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Review Article

Intraoperative Goal-Directed Perfusion in Cardiac Surgery with Cardiopulmonary Bypass: The Roles of Delivery Oxygen Index and Cardiac Index

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Purpose: Goal-directed perfusion (GDP) refers to individualized goal-directed therapy using comprehensive monitoring and optimizing the delivery of oxygen during cardiopulmonary bypass (CPB). This study aims to determine whether the intraoperative GDP protocol method has better outcomes compared to conventional methods.

Methods: We searched the PubMed, Central, and Scopus databases up to October 12, 2023. We primarily examined the GDP protocol in adult cardiac surgery, using CPB with oxygen delivery index (DO2I) and cardiac index (CI) as the main parameters.

Results: In all, 1128 participants from seven studies were included in our analysis. The results showed significant differences in the duration of intensive care unit (ICU) stays (p = 0.01), with a mean difference of −0.33 (−0.59 to 0.07), and hospital length of stay (LOS) (p = 0.0002), with a mean difference of −0.84 (−1.29 to −0.39). There was also a notable reduction in postoperative complications (p <0.00001), odds ratio (OR) of 0.43 (0.32–0.60). However, there was no significant decrease in mortality rate (p = 0.54), OR of 0.77 (0.34–1.77).

Conclusion: Postoperative acute kidney injury and ICU and hospital LOS are significantly reduced when GDP protocols with indicators of flow management, oxygen delivery index, and CI are used in intraoperative cardiac surgery using CPB.

Keywords: cardiopulmonary bypass, goal-directed perfusion, delivery oxygen index, cardiac index

List of Abbreviations:

CPB = cardiopulmonary bypass
DO2 = oxygen delivery
VO2 = oxygen consumption
ICU = intensive care unit
AKI = acute kidney injury
GDP = goal-directed perfusion
CI = cardiac index
MAP = mean arterial pressure
RCTs = randomized controlled trials
PROSPERO = the international prospective register of systematic reviews
PRISMA = preferred reporting items for the systematic reviews and meta-analyses
PIC = population, intervention, control
DO2I = oxygen delivery index
LOS = length of stay

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ISRCTN = international standard randomised controlled trial number
RoB = risk of bias
CABG = coronary bypass surgery
OR = odds ratio
CO = cardiac output
IABP = intra-aortic balloon pump
SVV = stroke volume variation
VCO2 = carbon dioxide production
HCT = hematocrit
BSA = body surface area
SVI = stroke volume index
SVRI = systemic vascular resistance index
BNP = brain natriuretic peptide
NGAL = neutrophil gelatinase-associated lipocalin
SCVO2 = central venous oxygen saturation
SVO2 = venous oxygen saturation
TEE = transesophageal echocardiogram
SOFA = sequential organ failure assessment score
RRT = renal replacement therapy
RSCO2 = regional cerebral oxygen saturation

Introduction

Cardiopulmonary bypass (CPB) has undergone consistent improvements over the years. The current focus is on specific oxygen delivery (DO2) with lower flows compared to conventional methods that use higher flows, which can be detrimental to blood. Monitoring includes assessing mixed venous and cerebral blood saturations to evaluate the adequacy of DO2.[1] The critical DO2, which represents the minimum safe DO2 during CPB, matches the point with oxygen consumption (VO2). Beyond this point, whole-body VO2, tissue oxygenation, and anaerobic metabolism start to decline, leading to the onset of lactic acidosis.[2]

The utilization of a CPB apparatus, the application of mechanical force, hypothermia, and dilution of blood results in a range of consequences, including harm to red blood cells and an inflammatory reaction. Blood damage can also occur due to the pressure exerted by the rotating blood conduit pipes, which aim to generate blood flow, known as shear stress. As a consequence, the duration of CPB increases, and the detrimental impacts it induces worsen.[3] CPB usage is related to microcirculatory perfusion disruptions, which are frequently linked to higher rates of morbidity and mortality in the intensive care unit (ICU). These damages in microcirculation may cause cardiogenic shock or sepsis, mediastinitis, permanent stroke, acute kidney injury (AKI), and acute lung injury.[4]

Goal-directed perfusion (GDP), which adapted Shoemaker's research findings in 1988 on goal-directed therapy for the management of critically ill patients, involves implementing successful DO2 management to improve patient outcomes. It aims to restore optimal tissue perfusion by utilizing aggressive monitoring parameters, including cardiac index (CI), DO2, mean arterial pressure (MAP), oxygen, inotropic therapy, and vasopressors. The effectiveness of GDP, which focuses on keeping the optimum DO2 during CPB above the critical threshold, has been demonstrated in reducing complications, morbidity, and mortality after surgery.[5]

Over the past decade, a few studies have been conducted in this promising field. However, to our knowledge, no comprehensive review has been published specifically about the effects of GDP in adult cardiac surgery using CPB. Accordingly, we conducted this review and meta-analysis of randomized controlled trials (RCTs) to assess the impact of GDP on adult cardiac surgery with CPB in many aspects.

Materials and Methods

This systematic review has been registered in The International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023422556, which was submitted in May 2023. The Preferred Reporting Items for the Systematic Reviews and Meta-Analyses (PRISMA) statement was used to guide the search and development of the flowchart. The Cochrane Handbook for Systematic Reviews of Interventions version 6.2. was used as a guide in the preparation of this article.

Eligibility criteria

The ongoing study has certain eligibility criteria. To be included in the study, the studies must have met the minimum PIC (Population, Intervention, Control) criteria. The criteria were as follows: (P) adult cardiac surgery, (I) GDP with targeted CI and oxygen delivery index (DO2I), and (C) a group of patients receiving standard surgical care with CPB. The purpose of the study is to compare postoperative outcomes between the intervention and control groups, which includes the ICU and hospital length of stay (LOS), duration of mechanical ventilation, average of extra volume, and mortality rate. However, the selection process excludes cardiac surgery trials, such as those without

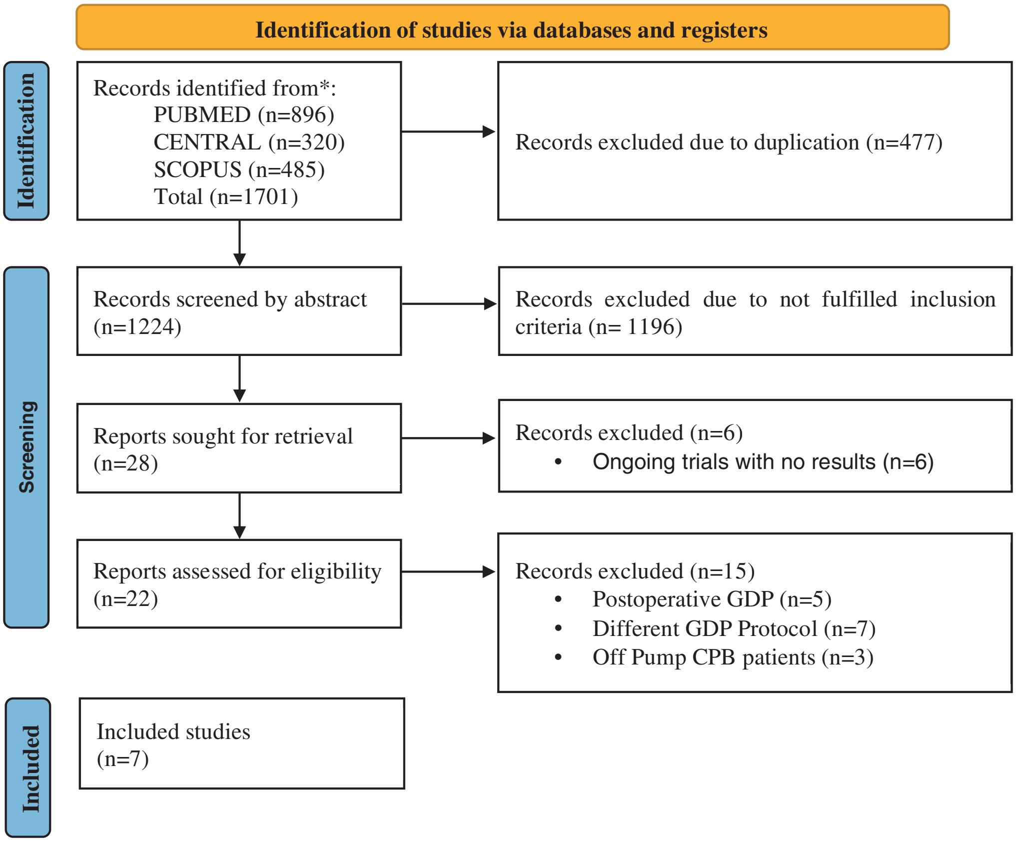


Fig. 1 PRISMA chart. This picture illustrates the flow of identification and selection of studies presented in the Prisma chart. PRISMA: Preferred Reporting Items for the Systematic Reviews and Meta-Analyses

the use of CPB (off-pump) and minimally invasive surgery. Moreover, the study excludes non-randomized and non-English studies.

Information sources and search strategy

The authors conducted a search of the CENTRAL, Scopus, and PubMed databases for potentially eligible trials until October 12th, 2023. We also searched for ongoing trials on clinicaltrials.gov and the International Standard Randomised Controlled Trial Number (ISRCTN) registry. The search was restricted to articles published in English, and the following keywords were used: “cardiac surgical procedures” AND “cardiopulmonary bypass” AND (“goal-directed therapy” OR “goal-directed perfusion”) AND (“cardiac index” OR “delivery oxygen index”).

Study selection

Five authors conducted a search of titles and abstracts of articles that were potentially eligible, and they reviewed them independently. The same authors retrieved the full text of the articles and evaluated them for eligibility using predetermined inclusion and exclusion criteria. Each therapy related to CPB in the study was assessed after collecting the full text. Co-interventions were permitted, provided that all randomized allocation arms received the same co-interventions. The main authors and co-authors engaged in discussions and consultations to resolve any disputes that arose during the selection process. The number of articles that passed each screening was recorded. A more comprehensive overview of the study selection process can be found in the PRISMA flow chart[6] shown in **Fig. 1**.

Data collection process

The necessary data from the eligible RCT were organized in a table format, and the full text of all studies was examined to collect the following information: author, publication year, sample size, study population, type of intervention, intraoperative and postoperative data, and definition of the GDP for each center. Detailed information on the characteristics of the studies is found in **Table 1,** and protocol details are available in **Supplementary Table 1** online.

Table 1 Study characteristics

Study	Year	Population	Intervention	(n)	Control (n)	Targeted GDP parameters
Goepfert[7)]	2013	AVR/CABG with CPB	Optimized hemodynamic therapy	46	46	Stroke volume variation, end-diastolic volume index, mean arterial pressure, cardiac index
Fellahi[8)]	2015	CABG with CPB	Early goal-directed therapy with ECOM	48	44	SVV and cardiac index
Kapoor[9)]	2016	CABG with CPB	Goal-directed therapy with FloTrac	60	60	Cardiac index, stroke volume index, systemic vascular resistance index, oxygen delivery index, central venous oxygen saturation, stroke volume variation
Ranucci[2)]	2018	Cardiac surgery with CPB	GDP	156	170	Oxygen delivery index
Kapoor[10)]	2019	CABG with CPB	Goal-directed therapy with FloTrac	54	56	Mean arterial pressure, central venous pressure, urine output, oxygen saturation, hematocrit, central venous oxygen saturation, cardiac index, stroke volume variation, systemic vascular resistance index, oxygen delivery index, stroke volume index
Tribuddharat[11)]	2021	CABG with CPB	Early goal-directed therapy with FloTrac	44	42	Stroke volume variation, stroke volume index, cardiac index, systemic vascular resistance index
Mukaida[12)]	2023	Cardiac surgery with CPB	Oxygen delivery-guided perfusion	137	138	Oxygen delivery index

This table illustrates the characteristics of the included studies that will undergo further review and/or meta-analysis. AVR: Aortic valve replacement; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; GDP: goal-directed perfusion

Table 2 Risk of bias of the study

Risk of bias						
Study	D1	D2	D3	D4	D5	Overall
Fellahi,[8)] 2015	+	!	+	!	+	!
Goepfert,[7)] 2013	+	+	+	+	+	+
Kapoor,[9)] 2016	+	+	+	+	+	+
Kapoor,[10)] 2019	+	+	+	+	+	+
Mukaida,[12)] 2023	+	+	+	+	+	+
Ranucci,[2)] 2018	+	+	+	+	+	+
Tribuddharat,[11)] 2021	+	+	+	+	+	+

This table illustrates the risk of bias for each of the included studies. D1: randomization process; D2: deviations from the intended interventions; D3: missing outcome data; D4: measurement of the outcome; D5: selection of the reported result

Risk of bias

Seven authors independently evaluated the methodological quality of the studies using the Risk of Bias (RoB) Assessment 2.0 Tools. The authors assessed various items, including the randomization process, deviation from intended intervention, missing outcome data, outcome measurement, and selection of reported outcome. Each study was categorized as having a low, some concern, or high RoB for each area of bias. A study was marked as "low risk" if the information provided was clear and complete, "high risk" if there was no information on some items or if the information provided indicated a clear RoB, and "some concerns" if the information provided was incomplete. The RoB for each study is presented in graphical form in **Table 2**.

Summary measures and synthesis of results

In this systematic review and meta-analysis, the primary outcomes assessed included ventilation duration (hours), mortality, ICU and hospital LOS (days), delta hemoglobin, units of red blood cell transfusion needed, extra volume (mL), and postoperative complication occurrences. Data were typically presented as mean with standard deviation. In cases of incomplete or missing data, a descriptive narrative was used. All statistical calculations employed a 95% confidence interval. Review Manager 5.4 software was utilized for combining analyses with a random effects model to assess potential clinical heterogeneity. The I^2 value determined the level of statistical heterogeneity, with 25% indicating low, 25%–50% moderate, and above 50% high heterogeneity.

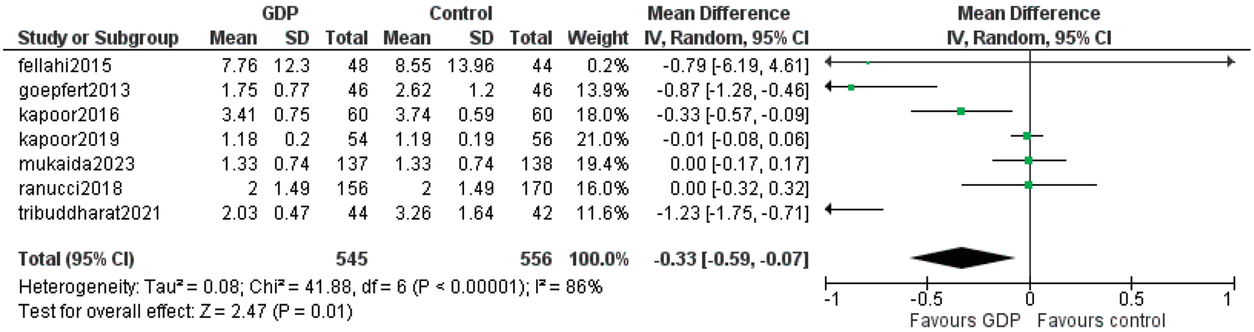


Fig. 2 Duration of ICU length of stay (days). This picture illustrates the impact of the GDP group compared to the control group on the duration of ICU length of stay. ICU: intensive care unit; GDP: goal-directed perfusion

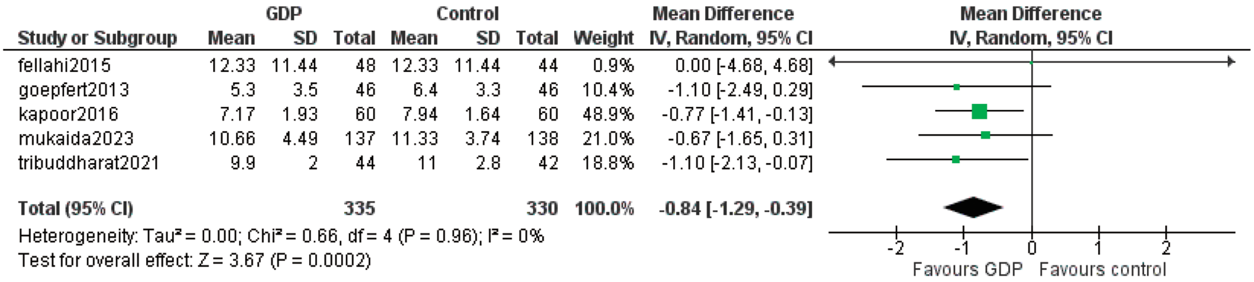


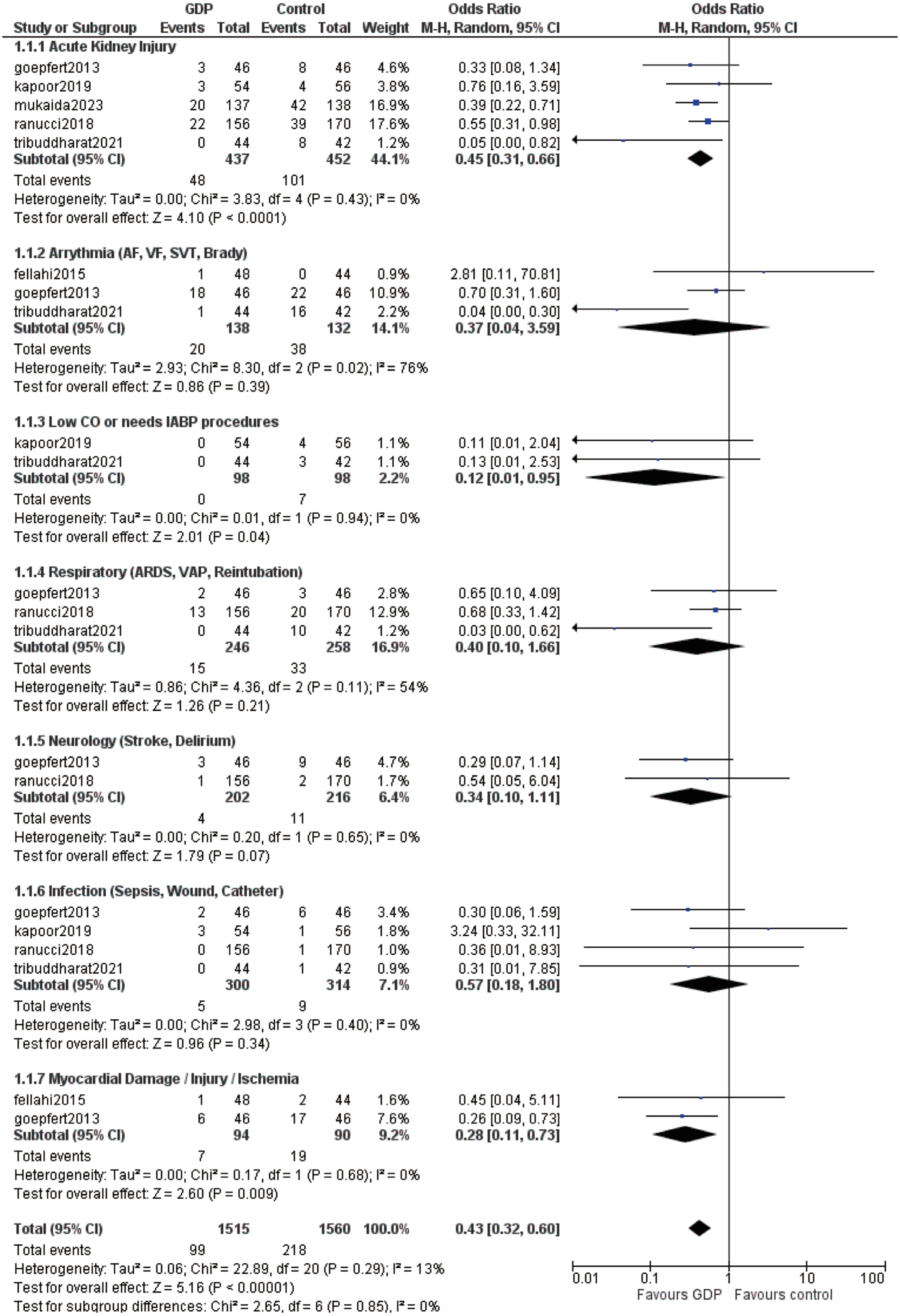
Fig. 3 Duration of hospital length of stay (days). This picture illustrates the impact of the GDP group compared to the control group on the duration of hospital length of stay. GDP: goal-directed perfusion

Results

There were initially 1701 studies found in total, and 477 duplicates were removed. The remaining 1224 studies' titles and abstracts were thoroughly scrutinized for inclusion. We found that 1196 studies did not fulfill the inclusion criteria. In all, 28 of these papers received full-text reviews; however, six of them involved ongoing trials with no results yet. Following additional selection, it was decided that a total of 7 studies[2,7–12] matched the predetermined inclusion criteria and were consequently included in the meta-analysis.

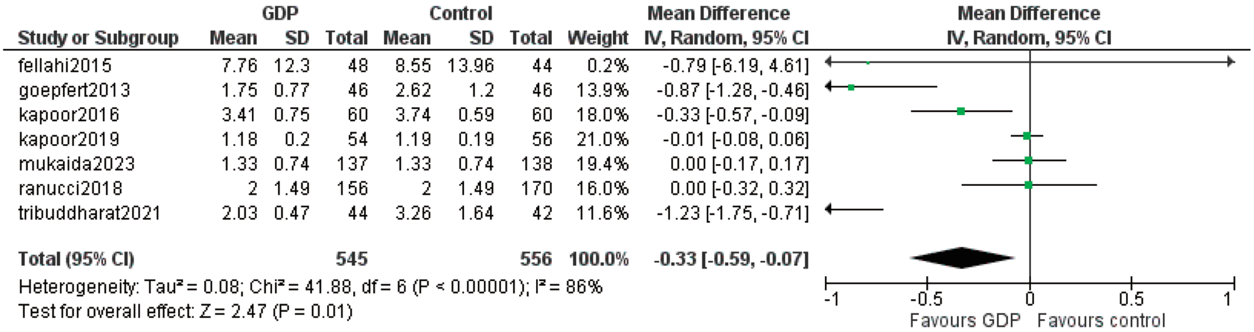
In these 7 studies, a total of 1128 adult patients who underwent coronary artery bypass graft (CABG), valve repair, or a combination of both procedures were included. The differences between protocols among these studies are listed in **Supplementary Table 1**. Among these patients, 545 were in the GDP group, whereas the other 556 were in the control or conventional group. GDP in this context refers to intraoperative management in cardiac surgery patients utilizing a CPB machine. The management approach is individualized, with different interventions tailored to each patient's specific condition. The goal-directed approach utilizes parameters such as CI or DO2I. Interventions in the goal-directed group may involve volume expansion, the use of inotropic and vasoactive medications, or blood transfusions to increase hemoglobin levels. Among the seven journals to be analyzed, one was identified as having a moderate RoB due to issues with blinding and outcome measurement.[9] The study will examine outcomes in both groups, including the duration of ventilation, LOS in the ICU and hospital, as well as patient mortality during the hospital stay.

In our study, the implementation of goal-directed protocols resulted in significant improvements in various outcome measures. We observed a significant decrease in the duration of ICU and hospital length with a mean potential difference of −0.33 (ranging from −0.59 to −0.07), p = 0.01 and −0.84 (ranging from −1.29 to −0.39), p = 0.0002 respectively (**Figs. 2** and **3**). Furthermore, GDP appeared to reduce overall complications (**Fig. 4**), with an odds ratio (OR) of 0.43 (ranging from 0.32 to 0.60), p <0.00001. Significant reductions in the incidence of AKI, postoperative low cardiac output (CO) requiring intra-aortic balloon pump, and myocardial damage/reperfusion injury were observed, but no significant effects on other complications. We also did not find significant reductions in the duration of the ventilator (**Fig. 5**), mortality rate



Study or Subgroup	GDP Events	GDP Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Acute Kidney Injury						
goepfert2013	3	46	8	46	4.6%	0.33 [0.08, 1.34]
kapoor2019	3	54	4	56	3.8%	0.76 [0.16, 3.59]
mukaida2023	20	137	42	138	16.9%	0.39 [0.22, 0.71]
ranucci2018	22	156	39	170	17.6%	0.55 [0.31, 0.98]
tribuddharat2021	0	44	8	42	1.2%	0.05 [0.00, 0.82]
Subtotal (95% CI)		**437**		**452**	**44.1%**	**0.45 [0.31, 0.66]**
Total events	48		101			
Heterogeneity: Tau² = 0.00; Chi² = 3.83, df = 4 (P = 0.43); I² = 0%						
Test for overall effect: Z = 4.10 (P < 0.0001)						
1.1.2 Arrythmia (AF, VF, SVT, Brady)						
fellahi2015	1	48	0	44	0.9%	2.81 [0.11, 70.81]
goepfert2013	18	46	22	46	10.9%	0.70 [0.31, 1.60]
tribuddharat2021	1	44	16	42	2.2%	0.04 [0.00, 0.30]
Subtotal (95% CI)		**138**		**132**	**14.1%**	**0.37 [0.04, 3.59]**
Total events	20		38			
Heterogeneity: Tau² = 2.93; Chi² = 8.30, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.1.3 Low CO or needs IABP procedures						
kapoor2019	0	54	4	56	1.1%	0.11 [0.01, 2.04]
tribuddharat2021	0	44	3	42	1.1%	0.13 [0.01, 2.53]
Subtotal (95% CI)		**98**		**98**	**2.2%**	**0.12 [0.01, 0.95]**
Total events	0		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
1.1.4 Respiratory (ARDS, VAP, Reintubation)						
goepfert2013	2	46	3	46	2.8%	0.65 [0.10, 4.09]
ranucci2018	13	156	20	170	12.9%	0.68 [0.33, 1.42]
tribuddharat2021	0	44	10	42	1.2%	0.03 [0.00, 0.62]
Subtotal (95% CI)		**246**		**258**	**16.9%**	**0.40 [0.10, 1.66]**
Total events	15		33			
Heterogeneity: Tau² = 0.86; Chi² = 4.36, df = 2 (P = 0.11); I² = 54%						
Test for overall effect: Z = 1.26 (P = 0.21)						
1.1.5 Neurology (Stroke, Delirium)						
goepfert2013	3	46	9	46	4.7%	0.29 [0.07, 1.14]
ranucci2018	1	156	2	170	1.7%	0.54 [0.05, 6.04]
Subtotal (95% CI)		**202**		**216**	**6.4%**	**0.34 [0.10, 1.11]**
Total events	4		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.79 (P = 0.07)						
1.1.6 Infection (Sepsis, Wound, Catheter)						
goepfert2013	2	46	6	46	3.4%	0.30 [0.06, 1.59]
kapoor2019	3	54	1	56	1.8%	3.24 [0.33, 32.11]
ranucci2018	0	156	1	170	1.0%	0.36 [0.01, 8.93]
tribuddharat2021	0	44	1	42	0.9%	0.31 [0.01, 7.85]
Subtotal (95% CI)		**300**		**314**	**7.1%**	**0.57 [0.18, 1.80]**
Total events	5		9			
Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.1.7 Myocardial Damage / Injury / Ischemia						
fellahi2015	1	48	2	44	1.6%	0.45 [0.04, 5.11]
goepfert2013	6	46	17	46	7.6%	0.26 [0.09, 0.73]
Subtotal (95% CI)		**94**		**90**	**9.2%**	**0.28 [0.11, 0.73]**
Total events	7		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.60 (P = 0.009)						
Total (95% CI)		**1515**		**1560**	**100.0%**	**0.43 [0.32, 0.60]**
Total events	99		218			
Heterogeneity: Tau² = 0.06; Chi² = 22.89, df = 20 (P = 0.29); I² = 13%						
Test for overall effect: Z = 5.16 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.65, df = 6 (P = 0.85), I² = 0%						

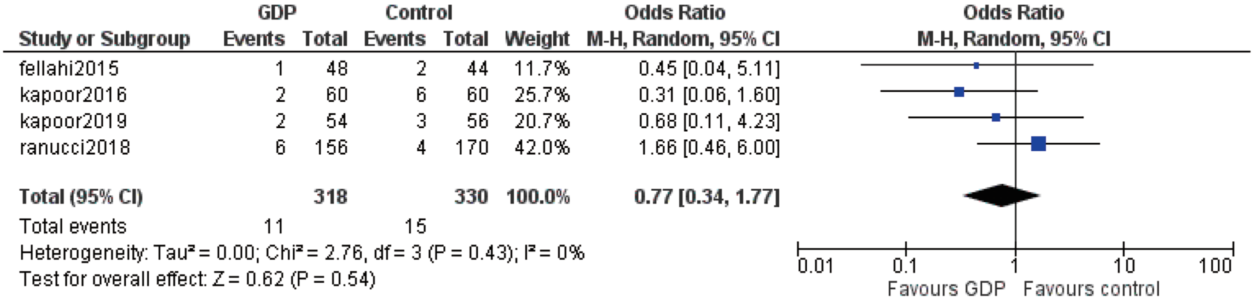
Fig. 4 Complications. This picture illustrates the impact of the GDP group compared to the control group on postoperative complications. GDP: goal-directed perfusion



Study or Subgroup	GDP Mean	GDP SD	GDP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
fellahi2015	7.76	12.3	48	8.55	13.96	44	0.2%	-0.79 [-6.19, 4.61]
goepfert2013	1.75	0.77	46	2.62	1.2	46	13.9%	-0.87 [-1.28, -0.46]
kapoor2016	3.41	0.75	60	3.74	0.59	60	18.0%	-0.33 [-0.57, -0.09]
kapoor2019	1.18	0.2	54	1.19	0.19	56	21.0%	-0.01 [-0.08, 0.06]
mukaida2023	1.33	0.74	137	1.33	0.74	138	19.4%	0.00 [-0.17, 0.17]
ranucci2018	2	1.49	156	2	1.49	170	16.0%	0.00 [-0.32, 0.32]
tribuddharat2021	2.03	0.47	44	3.26	1.64	42	11.6%	-1.23 [-1.75, -0.71]
Total (95% CI)			**545**			**556**	**100.0%**	**-0.33 [-0.59, -0.07]**

Heterogeneity: Tau² = 0.08; Chi² = 41.88, df = 6 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.47 (P = 0.01)

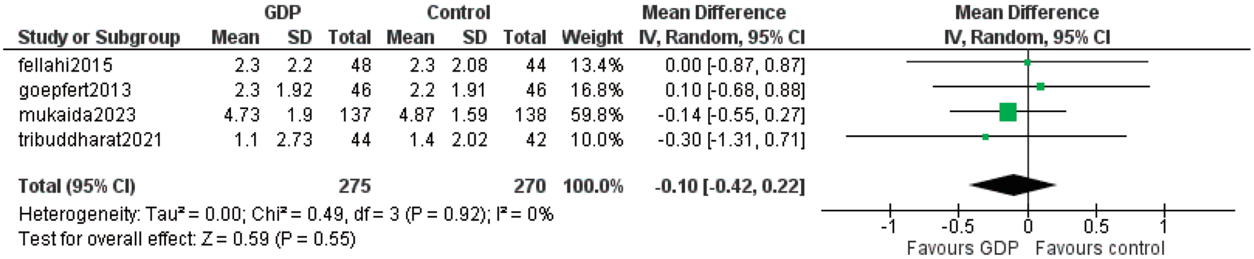
Fig. 5 Duration of ventilation (hour). This picture illustrates the impact of the GDP group compared to the control group on the duration of ventilator use. GDP: goal-directed perfusion



Study or Subgroup	GDP Events	GDP Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
fellahi2015	1	48	2	44	11.7%	0.45 [0.04, 5.11]
kapoor2016	2	60	6	60	25.7%	0.31 [0.06, 1.60]
kapoor2019	2	54	3	56	20.7%	0.68 [0.11, 4.23]
ranucci2018	6	156	4	170	42.0%	1.66 [0.46, 6.00]
Total (95% CI)		**318**		**330**	**100.0%**	**0.77 [0.34, 1.77]**
Total events	11		15			

Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)

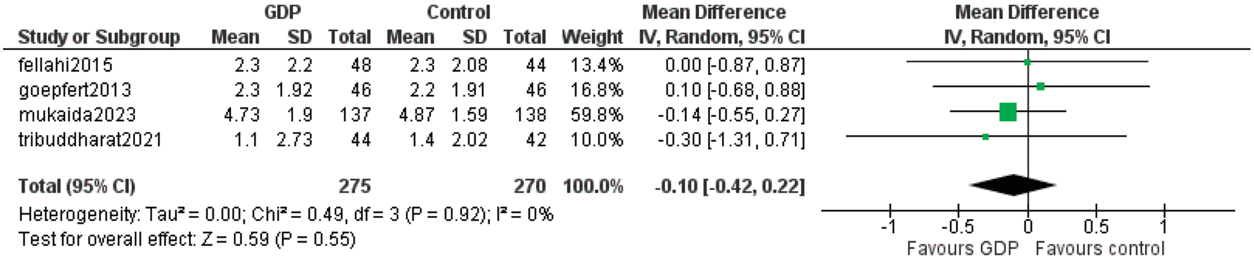
Fig. 6 Mortality rate. This picture illustrates the impact of the GDP group compared to the control group on the patients' mortality rate. GDP: goal-directed perfusion



Study or Subgroup	GDP Mean	GDP SD	GDP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
fellahi2015	2.3	2.2	48	2.3	2.08	44	13.4%	0.00 [-0.87, 0.87]
goepfert2013	2.3	1.92	46	2.2	1.91	46	16.8%	0.10 [-0.68, 0.88]
mukaida2023	4.73	1.9	137	4.87	1.59	138	59.8%	-0.14 [-0.55, 0.27]
tribuddharat2021	1.1	2.73	44	1.4	2.02	42	10.0%	-0.30 [-1.31, 0.71]
Total (95% CI)			**275**			**270**	**100.0%**	**-0.10 [-0.42, 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)

Fig. 7 Delta hemoglobin (g/dL). This picture illustrates the impact of the GDP group compared to the control group on the difference in patients' hemoglobin levels (delta hemoglobin) between preoperative and postoperative. GDP: goal-directed perfusion

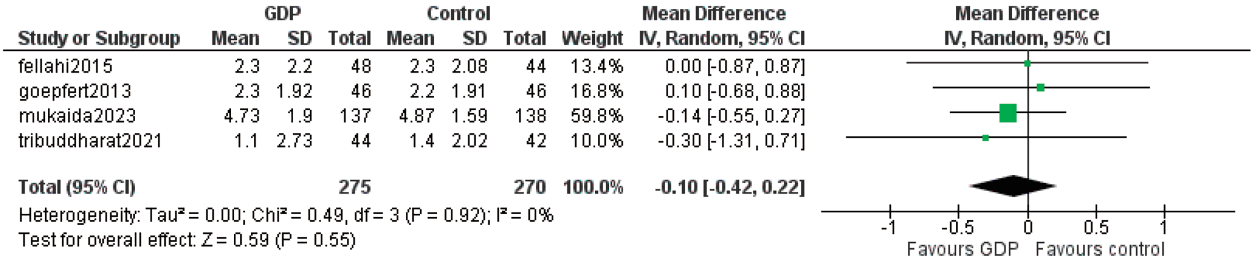


Study or Subgroup	GDP Mean	GDP SD	GDP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
fellahi2015	2.3	2.2	48	2.3	2.08	44	13.4%	0.00 [-0.87, 0.87]
goepfert2013	2.3	1.92	46	2.2	1.91	46	16.8%	0.10 [-0.68, 0.88]
mukaida2023	4.73	1.9	137	4.87	1.59	138	59.8%	-0.14 [-0.55, 0.27]
tribuddharat2021	1.1	2.73	44	1.4	2.02	42	10.0%	-0.30 [-1.31, 0.71]
Total (95% CI)			**275**			**270**	**100.0%**	**-0.10 [-0.42, 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)

Fig. 8 Average of extra volume (mL). This picture illustrates the impact of the GDP group compared to the control group on the amount of additional volume needed during the intraoperative period. GDP: goal-directed perfusion

(**Fig. 6**), the difference in hemoglobin levels between preoperative and postoperative (**Fig. 7**), volume expansion (**Fig. 8**), or the number of packed red cell units transfused (**Fig. 9**). It is important to note that there was considerable heterogeneity in the data for several outcome measures, with an I^2 value exceeding 50%, suggesting variations across studies in the observed effects.



Study or Subgroup	GDP Mean	GDP SD	GDP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
fellahi2015	2.3	2.2	48	2.3	2.08	44	13.4%	0.00 [-0.87, 0.87]
goepfert2013	2.3	1.92	46	2.2	1.91	46	16.8%	0.10 [-0.68, 0.88]
mukaida2023	4.73	1.9	137	4.87	1.59	138	59.8%	-0.14 [-0.55, 0.27]
tribuddharat2021	1.1	2.73	44	1.4	2.02	42	10.0%	-0.30 [-1.31, 0.71]
Total (95% CI)			**275**			**270**	**100.0%**	**-0.10 [-0.42, 0.22]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.49$, $df = 3$ ($P = 0.92$); $I^2 = 0\%$

Test for overall effect: $Z = 0.59$ ($P = 0.55$)

Fig. 9 Number of packed red cells (units) transfused. This picture illustrates the impact of the GDP group compared to the control group on the quantity of PRC required for intraoperative transfusion. GDP: goal-directed perfusion; PRC: packed red cells

Discussion

The concept of goal-directed therapy originated from the research conducted by Shoemaker et al. in 1988, which focused on supranormal oxygen values in high-risk surgical patients. The study utilized flow-based hemodynamic monitoring and therapeutic interventions to target specific CI and DO2 values, aiming to increase tissue oxygen perfusion. The target for VO2 was set above 170 mL/min/m^2. By achieving adequate tissue perfusion and meeting oxygen debt demands, the potential for tissue hypoxia and organ failures could be minimized.13,14) Subsequently, goal-directed therapy gained popularity for improving the survival of patients with septic shock and other critically ill patients, focusing on targeting CI and DO2. This was achieved by adjusting cardiac preload, afterload, and contractility to balance DO2 with oxygen demand and improve survival. Goal-directed therapy has been shown to reduce mortality in extremely high-risk patients and decrease complication rates.15,16) Early implementation of goal-directed therapy during the perioperative period, through the titration of fluid volume and the use of inotropic and vasoconstrictive medications to optimize flow, has been proven to reduce postoperative complications (including cardiogenic shock or sepsis, mediastinitis, permanent stroke, AKI, and acute lung injury), patient LOS, and surgical mortality.17) In non-cardiac surgical patients, goal-directed therapy protocols that assess fluid responsiveness and focus on optimizing CO, CI, DO2, and stroke volume variation (SVV) have been effective in reducing short-term mortality, lactate levels, complications, and ICU and hospital LOS.18,19)

The development from GDP was carried out by de Somer et al. who reported that the use of CPB in cardiac surgery could decrease DO2 to levels below 260 mL/min/m^2, DO2/VCO2 (carbon dioxide production) ratio below 5.3, and hematocrit (HCT) below 23.5%, which were associated with an increased incidence of AKI, hyperlactatemia, and increased VCO2 above 60 mL/min/m^2, which could endanger the patient's condition.20) The GDP strategy manages CPB pump flow/CO based on individualized body surface area and temperature, the use of inotropic and vasopressor according to individualized targeted CI, and balancing fluid including transfusion, which the use of fluids/fluid therapy and transfusion in accordance with the target HCT during CPB. Conditions of optimum oxygen content and delivery can be comprehensively addressed to optimize patient organ perfusion in critical conditions.21)

The GDP research in cardiac surgery is still limited, as evidenced by various meta-analysis studies.22–25) Nonetheless, there are differences between their studies and ours, which focuses on intraoperative GDP interventions during on-pump cardiac surgery. **Table 3** summarizes these distinctions. However, there are also some similarities in our findings. The adoption of GDP procedures can greatly shorten ventilator duration,8–11) hospital stay,7,9,11,23,25) and ICU stay duration.7,9,11) This improvement is because of the use of GDP during the pre-bypass period, which targeted individuals such as SVV, stroke volume index (SVI), CI, systemic vascular resistance index (SVRI), and MAP during surgery. This improves cardiac performance, resulting in lower medication requirements after bypass and before ICU transfer.7,11) GDP with maximum DO2 could minimize the occurrence of postoperative AKI.12) Furthermore, continuing goal-directed therapy in the ICU after surgery helps stabilize lactate, brain natriuretic peptide (BNP), and neutrophil gelatinase-associated lipocalin (NGAL) urine levels.9) In other studies, GDP does not significantly affect ventilator duration,7,12,25) hospital stay,8,12) and ICU stay.2,8,9,10,25) Two studies reported that the insignificance of the duration of the ventilator, length of hospital stay, and ICU stays may be attributed to insufficient statistical

Table 3 Differences with other meta-analysis study

	Key differences	Our study
Giglio,[22] 2012	There are two journals with off-pump cardiac surgery population	All study uses on-pump cardiac surgery population
Aya,[23] 2013	There are two journals with off-pump cardiac surgery population, and three journals with postoperative GDP	All study uses on-pump cardiac surgery population and intraoperative GDP
Osawa,[24] 2016	There are two journals with off-pump cardiac surgery population, and four journals with postoperative GDP	All study uses on-pump cardiac surgery population and intraoperative GDP
Li,[25] 2017	There are two journals with off-pump cardiac surgery population, and four journals with postoperative GDP	All study uses on-pump cardiac surgery population and intraoperative GDP

This table illustrates the differences between the meta-analysis studies discussing goal-directed therapy/goal-directed perfusion that have been previously published with our current study. GDP: goal-directed perfusion

power or limitations in hemodynamic optimization due to limited use of esophageal Doppler monitoring,[8,12] whereas the lack of significance in the study by Li et al. cannot be directly compared because it included patients undergoing off-pump cardiac surgery.[25] Our systematic review also discovered a non-significant reduction in pulmonary issues (OR = 0.46). Despite this, GDP lowers postoperative ventilator duration due to better oxygen supply after CPB.[26] CPB can result in decreased lung compliance and poor oxygenation, which may be related to extended breathing.[26,27]

In our systematic review, the use of GDP protocols resulted in a reduction in mortality with an OR of 0.55 among patients undergoing heart surgery, but statistically not significant. This result is similar to the findings in some meta-analyses such as Giglio et al. (OR 0.55), Aya et al. (OR 0.58), Li et al. (OR 0.58),[22,23,25] and RCT studies.[2,8,9,10] Intensive and specific monitoring-guided early therapies could potentially give more considerable benefits, particularly for individuals in the high-risk category, who often face increased morbidity and mortality concerns.[22,23,25]

GDP implementation has been conclusively proved to significantly reduce postoperative complications,[22,23,24] one of them is AKI.[2,7,11,12] Goal-directed protocol results in less organ damage and a decrease in indicators such as creatinine, lactate, NGAL, and BNP.[2,9,10] Furthermore, goal-directed therapy significantly reduces renal tubular injury, particularly beyond the first inflammatory response induced by CPB.[10] The efficacy of the DO2 method is particularly pronounced in patients with smaller body sizes, showing that it may be beneficial in this subgroup. A targeted DO2 index greater than 270/mL/min/^{2} has been shown to significantly reduce AKI incidence.[2,12]

The non-statistically significant result is also evident in other parameters such as the need for additional administered volume (p = 0.48), difference in hemoglobin levels (p = 0.55), and need for blood transfusion (p = 0.58), as reported in other studies.[7,10,11] This demonstrates that the GDP regimen does not eliminate the necessity for priming fluid volume, including blood transfusions, to maintain the patient's hemodynamic balance. The early goal-directed therapy protocol includes early fluid and drug administration in the pre-bypass phase to reach individualized objectives depending on specific patient characteristics.[7,11] However, monitoring SVV in patients allows for a more accurate prediction of fluid responsiveness and for more precise measurement of supplied oxygen patients.[8] Therefore, goal-directed therapy with fluid responsiveness parameters has been shown to improve patient outcomes.[28,29]

GDP is used in off-pump CABG to detect hemodynamic changes and oxygen transport during the perioperative period. Advanced monitoring using single transpulmonary thermodilution/pulse contour analysis (PiCCO device) with central venous oxygen saturation (SCVO2) and venous oxygen saturation (SVO2) parameters at a minimum of 60% helps optimize DO2. Studies have shown that increasing colloid fluid and dobutamine administration, higher intraoperative fluid balance, and reduced ephedrine requirements can enhance cardiac function and reduce postoperative hospital stay length.[30] The detection of elevated extravascular lung water values using the FloTrac sensor in conjunction with the EV-1000 device indicated the presence of fluid accumulation within interstitial and alveolar tissues. This fluid accumulation adversely affected gas exchange and lung compliance, leading to an extended need for inotropic support and prolonged stays in both the hospital and ICU. In addition, the duration of hospital stay has a negative correlation with SCVO2 and CI.[31] In a study utilizing comparable monitoring devices, the application of early goal-directed therapy led to decreased durations of ICU and hospital stays. This achievement can be attributed to the optimization of myocardial perfusion through the monitoring of SVV, CI, and SVRI using inotropic and vasoactive support.[32)]

GDP has proven advantageous in postoperative cardiac surgery patients, particularly in the ICU. A study employed SVV >10% on the pulmonary artery catheter for maintenance strategies, optimizing hemodynamic parameters, resulting in quicker recovery, lower complication rates, shorter inotropic agent use, and reduced ICU and hospital stays.[33)] The utilization of tools like transesophageal echocardiogram (TEE) with Doppler flowmetry facilitated the attainment of flow-based targets, including maintaining an SVI above 35 mL/m^2 and improving CI within the initial 4 hours in the ICU, indicating tissue perfusion enhancement. This intervention correlated with an 18% decrease in LOS and reduced complication rates.[34)] Achieving a target CI of 3.0 L/min/m^2 through TEE and CO monitoring led to lowered complication rates in postoperative patients. This strategy also resulted in reduced dependence on inotropic support during ICU monitoring, leading to shorter LOS. Furthermore, a decline in the Sequential Organ Failure Assessment score was observed in the 3 days following surgery.[24)] While protocol focused on maintaining SVO2 >70% and lactate levels <2.0 mmol/L, it demonstrated a significant reduction in hospital stay length, ICU readmissions, and lower incidence of organ dysfunctions upon hospital discharge.[35)] Recent Flotrac sensors and EV-1000 devices have enhanced CO and SVV monitoring for fluid guidance, leading to reduced fluid needs in the ICU and associated with shorter stays. This advanced hemodynamic monitoring approach, coupled with precise fluid administration, offers significant benefits to patients.[29,36)]

The European Society of Anesthesiology's approval of goal-directed therapy for patients with high cardiac and surgical risk emphasizes the necessity of optimizing CO and oxygen supply earl.[37)] Goal-directed therapy has proved cost-effectiveness in addition to clinical benefits. This is attributed to cheaper costs as a result of lower complication rates and shorter hospital stays. Long-term cost savings of around $2060 per gained quality-adjusted life year are estimated.[38)] GDP over TP adoption considerably increases the possibility of meeting DO2 objectives, potentially saving roughly $3137 per patient. This might equate to 3.38 ward days and 1.11 ICU days saved per patient. Reduced AKI occurrences and associated renal replacement therapy needs also led to savings, but their impact was less significant. Notably, fluctuations in nadir HCT during CPB and other GDP-related costs had no effect on overall spending because hospital charges were reduced.[39)]

This study has a number of limitations. First, there is a chance that data selection bias exists because of the small amount of research used in the study. Second, there was a noticeable amount of heterogeneity between the trials, which may have been caused by changes in the length of the observation periods, the severity of the diseases, the various CPB protocols used in the various centers, as well as variances in the methods of optimization and monitoring. These differences could introduce confounding variables into the findings, as indicated by the high heterogeneity and inconsistency. However, the overall degree of variability remained within an acceptable range, preserving the clinical significance of the pooled study. Third, we did not look into or analyze RCT involving cardiac surgery patients in the pediatric population, in patients who underwent off-pump procedures, postoperative GDP protocols, or GDP protocols using additional parameters like cerebral oxygen balance, colloid osmotic pressure, MAP, or fluid/volume monitoring. Our investigation uncovered a scarcity of research exploring the implementation of GDP within the pediatric cardiac surgery cohort.

Nonetheless, recent protocol advancements and the latest RCT have introduced a GDP strategy anchored in HCT values, DO2I parameters of ≥360 mL/min/m^2, regional cerebral oxygen saturation, baseline MAP, or SVV. This innovative approach seeks to evaluate the effect of these specific markers on patient outcomes to maximize their effectiveness in optimizing tissue perfusion and reducing postoperative complications.[40,41)]

Conclusion

Postoperative AKI, ICU, and hospital LOS are significantly reduced when GDP protocols are used in intraoperative cardiac surgery using CPB in conjunction with flow management and the use of DO2I and CI as hemodynamic indicators. Additional trials with bigger participant populations and standardized CPB protocols are required to properly evaluate the advantages of GDP protocols in CPB, as well as other parameters.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

The data underlying this article will be shared upon reasonable request with the corresponding author.

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Disclosure statement

The authors declare that there is no conflict of interest.

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