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EDITORIAL

Triluminate pivotal trial: Another brick in the wall?

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Key words: Tricuspid valve; Tricuspid valve regurgitation; Transcatheter edge-to-edge tricuspid repair.

Palabras clave: Válvula tricúspide; Insufiiencia de la válvula tricúspide; Reparación transcatéter borde-a-borde.

Cir Card Mex 2024; 9(1): 1-2.

The Triluminate Pivotal (NCT03904147) is a trial comparing the effectiveness of using transcatheter edge-to-edge therapy in tricuspid valve regurgitation (T-TEER) versus isolated medical treatment. Recently, Sorajja et al [1] have published the results after one year of follow-up. In this study, a total of 350 patients were included; out of them, 175 were assigned to the device arm (T-TEER), and 175 to the medical treatment arm. Although 153 (87%) in the T-TEER group had preoperative atrial fibrillation, the authors do not mention whether any cases were due to atrial functional tricuspid regurgitation. Therefore, we assumed that 100% of the cases were due to secondary or functional tricuspid regurgitation due to right ventricular (RV) dysfunction, elevated pulmonary pressures, or both as predominant factors.

The primary endpoint was composed of three items; namely, a) all-cause death or tricuspid-valve operation, b) hospitalization for heart failure, and c) improvement in quality of life (QoL) as measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ-12). The authors conclude that the results of the primary composite endpoint were favorable to the T-TEER group. However, it is important to mention that both death from any cause (8.8% vs 7.7%) and the hospitalization for heart failure (14.9% vs 12.1%) were unchanged in favor of either group. The favorable result for the device, according to this trial, is based exclusively on the fact that the QoL measured by KCCQ-12 was favorable for T-TEER ($p<0.001$). However, it is quite striking that the 6-minute walk test did not present changes in favor of T-TEER ($p=0.25$).

With all of the above, and given the ambiguous of the situation, we must take the results of this trial with all necessary reservations. At the same time, it is necessary to carry out a rough analysis of this trial, as well as the narrative, which can be confusing for the readers.

Primary composite endpoint by three items

A composite endpoint is one that is composed by several different criteria. Although the use of these primary composites may have advantages for researchers, some requirements must be met when using composite outcomes in decision making [2]. There are some criteria to be met. Otherwise, there is a high risk that clinical decisions will become difficult or impossible. When interpreting the results, it is evident that the frequency of occurrence of the different components is not the same, and that the effect of the intervention (T-TEER) on the different components is not the same. Thus, deciding based on a primary composite endpoint may be difficult or impossible. At the same time, in order to evaluate this primary composite endpoint, it is essential that researchers clearly report the results of each component separately. In this trial, the results are not reported individually in the main article, but only in a loose way in the supplementary material [3].

Therefore, in the Triluminate trial, the effectiveness of using T-TEER is based exclusively on the fact of a better QoL measured through the KCCQ-12. Contrariwise, it should be highlighted that the 6-minute walk test was not favorable for T-TEER. The implications derived from the above have a lot to do with the objectivity of the test, given that while the 6-minute walk is a totally objective test, the KKCQ-12 is a test based on 8 questions resulting in a test totally subjective [4]. Although clinical trials have increasingly used it to evaluate the cutting-edge catheter-based techniques, the level of objectivity of KCCQ-12 can be considered ambiguous. In summary, it would appear that the primary composite endpoint by three items in the Triluminate pivotal trial was created “ad hoc” to justify and ensure the results in favor of T-TEER.

What is the level of objectivity of the KCCQ-12?

As formerly explained, The KCCQ-12 is the short version of the original questionnaire [4]. It is composed of 8 questions, which are answered through an “option to choose” from, but always based on “only appreciative” ranges, that is, “qualitative”. There is no value in such evidence that can be measured tangibly and objectively. The above becomes particularly important when the results of T-TEER are compared through the 6-minute walk test, which in turn, unlike the KCCQ-12, is a completely objective test.Thus, there was no significant difference between the T-TEER arm and the medical treatment arm ($p=0.25$). In conclusion, Triluminate pivotal trial failed to demonstrate with objective data any benefit after T-TEER.

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Placebo effect of T-TEER

To rule out any placebo effect ofT-TEER, it is necessary a double-blind trial, where neither the researchers nor the patients know the treatment applied in the various comparative groups. In the case of Triluminate pivotal trial, due to the characteristics of the trial, it was an open label trial, in which the patient is perfectly aware that an invasive procedure (placement of the clip) has been performed to improve their cardiovascular and health status. As a result, the approach of this trial is totally deficient. In order to eliminate any placebo effect, it would have to be a comparator arm in which the patient underwent a groin puncture or catheterization (without clip installation), in order to have realistic and objective comparisons.Therefore, in the Triluminate pivotal trial, the placebo effect in favor of T-TEER arm cannot be ruled out.

No improvement in death from any cause and hospitalization for heart failure

Commonly, secondary or functional tricuspid regurgitation is due to an alteration in the function or three-dimensional geometry of the RV. In this sense, it is understandable that simply applying the clip to the regurgitant tricuspid valve cannot solve the underlying RV contractile muscle problem. The negative implication on the final outcome of the patient in terms of survival or rehospitalization for heart failure is more than evident in this study [death from any cause (8.8% vs 7.7%), the rate of hospitalization for heart failure (14.9% vs 12.1 %) for T-TEER arm and isolated medical treatment arm, respectively] [1]. Thus, it remains to be defined in which specific group of patients T-TEER would have any usefulness.

Echocardiographic parameters of irreversibility of right ventricular function

As stated by the authors in Triluminate trial, "The majority of participants in this trial had secondary tricuspid regurgitation" [2]. In cardiac surgery, irreversible RV dysfunction in patients with severe tricuspid regurgitation undergoing left-sided valvular surgery is of paramount importance. At present, we know some parameters related to right ventricular (RV) dysfunction. Tricuspid annular plane systolic excursion (TAPSE) (<15 mm), tricuspid annulus systolic velocity (<11 cm/s), and RV end-systolic area (>20 cm2) have been identified as such [5]. Surprisingly, none of the above is included into the exclusion criteria in Triluminate pivotal trial [3].

In conclusion, the Triluminate pivotal turns out to be a poorly objective trial in terms of the real usefulness of T-TEER in patients with isolated tricuspid regurgitation. At one-year follow-up, it failed to prove any utility of T-TEER on patient survival and heart failure rehospitalization rate. The only parameter in favor of T-TEER was QoL. The improvement in QoL measured only by the KCCQ-12 is controversial, as it does not have sufficient objectivity. In contrast, the 6-minute walk test (objective) failed to demonstrate any benefit for T-TEER. The weakness in the exclusion criteria, from the point of view of RV dysfunction, makes the applicability of this trial extremely limited when it comes to moving from theory to practice.

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Contenido

ORIGINAL ARTICLE

Outcomes of extracorporeal membrane oxygenation use in postcardiotomy shock at a single center

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Objective. *The primary objective of this study was to describe the outcomes of patients who underwent extracorporeal membrane oxygenation (ECMO) following postcardiotomy shock at a single center.* ***Material.*** *In this retrospective study, we reviewed the records of patients who had received postcardiotomy ECMO therapy from July 1, 2015 to December 31, 2019. The demographic characteristics and perioperative conditions were described.* ***Results.*** *We included 31 patients, 51.6% female. The median age of 26 years (IQR 12-54.5). Postcardiotomy venoarterial ECMO was used in 1.2% of all operations. Congenital procedures were the type of surgical procedure most associated with using ECMO (61.3%). The most common complication was renal failure (35.4%). The median duration of therapy in patients with successful and unsuccessful withdrawals was 5 and 6 days, respectively. Successful ECMO withdrawal was achieved in 38.7% of patients and 29.1 % at hospital discharge. Cardiogenic shock was the most prevalent cause of death (54.8%).* ***Conclusions.*** *ECMO contributes to improved outcomes in cases where alternative supportive measures are inadequate. The results from our center are similar to published reports supporting the use of postcardiotomy ECMO therapy as a feasible option for critically ill patients.*

Key words: Extracorporeal membrane oxygenation; Postcardiotomy shock; Congenital heart disease.

Objetivo. *El objetivo principal de este estudio fue describir los resultados de los pacientes que se sometieron a oxigenación por membrana extracorpórea (ECMO) en choque posterior a cirugía cardíaca en un solo centro.* ***Material.*** *Es este estudio retrospectivo, revisamos los expedientes de los pacientes que habían recibido terapia ECMO posquirúrgica desde el 1 de julio de 2015 hasta el 31 de diciembre de 2019. Se describieron las características demográficas y las condiciones perioperatorias.* ***Resultados.*** *Se incluyeron 31 pacientes, 51.6% fueron mujeres. La mediana de edad fue de 26 años (RIC 12-54.5). La terapia ECMO postcardiotomía se utilizó en el 1.2% de todas las cirugías. Los procedimientos congénitos se asociaron con más frecuencia en el uso de ECMO (61.3%). La complicación más común fue la insuficiencia renal (35.4%). La mediana de duración de la terapia en pacientes con retiro exitoso y no exitoso fue de 5 y 6 días, respectivamente. Se retiro el ECMO con éxito en 38.7% de los pacientes y 29.1% fue dado de alta. El choque cardiogénico fue la causa de muerte más frecuente de muerte (54.8%).* ***Conclusiones.*** *La terapia ECMO contribuye a mejorar los resultados en los casos en que las medidas de apoyo alternativas resultan inadecuadas. Los resultados de nuestro centro son similares a informes publicados, lo que respalda el uso de la terapia ECMO postcardiotomía como una opción factible para pacientes en estado crítico.*

Palabras clave: Oxigenación por membrana extracorpórea; Choque postcardiotomía; Cardiopatias congénitas.

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Postcardiotomy shock is a complication of cardiac surgery with an incidence of 0.5% to 6% and is associated with a poor prognosis. It is characterized by the inability to wean from cardiopulmonary bypass in the operating room or deterioration of myocardial function during the initial postoperative days and is a life-threatening complication associated with mortality rates ranging from 50% to 80%. After cardiac surgery, VA (venoarterial) ECMO (extracorporeal membrane oxygenation) is initiated in approximately 0.6% to 2.9% of patients [1].

However, despite postcardiotomy VA ECMO support, the in-hospital mortality rate ranges from 53% to 84% and is influenced by patient characteristics and the surgical case mix [1]. Approximately 3.2%–8.4% of children undergoing cardiac surgery may require circulatory support with ECMO owing to cardiogenic shock refractory to optimal medical treatment [2,3]. VA ECMO is intended to completely replace

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cardiac and pulmonary function, maintain continuous tissue perfusion, and allow the heart to recover. When recovery of cardiac function does not occur, VA ECMO can serve as a bridge to a left ventricular assist device, total artificial heart, or heart transplant [1]. In the United States and other developed countries, tertiary care hospitals have extensive experience using this therapy. However, its use in Mexico is relatively recent, considering it was established in 2013 [4,5].

The primary objective of this study was to describe the outcomes of patients who underwent ECMO following postcardiotomy shock at a single center.

MATERIAL

The local institutional review board approved the study, waving the need for patient consent. We conducted a descriptive and cross-sectional study to review the results of VA ECMO use in patients with postcardiotomy shock. We reviewed the records of patients who had received this therapy and met the inclusion criteria between July 1, 2015, and December 31, 2019. The inclusion criteria encompassed the presence of postcardiotomy shock and the use of ECMO for circulatory support. Patients whose clinical records did not include information essential for this study were excluded.

Statistical analysis

We used descriptive statistics for continuous variables, with measures of central tendency (mean, median, and mode), standard deviation, and range. Distributions were evaluated using the Shapiro–Wilk test. Asymmetric data were measured with Fisher's coefficient, and the degree of concentration or Kurtosis was determined. We evaluated quartiles and percentiles. For categorical variables, frequency distributions were shown using box-and-whisker plots. The data were visualized using bar graphs and histograms. The software used was SPSS version 24.0, SPSS Inc., Chicago, IL.

Table 1. Overall patient characteristics

Age (years)	Gender	BSA (kg/m2)	SAH	DM	Reoperation[a]	Aristotle[b]	EuroScore II
11	F	0.86	No	No	Yes	8.5	-
13	F	1.25	No	No	Yes	7.5	-
13	M	1.64	No	No	No	7	-
11	F	1.08	No	No	No	11	-
66	M	1.70	Yes	No	No	-	6.9
13	F	1.40	No	No	No	9	-
12	M	1.37	No	No	Yes	7	-
66	F	1.54	Yes	No	Yes	-	11
40	F	1.67	Yes	No	No	10	-
33	F	1.57	No	No	Yes	-	2
06	F	0.68	No	No	No	3	-
14	F	1.39	No	No	No	12	-
54	M	1.98	No	No	No	-	0.8
58	F	1.49	Yes	No	No	-	4.9
17	M	1.35	No	No	Yes	10	-
57	M	1.93	No	No	No	-	0.67
29	F	1.68	No	No	No	10	-
12	M	1.40	No	No	Yes	11	-
55	M	1.89	No	No	Yes	-	3.09
35	M	2.18	No	No	No	-	12.5
04	F	0.67	No	No	No	3	.
35	M	2.00	Yes	No	No	13	-
57	F	1.58	No	No	No	-	0.9
56	M	2.00	Yes	No	No	-	1.59
59	M	2.07	No	Yes	No	-	1.73
31	F	1.47	No	No	No	6	-
14	F	1.29	No	No	Yes	11	-
07	M	0.73	No	No	No	7.5	-
26	M	1.99	No	No	No	-	7.5
09	F	0.79	No	No	Yes	8	-
12	M	1.74	No	No	No	7	-

BSA: body surface area; DM: diabetes mellitus; F: female; M: male; SAH: systemic arterial hypertension. [a]History of cardiac surgery with a conventional sternotomy approach. [b]Comprehensive Aristotle Score.

RESULTS

A total of 31 patients were included, 16 (51.6%) female and 15 (48.4%) males. Four patients were excluded because of incomplete records (**Table 1**). The median age was 26 years (IQR 12 - 54.5). The youngest patient was 4 years, while the oldest was 66 years. The mean body mass index was 22.5 kg/m2 (SD 5.5]; the most frequent body mass index was 29.3 kg/m2, with a minimum of 13.6 kg/m2 and a maximum of 32 kg/m2. The mean weight was 54.7 kg (SD 23.5); the most frequently reported was 64 kg, with a minimum of 16 kg and a maximum of 95 kg. The median height was 157 cm (IQR 145–168), ranging between 100 cm and 180 cm. The mean body surface area was 1.5 m2 (SD 0.4); the most frequent was 1.4 m2, with a minimum of 0.67 m2 and a maximum of 2.1 m2 (**Fig. 1**). The expected mortality for the different types of surgical procedures was established using the Comprehensive Aristotle Risk Score for congenital procedures. The mean score was 8.5 points (SD 2.7), yielding a surgical risk level of 3 (out of 4); 7.0 points was the most frequent score, with a minimum of 3.0 and a maximum of 13.0 points. For non-congenital surgical procedures, the EuroSCORE II risk scale was used. The median score was 2.5 points (IQR 1.4–7.0), indicating a low surgical risk (<5 points). The lowest patient score was 0.6, and the highest was 12.5. We evaluated cardiac function on initiation of ECMO using four echocardiographic parameters. The median left ventricular ejection fraction was 21% (IQR 15.0–21.0), ranging from 5% to 60%. The median tricuspid annular plane systolic excursion was 5 mm (IQR 15–26.5), ranging from 2 mm to 10 mm. The median aortic velocity-time integral was 4.7 cm (IQR 4.1–5.6), ranging from 1.9 cm to 16 cm. The median cardiac output on initiation of ECMO was 1.8 l/min (IQR 1.7–2.5), ranging between 1.50 l/min and 3.1 l/min. Most patients, 30 (96.8%), were not diagnosed with diabetes mellitus or systemic arterial hypertension 26 (80.6%). Among the included patients, 10 (32.2%) had previous cardiac surgery.

Contenido

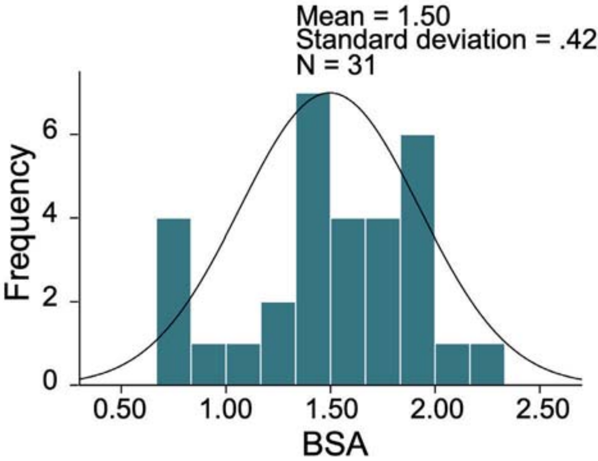

Figure 1. Frequency distribution intervals in comparison with normal distribution. BSA: body surface area.

74.1% of patients were treated using Cardiohelp (Getinge AB, Rastatt, Germany) and 25.9% with Sorin SCP (LivaNova PLC, Mirandola, Italy) systems; the latter used Dideco Membranes (LivaNova PLC, Mirandola, Italy). Congenital procedures were the type of surgical procedure most associated with using ECMO; the therapy was used in 19 (61.3%) patients. Other types of procedures included were isolated valve surgery 7 (22.6%), isolated myocardial revascularization 2 (6.5%), and other procedures 2 (6.5%). Only one patient (3.2%) with a mixed procedure (valve surgery and coronary artery bypass graft) required circulatory support (**Fig. 2**).

Peripheral cannulation was the most frequently used 14 (45.1%). A central approach and hybrid cannulation were used in 12 (38.7%) and 5 (16.1%). The most used left ventricular venting method was double inotropic therapy in 10 (32.3%), followed by surgical atrioseptostomy 6 (19.4%) and drainage catheter in the right superior pulmonary vein was used in 6 (19.4%). No venting method was used in 4 (12.9%); intra-aortic balloon pump was used in 2 (6.5%). The mixed form (surgical atrioseptostomy plus drainage catheter in the right superior pulmonary vein) was used in 2 (6.5%), and only one patient underwent percutaneous atrioseptostomy (3.2%).

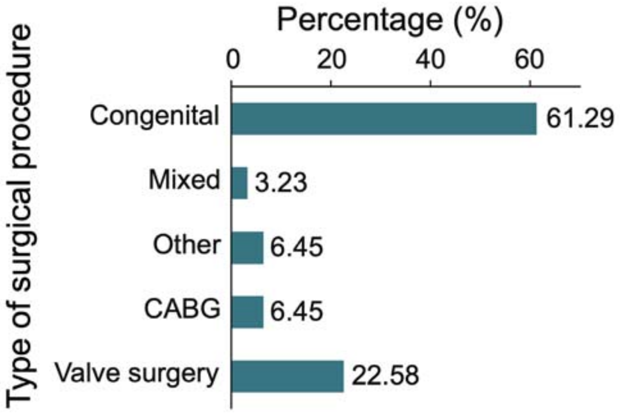

Figure 2. Surgery to treat congenital heart disease is noteworthy for its greater use of circulatory therapy. Mixed indicates valve surgery plus CABG. CABG: coronary artery bypass graft.

Among complications that occurred with the use of ECMO, the most frequent was renal failure 11 (35.4%); major bleeding with central cannulation 10 (32.2%); and infections 10 (32.2%), all respiratory origin; and two of the latter patients (6.4%) developed sepsis. Cardiac tamponade occurred in 5 (16.1%) cases, and injury to an artery or vein of the lower extremities occurred in 4 (12.9%). Cerebrovascular events during postcardiotomy VA ECMO occurred in 3 (9.6%), all of whom were hemorrhagic. Bleeding at the peripheral cannulation site was seen in 2 (6.4%) of patients. Hemolysis was observed in only two patients (6.4%).

The median duration of postcardiotomy VA ECMO in patients with successful and unsuccessful withdrawal was 5 days (IQR 3.5–9.0) and 6 days (IQR 3–12.5), respectively. The shortest duration of ECMO therapy was 3 days in the first group and one day in the second group, whereas the longest durations were 20 and 25 days, respectively (**Fig. 3**).

After ECMO withdrawal, echocardiographic parameters were as follows. The mean left ventricle ejection fraction was 51.6% (SD 12.1%); the most frequent value was 23%, with a minimum of 23% and a maximum of 68%. The mean tricuspid annular plane systolic excursion was 12.0 (SD 3.4) mm; the most frequently reported value was 11 mm, with a minimum of 7.5 mm and a maximum of 20 mm. The mean aortic velocity time integral was 18.2 (SD 5.1) cm; the most frequent value was 22 cm, with a minimum of 8.9 cm and a maximum of 25 cm. The median cardiac output was 4.5 l/min (IQR 4.4–5.2 l/min). The lowest cardiac output was 4.2 l/min, and the highest was 5.5 l/min.

Withdrawal of postcardiotomy VA ECMO was successful in 12 (38.7%) patients and 9 (29.1%) at hospital discharge. Regarding patients in whom ECMO was unsuccessful, the most frequently reported cause of mortality was cardiogenic shock 17 (54.8%). Two patients (6.4%) died of hypovolemic shock.

DISCUSSION

VA ECMO postcardiotomy shock has a reported success rate at hospital discharge of approximately 40% [4, 5]. Although still not optimal, the success rate at our hospital was acceptable (38.7% at withdrawal and 29% at hospital discharge). Furthermore, the number of cases with satisfactory outcomes has been increasing as the center acquires experience in patient selection, decision-making, cannulation techniques, and care of the patient during ECMO therapy. Throughout the study period, ECMO employment for postcardiotomy shock constituted 1.2% of all performed surgeries, consistent with global findings reported in other studies [1, 4].

Surgical treatment for congenital heart defects is highly complex, particularly when two or three-stage procedures must be performed. The patients in this study had a mean Comprehensive Aristotle Score of 8.5 points, representing greater complexi-

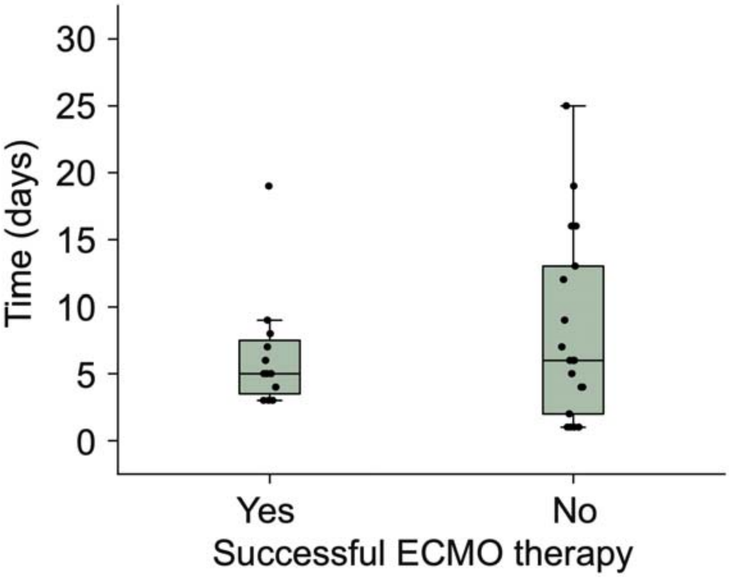

Figure 3. Box-and-whisker plots of the duration of ECMO therapy in successful and unsuccessful cases. ECMO: extracorporeal membrane oxygenation.

ty. This coincided with the greater use of ECMO therapy in these procedures [6,7].

The factors that most influence the prognosis of patients treated with ECMO are the timing of initiation and the parameters evaluated before cannulation [8-12]. We found that in our cases treated during 2015 and 2016, the optimal echocardiographic evaluation was not conducted, and the initiation of therapy was delayed in some cases. We also identified that a left ventricular venting technique was rarely used. The relationship between left ventricular venting and favorable outcomes is well-documented [13]. The Impella Device (Abiomed Inc, Danvers, MA) in ECMO is a good option for unloading the left ventricle but is very expensive for routine use. After the training of the ECMO team, we decided to use an unloading left ventricle method routinely. The best results were related to this strategy, among other modifications in the patient's care with ECMO. We generally use double inotropic therapy, surgical atrioseptostomy, or a drainage catheter in the right superior pulmonary vein. Our approach to surgical atrioseptostomy is distinctive. We place a purse in the right atrium with a polypropylene suture, then insert a 5 mm thoracoscopy trocar through the purse, ensuring a procedure is airtight all the time. Then a puncture of the oval fossa is performed, guided by reconstruction in 3D rendering of the atrial septum by transesophageal echocardiography. The benefit of this approach is reducing the risk of iatrogenic injuries to adjacent structures without needing catheterization to perform atrioseptostomy.

The duration of ECMO support has been correlated with the prognosis of patients. In VA ECMO, the ideal treatment duration is no longer than 3–5 days; survival after 10 days is very low [11, 14]. We showed that in most patients with successful outcomes, the duration of ECMO was between 3 and 9 days. Cardiogenic shock was the main cause of death among patients with unsuccessful ECMO. Two patients died of hypovolemic shock, a complication that is very difficult to treat in these patients and has been the subject of multiple recent studies [7, 11, 15].

Renal failure and bleeding at the cannulation site are the most common complications among patients receiving ECMO. Acute kidney failure is as high as 70% to 85%. Acute renal failure in ECMO is associated with higher mortality rates of up to 80% [16-19]. Bleeding is more common in postcardiotomy therapy, ranging between 10% and 30% [15,19]. Consistent with other reports, kidney failure and bleeding were the predominant complications observed at our center. Infectious complications are reported worldwide in approximately 13% of cases. Infection mainly originates in the respiratory and urinary systems and is often associated with sepsis [19, 20]. In our study, infection occurred in 32.2% of the patients. Among these, two patients developed sepsis. We showed that hemolysis was among the less common complications (6.4%). We believe this complication may be underdiagnosed because, at our hospital, there is no free hemoglobin in the plasma test [21, 22]. Limb ischemia complications were not frequent, which could be explained by the greater number of cases with central or hybrid cannulation and the routine use of distal perfusion cannula in the femoral artery in peripheral cannulation patients. Cerebrovascular events were also rare (9.6%), and they were all related to supra-anticoagulation, which resulted in hemorrhagic events.

Echocardiographic evaluation to decide on ECMO cannulation is very important. Past studies reported the need to assess left and right ventricular morphology and function, the dimension and volume of the right atrium, valve pathology, and other factors such as the presence of patent foramen ovale, aortic dissection or atheroma, and the Chiari network [12]. We collected data on left ventricle ejection fraction, tricuspid annular plane systolic excursion, aortic velocity time integral, and cardiac output. These parameters at the initiation of ECMO were as follows: median left ventricle ejection fraction was 21%, median tricuspid

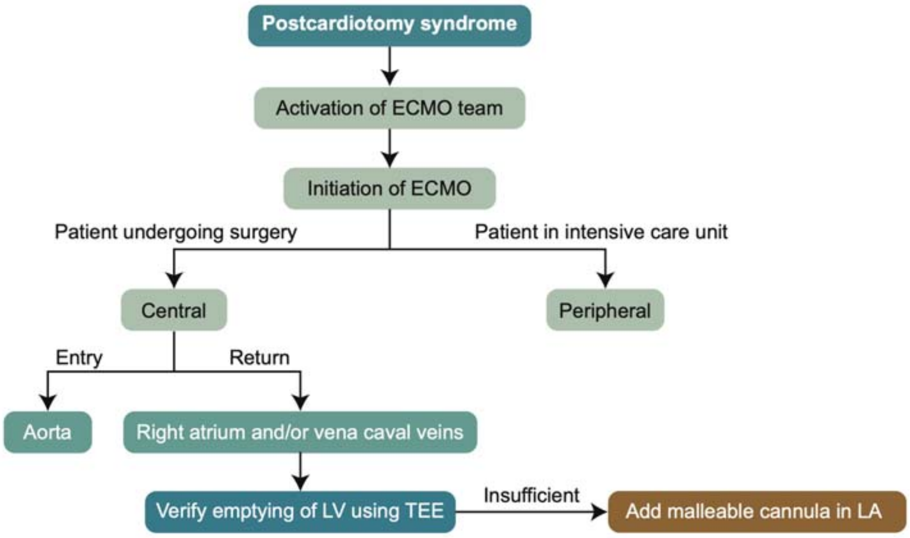

Figure 4. Algorithm to decide the configuration of cannulation in postcardiotomy shock. ECMO: extracorporeal membrane oxygenation; LA: left atrium; LV: left ventricle; TEE: transesophageal echocardiography.

annular plane systolic excursion was 5 mm, aortic velocity time integral was 4.7 cm, and cardiac output was 1.8 l/min. These were undoubtedly very low values, indicating poor cardiac function and contributing to the decision to use circulatory therapy. These same parameters were measured upon therapy withdrawal, revealing the following values: mean left ventricle ejection fraction was 51.6%, mean tricuspid annular plane systolic ejection was 12 mm, mean aortic velocity time integral was 18.2 cm, and cardiac output was 4.5 l/min. Most patients had records with target echocardiographic parameters, but some patients could not complete echocardiographic evaluation.

Importantly, the current patient assessment carried out by the ECMO team at this center is comprehensive and includes additional parameters such as the Interagency Registry for Mechanically Assisted Circulatory Support classification, age, type of pathology, evaluation of chronic or acute irreversible organic conditions, absence of contraindications, and team consensus.

Furthermore, we have decision algorithms for VA ECMO weaning and cannulation configuration in postcardiotomy shock. For a patient with postcardiotomy syndrome, we activate an ECMO alert to make the equipment available as soon as possible. We use central or hybrid cannulation if the patient is in the operating room. Our hybrid configuration consists of aortic cannulation with a polytetrafluoroethylene tubular, which is across through skin below the xiphoid appendix, and then is connected to the aortic cannula; this maneuver allows definitive sternal close. Venous drainage is carried out with a femoral or jugular cannula. If the patient is in intensive care and his clinical state is critical, we opt for peripheral femoral cannulation. We verify in all cases that the left ventricle is decompressed. The weaning begins when the patient presents data of cardiac recovery with adequate pulse pressure, mean arterial pressure over 60 mmHg with low dose or no vasopressor support, and without metabolic complications. We generally perform this protocol after 72 hours of placing the ECMO.

Our approach involves a gradual reduction in ECMO flow followed by a comprehensive hemodynamic evaluation. If hemodynamic deterioration occurs, the previous flow supply is reinstated, and subsequent weaning attempts are made (**Fig. 4**) (**Fig. 5**). The ECMO team was better trained in all aspects during the second half of the study period, which coincided with the better results obtained in the latest cases. In-hospital staff training began in 2017; from then on, theoretical-practical seminars are held every six months, allowing team members to transmit knowledge and experience.

Information regarding the outcomes of ECMO use in the context of cardiac surgery remains limited. While a few large series have reported results on ECMO therapy over the past three decades [23], its application has increased in the post-cardiac surgery setting. Remarkably, despite its widespread use, ECMO therapy after cardiac surgery has not shown a clear association with improved outcomes [24, 25].

As a conclusion, postcardiotomy VA ECMO was utilized in just over 1% of cardiac surgery patients experiencing postcardiotomy shock. Circulatory therapy was commonly required during congenital malformation procedures, particularly in high-risk patients. Successful ECMO cases demonstrated shorter therapy durations, typically within 7 days. Our center's outcomes align with numerous published reports, further supporting VA ECMO as a viable option for critically ill patients. VA ECMO improves outcomes by providing circulatory support in cases where alternative support measures prove inadequate.

Study limitations

As limitations in this study, the data used in this study were based on the clinical records; however, bias related to variability in inter-rater reliability may be present. The sample size was small because postcardiotomy VA ECMO is performed infrequently at our center, which limited our ability to calculate measures of association. However, this descriptive study fulfilled our objectives and must be understood from this perspective.

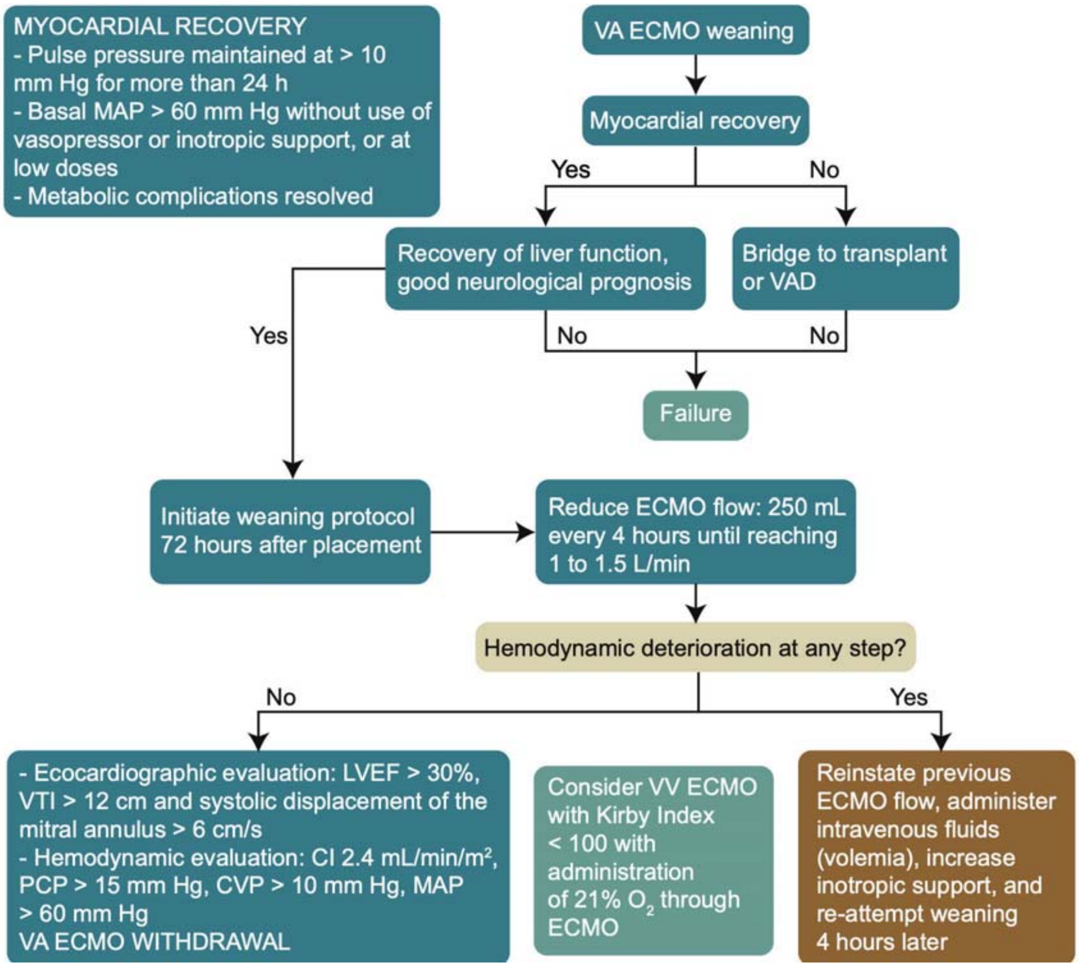

***Figure 5.** Venoarterial ECMO weaning algorithm. CI: cardiac index; CVP: central venous pressure; ECMO: extracorporeal membrane oxygenation; MAP: mean arterial pressure; PCP: pulmonary capillary pressure; VA: venoarterial; VAD: ventricular assist device; VV: venovenous.*

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REVIEW ARTICLE

Regulatory T cells in the "inflammatory balance" as a response to extracorporeal circulation in cardiac surgery. A narrative review

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Extracorporeal circulation (ECC) offers the benefit of maintaining a bloodless and still surgical field, providing a suitable surgical scenario for the performance of the surgical procedure. It is an essential procedure in virtually all heart surgeries, aiming to temporarily replace the function of the cardiopulmonary system, thus maintaining blood perfusion to organs and body tissues. Unfortunately, the use of this procedure triggers an inflammatory cascade, with endothelial dysfunction being the main triggering mechanism. This damage is a result of the contact between blood components with synthetic plastic surfaces, activating an intense inflammatory response, impacting the postoperative outcomes of patients undergoing this procedure. Regulatory T cells (Tregs) are a subtype of T lymphocytes that play a role in modulating the inflammatory response, specially by activation of a transcription factor called FOXP3. In this revision was identified that the understanding of Treg lymphocytes T and ECC interaction will improve an opportunity to comprehend the physiopathology of development and activation of inflammatory process into cardiac surgery, although ECC has generated an impact on cardiac surgery, also has a price to pay associated to inflammatory phenomenon with negative effect on postsurgical evolution in patients that underwent to cardiac surgery and the recognition of the lymphocytes TregFoxP3 regulatory capacity offer to develop future strategies that promote activation and it´s preservation during ECC through immunomodulatory drugs, such as corticosteroids and adrenergic receptor agonists will to help improve the outcomes of heart surgery.

Key words: Extracorporeal circulation; Inflammatory response; T regulatory lymphocites; Transcription factor FOXP3.

La Circulación Extracorpórea (CEC) ofrece el beneficio de mantener un campo quirúrgico exangüe que aporta un escenario quirúrgico apropiado para la realización del procedimiento intracardiaco, condición indispensable en prácticamente todas las cirugías de corazón. Desafortunadamente, este procedimiento desencadena una cascada inflamatoria debido al contacto de la sangre con las superficies de la CEC. Esta inflamación puede tener un impacto negativo en la recuperación del paciente. Los linfocitos T reguladores son un subtipo de linfocitos T que intervienen en la modulación de la respuesta inflamatoria, especialmente a través de la activación de un factor de transcripción denominado FOXP3 que participa como el principal regulador transcripcional de los linfocitos Tregs. En esta revisión se identificó que la comprensión de la interacción entre los linfocitos Tregs y la CEC ofrece la oportunidad de entender la fisiopatología involucrada en la activación y desarrollo de la inflamación en la cirugía cardíaca, que a pesar que la CEC ha generado un gran impacto en el desarrollo de la cirugía a corazón abierto hay un precio que pagar, asociado al fenómeno inflamatorio que desencadena y finalmente afectando la evolución posquirúrgica del paciente sometido a dicho procedimiento y adicionalmente se reconoce que la capacidad reguladora de inflamación de los linfocitos TregFoxP3 ofrece la oportunidad de desarrollar estrategias futuras que propicien su activación, preservación de su función durante la CEC mediante fármacos inmunomoduladores, como corticosteroides y agonistas de receptores adrenérgicos, para coadyuvar en la mejora de resultados de la cirugía cardiaca.

***Palabras clave**: Circulación Extracorpórea; Respuesta inflamatoria; Linfocitos T reguladores; Factor de transcripción FOXP3.*

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Contenido

Cardiac surgery has experienced significant advancements in recent decades, due to the introduction and refinement of surgical techniques and innovative technologies. Among these techniques, extracorporeal circulation (ECC) has become a fundamental tool in performing complex cardiac procedures. ECC allows for the adequate perfusion and oxygenation of vital organs while surgical correction is being performed on the heart, such as in the repair of congenital heart defects, coronary revascularization, heart transplantation, and valve correction [1].

Despite its undeniable utility, ECC triggers a systemic inflammatory response associated with coagulopathy, neurological, pulmonary, and renal dysfunction, with hemodynamic effects and a negative impact on the patient's recovery and outcomes. Therefore, it is crucial to thoroughly understand the technical and pathophysiological aspects of ECC, as well as identify strategies to mitigate and prevent complications.

Recently, the possibility of a regulatory response of the body's inflammatory process has been identified, which may also be present during extracorporeal circulation [2]. This review will examine some components involved in extracorporeal circulation, the inflammatory process it triggers, as well as the role of regulatory T lymphocytes (Tregs) as a possible regulatory response to the immune response triggered by ECC and their potential implications in clinical outcomes.

Components of extracorporeal circulation

ECC is an essential procedure for virtually all interventions in cardiac surgery, temporarily replacing the function of the cardiopulmonary system to maintain blood oxygenation and perfusion of the organs and tissues of the body. The device or pump diverts deoxygenated venous blood from the right atrium of the heart through cannulas (made of polyurethane) and plastic tubing (PVC or polyvinyl chloride) to a reservoir that is connected to a pump. Depending on its mechanism of action, the pump directs the blood either to a membrane oxygenator to carry out gas diffusion or through the tubing and another cannula inserted directly into the ascending aorta or another medium-sized artery, subsequently supplying the entire body, maintaining aerobic metabolism, and ensuring perfusion to all organs. This procedure offers the benefit of maintaining a bloodless and motionless surgical field, providing an appropriate setting for the surgical procedure [1].

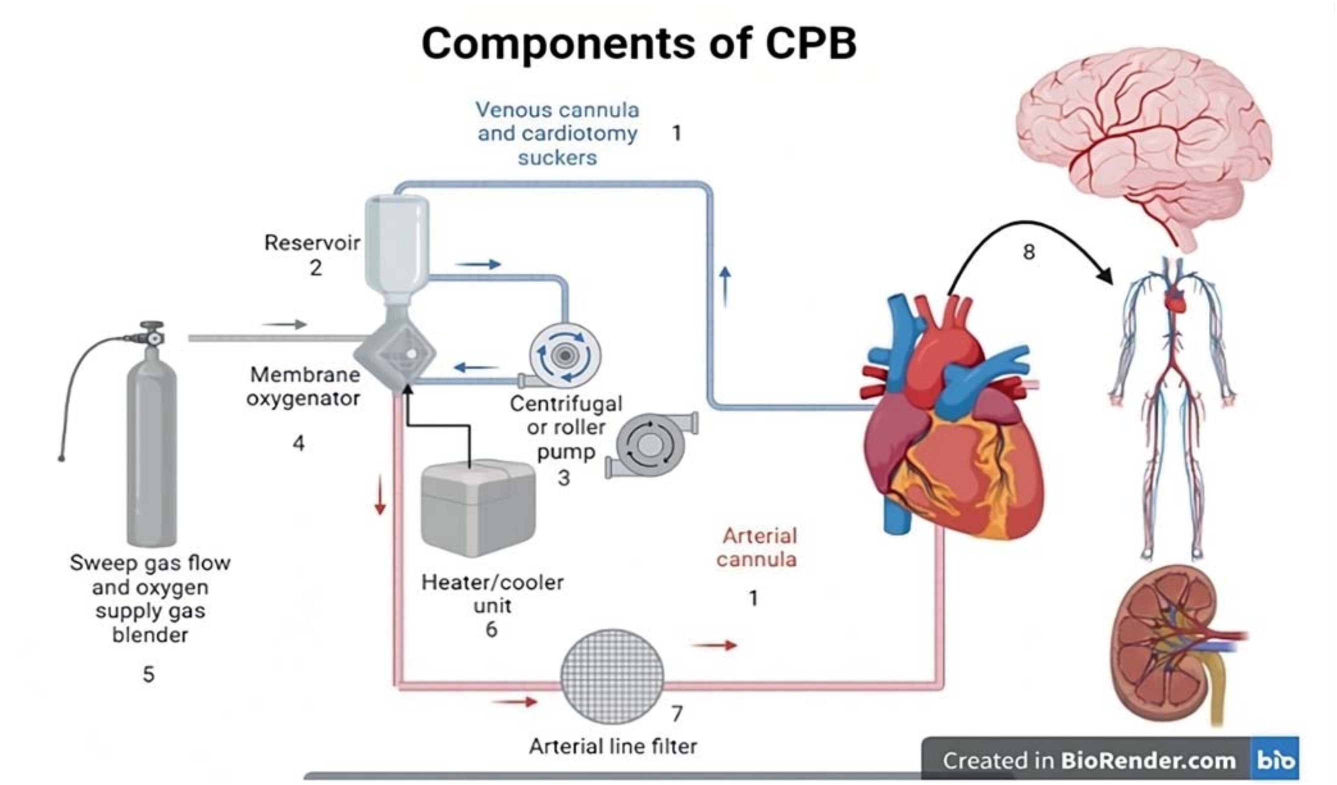

Figure 1. Components of conventional extracorporeal circulation. 1) Venous cannula, cardiotomy suction and arterial cannula. 2) Venous reservoir. 3) Centrifugal/roller pump. 4) Membranae oxygenator. 5) Sweep flow and oxygen mixer blender. 6) Heating/cooler unit device. 7) Arterial line. 8) Systemic blood distribution to vital organs. The components mentioned above are commonly used in conventional extracorporeal circulation. However, variations in the specific equipment and configurations may exist depending on the surgical procedureand individual patient needs.

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Contenido

In recent decades, numerous advances in equipment and techniques have been introduced, resulting in notable improvements in the morbidity and mortality of patients undergoing ECC (**Fig. 1**) [2-4].

The main components of extracorporeal circulation are:

1. Arterial and venous cannulas: These are flexible PVC (polyvinyl chloride) and/or polyurethane tubes used to connect the extracorporeal circulation system to the patient's arterial and venous system. The venous cannula is inserted into a vein to drain deoxygenated blood to the ECC machine, while the arterial cannula is placed in an artery (ascending aorta in central cannulation or axillary/femoral artery in peripheral cannulation) to return oxygenated blood to the body. The inflammatory response associated with cannulas is primarily due to their interaction with blood and foreign material surfaces. Their surface, especially if made of non-biocompatible materials like PVC, can trigger an immune response. Blood cells and proteins can adhere to such surface, activating inflammatory pathways and leading to the release of inflammatory mediators, initiating a cascade known as the contact activation pathway and promoting leukocyte activation and adhesion [5-6].

The composition of the cannula material can influence the magnitude of the inflammatory response. For example, cannulas made of more biocompatible materials, such as polymers with hydrophilic coatings, have been developed to reduce the inflammatory reaction. Additionally, the design of the cannula can also affect this response. Smooth and rounded cannula tips and a reduced contact surface can minimize blood flow disruption and decrease inflammation [7].

The modification of the circuit surface, aiming to replicate the antithrombotic and anti-inflammatory properties of the endothelium, includes the application of biomimetic surfaces (e.g., using heparin or direct thrombin inhibitors), biopassive surfaces (by using phospholipid-like phosphocholine or albumin), and more experimental attempts at endothelialization of circuit components. The most used biomimetic approach, which seeks to replicate the antithrombotic and anti-inflammatory properties of the endothelium, is heparin coating, which has shown to reduce cellular activation and release of inflammatory mediators in clinical studies of extracorporeal membrane circulation, as well as in in vivo models, and is even associated with better clinical outcomes such as shorter ICU stays and lower incidence of postoperative atrial fibrillation. Preparing the circuit with a heparin-albumin solution can have a similar effect, as PVC can absorb plasma proteins. On the other hand, biopassive approaches aim to make the circuit more inert. A common technique is coating with phospholipid-like phosphocholine, which is the main component of cell membrane phospholipids. It is believed that the formation of a biomembrane-like surface reduces thrombin formation, although its effect on inflammation is not well understood [8].

2. Venous reservoir: It is a reservoir that stores deoxygenated blood returning from the patient. The venous reservoir has the capacity to collect and filter the blood before sending it to the oxygenator for gas exchange. The flow dynamics within the venous reservoir can generate mechanical stress and turbulence, which can contribute to inflammation. Turbulent flow patterns and high shear stress can activate endothelial cells and trigger an inflammatory response. Design modifications in the venous reservoir, such as optimizing flow patterns and reducing turbulence, can help mitigate this effect. Changes in geometry can be made to improve flow and reduce turbulence. Proper sizing and strategic placement of these connections can facilitate more uniform flow and reduce turbulence. The use of biocompatible materials in constructing the reservoir can also reduce the inflammatory response and promote a more laminar flow [9].

3. Blood pump: It is a component responsible for propelling oxygenated blood from the oxygenator back into the patient's body. The blood pump can be either a roller pump or a centrifugal pump, and its function is to maintain adequate blood flow during surgery while the patient's heart is stopped. While both types of pumps are effective in providing blood circulation, they may differ in their impact on inflammation. The roller pump operates by compressing flexible PVC tubes to propel the blood forward. It is a pulsatile pump that generates an intermittent flow. The roller pump has been associated with a higher degree of shear stress and turbulence compared to centrifugal pumps. These factors can activate endothelial cells and trigger an inflammatory response. The increased presence of these factors may contribute to a higher risk of hemolysis and platelet activation, potentially leading to increased inflammation. On the other hand, the centrifugal pump utilizes rotational forces to propel the blood forward. It provides a continuous flow with less pulsatility compared to roller pumps. Centrifugal pumps generally generate less shear stress and turbulence, theoretically resulting in less endothelial cell activation and a potentially milder inflammatory response compared to roller pumps.

It is important to note that the choice between a roller pump and a centrifugal pump in cardiac surgery is based on various factors, including surgeon preferences, patient characteristics, and specific procedure requirements. It should be mentioned that research and some clinical studies have examined the impact of pump types on inflammation, but specific findings and conclusions may vary among studies.

Passaroni et al. [10] analyzed 60 patients undergoing coronary artery bypass grafting (CABG) surgery with ECC. The patients were randomly assigned to two groups: Group 1 (roller pump) and Group 2 (centrifugal pump). Measurements of haptoglobin and lactate dehydrogenase (LDH) were performed to evaluate hemolysis, and levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) were measured to assess the inflammatory response. No significant differences were found in the incidence of hemolysis and inflammatory response between the roller and centrifugal pumps. However, significant differences were observed in haptoglobin, LDH, and CRP levels at different time points, indicating hemolytic and inflammatory changes during the perioperative period.

Keyser et al. [11] conducted a prospective, randomized study involving 240 adult patients undergoing CABG surgery with ECC, where five different types of arterial pumps were used: roller pump, peristaltic pump, Sarns Delphin centrifugal pump, Rotaflow centrifugal pump, and Bio-Medicus Bio-Pump BP 80 centrifugal pump. The results showed a decrease in hemoglobin levels, hematocrit, and red blood cell count after surgery, which then recovered on the third postoperative day. There were no significant differences between the groups in these parameters. Platelet count decreased after surgery and recovered on the third postoperative day, with no significant differences between the groups. In terms of clinical outcomes, there were no significant differences between the groups in terms of mechanical ventilation time, ICU stay, and hospitalization duration. There were also no significant differences in intraoperative blood loss, amount of postoperative blood drainage, or transfusion of red blood cell concentrates or fresh frozen plasma.

While one of the studies carrying significant weight is the meta-analysis conducted by Saczkowski et al. [12], where they evaluated 18 randomized clinical trials that met their inclusion criteria and represented 1868 patients (Centrifugal pump= 961, Roller pump= 907). The predominant operation was coronary artery bypass grafting, and fixed-effect pooled estimates were performed for the end of ECC and the first postoperative day for platelet count (ECC: $P = 0.51$, first postoperative day: $P = 0.16$), free plasma hemoglobin (ECC: $P = 0.36$, first postoperative day: $P = 0.24$), white blood cell count (ECC: $P = 0.21$, first postoperative day: $P = 0.66$), and hematocrit (ECC: $P = 0.06$, first postoperative day: $P = 0.51$). No difference was demonstrated in postoperative blood loss ($P = 0.65$) or red blood cell transfusion ($P = 0.71$). The duration of ICU stay ($P = 0.30$), hospital stay ($P = 0.33$), and mortality ($P = 0.91$) were similar between both groups, with no significant differences in the evaluated variables.

Roller pumps and centrifugal pumps produce non-pulsatile flow (NPF) by default, and this remains the most used mode of perfusion. The development of pulsatile pumps has allowed for comparisons with NPF. Pulsatile flow (PF) mimics the arterial pulse generated by the heart and is considered more physiological by some.

Most of the articles reviewed by Tan et al. [13] in their review article on PF were randomized controlled trials. However, there was wide variation in study methodology, pulse-generating method, and how pulsatility was measured. Most of the evidence in favor of PF showed marginal improvement in renal and pulmonary outcomes. Although there is a lack of high-quality randomized clinical trials that can inform short- and long-term clinical outcomes of PF, further research is needed to reach a conclusion regarding its benefits on organ function. Pulsatility is an important factor for maintaining vascular function and homeostasis during cardiac surgery with ECC. Lack of pulsatility can have detrimental effects on the endothelium and organ perfusion, while pulsatile circulation may be beneficial. This alternating cycle of pressure and flow generates different hemodynamic forces, such as pulse pressure, cyclic shear stress, and cyclic strain, which are sensed at the cellular level and give rise to a variety of physiological responses. The endothelial glycocalyx (EG) is a critical component of endothelial cells and is a primary sensor of shear stress, vital for endothelial nitric oxide (NO) production [14,15], which tends to maintain endothelial homeostasis, including regulation of vasomotor tone, vascular permeability, and acts as an important antioxidant. Additionally, the EG plays a critical role in modulating inflammatory responses, acting as a physical barrier for leukocyte recruitment and extravasation. Loss of pulsatility can induce endothelial injury, demonstrated by degradation and release of the EG through markers such as heparan sulfate and syndecan-1, lasting up to 3 days after an average of approximately 100 minutes of pulsatile-free ECC [16].

At least in theory, pulsatile circulation should avoid the detrimental effects of non-pulsatile circulation on the endothelium.

4. Membrane oxygenator: It is a medical device used in ECC to provide oxygenation and remove carbon dioxide from the blood during cardiac surgical procedures. It consists of a hollow fiber membrane that serves as a gas exchange interface, separating the patient's blood and facilitating the interaction between blood and air, allowing the transfer of oxygen from the gas to the blood and the removal of carbon dioxide from the blood into the gas. The membrane is designed to be gas-permeable, meaning it allows oxygen and carbon dioxide molecules to diffuse through it. This is achieved by selecting suitable materials for membrane fabrication, such as polypropylene, polysulfone, or polymethylpentene. The gas exchange membrane has a porous or microporous structure that provides a large surface area for gas exchange. This structure allows gas molecules to pass through the membrane pores while preventing blood cells or larger particles from doing so [17]. Additionally, advanced oxygenators now incorporate the necessary materials for the heating/cooling unit and arterial line filters within their design, improving outcomes in cardiac surgery by reducing some of the complications triggered by ECC use (macro and micro systemic emboli) [18].

To reduce the inflammatory response during ECC, strategies such as the use of biocompatible surface-coated oxygenators, chemical modifications, and modified perfusion techniques have been implemented. These measures aim to minimize blood cell activation, oxidative stress, and clot formation [19].

Through the history of cardiac surgery with ECC, various types of oxygenators have been developed to facilitate gas exchange and improve oxygenation efficiency. These range from bubble oxygenators, which were the first to be used, to screen oxygenators, disc oxygenators, and the development of membrane oxygenators and high-performance oxygenators used in extracorporeal membrane oxygenation, designed for longer operating times due to their greater surface area for gas diffusion, durability, and biocompatibility in this type of extracorporeal oxygenation therapy [20].

The evolution of oxygenators used in ECC has been driven by the search for more efficient and biocompatible devices that reduce the inflammatory response and improve clinical outcomes. Technological advancements continue in this field, aiming to further enhance the safety and performance of oxygenators in cardiac surgery and other procedures requiring extracorporeal circulation. The latest data demonstrate that there is no single superior product in all aspects. Biochemically, there are small differences among oxygenators that do not translate into clinical differences in outcomes. The design and selection of the ideal oxygenator depend on the specific performance aspects that the perfusion team and surgical team consider relevant in the decision-making process [21–31].

5. Oxygen blender and sweep flow system: The oxygen blender is a critical component of ECC that precisely controls the ratio of oxygen and other gases in the mixture to ensure that the blood receives the appropriate amount of oxygen according to the patient's needs. This is important for maintaining adequate oxygenation levels and preventing hypoxemia (low blood oxygen levels) or hyperoxemia (excessively high blood oxygen levels) during the procedure. While there is no universally accepted strategy for managing oxygen metabolism during ECC, the trend, particularly among surgical teams and perfusionists, leans towards hyperoxemia in a significant number of centers

performing cardiac surgeries with ECC [32]. The discrepancy in preferences has been examined through surveys on oxygen administration during cardiac surgery with extracorporeal circulation. The survey included 317 anesthesiologists and 237 perfusionists, and revealed differences in oxygenation preferences between the two groups. Anesthesiologists were more comfortable with lower oxygen tension (90-250 mmHg PaO2), while perfusionists preferred higher levels (150-325 mmHg PaO2). This discrepancy is due to the availability of real-time peripheral oxygen saturation monitoring for anesthesiologists, which allows for more precise adjustment of oxygen administration. On the other hand, perfusionists lack this advantage during extracorporeal circulation and tend to titrate toward higher oxygen levels to avoid hypoxemia. Additionally, perfusionists also considered the presence of gas microemboli as a factor influencing their preference for higher oxygen levels [33].

There are potential risks and adverse effects associated with hyperoxemia (exposure to elevated oxygen levels) during ECC, with one of the main concerns being the threshold for determining hyperoxemia levels. While it is claimed to have therapeutic benefits such as myocardial preconditioning to better tolerate ischemia, reduced rates of postoperative wound infection, and decreased generation of gas microemboli during ECC, there are concerns about the negative impact of high partial pressures of oxygen on cardiac, vascular, neurological, respiratory, and renal function, as well as the possibility of exacerbating ischemia-reperfusion injury by altering the production of reactive oxygen species (ROS) that can accelerate the established inflammatory process [34].

One recent study by Douin et al. [35], a multicenter cohort study involving 21,632 patients undergoing ECC, demonstrated that hyperoxemia occurred over 96% of the time before, during, and after extracorporeal circulation. Cumulative intraoperative exposure to hyperoxemia, assessed continuously as the area under the curve, was associated with the development of postoperative pulmonary complications in a linear relationship during ECC. Increasing exposure to hyperoxemia before and during ECC was associated with a higher risk of postoperative pulmonary complications, while lower levels of hyperoxemia exposure after ECC were associated with a lower risk. Prospective clinical trials are needed to determine the causal relationship between hyperoxemia and not only postoperative pulmonary complications but also to establish optimal oxygenation targets during cardiac surgery. The upcoming "Risk of Oxygen during Cardiac Surgery" trial [36] may reveal optimal oxygenation goals for both cardiothoracic anesthesiologists and perfusionists.

Based on current evidence, normoxemic management may also reduce oxygen-derived free radicals during ECC, as well as reduce inflammatory cytokines. Completely preventing systemic inflammatory response syndrome (SIRS) is challenging as it is related to multiple factors, including direct contact of blood cells with artificial surfaces followed by leukocyte activation, ischemia-reperfusion injury to the heart and lungs, and oxidative injury. However, we can minimize SIRS by reducing oxidative injury, ischemia-reperfusion injury, and the production of anti-inflammatory cytokines [38].

The sweep flow system refers to a component used to remove exhaled carbon dioxide (CO2) and other residual gases from the ECC circuit during blood oxygenation. It works by extracting a small amount of gas from the oxygenator or venous return line and subsequently eliminating it from the circuit by connecting it to a CO2 removal device such as a CO2 absorber or filter. While this is not directly related to inflammation, efficient removal of CO2 and residual gases can help maintain proper homeostasis and reduce oxidative stress in the cardiovascular system. The gas removed through the sweep flow system contains CO2 exhaled by the patient and other residual gases. Its elimination helps maintain adequate CO2 levels in the oxygenated blood that is returned to the patient during ECC. This contributes to maintaining acid-base balance and ensures that the circulating blood is properly oxygenated and free from undesirable residual gases.

Some authors follow strategies for pH management through sweep flow and have found differences in pediatric and adult management. Thus, the trend is to make the necessary adjustments and modifications based on goal-directed therapy, which in this case would involve maintaining a pH range of 7.35-7.45 depending on the clinical context. Karabulut et al. [39] evaluated thirty patients undergoing isolated coronary artery bypass grafting and randomly and equally assigned them to three groups. The sweep flow to the oxygenator was maintained at 1.35 Lt/min/m2 in Group 1, 1.60 Lt/min/m2 in Group 2, and 2.0 Lt/min/m2 in Group 3. Blood gas samples were taken at the following time points: T1: before ECC; T2: 5 minutes after the start of ECC; T3: just before rewarming; and T4: at the end of rewarming. At 5 minutes after the start of ECC (T2), pCO2 significantly decreased in Groups 2 and 3 compared to Group 1 ($p < 0.02$). With the addition of hypothermia (T3), changes in pH and pCO2 became more profound, and during this period, levels in Group 3 exceeded physiological limits, with pCO2 and pH values of 28 ± 3 mmHg and 7.50 ± 0.04, respectively. At the end of the rewarming period (T4), despite increased carbon dioxide production, pCO2 values were below physiological limits in Groups 2 and 3. They concluded that the gas sweep flow to the oxygenator should be maintained between 1.35 and 1.60 L/min/m2 during ECC to avoid hypocapnia, which leads to alkalosis and has detrimental effects on pulmonary, cerebral blood flow, and the cardiovascular system.

On the other hand, Clingan et al [38]. retrospectively analyzed 1,077 cases in which PaCO2 values were not lower than 30 mmHg or higher than 50 mmHg in preoperative blood gas results. They examined the respiratory-to-blood flow ratio (V/Q) within the first few minutes of initiating ECC. A V/Q of 0.6 had an odds ratio (OR) of 1.57 for achieving a PaCO2 value between 35 and 45 mmHg in the initial blood gas analysis during ECC compared to a V/Q of 0.4. A V/Q of 0.9 had an OR of 1.76 compared to a V/Q of 0.4 and an OR of 1.12 compared to 0.6. Using a V/Q ratio of 0.6 achieved a PaCO2 value within normal physiological limits without a significant advantage compared to a higher V/Q ratio overall. However, younger or smaller patients required a higher V/Q ratio to achieve similar odds and PaCO2 values compared to larger or older patients. They contrast this ratio with the previous study by Karabulut [39] and compare sweep flow rates of 1.35, 1.6, and 2 Lt/min/m2, which would translate to V/Q ratios of 0.675, 0.8, and 1, respectively.

Although these are observational studies, the information described allows for an analysis of the situation. Depending on the experience of the surgical team, hospital infrastructure, and available resources, goal-directed therapy based on physiological parameters should be the trend in managing ECC circuit components.

6. Heating/Cooling Devices: During ECC, the blood circulating outside the patient's body tends to cool down. To maintain proper body temperature, a device is used to heat the blood before reintroducing it into the body. This helps prevent hypothermia and maintain normal metabolic function.

These first-generation devices control temperature by heating or cooling water and circulating that water through water lines to a disposable heat/cold exchanger located in the ECC oxygenator. Typically, they consist of at least two circuits: a patient circuit, responsible for maintaining the patient's body temperature, and a cardioplegia circuit, responsible for cooling a solution directly administered to the heart [40]. Due to the presence of a water reservoir in these devices, they have long been postulated as a potential source of infection, especially Mycobacterium chimaera, a member of the Mycobacterium avium complex, a group of slow-growing nontuberculous mycobacteria [41]. In 2015, a deadly outbreak of Mycobacterium chimaera was attributed to the use of heating/cooling units during extracorporeal circulation [42]. It was confirmed that the transmission route for these bacteria was aerosolization through the device's exhaust fan, which dispersed bacteria into the operating room air. Since this discovery, multiple cases of M. chimaera infections have been attributed to heating/cooling units, causing significant harm and even death to patients [43].

As a result, the US Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) recommended strictly following a cleaning, disinfection, and maintenance protocol provided by the device manufacturers, as well as water sampling and monitoring. The protocol involves cleaning and disinfecting the equipment following the manufacturer's instructions, environmental testing, measures to be taken in case of positive results, reporting instructions, task allocation among hospital departments (preventive medicine department, clinical microbiology and parasitology department, and cardiac surgery department), and case identification standards. According to the protocol, the Sorin system (LivaNova) cleaning and disinfection include the following: surface and water circuit disinfection (before first use, before storing the device, and during regular use), surface disinfection after each use, water replacement (adding hydrogen peroxide to tanks), and overflow bottle disinfection every 7 days, water circuit disinfection every 14 days, tube replacement every year, and annual cleaning and disinfection by the manufacturer [43].

The second-generation glycol exchange system is a widely accepted technology used in applications requiring biostatic capacity. The solution involves reformulating the biostatic thermal fluid into a biocidal thermal fluid. This is achieved by adding monomeric glutaraldehyde (Quantum, Medtronic) and has the potential to eliminate aerosolization-related infections, such as those caused by M. chimaera, avoiding the use of chemical agents for disinfection. Although it requires the use of an additional disposable heat exchanger and manipulation of the glycol by the operator, it offers greater control and lower risk of malfunctions. However, its recharge is not automated and requires the physical presence of the user. These technological improvements are important for safety and efficiency during cardiac surgery [43].

Regarding inflammation during ECC, the patient's body is cooled to a lower temperature to decrease metabolic demand and protect vital organs. This hypothermia can have anti-inflammatory effects by reducing the release of inflammatory mediators and attenuating the immune response. Low temperatures can also decrease cellular metabolism, reducing tissue injury and inflammation. On the other hand, warming the patient after the hypothermic period can trigger an inflammatory response. The sudden increase in temperature during rewarming can activate inflammatory pathways and promote the release of pro-inflammatory cytokines. This response is known as reperfusion injury and can contribute to inflammation and tissue damage. The use of this device in ECC allows precise control of the patient's body temperature. Gradual rewarming is often employed instead of rapid rewarming to minimize the inflammatory response. By controlling the rewarming rate and maintaining a stable temperature, the inflammatory cascade can be attenuated, reducing the risk of complications associated with excessive inflammation [44-46].

7. Arterial line filter: It is a device used to remove any particles or microemboli before they return to the patient, helping to prevent systemic macro and microembolism during cardiac surgery. The efficacy of the arterial line filter in ECC has been the subject of research, and studies have been conducted to evaluate its impact on various aspects, including the inflammatory response. According to the available evidence, the use of an arterial line filter during ECC can help reduce the burden of microemboli and particles in the patient's circulation. This can have a beneficial effect by decreasing the inflammatory response and preventing potential complications related to inflammation [47].

The particles present in the bloodstream during ECC can vary in size. Generally, smaller particles are considered to have a greater potential for causing harm as they can pass through filters and access organs and tissues. The retention capacity of these filters typically ranges from particles of approximately 40 micrometers (µm) to particles of around 20 µm [48].

The oxygenator and arterial line filter have been integrated into a single device as a method to reduce priming volume and surface area, as mentioned earlier. The instructions for use of a currently available oxygenator with an integrated arterial line filter recommend incorporating a distal recirculation line at the outlet of the oxygenator. However, according to a non-scientific survey, 70% of respondents use ECC circuits that incorporate these integrated filters without a distal recirculation pathway at the oxygenator outlet. Considering this circuit design, the ability to quickly eliminate a large air bubble in the blood path distal to the oxygenator outlet may be compromised. Reagor et al. [49] concluded in that a distal recirculation line to an oxygenator with an integrated arterial line filter significantly reduces the time required to remove an air bubble from the ECC circuit and may be safer for clinical use than the same circuit without a recirculation line.

8. Anticoagulants: ECC is a process in which blood flow is diverted outside the body to perform complex cardiac surgical procedures. During ECC, heparin is used as a systemic anticoagulant to prevent clot formation in the extracorporeal circuit and ensure adequate blood flow. Heparin belongs to the family of glycosaminoglycan (GAG) molecules, which consist of repeated disaccharide units of uronic acid residues (L-iduronic acid or D-glucuronic acid) and N-acetyl-D-glucosamine. Un-

fractionated heparin (UFH) is the least processed form of natural GAG and is derived from purified porcine intestinal tissue. It has a molecular weight of 3 to 30 kDa [50].

The pentasaccharide sequence-containing unfractionated heparin is responsible for its interaction with antithrombin (AT) on thrombin. Heparin is anionic and binds to the positively charged residues of the protease inhibitor AT. This causes a conformational change in the reactive arginine center of AT and an increase in the rate and binding activity of AT by up to 1000-fold. Furthermore, the reactive arginine center of AT covalently binds to the active serine protease center of thrombin (factor IIa), factor Xa, and other serine proteases, irreversibly inhibiting their procoagulant activity. Heparin molecules containing the pentasaccharide sequence have strong anticoagulant effects through their binding with AT, facilitated by binding to exosite II. Because access to exosite II is obstructed, heparin does not act on fibrin-bound thrombin, unlike direct thrombin inhibitors [51].

Recent guidelines from the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA) in 2018 have provided recommendations on the dosing and monitoring of heparin for CPB. The key principles from this document are as follows [52-55]:

Before initiating CPB, adequate anticoagulation should be demonstrated through an activated clotting time (ACT). Heparin doses for CPB start at 300-400 IU per kg of total body weight, but individual response to heparin is heterogeneous. Adequate anticoagulation is considered when the activated clotting time (ACT) is above 480 seconds. There is significant molecular variability in unfractionated heparin (UFH); therefore, the dose-response relationship is complicated.

Alternative methods exist to calculate the initial heparin dose, such as ex vivo heparin response curves, which compare ACTs with added UFH concentrations. The HepCon heparin response model is based on adding two heparin concentrations, 1.7 IU/ml and 2.84 IU/ml, to the patient's blood plasma and assumes a linear dose-response relationship. It then estimates the heparin dose needed to achieve concentrations of 2 IU/ml, which falls between the two used heparin concentrations. However, studies have shown poor correlation between the calculated in vitro heparin response curve and the actual patient response to heparin.

Activated clotting time (ACT) is considered the "standard of care" for assessing anticoagulation during CPB. In the clinical context of an ACT for safe anticoagulation during CPB, heparin concentration and ACT maintain an approximately linear relationship. All tests operate with different methodologies (amount/type of activator).

Protamine reverses the anticoagulant effect of heparin by forming an ionic bond between the anionic charge of heparin and the cationic charge of protamine. This new complex prevents heparin from binding to antithrombin (AT) and causes dissociation of heparin already bound to AT, allowing AT function to return to normal. The neutralization of heparin by protamine is amplified by platelet factor 4 (PF4) activity. Platelet factor 4 is released by platelets that are activated during CPB and acts to stabilize the heparin-protamine complex. The protamine-heparin complex is cleared through the reticuloendothelial system. The elimination half-life is 7.4 minutes, so most protamine is cleared from the body after 15 minutes.

Protamine has a range of unwanted effects that vary in severity and morbidity. The rate of adverse reactions is documented between 0.1% and 13% and includes hypotension, pulmonary hypertension, and anaphylaxis. Most severe reactions occur within the first 10 minutes of injection. Independent risk factors for protamine reaction include the use of insulin containing protamine (NPH insulin), previous reaction to protamine, allergy to protamine or fish, and any history of non-protamine drug allergies.

Hypotension is the most common hemodynamic effect and varies in severity from mild instability to cardiovascular collapse. It is defined as a systolic blood pressure (SBP) <100 mmHg or a reduction in mean arterial pressure (MAP) >10 mmHg.

Anaphylaxis associated with protamine has an incidence of 0.19%. Both immunoglobulin E (IgE)-mediated and IgG-mediated anaphylaxis have been described. Severity and incidence are related to the presence of specific antibodies against protamine. Heparin-protamine complexes are known to activate the classical complement pathway, leading to basophil and mast cell degranulation through C3a and C5a.

To achieve successful anticoagulation during CPB, it is necessary to reverse anticoagulation both at the end of CPB and during the postoperative period. Insufficient doses of protamine have been shown to increase postoperative bleeding; however, high doses of protamine have also been associated with increased postoperative bleeding.

Regimens based on the initial heparin dose result in prolonged clotting times and microvascular bleeding compared to protamine based on the measured heparin concentration. Additionally, protamine/heparin ratios greater than 1.3 are associated with increased postoperative bleeding compared to 0.8, without affecting ACT or heparin rebound. Furthermore, a protamine/heparin ratio of 0.6 may be better than a ratio of 0.8. At lower doses, a protamine/heparin ratio <0.6 is associated with increased blood loss in the first 12 hours after surgery.

The recommendations from the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA) [64] advise a lower total dose and emphasize that the protamine dose should match the actual heparin concentration after CPB. They also suggest low-dose protamine infusion (25 mg/h) for up to 6 hours to reduce the risk of heparin rebound.

The EACTS and EACTA guidelines recommend a total dose lower than the dose recommended by the STS/SCA [64] and stress that the protamine dose should match the actual heparin concentration after CPB. It is also advised that the protamine dose not exceed a ratio of 1:1 with respect to the initial heparin bolus.

9. Monitoring and Control: During extracorporeal circulation, it is crucial to monitor and control various parameters to ensure patient safety and well-being. This includes monitoring blood pressure, temperature, blood flow, gas concentration, and other vital indicators. Monitoring and control

devices provide real-time information to the medical team to make appropriate decisions during surgery [56].

This leads us to one of the main pillars within the multidisciplinary surgical team responsible for managing ECC, which is the perfusionist. Considered a specialist technician, the perfusionist is a clinical scientist who directs extracorporeal circulation towards goal-directed perfusion. This involves maintaining hemodynamic stability by keeping mean arterial pressure (MAP) above 65-70 mmHg, cardiac index >2.4 l/min/m2 and ensuring an adequate oxygen supply essential for tissue metabolism with indexed oxygen delivery (iDO2) >272 ml/min/m2. Monitoring parameters such as arterial oxygen saturation (SaO2) >94%, central or mixed venous oxygen saturation (SvO2) >65-70%, adjusting pump flow rate to meet the patient's metabolic demands, and maintaining an appropriate hematocrit level above 25% during ECC are important for oxygen transport capacity. Achieving optimal body temperature without compromising tissue perfusion and oxygenation through mild hypothermia and/or normothermia, as well as evaluating the function of end organs during ECC, such as renal function with urine flow >0.5 ml/kg/min and neurological function using near-infrared spectroscopy (NIRS), all this parameters help to identify any perfusion-related complications and guide interventions to optimize tissue perfusion in a preventive rather than corrective manner [24,57-60]. Continuous monitoring and adjustment of parameters help ensure tissue perfusion and prioritize preventive measures over correcting alterations in these objectives, focusing on the support of clinical guidelines for temperature management (61), anticoagulation management, blood component management [62], as well as the most recent guidelines for ECC management and conduct [63,64], in order to timely perform interventions and reduce potential complications that can be triggered by poor practice.

Understanding all relevant aspects of technological advancements for better clinical outcomes is of fundamental importance in evidence-based medicine applied to the science of extracorporeal circulation in cardiac surgery.

So far, some of the most important innovations in the clinical practice of conventional cardiac surgery with extracorporeal circulation have been reaffirmed. However, over the past two decades, an exceptional practice has emerged and has been increasing in developed countries, mainly due to the good results obtained in cardiac surgery. Despite being a low, intermediate, or high-risk intervention, it is associated with complications and postoperative sequelae that affect the quality of life of patients. This technique, known as Minimally Invasive Extracorporeal Circulation (MiECC), aims to minimize the invasiveness of ECC procedures (**Fig. 2**) [65], involving the use of specialized equipment and strategies to reduce the size of conventional circuits and the associated inflammatory response.

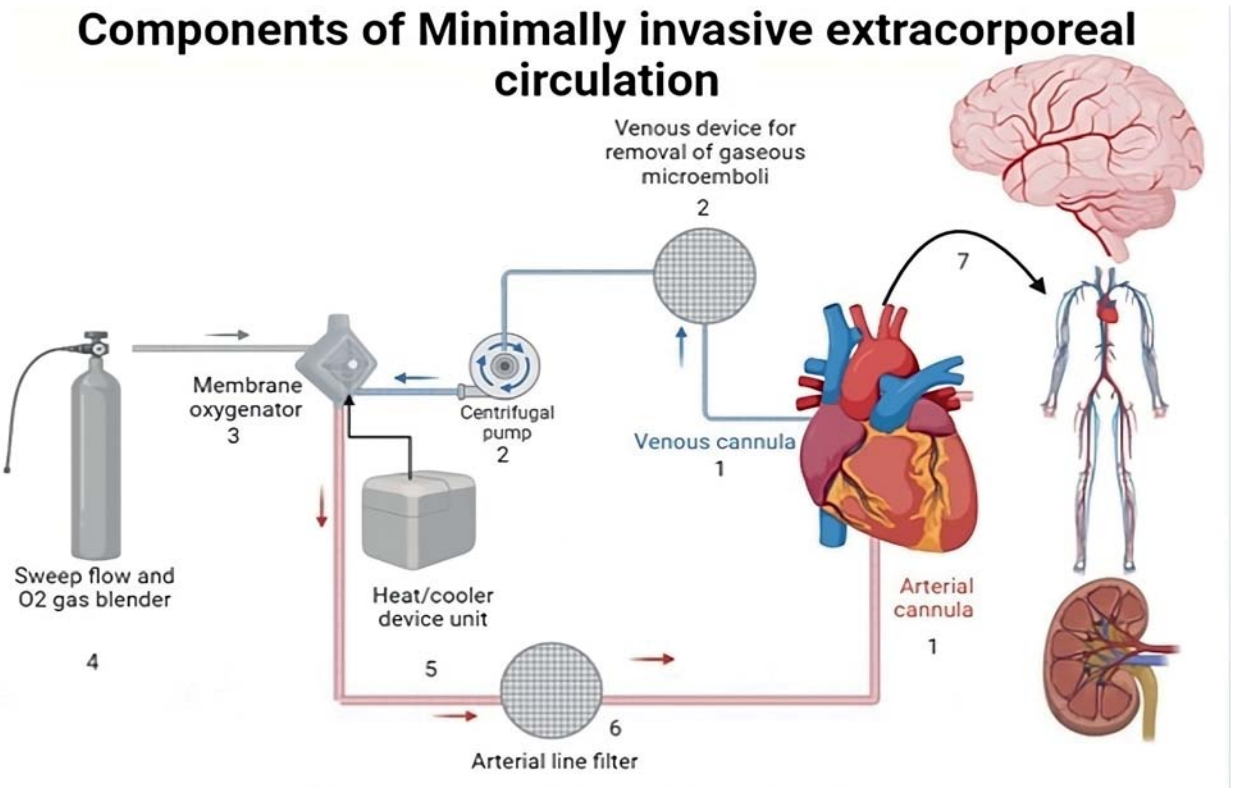

Figure 2. Components of Minimally Invasive Extracorporeal Circulation. This illustration depicts the configuration of this technique, particularly one of the most used circuits, which is Circuit II (Air Management). Circuit I, on the standard circuit, lacks the venous air removal device. Circuit III adds a collapsible venous reservoir to the Circuit I configuration and is used for volume management. Finally. Circuit IV (Blood Volume Management) adds a rigid reservoir as an additional component ingertated into the venous cannula, allowing it to convert to an open circuit and facilitate blood volume management in case of an emergency. 1) Venous and arterial cannulae. 2) Venous air removal device. 3) Centrifugal pump. 4) Membrane oxygenator. 5) Sweep flow and oxygen blender. 6) Heating/cooler device unit. 7) Arterial line filter. 8) Systemic blood distribution to vital organs.

The techniques and strategies of MiECC focus on minimizing circuit size, primordiality reducing the alteration of microcirculation triggered by conventional ECC, such as decreased blood contact with non-endothelialized surfaces, blood/air interface contact, patient hemodilution, use of cardiotomy suction and venous reservoir. All of these contribute to reducing blood trauma and decreasing the activation of inflammatory mediators, resulting in better outcomes in terms of renal function by reducing the incidence of renal injury, neurological function with reduced neurocognitive disability, postoperative arrhythmias, especially atrial fibrillation, erythrocyte physiology by reducing hemolysis and hemodilution, minimizing the need for blood transfusion and its related complications, immune function by reducing the activation of proinflammatory factors, and coagulation physiology by decreasing activation of both the intrinsic pathway in response to contact activation with non-endothelialized surfaces and the extrinsic pathway by reducing tissue factor response in this closed circuit. Furthermore, without the use of blood from cardiotomy suction, which contains large amounts of tissue factor, there is a decrease in thrombin generation, resulting in reduced platelet activation and, therefore, lower consumption of coagulation factors. Despite the extensive scientific literature available on ECC pathophysiology, better results in cardiac surgery are achieved when the surgical team applies these techniques [66-72].

Another vitally important specialty in cardiac surgery is cardiovascular anesthesia, which plays a fundamental role in ECC as it is necessary to ensure patient safety and well-being during the surgical procedure. It is primarily involved in anesthetic induction, monitoring and management of hemodynamic parameters, maintenance of an appropriate anesthetic level, among others [73-76].

Myocardial protection

Myocardial protection is a fundamental measure in initiating CPB in cardiac surgery procedures. During CPB, a variety of strategies are used to safeguard the cardiac tissue and prevent ischemic-reperfusion injury. These strategies are designed to preserve the function and viability of the myocardium during the period when the heart is disconnected from the blood flow and include temperature management, cardioplegia, and controlled ischemia-reperfusion environment, among others.

Among these strategies, Yamamoto [77] describes a series of experimental studies on myocardial protection, and one of the main techniques used is the induction of hypothermia [78]. By reducing the body temperature below 35°C, the metabolism of the heart is decreased, which helps protect it against ischemic-reperfusion injury. Hypothermia also reduces the oxygen demand of the myocardium and prolongs the time that the heart can tolerate the lack of blood flow [79]. However, this can have metabolic consequences that may affect the postoperative evolution of patients. Abassciano et al. [80], in their systematic review and meta-analysis, concluded that the protective effects of hypothermia in CPB are inconsistent and of low quality. Regardless, the strategy depends on the surgical team and the conditions and pathology of the patient. In some types of surgery, temperature management during CPB is divided into mild hypothermia (32°-35°C), moderate hypothermia (26°-31°C), and deep hypothermia (<25°C) (81). In a cohort study of 6,525 patients, Bianco et al. [82] found that patients with mild hypothermia (3,148) compared to normothermia (3,337) during CPB experienced increased postoperative renal failure (3.7% vs. 2.4%; P = .03) and longer stay in the intensive care unit (46.5 hr vs. 45.1 hr; p=0.04). However, they did not observe differences in long-term survival (82.6% vs. 81.6%; p=0.81). In addition to hypothermia, cardioprotective agents are used to minimize myocardial damage. These agents can include cardioplegia solutions, which are crystalloid, or blood solutions administered directly to the heart to induce temporary cardiac arrest and protect the tissue. Cardioplegia contains a combination of nutrients and chemicals that help preserve cardiac function [83].

Here are the key aspects of cardioplegia solutions:

Composition: They usually contain a combination of components that have various protective effects. This includes agents that stop the electrical and metabolic activity of the heart, such as adenosine and calcium channel blockers. They may also contain antioxidants to combat oxidative stress and energy substrates to provide nutrients to the myocardium during cardiac arrest.

Cooling: They are usually administered in the form of cold solutions (4°C) to cool the heart and reduce its metabolism during cardiac arrest.

Administration: They are administered directly into the coronary arteries to ensure adequate distribution in the myocardial tissue. This can be achieved through infusion of the solution into the aorta or by placing special cannulas in the coronary arteries.

Duration of action: They have a limited duration of action and, therefore, must be administered periodically during the period of cardiac arrest to maintain myocardial protection. The frequency of administration depends on various factors determined by the manufacturer, such as the temperature and composition of the solution [84].

Selection of the solution: The choice depends on the type of cardiac surgery, surgeon preference, and patient characteristics. There are different formulations of cardioplegia solutions available in the market, and the surgical team will select the most suitable one for each case. Zhou et al. [85], in their meta-analysis, included a total of 47 studies with 4,175 patients evaluating up to 7 types of cardioplegia solutions. They concluded that all solutions had protective effects after CPB, although the use of terminal warm blood cardioplegia had a lower concentration of markers of myocardial necrosis such as CK-MB at 2 hours (Mean Difference: 213.56; 95% CI: -25.79 to -1.59) and cTnT at 24 hours (Mean Difference: -1.50; 95% CI: -2.69 to -0.31) post-surgery when compared to crystalloid cardioplegia.

Inflammatory response triggered by cardiopulmonary bypass.

As discussed throughout this review article, cardiac surgery with cardiopulmonary bypass is one of the most physiopathological phenomena in medical literature, and the development of inflammation is practically involved in every component that has been developed and innovated over the past seven decades. Multiple cellular and humoral components are altered and contribute to systemic inflammatory response syndrome (SIRS) triggered by CPB, including blood contact with non-endothelial surfaces, changes in pressure and reduced temperature activating pathophysiological cascades within the body. This results in the production of an inflammatory storm characterized by the release of proinflammatory cytokines (IL-1, IL-6, and TNF-α) and activation of endothelial cells, neutrophils, macrophages, lymphocytes, and platelets. Prolonged exposure to these effects leads to disturbances in redox processes, resulting in increased production of oxygen free radicals with a negative impact, particularly on the cardiovascular, neurological, renal, and respiratory systems, leading to a scenario of multiorgan dysfunction and consequently increased postoperative morbidity and mortality.

As previously described, the combination of all these interrelated factors required to perform cardiac surgery leads to a myriad of outcomes that determine the likelihood of successful cardiac surgery. However, the injury to the vascular endothelial layer, coupled with blood components contacting the CPB circuit, intensifies the inflammatory process. The initial local inflammatory response eventually disseminates and becomes systemic [86-89].

This is an inherently unnatural process that magnifies this reaction. The pump and oxygenator function in a non-physiological manner, without feedback from normal homeostatic mechanisms, resulting in deviations from normal intravascular pressures and blood gas composition. Significant blood dilution occurs, leading to changes in intracellular/extracellular compartments, significant fluid retention, dilution, and denaturation of important plasma proteins. Blood encounters non-endothelial surfaces and experiences abnormal shear stress, which activates blood elements to produce various vasoactive mediators, altering capillary permeability and causing hemolysis. Simultaneously, the coagulation system is both activated and inhibited.

In summary, the body's homeostatic mechanisms become imbalanced, resulting in systemic inflammatory response syndrome (SIRS) [90,91].

Bone [92] postulated that there is already a powerful anti-inflammatory response to balance the destructive proinflammatory response, and agents that disrupt the balance in either direction could lead to death, either through uncontrolled inflammation or an inability to defend against infectious organisms. Unlike previously thought, SIRS is not a single, uncontrolled response; a compensatory anti-inflammatory response (CARS) occurs alongside SIRS. CARS is considered a late response to SIRS, although some argue it occurs simultaneously with the onset of SIRS. The concept of CARS was proposed in 1997 and is defined as an adaptive reprogramming of the immune state that attempts to regulate the acute proinflammatory response. The compensatory phase appears to play a prominent role in generalized postoperative immunosuppression and the development of infectious complications after CPB. It is speculated that regulatory T cells (Tregs) may be the main trigger of CARS. Tregs are a specialized subset of T cells that play a crucial role in maintaining immune homeostasis, controlling acute and chronic inflammation, and are characterized by the presence of the transcription factor FOXP3 [93-95].

Systemic inflammation following major surgery is the initial result of the highly conserved innate immune response.

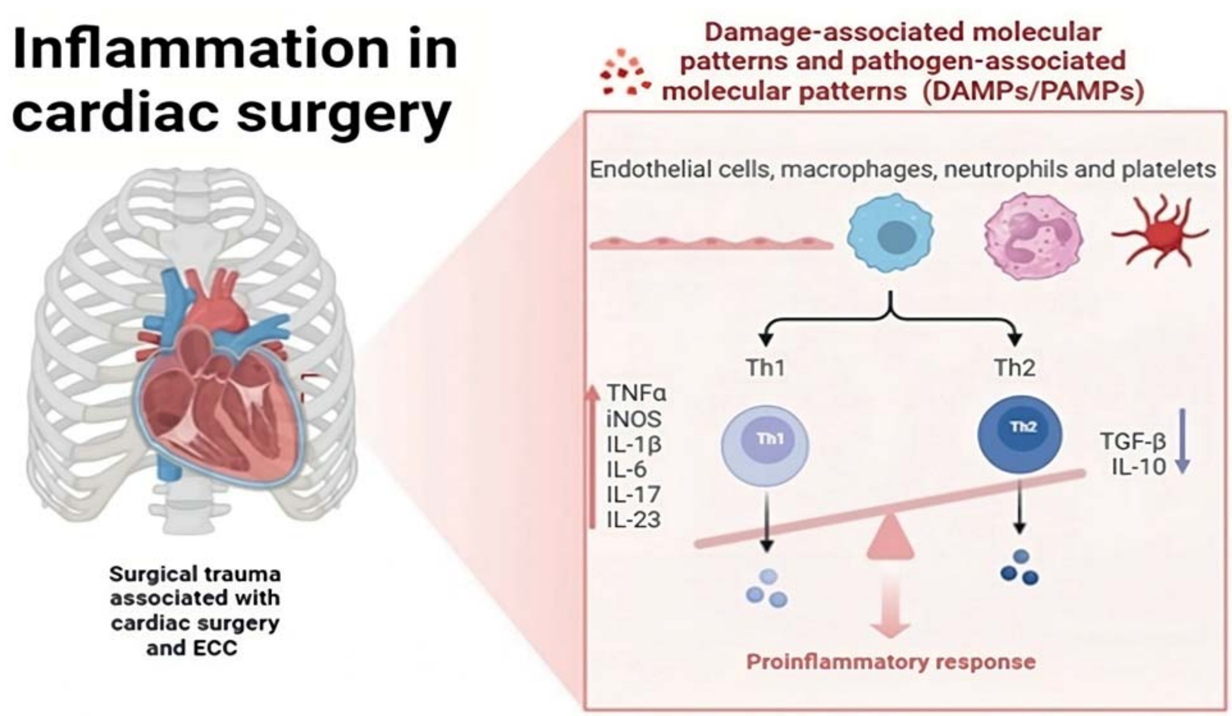

Figure 3. Cellular components in inflammation in cardiac surgery. Inflammation in cardiac surgery triggers a cascade of proinflammatory phenomena, disrupting the physiological balance when blood and its formed elements encounter proinflammatory stimuli, such as the surgical stress response, activation of cellular subgroups, and the release/activation of humoral factors, leading to a series of pathophysiological events throughout the body. If not self-limiting, this process can result in multiorgan failure and death. TNF-α: Tumoral Necrosis factor-alpha; iNOS: inducible Nitric Oxide Shyntase; IL-1β: Interleukin-1beta; IL-6: Interleukin-6; IL-17: Interleukin-17; IL-23: Interleukin-23; TGF-β: Transformig Growth Factor-beta; IL-10: Interleukin-10.

Contenido

The magnitude of the response varies widely depending on the surgical environment and is proportional to the degree of surgical injury [96]. Cellular injury is detected at the molecular level by pattern recognition receptors in innate immune cells. These receptors recognize molecules released by damaged and necrotic cells, known as damage-associated molecular patterns (DAMPs) or alarmins. They also recognize highly conserved molecules derived from exposed microorganisms, known as pathogen-associated molecular patterns (PAMPs) [97]. DAMPs are the key molecular ligands responsible for triggering the inflammatory and immune response to surgical injury [98]. At the site of injury, DAMPs bind to pattern recognition receptors, activating multiple signaling pathways that result in the production and release of proinflammatory cytokines and chemokines. This leads to increased production and recruitment of immune cells, such as neutrophils and monocytes, to the site of injury [99].

Natural killer cells are also activated, reactive oxygen species are released, and endothelial permeability is modified. The inflammatory and immune response is balanced as immune suppression processes are simultaneously activated. Interleukin-6 (IL-6) is the dominant inflammatory cytokine in this response, and its levels strongly correlate with the severity of the injury and the synthesis and secretion of acute-phase reactants, such as C-reactive protein (CRP) and procalcitonin. However, along with other proinflammatory cytokines, IL-6 directly stimulates the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol secretion and influencing cortisol-mediated immune regulation. Additionally, IL-6 induces the release of prostaglandin E2, a potent immunosuppressor, from macrophages, which negatively regulates the function of monocytes, macrophages, and T cells. The balance between type 1 helper T cells (Th1) and type 2 helper T cells (Th2), represented by the Th1/Th2 ratio, is an important factor in maintaining immunological balance, and suppression of Th1-mediated immunity has been associated with an increased risk of infectious complications [100]. IL-10 plays a significant role in regulating the Th1/Th2 balance, limiting excessive immune activation and uncontrolled inflammation. However, IL-10 can also induce profound immunosuppression by deactivating monocytes and cytotoxic T cells, as well as affecting antigen presentation [101]. (**Fig. 3**)

During CEC, different phases of activation occur, triggering inflammatory and other biological responses. These phases can be classified as early and late activation [90].

Early activation phase

The early phase of the inflammatory response occurs at the initiation of extracorporeal circulation and is believed to be caused by the contact of blood components (both cellular and humoral) with the synthetic material of the extracorporeal circuit. Under normal circumstances, blood only meets the endothelial cell lining of blood vessels, a surface with an important role in maintaining circulatory balance. By producing balanced amounts of procoagulant and anticoagulant substances, en-

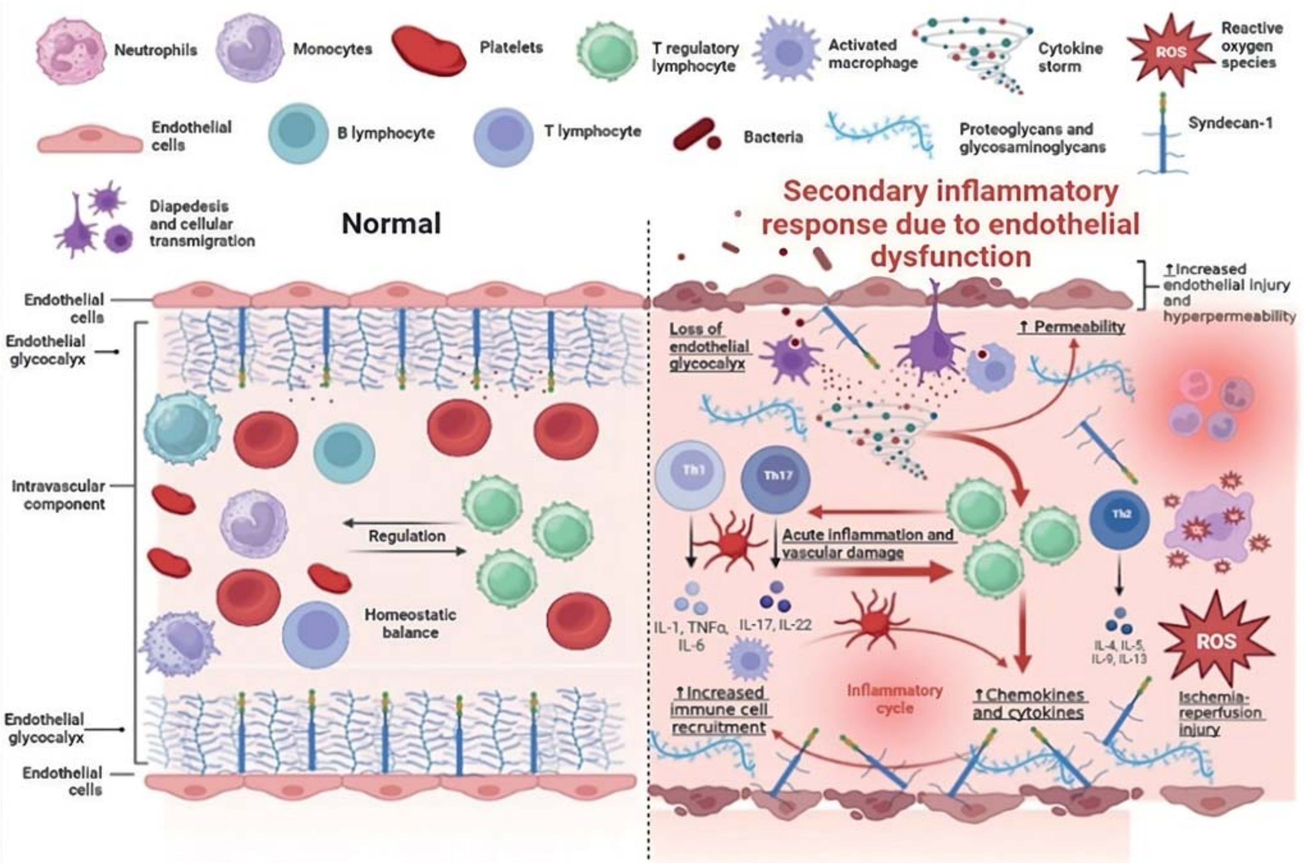

Figure 4. Early and Late Activation Phases in Cardiopulmonary Bypass. Read the text for a more detailed description [90].

dothelial cells ensure that blood remains in its fluid state until vascular injury occurs, and blood clot formation is favored. The non-endothelial surfaces of the extracorporeal circulation machine disrupt this balance towards thrombosis, making it essential to administer appropriate doses of heparin before initiating extracorporeal circulation. When heparinized blood encounters the tubing of the extracorporeal circulation circuit, plasma proteins instantaneously adsorb to the circuit, forming a monolayer. Some of these proteins undergo conformational changes that expose receptors to circulating proteins and cells in the blood. This leads to the activation of 5 plasma protein systems (contact system, intrinsic and extrinsic coagulation cascade, fibrinolytic system, and complement cascade) and 5 cellular groups (endothelial cells, lymphocytes, monocytes, neutrophils, and platelets). The roles of these protein systems and cellular groups are interconnected, complex, and not yet fully understood. However, vasoactive substances, enzymes, and microemboli produced by these activated mediators initiate the "systemic inflammatory response" and are responsible for the major complications associated with extracorporeal circulation, such as coagulopathy, tissue edema, and temporary organ dysfunction (**Fig. 4**) (**Fig. 5**).

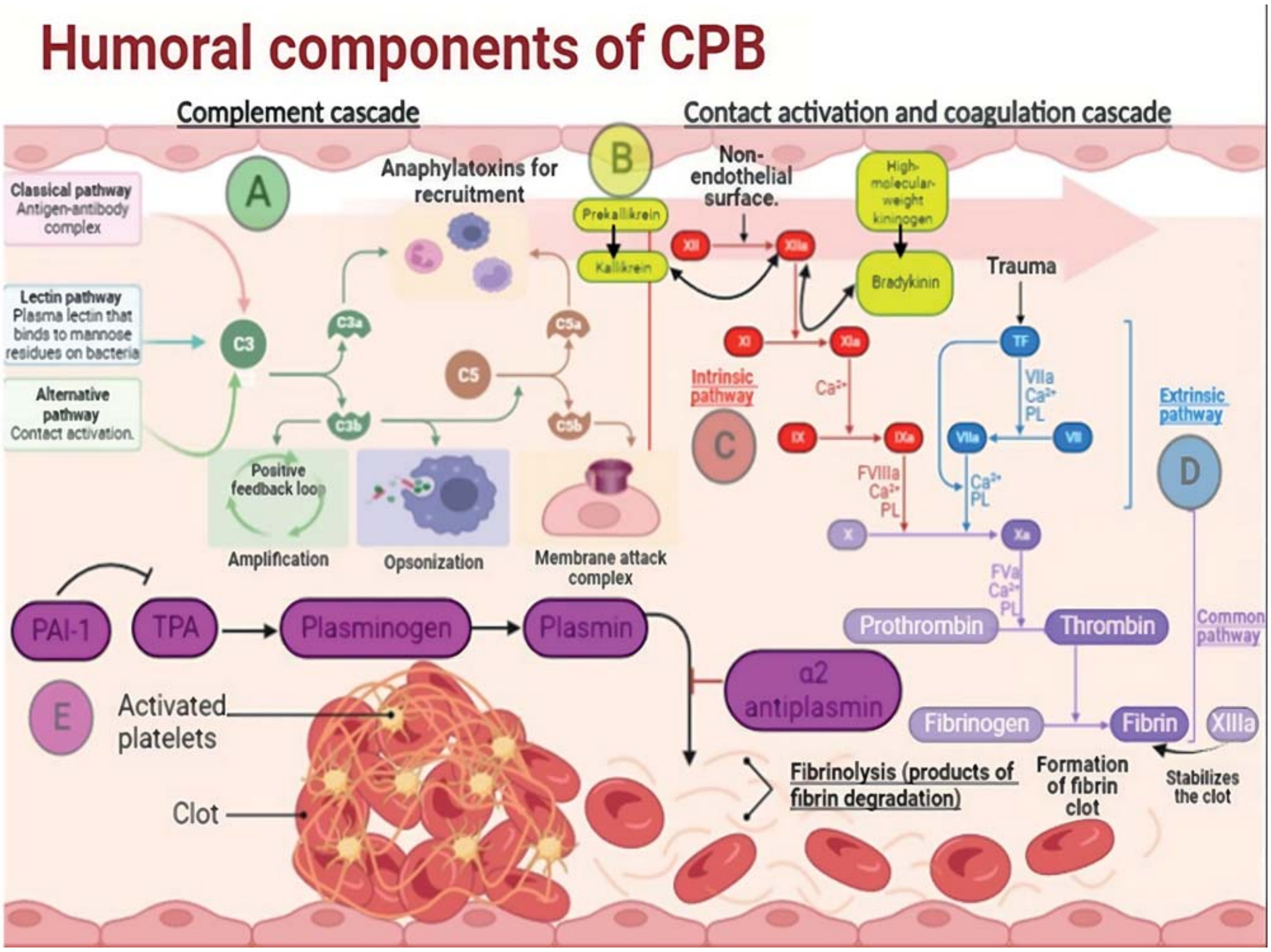

Figure 5. Humoral Components in CPB. A. Complement Cascade: It is a system of over 35 plasma proteins activated by all three pathways in ECC; however, the alternative pathway is predominantly activated due to contact of proteins with non-endothelial surfaces, the common pathway is triggered by the formation of heparin/protamine complexes with C1q, and the lectin pathway through mannose residues with plasma lectins. B. Contact Cascade: The contact system consists of 4 plasma factors activated when blood meets a non-endothelial cell surface. This activation triggers a series of reactions including the generation of vasoactive peptides, coagulation activation, and amplification of the inflammatory response. Bradykinin, generated from the activation of high molecular weight kininogen, causes vasodilation and smooth muscle contraction. Additionally, kallikrein activation promotes neutrophil activation and accelerates factor XII degradation. C. Intrinsic Coagulation Pathway: Activation of the contact system initiates the intrinsic coagulation pathway when blood contacts a non-endothelial surface. This pathway involves the activation of factors like factor XII and XI, prekallikrein, and high molecular weight kininogen. Activation of this pathway leads to thrombin generation, which plays a crucial role in blood clot formation and the inflammatory response. Thrombin has multiple effects, including the activation of coagulation factors, stimulation of smooth muscle cells, and production of substances that promote inflammatory cell adhesion and increase vascular permeability. D. Extrinsic and Common Coagulation Pathway: This pathway is activated when there is damage to the wall of a blood vessel and is the primary pathway involved in wound hemostasis. It begins when tissue factor (TF), present in exposed tissue cells, binds to circulating factor VII to form a TF-FVIIa complex. This complex catalyzes the conversion of factor X into its active form (Xa), which is crucial for thrombin formation. TF can come from various sources, such as blood cells from the pericardium or soluble fragments. The generation of factor Xa and thrombin triggers a cascade of coagulation that can result in consumption coagulopathy and complications of thrombosis and bleeding. E. Fibrinolysis Cascade: This fifth system of plasma proteins limits this process, localizing blood clot formation at the site of tissue or vascular injury and preventing widespread thrombotic occlusion of vessels and secondary tissue ischemia. Plasminogen, an inactive protein, is converted to plasmin, an enzyme that breaks down fibrin in blood clots. Fibrinolysis occurs continuously, especially at the pericardial wound, and is regulated by t-PA and other proteins. Fibrinolysis activation is associated with higher levels of bleeding during surgery. t-PA: Tissue Plasminogen Activator; PAI-1: Plasminogen Activator Inhibitor 1.

Late activation phase (**Fig. 4**)

As the duration of extracorporeal circulation increases, the activation of the previously described humoral and cellular components decreases. However, a second phase of the inflammatory response has been demonstrated, which is believed to be related to ischemia-reperfusion injury during and after extracorporeal circulation and endotoxemia, likely following the release of endotoxins by the intestinal microflora. During surgery, aortic clamping interrupts the blood supply to the heart and, to a lesser extent, the lungs, resulting in ischemia. Once the clamp is released, reperfusion occurs, involving the restoration of blood flow to these organs. However, this reperfusion also triggers an additional inflammatory response. Ischemia and reperfusion cause injury to the vascular endothelium, leading to activation and sequestration of neutrophils at the site of injury. Additionally, the generation of highly toxic reactive oxygen species (ROS), such as superoxide anions and hydrogen peroxide, occurs.

These ROS, along with the release of other molecules, amplify the already implemented inflammatory process. The reintroduction of oxygen during reperfusion creates a highly oxidative environment within the cells that experienced ischemia, leading to cellular damage. Endothelial cells in the microcirculation are particularly susceptible to damage caused by ROS. These free radicals can damage cell membranes and denature proteins, contributing to endothelial dysfunction and local structural alterations.

Endotoxin, which is a component of gram-negative bacterial cell walls, is considered a significant stimulus for the development of SIRS. The magnitude of endotoxin elevation during extracorporeal circulation can vary in different studies, which may be due to the heterogeneity in the existing literature. One possible source of endotoxin release during extracorporeal circulation is intestinal translocation, due to splachnic vasoconstriction that occurs during this procedure, which can lead to ischemia of the enteric mucosa and changes in microbial viability and intestinal permeability. However, it should be noted that establishing a clear relationship or causality between variables such as the duration of extracorporeal circulation, intestinal permeability levels, and endotoxin levels at the end of extracorporeal circulation has proven to be a challenge in research. Although it is recognized that elevated levels of endotoxin during extracorporeal circulation can activate the complement system, stimulate the release of proinflammatory cytokines, and increase postoperative oxygen consumption, further research is still needed to fully understand the underlying mechanisms [102-105].

Microcirculatory dysfunction resulting from endothelial dysfunction

CEC is associated with microvascular changes in various pathological aspects. Endothelial cell injury and subsequent acute inflammation with vascular damage, impairment of the coagulation cascade, ischemia-reperfusion injury, endothelial hyperpermeability, glycocalyx impairment, and gas microemboli all work together on the same team towards CEC-induced organ dysfunction [106].

Several studies in animal models and patients have demonstrated that cardiac surgeries, especially those involving cardioplegia and CPB, induce extensive vascular dysfunction. This dysfunction affects both large and medium-sized vessels, as well as the microcirculation, which is the terminal vascular network of the circulatory system comprising a wide variety of microvessels with a diameter of less than 200 micrometers. Microvessels can be subdivided into arterioles, capillaries, and venules, all of which play important roles in maintaining organ function. Microvascular dysfunction following cardiac surgery is characterized by changes in myogenic and vasomotor tone, as well as generalized endothelial dysfunction that clinically manifests as systemic hypotension and organ damage. For example, intra- and postoperative inflammation in the microcirculation triggers leukocyte activation, initiating the coagulation cascade in venules. Alternatively, coagulation cascade activation in capillaries restricts the available surface for diffusion, resulting in impaired nutrient and gas exchange. Patients may require vasopressors and/or aggressive fluid therapy to overcome these clinical consequences (**Fig. 6**).

Endothelial cell injury can be dependent and independent of neutrophils. In the former case, neutrophils express adhesion molecules on their surface, such as the integrins CD11a/CD18 (LFA1) and CD11b/CD18 (Mac1). The specific endothelial cell molecule, endocan, represents a novel endothelial cell stress signal and is released when the cells are activated. Free endocan binds to human leukocytes via the LFA1 integrin, inhibiting the interaction of LFA1 with ICAM1 and thus protecting endothelial cells from binding to inflammatory leukocytes [107]. Under physiological conditions, low levels of Mac-1 and LFA-1 are expressed. Neutrophil activation leads to the fusion of cytoplasmic granules with the cell membrane and an increase in Mac-1 expression on the surface. Mac-1 and LFA-1 interact with their endothelial "counter-receptor," ICAM-1. If the endothelial cell meets cytokines such as tumor necrosis factor-alpha (TNF-α) and/or interleukin-1 (IL-1), the expression of ICAM-1 significantly increases, facilitating adhesive interactions with neutrophils. Neutrophil-released elastase penetrates endothelial cells, where it converts xanthine dehydrogenase (x.d.) to xanthine oxidase (x.o.). In turn, x.o. can react with its substrate, xanthine (a breakdown product of ATP), leading to intracellular generation of superoxide anion (O2-), which then causes the conversion (reduction) of ferritin-bound Fe3+ to Fe2+, an unstable and transient form of iron [108].

Neutrophil-mediated endothelial cytotoxicity can also be influenced by intracellular mechanisms involving nitric oxide synthase (NOS) present in endothelial cells. NOS interacts with L-arginine to generate nitric oxide (NO), which is known to decrease the expression of adhesion molecules on endothelial cells and reduce adhesive interactions between neutrophils and endothelial cells. Additionally, NO can "scavenge" O2- by reacting with it to form the peroxynitrite anion (ONOO-). Therefore, if O2- is eliminated through this mechanism, the ability to reduce intracellular Fe3+ to Fe2+ may be compromised, resulting in increased resistance of endothelial cells to neutrophil-induced cytotoxicity.

In the case of a neutrophil-independent pattern, endothelial cells can also be directly damaged by soluble mediators produced during acute inflammation. In vitro studies have demonstrated that proinflammatory cytokines such as TNF-α and IL-1 directly harm endothelial cells, resulting in increased monolayer permeability. The direct injury of endothelial cells by these mediators can occur through the induction of apoptosis, especially in the case of TNF-α. All these observations may

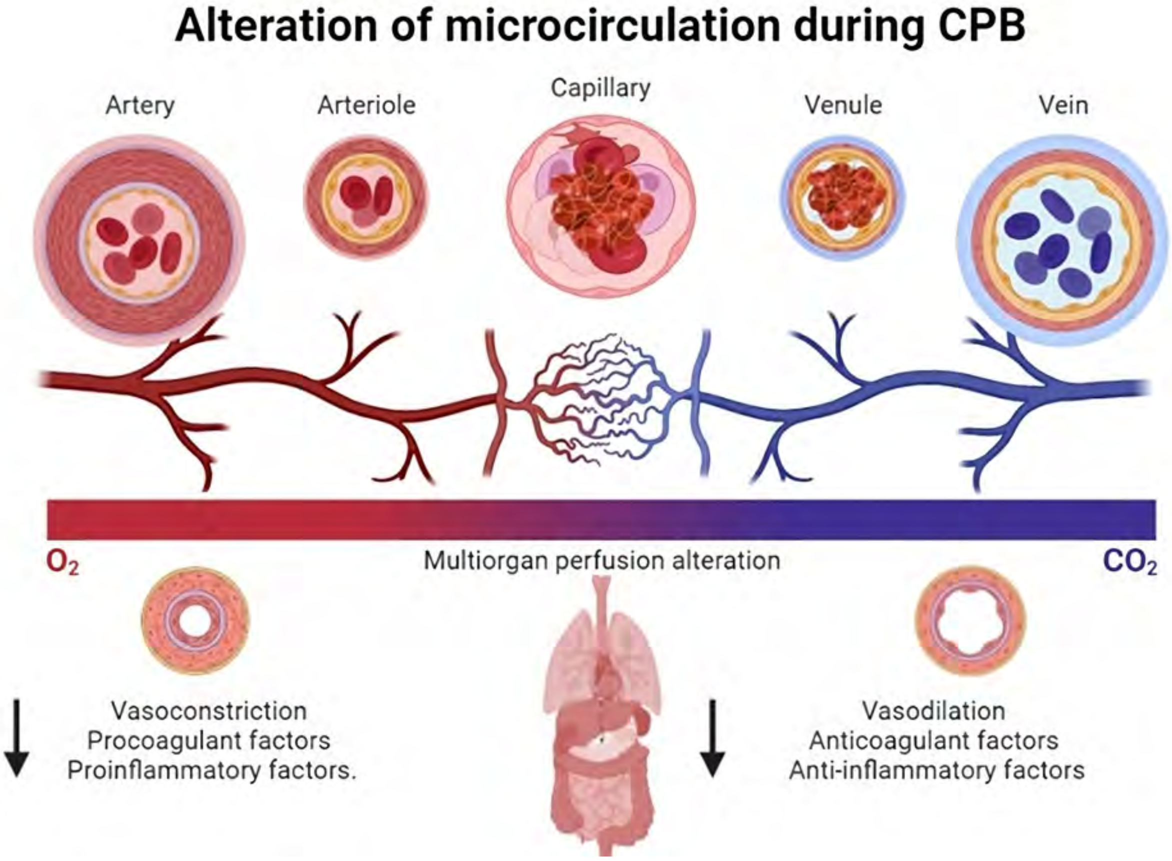

Figure 6. Impairment of microcirculation in cardiopulmonary bypass. The consequences of endothelial dysfunction and microcirculatory impairment during cardiopulmonary bypass include reduced blood flow to organs and tissues, increased risk of thrombosis, decreased tissue oxygenation, and enhanced inflammatory response. These factors can contribute to complications following cardiac surgery, such as organ dysfunction, postoperative bleeding, and prolonged recovery times.

be related to intracellular production of oxidants in stimulated endothelial cells triggered by TNF-α or IL-1. Furthermore, the production of cyclooxygenase products by endothelial cells increases when they meet TNF-α or IL-1. Several studies have revealed that angiopoietins-1 and -2 (Ang-1 and Ang-2) target key mechanisms contributing to the maintenance of endothelial barrier function. Ang-1 promotes junctional integrity by regulating the accumulation of adhesion proteins, especially VE-cadherin, at endothelial cell-cell junctions. Conversely, Ang-2 is increasingly expressed during endothelial activation and, by competing with Ang-1, may counteract endothelial stabilization [109].

The endothelial glycocalyx (EG) is a layer that coats endothelial cells inside blood vessels and organs. It is composed of glycoproteins that retain a non-circulating plasma volume of approximately 700 to 1,000 mL. This intraluminal layer maintains its own colloid osmotic pressure (COP) due to its content of plasma proteins, primarily albumin, which become trapped within the endothelial glycocalyx. The EG is estimated to contribute approximately 60% of intravascular COP. Structurally, the EG is a gel-like layer with a negative charge composed of an intricate matrix of oligosaccharide and polysaccharide chains called glycosaminoglycans, which covalently bind to glycosylated membrane proteins called proteoglycans, as well as membrane proteoglycans such as syndecans, glypicans, perlecans, and other plasma proteins. In the presence of an intact EG, water and electrolytes can freely pass through this layer and beyond the endothelial cells via intercellular gaps. Except for albumin, this exclusion zone also prevents high molecular weight colloids (>70 kDa) from contacting the endothelial cells. Albumin is the only significant plasma protein that can easily move between plasma and the EG due to the selectively permeable nature of the glycocalyx to naturally occurring colloids with molecular weights <70 kDa. However, it is noteworthy that the EG is susceptible to damage and degradation, especially under conditions of high transendothelial pressures. This may result in the loss of its protective function and the release of colloids into the extravascular space [110, 111].

Recently, it has been shown that loss of the endothelial glycocalyx, including syndecan-1, is associated with microcirculatory perfusion disorders following coronary artery bypass surgery [15]. Robisch et al. [112] found that prolonged CPB time contributes to elevated levels of syndecan-1, which may promote the mobilization of neutrophils from the bone marrow, resulting in leukocytosis. Neutrophils are equipped with a wide variety of bioactive factors that can contribute to the amplification of local inflammation. These neutrophils can access vulnerable endothelial cells, bypassing the compromised protective barrier of the endothelial glycocalyx and transmigrating into the extracellular space through intracellular gaps. Therefore, it is speculated that prolonged CPB-associated cardiac surgery is associated with loss of the endothelial glycocalyx and mobilization of neutrophils from the bone marrow, contributing to and amplifying a systemic inflammatory response.

Understanding the fundamental aspects of the pathophysiology involved in CPB, such as microcirculatory alteration due to endothelial dysfunction, highlights several mechanisms that contribute to it. Far from the balance of proinflammatory factors against the anti-inflammatory factors analyzed in this review, there is an alteration in the response of vasoactive mediators, disturbances in contact and coagulation cascades, but primarily the shedding of the glycocalyx and subsequent endothelial activation, disrupting the balance between vasodilatory and vasoconstrictive factors in the microcirculation, negatively affecting adequate tissue and organ perfusion. Hypoperfusion, ischemia-reperfusion, and microvascular inflammation are identified as common underlying themes in post-cardiac surgery kidney, brain, and lung injuries. These mechanisms can have significant consequences on organ function and integrity, increasing the risk of postoperative morbidity and mortality.

REGULATORY T LYMPHOCYTES IN INFLAMMATION

Regulatory T lymphocytes, also known as Treg cells, are a subtype of T cells in the immune system that play a crucial role in regulating and suppressing immune responses. In the body, there are modulatory mechanisms of inflammatory processes as a response to reduce the negative impact on organ function. Lymphocytes expressing cellular markers CD4, CD25, and the transcription factor FoxP3 participate in the modulation of the inflammatory response triggered by multiple causes. These regulatory T lymphocytes (Tregs) produce anti-inflammatory cytokines (IL-10 and TGF-β) that attenuate the activation of pro-inflammatory effector T lymphocytes and induce their apoptosis [113-115].

In the early 1970s, it was recognized that T cells not only had a helper function but could also modulate the inflammatory response, identifying a subpopulation of T cells with the ability to modulate excessive immune responses [116]. As an initial discovery, researchers began to identify the presence of suppressor cells in the immune system, which had the ability to inhibit excessive immune responses. In the early 1980s, studies in mice showed the existence of CD4+ T lymphocyte suppressor cells that could prevent autoimmune diseases. Through experiments in mice and other animals, researchers observed the existence of CD4+ T lymphocyte suppressor cells. These cells were shown to be capable of preventing autoimmune diseases in the animal models studied [117].

In the 1990s, significant advances were made in the characterization of regulatory T cells. It was discovered that these cells expressed the transcription factor FoxP3, which became a key marker for identifying and distinguishing Tregs. It was demonstrated that the absence or dysfunction of FoxP3 result-

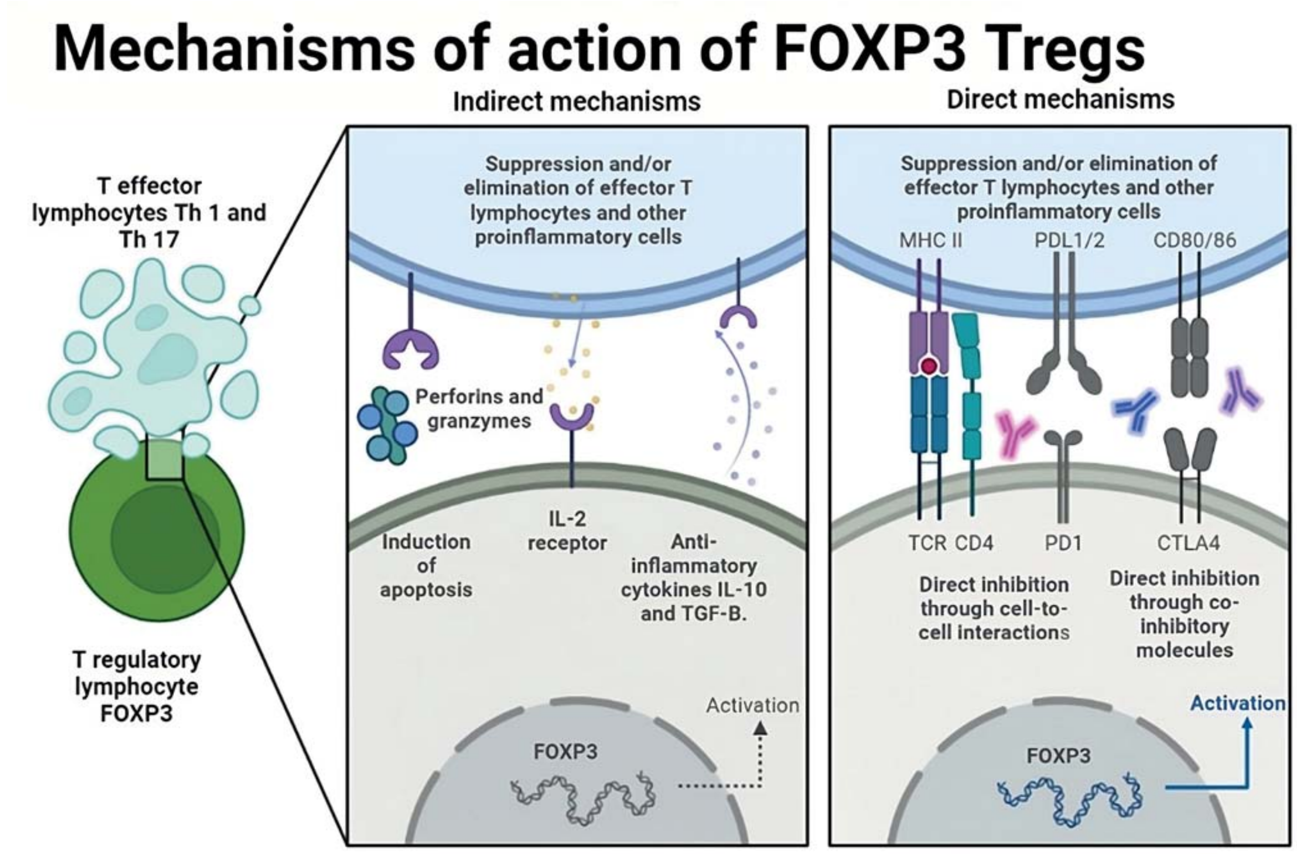

***Figure 7.** Mechanisms of action of FOXP3 Tregs. Tregs lymphocytes can suppress the immune response of effect cells through direft and indirect mechanisms.*

Contenido

ed in severe autoimmune disorders in animal models [118]. In the first decade of the 21st century, numerous studies were conducted to understand the mechanisms by which Tregs exert their suppressive function. It was found that Tregs can suppress the immune response in different ways, including the release of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), as well as direct inhibition of other immune cells [119].

In the past decade, there has been growing interest in the role of Tregs in various diseases, including autoimmune diseases, allergies, organ transplantation, and cancer. It has been shown that Tregs play a key role in maintaining immune tolerance and preventing excessive immune responses in these conditions. Furthermore, advances have been made in identifying specific biomarkers of Tregs and developing therapies based on the manipulation of these cells [120].

Lymphocytes marked with FoxP3 act as a transcription factor that regulates the expression of various suppressor genes, including anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Additionally, FoxP3 can suppress the expression of pro-inflammatory genes and co-stimulatory molecules in Tregs, thus contributing to their suppressive function through cytokine signaling pathways and interaction with other immune cells (Fig. 7) [121,122].

FoxP3 was discovered in 2001 by the research team led by Dr. Shimon Sakaguchi in Japan. It was identified as an essential gene for the function and stability of Tregs. FoxP3 expression was found primarily in Tregs, which helped distinguish them from other subsets of T cells. FoxP3 plays a fundamental role in the differentiation of Tregs in the thymus during the development of the immune system. Its expression is necessary for the generation of functional Tregs and proper immune suppression. The absence or dysfunction of FoxP3 results in severe autoimmune disorders in animal models and in the autoimmune immunodeficiency syndrome called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) [123].

The FoxP3 signaling pathway is crucial for the differentiation and function of regulatory T lymphocytes (Tregs), and activation of the FoxP3 signaling pathway is triggered through a combination of intracellular and extracellular signals. T cell receptor (TCR) signaling plays a fundamental role in FoxP3 activation. The interaction of the TCR with the major histocompatibility complex (MHC) on antigen-presenting cells (APCs) and the presentation of specific antigens are crucial for triggering the signaling pathway [124].

Activation of the mTOR pathway has been shown to be essential for Treg differentiation. mTOR signaling promotes the expression of the transcription factor FoxP3, which is a distinctive feature of Tregs. Additionally, the mTOR pathway is involved in the regulation of other transcription factors and key molecules in Treg differentiation and function, such as interferon regulatory factor 4 (IRF4) and interleukin-2 (IL-2). Manipulation of the mTOR pathway in Tregs has emerged as a potential therapeutic approach in various diseases. For example, mTOR inhibition in Tregs can be used in the treatment of autoimmune diseases to enhance the suppressive function of Tregs and reduce dysregulated immune response. Furthermore, mTOR activation in Tregs can be explored in the context of cardiopulmonary bypass (CPB) against the secondary inflammatory response to the activation of multiple interrelated factors in cardiac surgery to improve the understanding of the anti-inflammatory immune response [125-127].

Metabolism plays a crucial role in the function and survival of Tregs. These cells show a preference for aerobic metabolism, which is highly efficient in energy generation. This involves the utilization of glucose as the primary fuel source and energy production through glycolysis and oxidative phosphorylation in the mitochondria. The high activity of oxidative phosphorylation in Tregs enables efficient production of adenosine triphosphate (ATP), the main cellular energy source [128]. In addition to glucose, Tregs heavily depend on the amino acid glutamine to maintain their suppressive function. Glutamine is metabolized in the citric acid cycle in the mitochondria, generating key metabolic intermediates such as alpha ketoglutarate, which are necessary for Treg function and proliferation. Glutamine deficiency can compromise Treg function [129]. The mTOR signaling pathway plays a crucial role in Treg metabolism. mTOR activation promotes Treg proliferation and differentiation, as well as their suppressive function. The mTOR pathway regulates nutrient uptake, protein and lipid biosynthesis, and cytokine production in Tregs. Proper balance in mTOR activity is essential for maintaining Treg homeostasis and proper function [130]. Tregs interact with dendritic cells (DCs) and can modify their metabolism. It has been observed that Tregs can suppress the metabolism of DCs, reducing their capacity to effectively activate other T cells and thus promoting immune tolerance. This metabolic interaction between Tregs and DCs is important for maintaining immune system balance and preventing autoimmunity [131]. The composition and diversity of the gut microbiota can also impact Treg metabolism. It has been shown that the gut microbiota can influence Treg metabolism through the production of specific metabolites, such as short-chain fatty acids. These metabolites can directly affect Treg function and stability, as well as modulate the immune response in the gut [132,133].

Treg metabolism during cardiac surgery with CPB can be affected due to factors such as ischemia-reperfusion, the presence of numerous pro-inflammatory mediators, and metabolic stress. Stress can affect the regulation of key metabolic pathways, such as the mTOR pathway, which is critical for Treg function. Changes in stress response can influence the ability of Tregs to maintain their suppressive function and modulate the immune response during surgery.

Perspectives of Treg Lymphocytes

Tregs have promising therapeutic potential in the context of cardiac surgery with CPB. Manipulation of Tregs, either by increasing their numbers or enhancing their function, could be a therapeutic strategy to mitigate the inflammatory response and improve clinical outcomes in patients undergoing cardiac surgery with CPB [134]. Research is being conducted to identify specific biomarkers that can predict the inflammatory response during CPB and Treg function. This could enable more precise and personalized patient stratification, as well as the development of targeted therapeutic approaches. Furthermore, therapeutic approaches involving the expansion and activation of Tregs prior to surgery have been explored, aiming to enhance their ability to modulate the inflammatory response and protect against organ injury during CPB [135].

Pharmacological modulation of Tregs: Drugs and compounds that can directly modulate the function of Tregs, improving their suppressive and regulatory capacity, are also under investigation. These approaches could provide new therapeutic strategies to control the inflammatory response during CPB [136].

CONCLUSIONS

Understanding the interaction between Tregs and ECC provides an exciting opportunity to comprehend the pathophysiology involved in the activation and development of inflammation in cardiac surgery with the use of this device. While ECC has had a significant impact on the development of open-heart surgery, there is a price to pay due to its capacity to generate an inflammatory component that affects the postoperative evolution of patients undergoing this procedure. Several studies have explored strategies to preserve Treg function during ECC, including the use of immunomodulatory drugs such as corticosteroids and adrenergic receptor agonists, as well as modulating perioperative environmental conditions. Gaining more knowledge about the fascinating cellular biology of these regulatory T lymphocyte subtypes can provide relevant information on their interaction with all the factors required to perform heart surgery, ranging from identifying single-nucleotide polymorphisms in proinflammatory genes to the therapeutic potential in myocardial protection and ischemia-reperfusion mechanisms, as well as postoperative management and behavior in high-risk patients prone to developing an uncontrolled inflammatory response. Understanding the inflammatory balance in ECC and its potential outcomes on the morbidity and mortality of patients undergoing heart surgery can be of great significance.

It is worth noting that despite the numerous innovations in ECC components and techniques in cardiac surgery over the past years discussed in this review, there is limited information that considers the behavior of these important immune system cells and their relationship with each pathophysiological aspect triggered by these procedures, particularly in relation to inflammation, coagulation, and oxidative stress pathways.

In developed and some developing countries, minimally invasive cardiac surgery has been practiced, performed through small incisions instead of a full sternotomy, and using video-assisted thoracoscopy or robot-assisted techniques, reducing trauma and accelerating patient recovery. On the other hand, minimally invasive extracorporeal circulation, previously discussed, addresses some of the issues triggered by hemodilution, blood transfusions, and mainly inflammation due to the reduction in the contact surface area of these components with blood, resulting in better outcomes when compared to conventional ECC. The incorporation of both techniques can drive the evolution of minimally invasive cardiac surgery towards a more physiological approach aligned with current trends in cardiac care, known as physiological cardiac surgery [70].

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Optimizing outcomes in high-risk patients with low left ventricle ejection fraction undergoing coronary artery bypass grafting: a case report

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Managing patients with coronary artery disease and low ejection fraction remains a challenge despite medical advancements. Coronary artery bypass grafting has shown benefits for patients with reduced ejection fraction, but it also carries risks, such as post-cardiotomy shock. Pre and intraoperative strategies, like levosimendan preconditioning, on-pump beating-heart technique, comprehensive revascularization, and backup mechanical support, aim to optimize outcomes. Tailored multidisciplinary (Heart-Team) approaches minimize the risks while maximizing outcomes in high-risk patients.

Key words: Coronary artery bypass grafting; Left ventricle ejection fraction, low; on-pump beating heart surgery.

El manejo de pacientes con cardiopatía isquémica y fracción de expulsión reducida continúa siendo todo un reto a pesar de los avances médicos. La revascularización miocárdica ha demostrado ser de beneficio para pacientes con fracción de expulsión reducida, sin embargo, no está libre de riesgos, tales como el síndrome de estado de choque post-cardiotomía. Para optimizar resultados, se recomiendan múltiples estrategias prequirúrgicas e intraoperatorias, tales como pre-acondicionamiento con levosimendan, revascularización miocárdica con derivación cardiopulmonar a corazón latiendo, revascularización miocárdica completa, soporte mecánico circulatorio de respaldo. El abordaje individualizado por un equipo multidisciplinario (Heart-Team) reduce significativamente los riesgos, maximizando los resultados en este tipo de pacientes.

***Palabras clave**: Cirugía de revascularización coronaria; Fracción de expulsión del ventrículo izquierdo, baja; Cirugía en bomba a corazón latiendo.*

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Despite advancements in medical therapies and surgical techniques, managing patients with coronary artery disease (CAD) and low left ventricle ejection fraction (EF) remains a significant challenge. The current treatment options for these patients include intensive medical therapy, coronary artery bypass grafting (CABG), ventricular remodeling, and heart transplantation. In patients undergoing CABG, heart failure (HF) with reduced ejection fraction (HFrEF) is associated with a poor short-term and long-term prognosis, leading to an all-cause mortality rate of up to 7%. Consequently, it becomes a crucial factor in preoperative risk [1-3]. Studies from the 1980s, such as the Veteran Administration Cooperative Study, indicated that patients with reduced EF derive even greater benefits from surgical myocardial revascularization [4]. These findings were further supported by the long-term follow-up of the Surgical Treatment for Ischemic Heart Failure (STICH) trial, demonstrating a significant survival advantage for patients with poor ventricular function who undergo CABG [5].

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Patients with impaired left ventricular function undergoing CABG form a distinct subgroup, with mortality factors that may differ from those associated with traditional risk factors in CABG patients. Consequently, some surgeons may refrain from performing surgery on these patients due to the high risk of post-cardiotomy shock. While myocardial recovery following revascularization may take days to weeks to occur, patients may require high doses of inotropic and vasopressor support due to ongoing cardiogenic and/or metabolic shock, resulting in multiorgan failure and death. However, if patients can be preconditioned with levosimendan prior to surgery or receive appropriate support for early recognition of low cardiac output, excellent outcomes can be expected [6-8]. Yet, an absolute consensus on "the best" approach remains a topic of debate among experts. The use of cardiopulmonary bypass (CPB) and cardioplegic arrest during CABG can con-

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tribute to cardiac and systemic complications. Consequently, off-pump CABG has emerged as an alternative technique, particularly in cases of severely calcified ascending aorta. However, transitory hemodynamic instability caused by surgical manipulation, especially in severe coronary disease, may necessitate emergent conversion to on-pump conventional CABG, significantly increasing operative risk [9-11].

High-risk patients, such as those with recent myocardial infarction (MI), HFrEF, or poor hemodynamics, may benefit from an intermediate option that involves continuing to use CPB but eliminating the ischemic component of invasiveness by aboding aortic cross-clamping and maintaining a beating heart throughout the operation [12,13]. This CPB-assisted approach, introduced by Perrault et al. over 20 years ago [14], allows for the maintenance of coronary flow and reduced cardiac preload and afterload. Consequently, it decreases myocardial oxygen demand and provides a constant oxygen supply [15] leading to intraoperative hemodynamic stability without aortic cross-clamping and cardioplegic cardiac arrest. The mortality rate for patients with low LVEF undergoing on-pump beating-heart technique varies from 2 to 8% [9]. This case report aims to summarize and highlight our strategy for current surgical practice in high-risk patients.

CLINICAL CASE

We present a case of a 43-year-old male without any significant past medical history, who presented with progressively worsening dyspnea over the past 6 months. He also developed orthopnea, paroxysmal nocturnal dyspnea, and occasional effort-related epigastric pain in the 2 weeks prior to hospitalization. The patient underwent several diagnostic tests that revealed severe systolic dysfunction with an LVEF of 26% and multiple segmental contractility defects on echocardiography; coronary angiography revealed multivessel disease; nuclear medicine imaging also showed a reduced ejection fraction of 17% with territories of viable myocardium (**Fig. 1**) (**Fig. 2**). Given his severe symptoms and reduced EF, the patient was considered a high-risk candidate for CABG surgery. To optimize his hemodynamics and myocardial function, he was given levosimendan as a preconditioning agent prior to surgery.

With mechanical circulatory support device in standby in the operating theatre, operation was performed through median sternotomy. Anesthetic management included norepinephrine infusion at 0.05-0.2 mcg/kg/min for mean arterial pressure target above 65 mmHg; and glucose- potassium-insulin solution at an infusion rate of 1 ml/kg/hr. Internal thoracic artery (ITA) and saphenous vein were harvested. CPB was established using ascending aortic cannulation and a two-stage venous cannulation through the right atrium. Heparin was administered and CPB started. The left anterior descending artery was exposed in hemodynamic stabilization, so it was revascularized first with ITA; then the operation was continued with the assisted normothermic beating heart. The distal anastomoses were constructed before the proximal anastomoses followed by the circumflex and right coronary arteries with venous conduits. Regional myocardial coronary targets were achieved with the aid of epicardial stitch and mobilization with a large gauze within it. Regional myocardial immobilization was achieved with a suction stabilizer (Octopus, Medtronic; Guidant Acrobat, Guidant). We did not use the apical suction cardiac positioning device. During anastomoses, target vessel homeostasis was obtained with temporary occlusion of the proximal coronary artery or intracoronary shunts (when suitable) (**Fig. 3**). Distal anastomoses were made with running sutures of 7–0 polypropylene. The proximal anastomoses were created with 6–0 polypropylene sutures under a partial occlusion clamp. After weaning from CPB and decannulation, protamine was given. Due to his hemodynamic conditions and uneventful course, we performed ultrafast-track protocol and continue patient care process in the ICU.

Postoperatively, the patient had an uneventful recovery and was closely monitored for any complications. On the fourth day posterior to surgery the patient was started on guideline-directed medical therapy for heart failure, includ-

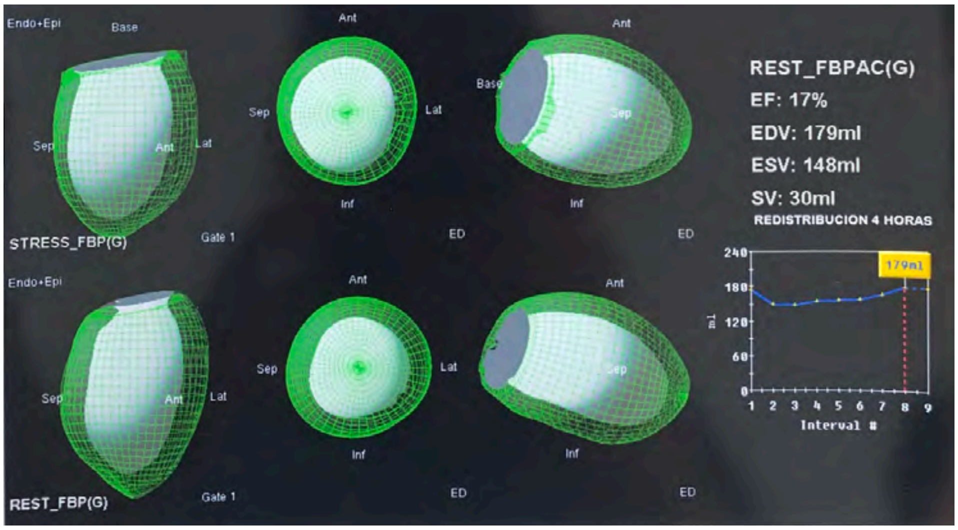

Figure 1. Nuclear medicine imaging showing a reduced ejection fraction of 17%.

ing a neprilysin inhibitor, angiotensin receptor blocker, beta-blocker, sodium-glucose co-transporter 2, diuretic and aldosterone antagonist. Symptoms improved significantly, and he was able to be discharged home in stable condition after a few days. He was advised to continue cardiac rehabilitation and to adhere to a heart-healthy lifestyle to optimize his long-term outcomes.

COMMENT

Patients who exhibit LV dysfunction, particularly those with significant areas of hibernating myocardium, tend to experience substantial improvements in LV function following CABG. Clinical trials conducted on randomized patient populations have highlighted the significant survival advantage observed in individuals with a low LVEF who undergo surgical revascularization [4,5]. It is worth noting that a dysfunctional LV with a low EF is a critical factor associated with higher risks of morbidity and mortality both during and after cardiac surgery [1-3]. At our center, we thoroughly assess patients with ischemic cardiomyopathy to determine their eligibility for CABG and anticipate the potential enhancement of myocardial function. This evaluation considers several factors such as the suitability of coronary arteries for distal anastomosis, the viability of myocardial tissue, the size and function of the left and right ventricles, as well as the patient´s functional status and symptoms. It is essential to emphasize the significance of a multidisciplinary (Heart-Team) approach in our center, where we conduct comprehensive reviews, assessments, and manage patients at every stage of diagnostic tests and treatment.

Coronary Assessment

The potential benefits of CABG rely heavily on two key factors: the quality of the coronary targets and the severity of coronary ischemia. For significant improvement to be expected after revascularization, it is crucial that dysfunctional segments of the myocardium correspond to the ischemic territories of the coronary arteries. Generally, target vessels with stenosis exceeding 70%, adequate blood flow, and diameter equal to or larger than 5F angiography catheter are consider suitable for revascularization. The more severe the stenosis and the larger the target vessel and blood flow, the higher the potential for enhanced myocardial function.

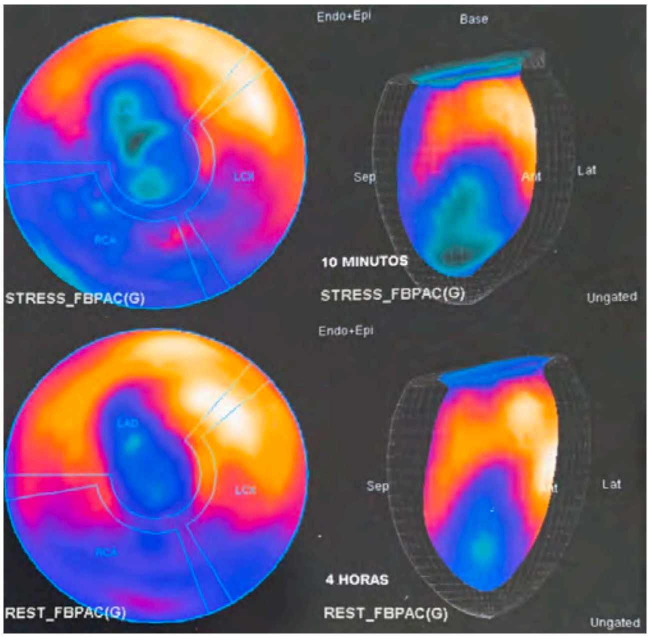

Figure 2. Nuclear medicine imaging showing viable myocardium.

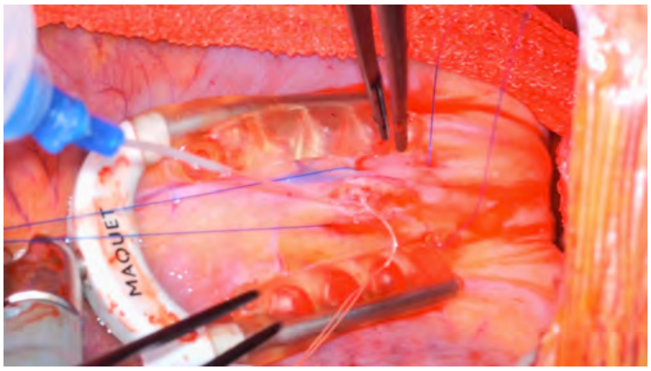

Figure 3. Mobilization of heart; exposure and stabilization of target vessel with techniques similar to those utilized in off-pump CABG; we can see the epicardial stitch with the gauze within, myocardial regional immobilization with a stabilizer, intracoronary shunt device.

Myocardial Viability Assessment [16,17].

In the context of ischemia, myocardial dysfunction undergoes a progression from stunning to hibernation and eventually leads to scar formation. Stunned and hibernating myocardium are considered viable and have the potential to improve upon revascularization, whereas myocardial scar tissue does not. The viability of myocardium can be assessed either physiologically or anatomically. Physiological assessment involves the use of resting and stress positron emission tomography (PET) with fluorodeoxyglucose, which evaluates both myocardial perfusion and metabolic activity. Normal perfusion indicates viable myocardium, while decreased perfusion with preserved metabolic activity suggests viable myocardium with delayed recovery. However, decreased perfusion along with decreased metabolic activity indicates myocardial scar that would not benefit from revascularization. Anatomical assessment of viability is best accomplished through magnetic resonance imaging (MRI) with delayed gadolinium enhancement. MRI provides the advantage of assessing the thickness of myocardial scar, which typically starts in a subendocardial pattern in ischemic cardiomyopathy. Mid-myocardial or epicardial distribution of scar suggests a different underlying cause than ischemia. Myocardium without scar or with scar limited to less than 25% of the full wall thickness has the greatest potential for improvement, whereas scar exceeding 50% of the myocardial thickness has limited potential for improvement. In cases where MRI is not available, echocardiography can provide information on the thickness of myocardium. While MRI is our preferred modality for viability assessment, it may be challenging to obtain in patients with incompatible implanted devices. In such cases, PET scans can serve as a reasonable alternative. It is important to note that even in the presence of viability, patients with left ventricular end-diastolic diameters greater than 65 mm may have a reduced likelihood of successful myocardial recovery, particularly when coupled with the presence of thinned myocardium.

Contenido

Levosimendan preconditioning

The efficacy of levosimendan in mitigating risk has been the subject of scrutiny in three recent large-scale randomized trials; namely, LICRON [18], LEVO-CTS [19] and CHEETA [20]. Despite the absence of conclusive evidence indicating a significant decrease in mortality among the levosimendan-treated group, a post hoc analysis of the LEVO-CTS study identified potential benefits exclusively for patients undergoing CABG [6].

The strategic initiation of levosimendan infusion 48 hours prior to surgery is designed to optimize the bioavailability of its active metabolites during a crucial timeframe characterized by intensified myocardial stunning. Specifically, this approach focuses on the initial 24 hours of the immediate postoperative phase, which is known to be particularly critical. By implementing this timing strategy, the prevention of postoperative low cardiac output is achieved, highlighting its positive impact across various stages of preoperative systolic dysfunction. In addition to its sustained hemodynamic effects, levosimendan exhibits an inhibitory effect on intramitochondrial calcium accumulation, a process associated with the ischemia-reperfusion phenomena encountered during extracorporeal circulation. This mechanism confers an additional myocardial protection [6].

Surgical preparation and conduct

We ensure the presence of a backup mechanical circulatory support device such as CardiohelpR ECMO (Maquet Getinge Cardiopulmonary AG, Rastatt, Germany) and/or IMPELLAR (Abiomed Inc., Danvers, MA, USA), as a precautionary measure, ready to be utilized if need arises. Its presence is crucial to address any potential requirements during the course of the surgery [8,21,22]. CABG is performed through a median full-sternotomy approach. We dissect the ITA as a pedicle, considering it the first choice for revascularization of the left AD coronary territory. For suitable cases, saphenous vein grafts and radial arteries are harvested using either open or endoscopic techniques. Our focus lies in achieving comprehensive revascularization across all coronary territories. To establish CPB, we initiate cannulation of the ascending aorta and right atrium after administering systemic heparinization, ensuring an Active Coagulation Time (ACT) of more than 480 seconds. We maintain normothermia without the use of aortic cross-clamp an strive to maintain arterial blood pressure above 50 mmHg. To expose the anterior, lateral, posterior, and inferior walls of the heart, we employ exposure, stabilization, and immobilization techniques similar to those utilized in off-pump CABG procedures [10,11,13,14]. In cases where required, we utilize a CO2 blower/mister device and/or intra-coronary shunts during grafting. Following weaning from CPB, we evaluate the need for mechanical circulatory support if patients exhibit moderate to high doses of two inotropic supports or high doses of a single inotropic support to achieve a cardiac index of 2.2 Lt/min/m2 [8]. In the postoperative period, we prioritize the timely extubation with ultra-fast track protocols, promoting early mobilization whenever feasible.

In conclusion, the decision to proceed with CABG in patients with impaired LV function can be challenging due to the associated risks, including post-cardiotomy shock. To optimize outcomes in high-risk patients, a multidisciplinary approach that includes careful coronary and myocardial viability assessments is essential. Surgical preparation and conduct for CABG in high-risk patients involve comprehensive revascularization, careful hemodynamic management, and the presence of backup mechanical circulatory support devices. The goal is to achieve successful myocardial recovery while minimizing operative risks and complications. At our Heart-Team, we prioritize incorporating the on-pump beating heart revascularization technique to optimize outcomes for high-risk, patients with low ejection fraction undergoing CABG. With this technique we provide a tailored approach aiming to maximize myocardial recovery and minimize the potential risks associated with cardioplegic arrest by performing revascularization on the beating heart with the assistance of cardiopulmonary bypass.

A comprehensive approach that combines careful patient selection, myocardial viability assessment, and the strategic use of adjunctive therapies such as levosimendan further contributes to successful outcomes in high-risk patients undergoing CABG. The choice of CABG technique for patients with low ejection fraction should be based on a collaborative decision-making among the multidisciplinary team that will optimize outcomes and enhance the quality of care provided to this specific patient population.

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IMAGES IN CARDIAC SURGERY

Applying the “resect” concept in mitral valve repair

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***Key words:** Mitral valve; Mitral valve regurgitation; Mitral valve repair.*

***Palabras clave**: Válvula mitral; Insuficiencia valvular mitral; Reparación de la válvula mitral.*

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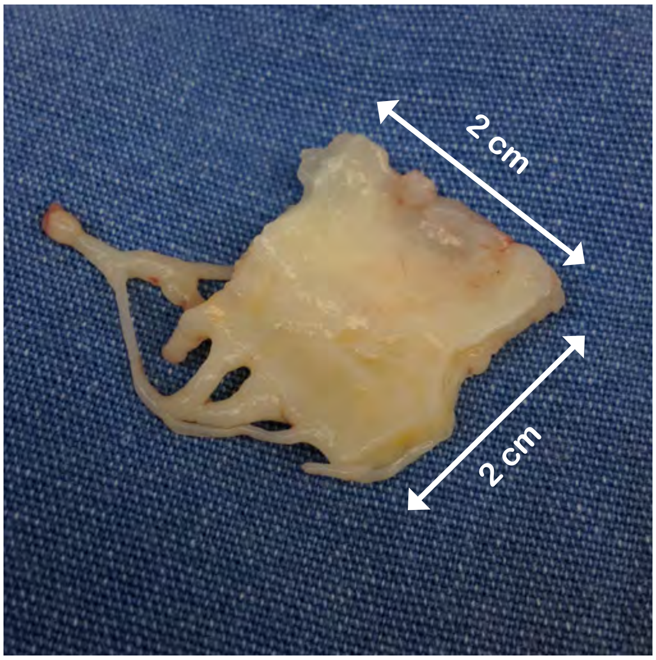
This is a case of mitral valve (MV) regurgitation in degenerative disease, in which p2 prolapse was originating a Carpentier’s type II insufficiency. In this case described here, we performed a posterior leaflet resection by means of quadrangular resection.

It has been said that MV repair by posterior leaflet resection is an art rather than a science. Certainly, leaflet posterior resection meets some basic principles. One-size-fits-all is not applicable for this resection. As a matter of fact, MV repair basic concepts have been previously published [1]. The key point is 2 centimeters in height and width in the MV posterior leaflet segment to be resected. Considering this point, triangular resection, quadrangular resection with or without unilateral or bilateral sliding posterior plasty, with or without reduction in height may be applicable in cases of leaflet posterior prolapse.

The image presented here represents a quadrangular resection of the MV posterior leaflet applying the concept of 2 cm in height and width.



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Peridevice leaks after left atrial appendage occluders. Frequency and relationship with stroke and systemic embolic events

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Key words: *Atrial fibrillation; Catheter-based techniques; Left atrial appendage; Left atrial appendage occluders; Stroke.*

Palabras clave: *Fibrilación auricular; Técnicas percutáneas; Orejuela izquierda; Oclusores de orejuela izquierda; Accidente vascular cerebral.*

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The results of the use of left atrial appendage occlusion devices in patients with atrial fibrillation have recently been reported. In the randomized controlled study Amulet IDE, 1,878 patients in 108 hospital centers were compared using two types of occluders. Although the 3-year results are quite encouraging from the point of view of freedom from the use of warfarin [Amulet (96.2%) vs Watchman (92.5%] [1], it is worth highlighting the rate of systemic embolism and/or stroke after the application of such devices (5.0% vs 4.6%, respectively). Of note, the peri-device leak (PDL) ≥3 mm is related to and can lead to ischemic events and/or stroke, as well as cardiovascular deaths [1].

The FDA has accepted a PDL≤5 mm as an adequate “closure” after application of the occluder, and allows the interruption of the use of warfarin, being replaced by dual antiplatelet therapy [2]. However, the clinical consequences of these PDLs may be devastating. A PDL≤5 at 1-year increases the 5-year risk of stroke or systemic embolism (HR: 1.94; 95% CI: 1.15-3.29; P = 0.014) [2].

To bear in mind the frequency of PDL after occlude devices. At 1-year, PDL was present in 32% of the series. Out of them, 36.8% were >3mm. In such cases, with any flow present, discontinued warfarin was related to stroke or embolism with a HR of 0.74 (CI: 0.31–1.79) versus 0.63 (0.14–2.71) with continued warfarin [3]. In such a way that incomplete closure of the left atrial appendage (LAA) seems to be an independent predictor of stroke or systemic embolism.

That goes without saying the results coming from surgical experience in LAA closure [4]. In a study by Aryana et al. demonstrated that the annualized stroke and systemic embolization risk was 6.5%; however, it can be increased up to 14.4% when not using warfarin, and up to 19.0% when a PDL ≤5.0 mm was present. Stroke risk was 5-fold higher than expected [5].

To sum up, PDL ≤5 mm can be seen up to one in three after LAA occluder devices. PDL ≤5 mm is associated with an increasing stroke and/or systemic embolism rates. In turn, it can be even worse when oral anticoagulants are interrupted after procedure.

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Contenido

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GENERAL INFORMATION

CIRUGÍA CARDIACA *EN* MÉXICO is the official journal the Mexican Society of Cardiac Surgery, A.C. and of the Mexican College of Cardiovascular and Thoracic Surgery, A.C. We publishe articles about diverse topics in cardiac surgery in the following modalities: Editorial, Original Articles, Review Articles, Viewpoint, Expert Opinion, Case Report, Surgical Technique, Images in Cardiac Surgery, New Technology, Historical Notes and Letters to the editor.

CIRUGÍA CARDIACA *EN* MÉXICO is adapted to the indications established by the International Committee of Medical Journal Editors. Manuscripts must be prepared in accordance with the Uniform Requirements for Sending Manuscripts to Biomedical Journals. The updated version is available at: www.icmje.org. All manuscripts, editorial material and correspondence should be sent by electronic email to: revmexcircard@gmail.com

Once accepted for pubication, all manuscripts will be property of **CIRUGÍA CARDIACA *EN* MÉXICO** and may not be published anywhere else without the written consent by the editor.

Each submission, regardless of its category, must include:
- a cover letter indicating the category of the article and the idea or justification of the authors to publish the manuscript.
- the complete manuscript including a front page, an abstract and keywords (in Spanish and English), text, tables, acknowledgments, declarations, references, and images and / or figures.
- Written permission from the editor for any table, image or illustration that has been previously published in print or electronic media.
- All authors must sign the Copyright Transfer Agreement, which is herein at the end of this document.

MANUSCRIPT PREPARATION PROCESS

All manuscripts must be prepared using Microsoft Word, 12-point Times New Roman or Arial font, single line spacing, letter size with 2.5 cm margins on all sides.
The manuscript should be arranged as follows:
1) Front page
2) Abstract and keywords (Spanish and English)
3) Text, acknowledgments, disclosure, references.
4) Tables
5) Figures
6) Figures Legends

Each section mentioned above should start on a separate sheet. All pages must be consecutively numbered at the center at the top, starting with the front page and ending with the figure legends. Do not list the lines. *Do not include the tables in the text.*

Original articles: should include front page, structured abstract including any background if necessary, objective, material and methods, results and conclusions (maximum 250 words) and key words (3 to 6), text (divided into introduction, material and methods, results and discussion), tables , figures and legends of figures. Number of references: Maximum 40.

Review articles. Expert opinion, or Viewpoint: front page, Non-structured abstract (maximum 250 words) and key words (3 to 6), text (divided into sections depending on the case), tables, figures and figures legends. Number of references: maximum 50.

Case report: front page, non-structured abstract (maximum 75 words) and key words (3 to 6), text (introduction, clinical case, comment), tables, figures and figures legends. Number of references: Maximum 8. Number of figures and / or tables: maximum 4 (altogether).

Surgical technique: front page, non-structured abstract (maximum 75 words) and key words (3 to 6), text (introduction, surgical technique, comment), tables, figures and figures legends. Number of references: maximum 8. Number of figures: unlimited.

Images in cardiac surgery: front page, non-structured abstract (maximum 75 words) and key words (3 to 6), text (exclusively to describe the case and the images presented, without introduction, or comments), figures and legends of figures. It should not include references or tables. Number of figures: Maximum 2.

New technologies: front page, non-structured abstract (maximum 75 words) and key words (3 to 6), text (divided into introduction, new technology, comments), tables, figures and figures legends. Number of references: Maximum 10. Number of Figures: Maximum 4.

Historical notes: front page, key words (3 to 6), text (free, divided into sections as considered), figures and figure legends. Does not include any abstract. Number of references: unlimited. Number of figures: unlimited.

Cartas al editor: front page, key words (3 to 6), text (free style, limited to 500 words). Does not include any abtract, tables or figures. Number of references: maximum 5.

Editorial (by invitation)**:** front page, key words (3 to 6), text (free style, divided into sections as considered). Does not include any abstract, tables or figures. Number of references: Maximum 10.

FRONT PAGE

Must include Title (Spanish and English) of up to 80 characters including spaces, Short title: up to 30 characters including spaces, Authors: list of all authors (maximum 6; in case of more than 6 it must be justified in the cover letter) Starting with the first name, middle initial, last names (in case of two surnames, both of them should be joined by an en-dash), Institution where the study was conducted (Department and Hospital Center; City and Country), connect the authors with the Departments by using superscripts if necessary, include if it has been presented at any congress, number of words in the abstract (not including key words), corresponding author (full name , phone number and contact email).

ABSTRACT

It must be provided in Spanish and English. See specifications in each item according to the type of article involved. It must be followed by the key words.

TEXT

See specifications regarding each of the article types.

ABBREVIATIONS

Abbreviations are not accepted in the abstract. Abbreviations in the text are allowed by using in parentheses after being cited the first time. Only 4 abbreviations per manuscript will be accepted. *Use abbreviations only if the term is repeated more than 4 times in the text.*

REFERENCES

Note the references by using arabic numbers between brakets [ ] at the end of the quote and before the point signal. DO not use superscripts.

List the references according the order they appear in the text. Journals abbreviations should be written according to the Index Medicus. Cite the authors (surname and initial of the name (s), title, abbreviated title of the Journal, year, volume, and initial and final pages. Example: Cox JL. Mechanical closure of the left atrial appendage: Is it time to be more aggresive? J Thorac Cardiovasc Surg 2013;146: 1018-1027.
JUST IF THE AUTHORS ARE MORE THAN SIX, CITE ONLY THE FIRST 3, AND INCLUDE THE SUFFIX "et al".
Within the bounds of possibility, include the doi of each article in the References.

Book References: Write down the author (s), book title, Publisher, year, and consulted pages. Example: Bonser RS, Pagano D, Haverich A. Mitral valve surgery. London: Springer Science & Business Media, 2010: 70-74.

Book chapter references: Write down the author (s) of the chapter, title of the chapter; then write “In” followed by the book reference (see book references). Example: Perier P. How I assess and repair the Barlow mitral valve: the respect rather than resect approach. In: Bonser RS, Pagano D, Haverich A. Mitral valve surgery. London: Springer Science & Business Media, 2010: 69-76.

Electronics references. Author, "Title of the contribution", Title of the serial publication. [type of support]. Edition. Location of the part within the source document. [Date of consultation]. Availability and access. Example: Gavela B. "The asymmetries of nature." The digital country [online]. October 15, 2008. [Query: October 15, 2008] http://www.elpais.com/articulo/futuro/asimetrias/natural eza / elpepusocfut / 20081015elpepifut_1 / Tes

TABLES

Each table must be numbered consecutively with Arabic numerals, and accompanied by a title. Explanatory notes should appear at the bottom, as well as the abbreviations used into. You should avoid supersaturation of information in it. They must be sent as part of the text, ***after the references,*** not as supplementary images.

FIGURES

Color images must be sent in TIFF, JPG, PSD, EPS, PNG format. Power point will not be accepted. For color images, a width size greater than 16.8 cm is recommended, File Format: CMYK, resolution: 300 DPI. For drawings or graphic images, it is recommended to send in TIFF format, width greater than 16.8 cm, File Format: CMYK, resolution: 1000 DPI.
The reproduction of the images will preferably be in color WITHOUT any extra charge.

Each of the images will be sent as a separate file, not as part of the text.
Resolution and quailty images must be as high as possible.

THIS IS THE MOST ATTRACTIVE PART OF THE CASE REPORT and SURGICAL TECHNIQUE sections. Therefore, the submission MUST BE EXCLUSIVELY in the FORMATS as MENTIONED ABOVE. Other than these, they will not be accepted.

VIDEOS

They will be accepted under the modality of Surgical Techniques in the written version, and the Video will be published in the electronic version of the magazine, by one link through the SMCC YouTube channel.

FIGURE LEGENDS

They should properly describe the figures. Each legend will correspond to the image described. It will consist of a title, and if the author considers it pertinent, a brief explanation. If abbreviations are handled in the images, these should be included at the end of the legend text.

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All manuscripts, editorial material and correspondence, including the AUTHOR COPYRIGHT TRANSFER AGREEMENT form must be sent by email to: ***revmexcircard@gmail.com***

Alternatively, for any submission, for greater convenience and user safety you can head to:
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