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CHAPTER 2

Gut permeability in paediatric cardiac surgery

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Background: Intestinal mucosal ischaemia can occur in infants and children during and after cardiac surgery. Severe decreases in mucosal perfusion may be a causative factor for postoperative mortality or complications such as necrotizing enterocolitis. We have investigated gut permeability in paediatric patients undergoing cardiac surgery using the dual sugar permeability test and absorption of two other saccharides.

Methods: Thirty-four patients undergoing palliative or corrective surgical procedures with and without cardiopulmonary bypass were investigated. Intestinal permeability was measured using 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose, given orally after induction of anaesthesia and 12 and 24 hours later.

Results: Lactulose/Rhamnose ratios were increased from the outset, 0.39 (0.07-1.8) (median CI) for patients undergoing operations without cardiopulmonary bypass and 0.30 (0.02-2.6) with cardiopulmonary bypass. The highest Lactulose/Rhamnose ratios were recorded 12 hours after surgery 0.32 (0.07-6.9), when cardiopulmonary bypass was used. This is approximately seven times the value expected in healthy children. There was an improvement in patients not undergoing cardiopulmonary bypass: 0.22 (0.03-0.85) 12 hours and 0.11 (0-0.48) 24 hours after induction of anaesthesia. Patients undergoing repair of aortic coarctation showed the fastest recovery: 0.09 (0.03-0.31) 12 hours and 0.07 (0.04-0.35) 24 hours after induction of anaesthesia.

Conclusions: Patients with congenital heart defects have abnormal gut permeability when compared to healthy children of similar age. Cardiopulmonary bypass seems to affect the intestinal barrier morphologically (lactulose and rhamnose absorption) and functionally (3-O-methyl-D-glucose and D-xylose absorption).

Intestinal mucosal ischaemia, although transient, can occur in infants and children during and after cardiopulmonary bypass (CPB).¹ Severe decreases in mucosal perfusion may be a causative factor for postoperative mortality or complications such as necrotizing enterocolitis (NEC). NEC can have devastating consequences, e.g. in patients undergoing repair of hypoplastic left heart syndrome² (mortality more than 90%). Neonates with aortic arch anomalies and infants subjected to CPB-induced profound hypothermia may be at particular risk of developing splanchnic ischaemia in the perioperative period.³ These studies used indirect indicators of intestinal mucosal perfusion (e.g. laser Doppler probe or gastric tonometry). Patients with coarctation of the aorta may, on the other hand, be exposed to reperfusion injuries after the surgical repair, manifesting as the postcoarctectomy syndrome.⁴

Intestinal permeability can be evaluated noninvasively by measuring the urinary excretion of orally administered water-soluble, non-degradable test molecules.^{5,6} This barrier function test is based on the comparison of intestinal permeation of larger molecules with that of smaller molecules by measuring the ratio of their urinary excretion. These two types of molecules follow different routes of intestinal permeation: the larger molecules are assumed to permeate paracellularly, and the smaller molecules transcellularly.

Preabsorption factors such as gastric emptying, dilution by secretion and intestinal transit time, and post-absorption factors such as systemic distribution and renal clearance are assumed to affect both molecules equally. Four saccharides, 3-O-methyl-D-glucose (molecular weight 194 Da), D-xylose (molecular weight 150 Da), L-rhamnose (R, molecular weight 164 Da) and lactulose (L, molecular weight 342 Da) are employed to assess active carrier-mediated, passive carrier-mediated, transcellular, and paracellular transport, respectively in the small intestine.

Intestinal permeability is considered to be normal if the lactulose (% recovery)/rhamnose (% recovery) (L/R) ratio is below 0.05.⁵ Intestinal absorptive capacity for saccharides is considered to be normal when the recoveries of D-xylose (passive carrier-mediated transport) and 3-O-methyl-D-glucose (active carrier-mediated transport) are around 10% and 30% respectively.⁷

The aim of our study was to observe the changes in gut permeability in paediatric patients undergoing cardiac surgery using the dual sugar permeability test (DSPT).

Materials and methods

After approval from the local ethics committee and informed consent from the parents or legal guardians, 34 patients were enrolled in this prospective, non-randomized observational study. Patients received a premedication consisting on oral atropine (0.02 mg kg^{-1}) and midazolam (0.5 mg kg^{-1}) 30 min before induction of anaesthesia. Anaesthesia was induced with sevoflurane followed by a bolus of sufentanil ($1 \mu\text{g kg}^{-1}$) and pancuronium (0.2 mg kg^{-1}). Maintenance of anaesthesia consisted on a combined continuous infusion of midazolam ($0.2 \text{ mg kg}^{-1} \text{ h}^{-1}$) and sufentanil ($2 \mu\text{g kg}^{-1} \text{ h}^{-1}$). The lungs of the patients were mechanically ventilated with a mixture of oxygen and air. Mechanical ventilation was maintained until cardiopulmonary bypass (CPB) commenced. After heparin administration (3 mg kg^{-1}) and aorta cannulation, CPB was instituted with a Dideco hollow fibre oxygenator with a blood flow between 200 and $300 \text{ ml kg}^{-1} \text{ min}^{-1}$. The prime volume, between 325 and 750 ml according to the patient's weight, contained lactate-free Ringer's solution, albumin, mannitol, blood and heparin. Patients underwent modified ultra-filtration at the end of the surgical procedure. The effect of heparin was reversed with protamine sulphate at a ratio of 1 mg protamine for 1 mg heparin.

After induction of anaesthesia, 2 ml kg^{-1} of the sugar solution was administered through a nasogastric tube. Urine was subsequently completely collected through a urinary catheter for 3 h, the total volume was recorded and samples were stored at -20°C until analysis. This process was repeated 12 and 24 h after induction of anaesthesia.

The sugar solution, prepared by the hospital pharmacy, contained 3-O-methyl-D-glucose (2 g litre^{-1}), D-xylose (5 g litre^{-1}), L-rhamnose (10 g litre^{-1}) and lactulose (50 g litre^{-1}). The osmolarity of the solution is approximately 240 mOsm l^{-1} .

Sugar concentrations in urine were determined by gas chromatography following a slight modification⁸ of the procedure described by Jansen and colleagues.⁹ Briefly, to an aliquot of urine corresponding to $0.5 \mu\text{mol}$ of creatinine $30 \mu\text{g}$ of ribitol and $10 \mu\text{g}$ of trehalose (Sigma-Aldrich, St. Louis, USA) were added as internal standards (ribitol for the determination of 3-O-methyl-D-glucose, D-xylose and L-rhamnose and trehalose for lactulose) for the determination of 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose.

The sample was dried, derivatized with 300µl Tri-Sil TBT (Pierce, Rockford, USA) at 100° C and partly hydrolyzed with water. Subsequently the intact sugar trimethylsilyl (TMS) derivatives were extracted with hexane and after concentrating, gas chromatographic analysis was performed on a 30 m capillary fused silica HP-1 column (Agilent, Palo Alto, USA) using split injection. Quantification was performed after the construction of standard addition calibration curves. The type of vasoactive drugs and their amount were recorded after admission to the intensive care unit and 24 h later. To quantify inotropic support, inotrope scores were calculated as the sum of all inotrope doses correcting for potency (dopamine, dobutamine =1, milrinone = 15, epinephrine = 100).^{10,11} Fluid intake (including crystalloids, colloids and blood products), output (urine, blood and serous fluid loss) and balance were recorded over a 36 h period following admission to the intensive care unit.

Statistical analysis

Data were analysed with the statistical package SPSS 10. Data are presented as median (95% confidence intervals). The data were not normally distributed and we used Mann-Whitney U-test for unpaired data and the Friedman test for sequential data. Values of $P < 0.05$ were considered significant. Based on a previous study⁶ that found a mean (SD) L/R ratio of 0.047 (0.018), a prospective analysis showed that we needed a sample size of 34 to detect a difference in the L/R ratio of 0.02, with $\alpha = 0.05$ and a power of 80%.

	No CPB	CPB	P value
Number of patients	17	17	
Age (months)	2 (0.2-24)	5 (2-47)	0.17
Sex (M/F)	8/9	6/11	0.72
Weight (kg)	4.8 (2.5-15)	6 (4-14)	0.24
Surgery time (min)	83 (45-160)	73 (176-360)	0.01
Bypass time (min)	0	105 (73-202)	
Aortic clamp time (min)	0 (0-21)	73 (0-150)	
Ventilator hours	24 (6-144)	48 (24-168)	0.11

Table 1: Patient characteristics. Values expressed as median (95% confidence intervals).

Results

Table 1 shows patients characteristics. The groups were comparable with respect to age, sex and weight. The type of operations performed in each group is shown in table 2. Table 3 shows the L/R ratios and percentage recovery of the four sugars throughout the study period. Figure 1 is a graphic representation of the L/R changes in both groups. Patients undergoing repair of aortic coarctation showed the fastest improvement in L/R ratios 0.52 (0.21-1.01) at T0, 0.09 (0.03-0.31) at T12 and 0.07 (0.04-0.35) at T24 ($P < 0.01$). Those patients receiving a Blalock-Taussig shunt or banding of the pulmonary artery had the following L/R ratios: 0.37 (0.06-1.81) at T0, 0.27 (0.12-0.85) at T12 and 0.14 (0-0.48) at T24 ($P < 0.04$). Inotropic scores (median 95% confidence intervals) on admission to the ICU 5 (0-59.7) were not significantly different from those at 24 h after admission 5 (0-54) in the CPB group. In the group without CPB inotropic scores were 0 (0-10) after admission and 0 (0-15) at 24 h.

No CPB		CPB	
Coarctation of the aorta	7	Aortic stenosis	1
Banding pulmonary artery	3	AVSD	2
Blalock-Taussig shunt	7	Glenn	2
		MVA	2
		TAPVC	2
		ToF	1
		VSD	7
Total	17		17

Table 2: Type of operations performed in each group. Atrioventricular septal defect (AVSD). Mitral valve anuloplasty (MVA). Total anomalous pulmonary venous connection (TAPVC). Tetralogy of Fallot (ToF). Ventricular septal defect (VSD).

Patients operated without CPB had a fluid intake of 79 ml kg⁻¹ (39-251) and output of 70 ml kg⁻¹ (22-176), with an overall fluid balance of 18 ml kg⁻¹ (-97 - 92). For those patients undergoing operations with CPB the fluid intake was 86 ml kg⁻¹ (41 - 147) and output 58 ml kg⁻¹ (23 - 110) with an overall balance of 31 ml kg⁻¹ (-41 - 121). Values between the two groups were not significantly different.

		T0	T12	T24
L/R	No CPB	0.39 (0.07-1.8)	0.22 (0.03-0.85)	0.11 (0-0.48)
	CPB	0.30 (0.02-2.6)	0.32 (0.07-6.9)	0.24 (0.05-3.2)*
Lactulose	No CPB	0.18 (0.02-0.73)	0.35 (0.01-1.2)	0.41 (0.2-0.92)†
	CPB	0.03 (0.01-0.3)*	0.29 (0.07-1.76)	0.82 (0.05-3.32) †
Rhamnose	No CPB	0.29 (0.04-1.56)	1.56 (0.12-11.1)	3.64 (1.2-17.6) †
	CPB	0.08 (0.03-1.14)*	1.17 (0.06-4.23)	3.8 (0.04-18.1) †
3OMG	No CPB	0.64 (0.11-9.21)	3.9 (0.11-25.34)	14.1 (2.2-55.3) †
	CPB	0.19 (0.04-1.88)*	1.31 (0.1-12.93)	7.4 (0.03-48.6)†
Xylose	No CPB	0.72 (0.17-2.89)	1.34 (0.27-14.81)	3.3 (0.92-38.31) †
	CPB	0.2 (0.04-1)*	0.73 (0.07-7.3)	2.1 (0.04-18.14) †

Table 3: Lactulose/rhamnose ratios (L/R) and percentage recovery for lactulose, rhamnose, 3-O-methyl-glucose (3OMG) and xylose without and with cardiopulmonary bypass (CPB). Values are expressed as median (95% confidence intervals). * Denotes statistical significance between groups. † Denotes statistical significance within groups.

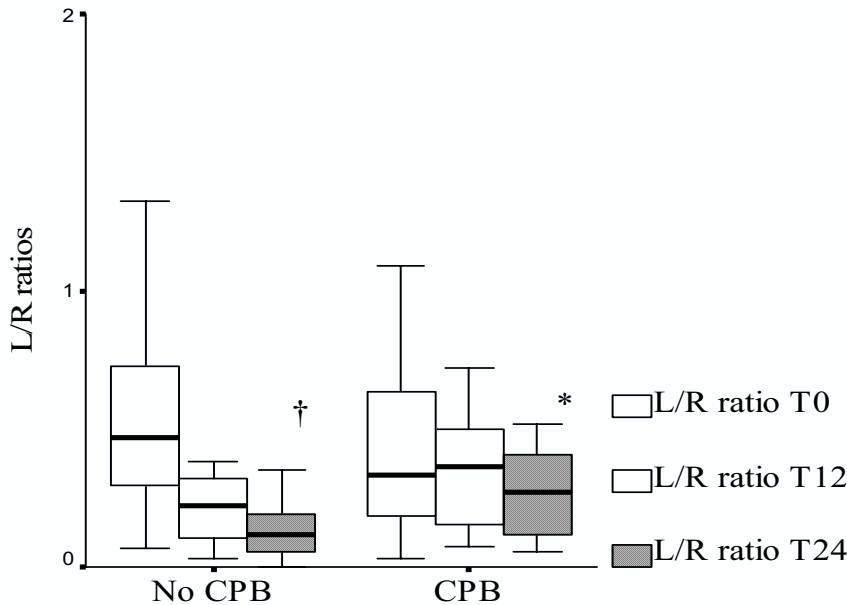


Fig 1: Changes in L/R ratios in both groups at induction of anaesthesia (T0), 12 hours (T12) and 24 hours (T24) after induction of anaesthesia. Values are expressed as median, 25th – 75th interquartile ranges (bars) and 2.5th and 97.5th percentile (error bars). * Denotes statistical significance between groups. † Denotes statistical significance within groups.

Discussion

To our knowledge this is the first report in the literature of changes in gut permeability in paediatric patients with congenital heart defects undergoing cardiac surgery. Our study shows that from the outset L/R ratios were well above the normal values expected in patients of similar age without cardiac defects.

Only patients undergoing repair of coarctation of the aorta had near normal L/R ratios 24 h after the surgical procedure. The DSPT has been used to assess intestinal function in healthy neonates, in whom the L/R ratios were around 0.05.⁵ Paediatric patients without intestinal pathology have a similar ratio; range 0.023 – 0.074 and mean (SD) 0.047 (0.018).⁶ Several studies have investigated the effect of cardiopulmonary bypass on intestinal permeability in the adult population.¹²⁻¹⁴ In all of them the investigators demonstrated an increase in gut permeability that reverted to normal during the postoperative period.

In animals, exposure to CPB induces a transient mesenteric endothelial dysfunction with an increased contractile response to an α 1-adrenergic agonist.¹⁵

Cyanotic patients may be at higher risk of developing intestinal mucosal ischaemia. This may also be true for patients with coarctation of the aorta because of a reduced blood flow through the descending aorta. Infants undergoing cardiac surgery often have chronic low arterial oxygen concentrations due to intra- or extra-cardiac shunting. Neonates with hypoplastic left heart syndrome have at times preferential blood flow to the pulmonary circulation at the expense of the systemic circulation. Those patients operated without CPB had either a total correction of their disease (coarctation of the aorta) or an improvement in the systemic oxygen delivery via a Blalock-Taussig shunt or a pulmonary banding. It is therefore logical in these patients to expect an improvement in the L/R ratios and recovery of single markers.

The accuracy of the DSPT relies on the complete collection of urine samples during the study period. This is a limiting factor on the applicability of the test in non-cooperative patients without a urinary catheter. A high percentage of patients are discharged to the ward the day after surgery with the consequent removal of urinary catheters. For this reason we performed the test during the first 24 hours after the operation.

There has been criticism concerning the interpretation and significance of the DSPT in the literature.^{16,17} In an animal model it was shown that fluid loading increased the L/R ratios independent of changes in intestinal permeability. Rats received in an 8-hour period a fluid bolus equivalent to twice the daily fluid oral intake. Put into perspective, this means an infant of 10 kg would receive in an 8-hour period approximately 2 litres fluid intravenously. We carefully documented the fluid balance during the study period. On average patients received less than the daily maintenance fluid expected for their age.

When lactulose and rhamnose are combined in the test solution at a fixed concentration ratio, the effect of preabsorption factors (gastric emptying, dilution by secretions, intestinal transient time) and postabsorption factors (systemic distribution and renal clearance) will apply equally to both. Therefore the L/R ratio is only influenced by the difference in gut permeability for each molecule.¹⁸ Pre and postabsorption factors may influence single markers such as D-xylose and 3-O-methyl-D-glucose. D-xylose is absorbed through a passive carrier-mediated transport and 3-O-methyl-D-glucose through an active carrier-mediated transport. These two single markers provide information about the functional state of the intestinal mucosa while the L/R ratio is a reflection of the mucosal integrity at the morphological level. Results of recovery of single markers should be always interpreted in conjunction with L/R ratios.

From the outset patients operated without CPB had better percentage recovery for both single markers although the differences were significant after induction of anaesthesia only. However the L/R ratio is worse in this group than in the one requiring CPB in the same period. It is difficult to draw conclusions at this point in time. Nevertheless the trend is towards a faster improvement of single markers in the group without CPB keeping in mind, that 24 h after the operation the values are far from normal.

We assume that the deterioration or lack of improvement in the L/R ratios 12 h after induction of anaesthesia must be related to the use of CPB. Interestingly CPB did not prevent a progressive and significant increase in the percentage recovery of D-xylose and 3-O-methyl-D-glucose. It appears that CPB damages temporarily the intestinal mucosa at the morphological level. At the functional level though, CPB may only delay a process that begins with the surgical correction and consequent improvement in arterial oxygen supply and/or systemic perfusion.

Inotropic support was necessary more often in the group undergoing CPB. It may be argued that this factor alone can explain the differences in L/R ratios between the two groups. However, inotropic support in the CPB group did not change between admission to intensive care and twenty-four hours later, while the L/R ratios did improve, although not significantly.

Used on a regular basis the DSPT may help us to identify the optimal time to reintroduce enteral feeding in the postoperative period. This indeed deserves further research. Novel surgical techniques or drugs aimed at protecting the splanchnic circulation can be tested against the DSPT as an end point. We are at present studying how the use of dexamethasone before CPB starts affects gut permeability in the postoperative period during paediatric cardiac surgery.

In conclusion, we have shown that paediatric patients undergoing cardiac surgery with CPB have median L/R ratios up to seven times the normal values expected in healthy children. Patients undergoing surgical repair of aortic coarctation show a swift return to near normal values twenty-four hours after the operation. From our results we can also conclude that the intestinal barrier is affected both at the morphological and functional levels. Measurement of mesenteric blood and oxygen supply in the paediatric population remains a difficult task. Only by using non-invasive, non-toxic surrogate markers of intestinal perfusion can we investigate and most importantly try to improve oxygen supply to the gut in the perioperative period.

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