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Microvascular endothelial dysfunction during cardiopulmonary bypass in surgery for correction of cyanotic and acyanotic congenital heart disease

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ABSTRACT

Objective: To evaluate endothelium-dependent microvascular reactivity during cardiopulmonary bypass (CPB) in surgery for the correction of cyanotic and acyanotic congenital heart disease (CHD) in children and infants using laser Doppler perfusion monitoring (LDPM).

Methods: This cross-sectional observational study included one hundred consecutive acyanotic (AC, n = 61) and cyanotic (C, n = 39) pediatric patients scheduled for cardiac surgery for correction of CHD. The endothelium-dependent microvascular vasodilation of the skin of the forehead was evaluated using a single-point LDPM coupled with local thermal hyperemia (LTH).

Results: LTH induced significant increases in microvascular conductance both in AC and C patients after the induction of anesthesia, during CPB and after weaning from CPB. Nevertheless, the vasodilation induced by LTH was significantly blunted during CPB when compared with values obtained after the induction of anesthesia both in AC and C patients. Microvascular endothelial reactivity nearly normalized after the discontinuation of CPB.

Conclusion: The evaluation of systemic microvascular reactivity on the forehead skin of infants and children using LDPM appears to be a valuable tool for optimizing microvascular perfusion during CPB in pediatric cardiac surgery.

1. Introduction

The use of cardiopulmonary bypass (CPB) during cardiac surgery is known to be associated with a wide range of alterations in microcirculatory perfusion and tissue oxygenation that may result in organ dysfunction (Koning et al., 2014). Even when the systemic hemodynamic parameters during CPB are maintained within the normal range, the microcirculation may be damaged and remain dysfunctional (Kara et al., 2016; Koning et al., 2014). Moreover, cardiac surgery for the correction of congenital heart disease (CHD) in infants and children leads to even more susceptibility to alterations in the microcirculatory perfusion because of specific anatomical and functional characteristics of these patients (Cordina and Celermajer, 2010). It is also noteworthy that endothelial dysfunction appears to result from chronic cyanosis in patients with CHD (Cordina and Celermajer, 2010).

Thus, monitoring the microcirculation during CPB may help anesthesiologists make interventions aimed at improving tissue blood flow and perfusion. In this context, with the introduction of noninvasive monitoring techniques for assessing microvascular flow and function, including laser-based methods, more insight has been gained into microvascular changes during and after cardiac surgery.

Laser Doppler perfusion monitoring (LDPM) coupled with physiologic or pharmacologic stimuli is a non-invasive methodology used in the clinical evaluation of systemic and local microvascular endothelial function (Cracowski and Roustit, 2016; Kaiser et al., 2013). Although LDPM does not provide an absolute measure of blood flow in volume per time, the existence of a linear relationship between the laser Doppler signal and the skin microvascular blood flow has already been demonstrated (Ahn et al., 1987). For that reason, LDPM is commonly coupled with reactivity tests, such as thermal or pharmacological provocation (Roustit and Cracowski, 2013). Local heating of the skin induces a microvascular response known as local thermal hyperemia (LTH), which is useful in the evaluation of systemic microvascular endothelial function (Cracowski and Roustit, 2016; Kaiser et al., 2013; Minson, 2010). This methodology is currently used in the clinical setting to evaluate endothelial-dependent microvascular reactivity in several clinical situations (Khan et al., 2000; Minson et al., 2002; Stewart et al., 2004). LTH elicits activation of TRPV1 (vanilloid receptor-1) receptors on local sensory nerves. This receptor stimulation releases neurotransmitters including calcitonin gene related peptide (CGRP), substance P, and others. Acting on endothelial cells, these neurotransmitters stimulate endothelial nitric oxide synthase (NOS) to

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Table 1
Clinical characteristics of patients.

Parameters	Acyanotic n = 61 n (%)	Cyanotic n = 39 n (%)	P value
Gender	38 F (62%) 23 M (38%)	14 F (36%) 25 M (64%)	0.0137
Age (months)			
All patients	16 (8.5–60)	30 (13–60)	0.3142
1–6 months	11 (18%)	8 (20.5%)	
> 6–12 months	14 (23%)	0	
> 12–24 months	13 (21%)	7 (18%)	
> 24–48 months	4 (6.5%)	11 (28%)	
> 48–108 months	19 (31%)	13 (33.3%)	
Weight (Kg)			
All patients	8 (5.75–16.9)	11.9 ± 5.5	0.3701
< 8 Kg	31 (51%)	9 (23%)	
8–16 Kg	15 (24.5%)	20 (51.3)	
> 16 Kg	15 (24.5%)	10 (25.6%)	
Type of cardiopathy N (%)			
Tetralogy of Fallot	–	20 (51.2%)	
Total/partial A-V canal defect	17 (27.9%)	–	
TGA	–	5 (12.8%)	
VSD simple	15 (24.6%)	–	
Pulmonary atresia	–	3 (7.6%)	
ASD-*OS*	4 (6.5%)	–	
Tricuspid atresia	–	2 (5.1%)	
Residual VSD	2 (3.2%)	–	
DORV	–	2 (5.1%)	
ALCAPA	1 (1.6%)	–	
Ebstein anomaly	–	1 (2.5%)	
Truncus arteriosus	1 (1.6%)	–	
Aortic arch interruption	1 (1.6%)	–	
TAPVR (> 30 days)	1 (1.6%)	–	
Mixed lesions	19 (31%)	6 (15.4%)	
RACHS-1 score N (%)			
Risk category 1	4 (6.5%)	No patients	
Risk category 2	29 (47.5%)	24 (58.97%)	
Risk category 3	26 (42.63%)	6 (15.38%)	
Risk category 4	2 (3.27%)	9 (23.07%)	

Data are presented as the mean ± SD or as medians (25th–75th percentiles) for values that did not fit a Gaussian distribution (by the Shapiro-Wilk normality test). P values were estimated using the Mann-Whitney *U* test. Gender was evaluated using Fisher's exact test (chi square).
Abbreviations: VSD, ventricular septal defect; ASD OS, atrial septal defect ostium secundum; ALCAPA, anomalous left coronary artery arising from the pulmonary artery; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; DORV, double-outlet right ventricle; RACHS-1, risk assessment category according to consensus-based method for risk adjustment for surgery for congenital heart disease (Jenkins et al., 2002)

produce nitric oxide. TRPV1 may be activated by a wide variety of exogenous and endogenous physical and chemical stimuli, including temperatures > 40 °C (Everaerts et al., 2011).

We have previously shown that the microcirculatory bed of the skin of the forehead is a suitable model for the study of microvascular reactivity and tissue perfusion in cardiovascular surgical procedures using CPB in adult patients (Salgado et al., 2014). Nevertheless, LDPM coupled with LTH has never been used to evaluate microvascular reactivity during pediatric cardiac surgery in infants and children for congenital heart defects under cardiopulmonary bypass.

Thus, the present study aimed to evaluate the microvascular reactivity during CPB in surgery for the correction of cyanotic and acyanotic CHD in children and infants using LDPM.

2. Research design and methods

This cross-sectional observational study included one hundred consecutive acyanotic (AC, n = 61) and cyanotic (C, n = 39) pediatric patients scheduled for cardiac surgery for correction of CHD at the National Institute of Cardiology, Ministry of Health, Rio de Janeiro, Brazil. The clinical characteristics are described in Table 1. The study was approved by the Institutional Review Board of the institution, and the parents or tutors of the participants were informed of the nature of the study protocol and provided written informed consent (protocol # CAAE 19201413.6.0000.5272); the study was registered and made public at ClinicalTrials.gov (NCT03144258). All anesthetic procedures were performed following a standardized protocol, under mild to moderate hypothermia [median temperature of 33 °C (32–34 °C)] on a non-pulsatile roller pump CPB [median pump flow rates of 125 (100–150) ml/kg/min]. The mean arterial pressure was maintained between 45 and 60 mmHg during CPB.

The endothelium-dependent vasodilation of the skin microcirculation was evaluated using a single-point LDPM system (Periflux 5001, Perimed, Järfälla, Sweden) for noninvasive and continuous measurements of systemic microvascular perfusion changes (in arbitrary perfusion units [APU] = 10 mV), as previously described (Cracowski and Roustit, 2016; Kaiser et al., 2013; Salgado et al., 2014). After measuring the resting microvascular flow using a heating laser probe (PF 457, Perimed) that was positioned on the skin of the forehead at the beginning of the anesthetic procedure, we investigated the maximal microvascular vasodilatation using prolonged (20 min) local heating of the laser probe to 42 °C (local thermal hyperemia, LTH), as previously described (Salgado et al., 2014). The maximal vasodilation was expressed as cutaneous vascular conductance (CVC) and was calculated as the ratio of the microvascular flow, in APU, to the mean arterial pressure (APU/mmHg). Three different instances of LTH were recorded: after the induction of general anesthesia (post-induction, PI), after 20 min from the beginning of CPB (CPB), and 20 min after the discontinuation of CPB (final, F).

The results are presented as the mean ± SD or as the median (interquartile range). The Shapiro-Wilk analysis was used to test the normality of the data. CVC values were analyzed using one-way ANOVA for repeated measures followed by Dunn's multiple comparisons test using GraphPad Prism 7.0 software (GraphPad Software INC., San Diego, California, USA). A P-value < 0.05 defined statistical significance.

3. Results

The median baseline microvascular flow did not differ between AC and C patients after the induction of anesthesia [0.48 (0.36–0.70) APU/mmHg and 0.49 (0.32–0.73) APU/mmHg, respectively; P > 0.05], during CPB [0.52 (0.33–0.80) APU/mmHg and 0.40 (0.26–0.56) APU/mmHg, respectively; P > 0.05] or after the discontinuation of CPB [0.75 (0.53–1.17) APU/mmHg and 0.60 (0.40–0.79) APU/mmHg, respectively; P > 0.05]. LTH induced significant increases in CVC both in AC and C patients at all time points (Fig. 1). Nevertheless, the vasodilation induced by LTH was significantly blunted during CPB when compared with values obtained after the induction of anesthesia both in AC and C patients (Fig. 1). In AC patients, the maximum increases in CVC induced by LTH after the induction of anesthesia [313% (171–604%)] were markedly reduced to 74% (9–156%) (P < 0.0001) during CPB. After the discontinuation of CPB, the response was partially reestablished [123% (34–227%)] but was still lower than the initial values (P < 0.0001). In C patients, the maximum increases in CVC induced by LTH after the induction of anesthesia [197% (86–485%)] were also reduced [120% (43–183%); P = 0.0037] during CPB. After the discontinuation of CPB, the response was partially reestablished [163% (62–310%)] but was still lower than the initial values (P = 0.0372). Finally, in AC patients, the baseline values of CVC after the discontinuation of CPB [0.75 (0.53–1.17) APU/mmHg] were higher than the values observed after the induction of anesthesia [0.49 (0.36–0.70) APU/mmHg; P = 0.0016] or during CPB [0.52 (0.33–0.80) APU/mmHg; P = 0.0013].