

Effect of Higher Mean Arterial Pressure with Norepinephrine on Tissue Oxygenation and Perfusion in Patients of Septic Shock

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ABSTRACT

The current survival sepsis guideline proposes the use of vasopressors and fluid resuscitation to maintain the mean arterial pressure (MAP) ≥ 65 mmHg. Titrating catecholamine infusion to achieve higher MAP has been demonstrated to improve tissue oxygenation, microcirculation, renal function and overall outcome of the patient in some studies and literature on actual hemodynamic goals is scarce. AIM: To study the influence of two MAP on tissue oxygenation and perfusion parameters in patients of septic shock on norepinephrine infusion. SUBJECT AND MATERIALS: Forty adult patients with the diagnosis of septic shock were enrolled. In all patients norepinephrine was titrated to first stabilize the MAP at 65 ± 5 mmHg (Set I), followed by MAP of 85 ± 5 mmHg (Set II). Heart rate (HR), Central venous oxygen saturation ($S_{CV}O_2$), Transcutaneous partial pressure of oxygen ($P_{tc}O_2$) by TCM 400/TINA (using miniature Clark electrode), Arterial partial pressure of oxygen (P_aO_2), P_tO_2/P_aO_2 ratio, Urine output and Serum Base deficit were recorded in each Set after 2 hr of stabilization. RESULTS: There was a significant increase in transcutaneous partial pressure of oxygen $P_{tc}O_2$ ($p < 0.0001$), P_tO_2/P_aO_2 ($p < 0.0001$), $S_{CV}O_2$ ($p < 0.0001$), urine output ($p < 0.006$) on increasing the MAP from 65 mmHg to 85 mmHg. Serum base deficit also improved ($p < 0.0001$). CONCLUSION: Higher MAP with norepinephrine is associated with better perfusion, oxygenation parameters in patients with established septic shock. These findings suggest that there is improvement in tissue oxygenation parameters using escalating doses of norepinephrine to achieve higher MAP without inherent adverse effect.

Keywords: Mean Arterial Pressure; Norepinephrine; Septic Shock; Tissue Oxygenation

1. Introduction

Despite many advances in understanding of pathophysiology of septic shock and its management, the mortality remains unacceptably high. In the year 1992 American College of Chest Physicians/Society of Critical Care Medicine consensus conference defined the septic shock as follows “...sepsis induced hypotension (systolic BP < 90 mmHg or reduction of ≥ 40 mmHg from baseline) despite adequate fluid resuscitation along with presence of perfusion abnormalities that may include but not limited to lactic acidosis, oliguria or an acute alteration in mental status” [1].

The current survival sepsis guideline in 2008 advocates the use of vasopressors and fluid resuscitation to maintain the mean arterial pressure (MAP) ≥ 65 mmHg. The recommended end points with regards to MAP to maintain tissue oxygenation and organ perfusion remain controversial and ranges from 60 mmHg (autoregulatory threshold below which organ blood flows become line-

arly dependent on perfusion pressure) to 90 mmHg. In septic shock this autoregulatory threshold shifts to a higher level. It can therefore be speculated that therapy should be aimed at providing an adequate organ perfusion pressure that is higher than the commonly targeted or achieved in the treatment of septic patients [2]. It is important to titrate the optimal dose of potent inotropic agents as both inadequate and excessive dosages can have deleterious consequences. Moreover the benefit of titrating catecholamine infusion to higher level has been demonstrated in a few studies [3-5] but not in others [2,6-8].

Transcutaneous partial pressure of oxygen ($P_{tc}O_2$) is used as a non-invasive technique to monitor tissue oxygenation and perfusion and early detector of shock and outcome [9]. Because $P_{tc}O_2$ reflects regional PO_2 , it changes in response to both regional perfusion and to global hemodynamic derangements [10]. When arterial partial pressure (P_aO_2) remains constant, a decrease in $P_{tc}O_2$ is probably due to changes in perfusion.

Hence, this single centre interventional study was planned to evaluate tissue oxygenation at two sets of mean arterial pressure of 65 mmHg and 85 mmHg (maintained with norepinephrine) in patients of septic shock, using transcutaneous partial pressure of oxygen.

2. Material and Methods

After Institutional Review Board (IRB) approval and written informed consent, this single centre prospective interventional study was conducted in 40 adult patients of either sex admitted in Multidisciplinary Intensive Care Unit (ICU) with the diagnosis of septic shock² (systolic BP < 90 mmHg or 40 mmHg less than patients normal BP for at least 1 hr after adequate fluid resuscitation) or those who develop septic shock during their stay in ICU.

Patients with acute myocardial ischemia, acute arrhythmia, pregnancy, diabetes, hypertension, peripheral vascular disease, those requiring inotrope agents other than norepinephrine and those on Renal Replacement Therapy (RRT) were excluded from the study.

Baseline values of heart rate (HR), Invasive Blood Pressure (IBP), Percent oxygen saturation of haemoglobin (SpO₂), Electrocardiography (ECG), Central Venous Pressure and Urine output in last one hour were recorded in all patients. The clinical management of each patient was determined by clinical staff in accordance with care bundles based on the current Survival Sepsis Guidelines.

No therapy was given during the study period that might influence the hemodynamics of the patient like hemofiltration, diuretics, other catecholamines etc.

After adequate fluid resuscitation (CVP = 8 - 12 mmHg in spontaneously breathing and 12 - 15 mmHg in mechanically ventilated patients) norepinephrine was started in all the patients. Patients acted as self control. First the NE infusion was titrated and stabilized at SET I pressures and then at Set II pressures as mentioned below.

SET I-Norepinephrine was titrated to achieve a MAP of 65 ± 5 mmHg.

SET II-Norepinephrine infusion was titrated to achieve MAP of 85 ± 5 mmHg.

After stabilizing the patient for two hours on above mentioned MAP, transcutaneous partial pressure of oxygen (P_{tc}O₂), P_aO₂, P_{tc}O₂/P_aO₂ ratio, Superior Vena Cava oxygen saturation (S_{cv}O₂), Heart rate (HR), Urine output (ml/hr) and Serum Base deficit were recorded.

After recording these variables the clinical management of the patient was continued as per determined by the clinical staff in accordance with the care bundles based on current survival sepsis guidelines.

Data was presented as mean (SD) where normally distributed. p < 0.05 was taken as significant. Paired t-test was applied for comparing the changes in HR, S_{cv}O₂,

P_{tc}O₂, P_aO₂, P_{tc}O₂/P_aO₂ ratio and urine output. Changes in base deficit were analyzed by wilcoxon signrank test.

3. Results

This single Centre prospective interventional study was conducted in 40 adult patients with septic shock with a mean age of 44.65yr (15 - 64 yr) of which 27 were male and 13 were female. Since, the patients acted as self-control the baseline demographic characteristics were same. (Table 1). Mean baseline SOFA score in our patients was 7.7 with a range of 5 - 11. Probable source of sepsis was abdominal in 67.5% of patients. There was statistically significant increase in transcutaneous partial pressure of oxygen P_{tc}O₂ (p < 0.0001), P_{tc}O₂/P_aO₂ ratio (p < 0.0001), S_{cv}O₂ (p < 0.0001), Urine output (p < 0.006) and Serum base deficit (p < 0.0001) on increasing the MAP from 65 mmHg to 85 mmHg. There was a significant fall in Heart Rate on increasing the MAP to 85 ± 5 mmHg (Table 2).

None of the patient developed tachycardia, arrhythmias, myocardial ischemia, signs of excessive vasoconstriction or any other adverse effect that could be attributed to the intervention.

Table 1. Baseline patient characteristics.

AGE (yr)	44.65 (15 - 64)
GENDER (M/F)	27/13
Time from onset of sepsis (days)	2.4 (1.37)
Mortality	21 deaths (52.5%)
Probable Source of Infection	Frequency (%)
Respiratory	13 (30)
Abdominal	26 (67.5)
Soft tissue	1 (2.5)
SOFA Score	7.7 (5 - 11)

Table 2. Hemodynamic and Perfusion parameters in the two groups.

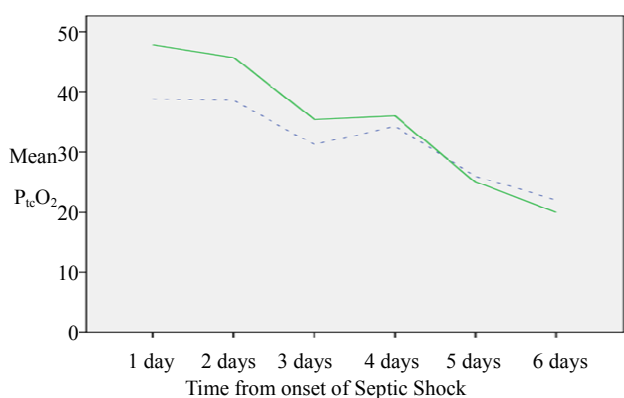
Parameter	MAP 65	MAP 85	p value
Heart rate (/min)	105.75 ± 17.27	101.1 ± 15.58	≤0.0001
S _{cv} O ₂ (%)	73.23 ± 4.00	75.11 ± 3.98	≤0.0001
P _{tc} O ₂ (mmHg)	35.75 ± 8.40	41.57 ± 11.42	≤0.0001
P _a O ₂ (mmHg)	109.11 ± 23.58	106.77 ± 23.31	0.0186
P _{tc} O ₂ /P _a O ₂	0.337 ± 0.084	0.3987 ± 0.11	≤0.0001
Urine output [‡] (mL/hr)	43.5 ± 18.70	50.2 ± 27.11	0.0068
Base deficit [†] (meq/L)	5.25 ± 2.29	4.65 ± 2.39	≤0.0001

Mean (SD). p value < 0.05 is taken as significant. Paired t test applied. [‡]normal distribution of data seen with Shapiro wilk test. [†]Wilcoxon signrank test applies.

The rise in $P_{tc}O_2$ on increasing the mean arterial pressure from 65 mmHg to 85 mmHg is less as the time from onset septic shock increases (Figure 1). It can be seen that as the duration of septic shock increases the response to increasing MAP is less or none at all. The time interval from the onset of septic shock to the start of our study varied from 1 - 6 days with mean of 2.4 days. 40 percent of patients (16) were included at day 2 of septic shock (Figure 2).

4. Discussion

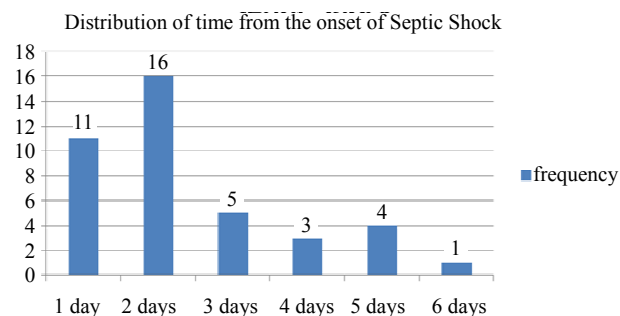
Septic shock is a life threatening complication of infection. Besides treatment of sepsis, hemodynamic management of the patient is mandatory to improve oxygen supply to tissues. Depending on the cardiac function, blood volume expansion and/or inotropic drugs are indicated. When fluid administration fails to restore adequate arterial pressure and organ perfusion, therapy with vasopressor agent is initiated [11].



--- mean transcutaneous partial pressure of oxygen at 65 ± 5 mmHg
 — mean transcutaneous partial pressure of oxygen at 85 ± 5 mmHg

Mean $P_{tc}O_2$ at 65 ± 5 mmHg (broken line) and 85 ± 5 mmHg (solid line) with respect to Time from onset of septic shock. As duration of septic shock increases, rise in mean $P_{tc}O_2$ decreases on increasing MAP.

Figure 1. Relation of change in mean $P_{tc}O_2$ for two sets of MAP to the time from onset of Septic Shock.



X-axis: Time from onset of septic shock; Y-axis: Number of patients. Number of patients with respect to Time from onset of septic shock.

Figure 2. Distribution of time from onset of sepsis.

Current survival sepsis guidelines for hemodynamic support of adult patients with sepsis recommend that vasopressor should be titrated to the minimum level required to provide an effective organ perfusion. The adequate arterial pressure is the endpoint of vasopressor therapy but does not always means adequate organ blood flow. The precise level of mean arterial pressure required to optimize tissue perfusion is still debated. Thus this single center prospective interventional study was conducted for comparative evaluation of tissue oxygenation using transcutaneous partial pressure of oxygen at two sets of mean arterial pressure of 65 mmHg and 85 mmHg maintained on norepinephrine infusion in patients of septic shock.

The principal finding of this study is that the use of incremental doses of norepinephrine to achieve higher MAP was associated with increase in oxygenation and perfusion parameters. In our study, tissue oxygenation parameters namely $P_{tc}O_2$, $P_{tc}O_2/P_aO_2$ and $S_{cv}O_2$ improved significantly at higher MAP. Since, $P_{tc}O_2$ is a direct measure of microvascular flow, it can be inferred that a higher MAP (85 mmHg) was associated with improvement in the tissue microcirculation and thus oxygenation. Jhanji S. *et al.* also found that titrating vasopressors to achieve higher MAP is associated with increase in global oxygen delivery, cutaneous microvascular flow and tissue oxygenation [3].

The perfusion parameters namely base deficit and urine output also showed significant improvement at higher MAP in our study. This improvement can be attributed to improved organ perfusion at higher MAP. Beneficial effects of higher doses of norepinephrine on renal perfusion (GFR and urine output) has been well documented [4,5,12]. Stephane Derudder *et al.* have also observed that on increasing the MAP from 65 to 75 mmHg with norepinephrine there was significant increase in urine output and decrease in renal resistive index [13].

However there are studies with contrasting evidence [2,6-8]. Amongst the most recent is the study by Aurelie bourgoin *et al.* in 28 patients which showed that increasing MAP from 65 mmHg to 85 mmHg with Norepinephrine neither affects metabolic variables nor improves renal function [2]. However the patients included in this study had severe form of septic shock (with 2 or more organ failure) and were sicker whereas our study excluded the patients with comorbid conditions. This might be the differentiating factor that can explain no improvement in tissue oxygenation and perfusion parameters in his group of patients.

Ledoux *et al.* [6] found out that on increasing MAP from 65 to 85 mm Hg with norepinephrine does not significantly affect systemic O_2 metabolism, skin microcir-

ulation, urine output or splanchnic perfusion. However the APACHE II score in his group of patients was 29 ± 2.1 which was more than in the study group of Aurelie bourgoin *et al.* [2] which was 27 - 28 in this study. In both studies the patient population belonged to a higher severity-of-illness score compared to our study which had a mean SOFA score of 7.7. Also the equilibration period in this study was only 60 minutes which was probably not sufficient to reflect changes in tissue oxygenation and perfusion parameters.

In the above mentioned studies the patients enrolled were older, in mid sixties compared to our patients, with mean age of 44 yr. Our results are applicable to younger population with recent onset of septic shock (67.5% patients with onset within 2 days) and primarily abdominal (65%) source of sepsis. This can be seen in **Figure 1** which shows that as the duration of septic shock increases, the rise in $P_{i_c}O_2$ decreases with increase in MAP.

5. Conclusion

Higher MAP with norepinephrine is associated with improved perfusion and oxygenation parameters in younger age group with septic shock when NE therapy is instituted early in the course of disease. Further research is required to know more about long term effects of higher arterial pressure targets in these patients.

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