Cardiopulmonary Bypass Settings for the Prevention of Early Hypotension During CABG

Giuseppe Nasso, MD, PhD[1]
Cardiac Surgeon

Giuseppe Speziale, MD, PhD[1]
Cardiac Surgeon

Francesco Bartolomucci, MD[2]
Cardiologist

Giovani Valenti, MD[2]
Cardiologist

Claudio Larosa, MD[2]
Cardiologist

Francesco Borrello, MD[3]
Cardiologist

Vincenzo Amodeo, MD[4]
Cardiologist

Flavio Fiore, MD[1]
Anesthetist

Ignazio Condello, PhD[1]
Chief of Perfusion Service

[1] Department of Cardiac Surgery, Anthea Hospital, GVM Care & Research, Bari, Italy
[2] Ospedale Lorenzo Bonomo, ASL BAT, Andria, Italy
[3] Division of Cardiology and Intensive Care Unit, Pugliese-Ciaccio Hospital, Catanzaro, Italy
[4] Department of Cardiology, Ospedale Santa Maria degli Ungheresi, Polistena, Italy

ABSTRACT

Background: Vasoplegic syndrome is a form of vasodilatory shock that can occur before, during or after cardiopulmonary bypass (CPB). We introduce a strategy to reduce the incidence of early hypotension phenomena during Coronary Artery Bypass Graft (CABG) procedures.

Materials and Methods: In this prospective cohort study, 100 patients underwent elective CABG with two perioperative CPB settings. The study group (50 patients) was managed with retrograde autologous priming (RAP), 3-minute stepwise for the institution of CPB, and pulsatile flow (PP). The control group (50 patients) was managed without RAP, with the rapid initiation of CPB, and non-pulsatile (NP) flow. The primary endpoints were MAP (mmHg), number of hypotensive phenomena (MAP < 50 mmHg for > 30 sec), the venous return volume on CPB (ml), the cardiac index (L/min/m^2), hemoglobin (g/dL), indexed oxygen delivery (DO2i, ml/min/m^2), the systemic vascular resistance index (SVRI, dynes s m^2/cm^5), number of 1-ml boluses of a vasoactive substance (norepinephrine), the positive fluid balance (ml), and the number of red blood cell units for transfusion.

Results: During CPB, the mean values in the study and control groups were as follows: MAP, 68± 7 vs 56 ± 7

(p-value, 0.0019); hypotensive phenomena, 3 ± 1 vs 8 ±2 (p-value, 0.019); venous return volume, 840±79 vs 1129 ±123 (p-value, 0.0017); cardiac index, 2.4 ± 0.4 vs 2.7 ±0.2 (p-value, 0.0023); hemoglobin, 9.13 ± 0.29 vs 7.8± 0.23 (p-value, 0.0001); DO2i, 301± 12 vs 276±23 (p-value, 0.0011); SVRI, 1879 ±280 vs 2210 ±140 (p-value, 0.0017); norepinephrine, 1±2 vs 8 ±3 (p-value, 0.0023); positive fluid balance, 750 ±212 vs 1450 ±220 (p-value, 0.005); and total number of red blood cell units for transfusion, 16 ±4.2 vs 27 ± 5.3 (p-value, 0.008).

Conclusions: In this prospective cohort study, during CPB, the study group showed a better preservation of MAP, SVRI, and DO2i, and a reduction of vasoconstrictor use in a CPB setting with the RAP technique, 3-minute stepwise for the initiation of CPB and pulsatile pump flow, compared to the control group. Further studies are needed to validate this perioperative approach to CPB.

INTRODUCTION

Vasoplegic syndrome is a common occurrence during and following cardiothoracic surgery and is characterized as a high-output shock state with poor systemic vascular resistance. The pathophysiology is complex and includes dysregulation of the vasodilatory and vasoconstrictive properties of smooth vascular muscle cells. Specific bypass-machine and patient factors play key roles in this syndrome.[1] While research into treatment of this syndrome is limited and extrapolated primarily from that pertaining to septic shock, our understanding is evolving. The mechanism by which cardiopulmonary bypass (CPB) leads to vasoplegia is multifactorial and depends on several patient characteristics as well as the nature of the surgical procedure. In healthy humans, vascular smooth muscle contracts as a response to rising levels of intracellular calcium. Increased levels of intracellular calcium cause a cascade of events, starting with myosin phosphorylation, leading to myosin-actin filament crosslinking and vasoconstriction. The influx of cytoplasmic calcium is generated by agonism of G-protein coupled receptors via catecholamines (alpha-1 adrenergic receptor), arginine vasopressin (vasopressin-1 receptor), and angiotensin II (angiotensin type-1 receptor). This mechanism is dysregulated during CPB, as the exposure of blood to foreign surfaces inside of the CPB circuit stimulates the release of inflammatory mediators, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF). These cytokines stimulate the locus coeruleus and the hypothalamic pituitary-adrenal axis in the paraventricular nucleus, which over time leads to adrenoreceptor desensitization and a proinflammatory state. These inflammatory mediators can also potentiate the production of nitric oxide (NO), which is vasodilatory and, when present in excess, can result in vasoplegic shock.[2] Consequently, norepinephrine is released from sympathetic nerves located in lymphoid organs, epinephrine and cortisol are released from the adrenal cortex, arginine vasopressin (AVP) is released from the hypothalamic axis, and angiotensin II is upregulated as part of the renin-angiotensin-aldosterone axis. As shock persists, there is a subsequent depletion of these hormones.

Despite the complexity of the mechanism of the vasoplegic syndrome, several studies show a correlation with the components of the extracorporeal circulation in relation to the characteristics of the patient, but not in relation to the management of CPB. In this context, we introduce a strategy and settings related to CPB with the goal to reduce the incidence of early hypotension phenomena during Coronary Artery Bypass Graft (CABG) procedures.

MATERIALS AND METHODS

Population and study design

Between March 2022 and June 2023, 100 patients aged > 18 years with a mean EuroSCORE II of 1.9–2.1% and LVEF > 45% underwent myocardial revascularization at our institution. The Internal Research Board (Anthea Hospital, GVM Care & Research, Bari, Italy) approved this research (February 2022) and all patients provided their written informed consent to use of their data. Patients with chronic renal failure, type 1 or 2 diabetes mellitus, septic shock or endocarditis, patients with hemoglobin values of <8 g/dL before the procedure and patients with hypotensive phenomena before establishment of the CPB were excluded. Prospective data collection was performed and we compared 100 consecutive patients who underwent isolated CABG surgery. The study group of 50 patients was managed with retrograde autologous priming (RAP), 3-minute stepwise for the institution of CPB, under pulsatile pump (PP) flow. The control group of 50 patients was managed without RAP, with the rapid institution of CPB (< 30 seconds), under non-pulsatile pump (NP) flow. The primary endpoints were MAP (mmHg), number of hypotensive phenomena (MAP < 50 mmHg for > 30 sec), the venous return volume on CPB (ml), the cardiac index (L/min/m^2), hemoglobin (g/dL), indexed oxygen delivery (DO2i, ml/min/m^2), the systemic vascular resistance index (SVRI, dynes s m^2/cm^5), number of 1-ml boluses of a vasoactive substance (norepinephrine), the positive fluid balance (ml), and the number of red blood cell units for transfusion.

CPB Setting

Only an open system (Removell II Venous Reservoir and Oxy AF PLUS, Eurosets, Medolla, Italy) was used for CPB. All patients were treated with mild hypothermic CPB (34–36 °C); 1250 mL crystalloid Ringer acetate solution was used for priming. The surgical procedures selected for this study do not justify the use of moderate hypothermia by falling below 34 °C. For this reason, in the event of an initial increase in anaerobic metabolism, the first compensation approach was not to lower the temperature; however, liquids or red blood cells may have been integrated. The hardware consisted of a Stöckert S5 heart-lung machine and a Stöckert 3T heater-cooler system (LivaNova Plc, London, UK), and the same cannulae were used in both groups. The venous drainage line (3/8 inch) and the arterial delivery line (3/8) were each 180cm long, the lines to the pump (3/8 and 1/2) were each 80 cm, and the car-

dioplegia line (1/16) was 190 cm. The aspiration lines were 1/4. This circuit uses a serial pump with VAVD. Roller pumps were used because aspiration has a management nadir from below 800 mL/min to >2 L/min. A negative pressure of −40 mmHg VAVD was applied to the reservoir. The intracavitary aspirator managed with a roller pump was channeled into a venous reservoir, and the extra-cavitary aspirator was managed with a roller pump.[3] The Landing monitoring system (Eurosets, SRL, Medolla, Italy) was used for DO_2 management during CPB. Metabolic parameters were monitored with a Landing system (Eurosets,SRL, Medolla,Italy); the nadir was higher than 280 mL/min/m^2. The security system used a level alarm, and a dissolved oxygen sensor was used to detect microbubbles leaving the venous reservoir. Anticoagulant therapy consisted of heparin sodium before CPB at 300 IU/kg to give an ACT of greater than 4 by 80 s. Cardioplegia was performed in an antegrade manner with normothermic blood in a 190 cm closed circuit with a bubble-trap filter by a serial micrometric pump, with St. Thomas solution with procaine, and repeated every 30 min.

Anesthetics and surgical procedures

Patients were monitored with 5-lead electrocardiography, a left radial artery catheter, capnography, pulse oximeter and rectal/urine bladder temperature sensors. Transoesophageal echocardiography was performed in all patients. Anaesthesia was induced with intravenous sufentanil (0.5–1 µg/kg) and midazolam (0.08–0.2 mg/kg), and tracheal intubation was facilitated with intravenous rocuronium (0.6–1 mg/kg).[2] Anaesthesia was maintained with propofol (2–5 mg/kg) and sufentanil (0.5–2.0 µg/kg), and the depth of anaesthesia was monitored using bispectral index values (BIS XP, Aspect Medical System, Newton, MA, USA). The dosage of propofol was titrated to maintain BIS values between 40 and 45. All operations were performed in median sternotomy and the CABG procedure was performed as routine by 2 surgeons.[3]

Perfusion techniques in the Study Group

Three-Minute Stepwise Approach to the Cardiopulmonary Bypass Setting.

To avoid early severe hypotension in the first phase of the intervention, we used a 3-minute stepwise approach to gradually empty the right sections of the heart by gradually providing flow in the arterial districts and at the same time gradually reducing the ventilation (Figs. 1a, 2).

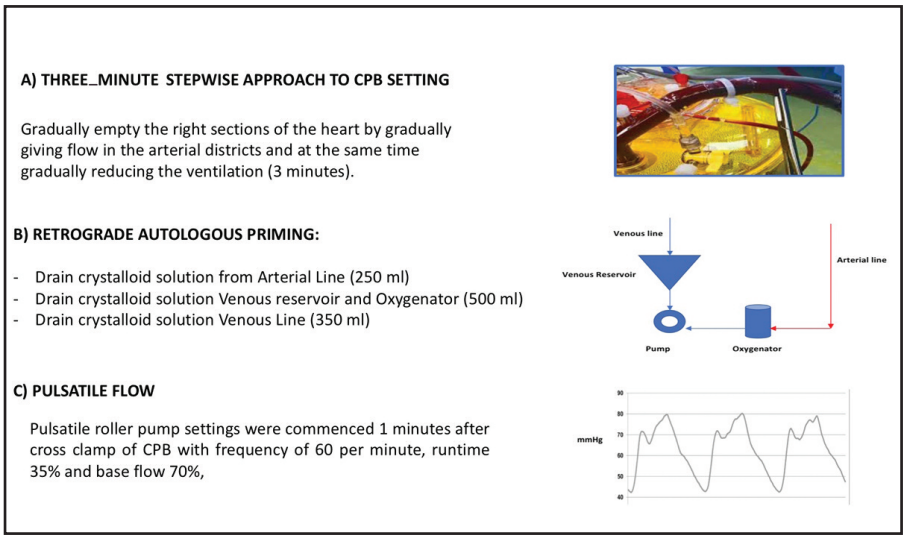

Figure 1. Study group setting for the prevention of early hypotension: a) Three-Minute Stepwise Approach to Cardiopulmonary Bypass Setting, b) Retrograde autologous priming setting, c) Pulsatile Flow setting.

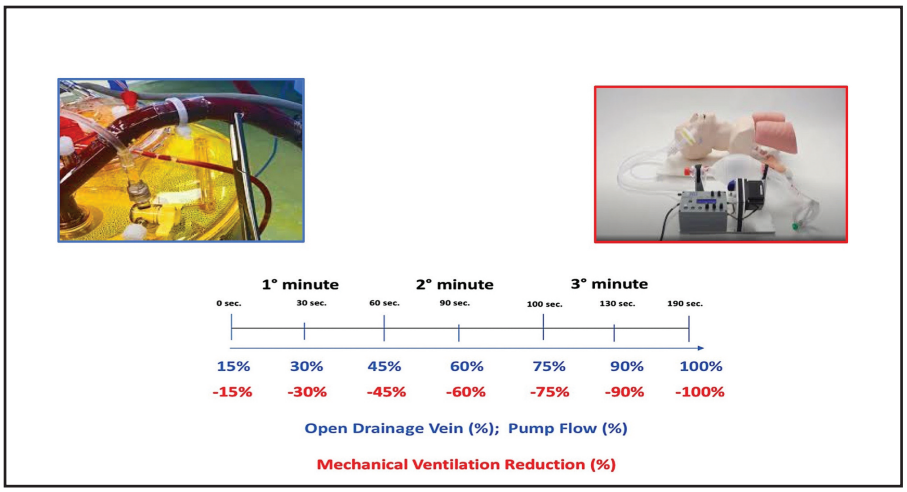

Figure 2. Three-Minute Stepwise Approach to Cardiopulmonary Bypass

RAP technique

Before initiating RAP, mean arterial pressure was elevated to approximately 80 mmHg with the aid of the Trendelenburg position.[4] The priming fluid in the arterial line of the CPB machine was replaced with patient's blood using arterial pressure while the venous line was drained by slowly rotating the arterial pump.[5] The priming fluid of the CPB circuit was slowly drained into the RAP bag. The RAP bag stayed connected to the venous reservoir for fluid replacement during CPB.[6]

Given the circuit length, which on average was longer than that used in sternotomy due to cannulation of the femoral vein, the RAP volume was expected to be between 400 and 600 mL. Nomograms were not used to calculate the intravascular volume after RAP (Fig. 1b).

Pulsatile roller pump flow

Pulsatile roller pump settings were commenced 1 minute after cross-clamp of CPB with a frequency of 60 per minute, runtime 35% and base flow 70% (Stockert S5 roller pump; LivaNova, London, UK) (Fig. 1c).

Goal-directed perfusion, mean arterial pressure management and transfusion trigger

In both the study and control groups, we used the Landing monitoring system (Eurosets, Medolla, Italy) for DO2 continuous monitoring during CPB with the

aim to keep the DO2i value > 280 mL/min/m^2. The Landing monitoring system provides data about oxygen consumption, transport, venous and arterial oxygenation, extracorporeal circuit pressure and blood flow with the ability to update data every 5 seconds; the Landing monitoring system is described in detail elsewhere.[3] The mean arterial pressure during CPB procedures used a cutoff between 50 and 70 mmHg. In both groups, bolus norepinephrine was administered if MAP decreased below 40 mm Hg during CBP.[1] The cardiac index (CI) target was set at 2.4-2.8 L/min/m^2 or above if the DO2i level was below 280 mL/min/m^2. An Hb value <7 g/dL was considered to be the trigger point for RBC transfusion during CPB. Hb levels higher than 7g/dL could also trigger RBC transfusion if DO2i was below 280 mL/min/m^2. An Hb value <7.5 g/dL or <9 g/dL in association with an SVO2 of less than or equal to 65% was considered to be the trigger point for RBC transfusion in the intensive care unit.[7,8]

Table I
Population characteristics

	Study group *(n=50)*	Control group *(n=50)*
Age (years)	73±8	69±9
Male sex (n)	28	27
BSA (m^2)	1.79±0.13	1.82±0.19
Pre-CPB hematocrit (%)	33.3 ± 0.3	33.4 ± 0.7
Pre-CPB Hb (g/dL)	11.1 ± 0.4	11.3± 0.9
Left ventricular ejection fraction (%)	48±5	49±3
EuroSCORE II (mean)	1.9±0.3	2.1±0.4

Values are presented as n (%) or mean ± standard deviation. CPB, cardiopulmonary bypass; Hb, hemoglobin; BSA, body surface area; CABG, coronary arteries bypass grafting.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation or the median with the interquartile range, and categorical data are expressed as percentages. Cumulative survival was evaluated by the Kaplan–Meier method. All reported *p*-values are two-sided, and *p*-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Preoperative demographic details of the patient population are shown in Table I. During CPB, the mean values in the study and control groups were as follows: MAP, 68± 7 vs 56 ± 7 (p-value, 0.0019); hypotensive phenomena, 3 ± 1 vs 8 ±2 (p-value, 0.019); venous return volume, 840±79 vs 1129 ±123 (p-value, 0.0017); cardiac index, 2.4 ± 0.4 vs 2.7 ±0.2 (p-value, 0.0023); hemoglobin, 9.13 ± 0.29 vs 7.8± 0.23 (p-value, 0.0001); DO2i, 301± 12 vs 276±23 (p-value, 0.0011); SVRI, 1879 ±280 vs 2210 ±140 (p-value, 0.0017); norepinephrine, 1±2 vs 8±3 (p-value, 0.0023); positive fluid balance, 750 ±212 vs 1450 ±220 (p-value, 0.005); and total number of red blood cell units for transfusion, 16 ±4.2 vs 27 ± 5.3 (p-value, 0.008) (Table II).

Table II
Population characteristics

	Study group (n=50)	Control group (n=50)	p-value
CBP Time (min)	121±8	110±13	0.83
Cross Clamp Time (min)	94±3	89±7	0.69
Hb (g/dL) during procedures	9.13±0.29	7.8±0.23	0.0001
Htc (%) during procedures	28.56 ± 0.59	24.19 ± 0.25	0.019
Cardiac index (L/min/m^2) during CPB	2.4 ± 0.4	2.7 ±0.2	0.0023
MAP < 50 mmHg events (n)	3 ± 1	8 ±2	0.019
MAP, mmHg	68 ± 7	56 ± 7	0.0019
SVRI (dynes s m^2/cm5)	1879 ±280	2210 ± 140	0.0017
DO2i (ml/min/m^2)	301± 12	276±23	0.0011
Positive fluid balance, ml on CPB (ml)	750 ±212	1450 ±220	0.005
Venous return volume in CPB (ml)	840±79	1129 ±123	0.0019
Total RBC units transfused (n)	16 ±4.2	27 ± 5.3	0.008
Perioperative RBC units transfused (n)	0	18± 3.3	0.0024
Postoperative RBC units transfused (n)	16 ±4.2	9±2.0	0.0019

Values are presented as n (%) or mean ± standard deviation. CPB, cardiopulmonary bypass; Hb, hemoglobin; Htc, hematocrit; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; DO2i, Indexed Oxygen Delivery; RBC, Red Blood Cells.

DISCUSSION

This study is the first to highlight how the synergy of multiple strategies during CPB can influence MAP maintenance and prevent early hypotension. The RAP technique, in addition to helping maintain an adequate DO_2 and reduce the need for transfusions, also helps to maintain both viscosity and osmotic colloid pressure in the vascular lumen, which, together with the vascular tone, helps to maintain the SVRI. The gradual approach to the institution of cardiopulmonary bypass over 3 minutes is not well described in the literature, even though it is good practice under elective conditions in terms of safety to evaluate the correct performance of the oxygenator and functioning of the heart lung machine (HLM). However, in our clinical protocol experience, the 3-minute time would seem to be useful for positively influencing the adaptation of the SVRI to CPB.[9]

The role of pulsatile flow during short-term and long-term extracorporeal support is still controversial.[10] To date, the precise mechanisms underlying the physiological effects of pulsatile and non-pulsatile perfusion are not well understood. Non-pulsatile flow is associated with lower mechanical energy transmission to the vascular wall, which results in decreased endothelial shear stress.[11] The mechanical unloading of arterial baroreceptors leads to a marked increase in sympathetic activity with further progressive vasoconstriction and worsening of peripheral blood flow. At the same time, the lower mechanical energy of non-pulsatile flow reduces the synthesis of shear-responsive, endothelial-derived vasodilators such as nitric oxide. It also contributes to progressive capillary collapse and microcirculatory shunting, and finally leads to tissue hypo-perfusion. Pulsatile flow seems to be more physiologic since it mimics the natural blood flow produced by the human heart.[12] The theoretical benefits of pulsatile perfusion consist of additional energy transmission to the vascular endothelium. This results in higher endothelial shear stress, the augmented release of vasodilative molecules and lower systemic vascular resistance with, consequently, better organ perfusion during and just after pulsatile CPB. Despite the complexity of the mechanism of the vasoplegic syndrome, several studies have shown a correlation with the components of the extracorporeal circulation in relation to the characteristics of the patient, but not in relation to the management of CPB.[13] Levin et al. retrospectively analyzed 2823 adult cardiac surgery cases.[1] Of these, 577 (20.4%) were vasoplegic after separation from CPB and 1645 (58.3%) had a clinically significant decline in MAP after starting CPB. These patients were also far more likely either to die in hospital or to have a length of stay >10 days (odds ratio, 3.30; 95% confidence interval, 1.44 to 7.57; P=0.005).[1] Numerous articles on the topic of vasoplegia and related hypotension during CPB have not described the technique of establishing cardiopulmonary bypass, which is inherent in the gradual emptying of the right sections and the gradual hemodynamic support. In this context, we introduce a strategy and settings through RAP, pulsed flow, and a 3-minute stepwise approach to establishing CPB with the aim of reducing the incidence of early hypotension phenomena during Coronary Artery Bypass Graft (CABG) procedures.

The main limitations of this study are its small sample size, the lack of biomarkers of endothelial reactivity, and the limited collection of data at the time of CPB. As noted in the literature, it is very important to manage hemoglobin levels, oxygen delivery and MAP within cut-offs during CPB for end-organ protection.

CONCLUSION

In this prospective cohort study, during CPB, patients in the study group had a better preservation of MAP SVRI, and DO2i and a reduction of vasoconstrictor use in relation to the CPB setting with the RAP technique (3-minute stepwise for the institution of CPB and pulsatile pump flow) compared to a control group. Further studies will be needed to validate this perioperative approach to CPB. STI

AUTHORS' DISCLOSURES

The authors declare that there are no conflicts of interest.

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Tel. 1 415 436 9790, Email: info@surgicaltechnology.com, Internet: www.surgicaltechnology.com
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