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Adrenaline in treatment of septic shock: effects on haemodynamics and oxygen transport

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Abstract. The effects of adrenaline on haemodynamics and oxygen transport were studied in 13 patients with septic shock persisting after optimal fluid loading. Adrenaline was administered by intravenous infusion at an increasing dose until no further benefit was seen. There were significant increases in mean arterial pressure, cardiac index, left ventricular stroke work index and oxygen delivery index. There was no significant change in oxygen consumption although the trend was towards an increase. There was a significant reduction in oxygen extraction ratio, but no change in shunt fraction. Adrenaline would appear to have beneficial haemodynamic effects in septic shock.

Key words: Adrenaline – Septic shock – Oxygen transport

The principal cardiorespiratory abnormalities in septic shock are myocardial depression [1], peripheral vasodilatation [2], and delivery dependent oxygen consumption [3]. It is logical therefore to base therapy on the correction of these abnormalities and there is evidence that achievement of supranormal values for cardiac index (CI), oxygen delivery (DO_2) and consumption (VO_2) whilst maintaining blood pressure may be associated with improved survival [4].

In most recently published work such therapy consists of optimal volume resuscitation, an inotrope (dobutamine) and a vasoconstrictor (noradrenaline) [4]. Independent manipulation of circulating volume, inotrope and vascular tone requires invasive cardiovascular monitoring including pulmonary artery catheterisation. This may not always be feasible in the first few minutes of resuscitation and so an agent which combines positive inotropic actions with vasoconstrictive properties has obvious attractions. Adrenaline has alpha- and beta-adrenergic actions [5] and is potentially such an agent. Although it is widely used to treat shock, its effects on haemodynamics and oxygen transport in septic shock have not been the subject of detailed investigation.

The aim of this study was to document the effects of adrenaline on the cardiovascular system and oxygen transport in septic shock, with a view to assessing its possible role as a primary agent in the treatment of this condition.

Patients and methods

For the purpose of this study, septic shock was defined as a mean arterial pressure (MAP) of less than 70 mmHg, and a urine output of less than 15 mls/hr in the presence of at least two of the following: (a) septic focus, (b) white cell count of greater than 10 or less than 4×10^6/ml, (c) temperature greater than 38 °C. Thirteen patients were included in the study and their details are summarised in Table 1.

All patients were mechanically ventilated with supplemental oxygen to achieve an arterial oxygen saturation (SaO_2) of greater than 95%. Central venous, systemic arterial (radial or femoral) and pulmonary arterial catheters were inserted. This enabled measurement of MAP, mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP). Cardiac output was measured by thermodilution being taken as an average of between three and five readings using 10 ml of ice cold 5% dextrose. Using these variables cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), right ventricular stroke work index (RVSWI) and left ventricular stroke work index (LVSWI) were calculated. Samples of simultaneously taken mixed venous and arterial blood were analysed for hydrogen ion concentration, blood gas tensions and, using a co-oximeter, total haemoglobin and oxyhaemoglobin saturation. From these, arterial and mixed venous oxygen content, oxygen delivery index (DO_2I), oxygen consumption index (VO_2I) and shunt fraction (Qs/Qt) were calculated. Heart rate was taken from the ECG.

Initial management consisted of fluid resuscitation. This was considered optimal when PCWP reached 15 mmHg or when no further increase in CI occurred. Where the haematocrit was less than 35%, concentrated red cells were used; otherwise human plasma protein solution was given. Thereafter a full haemodynamic and, except in patient 9, oxygen transport profile was performed as outlined above. No changes were made to sedation or ventilator settings and no further blood or colloid transfusions were given after this.

Adrenaline was commenced at a rate of 0.05 μg/kg/min and after 15 min the measurements were repeated. The dose was then increased, usually by increments of 0.05 μg/kg/min, and measurements per-

Table 1. Patient characteristics

No	Sex	Age	Diagnosis	Site of positive culture	Organism	Dose adrenaline μg/kg/min	Outcome
1	M	68	Pneumonia	Sputum	G +ve cocci	0.25	Survived
2	F	80	Pancreatitis	Intra-abdo	*Candida*	0.2	Died
3	M	63	Pneumonia	Sputum	*Legionella*	0.1	Survived
4	F	65	Pneumonia	Sputum	*Pneumococcus*	0.17	Survived
5	M	68	Ileal perforation	Peritoneum	*E. coli*	0.25	Died
6	F	46	Myasthenia	Sputum	*Pneumocystis; Candida*	0.05	Survived
7	F	74	Aspiration pneumonia	Sputum	*E. coli; Candida*	0.05	Died
8	M	77	Perforated oesophagus	Mediastinum	*E. coli; Candida Enterobacter cloacae*	0.05	Died
9	F	81	Biliary obstruction	Blood	*Pseudomonas*	0.2	Died
10	M	76	Catheter sepsis	Blood	*Coag. neg. staph*	0.08	Survived
11	M	81	Ischaemic bowel	Sputum	*Klebsiella*	0.1	Survived
12	F	87	Perforated DU	Peritoneum	*Candida*	0.15	Died
13	M	60	Pneumonia; Seminoma	Chest (PM)	*Pneumococcus*	0.42	Died

formed after each change. This protocol was followed until either the cardiac index exceeded 4.5 l/min/m^2 and the DO_2I 600 ml/min/m^2, no further increase in CI occurred, dysrhythmias or other side effects became apparent or a change of management was judged appropriate on clinical grounds. Subsequently, 3 patients received noradrenaline to increase SVR and MAP and two received dobutamine to further increase CI but the results presented are the effects of adrenaline alone before the introduction of other agents. Data was analysed by the Mann-Whitney U test assuming non-parametric data. All values are expressed as mean ± SE.

Results

The maximum dose of adrenaline ranged from 0.05 – 0.42 μg/kg/min (mean 0.16) (Table 1). The haemodynamic effects in 13 patients with septic shock are summarised in Table 2. There was a significant increase in MAP, CI and LVSWI. There was no consistent effect on SVR despite noticeable changes in individual patients as shown in Fig. 1. The shunt fraction was unaffected.

Oxygen transport was measured in 12 patients. The DO_2I increased significantly from 382 ± 41 ml/min/m^2 to 596 ± 43 (mean ± SE) ($p < 0.01$). The increase in VO_2I from 116 ± 8 ml/min/m^2 to 133 ± 11 ml/min/m^2 was not statistically significant but the fall in extraction ratio from 32.3 ± 2.5% to 23 ± 1.2% was significant ($p < 0.01$).

Table 2. Haemodynamic and oxygen transport changes with adrenaline

	Baseline (Mean ± SEM)	Adrenaline (Mean ± SEM)	Significance
Heart Rate	93 ± 5	102 ± 4	NS
PCWP (mmHg)	15.5 ± 1.5	15.5 ± 1.4	NS
MAP (mmHg)	55.5 ± 2.9	76 ± 2.5	$p < 0.01$
SVR (dynes·s/cm^5)	736 ± 93	687 ± 56	NS
CI (l/min/m^2)	2.8 ± 0.2	4.3 ± 0.2	$p < 0.01$
DO_2I (ml/min/m^2)	382 ± 41	596 ± 43	$p < 0.01$
VO_2I (ml/min/m^2)	116 ± 8	133 ± 11	NS
OER (%)	32.3 ± 2.5	23.0 ± 1.2	$p < 0.01$
Qs/Qt (%)	30.3 ± 2.9	34.6 ± 2.4	NS
LVSWI (g·m/m^2)	17.7 ± 1.6	34.6 ± 3.0	$p < 0.01$

The changes in individual patients are illustrated in Fig. 2.

Six of the patients survived, a hospital survival rate of 46%. One patient developed acute renal failure from which he made a full recovery.

Discussion

This study has demonstrated the beneficial effect of adrenaline on the cardiovascular system in 13 patients with severe septic shock. Following optimal volume loading, adrenaline infusion produced increases in MAP and CI with an associated increase in DO_2I. Although an increase in VO_2I was seen in some patients, this was not consistent and for the group as a whole the increase was not statistically significant.

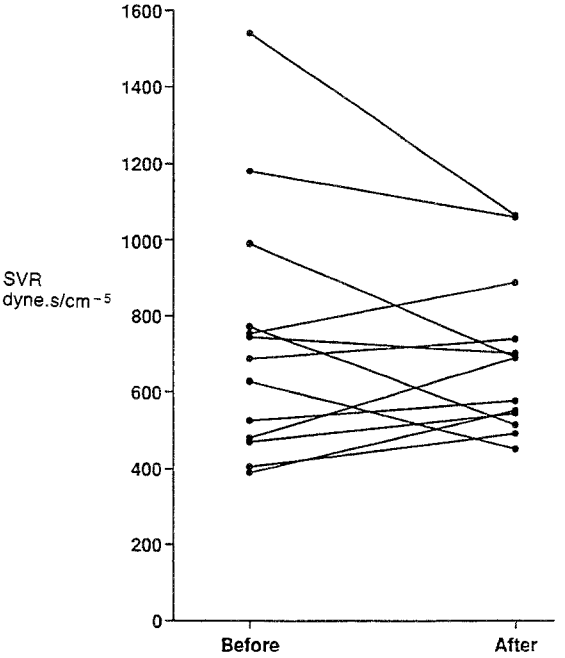

Fig. 1. Systemic vascular resistance before and after commencement of adrenaline

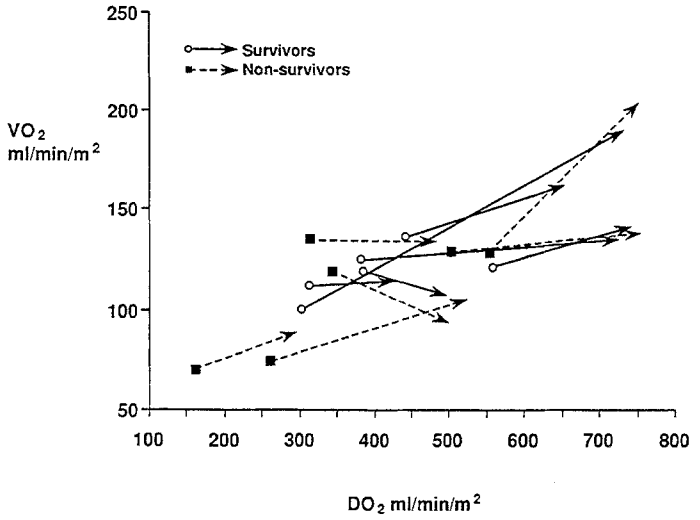

Fig. 2. DO_2I and VO_2I before and after commencement of adrenaline

MAP and CI both increased in every patient; there were no cases of excessive vasodilatation producing a reduction in filling pressure and MAP, nor did any patient suffer a fall in CI due to excessive vasoconstriction. It would appear that the SVR tended to rise if previously low, and to fall in those patients with a high initial value, usually those with a very low CI (Fig. 1). The patients in this study were in general elderly and the baseline values of cardiac index (CI) were heterogeneous with a low mean of 2.8 l/min/m^2. Clearly they were not all in the hyperdynamic phase of septic shock; indeed 3 were moribund and died within hours. This should be borne in mind when considering our results.

Most published work on the haemodynamic effects of adrenaline describes its use in situations other than septic shock and little is known of its effects on oxygen transport. Infusions of 0.15–0.3 μg/kg/min given to normotensive and hypertensive subjects produced an increase in cardiac output, systolic blood pressure and MPAP with a fall in SVR [6]. Coffin and co-workers found that a dose of 0.5–1 μg/kg/min reversed hypotension and oliguria in post cardiac surgical patients but they did not measure cardiac output [7]. Immediately after cardiopulmonary bypass, Steen and colleagues showed that a dose of 0.04 μg/kg/min increased cardiac output, MAP and pulse pressure with no effect on SVR [8].

Bollaert et al. [9] administered adrenaline at a rate of 1 μg/kg/min to 7 patients in septic shock. The degree of volume loading was less than in our study with a PCWP of 8.4±3.2 mmHg and the patients were all receiving dopamine at rates in excess of 15 μg/kg/min. The addition of adrenaline caused an increase in MAP, CI and DO_2I. VO_2I increased in some patients but not all and the change was not statistically significant. These results are similar to those we have documented using adrenaline alone in relatively low doses of 0.05–0.42 μg/kg/min.

Whilst the increase in CI, MAP and DO_2I achieved seem desirable, the failure to increase VO_2I consistently may be a cause for concern, given that VO_2I has generally been shown to be delivery dependent in septic shock.

Adrenaline may conceivably have a deleterious effect on tissue oxygen utilisation. In dogs, without septic shock, Coffin found that lactate concentrations were increased by adrenaline (1–2 μg/kg/min) despite an increase in splanchnic blood flow. When the dogs were placed on cardiopulmonary bypass, this rise in lactate did not occur, suggesting that the increased production might occur in the heart or lungs [8]. We were technically unable to measure blood lactate concentrations during this study and therefore cannot demonstrate either a beneficial or detrimental effect on tissue oxygenation and lactate production.

Alternatively it could be that in our study population there was not a significant tissue oxygen debt and therefore less scope for an increase in VO_2I. As we did not measure lactate we cannot comment on this. The results of some previous investigations suggest that delivery dependence of VO_2I is a phenomenon only associated with an elevated blood lactate concentration, reflecting tissue oxygen debt [10]. Another possible explanation for the failure to show a clear increase in VO_2 may simply be that the number of patients in our study is too small to achieve statistical significance.

All of the commonly used catecholamines have a mixture of desirable and undesirable effects. Dopamine has been shown to increase MAP, CI and DO_2I without necessarily increasing VO_2I [11]. The same study demonstrated an increase in the intrapulmonary shunt fraction. Others have found that dopamine may actually reduce CI in some patients [12].Neither of these undesirable effects were seen with adrenaline in our patients. Dopamine may possibly have specific advantages with regard to renal function. Dobutamine increases cardiac output and often causes vasodilatation. Whilst this may be beneficial in terms of microcirculatory flow, it may also cause serious hypotension especially in patients who are even slightly hypovolaemic. In the context of septic shock, monitoring of PCWP to exclude latent hypovolaemia is essential in conjunction with its use. Dobutamine has generally been found to increase VO_2I [13] although not all workers have confirmed this [14]. In a comparison of dopamine with dobutamine in critically ill, but not shocked, patients Shoemaker [15] found that VO_2I only increased with dobutamine and suggested that this might be due to beta-2 vasodilatation produced by dobutamine rather than the rise in DO_2I produced by both agents. Noradrenaline is primarily a vasoconstrictor with variable, but often detrimental effects on cardiac output. The fact that MAP may be maintained, or increased, at the expense of a reduction in CI, DO_2 and VO_2I illustrates the danger of titrating therapy against blood pressure alone [16].

Shoemaker and co-workers first suggested and validated the concept of therapeutic goals of supranormal cardiac index, DO_2I and VO_2I in high risk surgical patients, some of whom were septic [17]. Edwards et al. [4] have applied these concepts to severe septic shock. In a prospective but uncontrolled trial, they achieved their goals (CI greater than 4.5 l/min/m^2, DO_2I greater than 600 ml/min/m^2, VO_2I greater than 170 ml/min/m^2 with avoidance of hypotension) using fluid, dobutamine, nor-

adrenaline and dopamine to achieve a hospital mortality rate of 48%, a great improvement on previous experience. Our study mortality of 54% is similar despite an older study population. This may be partly because, like Edwards, we based management on haemodynamic and oxygen transport variables rather than blood pressure alone.

We have demonstrated that adrenaline can further increase CI and MAP when these remain low after fluid resuscitation in septic shock. Its reliable positive inotropic action and lack of unbalanced vasodilatory or vasoconstrictor effect suggests that adrenaline is indeed a suitable primary agent, particularly when full invasive monitoring is not possible during early resuscitation or patient transfer. We would emphasise however that full invasive monitoring of haemodynamics and oxygen transport should be instituted as soon as is practicable. As septic shock is a complex and dynamic condition, the approach to treatment must be flexible and tailored to the individual. When CI and MAP are low, adrenaline may be given but it will not be the correct choice in all patients. Therapy must in all cases be modified in the light of repeated haemodynamic and oxygen transport measurements. In the present series these led us to add either noradrenaline or dobutamine in 5 cases. We conclude therefore that adrenaline has a place in septic shock, as outlined above, but that a need for further research remains. This should focus particularly on hyperdynamic shock and also on tissue oxygenation and lactate metabolism.

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