The effects of different haemodynamic therapies on tissue microvascular flow and oxygenation in patients following major surgery and with sepsis

Introduction

Over 170,000 high-risk non-cardiac surgical procedures are performed each year in the UK with over 25,000 deaths before hospital discharge.[1] Those patients who develop complications but survive, suffer a substantial reduction in functional independence and one year survival.[2] A number of reports describe an association between derangements in systemic oxygen delivery (DO_2I) and poor outcome following major surgery.[3] Other investigators have suggested that tissue microvascular flow and oxygenation may be impaired following major surgery.[4, 5] In several small studies, the use of fluid and inotropic therapy to increase DO_2I has led to a reduction in post-operative complications.[6-8] It has been suggested that this beneficial effect may be the result of improved tissue microvascular flow and oxygenation. However, this hypothesis has yet to be investigated.

Derangements in microvascular flow in established sepsis are well recognised.[9] Efforts to improve survival from sepsis are focusing increasingly on intervention during the earliest stages of this disease.[10] Little data, however, is available to describe microvascular changes in early sepsis. Sepsis results in a combination of cardiovascular derangements which often result in arterial hypotension despite fluid resuscitation.[11] Vasopressor therapy is currently recommended to maintain mean arterial pressure at >65mmHg despite only limited evidence.[12]

Objectives

1) To confirm the existence, size and nature of the high-risk surgical population in our institution is representative of that described nationally and to describe critical care resource use for these patients.

2) To describe peri-operative changes in tissue microvascular flow and oxygenation in patients receiving usual care following major abdominal surgery.

3) To investigate the effects of flow targeted haemodynamic therapies on tissue microvascular flow and oxygenation and plasma markers of inflammation in patients following major abdominal surgery.

4) To investigate changes in sublingual microvascular flow in patients with sepsis and severe sepsis within 6 hours of hospital admission and compare these data to that of healthy volunteers.

5) To investigate the dose related effects of noradrenaline on tissue microvascular flow and oxygenation in patients with septic shock.

Methods and Results

All studies received relevant approvals from the local audit committee, Research ethics committees and the Medical and Healthcare products Regulatory Agency as appropriate. In each of the clinical investigations cutaneous PtO_2 was measured continuously using a Clark electrode (TCM400, Radiometer, Denmark). Microvascular flow was measured intermittently using cutaneous laser Doppler flowmetry (MoorLab, Moor Instruments, UK) and visualised using sublingual sidestream darkfield imaging (Microscan, Microvision Medical Netherlands). Cardiac output and DO_2I were

measured continuously using lithium indicator dilution and pulse power analysis (LiDCOplus, LiDCO Ltd, UK) in studies 2, 3 and 5 and supra sternal Doppler (USCOM Ltd, Australia) in study 4.

Study 1: Characterisation of the high-risk surgical population in a large NHS Trust

Data describing in-patient non-cardiac surgical procedures performed in our NHS Trust between April 2002 and March 2005 were obtained from hospital and critical care databases. Healthcare Resource Groups (HRG) codes were extracted and then ranked according to mortality rates. HRGs with ≥5% mortality were prospectively defined as high-risk. The high-risk surgical population accounted for 75.4% of deaths in hospital but only 9.3% of admissions. Although the high-risk population accounted for less than 10% of cases they utilised 23% of in-patient bed days. Only 35.3% of the high-risk patients were admitted to a critical care unit at any stage after surgery. Of 294 high-risk patients who died, only 144 (49.0%) were admitted to critical care at any time. Mortality rates were high amongst patients admitted to critical care following initial management on a standard ward (29.9%).

Study 2: Observational study of peri-operative changes in tissue microvascular flow and oxygenation

Measurements were made prior to and at 0, 2, 4, 6 and 8 hours after major abdominal surgery. Patients received usual clinical care. Of 25 patients recruited, two died (8%) and 14 (56%) developed post-operative complications. In patients who developed complications, sublingual microvascular flow index (MFI) (small vessels <20μm) was lower both before and after elective surgery (figure 1). The proportion of perfused vessels ($p<0.01$) and perfused vessel density ($p<0.01$) were also lower post-operatively in those patients who developed complications. There were no associated differences in DO_2I, cutaneous microvascular flow or cutaneous tissue oxygenation.

Study 3: Randomised trial of the effects of post-operative haemodynamic therapy on tissue microvascular flow & oxygenation and plasma inflammatory markers

135 patients undergoing major elective abdominal surgery involving the gut were randomised to one of three groups (n=45 per group) and stratified according to surgical procedure. Control group patients (Control) received colloid boluses titrated against central venous pressure. One intervention group received colloid boluses titrated against stroke volume (SV). The other intervention group received colloid boluses titrated against stroke volume and a fixed dose infusion of dopexamine at 0.5 mcg/kg/min (SV + Dopex). Intervention protocols commenced immediately after surgery and were continued for eight hours. Il-1β, Il-6, Il-8 and TNF-α were measured using a multi-array electrochemiluminescence technique (Mesoscale Discovery). There were significant improvements in DO_2I, cutaneous hyperaemic response, sublingual microvascular flow and tissue oxygenation in the SV + Dopex group compared to the Control and SV groups (figure 2). There were no significant differences in serum inflammatory markers, post-operative complications, hospital stay or mortality between groups.

Study 4: Early microvascular changes in sepsis and severe sepsis

Observational data were collected in healthy volunteers and within six hours of presentation in patients with sepsis and severe sepsis. 28 patients diagnosed with sepsis, 19 with severe sepsis and 16 healthy volunteers were recruited. Eight patients (17%) did not survive to leave hospital. Microvascular flow index ($p<0.05$), heterogeneity index ($p<0.05$) and the proportion of perfused vessels ($p<0.05$) were lower in patients with sepsis and severe sepsis compared to healthy volunteers. Perfused vessel density ($p<0.05$) was lower in the severe sepsis group compared to

the sepsis group. The proportion of perfused vessels ($p<0.01$) and mean arterial pressure ($p<0.05$) were lower in non-survivors compared to survivors.

Study 5: The effects of incremental increases in norepinephrine dose on tissue microvascular flow & oxygenation

The dose of norepinephrine was adjusted to achieve a mean arterial pressure (MAP) of 60 mmHg. Measurements were made following a 45 minute stabilisation period. This process was repeated at MAPs of 70, 80 and 90 mmHg. Patients otherwise received usual clinical care. 16 patients were recruited (age 67 [55-72], APACHE II 23 [17-30]) of whom ten (63%) subsequently died. Significant increases in DO_2I, cutaneous tissue microvascular flow & oxygenation were observed as the dose of norpeinephrine was increased (figure 3).

Conclusions

The high-risk surgical population in our institution is comparable to that previously identified in national studies. In line with national figures, only one third of high-risk patients were admitted to critical care at any stage following surgery, perhaps contributing to the poor outcomes for these patients. Sublingual microvascular flow was impaired both before and after surgery in those patients who subsequently developed complications. Post-operative flow targeted haemodynamic protocols were associated with improved tissue microvascular flow & oxygenation, most significantly in patients receiving low dose dopexamine. Despite these potentially beneficial effects, there were no significant differences in systemic inflammatory markers between groups. This randomised trial was not powered to identify differences in clinical outcomes. Sepsis results in derangements of microvascular flow which can be identified in the early stages of this disease. These abnormalities are more marked in the most severely ill patients. Increasing the dose of norepinephrine administered to

patients with septic shock resulted in increases in DO_2I, tissue microvascular flow and oxygenation, without adverse effects on the sublingual microcirculation.

A large clinical trial is required to confirm or refute the suggested survival benefit of haemodynamic therapies intended to increase DO_2I in high-risk surgical patients. Further detailed investigations of tissue microvascular flow & oxygenation in critically ill patients are also required.

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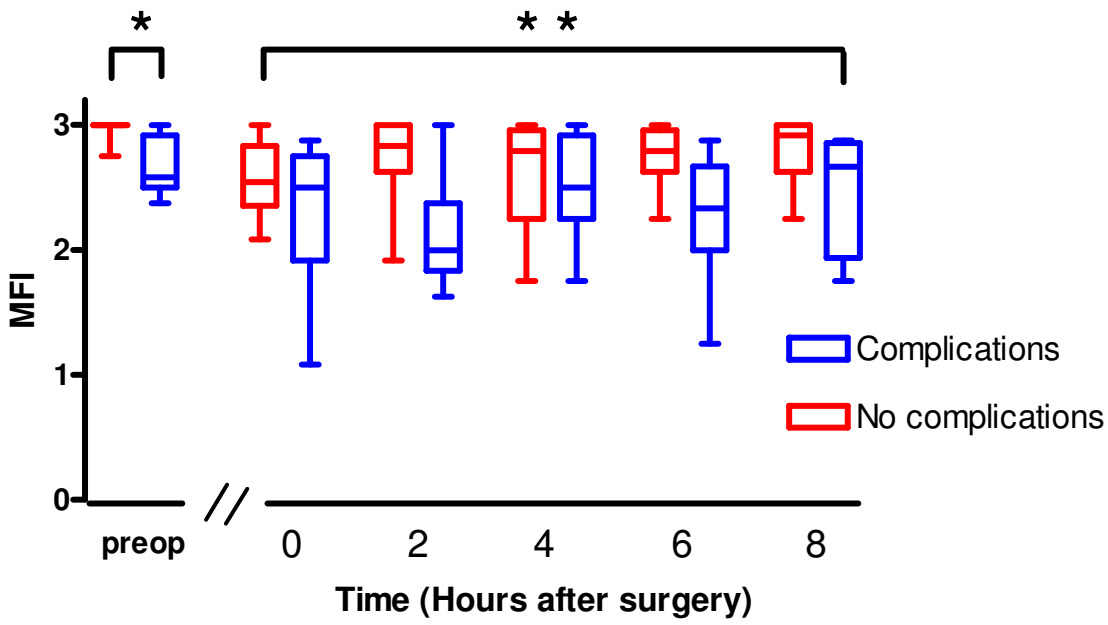

Figure 1 (Study 2) Sublingual microvascular flow index (MFI) of small vessels (<20µm) in patients receiving usual care before and after major abdominal surgery who did or did not develop complications). * p< 0.05 between groups before surgery (t-test). ** p<0.0001 between groups over 8 hours following surgery (two-way repeated measures ANOVA) (from Jhanji et al, ICM 2009).

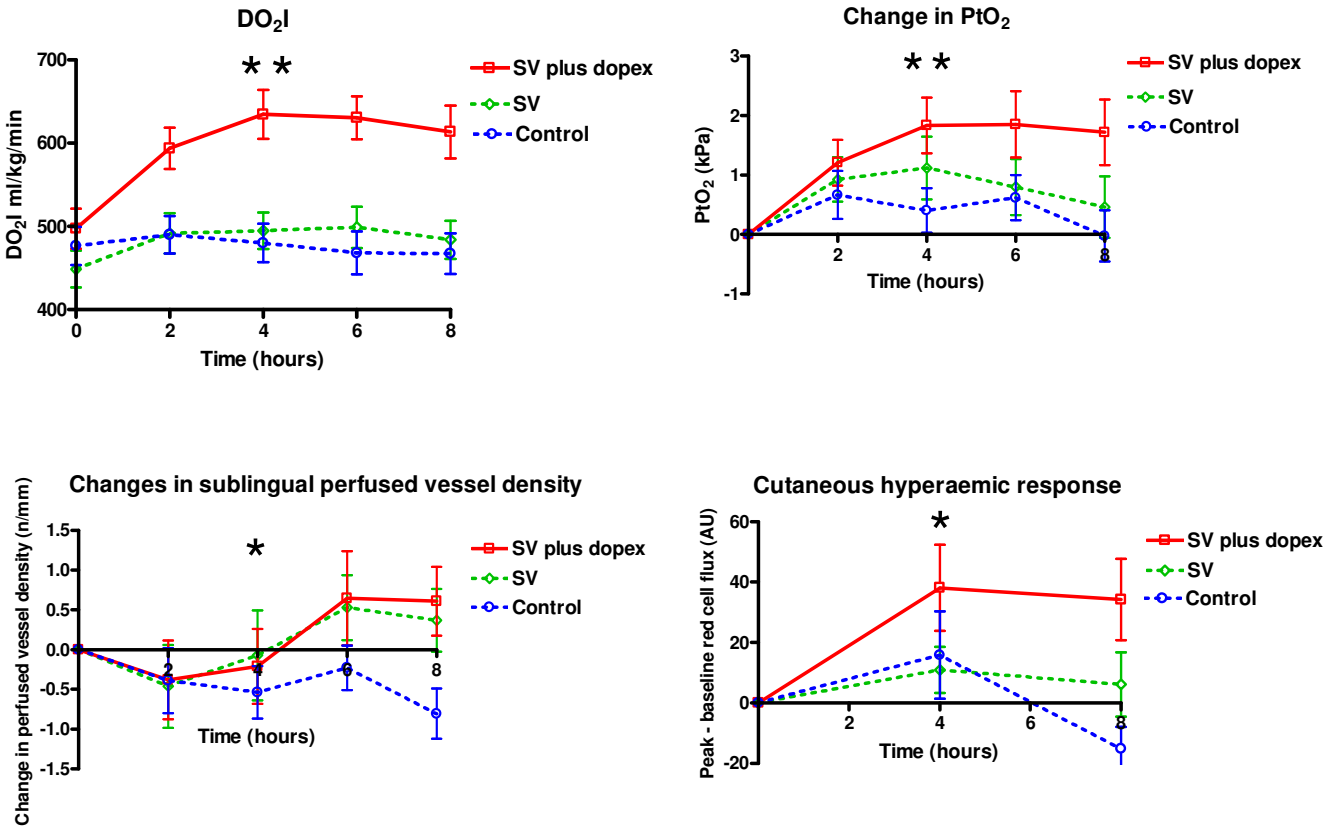

Figure 2. (Study 3) Increases in global oxygen delivery (DO_2I), tissue oxygenation, sublingual microvascular flow and cutaneous hyperaemic response in response to flow targeted therapies. * $p< 0.05$, ** $p<0.001$ (two way repeated measures ANOVA) (from Jhanji et al, Crit Care 2010).

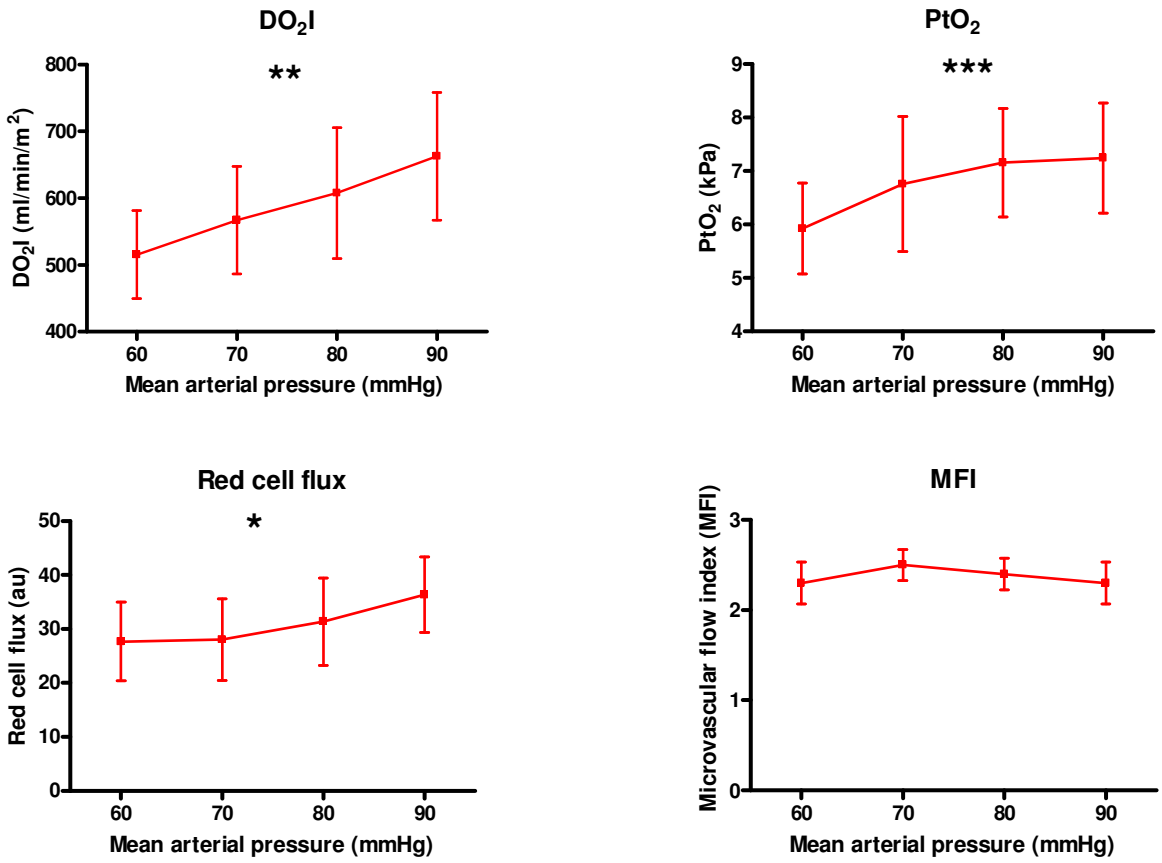

Figure 3 (Study 5). Increases in oxygen delivery index (DO_2I), cutaneous tissue oxygenation (PtO_2) and red cell flux with increasing mean arterial pressure in patients with septic shock. * $p<0.05$, ** $p<0.01$, *** $p<0.0001$ (from Jhanji et al, CCM 2009)

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Peer reviewed publications associated with this body of work

Original articles

1) **Jhanji S**, Smith A, Lucena-Amaro S, Watson D, Hinds CJ, Pearse RM. A randomised controlled trial of the effects of three haemodynamic therapies on microvascular flow, tissue oxygenation and inflammatory markers after major abdominal surgery. *Crit Care* 2010; 14:R151

2) Spanos A, **Jhanji S,** Smith A, Harris T, Pearse RM. Early microvascular changes in sepsis and severe sepsis. *Shock* 2010; 33:387-91.

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Review articles

1) Rampal T, **Jhanji S,** Pearse RM. Using oxygen delivery targets to optimise resuscitation in critically ill patients. *Current opinions in Critical Care* 2010; 16:244-9.

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3) **Jhanji S**, Dawson J, Pearse RM. Cardiac output monitoring: basic science and clinical application. *Anaesthesia* 2008; 63: 72-81.