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The Effects of Short-Term Norepinephrine Up-Titration on Hemodynamics in Cardiogenic Shock

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Summary

A higher mean arterial pressure (MAP) achieved by norepinephrine up-titration may improve organ blood flow in critically ill, whereas norepinephrine-induced afterload rise might worsen myocardial function. Our aim was to assess the effects of norepinephrine dose titration on global hemodynamics in cardiogenic shock. We prospectively evaluated 12 mechanically ventilated euvolemic patients (aged 67±12 years) in cardiogenic shock (10 patients acute myocardial infarction, 1 patient dilated cardiomyopathy, 1 patient decompensated aortic stenosis). Hemodynamic monitoring included arterial and Swan-Ganz catheters. The first data were obtained at MAP of 65 mm Hg, then the norepinephrine dose was increased over 40 min to achieve MAP of 85 mm Hg. Finally, the norepinephrine-dose was tapered over 40 min to achieve MAP of 65 mm Hg. Norepinephrine up-titration increased MAP to the predefined values in all patients with concomitant mild increase in filling pressures and heart rate. Systemic vascular resistance increased, whereas cardiac output remained unchanged. During norepinephrine down-titration, all hemodynamic parameters returned to baseline values. We observed no changes in lactate levels and mixed venous oxygen saturation. Our data suggest that short-term norepinephrine dose up-titration in cardiogenic shock patients treated or pretreated with inotropes was tolerated well by the diseased heart.

Key words

Norepinephrine • Cardiac function • Shock • Hemodynamics • Pressure

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Introduction

Neurohumoral activation, including increased endogenous catecholamine levels (norepinephrine and epinephrine), is a hallmark of pathophysiological condition in chronic heart failure patients and it has several long-term harmful effects (Francis 1985). Conversely, exogenous catecholamines are widely administered to well volume-resuscitated critically ill patients in various clinical scenarios. The primary aim of this treatment is the preservation of adequate organ blood flow keeping mean arterial pressure (MAP) above the autoregulatory organ perfusion pressure threshold (Albanese *et al.* 2004, Matějovič 2005, Ďurišová *et al. 2008*). In physiological conditions, the organ blood flow is usually preserved over a wide MAP range. When MAP is less than 65 mm Hg, the organ blood flow may be compromised. In certain subgroups of intensive care unit patients (e.g. patients with preexisting arterial hypertension, after cardiopulmonary resuscitation, sepsis etc.), the optimal target value of MAP may be even higher than usually accepted values of 65-70 mm Hg (i.e. above 80-90 mm Hg) (Matějovič 2005, Marik 2004, Tamborini *et al.* 2001). The influence of norepinephrine dose up-titration (resulting in a higher MAP usually within physiological range) on global and regional hemodynamics in sepsis (high cardiac output at baseline) has been assessed in several experimental and clinical studies showing no detrimental effects on global hemodynamics or cardiac function (Bourgoin *et al.* 2005,

LeDoux *et al.* 2000, Di Giantomasso *et al.* 2003, Kroužecký *et al.* 2006). However, such an approach might worsen myocardial performance in critically ill patients with a failing or injured heart due to norepinephrine induced rise in afterload (Heusch 1990, de Zeeuw *et al.* 2001). To our knowledge, hemodynamic studies on MAP changes within physiological range induced by norepinephrine titration in patients with acute forms of ischemic heart disease or low cardiac output states are lacking. Therefore, we have conducted a prospective clinical trial to assess the short-term effects of various norepinephrine doses (leading to clinically significant MAP changes) on global hemodynamics in cardiogenic shock patients.

Table 1. Patients´characteristics.

Pt.	Age	Diagnosis	LVEF/RVEF (%)	MR	APACHE II score	SOFA score	ICCU survival
1	79	STEMI	35/55	2/4	14	7	0
2	78	STEMI	30/30	1/4	20	12	0
3	75	STEMI	25/60	2/4	14	4	0
4	73	Non-STEMI	30/50	2/4	16	8	0
5	61	DCMP	25/35	3/4	13	12	0
6	59	STEMI	25/55	2/4	9	6	1
7	70	Aortic stenosis	20/45	1/4	24	10	1
8	65	STEMI	40/55	2/4	22	6	1
9	32	STEMI	20/45	0	20	9	1
10	70	STEMI	30/50	1/4	23	7	1
11	74	Non-STEMI	45/60	1/4	20	9	1
12	68	STEMI	30/45	1/4	25	10	0

LVEF/RVEF – left/right ventricular ejection fraction, MR – degree of mitral regurgitation, SOFA – sequential organ failure assessment, ICCU survival: 0 – no, 1 – yes, STEMI – ST elevation myocardial infarction, DCMP – dilated cardiomyopathy

Methods

The study followed the principles established in the Declaration of Helsinki. The protocol was accepted by the local ethics committee and informed consent was obtained from the patients or next of kin. This study was performed in intensive cardiac care unit in a tertiary medical center.

Patients

We evaluated 12 patients (age 67±12 years, male/female 8/4, for patients´ characteristics see Table 1) fulfilling the following inclusion criteria: 1) pulmonary arterial occlusion pressure (PAOP) $\geq$ 15 mm Hg, 2) the need for catecholamines to maintain MAP $\geq$ 65 mm Hg, 3) cardiac index $\leq$ 2.5 l/min/m^2, and 4) age 18-80 years.

The exclusion criteria were major hemodynamic and/or electrical instability. All patients were mechanically ventilated (no ventilatory changes during the study) and sedated with midazolam and fentanyl. Three patients had atrial fibrillation and 9 patients had sinus rhythm throughout the study. All but one patient with ST elevation myocardial infarction (STEMI) were treated with primary percutaneous coronary intervention (PCI) with stent implantation. Three patients were on intraaortic balloon counterpulsation. Six patients were given dobutamine in constant dosages (2-10 μg/kg/min) during the study and 8 patients received levosimendan in previous days in the intensive care unit.

Methods

Hemodynamic monitoring included arterial and pulmonary arterial thermodilution catheters (Swan-Ganz hands-off infusion port catheter 7, 5 Fr, Arrow®, Reading, USA). Both pulmonary arterial occlusion pressure (PAOP) and cardiac output (CO) were measured at end-expiration. Cardiac output was measured in triplicate at each time point (10 ml of room temperature saline, CO-set + closed injectate delivery system, Edwards Lifesciences, Unterschleissheim, Germany) and

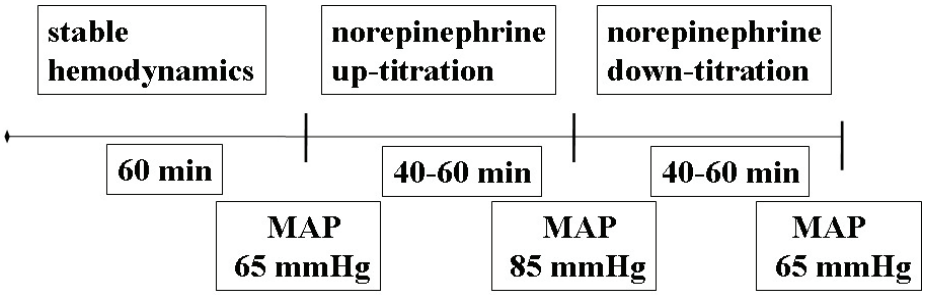

Fig. 1. Study flow chart. MAP – mean arterial pressure

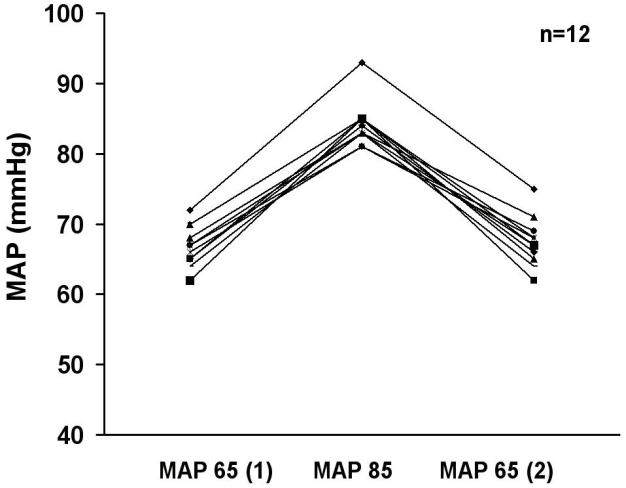

Fig. 2. Time course of mean arterial pressure. MAP – mean arterial pressure: individual changes

the mean of the three measurements was taken for calculations. Systemic and pulmonary vascular resistances (SVR and PVR) as well as left ventricular stroke work index (LVSWI) were calculated according to standard formulae. Blood gases were measured using a blood gas analyzer (ABL 520®, Radiometer, Copenhagen, Denmark), and hemoglobin oxygen saturation was determined by a co-oximeter (OSM-3, Radiometer).

Protocol (Fig. 1)

Before the study, adequate fluid resuscitation was ensured on the individual basis by monitoring filling pressures (central venous pressure and pulmonary arterial occlusion pressure) and cardiac output with eventual subsequent fluid challenge. Afterwards, norepinephrine (NE) dose was titrated over approximately 40 min to achieve mean arterial pressure (MAP) 65 mm Hg (at least 30 min in a steady state). At MAP of 65 mm Hg, the first data set was obtained, then NE dose was increased over 40 min to achieve MAP of 85 mm Hg (the second data set). Finally, the NE dose was tapered down over 40 min to achieve again MAP of 65 mm Hg (the third data set). During the study fluid infusion rates were kept constant, no red blood cells were given and no nursing procedures were performed.

Statistics

All values shown are medians; 25th and 75th percentiles if not otherwise stated. The differences between the periods were analyzed by the Friedman Repeated Measures Rank Sign Analysis of Variance and a subsequent Dunn's test for multiple comparisons when appropriate. The patients served as their own controls. Statistical significance was considered at $p<0.05$.

Results

The study was performed on the Day 1-5 of the intensive care unit stay. All patients required norepinephrine before the study to achieve mean arterial pressure $\geq$65 mmHg. No clinical adverse effects were registered during NE titration. NE up-titration (to approximately double dose vs. baseline in the majority of patients, Table 2) increased MAP to the predefined values in all patients (Fig. 2). We observed a mild increase in cardiac filling pressures (Table 2, Fig. 3). Systemic and pulmonary vascular resistances increased at a higher MAP. This response with a subsequent return to baseline values at NE down titration was uniform in all patients. The observed changes in heart rate and stroke volume did not reach statistical significance. Cardiac output (CO) increased or remained unchanged in 10 patients during NE up-titration (Fig. 4). In 2 patients (No. 5 and No. 10), we observed CO decrease at a higher MAP due to the worsening of mitral regurgitation (W vawe increase). Neither arterial lactate levels, nor mixed venous oxygen saturation changed during the study.

Discussion

The main finding of our study was that norepinephrine (NE) induced rise of systemic vascular

Table 2. Results.

	MAP 65 (1)	MAP 85	MAP 65 (2)	P
NE dose (μg/kg/min)	0.13 (0.10;0.20)	0.25 (0.21;0.34)*	0.14 (0.12;0.21)**	< 0.001
Heart rate (b.p.m.)	83 (80;102)	90 (81;101)	85 (80;100)	0.49
MAP (mmHg)	67 (65;69)	84 (83;85)*	67 (66;69)**	< 0.001
CVP (mmHg)	12 (11;14)	14 (12;15)	12 (10;14)**	< 0.001
PAOP (mmHg)	19 (18;20)	23 (21;28)*	19 (17;19)**	< 0.001
MPAP (mmHg)	28 (25;30)	33 (29;40)*	28 (25;32)**	< 0.001
SVR ($dyn*s/cm^5*m^{-2}$)	2441 (2039;2764)	2893 (2332;3869)*	2423 (2008;2725)**	< 0.001
PVR ($dyn*s/cm^5*m^{-2}$)	340 (244;463)	554 (307;748)*	396 (233;513)**	< 0.001
Stroke volume (ml/m^2)	22 (18;25)	21 (18;24)	22 (19;25)	0.98
Cardiac index ($l/min/m^2$)	1.9 (1.6;2.3)	1.9 (1.6;2.4)	1.9 (1.6;2.4)	0.90
LVSWI ($gm/m^2/HR$)	15 (11;17)	17 (14;22)*	14 (12;18)	< 0.05
Lactate (mmol/l)	1.54 (1.43;1.92)	1.50 (1.46;1.85)	1.40 (1.31;1.85)	0.33
SvO_2 (%)	64 (62;69)	64 (62;67)	65 (62;69)	0.79

MAP – mean arterial pressure, NE – norepinephrine, CVP – central venous pressure, PAOP – pulmonary arterial occlusion pressure, MPAP – mean pulmonary arterial pressure, SVR – systemic vascular resistance, PVR – pulmonary vascular resistance, LVSWI – left ventricular stroke work index, SvO_2 – mixed venous hemoglobin oxygen saturation. * vs. MAP 65 (1), ** vs. MAP 85, NS = nonsignificant

resistance and mean arterial pressure (MAP within a normal range of 65-85 mm Hg) did not compromise cardiac output in the majority of our patients.

In our study, all patients were euvolemic (individual preload optimization before the study). During norepinephrine up-titration, we observed a mild increase in both central venous and pulmonary arterial occlusion pressures (PAOP) which may be explained by the rise in systemic venous tone and pulmonary vascular tone and partly by a shorter diastole due to a mild heart rate increase. Cardiac output remained unchanged despite the rise of both systemic and pulmonary vascular resistances presumably due to the combined effect of norepinephrine both on alfa- and beta-adrenergic receptors. Nevertheless, the hemodynamic response to increased MAP in our study might have been influenced by the treatment with positive inotropic drugs (dobutamine in moderate stable doses and/or levosimendan in previous days) and thus we cannot exclude that cardiac output changes could be different in patients without previous or concurrent inotropic support.

During NE up-titration, clinician may expect hemodynamic deterioration in patients with severe mitral regurgitation (MR), where norepinephrine induced rise in systemic vascular resistance may lead to cardiac output decrease (afterload mismatch). We observed a mild cardiac output decrease in two patients during NE up-titration due to the worsening of mitral regurgitation (W wave increase/appearance). One patient had moderate to severe MR (3/4) already at baseline, whereas the second patient had only mild MR (1/4) at baseline. Therefore, before norepinephrine up-titration, a caution is needed when MR is detected on echocardiography and/or W wave is present during pulmonary arterial occlusion pressure measurement.

It is assumed that certain subgroups of critically ill patients might benefit from higher organ perfusion pressures, at least during limited time periods (Albanese *et al.* 2004, Marik 2004). The optimal MAP value may differ in 1) different patient populations (e.g. preexisting arterial hypertension, when autoregulatory renal perfusion pressure is shifted to higher values), 2) various stages of critical illness, e.g. the early phase in patients after cardiopulmonary resuscitation, when higher cerebral perfusion pressure is required or during sepsis when vasoplegia and altered vascular reactivity may result in a shift of the autoregulatory threshold to higher values), and 3) various organs also depending on different degree of stenotic atherosclerotic process (Marik 2004, Tamborini *et al.* 2001, Koužecký *et al.* 2006, Martin *et al.* 1999).

In a healthy heart, coronary blood flow remains stable within a wide range of coronary perfusion pressures (50-70 to 110-130 mm Hg) (Bourdarias 1995,

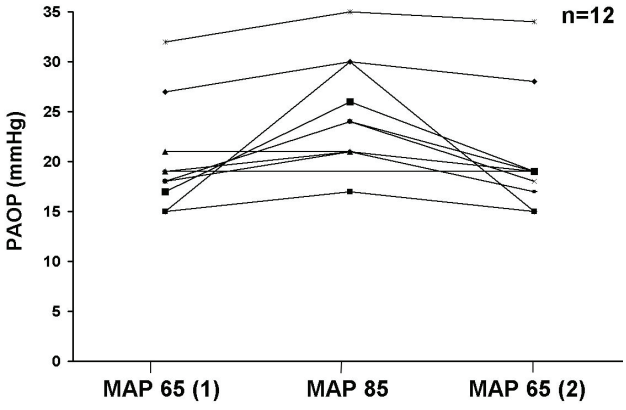

Fig. 3. Time course of pulmonary arterial occlusion pressure. PAOP – pulmonary arterial occlusion pressure, MAP – mean arterial pressure

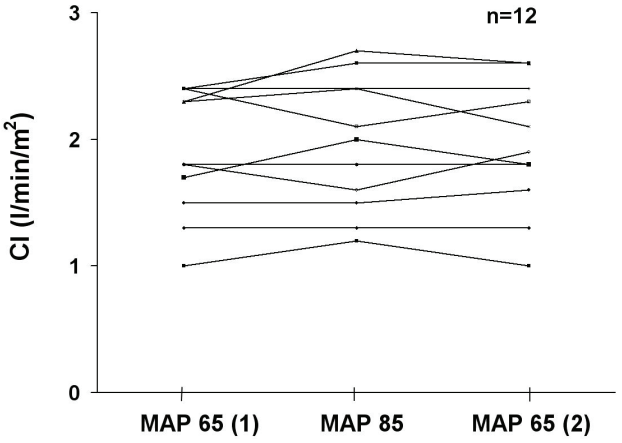

Fig. 4. Time course of cardiac index. CI – cardiac index, MAP – mean arterial pressure

Jones *et al.* 1995, Bellomo 2003). Norepinephrine leads to vasoconstriction of coronary arteries and coronary perfusion pressure (CPP) elevation (Heusch 1990). In experimental studies in sheep, short-term NE up-titration significantly increased coronary blood flow (Di Giantomasso *et al.* 2003, Bellomo 2003). In our study, we did not measure coronary blood flow directly. NE induced a significant MAP rise and a mild increase in PAOP, thus presumably also a mild increase of left ventricular end-diastolic pressure (LVEDP). Hence, we can assume that CPP (MAP-LVEDP) rose since the shortening of diastole (only mild heart rate increase) was not clinically significant (Vis *et al.* 1997). Importantly, the majority of our patients had successful percutanous coronary revascularisation with stent implantation before the study. We can only speculate that the effect of NE may be different in patients with persistent significant coronary artery stenosis, when the autoregulatory threshold of CPP may be shifted to higher values (Marik 2004).

Study limitations

Our study has certain limitations. First, the time periods for norepinephrine up- and down-titration were short and the increase of NE dose was relatively mild. Exposure to higher NE doses with more pronounced LV and RV afterload and/or heart rate increase might worsen cardiac performance due to the rise in myocardial oxygen demand or due to catecholamine-induced myocardial stunning (de Zeeuw e*t al.* 2001, Bolli and Marban 1999). Moreover, using isolated rabbit hearts, Rump *et al.* (2002) demonstrated direct cardiotoxic effects of NE mediated by superoxide anion radicals depending on the dose of exogenous NE. In experimental studies it has also been shown, that long-term NE administration may induce cardiac fibrosis and/or left ventricular hypertrophy contributing to functional deterioration and heart failure exacerbation (Briest *et al.* 2001, Meier *et al.* 2007).

Second**,** our analysis was focused only on global hemodynamics and metabolism and not on regional hemodynamics. In previous studies, it has not been convincingly shown that higher MAP values improves regional blood flow (Zhang *et al.* 1997). In our recent experimental study in pigs with hyperdynamic septic shock, we have shown that neither intestinal macro- nor microcirculation was compromised by norepinephrine up-titration (Kroužecký *et al.* 2006). In the present human study, we found that the indices of global oxygen kinetics and metabolism were unaltered, but we cannot make any conclusion concerning regional blood flows and metabolism. Due to the short-term protocol of this study, we did not measure potential urine output changes.

Conclusions

We conclude that short-term norepinephrine dose up-titration leading to mild mean arterial pressure rise in euvolemic cardiogenic shock patients treated or pretreated by inotropes was tolerated well by the diseased heart. Our observation may be in favor of possible safe norepinephrine use in order to achieve a higher organ blood flow also in critically ill patients with compromised cardiac function under careful hemodynamic monitoring. Caution is needed in patients with mitral regurgitation. However, the impact of long-term norepinephrine infusion on cardiac function in this patient population requires further studies.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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