The predictive value of Pressure Recording Analytical Method for the duration of mechanical ventilation in children undergoing cardiac surgery with an XGboost based machine learning model

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Abstract

Background

Prolonged mechanical ventilation in children undergoing cardiac surgery is related to the decrease of cardiac output during the postoperative intense care time, which often induced serious complications. Pressure Recording Analytical Method (PRAM) is a minimally invasive system for continuous hemodynamic monitoring, which can timely record the presence of lower cardiac function. This study is aimed to evaluate the predictive value of the several hemodynamic parameters for the duration of mechanical ventilation (DMV).

Methods

This retrospective study included 60 children under 1-year-old who underwent cardiac surgery between 2017 and 2021. CI, CCE and dp/dt_{max} derived from PRAM was documented in each patient 0, 4, 8 and 12 hours (T0, T1,T2, T3 and T4 respectively) after admission to the intensive care unit (ICU). A linear mixed model were used to deal with the repeated measurement on hemodynamic data. Correlation analysis and Receiver operating characteristic (ROC) curves were used to show the predictive value. XGBoost machine learning-based mode which produces a decision tree-heat map was used to find the key characteristics of the data in predicting the outcome.

Results

There were 35(58%) children in DMV≤24 h group and 25(42%) were in DMV>24h. Prolonged DMV caused longer ICU stays and postoperative hospital stays. Linear mixed model revealed significant time and group effect in CI and dp/dt_{max}. Prolonged DMV also have negative correlations with age, weight, CI at T2 and dp/dt_{max} at T2. dp/dt_{max} outweighing CI were the strongest predictors of prolonged DMV(AUC of ROC: 0.978 vs 0.811, respectively, $p<0.01$). The XGboost based learning machine model (Balance Accuracy=0.92, AUC of ROC=0.856) suggested that dp/dt_{max} at T2 ≤1.049 or >1.049 in combination with CI at T0 ≤2 or > 2 can predict prolonged DMV.

Conclusions

Hemodynamic monitoring in infants with PRAM after the cardiac surgery shows that the cardiac function can predict the prolonged duration of mechanical ventilation. CI measured by PRAM immediately after ICU admission and dp/dt_{max} that 8h later are 2 key factors in predicting prolonged DMV with the application of XGboost based machine learning model.

Introduction

Myocardial dysfunction is a critical factor for hemodynamic management after cardiac surgery. For infants with an undeveloped cardiovascular system and deteriorated by congenital heart disease, the

continuous decline in cardiac performance may remain long after cardiopulmonary bypass (CPB)[1–2]. Cardiac index(CI) decreased around 30% postoperatively in neonates, reaching the lowest point 9–12 hours after surgery[1]. In contrast to neonates, adults with initially satisfactory CI postoperatively show a decreasing trend over the first 4–8 hours in the ICU, but immediately recover to the baseline within 24 hours[3]. Hemodynamic instability and myocardial dysfunction often cause serious complications. For example, low cardiac output syndrome(LCOS) incurs higher mortality, prolongs the duration of cardiopulmonary support, and even leads to weaning failure[4–5].

Most of previous reports focus on the influence of the respiratory condition on mechanical ventilation[6–8], concern not much about that of the hemodynamic changes. Weaning failure is associated with increased left ventricular end-diastolic pressure (LVEDP) and left ventricular dysfunction[9, 10] and tools for evaluating this process include B-type natriuretic peptide (BNP) and PiCCO2 [11–12]. Clinical exploration based on the theory of the heart-lung interactions in the perioperative period still lacks data collection and analysis.

With the benefits of early extubation well established, fast-track anesthesia is now widely used in cardiac surgery in adult, but less well described in children[13–15]. In this case, the evaluation of cardiac function with the hemodynamic management after the surgery is of great necessity for predicting the postoperative course of mechanical ventilation.

Since the Fick principle was developed[16], many technological methods has been invented to measure the cardiac output and other hemodynamic parameters. MostCare(Vygon Vytech, Padova, Italy) uses the pressure recording analytical method (PRAM) for direct monitoring based on pulse spectrum analysis methods in the same way as PICCO2. It is a minimally invasive real-time method recorded at a high sampling rate (1000 pressure/time points) without the need of calibration[17–18]. Most care has been shown a good level of agreement with the Fick method measurements and and widely studied in animals and adults but rarely in infants after cardiac surgery[19].This study provides new insights into the cardiac function and early postoperative hemodynamic management in the ICU to make assessments of the prognosis for infants.

Patients And Method

Patients

This retrospective study was approved by the ethics committee and was waived by informed consent since PRAM monitoring by MostCare is our clinical routine, including 60 infants under the age of 1 year old who underwent heart defect repaired surgeries in our hospital between January 2017 and March 2021. Patients who expired during hospitalization were excluded. All the open heart surgeries were performed through standard procedures of CPB with oxygenation and moderate hypothermia.

Postoperatiive Managemnet

Mechanical ventilation was initiated immediately when the patient arrived at the ICU after surgery. Ventilation settings are adjusted to maintain PaO_2 at ≥60 mmHg, $PaCO_2$ at 35-45 mmHg, SpO_2 at 95%-100%, and pH at 7.35-7.45. The rectal temperature is maintained at 36–38∘C management consists of continuous intravenous infusion of sufentanil, dexmedetomidine, or midazolam. Inotropic and vasoactive drugs include dopamine, milrinone, epinephrine, norepinephrine, or Levosimendan to maintain arterial blood pressure. Anti-infective treatment is routinely performed with the intravenous antibiotic. Extubation was performed when the patients met the standard criteria:

(1) hemodynamic stability with reasonable urination and warm peripheral extremities; (2) $PaO_2 \geq 75$ mmHg and $PaCO_2 \leq 50$ mmHg with adequate spontaneous respiration under $FiO_2 \leq 40\%$ and end of expiratory pressure ≤ 5 cm H2O; (3) awake and able to respond to commands without new neurological symptoms; (4) no active bleeding with a reasonable change in hemoglobin and no requirement for volume replacement; and (5) no reasonable fear of re-intubation. Duration of mechanical ventilation (DMV) over 24 hours was considered delayed extubation. A MostCare device based on PRAM was used for hemodynamic monitoring during their first 24 postoperative hours as one critical part of our regular postoperative management. Hemodynamic parameters concerned in this study include Cardiac Index (CI), the maximal slope of systolic upstroke (dp/dt_{max}), and cardiac cycle efficiency(CCE). Data were collected and recorded by the device 0, 4, 8, and 12 hours after radial artery cannulation was established (T0, T1, T2, and T3, respectively) and stopped just before extubation.

Analysis Method

Statistical Analysis

The Shapiro-Wilk method was used to test whether the data followed the normal distribution. Demographic data are presented as mean values with standard deviation(mean ± SD) for variables that were normally distributed and median values with interquartile range (IQR, 25th–75th percentile) for variables that were not normally distributed, and as the frequency with percentage(%) for categorical variables. Hemodynamic data recorded by MostCare are presented as mean ± SD. In univariate analysis, differences between groups were evaluated using the Wilcoxon rank-sum test or T-test for continuous variables according to distribution. Chi-Square test and Fisher's exact test are used for categorical variables.

Linear mixed models were used to deal with the repeated measurement of hemodynamic data. For each CI, CCE, and dp/dt_{max}, we tested for interactions between group (DMV ≤ 24h or > 24h) and time (T0, T1, T2, T3). In fitting the model, we entered time and group as fixed effects. Random effect included individual differences (patients' ID) entered as a random intercept and individual bias influenced by DMV group entered as random slope. The model equation is shown as follows

$$\mathrm{Y_{i,j}}\tilde{\beta}_0 + \beta_1(\mathrm{Time}) + \beta_2(\mathrm{Group}) + \beta_3(\mathrm{Time*Group}) + \mathrm{b_0(ID)} + \mathrm{b_1(Group|ID)} + \mathrm{e_{i,j}}$$

Where $Y_{i,j}$ is the hemodynamic (CI, CCE, or dp/dt max) value for patients at Time j (i = 1,2...60. j = 0,1,2,3); Time is the time point recorded by PRAM; Group is DMV ≤ 24h or > 24h; Time∗Group is the interaction between the group term and the time term. ID is the patients i. β_0, β_1, β_2 and β_3 are the fixed effect coefficients: β_0 is the intercept; β_1 is the linear slope for Time; β_2 is the linear slope for Group; β_3 is the coefficient for the interaction term (Time∗ Group); b_0 and b_1 are the random effect coefficients:b_0 is the random intercept for patients i; b_1 is the random linear slope for patients i by Group; and $e_{i,j}$ is the error for participant i at Time j.

The Pearson correlation coefficient was calculated to assess the relationship between cardiac functions (selected hemodynamic parameters) and postoperative course (DMV). ROC curves are used to assess the diagnostic performance of the variable for predicting DMV. *p*-value < 0.05 was considered statistically significant. Statistical analyses and data processing were performed with R, version 4.2.0.

Machine Learning Model

Li Yan etc.[20] have designed an XGBoost machine learning based model that can predict the mortality rates of patients with more than 90% accuracy for COVID-19 prognostic prediction. The *treeheatr. R* package creates interpretable decision tree visualizations with the data represented as a heatmap at the tree's leaf nodes[21]. XGBoost algorithms are based on recursive decision tree building from past residuals and can identify those trees that contribute the most to the decision of the predictive model. The leaf nodes are labeled based on their majority votes and colored to correlate with the true outcome in the decision tree. The models were evaluated by assessing the classification accuracy (ratio of true predictions overall predictions), the precision, sensitivity/recall, and defined scores[20]. The importance of individual feature in XGBoost is determined by its accumulated use in each decision step in trees, computing the relative importance of each feature.[21] Hence, it can estimate features that are the most discriminative of model outcomes. Using this machine learning model, we construct a clinically operable decision model.

Results

Patients' Characteristics and Perioperative Changes

Demographic characteristics are shown in Table 1. A total of 60 children was included in the study, among which 35(58%) children were extubated within 24 hours (DMV ≤ 24h group), while 25(42%) were over 24 hours (DMV > 24h group), with 12 hours and 49 hours median ventilation time respectively (p < 0.05). According to the pathophysiology, congenital heart disease is divided into left-right shunt congenital heart disease and right-left shunt congenital heart disease. 53 patients in this study had the main defect for the former, including ASD, VSD, PDA, and simple valvular disease, and 7 for the latter, namely TFO, DORV, and Complete endocardium pad defect. No significant difference of whether had

prolonged DMV between the two types of CHD patients ($P > 0.05$) or patients with different cardiac function (over NYHA II or not). When admitted to the hospital, there were 27 cases diagnosed with mild to moderate respiratory disease, namely respiratory tract infection, pneumonia, and tracheal chondromalacia. It also shows no significant difference in whether prolonged mechanical ventilation time was prolonged between patients with preoperative respiratory disease and those without ($P > 0.05$). 35 patients were subjected to one or some of the following postoperative complications during the hospitalization: Low Cardiac Output Syndrome, pleural effusion, ascites, arrhythmia, infection, or pneumonia. These adverse events were found in 17 of 25 (68%) patients with prolonged DMV and 18 of 35 (51%) patients without (DMV ≤ 24h), however, no significantly prolonged ventilation time was found between the adverse-events group and no-adverse-events group ($P > 0.05$).

Children with younger ages(4.77 (3.50, 6.86) vs 2.00 (1.57, 4.53)month), lower heights (64.51 ± 5.75 vs 58.76 ± 7.45 cm) or weights (6.2 (5.50, 7.40) vs 5.00 (4.20, 6.20) kg) are more likely performed extubation over 24h after surgery($P < 0.05$). Longer CPB time (76 (66, 92) vs 104 (86, 136) min) and ACC (aortic cross clamp) time (45 (36, 56) vs 55 (50, 79)min) are also associated with prolonged ventilation time($P < 0.05$). As for prognosis, Patients with prolonged ventilation time have longer ICU (2(1, 3) vs 5 (4, 7) days) and postoperative hospital stays (10 (9, 12) vs 14(12, 18) days), which conforms to the previous study($P < 0.0001$)[8, 14].

Table 1
Baseline characteristics

Characteristics	DMV ≤ 24h (n = 35)	DMV > 24h (n = 25)	p-value
Age (month)	4.77 (3.50, 6.86)	2.00 (1.57, 4.53)	**< 0.001**
Sex			0.5
Female	11 (31%)	10 (40%)	
Male	24 (69%)	15 (60%)	
Height (cm)	64.51 ± 5.75	58.76 ± 7.45	**0.002**
Weight (kg)	6.2 (5.50, 7.40)	5.00 (4.20, 6.20)	**0.001**
CHD*			> 0.9
Left-Right	31 (89%)	22 (88%)	
Right-Left	4 (11%)	3 (12%)	
NYHA			0.7
≤II	19 (54%)	15 (60%)	
>II	16 (46%)	10 (40%)	
Preoperative Respiratory disease**			0.4
Yes	14 (40%)	13 (52%)	
No	21(60%)	12(48%)	
CPB time(min)	76 (66, 92)	104 (86, 136)	**0.004**
ACC time(min)	45 (36, 56)	55 (50, 79)	**0.016**
Ventilation time(h)	12 (8, 20)	49 (45,72)	**< 0.001**
Adverse events***			0.2
Yes	18 (51%)	17 (68%)	
No	17 (49%)	8 (32%)	
ICU stay (days)	2 (1, 3)	5 (4, 7)	**< 0.001**
Postoperative hospital stay (days)	10 (9, 12)	14 (12, 18)	**< 0.001**

Characteristics	DMV ≤ 24h (n = 35)	DMV > 24h (n = 25)	p-value

Data is presented as mean(IQR)/ n(%)/ mean ± sd

DMV, duration of mechanical ventilation. CPB, cardiopulmonary bypass. ACC, aortic cross clamp. NYAH, NYAH class.

**CHD, congenital heart disease includes left-right shunt congenital heart disease and right-left shunt congenital heart disease.*

***Preoperative Respiratory disease includes respiratory tract infection, pneumonia, and tracheal chondromalacia.*

****Adverse events, whether the patient is subjected to one of the following postoperative complications during the hospitalization: Low Cardiac Output Syndrome, pleural effusion, ascites, arrhythmia, infection, or pneumonia.*

Cardiac function reflection on different mechanical ventilation condition

Mean ± SD of hemodynamic monitoring in the ICU at different time points for each DMV group were recorded (Supplementary Table 1), and the changes in cardiac function over time were shown (Fig. 1). Results from the linear mixed model revealed significant main effects of time and group in CI and dp/dt_{max}, but not CCE (Table 2). DMV≤24h group showed significant increase in CI and dp/dt_{max} from T0 to T2 (CI, β1=0.44, SE=0.09, p<0.001; dp/dt_{max}, β1=0.182, SE=0.049, p<0.001) and from T0 to T3 (CI, β1=0.35, SE=0.09, p<0.001; dp/dt_{max}, β1=0.096, SE=0.049, p<0.05). T0 observed a significant difference between the two groups with decreased CI and dp/dt max in patients with prolonged DMV (CI, β2=-0.27, SE=0.12, p<0.05; dp/dt_{max}, β2=-0.182, SE=0.058, p<0.01). Besides, there were significant group × time interaction effects in dp/dt_{max} from T0 to T2 (β3=-0.152, SE=0.075, p<0.05) but not CI or CCE. For further correction, Time was changed from a classified variable into a continuous variable, and fixed effects were taken into consideration only. We found that the latter models' AIC (Akaike information criterion) reduced insignificantly in CCE but improved significantly in CI and dp/dt_{max}, indicating the previous type of model fitting in CI and dp/dt_{max}better. The equivalent new model of CCE showed group × time interaction effects but no main effects of time and group independently (Supplementary Table 2).

Table 2
Linear mixed effects in hemodynamic variables

	CI	CCE	dp/dt
Fixed effects			
T0	2.55(0.08)	-0.327(0.057)	1.113(0.035)
T0-T1	0.04(0.09)	0.090(0.065)	0.034(0.048)
T0-T2	0.44(0.09)***	0.031(0.065)	0.182(0.049)***
T0-T3	0.35(0.09)***	0.028(0.065)	0.096(0.049)*
Group×T0	-0.27(0.12)*	-0.148(0.091)	-0.182(0.058)**
Group×T0-T1	-0.004(0.14)	0.070(0.100)	-0.038(0.075)
Group×T0-T2	-0.21(0.14)	0.128(0.100)	-0.152(0.075)*
Group×T0-T3	0.08(0.14)	0.192(0.100)	0.036(0.075)
Random effects			
Individual	0.08(0.28)	0.042(0.20)	0.002(0.046)
Group | Individual	0.29(0.54)	0.064(0.27)	0.022(0.148)
Corr.	-0.96	-0.52	-1.00
Log Likelihood	-154.1	-75.41	15.37
AIC	332.21	174.81	-6.73
BIC	373.98	216.58	35.03

Values indicate the estimated effect (β), and corresponding standard error (SE). *Group, divides patients into duration of mechanical ventilation ≤ 24h and > 24h. CI, cardiac index. CCE, cardiac cycle efficiency. dp/dtmax, the maximal slope of the systolic upstroke.*

$*p < 0.05$.

$**p < 0.01$.

$***\ p < 0.001$.

Correlation analysis

Age, height, weight, CPB, ACC, which showed a significant difference between different DMV groups by univariate analysis (Table 1), and CI and dp/dt a_{max} at T0, T2, and T3, which showed significant effects of time or group in the linear mixed models (Table 2), were entered for correlation analysis. Figure 2

shows prolonged DMV have significant and negative correlation with age (r=-0.48, $p < 0.01$), weight (r=-0.42, $p < 0.05$), CI at T2 (r=-0.53, $p < 0.001$) and dp/dt_{max} at T2 (r=-0.82, $P < 0.001$). There was no significant correlation in CPB or ACC. dp/dt_{max} at T2 has a strong correlation, whereas age, weight. and CI at T2 have a moderate correlation.

Predictive values

In the ROC analyses, as shown in Fig. 3, dp/dt_{max} outweighing CI at T2 were the strongest predictors of prolonged DMV(AUC: 0.978 vs 0.811, $p < 0.01$). dp/dt_{max} at T2 < 1.052 (sensitivity = 1.000, specificity = 0.840), CI at T2 < 2.67(sensitivity = 0.800 specificity = 0.800) could predict prolonged DMV.

XGBoost machine learning based model

Age, height, weight, CPB, ACC, CI, and dp/dt_{max} at T0, T2, and T3 were also entered into the XGBoost machine learning based model, *treeheat* package in R language, and it produced a decision tree-heat map[20]. As Fig. 4a shows, the model suggested that patients with dp/dt_{max} less than 1.049 at T2 were classified as DMV > 24h. but those whose dp/dt_{max} exceeded 1.049 at T2 were DMV ≤ 24h. On the split of CI at T0 (T0_CI ≤ 2 and T0_CI) > 2), although individuals of both branches are all predicted to DMV ≤ 24h by majority voting, the leaf nodes have different purity, indicating different confidence levels the model has in classifying samples in the two nodes[20]. Therefore, patients with CI ≤ 2 at T0 can not easily exclude the possibility of DMV > 24h, which conforms to the results of T0-CI ROC curves (Fig. 4d) that the cut-off value of CI > 2.2 has plausible specificity = 0.857 for predicting DMV ≤ 24h, but quite uncertain to predict DMV > 24 if CI < 2.2 at T0 (sensitivity = 0.56). The whole model has excellent accuracy and predictive value (Accuracy = 0.933, Balance Accuracy = 0.920, Kappa = 0.860, AUC of ROC = 0.856, AUC of PR = 0.907).

When another more specific classification of DMV was added in the model (Fig. 4b), that is divided DMV into three groups, namely ≤ 12h, 12h ~ 24h and > 24h, dp/dt_{max} at T2 became the only dominant parameters for prediction, which split the three DMV groups by 1.049 and 1.233 for prediction. The model still had a good predictive value in spite of the accuracy decrease (Accuracy = 0.783, Balance Accuracy = 0.830, Kappa = 0.671, AUC of ROC curve = 0.880, AUC of PR curve = 0.824).

T2_dpdt, dp/dt_{max} (the maximal slope of systolic upstroke) at T2. T0_CI, CI (Cardiac index) at T0. DMV, duration of mechanical ventilation.

BAL_ACCURACY, balance accuracy, KAP, kappa.

a) Tree-heat map of XGboost machine learning model for predicting 24h DMV. Red column, DMV>24h; green column DMV≤24h.

b) Tree-heat map of XGboost machine learning model for predicting 12 and 24h DMV. Red column, DMV>24h; green column, 24h≤DMV<12h; yellow column, DMV≤12h.

Discussion

The parameters of PRAM proved to correlate well with 'gold standard' thermodilution [3] and many other examination results such as Fick, Doppler echocardiography, BNP, and lactate levels in assessing cardiac output[19, 22]. With relevant trial validation, Most-care has been widely used for monitoring hemodynamic variations of the CHD patients in the perioperative period. On the other hand, although the prolonged DMV is a significant sign of worse prognosis and successful early extubation is a goal to promote recovery after cardiac surgery with both medical and economic benefits[13–14, 23], few previous reports have a focus on the heart-lung interaction or explore the influence of cardiac function on it. Our study initiatively found correlations between the cardiac function presented by hemodynamic parameters and mechanical ventilation status. Further, we proved their good predictive value and provided a visualized decision-making map with the application of machine-learning model.

Hemodynamic management with PRAM in the postoperative process

Hemodynamic monitoring is instantaneous feedback, but it also can reflect a certain period of cardiovascular stability by repeatedly collecting the data. The linear mixed model showed time effects of hemodynamic parameters, indicating that cardiac function presented a significant increase over time in the first 4-8h after the surgery (Fig. 1 and Table 2), which contradicted the classic conclusion that CI decreased and reached a nadir at 9-12h postoperatively[1]. Some recent reports of postoperative hemodynamic monitoring also observed different trends from the classic one. Anton et al.[4] measured CI of children with CHD 24 hours after surgery by femoral arterial thermodilution and found no obvious changes between CI over time. Another exploration of trends of the postperative hemodynamic based on PRAM found gradual improvement in overall myocardial status with the indication of the increase in CCE and dp/dt_{max} and stabilization in CI in 48 hours postoperatively[24]. The opposite tends of postoperative cardiac function between the early study and later ones perhaps resulted from the developed CPB techniques, for example, modified ultrafiltration[25] and dexmedetomidine sedative[26–27] have been reported to do with less CPB related inflammatory responses and better hemodynamic outcomes. Besides, the use of vasoactive agents has proven to be another key factor contributing to improving postoperative cardiac function[28–30]. Though risk factors or preventive methods have been widely reported, they are incomprehensive. With recently inspiring new trends of increasing cardiac function after the operation of CHD, we should keep in mind that LCOS is still a common severe complication whose incidence could be up to 21.25% [2, 31] and there happened to be one case in our study.

Cardiac function in predicting DMV

The group effect on hemodynamic parameters revealed by the linear mixed model suggests that patients with prolonged DMV showed significantly lower CI and dp/dt_{max} after the surgery, although not all the time but at a certain time point (Table 2, Fig. 1). Therefore, Cardiac dysfunction is associated with prolonged ventilation. It is acknowledged that the preload and afterload increase due to the decrease of intrathoracic pressure premature in the process of extubation and increase cardiac work and myocardial oxygen consumption. As a result, premature extubation deteriorates patients' condition by inducing pulmonary edema, pulmonary artery spasm, severe anoxia, heart failure, and reintubation. Cardiac dysfunction is the main risk factor for 80% weaning failure[5]. Although the pulmonary injury after CPB and anesthesia effect are the direct factors derived from the extubation criteria and have a strong correlation with the ventilation duration[5–7, 14], the process of cardiac function restoration plays a more crucial role in determining the timing for extubation than we think in infants undergoing CHD surgery. Many reports have found that cardiac dysfunction is associated with longer mechanical ventilation duration, over 12h, 24h, or even longer in comparison to the normal group [4, 8, 13, 32, 33], yet a consensus on a definite concept for prolonged DMV has not been made. DMV as a crucial index for prognosis still needs more study and data collection.

dp/dt_{max}

The linear mixed model revealed the group and time interaction in dp/dt max only at T2 (Table 2), but the significant increase in dp/dt_{max} from T0 to T3 in DMV ≤ 24h group. In combination with the changes of time-depending hemodynamic value (Fig. 1), there was an obvious increase in cardiac function in the DMV > 24h group that compensated the previous gap with DMV ≤ 24h group from T2 to T3. dp/dt_{max} measured 8h after the surgery had strongest correlation with prolonged DMV and was the best hemodynamic predictor (Fig. 2–4). We suspect the reasons are as follows: On the one hand, dp/dt_{max} has generally been used as a sensitive index of cardiac contractility[34]. Arterial dp/dt_{max} tracks the left ventricular contractility changes and is mainly determined by myocardial contractility with very limited influence by loading conditions [35–37]. A recent report shows that the decreased dp/dt_{max} is associated with a myocardial injury even in extracardiac surgery using PRAM[38]. Other hemodynamic parameters like CI are dependent more on heart rate, preload, and afterload. It has also been found that not CI but dp/dt_{max} have a higher correlation with BNP when used PRAM after CHD operation[22].

On the other hand, the exact 8 h after the surgery may be a turning point for restoring cardiac function. Our study showed that prolonged DMV patients' distinctively poor CI and dp/dt max appeared only 0h or 8h after the surgery. Some reports also observed the nadir of cardiac output, the minimal central venous oxygen saturation, and the peak of BNP and lactate level at 8h after the surgery[22, 39]. Jennifer et al. [40]revealed that the increase of Troponin-I beyond 8h after CPB was a strong predictor of postoperative hypoperfusion in infants. Therefore, the myocardial status represented by dp/dt_{max} at 8h after the surgery may significantly affect the overall postoperative cardiac function and prognosis indexes such as ventilation duration. dp/dt_{max} is also related to the cardiac reserving ability[34]. In this case, active

enough cardiovascular management should be performed earlier in the postoperative 8h in infants with CHD.

CI

CI reflects the complex outcomes of the endogenous cardiac, neurohumoral responses and the exogenous inotropic and vasoactive drugs. Based on the heart-lung interaction theory that an increase in cardiac output is considered a positive response to a volume challenge[9], pulse pressure variation (PPV), stroke volume variation (SVV), and aortic velocity-time integral (delta VTI) should also be incorporated into making the assessment of a patient's cardiac function and direct fluid infusion[41–42]. CI is greatly affected by the early unstable hemodynamic process and loading condition after the surgery. Although it didn't have a linear correlation with delayed extubation, CI measured at T0 is a predictor that could not be neglected (Table 2, Fig. 3d, 4). Further, the difference of CI and dp/dt_{max} in DMV groups at T0 alarmed us that even very early stages of cardiac dysfunction also makes sense and inotropic, and vasoactive drugs should be used as early as possible, not postoperatively but intraoperatively.

CCE

CCE is a unique parameter derived from PRAM, which evaluates the compensating interplay of different cardiovascular system compartments, including left and right ventricular contractility, preload and afterload, heart rate, reflected waves, as well as elasticity of great arteries and the ventricular-arterial coupling.[24, 41]. The negative value of CCE with no significant changes over time in our study (Table 2) indicates the constant rather than worsening condition of cardiac energy expenditure for compensation to maintain cardiovascular homeostasis after the surgery[32, 43]. However, CCE can be influenced by many factors. For example, the inability of Negative-pressure ventilation to reduce HR in sedated extubated patients meant that other hemodynamic benefits increases did not translate into the improved CCE[44]. CCE is too sensitive and variable that its instantaneous value may not precisely reflect the different hemodynamic conditions between the patients with different DMV as CI or dp/dt_{max} does. But in our study, CCE showed group × time interaction effects when *Time* was entered in the linear mixed model as a continuous variable (Supplementary Table 2). Therefore, it suggests that constant hemodynamic monitoring of CCE is still meaningful, and the actual changes of CCE during a period should be considered.

XGBoost machine learning based model

XGBoost machine learning model is a widely used technique for a predictive model for its significant accuracy, which is better than many linear models. It is well designed to prevent overfitting by cross-validation and regularization. The leaf nodes are labeled based on their majority votes and colored to correlate with the true outcome. Further, the more extended corresponding color column of the outcome means more cases of the event and more substantial predictive value of these branches in our XGboost based model. Heat map colors present the relative value of compared to the rest of the group on each feature. Higher values are associated with lighter colors[20]. Although CI at T2 had good performance in ROC curves, dp/dt at the same time point probably substitute for it completely, while later CI at T0

improved the predictive model when added into the algorithm. XGBoost machine learning model has been more prevalent in dealing with clinical problems such as treatment evaluation and disease risk management[45]. Nevertheless, our XGBosst based model did not show improved fitting when the binary classification advanced to the next dimension.

Other factors affecting DMV in infants

Age and weight are important factors for both early extubation in fast-track management and delayed extubation after congenital heart surgery in children[46]. Our study also showed that these two factors have correlations with prolonged DMV. The infants' left ventricle have altered relaxation characteristics that progressively change over the first year of life and reach adult level[47]. The less proliferation of cardiomyocytes and sarcoplasmic reticulum in the myocardium contributes to the lower cardiac contractility. Younger infants with a lower cardiac reserve and poorer compensatory regulation ability are susceptible to surgery impairment. Besides, infants with lower body weight had a higher frequency of adverse events and longer DMV, ICU stay and, hospital stay[48], and body weight < 4 kg was considered to be a risk factor for complete heart block[49].

Cardiac surgery often necessitates a period of myocardial ischemia during CBP and cardioplegic arrest, followed by reperfusion after aortic cross-clamp(ACC) removal. This myocardial ischemia–reperfusion can induce oxidative stress and ventricular dysfunction[50]. Children with prolonged DMV undergo longer CBP and ACC during the Surgery (Table 1). However, CBP and ACC did not correlate with prolonged DMV and could not use for prediction (Fig. 2, 4). Some studies have also reported a similar irrelevance to the mechanical ventilation condition [13, 46, 51]. But other conflicting data[52] suggests complex cardiopulmonary interactions, and it is impossible to list all the risk factors for this multifactorial phenomenon.

Limitation

There are several limitations to this study. First, other factors probably associated with prolonged DMV such as pulmonary condition, ventilator parameters, vasoactive drug, renal function were not considered. Other Hemodynamic parameters with PRAM are also needed further exploration. Second, many infants included in the study did not have complex CHD, and a more extensive multi-center cohort study including complicated cases and using more advanced techniques is warranted to confirm our findings. At last, The assessment and the modification of machine learning model applied to solving the clinical problems need further discussion.

Conclusion

In summary, postoperative hemodynamic management with PRAM shed light on the interconnection between cardiac function and mechanical ventilation. CI measured by PRAM immediately after ICU admission and dp/dt_{max} that 8h later are 2 key factors in predicting prolonged DMV with the application of the machine learning model.

Abbreviations

PRAM: Pressure Recording Analytical Method; DMV: duration of mechanical ventilation; ICU: intensive care unit. CHD: congenital heart disease; CI: Cardiac Index; dp/dt max, the maximal slope of systolic upstroke. CCE: cardiac cycle efficiency; CPB: cardiopulmonary bypass; ACC: aortic cross clamp; XGBoost: Extreme gradient boosting.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Capital Institute of Pediatrics. The informed consent was waived considering the retrospective data collected.

Consent for publication

Not applicable.

Availability of data and materials

The code of the machine learning model is available at https://github.io/HAIRLAB/Pre_ Surv_COVID_19 under an MIT licence (https://doi.org/10.5281/ zenodo.3758806). Related raw documents are available by submission of a request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Mingwei Li and Shuangxing Wang conceived the idea, performed the analysis, and drafted the manuscript. Hui Zhang helped to analyze the data and revise the manuscript. Danlei Chen, Hongtao Zhang, Yongjie Wu, Xinpeng Qu and Bing Meng helped to collect the data and frame the idea of the study. All authors read and approved the final manuscript.

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Figures

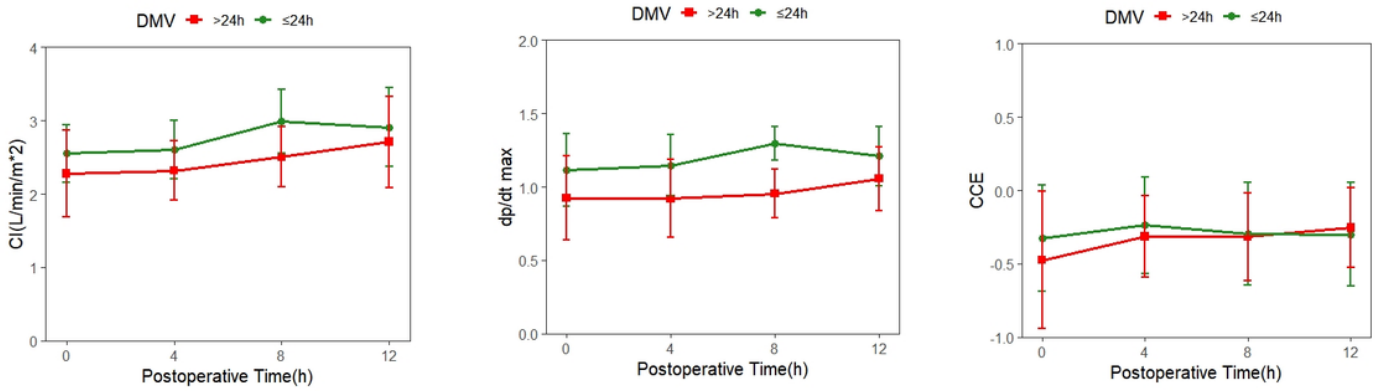

Figure 1

Trends of systemic hemodynamic value over time in patients with different duration of mechanical ventilation (DMV), the red line represents DMV>24h, the green line represents DMV≤24h.

a)Time-dependent changes in CI, cardiac index.

b)Time-dependent changes in dp/dt max, the maximal slope of the systolic upstroke.

c)Time-dependent changes in CCE, cardiac cycle efficiency.

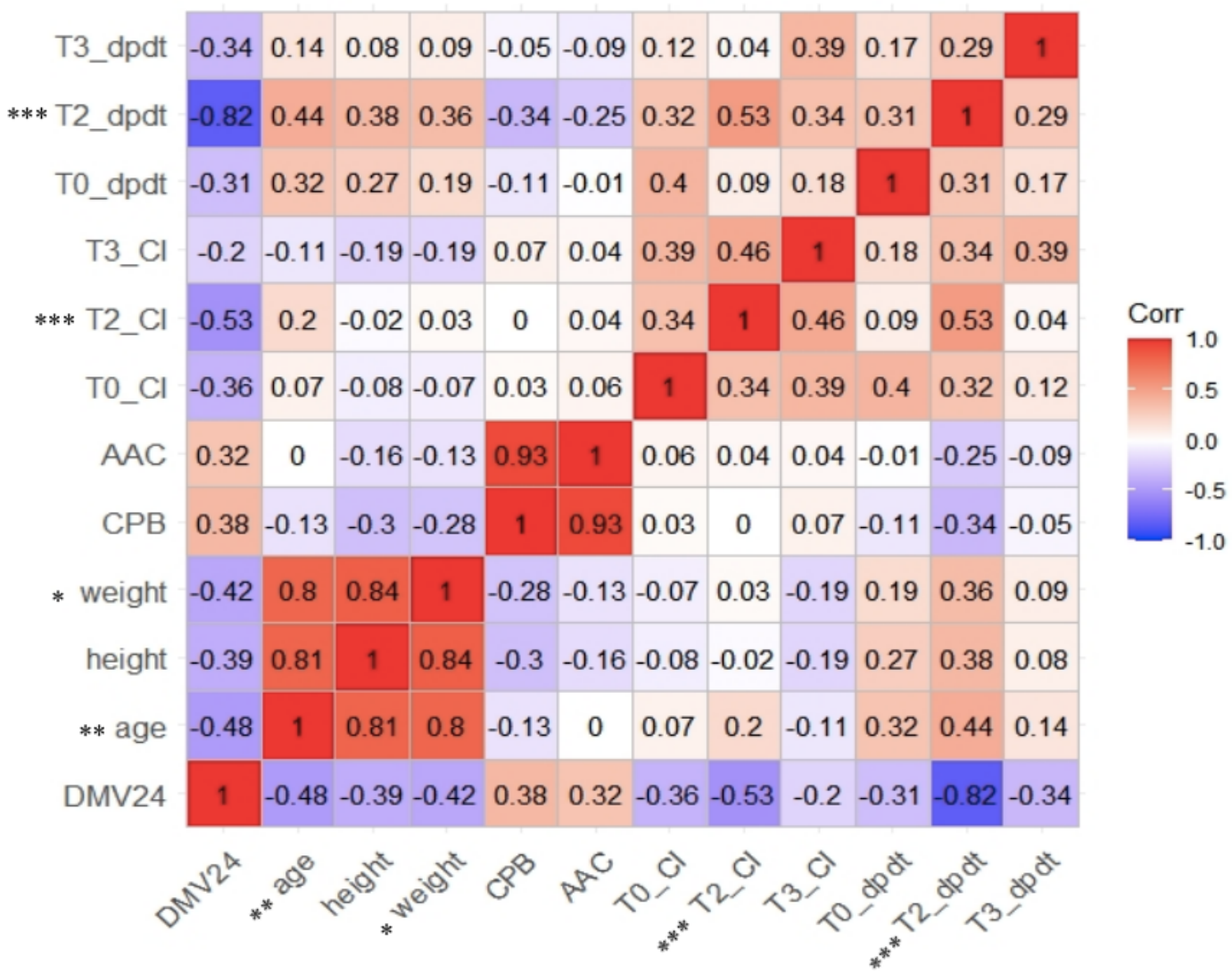

Figure 2

Correlation analysis heat map for relationship between selected the characteristics , hemodynamic parameters and prolonged DMV. CI, cardiac index. dp/dt $_{max,}$ the maximal slope of systolic upstroke. DMV24, binary-classified variable, duration of mechanical ventilation ≤24h or >24h.

∗$p < 0.05$.

∗∗$p < 0.01$.

∗∗∗ $p < 0.001$.

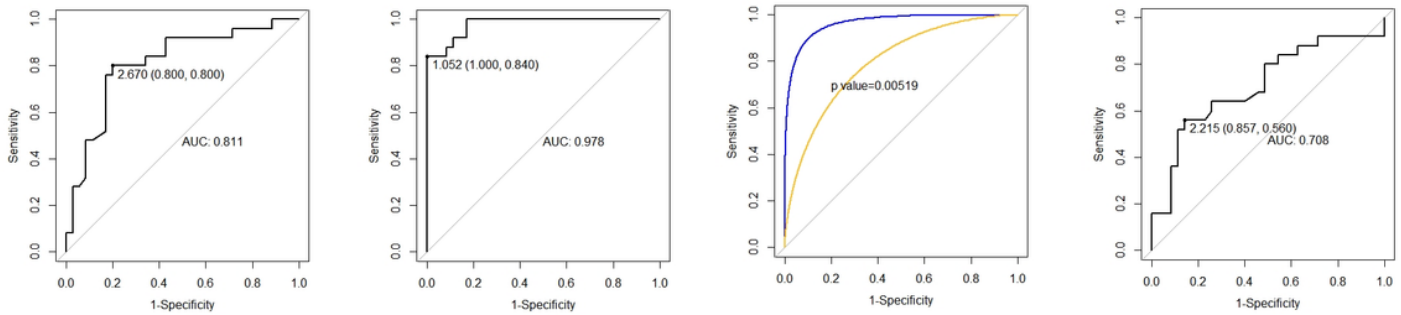

Figure 3

ROC curves for predicting prolonged duration of mechanical ventilation (DMV).

a) CI, Cardiac index, measured at T2 for predicting DMV>24h.

b) dp/dt $_{max}$, the maximal slope of the systolic upstroke, measured at T2 for predicting DMV>24h.

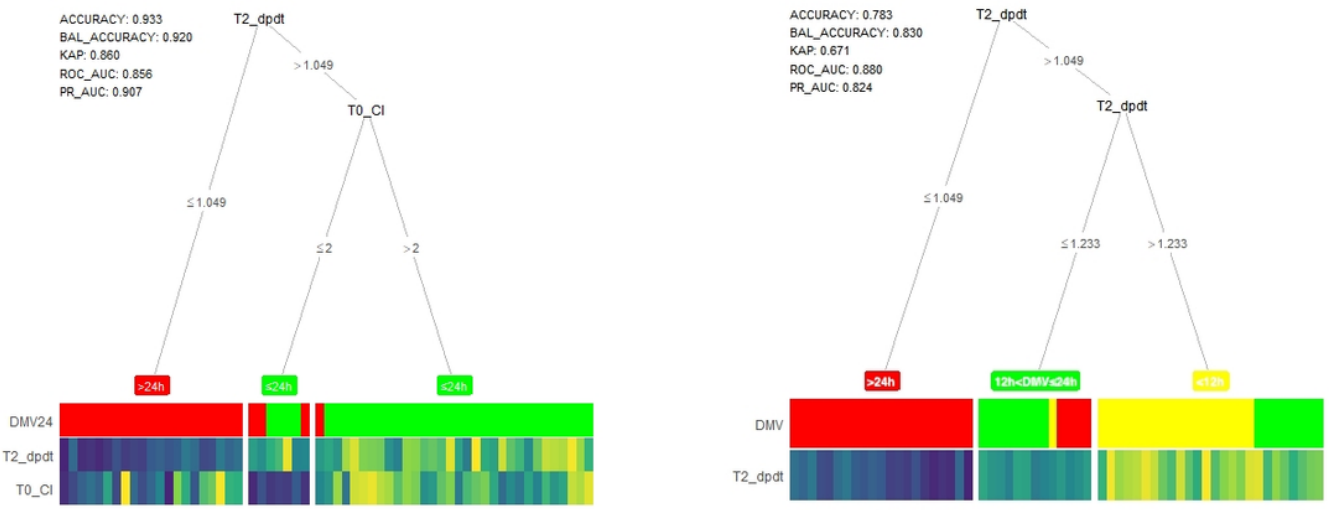

Figure 4

Tree-heat map of XGboost machine learning model for prediction

Supplementary Files

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- SupplementaryTable12.docx