312:1215–1218
17. Ensinger H, Lindner KH, Goertz A, et al: Metabolic and haemodynamic effects of dopamine plus domperidone in volunteers. *Res Exp Med (Berl)* 1993; 193:241–254
18. MacGregor DA, Smith TE, Prielipp RC, et al: Pharmacokinetics of dopamine in healthy male subjects. *Anesthesiology* 2000; 92: 338–346
19. Beloeil H, Mazoit JX, Benhamou D, et al: Norepinephrine kinetics and dynamics in septic shock and trauma patients. *Br J Anaesth* 2005; 95:782-788
20. Lieverse AG, Lefrandt JD, Girbes AR, et al: The effects of different doses of dopamine and domperidone on increases of plasma norepinephrine induced by cold pressor test in normal man. *Hypertens Res* 1995; 18(Suppl 1):S221–S224
21. Leone M, Vallet B, Teboul JL, et al: Survey of the use of catecholamines by French physicians. *Intensive Care Med* 2004; 30: 984–988
22. Bailey JM: Dopamine: One size does not fit all. *Anesthesiology* 2000; 92:303–305
23. Jones D, Bellomo R: Renal-dose dopamine: From hypothesis to paradigm to dogma to myth and, finally, superstition? *J Intensive Care Med* 2005; 20:199–211
24. Kellum JA, M Decker J: Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; 29:1526–1531
25. McDonald RH Jr, Goldberg LI, McNay JL, et al: Effect of dopamine in man: Augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. *J Clin Invest* 1964; 43:1116–1124
26. Chan L, Shapiro JI: Contributions of nuclear magnetic resonance to study of acute renal failure. *Ren Fail* 1989; 11:79–89
27. Beale RJ, Hollenberg SM, Vincent JL, et al: Vasopressor and inotropic support in septic shock: An evidence-based review. *Crit Care Med* 2004; 32:S455–S465
28. Harvey S, Harrison DA, Singer M, et al: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): A randomised controlled trial. *Lancet* 2005; 366: 472–477
29. Gnaegi A, Feihl F, Perret C: Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act? *Crit Care Med* 1997; 25:213–220
30. Iberti TJ, Fischer EP, Leibowitz AB, et al: A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. *JAMA* 1990; 264:2928–2932
31. Bouchard MJ, Denault A, Couture P, et al: Poor correlation between hemodynamic and echocardiographic indexes of left ventricular performance in the operating room and intensive care unit. *Crit Care Med* 2004; 32: 644–648