Fluid bolus of 20% Albumin in post-cardiac surgical patient: 
a prospective observational study of effect duration

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Fluid bolus therapy (FBT) is commonly used as the first line therapy for the treatment of haemodynamic instability in patients post cardiac surgery\(^1\). The physiologic rationale for FBT is that the fluid will lead to an increase in stroke volume via the Frank-Starling mechanism, and therefore increase cardiac output and blood pressure.

The concept of *fluid responsiveness* is commonly used to determine the impact of FBT and patients are typically considered to be *responders* if there is an increase of at least 10% to 15% in their stroke volume after the administration of a fluid bolus\(^2\text{-}^4\). Currently however, there is no consensus definition as to what volume of fluid should be administered as a bolus, the timescale over which it should be administered and the time, post-bolus, at which fluid responsiveness should be assessed\(^5\text{-}^6\).

Recent studies have suggested that the haemodynamic effect of fluid boluses may be short-lived\(^7\text{-}^8\) and that patients who are considered to be *responders* at the end of a fluid bolus may be classed as *non-responders* in as little as ten minutes after the bolus\(^7\). These studies have reported short periods of continuous observation following FBT or longer periods of intermittent observation following FBT. Furthermore, the fluid boluses used in some cases have been relatively small (circa 3ml/kg).

It is important to note that FBT is normally part of a complex intervention\(^6\) that frequently occurs in concert with numerous other haemodynamic confounders. To date, no studies have interpreted the physiological effects of fluid bolus therapy in setting of day-to-day clinical practice, when the fluid bolus utilized 20% albumin as the solution of choice.

Accordingly, we sought to continuously measure the haemodynamic impact of a 100 ml fluid bolus of 20% albumin following completion of the bolus. Our aim was to quantify the dissipation of the haemodynamic effect of FBT with 20% albumin with as much fidelity as possible.
References


Methods

The study was approved as a service evaluation by the Ethics Committee of the Austin Hospital in Melbourne, Australia (reference number LNR/16/Austin/358). The need for informed consent was waived due to its purely observational nature.

This was a prospective, single-centre, observational study performed in the cardiothoracic ICU of a tertiary university hospital between December 2016 and June 2017. All ventilated patients aged over 18 years who were admitted to the ICU following cardiac surgery were considered for inclusion in the study. Patients were included if the treating clinician decided to prescribe a bolus of fluid in the first 12 hours on arrival to the ICU and if a member of the research team was available at the bedside to observe the patient’s haemodynamic parameters for one hour post bolus. Patients were excluded from the study if they did not have invasive blood pressure monitoring or a pulmonary artery catheter in-situ. Patients who were known to be pregnant or who required mechanical haemodynamic support (intra-aortic balloon pump or extracorporeal membrane oxygenation (ECMO) were also excluded.

Cardiovascular Monitoring

All patients were monitored using Philips Intelliview MP70 (Philips Healthcare, Best, Netherlands) bedside monitors with continuous arterial blood pressure monitoring from either a radial or brachial artery catheter and continuous central venous pressure measurement via an internal jugular catheter. Pulmonary artery (PA) pressures and blood temperature were recorded from PA catheters (Edwards Lifesciences, Irvine, CA) inserted via the internal jugular vein. Depending on the variety of PA catheter, intermittent or continuous measurements of cardiac output were recorded using a thermodilution technique. In the case of intermittent cardiac output catheters, all measurements were performed by the patient’s bedside nurse or a member of the research team. 10ml boluses of room temperature saline were used for each cardiac output measurement.
and the recorded values were based on the average of three measurements (or two measurements when there was less than 10% difference between the two values). All pressure measurements were referenced to the intersection of the anterior axillary line and the fifth intercostal space.

**Fluid Challenge**

Fluid challenges were only administered if deemed necessary by the clinical team but clinicians were asked to use a bolus of 100 mls of 20% albumin solution. The research team recorded the indication for the fluid bolus according to a list of pre-defined indications (ESM Appendix 1, supplemental digital content).

All fluid boluses were given using a hand pump via an intravenous giving set connected to the central venous catheter or a large bore peripheral cannula. No guidelines were given regarding the speed of fluid administration although patients were excluded from further analysis if administration of the bolus took greater than 30 minutes.

**Haemodynamic Observation**

Haemodynamic data were recorded on a second-by-second basis using Medicollector data logging software (Medicollector LLC, Boston, MA) connected to the Phillips MP70 bedside monitors via a RS232 serial port connection.

Where possible, baseline haemodynamic parameters were recorded for a minimum of ten minutes prior to commencement of the fluid bolus. Baseline ventilator parameters and the rates of any sedative and vasoactive infusions were also noted during this period. In addition, arterial blood gas results from within 2 hours prior to the fluid bolus were recorded.
A member of the research team was present at the bedside throughout fluid bolus administration and for one hour afterwards. Following commencement of the fluid bolus, the clinical team were asked to avoid any interventions (haemodynamic confounders) that may alter the patient’s haemodynamic status provided that doing so would not be detrimental to patient care. When this was not possible, the researcher contemporaneously recorded the nature of the confounder by electronic annotation of the Medicollector datafile.

When patients did not have pulmonary artery catheters that were capable of continuous cardiac output measurements, measurements of cardiac output were performed within 15 minutes prior to the fluid bolus, immediately after completion of the bolus and then, as a minimum, at 30 minutes and post bolus.
**Statistical Analysis Plan (SAP)**

**Primary Hypothesis**

In post-cardiac surgery patients with a decision to administer a fluid bolus by an independent clinician, compared with baseline, at 30 minutes after the administration of a 100 ml of 20% Albumin (fluid bolus), more than 50% of patients will have a persistent increase in Cardiac Index (CI) >15% (persistent responders).

**Secondary Hypotheses**

- In responders (CI>15% above baseline at the end of the bolus), the median time to dissipation of CI effect will be >30 minutes
- In responders (MAP>10% above baseline at the end of the bolus), the median time to dissipation of MAP effect will be >30 minutes
- CI will increase by >15% above baseline in ≥ 80% of patients at the end of the fluid bolus (early responders)
- MAP will increase by >10% above baseline in ≥ 80% of patients at the end of the fluid bolus (early responders)
- Overall, irrespective of response, MAP will be >10% above baseline in >20% of patients at 30 minutes after the fluid bolus (persistent MAP responders)
- Central Venous Pressure (CVP) will be >2 mmHg above baseline in ≥80% of patients at the end of the bolus and in >50% of patients at 30 minutes
- Organ perfusion pressure (MAP-CVP) will increase by >5% of baseline in >50% of patients at the end of the fluid bolus
**Planned Tables description**

**Table 1.** Demographic characteristics of the 20 patients enrolled

**Table 2.** Fluid bolus indications, median [IQR] duration of infusion, percentage of responders at the end of the bolus and 15 minutes and 30 with median [IQR] time to dissipation overall and then split for responders and non-responders (3 columns)

**Table 3.** Mean haemodynamic variables at baseline, end of the bolus, 15 minutes and 30 minutes overall and for responders and for non-responders (3 columns).

**Planned Figures description**

**Figure 1.** The box plot shows mean CI change at the end of the bolus, 15 minutes and 30 minutes split for responders and non-responders

**Figure 2.** The box plot shows mean changes in MAP at 2 minutely interval since the end of the bolus split for responders and non-responders

**eFigure 1.** The box plots show mean changes of heart rate (HR), SAP, diastolic arterial pressure (DAP), CVP, organ perfusion pressure (MAP-CVP), systolic pulmonary arterial pressure (SPAP), diastolic pulmonary arterial pressure (DPAP), mean pulmonary arterial pressure (MPAP), peripheral O2 saturation (SpO2), mixed venous O2 saturation (SvO2), blood temperature (Tb) at the end of the bolus, 15 minutes and 30 minutes for responders and non-responders

**eFigure 2.** The line plots show mean changes of CI, HR, SAP, DAP, CVP, SPAP, DPAP, MPAP, MAP-CVP, SpO2, SvO2, Tb at the end of the bolus, 15 minutes and 30 minutes for each patient.
**Planned statistical analysis approach**

According to the changes in CI after the administration of the fluid bolus, patients will be classified as responders (ΔCI > 15% above baseline) or non-responders. Cardiovascular measurement will be obtained at:

- Baseline: within 3 minutes before the commencement of the fluid bolus.
- End of the bolus: for continuous measurement, mean value within 3 minutes post bolus.
- 15’ post bolus: for continuous measurement, mean value within 28’ and 32’ post bolus.
- 30’ post bolus: for continuous measurement, mean value within 58’ and 62’ post bolus.

We will define the time to effect of dissipation as the time:

- when a patient’s CI is < 5% than baseline for at least two consecutive minutes.
- when a patient’s MAP is <3 mmHg than baseline for at least two consecutive minutes

Data will be expressed as Mean (Standard Deviation) or Median (25%-75% Interquartile Range).

Normal distribution of the data will be evaluated using the Kolmogorov-Smirnov test.

Difference between responders and non-responders will be assessed by two-tailed Student’s t-test or Mann-Whitney U-test or repeated measures ANOVA, as appropriate.

Comparison of responders vs. non-responders will be performed with RM ANOVA for hemodynamic variables and by Mann-Whitey or Fisher’s exact test for other variables.

Analysis of categorical data will be performed using Fisher’s exact test.

Correlations will be tested by Spearman’s correlation test.