Haemodynamic response to fluid boluses in children after cardiac surgery: a technical report

Ben Gelbart, Laurent Bitker, Ahuva Segal, Adrian Hutchinson, Norman Soh and Tim Maybury

Fluid boluses (FB) are a ubiquitous intervention in the management of critically ill children; however, there are few data on the haemodynamic response to this therapy. In part, this relates to the difficulty in defining fluid responsiveness but also to the infrequency of invasive monitoring in children. In recent times, FB has been the subject of increased scrutiny in the context of studies suggesting associated harm. For instance, the FEAST (Fluid Expansion as Supportive Therapy) study showed increased mortality with FB in African children with sepsis, and in paediatric intensive care, excessive fluid therapy has been associated with renal and pulmonary morbidity as well as with increased mortality. Despite the widespread use of FB in paediatric critical care, an understanding of the haemodynamic response in terms of magnitude and duration remains poorly described.

Vital signs such as heart rate and blood pressure are preferred triggers for FB among paediatric intensive care doctors and emergency department physicians rather than central venous pressure (CVP) and dynamic measures such as straight leg raise. Volume responsiveness in children has been described using cardiac output monitoring and echocardiographic measures, including pulse pressure and stroke volume variation. Assessment of volume responsiveness in children during cardiac surgery shows that pulse pressure variation and respiratory variation in stroke volume are superior markers; yet, these are uncommonly used in clinical practice. Routine bedside haemodynamic monitoring remains the most common way to assess the need for and response to FB; therefore, it is prudent to describe this response.

After congenital heart disease surgery, children commonly receive FB when managing low cardiac output syndrome. This population is unique in paediatric intensive care for several reasons. Firstly, invasive haemodynamic monitoring is commonplace to monitor and guide therapy. Secondly, exposure to cardiopulmonary bypass inflicts an inflammatory response leading to circulatory compromise often requiring FB. The combination of invasive monitoring and frequent use of FB makes this population ideal to examine haemodynamic interventions. The introduction of an electronic medical record in 2016 has enabled the collection and storage of bedside monitor data. In this technical report, we describe the methodology for assessing the response to FB in children and aim to report the haemodynamic response in children admitted to a cardiac intensive care unit.

Abstract

Objective: To describe the haemodynamic response to fluid boluses (FB) in children after cardiac surgery.

Design: A prospective observational pilot study.

Setting: Single-centre, paediatric cardiac intensive care unit.

Participants: Children after cardiac surgery.

Interventions: FB of 0.9% saline, 4% albumin or modified ultrafiltrate blood administered in less than 30 minutes.

Main outcome measures: Heart rate, arterial blood pressure, central venous pressure, oesophageal temperature, and end-tidal carbon dioxide were measured continuously and reported minutely from 5 minutes before and 30 minutes after FB. A mean arterial pressure (MAP)-responsive episode was defined as a 10% increase in MAP from baseline.

Results: There were 21 FB recorded in 9 patients. Most patients \((n = 8)\) weighed \(\leq 6\) kg, and three had univentricular circulation. Fourteen FB (67%) were 4% albumin and 15 (71%) were \(\leq 7.5\) mL/kg. There were nine MAP-responsive episodes (43%). Episodes of MAP responsiveness had a median MAP increment from baseline of 5 mmHg (interquartile range [IQR], 5–7) and 5 mmHg (IQR, 2–17) at 15 minutes and 30 minutes, respectively, significantly higher when compared with non-responsive episodes (median, 1 mmHg [IQR, –2 to 3]; and median, –1 mmHg [IQR, –3 to 1]; \(P < 0.01\)). In MAP-responsive episodes, median time to response was 6 minutes (IQR, 3–12) and seven episodes (78%) dissipated at a median of 2 minutes after response (IQR, 1–8). MAP response was not associated with fluid volume nor fluid composition.

Conclusion: In this study, the haemodynamic response to FB in children is infrequent and unsustained. Larger studies are required to demonstrate the pattern of haemodynamic response of FB in critically ill children.
Methods
We conducted a prospective observational pilot study of FB in children after congenital heart disease surgery admitted to the paediatric intensive care unit (PICU) of the Royal Children’s Hospital, Melbourne, VIC, Australia, over a 2-week period in March 2018. The Human Research Ethics Committee at the Royal Children’s Hospital approved the study and waived the requirement for informed consent (RCH HREC reference no. 36056A).

All children who received FB of sodium chloride 0.9%, 4% albumin or modified ultrafiltrate blood administered in less than 30 minutes duration were included. We excluded children who were on extracorporeal membrane oxygenation at the time of FB or for whom the chest remained open after the operation. All fluid was administered at room temperature.

Physiological and fluid bolus data capture
The indication, prescription and administration of FB were at the discretion of the clinical staff. A case report form was used to collect fluid composition, volume, the exact minute the FB was administered (starting time), and its duration (in minutes). Continuous haemodynamic data were collected from the bedside monitor (Phillips Intellivue, Amsterdam, The Netherlands). Minutely data were extracted commencing 5 minutes before and 30 minutes after each FB starting time using a medical device integration system (SmartLinx Advanced Integration, Capsule by Qualcomm Life, California, USA). We recorded heart rate, all invasive blood pressures (CVP, right atrial pressure, arterial systolic, mean and diastolic blood pressure, left atrial pressure) when present, as well as end-tidal carbon dioxide (ETco2) level and oesophageal temperature. Multiple FB occurring in a single patient could be included in the final analysis, so long as each FB was separated by 30 minutes before and after.

Definition of study endpoints
Mean arterial pressure (MAP) responder was defined as an individual FB episode that led to an increase in MAP of a pre-specified threshold above baseline for a duration of 2 minutes. We tested the proportion of MAP responders at MAP thresholds of 5%, 10% and 15%. MAP response was defined at the 10% threshold as the optimal cut-off.

Time to response was defined as the elapsed time from the start of the FB to the time at which MAP response was first achieved. In responders, we defined dissipation as the fall in MAP below the 10% response during a proceeding 3-minute interval. Time to dissipation was the elapsed time between MAP response and dissipation of effect.

Demographic and clinical data
Demographic and clinical data including age, weight, diagnosis, and Risk Adjustment for Congenital Heart Surgery (RACHS) score were collected from the PICU database and electronic medical records.

Statistical analysis
Demographic and clinical characteristics were described using frequency and proportions. Median and interquartile range (IQR) were used to describe non-parametric data. The study’s statistical unit was the FB episode, and all analyses accounted for the repetition of FB episodes in an individual.

We first compared baseline episode characteristics based on MAP response, fluid composition and volume. We then compared the effect of FB on recorded haemodynamic variables (expressed as the absolute changes from baseline) over the observation period, using mixed effect linear regression models accounting for the repetition of measurements within each FB episode. Finally, we performed a univariate logistic regression of variables associated with MAP response. All analyses were performed using the R software, version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided \( P < 0.05 \) was considered statistically significant.

Results
There were 21 FB episodes administered to 9 children — Table 1 shows the demographic and clinical characteristics of the 9 patients. Most patients \( (n = 8) \) weighed \( \leq 6 \) kg, and 3 had a univentricular circulation. Children were mechanically ventilated for all but one FB episode, and for two episodes temporary pacing was present.
Fluid composition, duration and volume
The characteristics of FB are shown in Table 2. The predominant characteristics were a composition of 4% albumin, a volume of ≤ 7.5 mL/kg and a duration < 10 minutes.

Mean arterial pressure response and baseline characteristics
MAP response of 10% after a FB occurred in 9 episodes (43%). There were no significant differences in FB characteristics between responsive and non-responsive episodes (Table 2). Nor were there differences in haemodynamic parameters apart from higher baseline ETco₂ level in MAP-responsive episodes (Table 3).

Mean arterial pressure response and dissipation
MAP responses over time for both responsive and non-responsive episodes are shown in Figure 1. MAP response occurred at a median time of 6 minutes (IQR, 3–12) after the start of the FB. The response dissipated in seven responders (78%) at a median of 2 minutes (IQR, 1–9) minutes after MAP response. For a threshold MAP response of 5% and 15% from baseline, the proportion of responders were 15/21 (71%) and 6/21 (29%), respectively (online Appendix, figure 1; available at cicm.org.au/Resources/Publications/Journal).

Other haemodynamic and physiological parameters
The change in systolic and diastolic blood pressure increased significantly in MAP responders compared with non-responders at 5, 15 and 30 minutes after FB (Figure 2). There was a statistically significant yet not clinically relevant difference in heart rate change from baseline at 30 minutes in MAP responders compared with non-responders (online Appendix, figure 1). There were no significant differences in CVP, ETco₂ and oesophageal temperature between MAP responders and non-responders at any time point compared with baseline ($P = 0.24$, $P = 0.90$, $P = 0.77$, respectively).

Discussion
Key findings
In this technical report, we describe the methodology for analysing commonly measured physiological and haemodynamic variables in children receiving FB and show patterns of response and dissipation. We showed that MAP response, defined by a 10% increment from baseline MAP, occurred in less than half of fluid bolus (FBT) episodes. Dissipation occurred in 78% of episodes at a median time of 2 minutes after response. Systolic, diastolic and pulse pressure responses all significantly increased in MAP responders, but no discernible changes in heart rate, oesophageal temperature and ETco₂ level were observed. We have shown that it is feasible to describe the haemodynamic changes of commonly measured variables on a minutely basis.

Our study shows that less than half of children responded to FB with an increase of 10% in MAP from baseline. We chose 10% as a threshold defining MAP responsiveness as it exists in a range preferred by paediatric intensive care physicians. Using a 15% threshold meant that less than 30% of episodes were responsive. Although the present study was not designed to define an optimal threshold, future studies may answer this by investigating how different thresholds may be associated with patient-centred outcomes or more invasive markers of cardiac output.

The relationship between blood pressure response to FB and increase in stroke volume in children is poor, highlighting the difficulty in relying on blood pressure as an endpoint. In children, dynamic measures that rely on cardiopulmonary interactions such as respiratory variation in aortic blood flow velocity appear more predictive of fluid responsiveness than static measures. This has also been observed in children after cardiac surgery. A study of 26

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<th>Table 2. Characteristics of fluid boluses and comparison based on mean arterial pressure response</th>
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<td><strong>Whole cohort</strong></td>
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<td>Number of patients</td>
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<td><strong>Fluid composition</strong></td>
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<tr>
<td>0.9% Saline</td>
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<td>4% Albumin</td>
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<td>Modified ultrafiltrate blood</td>
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<td><strong>Fluid volume</strong></td>
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<td><strong>Fluid duration</strong></td>
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* $P$ value reflects the significance between responders and non-responders.
anaesthetised infants who were administered FB before and after repair of atrial and ventricular septal defects showed that, in contrast to CVP, dynamic measures, such as pulse pressure variation, were highly correlated with an increase in echocardiographic-derived stroke volume. However, these measures are rarely relied upon to determine response to fluid, thus supporting less invasive parameters as surrogates. We did not assess pulse pressure variation in the present study, but static pulse pressure was significantly higher in MAP-responsive episodes. It may be that more granular, minutely data such as these can highlight early, brief responses with greater fidelity.

Dissipation in responsive episodes occurred frequently and relatively quickly, in keeping with other studies of physiological responses to FB in adults. Dissipation has not been widely explored in paediatrics. In a recent, prospective, observational study in children with sepsis, Long and colleagues showed that about two-thirds of patients had an increase in cardiac index (measured using echocardiography) greater than 10% by 5 minutes, and the

| Table 3. Baseline haemodynamic and physiological values based on mean arterial pressure (MAP) response* |
|-------------------------------------------------|-----------------|-----------------|-----------------|-------|
| Number of patients                              | Whole cohort    | Non-responsive  | Responsive      | P     |
| Systolic blood pressure (mmHg), median (IQR)    | 71.2 (60.0–76.7)| 71.0 (59.1–76.2)| 71.2 (62.8–77.0)| 0.25 |
| Diastolic blood pressure (mmHg), median (IQR)   | 43.6 (35.8–48.0)| 44.7 (31.9–50.5)| 43.6 (36.6–44.0)| 0.10 |
| Mean blood pressure (mmHg), median (IQR)        | 52.6 (47.2–56.8)| 52.9 (45.6–58.9)| 52.0 (47.6–55.0)| 0.15 |
| Heart rate (beats/min), median (IQR)            | 150.0 (136.5–167.0)| 153.0 (140.4–167.6)| 140.0 (131.4–160.2)| 0.58 |
| Etco₂, median (IQR)                              | 33.0 (30.6–38.4)| 31.3 (30.4–33.8)| 35.6 (33.0–40.0)| 0.03 |
| Pulse pressure (mmHg), median (IQR)             | 26.0 (18.8–32.0)| 26.3 (20.9–30.2)| 23.2 (18.8–35.0)| 0.63 |
| Central venous pressure (mmHg), median (IQR)    | 7.0 (6–9.4)     | 8.5 (6.6–9.4)   | 6.0 (5.1–8.4)   | 0.74 |
| Oesophageal temperature (°C), median (IQR)      | 36.7 (36.5–37.6)| 36.7 (36.5–37.6)| 37.6 (37.0–37.7)| 0.54 |

Etco₂ = end-tidal carbon dioxide. * MAP response was defined as an individual fluid bolus episode that led to an increase in MAP of 10% above baseline.
The figure shows the course of systolic arterial pressure (A), diastolic arterial pressure (B), pulse pressure, (C) and heart rate (D) at three time points of the observation period. Response in MAP was defined using a threshold of a 10% increase in MAP above its baseline value. MAP responders are depicted by grey boxes and non-responders by white boxes. The P value reflects the overall difference between groups over the whole observation period, and accounts for the repetition of measurements and fluid bolus episodes in a given individual. Asterisks reflect a significant difference (P < 0.05, after adjustment for multiple comparisons) between groups at a given time point.

The median cardiac index at 60 minutes after FB was less than baseline. Only 13% of responders had a sustained response at 60 minutes. Others have performed similar studies in adults with sepsis and have shown transient changes in MAP and CVP. No standardised definition of “dissipation” exists. We hypothesise that it may reflect rapid redistribution of the fluid volume from the intravascular space or blunting of endogenous sympathetic activity to either vasomotor tone or cardiac contractility. Although these are pilot data with undefined criteria for administration of FBT or for standardised dosing, there is a signal that the response to FB is infrequent and unsustained.

It is not clear why no commensurate drop in heart rate was observed. It is likely that other factors influencing heart rate may have contributed to this. Importantly, in this study, temporary pacing was not likely to be contributory, as only...
a small proportion of FB occurred in this context. Finally, baseline ETco₂ level was significantly lower in non-responsive episodes, suggesting that cardiac output may have been more depressed for this group of FB, with perhaps a lower potential to respond to preload-dependant improvement in haemodynamic parameters.

The optimal composition, volume and duration of FB are unclear; however, a number of studies have sought to test this, albeit with methodological limitations. A small randomised study in children with septic shock in India, despite being stopped prematurely, showed that rapid administration of FB increased the risk of intubation compared with those who received it over 15–20 minutes. A retrospective study of cardiac surgical patients comparing crystalloids and colloids for fluid resuscitation interestingly showed that when compared with colloids, patients receiving crystalloids received less total daily fluid on the second and third post-operative day. There were insufficient data in this study to determine whether fluid composition or rate affected responsiveness. Describing the response to FBT can inform clinicians on the range of expected magnitude and duration of therapy and may guide appropriate fluid administration. What remains unclear is how to better define when, how quickly, how much, which composition and to what endpoints.

Strengths and limitations

The strengths of this study are that it utilises the minutely, averaged haemodynamic data to analyse the response to FBT in a real-world setting using routine invasive haemodynamic monitoring. This has the advantage of being able to monitor changes of commonly used signs on a minutely basis and does not rely on interobserver agreement. The timing of FB administration and haemodynamic data were time-matched. Studying the physiological and haemodynamic response to FBT in children after congenital heart disease surgery has the advantage of availability of broad invasive monitoring but represents a niche population with diverse circulatory anatomy. There are, however, significant limitations. In the first instance, in this single-centre study, the indication for and administration of FB was not standardised. The confounding effects of vasoactive therapies, mechanical ventilation and other stimuli of haemodynamic alterations were not accounted for. While accuracy of parameters such as ETco₂, level, heart rate and continuously monitored pressures could be confirmed, continuous CVP monitoring may have been subject to error during drug administration and line occlusion. The definition of “fluid responders” is based on arbitrary increments, albeit within the expected range of paediatric intensivists in Australian and New Zealand. The small sample size and variability in intracardiac anatomy as well as the presence of systemic to pulmonary shunts limit the broader applicability of these results but provide a baseline for defining threshold responses and a framework for investigating FBT with a larger sample size.

Future direction

Analysing the response to FBT in a larger, broader population of children will provide the ability to compare responses by volume, rate and fluid composition — none of which could be evaluated in this technical report. Further research could also assess the impact on vasoactive medication administration, other physiological endpoints such as urine output, and total fluid administration. Understanding the response to FBT in terms of the macrovascular haemodynamic response as well as its effect on the microvascular components of the circulation are important future considerations.

Conclusion

In this cohort of children after cardiac surgery, response to FBT occurs infrequently and the effects dissipated rapidly. Understanding the timing and magnitude of response and dissipation of FBT is informative and will identify key haemodynamic patterns for trials comparing fluid compositions and fluid volumes.

Competing interests

None declared.

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