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Pilot alternating treatment design study of the splanchnic metabolic effects of two mean arterial pressure targets during cardiopulmonary bypass

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Editor's key points

- The optimum arterial pressure to maintain splanchnic perfusion during cardiopulmonary bypass is unknown.
- These authors used norepinephrine to manipulate mean arterial pressure to 60–65 and 80–85 mm Hg.
- Splanchnic oxygenation, acid–base balance, and cytokine release remained similar.
- There was no advantage or disadvantage for splanchnic metabolic function in targeting a higher arterial pressure using norepinephrine.

Background. The arterial pressure target for optimal splanchnic function during cardiopulmonary bypass (CPB) is uncertain. Thus, we aimed to compare the effects of two different arterial pressure targets during CPB on trans-splanchnic oxygenation, acid–base regulation, and splanchnic interleukin-6 (IL-6) and interleukin-10 (IL-10) flux.

Methods. Sixteen patients undergoing cardiac surgery with CPB in a university affiliated hospital were subjected to a prospective alternating treatment design interventional study. We measured arterial and hepatic vein blood gases, electrolytes, IL-6, and IL-10 while targeting a mean arterial pressure (MAP) of between 60 and 65 mm Hg for 30 min, a MAP of between 80 and 85 mm Hg for 30 min (using norepinephrine infusion), and finally 60–65 mm Hg MAP target for 30 min.

Results. The MAP targets were achieved in all patients [65 (4), 84 (4), and 64 (3) mm Hg, respectively; $P<0.001$] with a greater dose of norepinephrine infusion during the higher MAP target ($P<0.001$). With longer time on CPB, hepatic vein O_2 saturation decreased, while magnesium, lactate, glucose, IL-6, and IL-10 increased independent of MAP target. The decrease in hepatic vein saturation was greater as the temperature increased (re-warming). Overall, there was trans-splanchnic oxygen, chloride, lactate, and IL-6 removal during CPB ($P<0.001$) and carbon dioxide, bicarbonate, glucose, and IL-10 release ($P<0.001$). Such removal or release was not affected by the MAP target.

Conclusions. Targeting of a higher MAP during CPB by means of norepinephrine infusion did not affect splanchnic oxygenation, splanchnic acid–base regulation, or splanchnic IL-6 or IL-10 fluxes.

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Maintaining adequate mean arterial pressure (MAP) during cardiopulmonary bypass (CPB) is considered important because MAP is a key determinant of vital organ perfusion.[1 2] In this context, adequate splanchnic perfusion and oxygenation is believed to be particularly important.[2] This is because right heart cannulation is likely associated with a degree of splanchnic congestion; lack of pulsatile flow may further jeopardize the gut and liver blood flow, and gastrointestinal complications are relatively common and sometimes clinically important after cardiac surgery.[3 4] Moreover, splanchnic hypoperfusion and hypoxia may cause subclinical injury secondary to translocation of bacteria, endotoxin, or both from the splanchnic bed into the systemic circulation.[5] Such translocation may, in turn, contribute to systemic inflammation and infection, splanchnic cytokine release, and delayed recovery in ways that are not appreciated or detected clinically.

Despite the above concerns, it is unclear what level of MAP might best maintain splanchnic perfusion at a given pump flow during CPB. This is because perfusion pressure can only be reliably increased by the administration of vasopressor drugs. Vasopressor drugs, in turn, may induce splanchnic vasoconstriction and decrease perfusion.[6] In particular, norepinephrine, probably the most commonly used vasopressor drug, has been reported to cause mesenteric vasoconstriction.[7] Thus, increasing MAP and perfusion pressure may prove beneficial to splanchnic oxygenation but giving norepinephrine to increase MAP may prove detrimental to

such oxygenation. Whether the gains are greater than the losses or vice versa remains uncertain.

Accordingly, we conducted an alternating treatment design over study where 16 patients were subjected to 30 min periods of lower, higher, and then lower arterial pressure during CBP. We evaluated oxygen saturation in the hepatic veins, trans-splanchnic acid–base and electrolyte balance, and trans-splanchnic cytokine release as markers of splanchnic well-being. We hypothesized that increasing MAP with norepinephrine might significantly decrease hepatic vein oxygen saturation and increase both trans-splanchnic acidification of blood and cytokine release.

Methods

Design overview

This study was an alternating treatment design, single-centre, open-label, controlled trial. The Human Research Ethics Committee of the Austin Hospital approved this study (Austin Hospital HREC number: H99/00667). Written informed consent was obtained from each patient. The study is reported using the recommendations of the CONSORT statement[8] and was registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12611001107910).

Setting and participants

We enrolled a cohort of patients who were undergoing elective or urgent cardiac surgery necessitating the use of CPB at a university tertiary referral hospital.

Clinical practice was not changed or modified for the purpose of the study and followed the same standard protocols as previously described.[9 10] In brief, all preoperative medications were routinely omitted on the day of surgery. Aspirin was stopped 1 week before surgery. Angiotensin-converting enzyme inhibitors were withdrawn on hospital admission (generally 1 day before surgery). The surgical approach in all patients was by median sternotomy. The CPB circuit consisted of a roller pump (Stoeckert S3, Munich, Germany), tubing (Lovell Uncoated Tubing, Lovell, Melbourne, Australia, or Cobe Smart Tubing, Cellplex, Melbourne, Australia), a membrane oxygenator (Affinity Trillium Coated Oxygenator, Medtronic, Minneapolis, MN, USA, or Monolyth-Pro, Sorin, Saluggia, Italy), and an arterial filter (Pall, Melbourne, Australia). The pump prime solution was made up with 2 litres of crystalloid solution (Plasmalyte, Baxter, Sydney, Australia). CPB was managed with a pump flow of 2.4 litre min^{-1} m^{-2} and moderate hypothermia (28°–30°C). Acid–base management involved the α-stat method (with no correction for temperature). Myocardial protection during aortic cross-clamping was with antegrade and retrograde blood cardioplegia, and all proximal graft anastomoses were performed during the period of complete aortic clamping.

Intraoperative fluid management was at the discretion of the anaesthetist and was documented. For fluid administration, a crystalloid solution (Compound Sodium Lactate, Baxter, Old Toongabbie, Australia) or gelatine-based colloid solution (Gelofusine®, Braun, Bella Vista, Australia) was used. Blood glucose levels between 5 and 10 mmol $litre^{-1}$ (90–144 mg dl^{-1}) were achieved using insulin bolus or infusions.

Intervention

Cardiovascular monitoring for all patients included radial arterial cannulation and a thermodilution pulmonary artery catheter (Baxter-Edwards Oximetry TD Catheter 93A-741H, 7.5 F) inserted via the right internal jugular vein. After induction of anaesthesia, a hepatic venous catheter (Baxter-Edwards Oximetry TD Catheter 93A-741H, 7.5 F) was inserted through the femoral vein using fluoroscopy. Fluoroscopy was repeated at the end of surgery to confirm that the hepatic venous catheter had remained in place during the study period. Baseline haemodynamic measurements were obtained. Blood was drawn from the arterial line and from the hepatic vein for the measurement of biochemistry, blood gases, and cytokines [interleukin (IL)-6 and IL-10].

Once the patient was on CPB, a MAP of between 60 and 65 mm Hg was targeted using an infusion of norepinephrine. After 30 min at this target MAP, samples and haemodynamic measurements were obtained for repeat measurements. After obtaining the samples, MAP was increased using an infusion of norepinephrine to a value between 80 and 85 mm Hg. After 30 min at this increased MAP, all measurements were repeated. After the samples were obtained, the MAP was allowed to return to a target of 60–65 mm Hg. After 30 min at this lower MAP, measurements and sampling were repeated once more.

Outcome measures and follow-up

The primary study outcome measure was hepatic venous saturation. Secondary outcomes included trans-splanchnic changes in lactate levels, trans-splanchnic changes in pH, trans-splanchnic changes in other markers of metabolic acid–base status (base excess and bicarbonate), and trans-splanchnic changes in IL-6 and IL-10 levels. Trans-splanchnic changes were calculated by subtracting the hepatic vein values of the relevant variables from their arterial values. A positive value indicated a trans-splanchnic increase (release) and a negative value trans-splanchnic decrease (removal).

Power of the study and statistical analysis

After log transformation of the data, this study had a >80% power to detect a difference between the low and high MAP period equal to the standard deviation at an α of 0.05. Continuous data were tested for normal distribution. Between-group comparisons for continuous data were performed with the use of the *t*-test or the Mann–Whitney *U*-test. One-way analysis of variance (ANOVA) and Friedman's ANOVA were used to assess change over time for parametric and non-parametric data, respectively. Correlation coefficients were calculated with the Spearman rank correlation test. All tests were two-tailed and we considered a *P*-value of <0.05 to indicate statistical significance. We report values as means with standard deviation (SD) and mean difference, or medians with inter-quartile ranges (IQR) as