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Clinical Investigation

CLINICAL INVESTIGATION

Norepinephrine exerts an inotropic effect during the early phase of human septic shock

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Abstract

Background: We conducted this study to investigate whether norepinephrine increases cardiac contractility when administered during the early phase of septic shock.
Methods: We studied 38 patients with septic shock who had been resuscitated for <3 h and whose mean arterial pressure (MAP) remained <65 mm Hg. Echocardiographic variables were obtained before (T_0) and after either initiation or an increase in the dose of a norepinephrine infusion to increase MAP to ≥ 65 mm Hg (T_1). We collected left ventricular ejection fraction (LVEF), velocity-time integral of the left ventricular outflow tract (VTI), tissue Doppler imaging of mean systolic velocity of the lateral tricuspid annulus (S_a) and of the lateral mitral annulus (S_m), and tricuspid annular plane systolic excursion (TAPSE).
Results: There were significant ($P<0.05$) increases from T_0 to T_1 in MAP [mean (SD): from 56 (7) to 80 (9) mm Hg], LVEF [from 49 (13) to 56 (13)%], VTI [from 18 (5) to 20 (6) cm], S_m [from 10.8 (5.1) to 12.1 (5.0) cm s^{-1}], TAPSE [from 1.8 (0.5) to 2.0 (0.5) cm], and S_a [from 13.0 (5.6) to 15.1 (6.4) cm s^{-1}]. In the subgroup of 15 patients with LVEF ≤45%, significant increases in VTI [from 16 (8) to 18 (7) cm] and in LVEF [from 36 (7) to 44 (10)%] were observed.
Conclusions: Norepinephrine administration during early resuscitation in patients with septic shock increased the cardiac systolic function despite the presumed increase in left ventricular afterload secondary to the increased arterial pressure. Whether such an effect persists over time remains to be evaluated.
Clinical trial registration: NCT02750683.

Key words: echocardiography; left ventricular function; norepinephrine; septic shock

Norepinephrine (NE) is a potent vasopressor used in septic shock to reverse hypotension resulting from a deeply depressed arterial tone. However, there is concern over a negative effect of NE on cardiac function through an increase in left ventricular afterload,[1] especially when cardiac function is already impaired. Nevertheless, by restoring arterial tone NE may restore diastolic arterial pressure (DAP), hence the coronary perfusion of the left ventricle.[2] This might reduce some degree of the ischaemic myocardial dysfunction that can occur in patients with prior coronary artery disease and low

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Editor's key points

- Some of the effects of norepinephrine in sepsis may be related to β_1-adrenergic effects, but few specific data are available.
- In this study of patients with septic shock, early administration of norepinephrine was associated with increased arterial pressure and echocardiographic indices of cardiac function, suggesting increased myocardial contractility.
- Possible mechanisms include increased coronary perfusion, direct myocardial β_1-adrenergic effects, or possibly, increased preload.
- Data were restricted to before and after restoration of arterial pressure, and it is not known whether these effects would persist.
- The study was not designed to evaluate continuing cardiovascular effects or clinical outcomes.

DAP. In addition, NE may exert a positive effect on cardiac contractility through β_1-adrenergic stimulation.[3] Although sepsis-induced downregulation of β_1-adrenergic receptors may occur,[4 5] it may be relatively late,[6] and thus, not observed when NE is administered early. However, the effects of early administration of NE on cardiac systolic function in human septic shock have not been studied specifically.

The aim of this study, therefore, was to test the hypothesis that early administration of NE in septic shock patients with severe hypotension might enhance left ventricular systolic function.

Methods

This prospective observational study was performed between October 2014 and January 2016 in two 15-bed intensive care units. The study was approved by the institutional review board of our institution (Comité de Protection des Personnes, Paris-Ile-de-France VII). Informed patient (or next-of-kin) consent was obtained from all patients. Our study was registered in ClinicalTrials.gov (NCT02750683).

We included adult patients with septic shock who had a mean arterial pressure (MAP) <65 mm Hg (measured by an intra-arterial catheter) within the first 3 h after the start of resuscitation. In the two units, no fixed predefined fluid management protocol is used. Instead, fluid management is personalized and decided by the physician in charge and in consideration of the patient's past medical history, clinical signs, and dynamic indices of fluid responsiveness when available or results of a fluid challenge, according to the current European recommendations.[7] For every patient, early initiation of NE was decided by the physician in charge on the basis of lifethreatening hypotension even if hypovolaemia had not been totally resolved, as recommended.[8]

Before starting the study, patients could have received NE already, but the desired target value of MAP had not yet been achieved. For every patient included (time T_0), NE was either initiated or its dose increased in order to achieve the desired MAP target value ($\geq$65 mm Hg, or more in the event of a history of chronic hypertension). Time T1 was defined as the time when the desired MAP target was achieved. If a change of the associated therapy (fluid administration, ventilator settings, and other drugs) was decided by the attending physician, the patient was not included.

Data collection

Clinical information, the volume of fluids administered before inclusion, use of mechanical ventilation, the time interval between the start of resuscitation and T_0, and the time interval between T_0 and T_1 were noted.

Haemodynamic data

At T_0 and at T_1, we recorded heart rate (HR), systolic arterial pressure (SAP), DAP, MAP, and the blood lactate concentration.

Transthoracic echocardiographic data

Transthoracic echocardiographic (TTE) examination was performed at T_0 and T_1 with a 3.75 MHz probe using a CX50 Philips (Philips Healthcare, DA Best, Holland) and a Vivid i (GE Healthcare, Freiburg, Germany) machine. There was one echocardiographic operator in each intensive care unit, both of them (O.H., M.J.) physicians with a national echocardiographic diploma and $\geq$3yr training.

Patients were in supine flat or lateral supine positions depending on their respiratory tolerance. Two-, four-, and five-chamber apical views were used in order to determine the left ventricular ejection fraction (LVEF), calculated by the biplane method of disc summation (modified Simpson's rule), and the following other indices of right or left ventricular systolic function: tissue Doppler imaging of mean systolic velocity of the lateral tricuspid annulus (S_a), tricuspid annular plane systolic excursion (TAPSE) measured by M-mode echocardiography, and tissue Doppler imaging of mean systolic velocity of the lateral mitral annulus (S_m). We also collected the velocity-time integral of the flow in the left ventricular outflow tract (VTI), and we calculated cardiac output (CO) by multiplying the heart rate by the stroke volume. The latter was calculated as the product of VTI by the area of the left ventricular outflow tract. We also collected the left ventricular end-diastolic area (LVEDA) from the four-chamber apical view, the peak early (*E*) and late (*A*) transmitral flow velocity, tissue Doppler imaging of the mean early diastolic velocity (*E'*) of the lateral mitral annulus, and the ratios *E/A* and *E/E'*. All the variables were averaged over three beats, or over five beats in the event of atrial fibrillation.

We also calculated an estimate of the effective arterial elastance (E_a). The E_a is generally calculated using the following formula: 0.9 $\times$ aortic end-systolic pressure/stroke volume.[9] As we inserted the arterial catheter in the femoral artery, and given the low pulse wave amplification phenomenon between the aorta and the location of catheter's tip (normally close to the iliac artery), we made the reasonable assumption that the SAP approximated the aortic end-systolic pressure, so that the estimated E_a was calculated as 0.9 $\times$ SAP/stroke volume. We also estimated the left ventricular end-systolic elastance (E_{es}) by applying the estimation previously proposed by Robotham and colleagues:[10] estimated $E_{es}=E_a/(1/\text{LVEF})-1$.

Statistical analysis

In order to calculate the number of patients needed for our study, we estimated from the previous literature[11] that an

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