Strong vasopressor support may be futile in the intensive care unit patient with multiple organ failure

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Objective: The aim of the study was to determine the prognosis in patients who needed norepinephrine treatment in our institution in relation to the degree of organ failure and the evolution of the disease process.

Design: Retrospective case note analysis of outcome of those patients who needed norepinephrine according to our institutional regimen.

Patients: A total of 100 consecutive patients admitted to our 31-bed medical-surgical intensive care unit (ICU) who were treated with norepinephrine for severe hypotension and evidence of end-organ hypoperfusion unresponsive to both fluid resuscitation and dopamine treatment at 20 μg/kg/min.

Measurements: The degree of organ dysfunction at the time of starting norepinephrine treatment was assessed by the sequential organ failure assessment (SOFA) score. The time before starting norepinephrine treatment was defined as the time elapsed between ICU admission and that of starting norepinephrine administration. The patients were defined as survivors or nonsurvivors according to their ICU outcome.

Results: There were relationships between mortality and the degree of organ dysfunction and mortality and the duration of ICU stay before starting norepinephrine treatment. The mortality rate was 100% in the 30 patients with a total SOFA score of >12 and a delay before starting norepinephrine treatment of >1 day. The mortality rate of the other patients was 63%. The lowest mortality was seen in patients with lower SOFA scores and early norepinephrine administration after admission.

Conclusions: Both the time of starting norepinephrine treatment after admission to the ICU and the degree of organ dysfunction have an important bearing on subsequent outcome. Although norepinephrine may be a lifesaving catecholamine in some cases, its administration to patients who have already developed multiple organ failure during their stay in the ICU is associated with a poor outcome.

Key Words: adrenergic agents; catecholamines; circulatory shock; arterial hypotension; end of life; ethics; multiple organ failure; life support.

Severe acute circulatory failure is a common and frequently fatal condition despite early recognition and treatment in the intensive care unit (ICU) setting. This is especially true when the shock state is refractory to standard doses of vasopressor agents. In such cases, particularly in the presence of multiple...
organ failure (MOF), increasing the level of treatment may even be considered futile. The modern ICU is able to sustain life for prolonged periods of time and, in fact, the majority of deaths in the ICU today occur after the withdrawing or withholding of treatment (1, 2). In the critically ill patient, the decision to start or continue treatment with a particular agent may thus become an ethical issue, one of many ethical dilemmas facing the ICU physician. Such decisions must be based on reasonable evidence that the drug in question will be of benefit to that patient.

In our institution, treatment of circulatory shock follows a standard regimen. Briefly, cardiovascular resuscitation is based on fluid administration whenever possible and the early use of dopamine. Norepinephrine infusion is administered only in cases of hypotension refractory to such initial treatment.

The aim of this study was to evaluate the prognosis of patients who needed norepinephrine administration according to this therapeutic protocol. We reviewed the outcome of patients who needed norepinephrine in our department looking at the presence of organ failure and the time that elapsed after admission to the ICU before starting such treatment.

## PATIENTS AND METHODS

We analyzed the records of 100 consecutive patients admitted to our 31-bed medical-surgical ICU in 1996 who were treated with norepinephrine for severe hypotension. All patients had signs of circulatory shock, including arterial hypotension (mean arterial pressure, <70 mm Hg), associated with evidence of altered organ perfusion, such as altered mental status, oliguria (as defined by a urine output of <20 mL/hr), or a blood lactate level of >2 mEq/L. In our institution, the treatment of circulatory shock follows a standard regimen. When possible, the original cause of shock is identified and treated appropriately. A source of sepsis is sought, treated with appropriate antibiotics, and surgically drained if possible. Oxygen is administered early and mechanical ventilation initiated whenever needed. Arterial pressure is monitored via an intra-arterial catheter. Hemodynamic resuscitation consists first of fluid administration guided by the central venous pressure. If hypotension persists, administration of dopamine is started. All patients have pulmonary artery flotation catheters inserted for the measurement of pulmonary artery pressures, pulmonary artery occlusion pressure, and cardiac output. A dobutamine infusion is started if the cardiac output is found to be inadequate. Norepinephrine is administered only to patients with hypotension resistant to both fluid administration and dopamine at a dose of 20 μg/kg/min.

In this study, we used the sequential organ failure assessment (SOFA) score (3, 4) to assess the degree of organ dysfunction. The SOFA score was calculated at the time of starting norepinephrine treatment. The time before starting norepinephrine treatment was defined as the time that elapsed between ICU admission and the start of norepinephrine administration. The patients were defined as survivors or nonsurvivors according to their ICU outcome. Differences of the medians between groups were analyzed by the Mann-Whitney U test. For comparison of proportional data, a chi-square statistical analysis was performed. A p of <.05 was considered statistically significant.

## RESULTS

The study included 64 medical and 36 surgical patients. Their median age was 65 yrs (range, 10-86 yrs) (Table 1). The indications for norepinephrine treatment are listed in Table 2. The time that elapsed before starting norepinephrine treatment after admission to the ICU was significantly longer in nonsurvivors.
than in survivors (40 hrs vs. 8 hrs, \( p < .05 \)) (Table 1). There was a statistically significant difference between total SOFA scores of survivors and nonsurvivors (11 [range, 8-21] vs. 13 [range, 8-19]; \( p < .05 \)). The development of each organ failure was more common in nonsurvivors than in survivors (Table 3).

Table 1. Demographics of study population

Table 2. Indication for norepinephrine treatment

Table 3. Types of organ failure in survivors and nonsurvivors

There was a relationship between mortality and both total SOFA score and the time before starting norepinephrine treatment (Fig. 1). The mortality rate was 100% in the 30 patients with a total SOFA score of >12 who started norepinephrine treatment >1 day after admission to the ICU. The mortality rate of the other patients ranged from 55% to 71% depending on the degree of organ dysfunction and the length of ICU stay before norepinephrine. The lowest mortality (55%) was seen in patients with lower SOFA scores and early norepinephrine administration after ICU admission. The difference in the mortality rate between these groups was not statistically significant.

Figure 1. Mortality rate according to total sequential organ failure assessment (SOFA) score and time of starting norepinephrine treatment, for survivors (triangles) and nonsurvivors (circles). If the time is >1 day (vertical dotted line) and the total SOFA score is >12 (horizontal dotted line), the mortality is 100% (\( p < .05 \)).

**DISCUSSION**

Norepinephrine is a potent vasopressor agent with both alpha and beta-adrenergic effects. It produces arteriolar constriction in many vascular beds, thus increasing both systemic and pulmonary vascular resistance (5). As a result norepinephrine may further impair organ perfusion and worsen tissue ischemia in patients whose circulation is already compromised (6). However, some patients may need transient vasopressor support to sustain life while the cause of their condition is ascertained and treated. In particular, in patients with septic shock who have a normal or a high cardiac index and a greatly reduced systemic vascular resistance index, norepinephrine may be used safely to increase arterial pressure by increasing vascular resistance (6-9). In some of these patients, urine flow may increase secondarily (7-9). In severe sepsis, norepinephrine may not have deleterious effects on the hepato-splanchnic circulation (10, 11) and may even improve whole body and liver oxygen extraction capabilities (11).
The present study was not designed to assess the effects of norepinephrine per se but rather to reevaluate its use in very severe cases of circulatory failure in relation to the degree of organ failure. Our results show that all patients with a substantial degree of organ dysfunction (as reflected by a total SOFA score of >12) in whom norepinephrine treatment was started >24 hrs after admission to the ICU died. These observations may not readily apply to all ICUs because the use of adrenergic therapy and the management of different types of shock are variable. However, the treatment regimen for circulatory shock followed by our institution is the same as that currently used by several other centers (12-14) and has been recommended in a recent consensus conference (15). Also, the total mortality rate of 74% in this group of patients is similar to that of other reported series (14). Studies limited to patients with hyperdynamic septic shock have reported mortality rates of 60% if norepinephrine treatment is started after dopamine has been found to be ineffective (9). This rate is similar to those reported in studies using norepinephrine as the first agent (8, 16). In our study, the mortality rate from septic shock (85%) was higher because norepinephrine was not used as a first agent. We made no attempt in the study to relate the onset of norepinephrine administration to the onset of hypotension and are aware that the presence of a high SOFA score, although indicating marked organ failure at the time of starting the norepinephrine infusion, yields no information regarding the reversibility of the organ failure. However, although norepinephrine may be a lifesaving catecholamine in some cases, its administration to patients who have already developed MOF during their stay in the ICU seems to be associated with a poor outcome.

Although we do not imply that norepinephrine should never be used in these circumstances, in some patients norepinephrine treatment may simply be prolonging the process of dying rather than changing its outcome. This may be because the ultimate mortality is determined not by the circulatory status of the patient but by the degree and duration of concomitant MOF. The mortality rate of patients in the ICU is directly related to the degree of total and individual organ dysfunction as measured by a variety of different scoring systems (3, 17, 18). The scoring system used in this study, the SOFA score, is one such measure, providing an assessment of individual and global organ dysfunction (3, 4). The mortality rate after acute failure of three or more organ systems for >3 days is said to be 98% (17). Moreover, the mortality from MOF is dependent on the duration of the organ failure (17).

Do the results of this study mean that we should be withholding norepinephrine treatment from such patients? There is no compelling evidence that norepinephrine improves outcome. However, labeling any therapy, or any patient, as "futile" has serious ethical consequences. One of the major problems in discussing such issues is that there is little consensus regarding how futility should be defined in practice. The subjective nature of the concept of futility makes it difficult to provide a definition that will be acceptable to all (19, 20), and some would say that futility is simply the tail end of a spectrum of low-efficacy therapies (21). Studies showing negative outcomes may, for some, justify calling the treatment futile and vindicate the decision to withhold or withdraw that therapy even if it prolongs life (22, 23). However, the effectiveness or ineffectiveness of any treatment must be rationally assessed in light of all available literature and clinical experience. An evidence-based approach will enable more objective decisions to be made in the frequently subjective medical arena. Our findings do not suggest that norepinephrine treatment is of no use in the ICU, but that it may be ineffective in certain patients with MOF. Perhaps the results suggest that, in these patients, interventions that are not just aimed at maintaining blood pressure should be sought.

Our study has several drawbacks, including that we did not try to separate patients according to primary...
disease processes, which is an important determinant of outcome. Also, the difference in the total SOFA score between survivors (11) and nonsurvivors (13), although statistically significant, is not great and these results should be interpreted with some caution. Indeed, as a retrospective study, any conclusions we may draw would need to be tested prospectively. Protocols are useful methods of providing standards of treatment but should be discussed regularly and altered in the context of new evidence. Any proposed intervention must be supported by reasonable evidence that it will be beneficial. In patients with MOF, treatment with norepinephrine or other strong vasopressor agents may not be beneficial.

REFERENCES [Click here for reference links. (22 references linked.)]


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