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PRESENTACIÓN DE CASOS

Goal directed perfusion: a systematic review

Perfusión dirigida por metas: revisión sistemática

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ABSTRACT

The concept of goal-directed perfusion consists in the use of variables derived from oxygen and carbon dioxide to optimize extracorporeal circulation, avoiding anaerobic metabolism and consequently the aggression to target organs. The objective of the present paper is to evaluate the impact of the use of goal-directed perfusion in the management of perfusion and in the postoperative period. For this, a systematic review of studies published over the past 10 years in the PubMed/MEDLINE database was performed using the descriptor "goal-directed perfusion". After the successive stages of analysis, 15 articles fit the objective of this study. Two of the articles included are randomized studies, the others correspond to observational studies, 10 were retrospective and 3 prospective. In total, the evaluated studies included 40 904 patients. Of the included articles, 11 had as main objective to evaluate the relationship between goal-directed perfusion strategies and the incidence of acute kidney injury, 3 evaluated the relationship of goal-directed perfusion with some predictive marker of neurological injury and 1 only evaluated the association of goal-directed perfusion with increased serum lactate. The qualitative analysis of the articles, included in this review, showed that the goal-directed perfusion technique can be considered a promising strategy to minimize organ dysfunction, especially acute kidney injury. However, it is important that the technique be better standardized, allowing greater reproducibility of such results in future studies.

Keywords: **ECMO, transporte aeromédico, insuficiencia cardiaca, trasplante cardíaco.**

SUMMARY

El concepto de perfusión dirigida por metas consiste en utilizar las variables derivadas del oxígeno y del dióxido de carbono para optimizar la circulación extracorpórea, y así evitar el metabolismo anaeróbico y consecuentemente el daño de los órganos. El objetivo del presente trabajo es evaluar el impacto de la utilización de estrategias de perfusión dirigidas por metas en el manejo de la perfusión y el postoperatorio. Se realizó una revisión sistemática de la literatura publicada en la base de datos de PubMed/MEDLINE en los últimos 10 años. Se utilizó el término de búsqueda: "goal-directed perfusion". Tras sucesivas etapas de análisis, se encontraron 15 artículos que se encuadran con el objetivo de nuestro estudio. Dos de los 15 artículos incluidos, son estudios aleatorizados y el resto corresponden a estudios observacionales, 10 retrospectivos y 3 prospectivos. En total, fueron 40 904 pacientes evaluados en esos estudios. Entre los artículos incluidos, 11 tenían como objetivo principal evaluar la asociación entre la perfusión dirigida por metas y la incidencia de insuficiencia renal aguda, 3 evaluaron la relación de la perfusión dirigida por metas con algun marcador predictivo de lesión neurológica y 1 evaluó la asociación de la perfusión dirigida por metas con el aumento del lactato sérico. El análisis cualitativo de los artículos incluidos en esta revisión demuestra que la perfusión dirigida por metas puede ser considerada una estrategia promisoria para minimizar disfunciones orgánicas, principalmente de la insuficiencia renal aguda. Entre tanto, es importante que esta técnica sea mejor estandarizada, lo que permitirá una mayor reproductibilidad de los resultados de estudios futuros.

Palabras clave: **Perfusión dirigida por metas. Circulación extracorpórea. Aporte de oxígeno**

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INTRODUCTION

Hemodynamic management of the patient in the perioperative period is considered one of the pillars of intensive therapy.[1] Oxygen supply to the tissues depends both on the respiratory system—responsible for oxygen (O_2) extraction and the elimination of carbon dioxide (CO_2), and the cardiovascular system, responsible for O_2 transport from the lungs to the tissues.[2]

The hemodynamic objective of macrocirculation is to generate oxygenated blood flow, that is, oxygen delivery (DO_2). DO_2 is defined as the amount of O_2 per unit of blood volume. Therefore, it depends on the arterial O_2 content (CaO_2) and cardiac output (CO). CaO_2., in turn, depends on hemoglobin (Hb) and arterial O_o saturation (SaO_2) while CO is influenced by the heart rate (HR) and systolic volume (SV).[3]

DO_2 is considered appropriate when it is equivalent to the metabolic needs of O_2, that is, O_2 consumption (VO_2). Reduction of DO_2 can initially be compensated by an increased O_2 extraction rate (ERO_2) to maintain aerobic metabolism. Still, when there is excessive decrease of DO_2, the increase of ERO_2 cannot do the compensation anymore, thus limiting aerobic cellular metabolism and resulting in cellular hypoxia, ischemia, production of lactate, and cellular death. When that point is reached, it is considered critical DO_2.[3]

Unbalance between the DO_2/VO_2 ratio can be identified through organ dysfunction, elevated plasma lactate levels or signs of excessive extraction of O_2 (low levels of venous O_2 saturation, SvO_2). With new concepts on cardiovascular pathophysiology, and consequently, new monitoring devices being incorporated to the routine clinical practice, demand that each situation should be managed based on the specific characteristics of each patient has grown. That is the origin of the term "goal-directed therapy" (GDT) in this context.

GDT consists of rigorously monitoring and actively managing the patient during intensive care periods (peri-, intra- and postoperative periods) to achieve better clinical outcomes.4 The main objective of GDT is to restore proper tissue perfusion by managing several parameters, which including the cardiac index (CI), DO_2, mean arterial pressure (MAP), and fluid therapy.[5]

In heart surgery, several studies have been published using the GDT principle to optimize perfusion parameters and improve clinical outcomes.[6-9] Over the oast few years, three meta-analyses on this topic have concluded that application of GDT reduces postoperative complications, morbidity, and the length of stay (LoS) in patients treated with heart surgery.[10-12]

At the same time, these studies used management based on GDT in pre- and postoperative times of ECC and excluded GDP management during the interval in which the patient is on ECC (extracorporeal circulation).

Therefore, although the concept of GDT was first described back in 1988 and its promising results in the perioperative period are well established, it has been adopted recently for the management of ECC. In 2005, Ranucci et al. demonstrated the importance of adequate DO_2 during ECC to reduce risk of postoperative kidney failure.[13] Based on this work and others by the same group, in 2011, De Somer first coined the term "goal-directed perfusion" (GDP) to describe the adaptation of ECC management individually based on the patient's metabolic parameters (DO_2 and CO_2 output (VCO_2)).[14]

Since then, other authors have used the definition to refer to ECC optimization to prevent anaerobic metabolism by adding continuous monitoring, in real time, of microparameters derived from O_2, and CO_2 like DO_2, VO_2, VO_2, and ERO_2.[15,16]

In addition, the guidelines on the management of ECC in adult heart surgery published in 2019 by the European Association Cardiothoracic Surgery (EACTS), the European Association of Cardiothoracic Anesthesia (EACTA), and the European Board Cardiovascular Perfusion (EBCP), recommends that pump flow should be adapted during ECC based on oxygenation and metabolic parameters (SvO_2, ERO_2, VCO_2, and lactate).

Also, that flow should be adjusted based on CaO_2 to maintain a minimum threshold of DO_2 (Class IIa Recommendation, Evidence Level B).[17] The clinical guidelines published by the American Society of Extracorporeal Technology (AmSECT), and the Brazilian Society of Cardiovascular Surgery (SBCCV) in association with the Brazilian Society of Extracorporeal Circulation (SBCEC) also recommend using DO_2 as one of the parameters that should be considered to determine the proper blood flow.[18,19]

These publications show the importance this issue has gained over the past few years. Despite of that, a broad search using the keywords "goal-directed perfusion" in the Pubmed database found 37 results only. Of these, 10 are just letters to the editor or comments. The preliminary analysis of original articles has proven that there are some differences in the methodologies mainly regarding the formula used to calculate metabolic parameters, the values considered critical, and the variables used to evaluate the results.

Despite the fact that the guidelines recently published mentioned the importance of using GDP, no specific instructions have been provided regarding their application. In addition, traditionally, the main determining factors to define adequate pump flow are the perfusionist's experience, SvO_2 monitorization, body surface, and temperature.[20] However, pump flow defined based only on these parameters does not guarantee, necessarily, proper DO_2 to the tissues.[21]

To this date, no systematic review on the topic has been published. Therefore, studies are needed that can collect the information available on GDP to spread the topic in the clinical setting, and facilitate standardization of future studies.

Therefore, this study endpoint is to assess the impacts of using GDP during the management of perfusion and in the postoperative period. The specific endpoints are:

1. To identify the differences among different methodologies.

2. To analyze the best critical values.

3. To identify the monitoring devices necessary for the application of GDP.

4. To evaluate the main clinical impacts.

METHODOLOY

This is a systematic bibliographic review work conducted following the recommendations of the guidelines: "Preferred reporting Items for systematic Reviews and Meta-Analyses: The PRISMA Statement." [22] Studies published over the past 10 years found on the PubMed/MEDLINE database were used. These studies influence patients who underwent heart surgery with ECC. Their objective was to evaluate their clinical impact on the use of GDP strategies.

The search was conducted using the term "goal-directed perfusion". However, there was also a manual search and reading of the references cited in the articles selected.

Clinical trials, cross-sectional studies, cohort studies, case and control studies and case series were included. Case studies, letters to the editor and comments were excluded, as well as literature reviews, and articles without full access to the content, those that were not published in English and those with animal models.

After the search in the database, the articles were selected through the following stages:

1. Reading of the title and abstract to identify possible eligible studies.

2. Reading the full text.

3. Data collection and setting up of the data bank.

4. The narrative synthesis to identify the main topics of the literature.

RESULTS

Initially, 37 references were found during the search of the database and with the manual reference search. Also, 5 additional references were identified. Overall, a total 15 articles matched the endpoint of this study, which is to evaluate the association between GDP management and clinical outcomes in patients who underwent ECC (Figure 1).

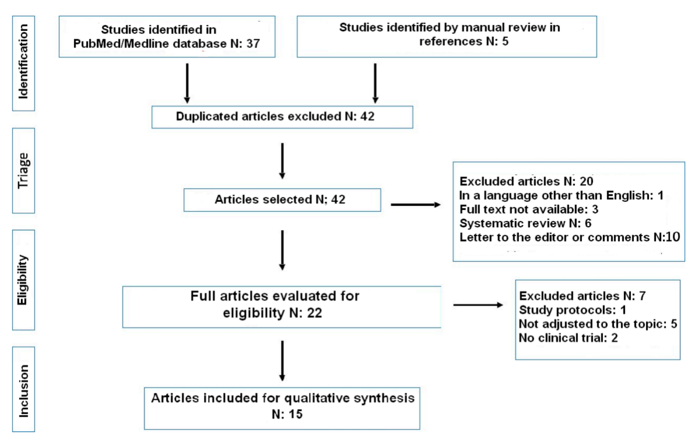

Figure 1. Study flow diagram (bibliographic analysis)

Two of the 15 articles included are randomized studies, the rest correspond to observational studies (10 retrospective, and 3 prospective). All in all, 40 904 patients were evaluated in these studies, of whom 1278 were specifically divided in the

GDP group (corresponding to 621 patients), and the control group with 657 patients. In the remaining patients (39 626), the parameters associated with GDP were assessed retrospectively without any other specific procedure in the ECC center protocols during the study period.

Among the articles included, 11 had the primary endpoint of evaluating the association between GDP management and rate of of AKI, 3 assessed the relation of GDP with some predictive markers of neurological damage and 1 assessed the association of GDP with elevated serum lactate levels only.

Regarding the types of surgeries included, they varied widely. Some of the studies used as criterion any heart surgery where ECC lasted for over 90 min; others included all heart surgeries with ECC performed at their institutes and still others coronary surgeries only. Only 1 study evaluated pediatric surgeries to correct congenital heart defects. The mean age of the population studied ranged from 60.5 to 71.3 years with the exception of the pediatric population study whose average age was 0.75 years. Regarding mean minimum temperature during ECC, it varied from 28ºC to normothermia.

Respecting the parameters associated with GDP, 13 of the 15 articles included in this review evaluated DO_2 only with critical values varying from 225 to 310 mL/min/m^2. The other two articles, in addition to DO_2, also evaluated the DO_2/VCO_2 ratio in one of them while the other evaluated DO_2/VCO_2 (QR).

The main characteristics obtained from each study are shown on table 1. Regarding the formulas used, despite the differences in the form of presentation, the main effective differences were the assessment of CaO_2:

1. Use of hemoglobin or hematocrit value.

2. Constant value of O_2 transport capacity of hemoglobin.

3. Use or not of PaO_2 and the constant of O_2 solubility (table 2).

Regarding the specific technologies for the analysis of GDP parameters, most studies used online monitoring of the variables and automatic calculation of DO_2. Somer et al., 2011,[14] Magruder et al., 2015.[26] Magruder et al., 2016,[15] Magruder et al., 2017,[27] Magruder et al., 2018, [28] and Newland et al., 2019.[17] used intermittent monitoring and manual calculation of the variables. Ranucci et al., 2015 has not mentioned how these parameters were assessed in their study.[29] In addition, the studies that evaluated variables associated with CO_2 also used the capnograph.

Regarding the treatment of the variables associated with GDP, 8 of the 15 studies conducted used only the mean of the minimum DO_2 value or the maximum VCO_2 value as a parameter. Newland et al., 2017,30 and Magruder et al., 2018 [28] used in addition to this critical value the area under the curve (AUC) as an analysis parameter. Katona et al., 2021 used the minimum DO_2, and also the mean DO_2.[19] Rasmussen et al., 2019 used the minimum DO_2 and the smallest DO_2 cumulative time of the critical value.[31] Leenders et al., 2018.32 Mukaida et al., 2019.16 and Mukaida et al., 2021[33] have already used the three parameters for the analysis of their results.

DISCUSSION

Organ dysfunction or failure in the postoperative period of heart surgery continues to be a complication of great clinical importance, which results in an increased postoperative morbimortality. Many of the risk factors are associated with the patient's medical conditions in the preoperative period and, therefore, cannot be modified, among them: chronic diseases with an impact on endothelial function such as diabetes mellitus and metabolic syndrome, prior heart surgery, stroke, preexisting renal failure, advanced age, and the presence of endocarditis.

A second group of risk factors included those that are potentially modifiable associated with the perioperative period like systemic inflammatory response syndrome, hypoperfusion of microcirculation, hemodilution, solid and gaseous microemboli, damage due to ischemia-reperfusion, prolonged ECC times and postoperative hypotension.[34] Regarding ECC, several modifiable factors have been studied over the past few years, especially their association with AKI and/or neurological damage, among them, DO_2 and other microparameters associated with oxygen consumption and CO_2 output.

1. Goal-directed perfusion and AKI

Out of the 11 articles included in this review with the main objective of evaluating AKI, 6 evaluated its relation to GDP parameters, mainly DO_2, while 5 evaluated its association with the application of GDP.

Out of the 6 articles that evaluated the relation between DO_2 and AKI,14.16.17.26.30.31 all of them obtained significant results,

Table 1. Characterization of the articles included in this study (n = 15)

1st author – Year (type of study)	Primary endpoint assessed	N Control GDP	Mean Age Control GDP	Type of surgery	Min mean temp.(°C)	GDP parameters evaluated	Criticalvalue	Main results
Somer - 2011 (control case)	AKI	359	66.1	Heart surgery with estimate of > 90 min ECC	30.9 °C	DO_2 DO_2/VCO_2	262 mL/min/m² 5.3	Minimum DO_2 <2 62 mL/min/m^2 and minimum DO_2/VCO_2 ratio value are independently associated with AKI. Minimum DO_2 was the most accurate predictor of stage 2 AKI in the postoperative period.
Ranucci – 2015 (control case)	AKI	16790	N/I	All surgeries with ECC (adults with congenital heart diseases)	32 °C	DO_2	270 mL/min/m²	The association between the minimum Hto value during ECC and AKI was confirmed in a multivariable analysis with relative risk of AKI increasing 7% per percent points of diminishment of minimum Hto value during ECC. The sensitivity analysis based on the differences before and after different procedures proved a beneficial effect of GDP application, with a 5.8% reduction in the AKI rate for 3.15 (P = .001).
Magruder – 2015 (control case)	AKI	170	69.5	Coronary artery valve	28 °C to 34 °C	DO_2	225 mL min/m²	The univariable analysis showed that patients with AKI have lower minimum DO_2 in ECC (208 vs 230 mL/min/m^2; P = .03). In the multivariable analysis, AKI predictors were DO_2 < 225 mL/min/m^2 in ECC (OR, 246; 95%CI, 1.21 TO 5.03; P = .01) and postoperative MAP < 60 mmHg for > 15 min. (OR, 3.96; 95%CI, 1.92 to 8.20; P < .001).
Ranucci – 2015 (control case)	AKI	16790	N/I	All surgeries with ECC (adults with congenital heart diseases)	32 °C	DO_2	270 mL/min/m²	The relation between the minimum Hto value during ECC and AKI was confirmed in a multivariable analysis with relative risk of AKI increasing 7% per percent points of diminishment of minimum value of Hto during ECC. The sensitivity analysis before and after different procedires proved a beneficial effect of GDP application, with a 5.8% reduction in the AKI rate for 3.15 (P = .001).
Magruder – 2016 (cohort)	L. cerebral	116	0.75 years	Septal defect, single ventricle, tetralogy of Fallot and others	29.2 °C	DO_2	Not evaluated	In univariable analysis, minimum DO_2 was significantly associated with GFAP values measured during rewarming in CEC (P = .005) and after weaning from ECC (P = .02). In the multivariable analysis that controls ECC time, deep hypothermic circulatory stop, and category of procedural risk, a negative and significant correlation remained between minimum DO_2 and GFAP post-CEC values (P = .03).
Magruder - 2017 (control case)	AKI	88 88	64 61	Coronary artery, valve, and ascending aorta	32 °C 33 °C	DO_2	300 mL/min/m²	The control group received more phenylephrine in ECC (mean, 2.1 vs 1.4 mg; P < .001) and showed lower DO_2 values (mean, 241 vs 301 mL/min/m^2; P < .001). Rate of AKI was 23.9% in the control group and 9.1% in the GDP group (P = .008); rates of stage I, II and III AKI were 19.3%, 3.4% and 1.1% in the control group and 5.7%, 3.4% and 0% in the GDP group, respectively. Control group patients showed mean percent increase beyond the creatinine baseline (27% vs 10%; P < .001).
Newland – 2017 (cohort)	AKI	210	64 and 68	Coronary artery, valve, coronary artery + valve and others	33.2 °C	DO_2	270 mL/min/ m²	Area under the curve (AUC) < 0 for minimum DO_2 of 270 mL/min/m^2 during ECC is an independent predictor of AKI after adjustment for Euroscore II and transfusion [OR, 2.74. CI, {1.01–7.41}; P =.047].
Ranucci - 2018 (randomized)	AKI	170 174	67	Heart surgery with estime of > 90min ECC	33 °C 33 °C	DO_2	280 mL/min/m²	Stage I AKI was less prevalent in GDP group (relative risk [RR], 0.45; 95%CI [IC], 0.25-0.83; P = .01). Stage II-III AKI was not any different between the 2 groups (RR, 1.66; CI 95%, 0.46-6.0; P = .528). There were no significant differences in secondary results. In prespecified analysis of patients with ECC time between 1 and 3 hours, the differences in GDP group were more pronounced with RR for AKI of 0.49 (95%CI, 0.27-0.89; P = .017).
Magruder – 2018 (cohort)	L. cerebral	43	65	Coronary artery, valve, aorta, coronary artert + valve	32.9 °C	DO_2	225 - 300 mL/min/m²	The mean UCH-L1 levels differed from the baseline up to 6 and 24 hours after ECC (40. 232 and 166 pg/mL, respectively; P < .001). In the multivariable linear regression analysis that controls baseline and surgical variables, AUC DO_2 < 225 was barely associated significantly with UCH-L1 levels of 6 hours (P < .001) while AUC DO_2 < 300 was barely significantly associated with 24-hour levels (P < .001). The 3 patients who suffered radiographic stroke showed UCH-L1 levels of 24 hours not significantly high compared to patients from the control group (585 and 151 pg/mL; P = .11).

Table 1. Characterization of the articles included in this study (n = 15)

1st author – Year (type of study)	Primary endpoint assessed	N		Mean Age		Type of surgery	Mean min Temp. (°C)	GDP parameters evaluated	Critical value	Main results
		GDP	Control	GDP	Control					
Leenders – 2018 (control case)	L. cerebral	357		65.5 y 71.3		Coronary artery	Normothermia	DO_2	272 - 310 mL/min/m²	Minimum mean DO_2 differed significantly comparing the group of patients with and without postoperative delirium. The multivariable analysis identified only age, preexisting cognitive deterioration, preoperative renal dysfunction and crossed clamping time as independent risk factors for delirium. The results indicated also that advanced age patients were more sensitive to lower DO_2 levels.
Newland – 2019 (control case)	AKI	19410		68		Coronary artery, valve or coronary + valve	34 °C	DO_2	270 mL/min/m²	Minimum DO_2 was significantly associated with any AKI stage, risk of AKI or higher class in both datasets representing a mean increase of 7% in the probability of AKI for each 10 mL/min/m^2 reduction in minimum DO_2. Diagnostic precision was the same for both datasets with a limit of minimum DO_2 of 270 mL/min/m^2. Chance of any AKI increased 52% in groups with DO_2 below the limit.
Mukaida – 2019 (control case)	AKI	112		65.2		Valve, valve + thoracic aorta, valve + coronary artery and others	34 °C a 36°C	DO_2	300 mL/min/m²	Patients who developed AKI with DO_2 below the limit of 300 mL/min/m^2 (1581 vs 632; $P < .01$) showed greater AUC and cumulative time (34.7 vs 15.3 min; $P < .01$). Minimum DO_2 was not significantly different between groups with or without AKI (263.4 vs 247.0 mL/min/m^2; $P = .291$).
Rasmussen – 2019 (control case)	AKI	1968		67.6		Coronary artery ± valve	36.5 °C a 37 °C	DO_2	272 mL/min/m²	The postoperative serum creatinine peak, rate of AKI, need for dialysis increased in a dose-dependent manner in relation to duration of mean oxygen supply < 272 mL/min/m^2. Using multiple regression analysis, exposure to, at least, 30 min was independently associated with increased PPSC and AKI. On the contrary, short exposure (1-5 min, OR, 2.58 [1.20. 5.54]; $P = .015$) and, at least, 30 min (OR, 2.85 [1.27-6.41]; $P = .011$), lower minimum DO_2 were associated independently with need for renal replacement therapy (RRT).
Overdevest - 2020 (control case)	Lactate	91		Not reported		Coronary artery	36 °C a 37 °C	DO_2 VCO_2 RQ DO_2/VCO_2	310 mL/min/m² 60 mL/min/m² 0.90 5	Increase of lactate concentrations remained clinically insignificant and showed low correlations with VCO_2i (rs, 0.277. $P = .008$) and RQ (rs, 0.346. $P = .001$). Patients with high VCO_2i (≥ 70 mL/min/m2) and RQ (≥ 0.82) showed a greater significant increase in lactate concentration compared TO patients with VCO_2i < 70 mL/min/m^2 ($P = .004$) and RQ < 0.82 ($P = .012$). Groups separated by a median DO_2/VCO_2 of 4.8 did not show any differences in increased plasma lactate concentrations.
Katona – 2021 (control case)	AKI	226 257		60.5 60.9		Coronary artery	34 °C	DO_2	270 mL/min/m²	Minimum DO_2 during ECC increased significantly after implementation of GDP ($P < .001$). In the pre-GDP group, 19.5% (50/257) of the patients reached the desired range of DO_2 > 270mL/min/m^2 for all the measurements obtained during ECC, compared to 50.9% (115/226) of patients from the post-GDP group. Implementation of GDP resulted in a postoperative increase, significantly reduced SCr, and the rate of AKI.
Mukaida – 2021 (randomized)	AKI	137 138		71	70	Valve, Valve + coronary artery, valve + thoracic aorta	34 °C	DO_2	300 mL/min/m²	AKI occurred in 20 patients (14.6%) who received the oxygen supply strategy and in 42 patients (30.4%) who received the conventional strategy (relative risk, 0.48; 95%CI, 0.30-0.77; $P = .002$). Secondary results were not significantly different between the strategies. In prespecified subgroup analyses of patients with minimum hematocrit < 23% or body surface area < 1.40 m^2. The oxygen supply strategy seemed to be superior to the conventional strategy and the existence of quantitative interactions was suggested.

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although critical values varied widely from 225 to 300 mL/min/m^2 (Table 1). We should also mention that the studies with the lowest DO_2 critical values correspond to the studies whose mean minimum temperature during ECC was also the lowest (Somer et al., 2011,[14] with a mean minimum temperature of 31ºC and DO_2 critical values of 262 mL/min/m^2 and Magruder et al., 2015,[26] ranging from 28ºC to 34ºC and critical values of 225 mL/min/m^2).

The association between a lower body temperature and O_2 metabolism, mainly on brain metabolic demand, is well known and justifies the use of hypothermia during ECC.35 Ashmore et al. have shown a 43% reduction in O_2 consumption in patients treated with surgery with ECC and 32ºC hypothermia.[36]

However, DO_2 critical value for each hypothermia level is not very well known yet and, therefore, studies that seek to analyze these parameters at different temperatures are necessary. Another important point in the study conducted by Magruder et al., 2015, is that the group without AKI, the mean of the DO_2 minimum value was also significantly lower compared to that of other studies (230 mL/min/m^2) making comparison difficult.[26]

Regarding the variables associated with CO_2. De Somer et al. 2011[14] and Newland et al., 201730 barely evaluated the association between DO_2/VCO_2 and AKI. Newland et al., 2017 did not find any significant differences of these variables among the groups with or without AKI.30 De Somer et al., 2011 found an independent association between DO_2/VCO_2 ratios <5.3 and AKI.[14]

VCO_2 can provide important information about adapting perfusion in relation with DO_2, since, under conditions of inadequate DO_2, there is an excessive CO_2 output as a result of lactic acid tamponade. Therefore, VCO_2 can be considered an indirect marker of lactate increase. In addition to an inadequate provision of O_2, other factors can lead to an increased $ePCO_2$ and consequently of VCO_2.

Among them, unclamping of the aorta (increase of anaerobic CO_2 due to myocardial reperfusion), rewarming the patient (increase of aerobic CO_2 based on the increased VCO_2) and change CO_2 solubility. Therefore, the DO_2/VCO_2 ratio has been introduced to emphasize the role of VCO_2 increase due to low DO_2 values. When DO_2 is in its lower limit, even though VCO_2 increase is not yet significant, it will cause a reduction that expresses the relation. On the other hand, although VCO_2 increases as a result of VO_2 increase or due to other causes, if DO_2 is adequate, the relation will remain > 5.37 The DO_2/VCO_2 ratio is a useful parameter to evaluate the O_2 supply in a more individualized manner and according each patient's metabolism at different moments.

Table 2. Variations in the formulas of GDP paremeters according to each study.

Authors	Formulas
Somer 2011	$DO_2 = IC (l/min/m2) \times CaO2 (mL/dL) \ x\ 10$ $CaO_2 = (Hb (mg/dl) \ x\ SaO2(\%) \ x\ 1{,}34) + (0{,}003 \ x\ PaO2 \ (mmHg))$ $VCO_2 = \frac{ePCO2 (mmHg) \times Ve (l/min) .\ 1000}{760 \ x\ SC (m2)}$
Ranucci 2015	Not informed
Magruder (2015, 2016, 2017, 2018)	$DO_2 = \frac{10 \ x\ Flujo (l/min) .\ [(Hb(g/dl) \ x\ 1{,}36 \ x\ SaO2(\%)) + (0{,}003 \ x\ PaO2 \ (mmHg)]]}{SC (m2)}$
Newland 2017	GDP por M4: $DO_2 = IC (l/min/m2) \cdot (Hb (g/dl) \ x\ 1{,}34 \ .\ \frac{SaO2}{100}) \ x\ 10$
Ranucci 2018	GDP calculado: $DO_2 = CaO2 (ml/dl) \ x\ IC (dl/min/m2)$ $CaO_2 = (Hb (g/dl) \ x\ SaO2 \ x\ 1{,}34) + (0{,}03 \ x\ PaO2 \ (mmHg))$ GDP por CONNECT: $DO_2 = IC (l/min/m2) \cdot (\frac{Ht}{2{,}94} \ x\ 1{,}36 \ x\ SaO2) + (0{,}03 \ x\ PaO2 \ (mmHg)) \ x\ 10$ GDP por M4: $DO_2 = IC (l/min/m2) \times (Hb (g/dl) \ x\ 1{,}34 \ x\ \frac{SaO2}{100}) \ x\ 10$
Leenders 2018 y Mukaida (2019, 2021)	$DO_2 = \frac{10 \ x\ Flujo (l/min) \times [(\frac{Ht}{2{,}94} \ x\ 1{,}36 \ x\ SaO2(\%)) + (0{,}003 \ x\ PaO2 \ (mmHg)]}{SC (m2)}$
Newland – 2019	$DO_2 = 10 \ x\ IC(l/min/m2) \ x\ ((Hb(g/dl) \ x\ SaO2 \ x\ 1{,}34) + (0{,}003 \ x\ PaO2))$
Rasmussen – 2019	$DO_2 = 10 \ x\ IC(l/min/m2) \ x\ [(\frac{Ht}{3} x\ SaO2 \ x\ 1{,}34) + (0{,}003 \ x\ PaO2)]$ $DO_2 = \frac{10 \ x\ Flujo (l/min) \times [(Hb \ x\ 1{,}36 \ x\ SaO2(\%)) + (0{,}003 \ x\ PaO2 \ (mmHg))]}{SC (m2)}$
Overdevest - 2020	$VO_2 = \frac{10 \ x\ Flujo (l/min) \times [(Hb \ x\ 1{,}36 \ x\ (SaO2 - SvO2)) + (0{,}003 \ x\ (PaO2 - PvO2))]}{SC (m2)}$ $VCO_2 = \frac{ePCO2 (mmHg) \times Ve (l/min) \ x\ 1{,}15}{SC (m2)}$
Katona – 2021	$DO_2 = IC \ x\ ((Hb \ x\ SaO2 \ x\ 1{,}34) + (0{,}003 \ x\ PaO2))$

The fact that Newland et al., 2017 did not find significant results for this variable can be explained by the methodological differences seen between the two studies. As opposed to De Somer et al., 2011, Newland et al. did not use a capnograph to measure VCO_2. Instead, they used the in-line M4 monitor. Therefore, the formulas used to calculate VCO_2 were different. In addition, it has been described that variations in the design of oxygenators interfere in the measurements of exhaled CO_2.[30]

Therefore, for future studies to assess more conclusively the role of the DO_2/VCO_2 ratio, better standardization of the formula is necessary.

Regarding the studies that evaluated the efficacy of GDP implementation in AKI reduction, 3 are retrospective studies 19.27.2, and 2 are randomized studies.[33.38]

Except for the study conducted by Ranucci et al., 2015,29 the other studies evaluated the efficacy of GDP increasing DO_2 values during ECC. They all obtained significant differences.19 Katona et al., 2021 obtained a mean minimum DO_2 of 238 mL/min/m² in the control group vs 278 mL/ min/m² in the GDP group; P < .001. Magruder et al., 201727 found a mean minimum DO_2 of 240 mL/min/m² vs 302 mL/min/m² in the control and GDP groups respectively; P < .001. Mukaida et al., 2021,33. obtained a difference in AUC and DO_2 time < 300 mL/min/m² among the control and GDP groups, 56 vs 703; P < .001, and 2.7 vs 20.3. P < .001, respectively. Ranucci et al. 201838 obtained a mean minimum DO_2 of 301 mL/min/m² in the control group and 315 mL/min/m² in the GDP group; P = .013.

All 5 studies19.27.29.33.38 have obtained significant reduction in the rate of AKI in the GDP group compared to the control group (Table 1). When AKI was categorized into stages 1, 2 and 3, Ranucci et al., 2018,38 Mukaida et al., 2021,33 and Katona et al., 2021,19 obtained significant inter-group differences in stage 1 only. Ranucci et al., 2018,[38] obtained a mean minimum DO_2 301 mL/min/m² in the group while Magruder et al., 2017,[27] did not find any differences in any subclassifications. These results can be explained by the rarity of events in these subgroups since Newland et al., 2019, who have a larger sample size compared to other studies, described significant associations between the minimum DO_2 < 270 mL/min/m² and AKI (P < .001).[17]

Assessment of secondary endpoints like mortality, morbidity, mechanical ventilation time, time of ICU stay and concentrated red blood transfusion has not shown any significant differences between GDP and control groups for any of the studies analyzed. De Somer et al., 2011, found a significant and negative association between the ICU stay and the length of stay (LoS) with minimum DO_2 during ECC.[14] In addition, the assessment of these results in groups with or without AKI revealed significant differences in the study conducted by Mukaida et al., 2021 among intubation time, ICU stay, LoS, and estimated glomerular filtration rate at discharge.[33] In the study conducted by Magruder et al. (2015) these differences were found among the ICU stay, LoS, and mortality.[26]

Heart surgery-related AKI is a common complication even stage 1 was associated with increase in morbimortality in the short and long heart surgery postoperative period.[39] Moreover, small increases in serum creatinine values showed a threefold increase in renal damage in the terminal stage and a higher mortality rate.[40] Absence of statistical significance for these variables can be justified by the insufficient sample size.

ECC includes a state of reduction of GC, Hb and MAP, which can contribute to AKI pathogenesis, because kidney function is highly dependent on oxygen supply, especially in conditions of non-pulsatile flow generated by ECC. Due to its unique blood supply, the kidney medulla enters a state of hypoxia under conditions of acute progressive anemia long before other organs, such as the intestine or the heart.[38] This way, extreme hemodilution can contribute to AKI, despite the theoretical benefits of kidney protection, such as a reduced blood viscosity and improved regional blood flow in the context of hypoperfusion and hypothermia.[41]

Lannemyr et al. showed that during ECC, renal DO_2 decreases down to 20% due to hemodilution and vasoconstriction, meanwhile, the glomerular filtration rate and renal VO_2 renal remain unchanged. Therefore, there is an increased renal ERO_2 of up to 45%, which indicates an unbalance of renal DO_2 and VO_2.[42] These pathophysiological concepts in association with the results revealed by the studies included in this review support the use of GDP as a practice that is potentially capable of minimizing the rate of AKI.

We should mention that for these studies to be more reproducible, some standardization is necessary, especially in relation with how variables are treated. Since some authors used intermittent monitoring, with calculation of parameters done manually at 10-and-30 min intervals, the use of AUC was not possible and, therefore, these studies used the mean minimum DO_2 or the mean as variables. Meanwhile, exposure time is an important risk component for AKI that is not considered in this type of treatment of the variables.

On the basis of previous studies that showed a relation between time-dose response of MAP and increased risk of AKI and taking into account that DO_2 levels during ECC are always

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changing dynamically, Mukaida et al have proposed that time-dose response of DO_2 is a better predictor for AKI than minimum DO_2.[16]

Moreover, another point of divergence that needs better standardization is the formulas. According to Newland et al, use of CONNECT or M4 monitoring to calculate DO_2 results in a variation of approximately 20 units that derives from variations in the formulas.[30]

1.1 Other clinical results.

Among the studies included, 4 did not have as its primary endpoint the assessment of AKI. Three studies evaluated neurological parameters and the other one evaluated hyperlactatemia. Regarding the studies that assessed neurological parameters, they are all retrospective studies.[15,28,32]. Magruder et al., 2016. assessed the association between DO_2 and glial fibrillary acidic protein (GFAP), a biomarker of astrocytes injury or necrosis, in patients treated with heart surgery under ECC.15 In a different study conducted by Magruder et al., 2018, the relation between minimum DO_2, the AUC of DO_2, and the biomarker of neurological injury ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) was evaluated in adult patients treated with heart surgery with ECC.[28]

Both studies obtained a significant association between the respective biomarkers and DO_2. However, no association between these findings and clinical neurological impacts possibly due to sample size.[15.28]

Leenders et al., 2018 evaluated the relation between GDP parameters and the occurrence of postoperative delirium in patients treated with cardiac revascularization with normothermic ECC. This study revealed significant differences between minimum DO_2 levels during ECC in patients with or without postoperative delirium. In a multivariate analysis, DO_2 parameters were not identified as independent predictors of delirium.[32]

The endpoint of the study conducted by Overdevest et al. was to assess the association between GDP parameters derived from CO_2 (VCO_2, QR, DO_2/VCO_2) with hyperlactatemia in patients treated with myocardial revascularization with normothermic ECC. Critical values to predict lactate increase, reported in other studies, were not confirmed in this study. $VCO_2 \geq 70$ mL/min/m^2 and QR ≥ 0.8 have been associated with increased lactate output. These differences in the data available on the medical literature can be explained by the fact that CO_2 output during ECC depends on the patient's temperature and, therefore, a different cut-off value should be used during normothermic ECC.18 We should mention that in the study at stake, the increased lactate concentrations remained without any clinical significance with barely 2 patients showing postoperative hyperlactatemia in cardiovascular surgery with ECC. All this makes it difficult to compare these results with previous studies.

CONCLUSION

There is still no consensus on the parameters to be evaluated and the critical values that should be considered during ECC. The qualitative analysis of the articles included in this review shows that GDP can be considered a promising strategy to minimize organ dysfunctions, especially AKI while the studies that evaluated other clinical results are preliminary and non-conclusive. It is important for the technique to be better standardized, which would allow greater result reproducibility in future studies

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