


Perioperative Echocardiographic Hemodynamic Parameters and Postoperative Outcome in Pediatric Congenital Heart Disease: A Descriptive Observational Prospective Pilot Study Protocol

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Abstract

Background: We have elaborated a randomized controlled trial (RCT) protocol in pediatric congenital heart disease patients scheduled for surgical repair. In this RCT protocol trans-thoracic echocardiography will be realized perioperatively to guide fluid and hemodynamic therapy in these patients. This RCT will determine the impact of goal directed therapy with echocardiography on postoperative outcome in terms of morbidity, length of intensive care unit stay (LOSICU), length of mechanical ventilation (LMV), length of hospital stay (LOS), fluid therapy and vasopressor-inotropic therapy. There are no trials in this population which have identified echocardiographic hemodynamic parameters predictive of postoperative outcome in terms of morbidity, LOSICU, LMV and LOS. The objective of this pilot observational prospective trial protocol is to describe the study which will determine echocardiographic hemodynamic parameters predictive of postoperative outcomes. These hemodynamic parameters will be integrated in the RCT which has the objective to determine the impact of goal directed fluid and hemodynamic therapy guided by trans-thoracic echocardiography on postoperative adverse outcome.

Methods: Patients aged less than 18 years with congenital heart disease admitted for surgical repair will be included. Trans-thoracic echocardiography will be realized to measure different hemodynamic parameters preoperatively and perioperatively after weaning from cardiopulmonary bypass until discharge from the ICU in included patients. Primary outcome will be postoperative morbidity, secondary outcomes will be LOSICU, LMV and LOS; tertiary outcomes will be fluid therapy, vasopressor and inotropic therapy. Primary outcome measure will be the presence of postoperative organ dysfunction. Secondary outcome measures will be the number of postoperative days spent in the intensive care unit (ICU), number of postoperative days spent on invasive or non-invasive mechanical ventilation and the number of postoperative days spent in the conventional hospitalization ward. Tertiary outcome measures will be the quantity of fluid administered and the vasopressor-inotropic score (VIS). The study will be monocentric. XLSAT 2018.3 or plus will be the software for statistic analysis. Results are expected in the first semester of 2021.

Conclusion: This pilot study will identify echocardiographic hemodynamic parameters predictive of postoperative adverse outcome which will be integrated in the second RCT where goal directed fluid and hemodynamic therapy will be guided with echocardiography.

Introduction

Perioperative goal directed fluid and hemodynamic therapy (PGDFHT) has been studied in adults where it has demonstrated its efficacy in terms of reduced postoperative complications and length of hospital stay (LOS) [1-7]. The objective of PGDFHT is to monitor fluid responsiveness and hemodynamic status with the aim to improve oxygen delivery to different systemic organs and to improve tissular perfusion [8]. Tissular hypoperfusion can have side effects in terms of organ failure. Unoptimal fluid and hemodynamic status (insufficient or plethoric) can alter tissular perfusion. Therefore monitoring fluid responsiveness and hemodynamic status using tools to assess adequate cardiac output to maintain sufficient tissular oxygen delivery is

mandatory. There are no studies in children demonstrating the impact of PGDFHT with echocardiography on postoperative outcome.

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However, there are studies in pediatric cardiac surgery mostly which identified perioperative biomarkers of postoperative adverse outcome [9]. These biomarkers were lactate levels, central venous oxygen saturation SCVO², regional cerebral, renal, splanchnic oxygen saturation and veno-arterial carbon dioxide gradient. Unoptimal values of these biomarkers predicted adverse postoperative outcome in terms of mortality, morbidity and length of hospital stay (LOS) [9]. Concerning the tool to assess cardiac output, fluid responsiveness and hemodynamic status, transthoracic echocardiography is a non invasive mean which can bring solutions and some parameter like the variation of peak velocity at the aortic annulus has been validated to predict fluid responsiveness in children [10]. There are no studies which have clarified echocardiographic hemodynamic parameters predictive of postoperative outcome in children scheduled for congenital heart disease surgical repair. Nevertheless, there is one retrospective study in pediatric and adult cardiac surgery which showed that intraoperative trans-oesophageal echocardiography after surgical repair in congenital heart disease reduced LOS [11]. We have elaborated a RCT trial where fluid and hemodynamic therapy will be guided with trans-thoracic echocardiography. In this RCT echocardiography hemodynamic parameters will be integrated in a protocol to guide fluid, inotropic and or vasopressive therapy [12]. To validate these echocardiographic hemodynamic parameters, we will conduct a pilot observational prospective study to identify those which are predictive of postoperative adverse outcome. We describe here this pilot trial.

The primary objective of this study protocol is to describe the pilot trial which will be undertaken to identify echocardiographic hemodynamic parameters predictive of postoperative outcome in terms of morbidity. The secondary objective is to clarify echocardiographic

hemodynamic parameters predictive of postoperative LOS/ICU, LMV and LOS. The tertiary objectives are to determine echocardiographic hemodynamic parameters predictive of fluid therapy, vasopressor and inotropic therapy. The primary outcome measures will be postoperative organ dysfunction until discharge from hospital. The secondary outcome measures will be the number of postoperative days spent in the intensive care unit (ICU), the number of postoperative days spent on invasive or non invasive mechanical ventilation and the number of postoperative days spent in the conventional hospitalization ward. The tertiary outcome measures will be the quantity of postoperative fluid administered in terms of crystalloids, colloids, blood product and postoperative vasopressor inotropic score.

Once the echocardiographic hemodynamic parameters predictive of postoperative outcome have been identified in this pilot study, they will be integrated in the randomized controlled trial entitled 'Perioperative Goal Directed fluid and Hemodynamic Therapy with Echocardiography in Pediatric Congenital Heart Disease', which is declared and registered at the ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé) under the number RCB : 2019-A02886-51 [12].

Methods and Materials

This trial has been declared at the French National Agency of Drugs and Medications Security, ANSM (Agence Nationale de Sécurité du Médicament et des produits de santé) and registered under the number RCB: 2019-A02925-52. After approval from the Ethics Committee, and after parents and or patients information, patients will be included prospectively in one cohort. The patients included will be managed according to the usual local practices. Echocardiography (Figure 1) will be realized in each patient preoperatively (to have

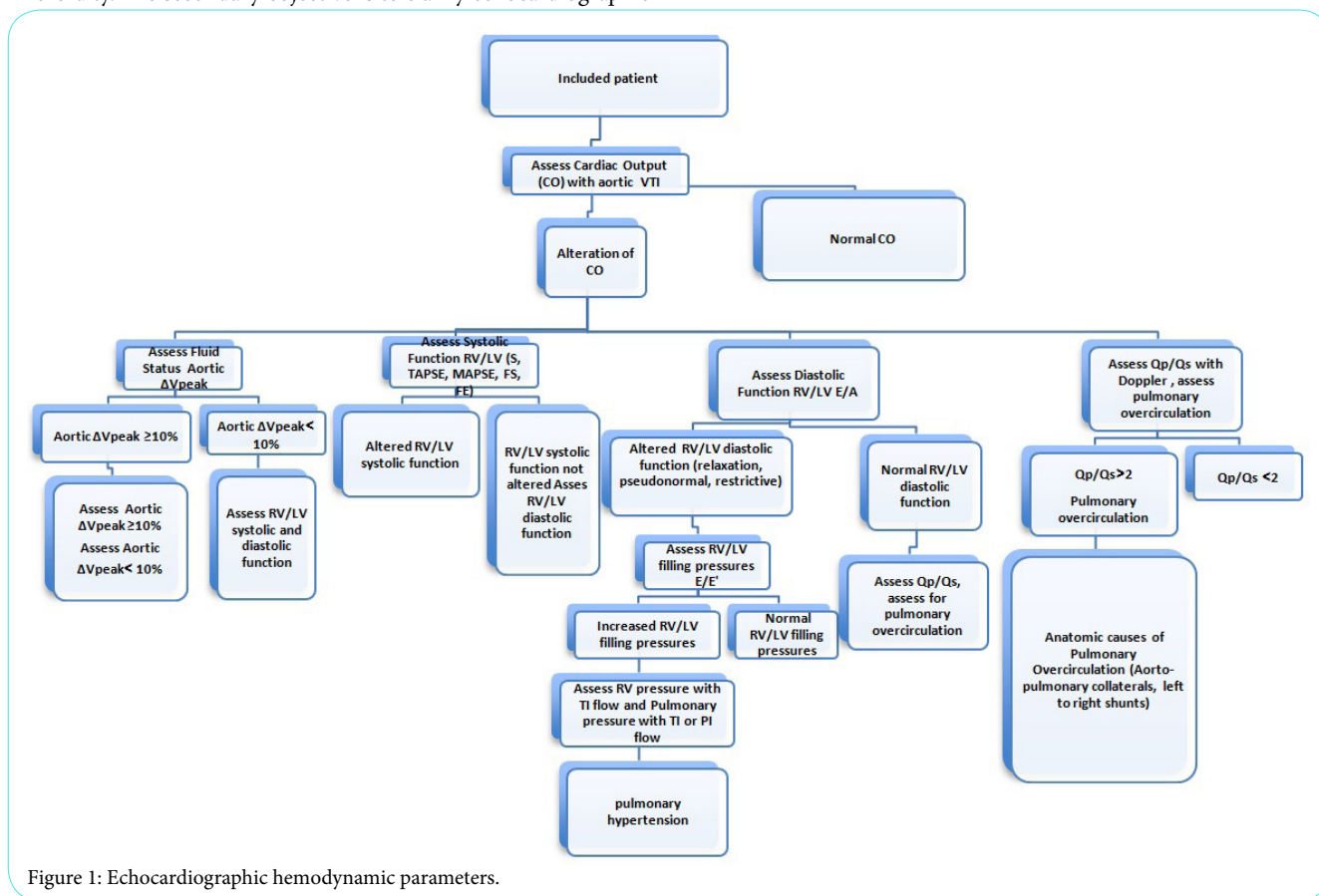


Figure 1: Echocardiographic hemodynamic parameters.

preoperative echocardiographic hemodynamic parameter values) and postoperatively after weaning from cardiopulmonary bypass (CPB) until discharge from the ICU. In the ICU, echocardiography will be realized daily and whenever necessary depending on the hemodynamic instability of the patient until discharge from the ICU. The echocardiographic hemodynamic parameters measured are precise below.

The patients included will be children aged less than 18 years with congenital heart disease (CHD) admitted for surgical repair.

General variables registered will be age, gender, type of CHD, surgery, elective or urgent surgery, redux, triduxor more, Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1), American Society of Anesthesiologists status (ASA), weight, height, prematurity, blood pressure, heart rate, hemoglobin levels, platelet count, leucocyte count, activated thromboplastin, prothrombin time, fibrinogen, blood urea nitrogen, serum creatinin levels, C-reactive protein levels (CRP), procalcitonin (PCT) levels, hepatic functional tests.

Preoperatively basal values of blood pressure, heart rate, core temperature, pulse oxymetry, mixed venous oxygen saturation (ScVO²), lactate levels, cerebral (ScO²) and renal oxygen saturation (SrO²), venous to arterial carbon dioxide gradient will be registered prior to anesthesia and surgery and intraoperatively during surgery hourly.

Intraoperative parameters registered will be time on cardiopulmonary bypass (CPB), aortic cross clamping, circulatory arrest, ultra filtration during CPB, blood product transfusion (packed red blood cells (PRBC), fresh frozen plasma (FFP), concentrated platelet units (CUP), fibrinogen, cryoprecipitate, concentrated complex of prothrombin (CPP) or other blood product derivatives, crystalloids and colloids or other fluids administered, priming volume of the CPB, CPB output during surgery, blood loss, urinary output, quantity of inotropes, diuretics, anesthetic drugs administered and mechanical ventilation parameters, central venous pressure, left intra-auricular pressure (LAP) and pulmonary artery pressure (PAP) if used. Normal blood pressure and heart rate values are those defined according to the patient age [13].

Pulse oximetry normal values will be considered according to the congenital heart disease (right to left shunts, left to right shunts), normal values of ScVO² will be considered $\geq 75\%$. 20% reduction of ScO² and SrO² under the basal levels will be considered abnormal [9]. Lactate levels above 2 mmol/L will be considered abnormal.

Concomitantly with echocardiographic hemodynamic parameters, postoperative variables registered will be blood pressure, heart rate, core temperature, pulse oxymetry, mixed venous oxygen saturation (ScVO²), lactate levels, cerebral (ScO²) and renal oxygen saturation (SrO²), venous to arterial carbon dioxide gradient, CVP, LAP and PAP if used, blood product transfusion (PRBC, FFP, CUP), fibrinogen, cryoprecipitate, concentrated complex of prothrombin, other blood product derivatives, crystalloids, colloids or other fluids administered, blood loss, urinary output, quantity of inotropes, diuretics, anesthetic drugs administered, mechanical ventilation parameters, hemoglobin, platelet, leucocyte levels, CRP, PCT, hepatic functional tests, blood urea nitrogen, serum creatinin levels. Trans-thoracic echocardiographic parameters measured preoperatively once and postoperatively daily and whenever there will be a hemodynamic instability or a variation in fluid, vasopressor inotropic, diuretic therapy until discharge from the ICU are described here after. Since echocardiography is operator dependent, all the echocardiographic hemodynamic parameters

will be measured by one experienced medical doctor in pediatric congenital heart disease echocardiography and validated by a second experienced medical doctor. Cardiac output measures will be realized with velocity time integral (VTI) at the aortic valve in the apical five chamber view. Normal values of aortic VTI have been defined in children [14]. Fluid responsiveness will be assessed with aortic peak velocity at the apical five chamber view with peak velocity variation (ΔV_{peak}) of $\geq 10\%$ defining responders to fluid therapy.

ΔV_{peak} is defined as $V_{\text{max}} - V_{\text{min}} / [(V_{\text{max}} + V_{\text{min}}) / 2] \times 100$ [10].

Right ventricular (RV) and left ventricular (LV) systolic function will be assessed in the apical four chamber view with lateral S (Slat) wave velocity in tissue Doppler, with mitral and tricuspid annular plane systolic excursion (MAPSE, TAPSE) in time motion mode (TM) and with ejection fraction EF with Simpson's method. Normal MAPSE, TAPSE and SI at values have been defined in children [15-20]. Fractional shortening (FS) will be assessed in the parasternal longitudinal axis view, normal values are the same as in adults (28-42%). Right ventricular and left ventricular diastolic function will be assessed in the apical four chamber view at the tricuspid and mitral valves with pulsed Doppler to assess for E wave velocity, A wave velocity and E/A ratio. E/A ratios will be analyzed according to age [21-28]. To assess for normal, relaxation alteration, pseudo normal and restrictive profiles. Right and left filling pressures will be assessed with tissue Doppler at the apical four chamber view at the tricuspid and mitral valves to assess lateral E' wave velocity and E'/E'latratio. Normal E'/E' and E'latvalues have been defined in children [21-28].

To assess for pulmonary over circulation, Qp/Qs ratio (where Qp is pulmonary output and Qs is systemic cardiac output) will be calculated using the formula $Qp/Qs = \text{Pulmonary VTI} \times \text{Area of the pulmonary annulus} \times \text{HR} / \text{Aortic VTI} \times \text{Area of the aortic annulus} \times \text{HR} = VTI_p \times \pi \times (D/2)^2 / VTI_{\text{a}} \times \pi \times (D/2)^2$, where D is the diameter of the annulus and HR the heart rate [29]. Pulmonary VTI and pulmonary annulus diameter will be assessed at the parasternal transverse axis view. Aortic VTI will be assessed at the apical 5 chamber view and the aortic annulus diameter at the parasternal longitudinal axis view.

Postoperative organ dysfunction until discharge from hospital will be registered to assess for primary outcome. The number of days spent in ICU, under invasive or non invasive mechanical ventilation and days in the conventional hospitalization ward postoperatively will be registered to assess for secondary outcomes. The quantity of postoperative fluid (crystalloids, colloids, blood products) administered and postoperative vasopressor inotropic score will be registered to assess for tertiary outcomes.

Statistic analysis will be used with XLSTAT 2018.3 or plus software. Normally distributed and non-normally distributed variables will be compared using Student t test and Wilcoxon test respectively. Normally distributed variables will be expressed in terms of means with standard deviation. Non-normally distributed variables will be expressed in terms of medians with interquartile ranges. Categorical variables will be compared with the exact Fisher's test or Chi squared test accordingly. Categorical variables will be expressed as percentages with confidence intervals. To assess for independent predictors of adverse postoperative outcome, multivariate analysis will be realized. A P-value ≤ 0.05 will be considered significant. Missing data will not be included.

The study is expected to begin second semester of 2020 and will terminate end 2020. The number of patients included will be 100-200

patients to have a normally distributed population. The study will be monocentric.

Results

Results are expected in the first semester of 2021.

Conclusion

This study protocol was designed to describe the pilot observational prospective trial which will identify echocardiography parameters predictive of postoperative outcome in terms of morbidity, LOSICU, LMV, LOS, fluid therapy and vasopressor inotropic score in children with CHD scheduled for surgical repair. These echocardiographic predictors of the above mentioned outcomes will be integrated in the randomized controlled mono-multicentric trial entitled 'Perioperative Goal Directed fluid and Hemodynamic Therapy with Echocardiography in Pediatric Congenital Heart Disease', which is declared and registered at the ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé) under the number RCB: 2019-A02886-51.

Disclosure

This study is part of the Thesis entitled 'Do goal directed therapies improve postoperative outcome in children? (Perioperative Goal Directed Fluid and Hemodynamic Therapy; Transfusion goal directed therapy using viscoelastic methods and enhanced recovery after surgery and Postoperative outcome)' [30-32]. This Thesis is registered online <http://www.theses.fr/s232762>.

Competing Interests

The authors declare that they have no competing interests.

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