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Early prediction of norepinephrine dependency and refractory septic shock with a multimodal approach of vascular failure☆

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ABSTRACT

Purpose: The purpose of the study is to improve our ability to detect catecholamine dependency and refractory septic shock.
Methods: Fifty-one patients with septic shock were studied within the first 4 hours of norepinephrine administration. Patients were divided into 2 groups according to their evolution in the intensive care unit, namely, group A, shock reversal, and group B, no shock reversal. *Reversal of shock* was defined as the maintenance of a systolic blood pressure greater than or equal to 90 mm Hg without vasopressor support for 24 hours or more. Vascular reactivity was tested using incremental doses of phenylephrine. Muscle tissue oxygen saturation and its changes during a vascular occlusion test were measured.
Results: Group B patients had a higher Sequential Organ Failure Assessment (SOFA) score and lactate level and more frequently received norepinephrine and renal replacement. Overall mortality was 100% in group B (16/16) and 20% (7/35) in group A. Phenylephrine increased mean arterial pressure in a dose-dependent manner more significantly in group A patients than in group B ($P = .0004$). Basal tissue oxygen saturation and the recovery slope after vascular occlusion test were lower in group B. In multivariate analysis, 4 parameters remained independently associated with mortality: the increase in mean arterial pressure at phenylephrine 6 μg/kg per minute, the recovery slope, SOFA score, and norepinephrine doses at H0.
Conclusions: The intensity of septic shock–induced vascular hyporesponsiveness to vasopressor is tightly linked to septic shock severity and evolution and may potentially be identified early with simple to obtain parameters such as near-infrared spectroscopy value, SOFA score, or norepinephrine dose.

1. Introduction

The persistence of arterial hypotension during septic shock is associated with mortality [1,2]. Increased nitric oxide production is a major component in sepsis-induced vascular hyporeactivity [3]. A persistent vascular hyporeactivity may lead to norepinephrine dependency defined by the failure to wean norepinephrine and is associated with mortality [1]. Death may occur from refractory septic shock, likely within the first 48 hours, or from multiple-organ failure including norepinephrine dependency [4]. Therefore, detecting norepinephrine dependency in the early phase of septic shock may be of valuable interest in instituting the use of innovative therapy.

At bedside, the criterion standard for detecting vasopressor hyporesponsiveness is to perform dose-response curves to an α agonist such as phenylephrine, to which a lower increase in arterial pressure is observed in septic shock patients comparatively to control subjects [5]. Nevertheless, from a practical standpoint, this technique is difficult to achieve in a clinical setting and hence the need to find suitable surrogates. Theoretically, the norepinephrine dose used to maintain mean arterial pressure (MAP) could be used as a substitute to the dose-response curve. However, norepinephrine dose may be influenced by local practices such as MAP level or volemia status.

Near-infrared spectroscopy (NIRS) is a noninvasive technique using the absorption of infrared light at 2 specific wavelengths (680 and 800 nm) by deoxyhemoglobin and oxyhemoglobin to define hemoglobin saturation (tissue oxygen saturation [StO_2]) in vessels less than 1 mm in size located in the volume of tissue illuminated by the probe [6]. The StO_2 recovery slope obtained during a vascular occlusion test (VOT) is likely to reflect the ability of microvessels to vasodilate and/or to be recruited in response to a local hypoxic stimulus. The StO_2 recovery slope is a prognostic factor in septic shock [6,7].

We therefore conducted a prospective study to (i) identify patients who will evolve toward refractory shock/norepinephrine dependency by using dose-pressure curves with phenylephrine within the first 4 hours of norepinephrine administration, and (ii) given that establishing dose-response curves with phenylephrine is complex and does not

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involve the microcirculation, a multivariate analysis was performed to identify practical surrogates including dynamic NIRS-derived parameters.

2. Methods

2.1. Septic shock patients

The study was approved by our ethics committee, and informed consent was obtained from each patient's next of kin. The study enrolled 51 consecutive septic shock patients treated with norepinephrine.

2.1.1. Control groups

This group was constituted of 20 healthy volunteers (median age, 28 years; interquartile range, 24-33 years) in whom NIRS measurements were performed. With regard to phenylephrine-MAP dose-response assessment, previously obtained data by Bellissant and Annane [8] from 12 healthy volunteers were used using the same methodology (see procedure further below).

2.2. Therapeutic protocol

The adequacy of intravascular volume was assessed by pulse pressure variation when possible [9] or when additional fluid infusion was no longer accompanied by an increase in cardiac index (CI) (>15%). Cardiac index was estimated by echocardiography, Swan-Ganz catheter, or transpulmonary thermodilution (PiCCO; Pulsion Medical Systems, Munich, Germany) monitoring combined with intermittent or continuous central venous oxygen saturation (SVO_2) measurement through the central catheter, according to the decision of the physician in charge.

Norepinephrine was started at 0.2 μg/kg per minute when MAP was less than 65 mm Hg despite adequate vascular filling. Infusion rate was rapidly increased and adjusted to maintain a MAP of 65 to 70 mm Hg. Dobutamine was added in instances of low CI associated with a hypokinetic echocardiographic state and/or signs of tissue hypoperfusion or low SVO_2.

Hydrocortisone (200 mg/24 h) and activated protein C administration was considered when patients remained vasopressor dependent after at least 6 hours of norepinephrine therapy and with at least 2 organ dysfunctions and persistent signs of hypoperfusion [10]. Antibiotics were given as soon as possible and adapted to the putative infection site.

Weaning of drugs was performed after a 12- to 24-hour period of hemodynamic stability, using decremental doses of norepinephrine every 30 minutes.

Table 1
Demographics and clinical characteristics of the study groups

	Group A (n = 35)	Group B (n = 16)	*P*
Age (y)	62 ± 15	66.8 ± 8	NS
SAPS II (points)	66 ± 14	90 ± 21	.002
SOFA at inclusion (points)	11 ± 3	15 ± 3	.002
Pao_2/Fio_2	203 ± 80	153 ± 80	<.05
Fluid loading before norepinephrine (mL)	3110 ± 1070	3070 ± 1060	NS
Norepinephrine, μg/kg/min	1.0 ± 1.2	2.6 ± 1.8	.003
Dobutamine, n (%)	7 (20)	6 (37)	NS
MAP (mm Hg)	71 ± 7	69 ± 4	NS
DAP (mm Hg)	52 ± 5	45 ± 4	NS
Heart rate (beats/min)	103 ± 26	113 ± 20	NS
SVO_2 (%)	76 ± 7	75 ± 12	NS
CI (L/min/m^2)	3.2 ± 0.5	3.9 ± 0.7	<.05
Lactate (mmol/L)	2.6 ± 2	6.1 ± 4	<.01
Hydrocortisone, n (%)	28 (81)	15 (94)	NS
Activated protein C, n (%)	11 (35)	6 (37)	NS
Renal replacement, n (%)	18 (51)	12 (75)	<.001
28-d mortality, n (%)	7(20)	16 (100)	<.0001

Fio_2 indicates fraction of inspired oxygen; DAP, diastolic arterial pressure; NS, nonsignificant.

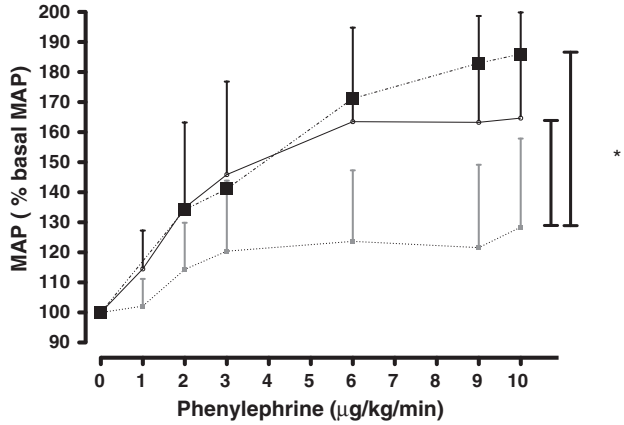

Fig. 1. Relative variations (vs basal values) in MAP induced by phenylephrine infusion in patients able to wean norepinephrine (group A, triangles), patients unable to wean norepinephrine (group B, dashed line and square), and healthy volunteers (black squares) [11]. *$P < .05$. Data are expressed as means ± SD.

2.3. Protocol

Patients were studied at bedside within the first 4 hours of norepinephrine administration.

2.4. Assessment of MAP dose-response to phenylephrine

To establish the MAP dose-response curve to phenylephrine, the protocol proposed by Bellissant and Annane [8] was used. Phenylephrine was infused in a stepwise manner (with each dose being maintained for 5 minutes) at 0, 1, 2, 3, 6, 9, and 10 μg/kg per minute. At each dose, systolic arterial pressure, diastolic arterial pressure, MAP, and heart rate were determined as the mean value recorded within the last minute of infusion. To be eligible for the phenylephrine test, patients had to have an ejection fraction greater than 45%. Phenylephrine was stopped if MAP is greater than 140 mm Hg or greater than 110 mm Hg when platelet count was less than 50000/mm^3 or in case of bradycardia or arrhythmia.

The norepinephrine dose was maintained constant throughout the phenylephrine test.

2.5. Near-infrared spectroscopy measurements

2.5.1. Tissue oxygen saturation measurement

Thenar StO_2 was measured by a tissue spectrometer (InSpectra Model 325; Hutchinson Technology, Hutchinson, MN). Probe spacing was set at 25 mm. The NIRS probe was placed on the skin of the thenar

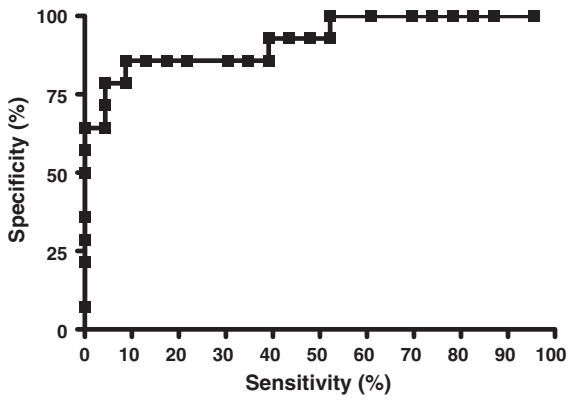

Fig. 2. Receiver operating characteristic curve established at phenylephrine 6 μg/kg per minute.