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Troponin-I: predictor of early postoperative outcome after repair of Tetralogy of Fallot

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Introduction

The tetralogy of Fallot is the most common cyanotic congenital cardiac disease with a prevalence of 3-6 per 10'000 live births (1,2). Its main features are: right ventricular outflow tract obstruction (RVOTO), ventricular septal defect (VSD), deviation of the origin of the aorta to the right, and right ventricular hypertrophy (3). This disease is lethal in the early infancy particularly and a surgical correction is thus necessary (4). Since this surgery is associated with early complications, such as an important need of ventilation, a long stay in the pediatric intensive care unit (PICU) or even death, it would be beneficial to research a plasmatic marker that could help predict the early post-operative prognostic. Troponin-I is an important and unique component of the cytoskeleton of the myocardial cells. For this reason its plasmatic level is used to determine the myocardial damage in myocardial ischemia. Surgical repair of the Tetralogy of Fallot is associated with a resection of the infundibulum depending on the severity of the RVOTO and with a closure of the VSD. Troponin-I is then released in the systemic circulation and continues to do so according to the severity of the locally induced ischemia. We can then imagine that the Troponin-I variables reflect not only the postoperative outcome directly caused by the operation but also the severity of the postoperative myocardial injury. Studies have shown that the pre- and postoperative Troponin-I is a good predictor of mortality in overall cardiac surgical repair, especially for its stability against impaired renal function and its myocardial specificity (5–8). This study will analyze a possible correlation between specific Troponin-I values (such as plasmatic peaks, area under the curve and others) and the early postoperative outcome of young patients operated for a Tetralogy of Fallot.

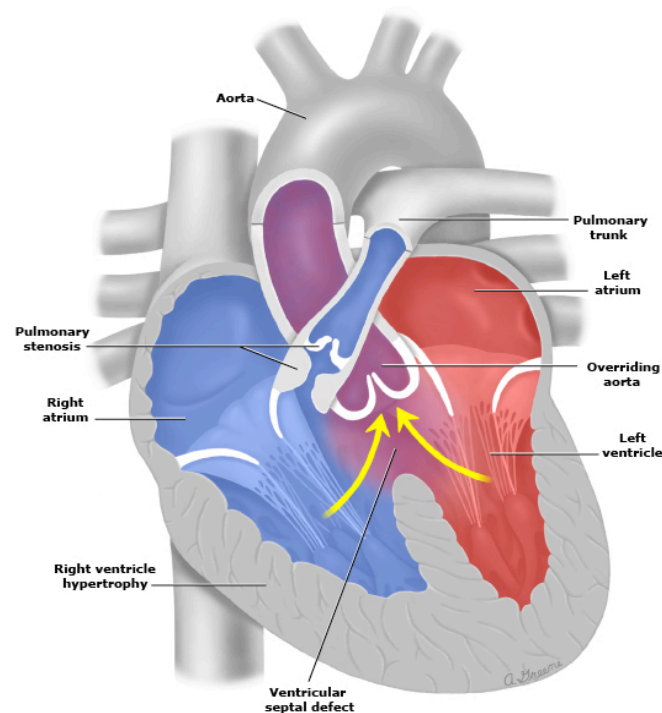


Figure 1: Anatomy of tetralogy of Fallot, published in Pathophysiology, clinical features, and diagnosis of tetralogy of Fallot in UpToDate (9)

Physiopathology

The exact cause of Tetralogy of Fallot is still unclear. The first step into the development of a Tetralogy of Fallot is a deviation of the infundibular septum, which is supposed to merge with the interventricular septum to completely separate both ventricles. It results in a malaligned VSD. Additionally, a malformation of the septoparietal trabeculations leads to the RVOTO (4). It is also important to note that this disease's defects vary on a wide spectrum, principally due to the severity of the RVOTO.

The VSD is in almost all cases non restrictive. Depending on the degree of RVOTO, the shunt at the level of the VSD can initially be left-to-right. However, with the increasing RVOTO over time, it can progressively lead to a right-to-left shunt with an increasing cyanosis (10). If RVOTO is severe already in utero, the neonates can be born with an already-deep cyanosis ("blue Fallot") or develop it soon after birth, as soon as the ductus arteriosus closes. The cyanosis can appear after months or even years, if the severity is lesser ("pink Fallot") (1,3).

Furthermore, the Tetralogy of Fallot can be part in 28% of cases of syndromes, such as Down or Di George syndromes; or be associated with other cardiac anomalies, like a right aortic arch in 25% of cases, or abnormalities in coronary arteries in 9% of patients. The Tetralogy of Fallot can also be sporadic with identified genetic anomalies (1).

Clinical presentation

The clinical presentation depends on the degree of RVOTO:

- cyanosis (permanent or appearing during an effort like sucking when breastfeeding),
- heart murmur (best heard along the left mid- to upper sternal border),
- cyanotic spells depending on the severity (10).

Diagnosis

The diagnosis is established with the echocardiography (figures 2 and 3). The complete assessment consists of a clinical examination, hematologic parameters (increased hemoglobin and hematocrit; lowered oxygen saturation and coagulation factors), arterial blood gas, electrocardiogram, echocardiography, even angiography (complex anatomy, coronaries' anomalies) and chest x-ray (boot-shaped heart, figure 4) (1).

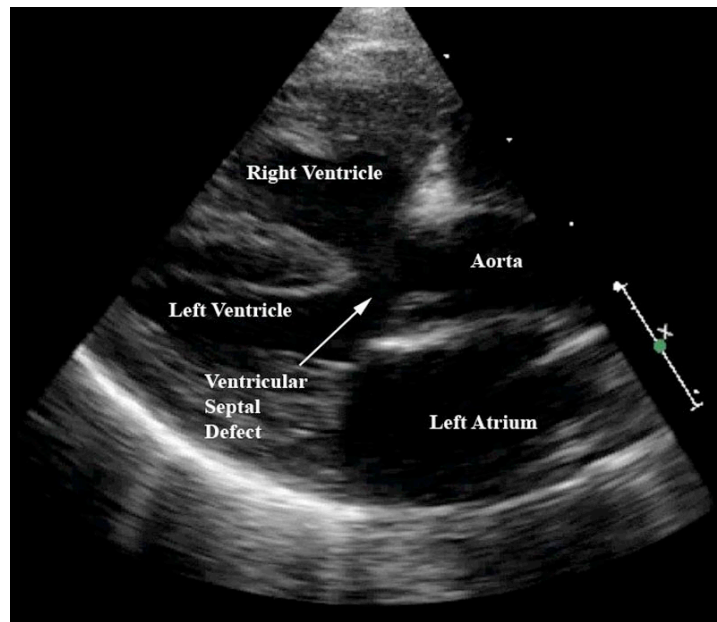


Figure 2: Still frame of the ventricular septal defect, aortic override and right ventricular hypertrophy in echocardiography (modified parasternal long axis view), published in Tetralogy of Fallot, in Orphanet (11).

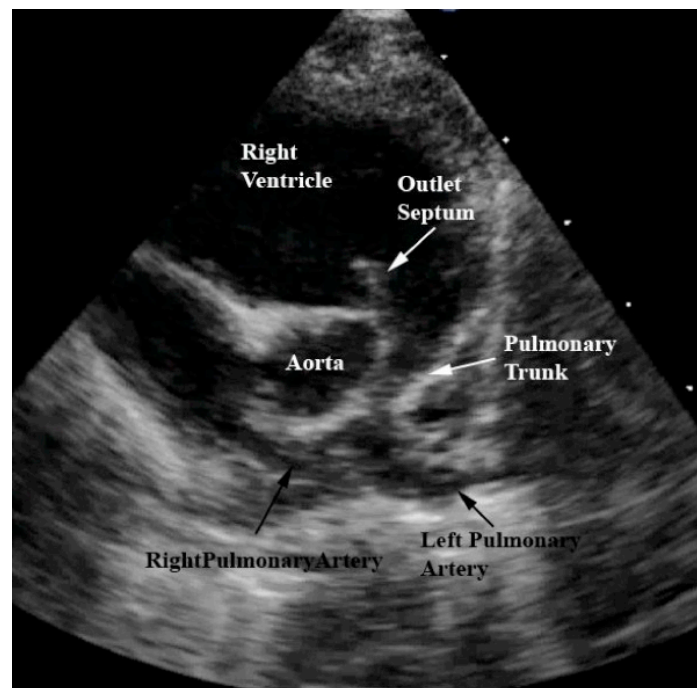


Figure 3: Still frame of the antero-cephalad deviation of the outlet septum into the right ventricular outflow tract in echocardiography (parasternal short axis view), published in Tetralogy of Fallot, in Orphanet (11).

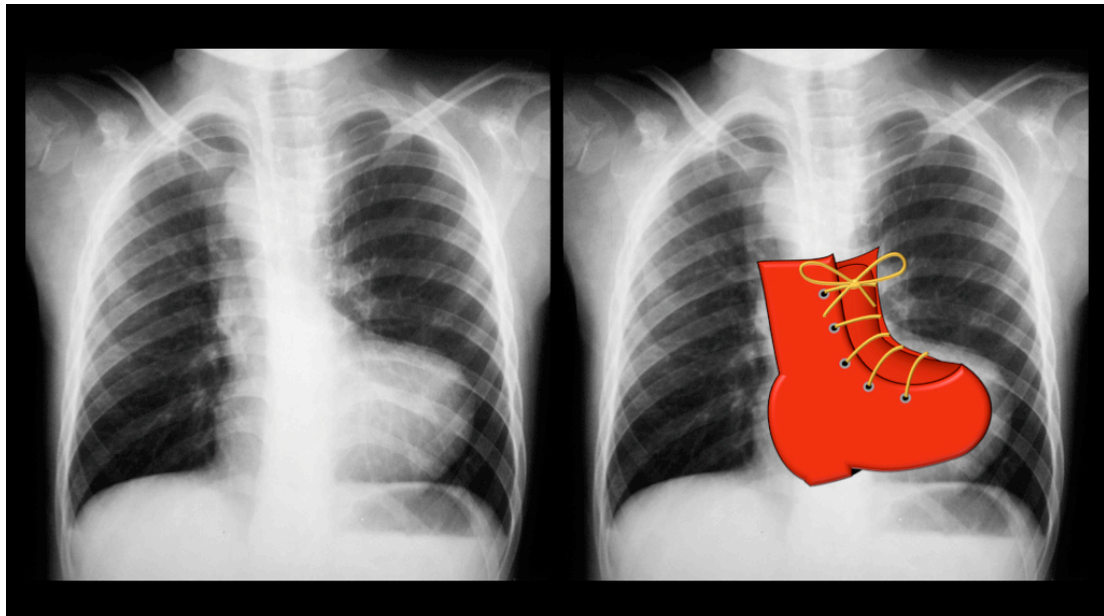


Figure 4: Boot-shaped heart in a thoracic radiography, published in Tetralogy of Fallot, in Radiopaedia (12).

Prognostic

The natural prognosis of patients not treated for their Tetralogy of Fallot is poor. The RVOTO is the principal factor leading to death in the first years (lowered oxygenation, cerebral thromboses, osteomyelitis). After potentially reaching adulthood, the main cause of death is then chronic heart failure (4).

The mortality rate gradually increases: 40% of death by age 3. Only 30% of patients reach the first decade alive and even fewer the second one. The mortality rate is the highest during the first year of life. A complete atresia has an extremely poor prognosis, with only 50% reaching the age of 1 (4). It is, however, important to note that those rates have been drastically lowered with the advancement of medical and surgical treatments (13).

Treatment

With such a poor natural prognosis, it is essential to correct the Tetralogy of Fallot in the first years of life through surgery. There are two types of surgical procedures: palliative shunts or complete repair.

Palliative shunt

The palliative shunt is used to stabilize the patient while waiting for a complete repair (eg. premature, severe pulmonary stenosis, spells), so as to maintain the ductus arteriosus open. The modified Blalock-Taussig shunt is usually chosen as the best technique, by creating a

communication between the subclaviar artery and the ipsilateral pulmonary artery via a synthetic graft (10).

Complete correction

The complete repair has the goals to relieve the RVOTO and to completely separate both ventricles (and thus the systemic and pulmonary circulations), while preserving the right ventricle's function and the pulmonary valve competence. Usually, the right ventricular outflow tract is reconstructed through the resection of the hypertrophic infundibular and subinfundibular muscle bundles via a transatrial approach. This part of the intervention is also associated with a valvulotomy and possible valve replacement in case of an abnormal pulmonary valve via a transpulmonary approach, and in some cases, with the addition of a small ventricular incision if necessary (3). The VSD is closed with a patch of pericardium. The approach to the VSD is transatrial, to avoid a ventriculotomy, which could lead to arrhythmias (3).

After surgery, the patients are sent to the pediatric intensive care unit (PICU), where they are supported with ventilation and vasopressor treatment until their vital signs stabilize. According to Davidson J et al (14), the vasopressor treatment can also be used as a predictor of the short-term post-operative outcome and will be taken into account for this study too.

The complete repair is associated with different complications. The perioperative ones include residual VSD and residual RVOTO (1). The short-term outcome is usually good with a low mortality rate between 1-5% (1,4). Long-term complications can arise, such as chronic pulmonary regurgitation, aneurysm of the right ventricular outflow patch, right ventricular dilatation and chronic heart failure, residual RVOTO, aorta dilatation and aortic valve insufficiency, arrhythmias or even sudden cardiac death (1,3). These complications can lead to a surgical reintervention.

Overall, the survival of repaired Tetralogy of Fallot is extremely good with 90% survival rate at 25 years' post-repair (1).

Therefore, a complete repair is essential for patients suffering from the Tetralogy of Fallot. The postoperative mortality is low but still exists; it would then be beneficial to find a special indicator that could help predict the early outcome after surgical repair. In this study, the Troponin-I, marker of myocardial damages, has been chosen as the plasmatic parameter which will be analyzed to determine a possible correlation between its different plasmatic values and the early postoperative evolution.

Methodology

The institutional research ethics committee approved this retrospective study based on the early postoperative outcome of patients operated for the Tetralogy of Fallot.

Data collected were classified into five types: population criteria, demographic data, surgical data, Troponin-I data and postoperative outcome data.

Population

The criteria of inclusion in the study were all patients who underwent cardiac repair surgery for a Tetralogy of Fallot in the Pediatric Cardiology Department in the Centre Hospitalier Universitaire Vaudois (CHUV) in Switzerland between 2003 and 2010. The only criterion of exclusion from this population was a preoperative Troponin-I level above 0.003 µg/l because of the possible bias that could be introduced in the analysis and calculation of the plasmatic parameters of the Troponin-I.

Demographic data

The following preoperative demographic data were collected: age, height and weight.

Surgical data

After surgery, the following surgical data were collected: duration of extracorporeal circulation (ECC) (= cardiopulmonary bypass), duration of aortic cross-clamping. The type of surgery according to the Risk Adjustment for Congenital Heart Surgery (RACHS-1) was recorded: the classical repair fell into RACHS-1 category 2, while the repair with the addition of a pulmonary valve replacement fell into RACHS-1 category 3, according to the quality of the pulmonary valve (15).

The cardioplegia and anesthesia followed the same routine, without a specific protocol, and the surgeon was the same for all operations.

Troponin-I data

Preoperative plasmatic Troponin-I concentration was measured as a routine analysis and later used to assure the inclusion in the study.

After surgery, Troponin-I values were collected at least 5 times without following a specific pattern of hours and were then exposed on a timeline like in a pharmacodynamic analysis so

as to calculate the area under the curve, half-life, maximal plasmatic concentration and constant of elimination of the plasmatic concentration of the Troponin-I.

Postoperative outcome data

The postoperative outcome data collected were the following: PRISM-II score, amount of vasopressor support, duration of mechanical ventilation, duration of stay in the PICU and deaths. Those variables were chosen as the ones reflecting the best the early postoperative prognostic. The criterion for extubation was let to the physician in charge in the PICU. The criteria of the duration of stay in the PICU were multifactorial and depended on the medical personal's decision.

As for the various scores, the PRISM-II score (Pediatric Risk of Mortality) was used to assess the postoperative mortality. A score above 10 was set as the threshold for a higher postoperative mortality risk (16,17).

The modified inotropic score, named vasoactive-inotropic score (VIS), estimates the maximal vasopressor support needed in the PICU in the 24 hours after surgery. A score above 20 was determined as a major vasopressor support (18,19).

Box 1

$$\begin{aligned} \text{Wernovsky IS} &= \text{dopamine dose } (\mu\text{g/kg/min}) \\ &+ \text{dobutamine dose } (\mu\text{g/kg/min}) \\ &+ 100 \times \text{epinephrine dose } (\mu\text{g/kg/min}) \\ \text{VIS} &= \text{IS} + 10 \times \text{milrinone dose } (\mu\text{g/kg/min}) \\ &+ 10,000 \times \text{vasopressin dose } (\text{U/kg/min}) \\ &+ 100 \times \text{norepinephrine dose } (\mu\text{g/kg/min}) \end{aligned}$$

Figure 5: Formulas of inotropic score according to Wernovsky and to Gaies, published in Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass, in Pediatric Critical Care Medicine (19).

Goal

For this study, the pharmacodynamic parameters of the plasmatic Troponin-I were described and correlated with the different postoperative outcome measurements.

For the analysis of all variables, we used the analytical program Stata 13.0. Data are presented as median (p50) with interquartile ranges (p25; p75). Wilcoxon's rank sum test was used to test associations between categories. The univariate logistic regression was used to prove the correlation between variables chosen from the results of the Wilcoxon's rank sum test and to give an odd ratio. A relation between two categories was considered significant when the p-value was under 0.05.

Results

Data collection

A total of 93 patients were included in this study, in the range of 0 to 16 years old (median at 4.1 years [2.05; 6.73]). Among those, 29 (31%) patients were operated with the addition of a biological pulmonary valve replacement. The demographic data along with the surgical ones are summarized in Table 1.

For the surgical data collected, the ECC duration ranged from 25 to 221 minutes (median at 114.0 minutes [96.0; 141.0]). The aortic clamping duration ranged from a minimum of 32 to 135 minutes (median at 63 minutes [53; 77]).

Table 1. Demographic and surgical data

N=93	Median [IQR]	
Age (year)	4.08	[2.05; 6.73]
Weight (kg)	13.5	[11.0; 17.0]
Height (cm)	98.0	[85.5; 114.0]
ECC time (min)	114.0	[96.0; 141.0]
Clamping time (min)	63	[53; 77]
RACHS-1 2	64 (69%)	
3	29 (31%)	

ECC, extracorporeal circulation; RACHS-1 2, cardiac repair not associated with pulmonary valve replacement; RACHS-1 3, cardiac repair associated with pulmonary valve replacement.

For the Troponin-I data compiled in Table 2, the area under the curve ranged from 45 to 6349 µg/l (median at 599.43 µg/l [353.04; 951.50]). The half-life covered a range from 11 to 108 hours (median at 28.22 h [20.90; 39.59]). The maximal concentration ranged from 2.7 to 103.0 µg/l (median at 25.55 µg/l [13.53; 38.34]). As for the constant of elimination, the range stretched from 0.36 to 3.6 µg/h (median at 1.2 µg/h [0.6; 1.8]).

Table 2. Troponin-I data

N=93	Median [IQR]	
AUC (µg/l)	599.43	[353.04; 951.50]
Half-life (h)	28.22	[20.90; 39.59]
Ke (µg/h)	1.20	[0.6; 1.8]
C _{max} (µg/l)	25.55	[13.53; 38.34]

AUC, area under the curve; Ke, constant of elimination; C_{max}, maximal concentration.

The postoperative data collected in Table 3 showed a PRISM-II score ranging from 0 to 25 and above 10 for 12 patients (13%). They were 2 deaths which occurred during the stay in the PICU. The vasoactive-inotropic score's range was from 3 to 124 points and its median was at 25 points [17; 58]. The ventilation time ranged from 0.4 to 42 days (median at 1.12 days [0.92; 4.98]). On the other side, the duration of stay in the PICU fluctuated between 2 to 43 days (median at 5.99 days [4.17; 9.07]).

Table 3. Postoperative outcome data

N=93	Median [IQR]	
PRISM-II ≤10	81 (87%)	
>10	12 (13%)	
Deaths	2 (2%)	
Vasoactive-inotropic score	25	[17; 58]
Ventilation time (day)	1.12	[0.92; 4.98]
Stay in PICU time (day)	5.99	[4.17; 9.07]

PRISM-II, pediatric risk of mortality; *PICU*, pediatric intensive care unit.

After collecting those data, we classified them according to the operative procedure (RACHS-1 categories) and postoperative parameters, including the duration of mechanical ventilation and duration of stay in the PICU, in Table 4, 5 and 6 respectively. To simplify comparisons we arbitrarily divided a few parameters according to the median p50.

For the data arranged according to the RACHS-1 categories in Table 4, only the duration of ECC and of clamping were notably different for the RACHS-1 category 3 vs RACHS-1 category 2, with a median of 108 minutes versus 136 minutes for the ECC time (*p-value*<0.0001) and 58 minutes versus 80 minutes for the clamping time (*p-value*<0.0001).

The rest of the *p-values* analyzed for the RACHS-1 categories were not significant.

Table 4. RACHS-1 categories versus demographic and surgical data, postoperative outcome and Troponin-I data

	RACHS-1 category 2 Median [IQR]		RACHS-1 category 3 Median [IQR]		P-value
N=93	62		29		
Age (year)	3.84	[1.95; 6.48]	4.72	[2.44; 8.04]	NS
Weight (kg)	13.35	[10.45; 16.40]	14	[12; 20]	NS
Height (cm)	96	[83; 113]	102	[87.5; 122]	NS
ECC time (min)	108.0	[93; 125.5]	136	[119; 152]	<0.0001
Clamping time (min)	58	[52; 67]	80	[63; 90]	<0.0001
PRISM-II	4	[2; 8.5]	4	[2; 7]	NS
Ventilation time (day)	1.10	[0.92; 4.96]	1.12	[0.92; 3.92]	NS
Stay in PICU time (day)	6.07	[4.18; 9.06]	5.89	[4.17; 9.98]	NS
AUC (µg/l)	604.81	[337.88; 881.64]	599.43	[458.32; 1144.26]	NS
Half-life (h)	29.63	[22.55; 39.32]	23.80	[19.63; 39.60]	NS
Ke (µg/h)	1.2	[1.2; 1.8]	1.8	[1.2; 1.8]	NS
C_{max} (µg/l)	25.37	[13.52; 40.01]	25.76	[16.30; 38.11]	NS

RACHS 2, cardiac repair not associated with pulmonary valve replacement; *RACHS 3*, cardiac repair associated with pulmonary valve replacement; *ECC*, extracorporeal circulation; *PRISM-II*, pediatric risk of mortality; *PICU*, pediatric intensive care unit; *AUC*, area under the curve; *Ke*, constant of elimination; *C_{max}*, maximal concentration. *NS*, non-significant.

In Table 5, we divided the data related to the ventilation time according to its median (p50 at 1.12 days), decreeing that a two-days or more duration of ventilation was an unusual evolution in this population. 54 patients needed ventilation for less than two days and 39 had a need for ventilation for more than two days. Some data were noticeably different for the group of patients having a ventilation time of two days or more, in comparison to the group having a ventilation time of less than two days: the age median was at 2.75 years old [0.88; 3.92] versus 6.07 years old [3.59; 8.52] (*p-value*=0.005), the weight was at 16 kg [13; 21] versus 11.5 kg [9.18; 13.5] (*p-value*<0.0001), the height was at 108.5 cm [94; 126] versus 90 cm [72.5; 98] (*p-value*<0.0001), the PRISM-II score was at 6 [3; 10] versus 2.5 [2; 6] (*p-value*=0.021), the median of the overall stay in the PICU was at 9.08 days [6.24; 11.14] versus 5.08 days [3.29; 6.06] (*p-value*<0.0001). The Troponin-I data which were also contrasting were the area under the curve with a median at 1011.61 µg/l [544.29; 1488.60] versus 470.92 µg/l [290.18; 680.83] (*p-value*<0.0001) and the maximal concentration with a median at 36.34 µg/l [20.24; 54.26] versus 20.45 µg/l [11.95; 31.48] (*p-value*=0.001).

The *p-values* for the extracorporeal circulation, the aortic clamping time, constant of elimination and half-life were not significant.

Table 5. Duration of ventilation in the PICU versus demographic and surgical data, postoperative outcome and Troponin-I data

	Ventilation time < 2 days		Ventilation time ≥ 2 days		P-value
	Median [IQR]		Median [IQR]		
N=93	54		39		
Age (year)	6.07	[3.59; 8.52]	2.75	[0.88; 3.92]	<0.0001
Weight (kg)	16	[13; 21]	11.5	[9.18; 13.5]	<0.0001
Height (cm)	108.5	[94; 126]	90	[72.5; 98]	<0.0001
ECC time (min)	110.5	[95; 139]	125	[99; 147]	NS
Clamping time (min)	63	[53; 79.5]	62.5	[52; 74]	NS
PRISM	2.5	[2; 6]	6	[3; 10]	0.004
PICU stay (day)	5.08	[3.29; 6.05]	9.08	[6.24; 11.14]	<0.0001
AUC (µg/l)	470.92	[290.18; 680.83]	1011.61	[544.29; 1488.60]	<0.0001
Half-life (h)	27.10	[20.59; 36.41]	35.63	[21.47; 41.94]	NS
Ke (µg/h)	1.2	[1.2; 1.8]	1.2	[1.2; 1.8]	NS
C_{max} (µg/l)	20.45	[11.95; 31.48]	36.34	[20.24; 54.26]	<0.0001

ECC, extracorporeal circulation; PRISM, pediatric risk of mortality; PICU, pediatric intensive care unit; AUC, area under the curve; Ke, constant of elimination; C_{max}, maximal concentration. NS, non-significant.

For the duration of stay in the PICU, the data were divided in Table 6 in two categories according to the median time of stay in the PICU: a stay longer than 6 days or more was considered as an unusual evolution for this population. For the group of patients that demonstrate a stay in the PICU longer than 6 days, there was a notable difference in outcome parameters compared to the group of patient that stayed less than 6 days in the PICU. The patient staying longer in the PICU were younger with a median age at 2.75 years old [1.15; 4.67] versus 6.17 years old [3.67; 8.81] (p -value=0.011), with a median weight at 16.4 kg [12.9; 21.0] versus 12.0 kg [9.6; 14.5] (p -value<0.0001) and a median height at 110.75 cm [92.5; 127.0] versus 94.0 cm [74.0; 100.0] (p -value<0.0001) as well. The duration of ventilation was also different for patients staying longer with a median at 4.98 days [1.12; 7.00] versus 0.92 days [0.73; 1.06] (p -value<0.0001). As for the Troponin-I variables, the area under the curve seemed to be divergent with a median at 939.97 µg/l [594.10; 1439.03] for a longer stay versus 431.76 µg/l [271.30; 619.09] (p -value<0.0001). Likewise, the maximal concentration's median was at 34.13 µg/l [23.79; 52.01] versus 19.46 µg/l [11.62; 29.40] (p -value<0.0001).

The p -values for the ECC and clamping time time, for the PRISM-II score and for the Troponin-I values half-life and constant of elimination were not significant.

Table 6. Duration of stay in the PICU versus demographic and surgical data, postoperative outcome and Troponin-I data

	PICU time < 6 days Median [IQR]		PICU time ≥ 6 days Median [IQR]		P-value
N=93	48		45		
Age (year)	6.17	[3.67; 8.81]	2.75	[1.15; 4.67]	<0.0001
Weight (kg)	16.4	[12.9; 21.0]	12.0	[9.6; 14.5]	<0.0001
Height (cm)	110.75	[92.5; 127.0]	94.0	[74.0; 100.0]	<0.0001
ECC time (min)	110.5	[93.5; 137.5]	122.0	[104.0; 147.0]	NS
Clamping time (min)	61.0	[53.0; 80.0]	64.5	[55.5; 73.5]	NS
PRISM	3.0	[2.0; 6.5]	4.0	[2.0; 9.0]	NS
Ventilation time (day)	0.92	[0.73; 1.06]	4.98	[1.12; 7.00]	<0.0001
AUC (µg/l)	431.76	[271.30; 619.09]	939.97	[594.10; 1439.03]	<0.0001
Half-life (h)	26.32	[20.56; 38.76]	32.96	[21.03; 40.41]	NS
Ke (µg/h)	1.8	[1.2; 1.8]	1.2	[1.2; 1.8]	NS
Cmax (µg/l)	19.46	[11.62; 29.40]	34.13	[23.79; 52.01]	<0.0001

ECC, extracorporeal circulation; PRISM, pediatric risk of mortality; PICU, pediatric intensive care unit; AUC, area under the curve; Ke, constant of elimination; Cmax, maximal concentration. NS, non-significant.

Categories testing

Univariate Logistic Regression

The next step in our study was to analyse correlation between early postoperative outcomes and Troponin-I pharmacological parameters. Our findings are summarized in Table 8. The threshold age above 1-year-old was decided on the basis of the literature regarding the best time of surgical correction of a Tetralogy of Fallot. The ECC time threshold was set at 120 minutes like in other studies (8,20–22).

Age seemed to be a significant factor for a longer ventilation time and a longer duration of stay in the PICU with an odd ratio of 20.82 (p -value= 0.005) and 15.21 (p -value=0.011), respectively. The PRISM-II score had a significant correlation with the duration of ventilation, with an odd ratio at 5.10 (p -value=0.021). The operative procedures, described by the RACHS, and the duration of ECC did not statistically have any impact on any of the three postoperative parameters.

As for the Troponin-I variables, the area under the curve showed a significant correlation with a longer ventilation time with an odd ratio of 7.27 (p -value<0.0001), longer duration of stay in the PICU with an odd ratio of 9.35 (p -value<0.0001) and increased vasopressor support, with an odd ratio of 5.00 (p -value=0.018). The maximal concentration had a significant correlation with the ventilation time with an odd ratio at 4.33 (p -value=0.001), and duration of stay in the PICU with an odd ratio at 6.05 (p -value<0.0001), but not with the vasopressor support. The half-life did not have any significant correlation with any of the three parameters.

Table 8. Univariate Logistic Regression with p-values and odd ratios

	Ventilation time: P-values	Duration of stay in PICU: P-values	Vasopressor support: P-values
Age < 1 year old	0.005 → OR = 20.82	0.011 → OR = 15.21	NS
PRISM >10	0.021 → OR = 5.10	NS	NS
RACHS-1 3	NS	NS	NS
ECC >120 min	NS	NS	NS
AUC >654 µl	<0.0001 → OR = 7.27	<0.0001 → OR = 9.35	0.018 → OR = 5.00
Half-life >28 h	0.168	NS	NS
C_{max} >25 µg/l	0.001 → OR = 4.33	<0.0001 → OR = 6.05	NS

PICU, pediatric intensive care unit; *PRISM*, pediatric risk of mortality; *RACHS-1 3*, cardiac repair associated with pulmonary valve replacement; *ECC*, extracorporeal circulation; *AUC*, area under the curve; *C_{max}*, maximal concentration. *NS*, non-significant p-value. Only odd ratios for significant relations were written in the Table.

Discussion

Overall Data

The overall demographic data collected showed quite an advanced age at the time of surgery, with a median at 4 years old. This particularity is due to the fact that our institution has a great number of patients coming from abroad for surgery corrections of congenital diseases. For our local patients who are diagnosed and followed from birth, the usual time for corrective surgery is between 3 to 6 months, but for the referred patients from abroad, it is clearly older. The length of cardiopulmonary bypass and aortic cross-clamping were similar to the duration recorded by other studies (8,22,23).

The RACHS-1 category 2 was more frequent and this result was expected as the replacement of the pulmonary valve (RACHS-1 category 3) is only reserved to patients whose valve is unsuitable for repair and preservation.

The Troponin-I variables were difficultly comparable to the ones appearing in other studies. Indeed, the half-life, constant of elimination and area under the curve did not seem to have been researched before. Only the maximal concentration of Troponin-I was used in other studies (5,6,22,24,25). In our study, the median of maximal concentration was at 25.5 µg/l. In the Bottio et al study, the median was also at 25.5 (5). In the Modi et al study, however, it was at 5.0 or 12.9 (depending on the right ventricular tract incision) (22). This difference could be explained by the use of a different analysis system for the plasmatic Troponin-I in each center. The other studies quoted above were not usable as the median was not communicated precisely in their article.

The PRISM-II score median was about 10, which is quite close to the score recorded in another study (21). This score predicts the early postoperative mortality rate. The greater the PRISM-II score (in particular if greater than 10) is the higher the mortality risk (16,17,26,27). However, this analysis could not be performed in our study as the number of deaths was insufficient.

Among our patients, only 2 died, which made the analysis of this variable impossible. However, this rate seems to be in agreement with the 0-3% mortality rate reported previously (1).

The median duration of mechanical ventilation time was similar to the one reported by other studies, which were between 61 and 72 hours (8,28,29).

As for the duration of stay in the PICU, the rate of 6 days seemed to be similar to other studies as well (5,8,26,29).

RACHS-1 categories

The Risk Adjustment for Congenital Heart Surgery (RACHS-1) predicts the postoperative mortality after a cardiac surgery. Its advantage is the categorization according to the surgery type and not according to the disease. The RACHS-1 category 2 contains the Tetralogy of Fallot repair and the category 3 contains the repair of Tetralogy of Fallot with the pulmonary valve replacement (15).

Our study does not show any difference of age at the time of surgery depending on the RACHS-1 categories. The ECC and aortic clamping time were longer for the RACHS-1 category 3 as the surgery lasts longer since it is associated with the valve replacement.

Furthermore studies brought forth the association between pulmonary valve replacement and a longer ventilation need (>48 hours) (28–31). In our study, the RACHS-1 category 3 was correlated neither with a longer ventilation time, nor with a longer stay in PICU nor greater inotropic support, and did not seem to have any association with the PRISM-II score either. This result contradicts studies mentioned above and the reason is unclear. Also, its correlation to postoperative mortality could not be determined as the total number of deaths was insufficient.

The RACHS-1 categories did not seem to be associated with the different plasmatic Troponin-I variables. This absence of association is understandable as the surgery is not coupled with a more important myocardial resection which would release more Troponin-I in the bloodstream.

Ventilation Support (± 2 days)

As for the ventilation need, age seemed to play an important role. The right timing of complete repair of Tetralogy of Fallot has always been a debated topic. Studies have shown that a repair during the neonatal period (versus infancy) was not associated with more reinterventions (32,33). Besides, it allowed a reduction of the right ventricle's hypertrophy, a protection against abnormal development of myocardium (and thus against arrhythmias) and against pathologic pulmonary gas exchange because of the reduced vascular pulmonary flow and pressure, and finally it diminished the length of hypoxemia on the brain (33,34). However, it also seemed that such an early operation resulted in longer ventilation support and stay in the PICU (20,21,26,35). This correlation could be explained by the immaturity of the respiratory system, with the absence of contribution of the thoracic cage, the weakness of respiratory muscles and narrow respiratory tracts (36). Our findings suggest the same correlation as well. Indeed, patients under 1-year-old had a significant higher risk to need a longer ventilation support and a longer stay in the PICU. The risks were 20 times and 15 times greater, respectively. Our group is also particular because of a significant proportion of patients with Tetralogy of Fallot coming from abroad for a corrective surgery. These patients are older with a longer period of cyanosis than the patient born and followed in our center. It means that these patients have a long-standing evolution with their initial disease, with all complications due to long standing cyanosis. It is then interesting to see that these patients do not have a longer stay nor a longer time of mechanical ventilation contrary to the patient who are younger than one-year-old, the genuine patients of our center.

In our study, the duration of ECC and aorta cross-clamping did not have any impact on the ventilation need. In the literature, both these variables are apparently correlated with an increased risk of longer mechanical ventilation of more than 61 hours (29) and 72 hours (6). This divergence could be explained by the different categorization of mechanical ventilation used: in our study, we chose to differentiate a ventilation of more or less 48 hours, in contrast to the studies mentioned above. Furthermore, the study from Egbe et al (20) seemed to support our findings as well.

Concerning the correlation between the ventilation time and the PRISM-II score, it seems that another study confers the utility to the the PRISM-II score to predict a longer mechanical ventilation support (21). Our study brought forth a risk 5 times greater of longer ventilation need with a score above 10.

As for the length of stay in the PICU, it seemed to be longer in case of an extended ventilation need, as studies also described (36). This relation looks logical as the ventilation support has to be applied in the intensive care unit.

Lastly, the Troponin-I variables seemed to play a major role in the determination of a longer ventilation need. The half-life and constant of elimination were uncorrelated to the mechanical ventilation support. However, the maximal concentration was associated with a risk 4 times greater to require a ventilation need for more than 2 days. This result confirms the conclusion of the studies of Immer et al. (6) and Hirsch et al (8). Furthermore, the area under the curve was significantly correlated to the ventilation support, as an area under the curve greater than 654 µg/l was associated with a risk 7 times more important to need mechanical ventilation for more than 2 days. This correlation support our hypothesis that the Troponin-I plasmatic levels reflect the initial surgical lesions and the management in the postoperative time, when the strategy is to protect the myocardium around resection lines to avoid secondary hypoperfusion scars. This result is new, as no other study seems to have research this specific parameter of the Troponin-I.

Pediatric Intensive Care Unit ($\pm$ 6 days)

As for the length of stay in the PICU, young age (linked with the height and weight) was a risk factor for a longer stay as explained above.

The duration of cardiopulmonary bypass and clamping time did not play any role in the duration of stay in the PICU. This result coincides with the research from Egbe et al. (20).

The PRISM-II score can predict the mortality, but seems to also predict a longer ventilation time, as explained above, and longer stay in the PICU (37). However, in our study, the latter correlation was not statistically significant and the reason is unclear.

Concerning the Troponin-I variables, the maximal concentration is again known to influence the duration of stay in the PICU (8,22). The half-life was not associated with the length of stay. The area under the curve, however, was strongly associated with the duration of stay in the PICU, as an area under the curve greater than 654 µg/l had a risk 9 times greater to need a longer stay in the PICU.

Vasopressor support

For the ventilation need and duration of stay in the PICU, age played an important role. However, no correlation to the vasopressor support was brought forth. This result seems to contradict the one from Pigula et al. (23), but this could be explained as their study focused on the difference between neonates and infants, while we were interested in a categorization of age between more or less than 1 year old.

As expected, the PRISM-II score did not have any association with the inotropic support. The RACHS-I category 3 and an ECC time longer than 120 minutes were not correlated either to the vasopressor need. This was actually expected, as they were not related to the ventilation support and length of stay in the PICU either.

Concerning the Troponin-I variables, only the area under the curve was correlated to the vasoactive-inotropic need, with a risk 5 times greater to need an increased support if the area under the curve was greater than 654 µg/l. The half-life and maximal concentration of plasmatic Troponin-I were not correlated to the vasopressor support. This last result is supported by the study from Hirsch et al (8) who recorded the same conclusion.

Limitation

The number of deaths in this study was too small (deaths = 2) to be taken into consideration as a usable postoperative data and was not analyzed.

The main limitation of our study was the imprecise pattern of sampling of the Troponin-I. Indeed, the samples were taken at least 5 times postoperative as a routine follow-up over the days after surgery but without an accurate strategy. This could have introduced an imprecision in the calculation of the area under the curve of the plasmatic Troponin-I. Consequently to this pilot study and when looking at all parameters of the Troponin-I plasmatic levels, we could propose that the pattern for a prospective study would be to sample the Troponin-I on the same hour in every patient, four times on day 0 post-surgery (3 hours, 6 hours, 12 hours, 24 hours for exemple), then three times on day 1, twice on day 2 and finally once on day 3.

Lastly, one of the actual problem is that many institutions use now the high-sensitive Troponin-T, since that analysis allows extremely accurate results for small values, with a coefficient of variance of <10% at the 99th percentile (38). This test is already in use for the earlier detection of myocardial infarct (39,40). However, the current Troponin-I assays are not standardized yet and results cannot be compared with other institutions, preventing their use for multi-centric studies (41). In our study, this new type of analysis would have probably not changed the results because of the high plasmatic concentrations' releases (median for the area under the curve around 650 µg/l). However, most institutions gradually use the high-sensitive Troponin-T solely and we cannot deny this change. Our study could then be used as a milestone for a possible prospective study using the high-sensitive Troponin-T as a main biomarker. New interesting findings could then be brought to light.

Conclusion

Our study demonstrates that the Troponin-I plasmatic values are indeed good markers to predict the length of ventilation support, the duration of stay in the PICU and the strength of the vasopressor support. The maximal concentration of plasmatic Troponin-I was significant for only two categories (length of ventilation support and duration of stay), while the half-life and constant of elimination were not correlated to any. On its side, the area under the curve showed a significant correlation to all three postoperative categories. An area under the curve greater than 654 $\mu\text{g/l}$ was associated with a risk of longer ventilation support 7 times greater, with a risk of longer stay in the PICU 9 times greater and with a risk of increased vasopressor support 5 times greater.

Then, the next hypothesis could be to research a specific postoperative time where the area under the curve greater than a certain amount would reflect an important myocardial necrosis and thus a worse postoperative outcome.

References

1. Stewart RD, Mavroudis C, Backer CL. Tetralogy of Fallot. In: Mavroudis C, Backer CL, Idriss RF, editors. *Pediatric Cardiac Surgery*. Blackwell Publishing Ltd; 2012. p. 410–27.
2. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth Prevalence of Congenital Heart Disease Worldwide: A Systematic Review and Meta-Analysis. *J Am Coll Cardiol*. 2011 Nov 15;58(21):2241–7.
3. Corno AF. *Congenital Heart Defects*. Heidelberg: Steinkopff; 2004.
4. Kouchoukos NT, Blackstone EH, Hanley FL, Kirklin JK. Ventricular Septal Defect with Pulmonary Stenosis or Atresia. In: *Kirklin/Barratt-Boyes Cardiac Surgery*. 4th Edition. Philadelphia, PA, USA: Elsevier Saunders; 2013.
5. Bottio T, Vida V, Padalino M, Gerosa G, Stellin G. Early and long-term prognostic value of Troponin-I after cardiac surgery in newborns and children. *Eur J Cardiothorac Surg*. 2006 Aug 1;30(2):250–5.
6. Immer FF, Stocker F, Seiler AM, Pfammatter J-P, Bachmann D, Printzen G, et al. Troponin-I for prediction of early postoperative course after pediatric cardiac surgery. *J Am Coll Cardiol*. 1999 May;33(6):1719–23.
7. Hirsch R, Landt Y, Porter S, Canter CE, Jaffe AS, Ladenson JH, et al. Cardiac troponin I in pediatrics: Normal values and potential use in the assessment of cardiac injury. *J Pediatr*. 1997 Jun;130(6):872–7.
8. Hirsch MBChB R, Dent MD CL, Wood RN MK, Huddleston MD CB, Mendeloff MD EN, Balzer MD DT, et al. Patterns and Potential Value of Cardiac Troponin I Elevations After Pediatric Cardiac Operations. *Ann Thorac Surg*. 1998 May;65(5):1394–9.
9. Doyle T, Kavanaugh-McHugh A. Pathophysiology, clinical features, and diagnosis of tetralogy of Fallot in UpToDate [Internet]. 2015 [cited 2016 Apr 26]. Available from: http://www.uptodate.com/contents/image?imageKey=PEDS/82493&topicKey=PEDS/5769&source=outline_link&search=tetralogy%20of%20fallot&utdPopup=true
10. Apitz C, Anderson RH, Redington AN. Tetralogy of Fallot with Pulmonary Stenosis. In: *Paediatric Cardiology*. 3rd ed. Philadelphia, PA, USA: Churchill Livingstone Elsevier; 2010. p. 753–73.
11. Bailliard F, Anderson RH. Tetralogy of Fallot. *Orphanet J Rare Dis*. 2009 Jan 13;4:2.
12. Tatco V. Tetralogy of Fallot | Radiology Case | Radiopaedia.org [Internet]. Radiopaedia. [cited 2016 Oct 25]. Available from: <https://radiopaedia.org/cases/tetralogy-of-fallot-6>
13. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: Trends in the US population from 1979 to 2005. *Am Heart J*. 2009 Nov;158(5):874–9.
14. Davidson J, Tong S, Hancock H, Hauck A, Cruz E da, Kaufman J. Prospective validation of the vasoactive-inotropic score and correlation to short-term outcomes in neonates and infants after cardiothoracic surgery. *Intensive Care Med*. 2012 Apr 14;38(7):1184–90.
15. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. 2002 Jan;123(1):110–8.

16. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med*. 1988 Nov;16(11):1110–6.
17. Pollack MMMF, Patel KM, Ruttimann UE. PRISM III: An updated Pediatric Risk of Mortality score. *Crit Care Med*. 1996 May;24(5):743–52.
18. Wernovsky G, Wypij D, Jonas RA, Mayer JE, Hanley FL, Hickey PR, et al. Postoperative Course and Hemodynamic Profile After the Arterial Switch Operation in Neonates and Infants. *Circulation*. 1995 Oct 15;92(8):2226–35.
19. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass*: *Pediatr Crit Care Med*. 2010 Mar;11(2):234–8.
20. Egbe AC, Mitnacht AJ, Nguyen K, Joashi U. Risk factors for morbidity in infants undergoing tetralogy of fallot repair. *Ann Pediatr Cardiol*. 2014;7(1):13–8.
21. Polito AM, Patorno EM, Costello JMM, Salvin JWM, Emani SM, Rajagopal S, et al. Perioperative factors associated with prolonged mechanical ventilation after complex congenital heart surgery *. *Pediatr Crit Care Med*. 2011 May;12(3).
22. Modi P, Imura H, Angelini GD, Pawade A, Parry AJ, Suleiman M-S, et al. Pathology-Related Troponin I Release and Clinical Outcome after Pediatric Open Heart Surgery. *J Card Surg*. 2003 Jul 1;18(4):295–300.
23. Pigula FA, Khalil PN, Mayer JE, Nido PJ del, Jonas RA. Repair of Tetralogy of Fallot in Neonates and Young Infants. *Circulation*. 1999 Nov 9;100(suppl 2):II-157-li-161.
24. Carmona F, Manso PH, Vicente WVA, Castro M, Carlotti APCP. Risk stratification in neonates and infants submitted to cardiac surgery with cardiopulmonary bypass: A multimarker approach combining inflammatory mediators, N-terminal pro-B-type natriuretic peptide and troponin I. *Cytokine*. 2008 Jun;42(3):317–24.
25. Siaplaouras J, Thul J, Will JC, Bauer J, Kreuder J, Valeske K, et al. [Cardiac troponin I after heart surgery corrective operation in infancy and childhood]. *Z Kardiol*. 2001 Jun;90(6):408–13.
26. Ödek Ç, Kendirli T, Uçar T, Yaman A, Tutar E, Eyileten Z, et al. Predictors of Early Extubation After Pediatric Cardiac Surgery: A Single-Center Prospective Observational Study. *Pediatr Cardiol*. 2016 Jun 6;1–9.
27. de Araujo Costa G, Delgado AF, Ferraro A, Okay TS. Application of the Pediatric Risk of Mortality Score (PRISM) score and determination of mortality risk factors in a tertiary pediatric intensive care unit. *Clinics*. 2010 Nov;65(11):1087–92.
28. Shi S, Zhao Z, Liu X, Shu Q, Tan L, Lin R, et al. Perioperative Risk Factors for Prolonged Mechanical Ventilation Following Cardiac Surgery in Neonates and Young Infants. *Chest*. 2008 Oct;134(4):768–74.
29. Székely A, Sági E, Király L, Szatmári A, Dinya E. Intraoperative and postoperative risk factors for prolonged mechanical ventilation after pediatric cardiac surgery. *Pediatr Anesth*. 2006 Nov 1;16(11):1166–75.

30. Manrique AM, Feingold B, Di Filippo S, Orr RAM, Kuch BAB, Munoz RM. Extubation after cardiothoracic surgery in neonates, children, and young adults: One year of institutional experience. *Pediatr Crit Care Med*. 2007 Nov;8(6):552–5.
31. Reddy NS, Kappanayil M, Balachandran R, Jenkins KJ, Sudhakar A, Sunil GS, et al. Preoperative Determinants of Outcomes of Infant Heart Surgery in a Limited-Resource Setting. *Semin Thorac Cardiovasc Surg*. 2015;27(3):331–8.
32. Kolcz J, Pizarro C. Neonatal repair of tetralogy of Fallot results in improved pulmonary artery development without increased need for reintervention. *Eur J Cardiothorac Surg*. 2005 Sep 1;28(3):394–9.
33. Jonas RA. Early Primary Repair of Tetralogy of Fallot. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2009;12(1):39–47.
34. Tamesberger MI, Lechner E, Mair R, Hofer A, Sames-Dolzer E, Tulzer G. Early Primary Repair of Tetralogy of Fallot in Neonates and Infants Less Than Four Months of Age. *Ann Thorac Surg*. 2008 Dec;86(6):1928–35.
35. van Dongen EI, Glansdorp AG, Mildner RJ, McCrindle BW, Sakopoulos AG, VanArsdell G, et al. The influence of perioperative factors on outcomes in children aged less than 18 months after repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2003 Sep;126(3):703–10.
36. Davis SM, Worley SM, Mee RBBM, Harrison AMM. Factors associated with early extubation after cardiac surgery in young children. *Pediatr Crit Care Med*. 2004 Jan;5(1):63–8.
37. Slonim AD, Marcin JP, Pollack MM. Chapter 6 - Outcomes in Pediatric Critical Care Medicine: Implications for Health Services Research and Patient Care A2 - Fuhrman, Bradley P. In: Zimmerman JJ, editor. *Pediatric Critical Care (Fourth Edition)* [Internet]. Saint Louis: Mosby; 2011 [cited 2016 Aug 10]. p. 59–66. Available from: <http://www.sciencedirect.com/science/article/pii/B9780323073073100060>
38. Apple FS, Collinson PO, Biomarkers for the ITF on CA of C. Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays. *Clin Chem*. 2012 Jan 1;58(1):54–61.
39. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016 Jan 14;37(3):267–315.
40. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J*. 2012 Sep 1;33(18):2252–7.
41. Sherwood MW, Newby LK. High-Sensitivity Troponin Assays: Evidence, Indications, and Reasonable Use. *J Am Heart Assoc*. 2014 Jan 3;3(1):e000403.