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Veno-arterial CO_2 difference and cardiac index in children after cardiac surgery

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Abstract

Veno-arterial CO_2 difference has been considered as a marker of low cardiac output. This study aimed to evaluate the correlation between veno-arterial CO_2 difference and cardiac index estimated by MostCare^{TM} in children after cardiac surgery and its association with other indirect perfusion parameters and the complex clinical course (vasoactive inotropic score above 15 or length of stay above 5 days).

Data from 40 patients and 127 arterial and venous CO_2 measurements for gap calculation taken 0–5 days postoperatively were available. The median (range) veno-arterial CO_2 difference value was 9 (1–25 mmHg). The correlation between veno-arterial CO_2 difference and cardiac index was not significant (r: −0.16, $p = 0.08$). However, there was a significant correlation between veno-arterial CO_2 difference and vasoactive inotropic score (r: 0.21, $p = 0.02$), systolic arterial pressure (r: −0.43, $p = 0.0001$), dP/dt_{MAX} (r: 0.26, $p = 0.004$), and arterio-venous O_2 difference (r: 0.63, $p = 0.0001$). Systolic arterial pressure (OR 0.95, 95% CI 0.90–0.99), dP/dt_{MAX} (OR 0.00, 95% CI 0.00–0.06), lactates (OR 1.87, 95% CI 1.21–3.31), and veno-arterial CO_2 difference (OR 1.13, 95% CI 1.01–1.35) showed a significant univariate association with the complex clinical course. In conclusion, veno-arterial CO_2 difference did not correlate with cardiac index estimated by MostCare^{TM} in our cohort of post-cardiosurgical children, but it identified patients with the complex clinical course, especially when combined with other direct and indirect variables of perfusion.

Assessment of cardiac function after paediatric cardiac surgery relies on echocardiography, on the combination of indirect signs of systemic perfusion (e.g. diuresis, lactates, acid-base balance, and superior caval vein oxygen saturation), and on standard (e.g. blood pressure) and advanced (e.g. stroke volume) haemodynamic parameters to provide an accurate picture of the haemodynamic state of the patient.[1] However, this evaluation can be extremely challenging since, first, echocardiography requires an expert operator, is not continuous, and in the first post-operative hours is not conducted as a routine exam; furthermore, indirect signs of systemic perfusion can be altered by many conditions (e.g. diuresis can be reduced due to acute kidney injury, regardless of cardiac function), and continuous advanced haemodynamic monitoring in children is not commonly applied due to the absence of a gold standard method.

Recently, the pressure recording analytical method, a non-calibrated pulse contour method, has been applied to children after cardiac surgery.[2–5] Pressure recording analytical method is powered with the MostCare^{TM} monitor (Vygon, Vytech, Padua, Italy). Pulse contour method application seems rational in children and neonates undergoing cardiac surgery since invasive blood pressure monitoring is part of the standard of care in all post-operative patients, and pressure recording analytical method estimates stroke volume from the analysis at a high sampling frequency (1000 Hz) of the arterial waveform.[6] Moreover, pressure recording analytical method does not require dedicated arterial catheters or calibration, and these characteristics make the application of this monitor particularly suitable in the paediatric setting. On the other hand, among all the signs of systemic perfusion routinely measured at bedside (i.e. blood pressure, heart rate, arterial blood gas analysis, lactates, superior caval vein oxygen saturation, and arterial pH), venous to arterial carbon dioxide difference is gaining attention as a promising marker of cardiac output adequacy.[7] Venous to arterial carbon dioxide difference represents the capability of venous blood flow (which equals cardiac output) to drag venous CO_2 from the peripheral tissues to the right atrium.[8] Essentially, the relationship between venous to arterial carbon dioxide difference and cardiac output reveals that when cardiac output is low, CO_2 stagnates at the venous side, venous CO_2 increases with respect to arterial CO_2, and, ultimately, the CO_2 gap (venous to arterial carbon dioxide difference) increases. Theoretically, for a given level of CO_2 production, a decrease in cardiac output results in an increased venous to arterial carbon dioxide difference and vice versa.[7,8] Differently, respiratory failure, hypoxia, and microcirculatory injury with impairment of oxygen extraction may affect parameters such as superior caval

vein oxygen saturation and arterial-venous oxygen difference, because oxygen delivery may be compromised even with normal cardiac output.[7,8]

This study aimed to evaluate the correlation between venous to arterial carbon dioxide difference and cardiac index estimated by MostCare™ in neonates and children after cardiac surgery, upon admission to the paediatric cardiac intensive care unit and in the following days, as well as to assess venous to arterial carbon dioxide difference in relation to other systemic perfusion parameters. Finally, we evaluated whether venous to arterial carbon dioxide difference and other direct and indirect perfusion signs at paediatric cardiac intensive care unit admission were predictive of complex clinical course in our patients.

Materials and methods

We conducted a retrospective study collecting data from all patients younger than 18 years of age with biventricular congenital heart diseases who underwent elective cardiac surgery, with cardiopulmonary bypass, between June 2019 and January 2020. Inclusion criteria were also the presence of a superior caval vein central venous catheter, the availability of at least one pair of simultaneous (within 30 minutes) withdrawals for arterial and venous blood gas analyses after paediatric cardiac intensive care unit admission, sedation, controlled mechanical ventilation, and Most-Care™ monitoring data. Exclusion criteria were gestational age <37 weeks, intracardiac or extracardiac shunts, haemodynamic instability (i.e. bleeding with transfusion of more than 20 ml/kg of packed red blood cells and an increase of adrenaline and/or vasopressin of more than 25% of admission dose in the first 2 hours), post-operative pulmonary damage (i.e. PaO_2/FIO_2 ratio < 100), and application of extracorporeal membrane oxygenation at any time in the post-operative phase. Standard continuous post-operative monitoring included electrocardiogram, invasive (systolic, diastolic, mean) arterial blood pressure, peripheral oxygen saturation, rectal and peripheral temperature, cerebral near infrared spectroscopy (all recorded in the electronic medical chart every hour and retrieved at the same time point of all blood gas analyses pairs), arterial blood gas analyses, sampled every 2 hours during the first post-operative day and about every 4 hours thereafter, and venous blood gas analyses, routinely sampled twice a day, unless further requests were made. In our unit, MostCare™ is applied at the discretion of attending physician, typically in post-operative patients for the first 24–48 hours, with particular attention to those who are expected to require mechanical ventilation for more than 24 hours. When applied, MostCare™ parameters (i.e. cardiac index estimated by MostCare™, systemic vascular resistances indexed, and dP/dt_{MAX}) are recorded every hour. dP/dT_{MAX} represents the measurement (not an estimation) of maximal pressure-to-time ratio or maximal slope of systolic upstroke. Previous studies have found dP/dt_{MAX} to be associated with heart contractility[9] and ventriculo-arterial coupling.[10] Arterial waveform is always carefully checked and MostCare™ is not applied in the case of an overdamped or underdamped signal that cannot be adjusted or when dicrotic notch is not correctly detected. For the purposes of this analysis, we retrieved the following blood gas analyses data: arterial and venous CO_2, arterial and venous oxygen saturation, arterial and venous pH, and arterial lactates. The following data were also collected: age and weight, cardiac diagnoses and surgical procedures, cardiopulmonary bypass duration, vasopressor doses (retrieved at the same time point of all blood gas analyses pairs) in order to calculate vasoactive inotropic score,[11] and length of paediatric cardiac intensive care unit stay.

We defined the complex clinical course as the requirement for a vasoactive inotropic score above 15 at any time during paediatric cardiac intensive care unit admission or a paediatric cardiac intensive care unit length of stay above the median value of 5 days.

The primary objective was to assess the correlation between venous to arterial carbon dioxide difference and cardiac index estimated by MostCare™ recorded at the same time point (with a tolerance window of ±30 minutes). The secondary objectives were to analyse the association of venous to arterial carbon dioxide difference with other perfusion markers: superior caval vein oxygen saturation, arterio-venous oxygen gap, lactates, cerebral near infrared spectroscopy, vasoactive inotropic score, systolic arterial pressure, diastolic arterial pressure, heart rate, peripheral temperature, systemic vascular resistances indexed, dP/dt_{MAX}, arterial pH, and venous pH. The behaviour over time of the main perfusion parameters (venous to arterial carbon dioxide difference, arterio-venous oxygen gap) was analysed. Finally, we evaluated whether direct and indirect perfusion signs recorded at paediatric cardiac intensive care unit admission were predictive of complex clinical course in our patients.

The institutional review board approved the protocol and waived the need for informed consent because of the retrospective design of the study.

Statistical analysis

Spearman's correlation and logistic regression were used to analyse the univariate associations when variables were continuous or dichotomous, respectively. Mixed effect analysis was utilised to assess the behaviour of repeated measures over time, with a post-test assessment for trend. Multivariable logistic regression was utilised to assess which variable (reporting OR and 95% CI) was associated with the achieved definition of the complex clinical course. An area under the receiver operator characteristic curve of this model was calculated to explore its performance in predicting the complex clinical course. All data are presented as median (range). A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed with the GraphPad Prism 8.0 software package (GraphPad Software, San Diego, CA).

Results

The flow chart of data collection is depicted in Figure 1. Analysed samples and all the collected clinical variables were retrieved between 0 and 5 days postoperatively. Ultimately, 127 venous to arterial carbon dioxide difference/cardiac index pairs were retrieved. Demographic data and baseline characteristics, including diagnoses, median (range) values of analysed parameters, and outcomes are reported in Table 1. All enrolled patients survived to paediatric cardiac intensive care unit discharge. The median venous to arterial carbon dioxide difference value was 9 and ranged from 1 to 25 mmHg. The correlation of venous to arterial carbon dioxide difference with cardiac index estimated by MostCare™ was not significant (r: −0.16, p = 0.08). It was generally weak with other clinical variables (Table 2) and significant, among other variables, with vasoactive inotropic score (r: 0.21, p = 0.02), systolic arterial pressure (r: −0.43, p = 0.0001), dP/dt_{MAX} (r: 0.26, p = 0.004), and arterio-venous oxygen gap (r: 0.63, p = 0.0001). Cardiac index estimated by MostCare™ showed additional significant correlations with lactates (r: −0.29, p = 0.0009) and systemic vascular resistances indexed (r: −0.59, p < 0.0001) (Table 2).

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Table 1. Demographic data, outcome, diagnosis, and perfusion variables. Data are expressed as absolute numbers or as median (range)

Demographic data and prognosis	
Patients #	40
Age (days)	215 (3–5600)
Weight (kg)	6 (2.3–47)
Neonates (Y/N)	11/29
CPB (minute)	148 (52–332)
VIS	12.5 (1–28)
PCICU LOS (days)	5 (1–44)
Poor outcome (Y/N)	24/16
Diagnoses	
o 2 Ventricular septal + atrial septal defect o Atrial septal defect + partial anomalous venous return o 2 Atrial septal defect + pulmonary stenosis o 2 Ventricular septal defect + pulmonary atresia o Ventricular septal defect + pulmonary atresia + MAPCAs o 8 Ventricular septal defect o 3 Tetralogy of Fallot o 3 Heart transplantation o 6 Transposition of the great arteries o Transposition of the great arteries + ventricular septal defect o Aortic valve insufficiency o Truncus arteriosus o 3 Mitral valve insufficiency o Aortic arch interruption + ventricular septal defect o 2 Aortic arch hypoplasia o 2 Pulmonary arteries stenosis o Total anomalous venous return	
Perfusion variables (all measurements)	
SAP/DAP (mmHg)	83 (55–127)/49 (27–76)
HR (bpm)	141 (62–183)
Central T°	36.7 (35–38.4)
Peripheral T°	34 (33–37)
CI (L/minute/m2)	2.4 (1.5–4.6)
SVRI (dyne*sec*m^2/cm^5)	1640 (1041–2975)
dP/dt_{MAX} (mmHg/ms)	0.89 (0.40–1.62)
Arterial/venous pH	7.47 (7.26–7.59)/7.40 (7.22–7.48)
$SaO_2/ScvO_2$ %	99.4 (93–100)/73.8 (46–89)
VA-CO_2 (mmHg)	9 (1–25)
AV-O_2 (mmHg)	25 (6–53)
cNIRS %	68 (42–86)
Lactates (mmol/L)	2.4 (0.6–10.6)

AV-O_2 = arterio-venous oxygen difference; CI = cardiac index; Cnirs = cerebral near infrared spectroscopy; CPB = cardiopulmonary bypass; HR = heart rate; PCICU LOS = paediatric cardiac intensive care unit length of stay; $SaO_2/ScvO_2$ = arterial/venous oxygen saturation; SAP/DAP = systolic/diastolic arterial pressure; SVRI = systemic vascular resistances indexed; VIS = vasoactive inotropic score; VA-CO_2 = veno-arterial CO_2 difference

The levels of venous to arterial carbon dioxide difference showed a significant decreasing slope over time (−0.9, p = 0.01). Differently, arterio-venous oxygen gap slope was not significant (−0.2, p = 0.73) (Fig 2). Systolic arterial pressure (OR 0.95, 95% CI 0.90–0.99), dP/dt_{MAX} (OR 0.00, 95% CI 0.00–0.06), lactates (OR 1.87, 95% CI 1.21–3.31), and venous to arterial carbon dioxide difference (OR 1.13, 95% CI 1.01–1.35) at paediatric cardiac intensive care unit admission showed a significant univariate association with the composite complex clinical course. None of these variables remained independently associated when multivariate logistic regression was built, even though this model produced an area under the receiver operator characteristic curve of 0.89 (p < 0.0001) (Fig 3).

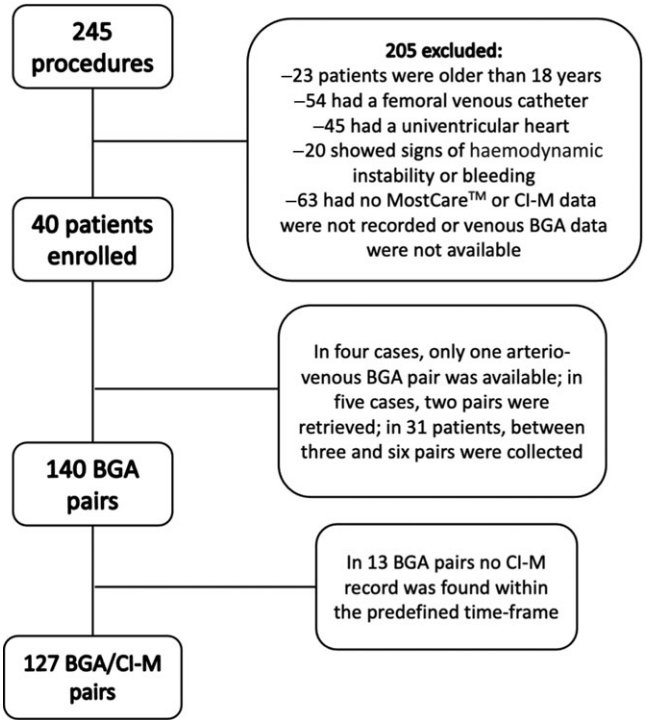

Figure 1. Flow chart of data collection. BGA = blood gas analysis; CI-M = cardiac index estimated by MostCare™.

Discussion

The key points of this study are 1) venous to arterial carbon dioxide difference did not correlate with cardiac index estimated by MostCare™. This could be due to the fact that it is a poor marker of organ perfusion. Alternatively, we can speculate that correlating blood gas analyses samples with a continuous monitoring (cardiac index with MostCare™) is wrong. In fact, it is possible that the changes in cardiac function are detected by these two variables at different time points. However, other perfusion variables appeared significantly associated with venous to arterial carbon dioxide difference, in particular arterial pressure and vasoactive inotropic score. It is possible that modifications of vasoactive drugs according to arterial pressure levels were effective to maintain a steady cardiac index, but some CO_2 "stagnation" was still present. Lactate levels, one of the most important indirect perfusion markers in these patients, did not show a direct correlation with venous to arterial carbon dioxide difference, similar to the results of Akamatsu[12] and Rhodes.[13] 2) On this line, based on trend analysis, we speculate that the progression of venous to arterial carbon dioxide difference from higher values to lower ones might express the "normalisation" of perfusion demands at the tissue level in the post cardiopulmonary bypass phase. Differently, arterio-venous oxygen gap did not appear to display a trend to normalisation. Venous oxygen saturation, as a surrogate variable of perfusion, may present significant pathophysiological limitations with respect to venous CO_2, as explained by Gavelli and coworkers.[8] 3) If one might imply

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Table 2. Correlation between veno-arterial difference of CO_2 ($VA\text{-}CO_2$)(left side of the table), cardiac index estimated by Mostcare™ (CI-M)(right side of the table) and other clinical variables

	$VA\text{-}CO_2$		CI-M	
	r	p value	r	p value
CPB duration	0.28	0.09	−0.16	0.33
age at surgery	−0.15	0.37	0.05	0.74
weight	−0.13	0.42	−0.01	0.97
length of stay	0.19	0.26	0.10	0.54
VIS	0.21	**0.02**	−0.23	**0.01**
SAP	−0.43	<**0.0001**	0.44	<**0.0001**
DAP	−0.38	<**0.0001**	0.28	**0.001**
HR	0.14	0.11	−0.33	**0.001**
Central T°	−0.08	0.38	0.07	0.42
Peripheral T°	−0.24	**0.01**	0.12	0.19
SVRI	−0.16	0.07	−0.59	<**0.0001**
Dp/Dt_{MAX}	−0.26	**0.001**	0.27	**0.001**
Lac	0.07	0.46	−0.29	**0.001**
HCO_3^-	−0.09	0.29	0.10	0.27
SaO_2	0.28	**0.001**	−0.09	0.32
$ScvO_2$	−0.61	<**0.0001**	0.08	0.40
Ph Ven	−0.21	**0.02**	0.05	0.57
pvO_2	−0.58	<**0.0001**	0.10	0.26
$pvCO_2$	0.46	<**0.0001**	0.04	0.65
$AV\text{-}O_2$	0.64	<**0.0001**	−0.08	0.35
cNIRS	−0.33	**0.02**	0.12	0.39
PIM3	0.09	0.57	0.00	0.98
SVI	−0.14	0.12	0.82	<**0.0001**
delta CO_2	–	–	−0.16	0.08
CI	−0.16	0.08	–	–

$AV\text{-}O_2$ = arterio-venous oxygen difference; cNIRS = cerebral near infrared spectroscopy; CPB = cardiopulmonary bypass; HCO_3^- = plasma bicarbonates; HR = heart rate; Lac = lactates; pH ven = venous pH; PIM3 = paediatric index of mortality 3; $pvCO_2$ = CO_2 venous partial pressure; pvO_2 = oxygen venous partial pressure; $SaO_2/ScvO_2$ = arterial/venous oxygen saturation; SAP/DAP = systolic/diastolic arterial pressure; SVI = stroke volume index; SVRI = systemic vascular resistances indexed; VIS = vasoactive inotropic score

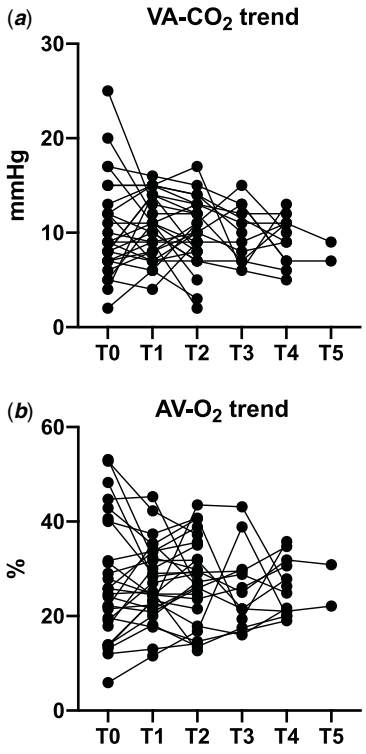

Figure 2. Representation of analysed data over time. (***a***) veno-arterial CO_2 difference ($VA\text{-}CO_2$): significant trend slope; (***b***) arterio-venous oxygen gap ($AV\text{-}O_2$): not significant trend slope.

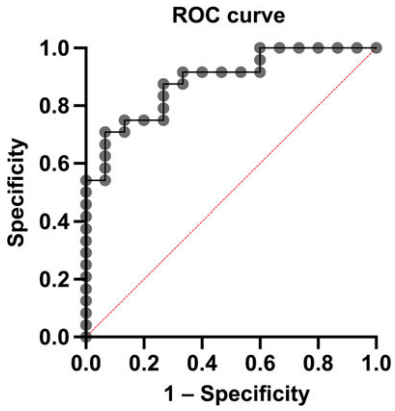

Figure 3. ROC graph of the prediction model: Systolic arterial pressure (OR 0.95, 95% CI 0.90–0.99), dP/dt_{MAX} (OR 0.00, 95% CI 0.00–0.06), lactates (OR 1.87, 95% CI 1.21–3.31) and $VA\text{-}CO_2$ (OR 1.13, 95% CI 1.01–1.35) at paediatric cardiac intensive care unit admission were able to predict a prolonged paediatric cardiac intensive care unit stay or a vasoactive inotropic score >15 at any time.

that cardiac index estimated by MostCare™ was not accurately estimated with the pressure recording analytical method, still dP/dT_{MAX} could be considered an interesting parameter.[10] dP/dT_{MAX} was associated with venous to arterial carbon dioxide difference and with the complex clinical course. Again, the association between cardiovascular function, vasoactive drugs administration, and systemic perfusion warrants further evaluation. 4) According to the results of this study, it would be difficult to propose cut off values for venous to arterial carbon dioxide difference; however, the median value of venous to arterial carbon dioxide difference of 9 in our patients could be used as a reference value between those with low and high venous to arterial carbon dioxide difference. It is also possible that the trend should be followed in these patients instead of an absolute value, with a reduction being a marker of an improving perfusion. 5) In particular, our data show a complex interaction between different variables. Possibly, the application of multimodal monitoring that included both direct and indirect perfusion parameters might improve prediction and management of low cardiac output in heart surgery children, as shown by the model's promising area under the receiver operator characteristic curve. Our results, following previous controversial findings, may warrant further research on venous to arterial carbon dioxide difference variations over time and their relationship with other variables.

Limitations

This study enrolled a relatively small sample of patients; it is possible that correlations might have been stronger with a higher

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number of patients. However, our aim was to include only patients with corrected biventricular anatomies in order to exclude the confounders of intra- or extracardiac shunting and to analyse the most homogeneous population possible. MostCare™ is not a validated monitoring system in children and our primary objective may have been biased by an imprecise estimation of cardiac index. Furthermore, even if we routinely carefully check arterial waveform before applying this monitor, a formal control (i.e. with fast flush Gardner's test[14]) was not performed and this is a major risk of inaccuracy when a pulse contour method is applied. However, there is currently no universally recommended monitor to measure cardiac index in children[15] and to apply as a gold standard. In our centre, MostCare™ has been repeatedly studied[2–5,10] and we have found cardiac index estimated by MostCare™ to be reliable in paediatric cardiac patients after surgery.[2] Finally, to add consistency, we analysed cardiac index estimated by MostCare™ associations with indirect perfusion parameters and found that it was also associated with lactate levels that are considered among the commonest variable utilised to estimate adequate oxygen delivery and patients outcome.[15,16] Our study was retrospective, and the enrolled patients could not be controlled for diagnosis and severity of disease or incidence of low cardiac output. It has to be acknowledged that about 10% of recorded cardiac indices estimated by MostCare™ for this study were below 2 L/minute/m,[2] which is the threshold for diagnosis of low cardiac output syndrome in our unit. Such percentage of low cardiac index estimated by MostCare™ should be adequate to assess correlation with venous to arterial carbon dioxide difference in an exploratory retrospective study. Finally, it might be interesting to include exclusively unstable patients, who were excluded in our study.

In conclusion, venous to arterial carbon dioxide difference did not correlate with cardiac index estimated by MostCare™ in our cohort of post-cardiosurgical children. Venous to arterial carbon dioxide difference showed a trend towards an improvement over time, and higher values were associated with the complex clinical course. Further evaluation of the exact clinical value of this parameter and its interaction with direct and indirect perfusion variables, especially over time, should be studied.

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Conflict of interests. None

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Comitato Etico Bambino Gesù).

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