DEL NIDO CARDIOPLEGIA VS CUSTODIOL© CARDIOPLEGIA IN CORONARY ARTERY BYPASS GRAFT SURGERY

A PROSPECTIVE RANDOMIZED CLINICAL TRIAL

BACHELOR THESIS

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INDEX

ABBREVIATIONS

ACR -> Albumin Creatinine Ratio

AEMPS -> Asociación Española del Medicamento y Productos Sanitarios

CABG -> Coronary Artery Bypass Graft

CAD -> Coronary Artery Disease

CEIC -> Comité de Ética de Investigación Clínica

CI -> Cardiac Index

CKD -> Chronic Kidney Disease

CPB -> Cardiopulmonary Bypass

CS -> Cardiogenic Shock

CVD -> Cardiovascular Disease

EACTS -> European Association for Cardio-Thoracic Surgery

ECMO -> Extracorporeal Membrane Oxygenation

ESC -> European Society of Cardiology

GFR -> Glomerular Filtration Rate

HTK -> Histidine-Tryptophan-Ketoglutarate

IABP -> Intra-Aortic Balloon Pump

LAD -> Left Anterior Descending artery

LCOS -> Low Cardiac Output Syndrome

LM -> Left Main artery

LV -> Left Ventricle

LVDD -> Left Ventricle Diastolic Dysfunction

LVSD -> Left Ventricle Systolic Dysfunction

MAP -> Mean Arterial Pressure

MR -> Myocardial Revascularization

PCI -> Percutaneous Coronary Intervention

REec -> Registro Español de estudios clínicos

RV -> Right Ventricle

SvO_2 -> Venous Oxygen Saturation

VF -> Ventricular Fibrillation

VT -> Ventricular Tachycardia

ABSTRACT

BACKGROUND: Coronary Artery Disease is one of the most prevalent conditions in our society, resulting in Coronary Artery Bypass Grafting being the most performed heart surgery and one of the most common surgeries in today's medical practice. From an anaesthesiologic point of view, cardioprotection of the heart is of the most importance during the procedure. The challenge of bringing the heart into an elective diastolic arrest has been in discussion since the first cardioplegic strategies were introduced in the 60s. Nowadays, single-dose hyperpolarizing cardioplegic solutions such as Del Nido cardioplegia and Custodiol© cardioplegia are part of the regular medical practice without enough evidence regarding its use in high risk patients, and with no quality clinical trials comparing the two solutions.

OBJECTIVE: The main objective is to asses which of the two cardioplegic solutions provides a better return to spontaneous sinus rhythm after the aortic cross-clamp removal in patients undergoing CABG surgery. Secondary objectives will be the comparison of LCOS incidence in the first 24 hours, need for defibrillation in the first 24 hours and mortality after 30-days in patients undergoing CABG surgery.

DESIGN: The study will be a prospective, randomized, double-blinded clinical trial carried out in the Dr. Josep Trueta University Hospital of Girona.

INTERVENTION AND METHODS: Patients over 18 years old scheduled for CABG surgery in University Hospital Dr. Josep Trueta of Girona will be identified in the pre-operatory anaesthesiology visit. Patients with acute kidney failure, chronic kidney disease in stages G4 or G5, dependent on dialysis or with an implanted peacemaker will be excluded. They will be randomly divided in two groups: group A (n=62) will receive Del Nido cardioplegia, and Group B (n=62) will receive Custodiol© cardioplegia. The spontaneous return to sinus rhythm after the aortic cross-clamp removal will be assessed. The incidence of LCOS in the first 24 hours, need for defibrillation in the first 24 hours and the mortality after 30 days will also be compiled as secondary objectives.

KEY WORDS: Cardioprotection, Coronary Artery Bypass Grafting, Cardioplegia, Custodiol Cardioplegia, Del Nido Cardioplegia, Sinus Rhythm, Defibrillation, Low Cardiac Output Syndrome, 30-Day Mortality.

INTRODUCTION

Definition and Epidemiology of Coronary Artery Disease

Coronary artery disease (CAD) is a concept that englobes different conditions that affect both the structure and function of the heart. It is mainly caused by the process of atherosclerosis, which consists on the build-up of atheromatous plaques in the vascular intima due to hyperlipidaemia and sclerosis (1). As a result, blood flow in the coronary arteries may be compromised, resulting in partial or complete occlusion of the coronary vessels that can induce myocardial ischemia (2,3).

It is one of the most prevalent and concerning conditions of our time, so much so that one could describe it as "the twenty-first century plague". It is estimated that the lifetime risk in the middle-aged American population is one in two for men and one in three for women (4,5), and in 2006 the American Heart Association stated that 1 of every 6 deaths in the United States of America is caused by CAD (6), which equals about one death every sixty seconds related to CAD in a first-world country with leading healthcare advances. In Europe, Cardiovascular Disease (CVD) accounted for 45% of all deaths and 37% of all deaths in countries member of the European Union in 2017 (7). Such high numbers make CAD and CVD one of the main targets in scientific research, aiming to understand this disease better, analysing new treatment options and questioning the procedures we take as the optimal intervention.

Coronary anatomy

It is important to know the coronary anatomy and the importance of dominance pattern when considering myocardial revascularization.

The heart is irrigated by two coronary arteries (left and right) that originate from the initial portion of the ascending aorta. Blood flow occurs mainly during diastole, as during systole the semilunar valves are closed and the heart contraction hinder blood flow.

The left main coronary artery originates from the left aortic sinus. It divides into two vessels when it reaches the coronary sulcus, the anterior interventricular artery and the left circumflex artery.

The anterior interventricular artery descends through the anterior interventricular sulcus and can give a terminal branch called the posterior recurrent artery, which can anastomose with the posterior interventricular artery. It gives the following branches:

- Diagonal branches
- Septal branches

The circumflex artery proceeds through the left atrioventricular sulcus until it reaches the posterior interventricular sulcus. Its collateral branches are:

- Atrial branches
- Ventricular branches

The right coronary artery originates from the left coronary sinus. When it reaches the crux cordis it is named as posterior interventricular artery. Its branches are:

- Atrial branches -> Originate the sinus node artery.
- Ventricular branches
- Septal branches

The coronary dominance is established by which of the two main coronary arteries originate the posterior interventricular artery. There are three main dominance patterns regarding coronary irrigation:

- Right dominance, when the posterior interventricular artery is originated from the right coronary artery. It is the pattern described above and the most common of them all. Approximately 50% of the individuals present this distribution.
- Left dominance presents in approximately 20% of the individuals. The left coronary artery originates the posterior interventricular artery and irrigates the left ventricle, the medial and inferior surfaces of the right ventricle and the whole of the interventricular septum.

- The intermediate pattern appears in about 30% of individuals. The right coronary artery originates the posterior interventricular artery. However, the left ventricle's inferior surface is irrigated by the left coronary artery (8,9).

Myocardial Revascularization

Nowadays, the gold standards in myocardial revascularization are considered to be Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Graft (CABG) (10). The aim of Myocardial Revascularization (MR) is the alleviation of the symptoms caused by the myocardial ischemia as well as the improvement of prognosis. The level of improvement of these two items will depend on the success of the revascularization together with the extent of the ischemia.

The European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines on Myocardial Revascularization (MR) recommend MR in patients with stable angina or silent ischemia in the following situations (10):

Extent of CAD (anatomical and/or functional)		Class[a]	Level[b]
For prognosis	Left main disease with stenosis >50%.[c] [68–71]	I	A
	Proximal LAD stenosis >50%.[c] [62,68,70,72]	I	A
	Two- or three-vessel disease with stenosis >50% with impaired LV function (LVEF ≤35%).[c] [61,62,68,70,73–83]	I	A
	Large area of ischaemia detected by functional testing (>10% LV) or abnormal invasive FFR.[d] [24,59,84–90]	I	B
	Single remaining patent coronary artery with stenosis >50%.[c]	I	C
For symptoms	Haemodynamically significant coronary stenosis[e] in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy.[e] [24,63,91–97]	I	A

Figure 1 Indications for revascularization in patients with stable angina or silent ischemia (10).

The optimal treatment for myocardial revascularization is still in discussion, especially when regarding multivessel occlusion (11). According to the 2018 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization, CABG should be preferred over PCI in the case of three-vessel CAD, whenever the proximal LAD is affected and with high risk LM CAD. It is important to note that even though the guideline recommendations are based on clinical evidence, they also insist on individualization of each case and the importance of multidisciplinary decision making through Heart Team taking into account predicted

surgical mortality, anatomical complexity, anticipated completion of revascularization and the consideration of periprocedural complications.

The anatomical complexity of each individual CAD can be estimated with the SYNTAX score (ANNEX 2) and should be taken into account. Predicted mortality should be considered using one of the variants of EuroSCORE or STS score. According to the ESC and EACTS 2018 guidelines the following characteristics should be taken into account when making a multidisciplinary decision:

Favours PCI	Favours CABG
Clinical characteristics	**Clinical characteristics:**
- Presence of severe co-morbidity. - Advanced age or reduced life expectancy. - Restricted mobility or compromised rehabilitation process.	- Diabetes - Reduced LV function (FEV <35%). - Contraindication for dual antiplatelet therapy. - Recurrent diffuse in-stent restenosis.
Anatomical and technical aspects:	**Anatomical and technical aspects:**
- Multivessel coronary disease with low SYNTAX score(0-22). - Problematic conduits for anatomical reasons regarding CABG. - Severe chest deformation, scoliosis or chest radiation sequalae. - Porcelain aorta.	- Multivessel coronary disease with high SYNTAX score (>22). - Problematic anatomy regarding PCI. - Severe calcification in the coronary artery lesions limiting expansion. - Need for concomitant interventions.

The following table summarizes the latest ESC and EACTS 2018 recommendations according to the extent of CAD when regarding the MR strategy selection (10) (ANNEX 1):

	PCI	**CABG**
One-vessel CAD	PCI indicated (Evidence IC)	CABG could be considered (Evidence IIbC)
One-vessel CAD with proximal **LAD stenosis**	PCI possible (Evidence IA)	CABG indicated (Evidence IA)
Two-vessel CAD	PCI indicated (Evidence IA)	CABG could be considered (Evidence IIbC)
Two-vessel CAD with proximal **LAD stenosis**	PCI possible (Evidence IC)	CABG indicated (Evidence IB)
Lefft main CAD (SYNTAX <22)	PCI indicated (Evidence IA)	CABG indicated (Evidence IA)
Left main CAD (SYNTAX 23-32)	PCI could be considered (Evidence IIaA)	CABG indicated (Evidence IA)
Left main CAD (SYNTAX >33)	PCI not recommended (Evidence IIIB)	CABG indicated (Evidence IA)
Three-vessel CAD without diabetes mellitus (SYNTAX <22)	PCI possible (Evidence IA)	CABG indicated (Evidence IA)
Three-vessel CAD without diabetes mellitus (SYNTAX >22)	PCI not recommended (Evidence IIIA)	CABG indicated (Evidence IA)

Three-vessel CAD with diabetes mellitus (SYNTAX <22)	PCI could be considered (Evidence IIbA)	CABG indicated (Evidence IA)
Three-vessel CAD with diabetes mellitus (SYNTAX >22).	PCI not recommended (Evidence IIIA)	CABG indicated (Evidence IA)

Table 1 Recommendations according to the extent of CAD (10):

Coronary Artery Bypass Graft surgery:

Coronary artery bypass graft (CABG) surgery is, still to this day, the most performed cardiac surgery both in Europe and USA. Despite being common, this procedure demands a high level of expertise from an anaesthesiologic point of view because of different factors, from the type of patients that are normally eligible for CABG which present several comorbidities, to the technique that the surgery itself involves (12). The current intraoperative mortality of CABG ranges between 1% and 2% (13) and 30-day mortality between 2% and 3% (14).

There are different iterations of CABG surgery, it can be performed on-pump, off-pump and endoscopically. The technique we are describing and using in this study is the most commonly used and the accepted to have better outcomes, which is on-pump open CABG surgery (15,16)

The surgery is performed with the patient lying in supine position, via a median sternotomy. Once the sternotomy is performed, the surgeons proceed to harvest the conduits via open or endoscopic technique. The most important criteria when selecting the conduit is graft patency at 5 and 10 years. It is also important to take into account the morphological similarity between the graft and the coronary artery in order to achieve a better durability, permeability and function (17). Nowadays, the best conduit available is considered to be both internal thoracic arteries, presenting a patency of 98% at 5 years and between 85 to 90% at 10 years. The internal thoracic artery can be used as a free graft or remain attached to the subclavian artery. The next best conduit is the radial artery, presenting a similar prevalence at 5 years of 98%, but a confirmation of

ulnar collateral flow to the hand by Allen's test or by ultrasound needs to be performed before harvesting the vessel. The greater saphenous vein offers a 86% patency at 5 years (15). Other vessels that can be used as conduits in CABG include the ulnar artery and the right gastroepiploic artery (17).

When the conduits are ready, the patient must be heparinized to initiate the cardiopulmonary bypass (CPB). CPB is designed to provide:

- Oxygenation and carbon dioxide elimination.
- Circulation of blood.
- Systemic cooling and rewarming.
- Diversion of the blood from the heart to provide a bloodless field (18).

The blood is drained from the right side of the heart, via an atrio-caval cannulation and returned to the body through the distal ascending thoracic aorta, bypassing the heart and lungs. It is important to note that with hypothermia the oxygen consumption is reduced by 50% every 10ºC drop, so the blood flow should be reduced from the 2.4L/min/m^2 in normothermia to approximately 1L/min/m^2 required at 18ºC.

Then the aorta is cross-clamped and cardioplegia is delivered by the surgeon and perfusionist. Coronary arteriotomies are made in order to perform distal anastomoses, and proximal anastomoses are performed to the ascending aorta or pre-existing grafts. It is advised to leave the left internal thoracic artery to left anterior descending (LAD) graft last to avoid disruption or blood flow compromise of this main conduit. When all grafts are placed, the cross-clamp is removed, washing out the cardioplegic solution and heart activity is restored, allowing the patient to be weaned from CPB. If the patient is hemodynamically stable chest tubes are placed, sternum is approximated with specific wires and the incisions are closed (15).

Cardioplegia

Once the surgical procedure is clarified, from an anaesthesiologic point of view, cardioprotection is one of the main concerns in open heart surgery. In this surgical context it can be defined as the techniques and drugs administered to the patient in

order to protect the heart from ischemic damage derived from the procedure. The main cardioprotection strategy used in CABG surgery is cardioplegia, an elective diastolic heart arrest achieved through a pharmacological solution (19). Cardioplegia indications include the need for myocardial protection and a motionless, bloodless field during on-pump surgery (20). All cardioplegic solutions focus on the elimination of free-radicals, promotion of anaerobic metabolism and prevention of intracellular Ca^{2+} accumulation.

Cardioplegia consists on a pharmacological solution that can be classified into different groups according to its characteristics and composition. By means of its main component they can be distinguished into hematic or blood cardioplegia, when its main component is blood from the patient even though there are formulas where the blood is diluted in a 4:1 proportion with crystalloid components (such as the Buckerg solution (21)) and crystalloid cardioplegia when it is solely based on crystalloids or diluted with a small proportion of blood (22).

According to its ionic composition, mainly sodium and potassium content, they can also be classified between extracellular solutions, with a high content of sodium, potassium and magnesium, and intracellular solutions containing low electrolyte concentration (22).

Regarding its mechanism of achieving heart arrest the solutions can also be differentiated as depolarizing if they positivize the resting membrane potential or hyperpolarizing if their mechanism consists on maintaining a negative resting membrane potential (23).

Finally, as for its delivery we can discriminate cardioplegia between anterograde, when the solution is administered into the root of a cross-clamped aorta, retrograde when the catheter is inserted via atriotomy in the right atrium into the coronary sinus or selective cardioplegia when the solution is administered individually to each coronary ostial with a specialized catheter (15). Retrograde or selective cardioplegia can be used mainly due to anatomical difficulties such as an incompetent aortic valve, severe coronary artery stenosis or previous CABG (20).

Focusing on the solutions reviewed in this study, Del Nido Cardioplegia and Custodiol©, also known as Brestchneider solution or Histidine-Tryptophan-Ketoglutarate (HTK) cardioplegia are two crystalloid hyperpolarizing solutions that have become very common in heart surgery during the last 4 years. Their main benefit is that a single dose administration provides up to 120 minutes of cardioprotection in the case of Custodiol© (24) and up to 90 minutes in Del Nido (25), compared to the need of redosing every 15-20 minutes of traditional hematic solutions such as Buckberg or Saint-Thomas solution. However, these limits are being questioned and when further trials are conducted this time limit could be enhanced..

This in turn, allows for shorter cross-clamp times and shorter total operation time as it has been observed in several studies comparing Del Nido cardioplegia with other cardioplegic solutions (26,27), but on the other hand some studies have found no significant difference in CPB and total surgery time with the Custodiol© cardioplegia (28). All of this while proving equal or non-inferior cardioprotection to hematic cardioplegia on both Custodiol© (29–31) and Del Nido (26,27).

Furthermore, cardioplegic solutions based on high potassium depolarization have been linked with post-cardioplegic ionic and metabolic imbalances, myocardial hypokinesia, higher incidence of arrhythmias and ischemic injury, tissue oedema, endothelial damage, increased free radical production and left ventricular dysfunction (32,33) thought to be associated with a decrease in the ATP content, increase in intracellular H^+ and Ca^{2+} concentration and an increased Na^+ current via the Na^+/H^+ exchanger. This is one of the main attractive features of Del Nido and Custodiol© cardioplegias, as they achieve elective heart arrest mainly via a polarization strategy, rather than a depolarization, aiming to solve the problems associated with traditional hyperkaliaemic cardioplegia.

Del Nido Cardioplegia

Del Nido cardioplegia can be defined as an extracellular solution due to its high concentration of sodium and potassium. The solution was invented by Dr. Pedro J. Del Nido and his team at Boston Children's Hospital and Stanford University. It has been successfully used in paediatric heart surgery for more than 20 years (34), which was its initial purpose. However, the solution was not started to be regularly used until 2012, as Stanford University held the rights to the solution.

It achieves diastolic heart arrest thanks to synergic depolarizing and hyperpolarizing mechanisms. The depolarization is achieved thanks to the high concentration of potassium in the extracellular space, depolarizing the cell membrane potential from -85mV to between -65mV to -40mV (35), which inactivates the fast Na^+ channels and blocks conduction of the myocardial action potential (36). The Del Nido cardioplegia includes depolarizing K^+ in order to achieve a quick cardiac arrest.

This can be achieved with concentrations of about 10-30mmol/L of potassium chloride, and it is important not to exceed this concentration, as it can surpass the -40mV threshold that can activate the L-type Ca^{2+}-channels, inducing calcium overload that can generate spontaneous contraction (23).

With an hyperkaliaemic arrest, the Na^+/K^+-ATPase pump remains inhibited by the generated extracellular hyperkalaemia and hypothermia, maintaining elevated intracellular sodium levels. The sodium current is exacerbated due to the activation of the Na^+/H^+ exchanger because of the intracellular acidosis caused by ischemia, and forcing the Na^+/Ca^{2+} exchanger in reverse mode (at membrane potentials more positive than -50mV) (37), pumping in calcium. Calcium overload can lead to contraction, reperfusion injury and cell death (FIGURE 2).

Composition of Del Nido Cardioplegia:

Carrier solution Plasmalyte-A (1000ml)
1:4 Blood:Crystalloid ratio
4mL of Potassium Chloride
16.3mL of Mannitol (20%)
13mL of Lidocaine (1%)
4mL of Magnesium sulfate (50%)
13mL of Sodium bicarbonate (8.4%)

Table 2 Composition of Del Nido Cardioplegia (38)

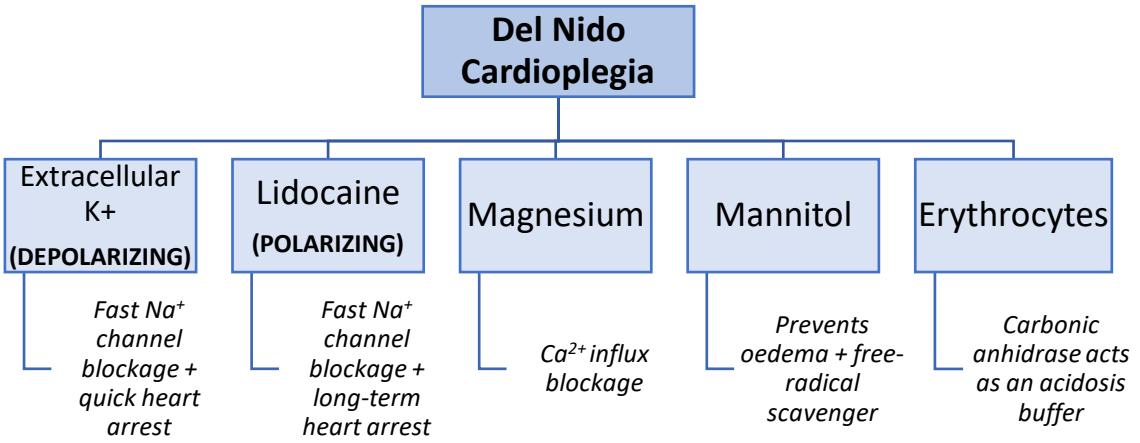

Figure 2 Del Nido cardioplegia components and function

In order to avoid the classic complications of hyperkalaemia cardioplegia stated above, the solution adds Lidocaine, a class IB antiarrhythmic that allows the polarization of the myocyte by blocking the fast Na^+ channels, providing additional protection when included in hyperkaliaemic cardioplegia (39). By blocking the Na^+ current induced by fast Na+ channels, it is able to maintain the membrane potential closer to the resting potential (around -70mV), avoiding the Na^+ window current and the Ca^{2+} loading caused by hyperkalaemia. By including Lidocaine, the solution is able to keep the heart in

diastolic arrest for a longer period of time as well as avoiding the Na^+ entry and, indirectly, avoiding the Ca^{2+} entry.

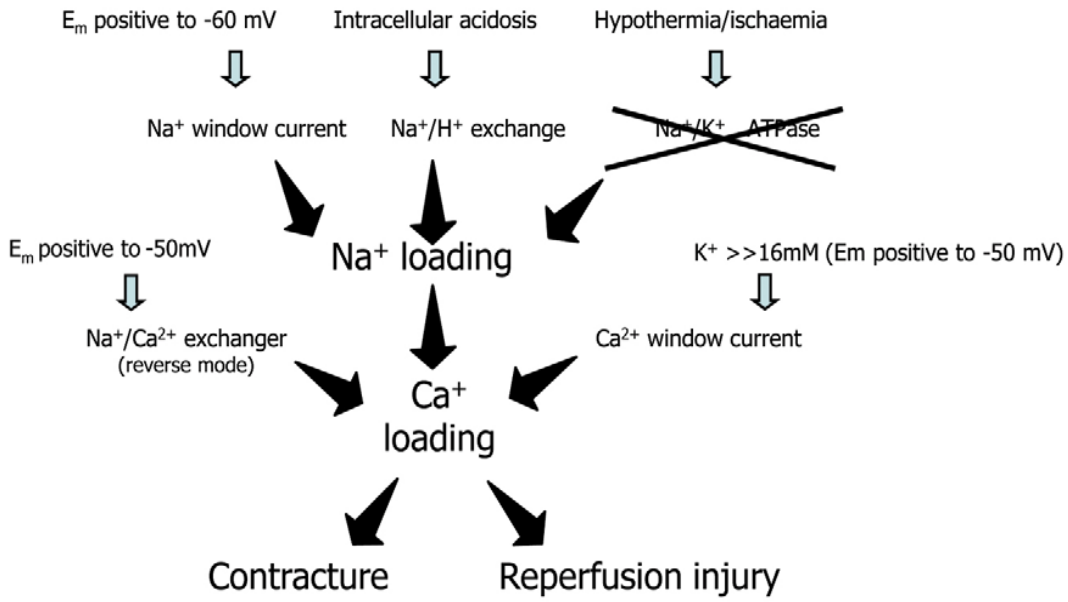

Figure 3: Mechanisms of Na^+ and Ca^{2+} loading in depolarized arrest (36)

Del Nido also adds magnesium, its main action is to competitively block the influx of calcium ions into the cardiomyocyte, as it is a natural Ca^{2+} channel blocker. And Mannitol acting to prevent hyperosmotic edema and free radical damage. The addition of red blood cells in a 1:4 ratio provides carbonic anhydrase for buffering acidosis (38). Finally, Del Nido Cardioplegia includes only a very small amount of glucose in the Plasmalyte solution. When entering the cell, glucose can also drag Na^+ with it. By only adding a minimal amount of glucose, we can achieve better surgical outcomes, reduce the need for postoperative insulin requirements and better intraoperative glucose levels (21).

The ionic components of Del Nido solution (sodium, potassium, magnesium) are cleared through the kidney. Lidocaine is cleared through the liver and Mannitol has a mixed liver and kidney clearance.

Custodiol© Cardioplegia

What we know today as Custodiol© cardioplegia was first proposed by Hans J. Bretschneider in Germany in 1975. It can be defined as an intracellular solution due to its low Na^+ and Ca^{2+} content. The low Na^+ content of the solution causes Na^+ depletion of extracellular space, resulting in hyperpolarization of the myocyte plasma that prevents the activation of the fast Na+ channel, thus allowing for diastolic heart arrest.

It also contains histidine, which buffers acidosis caused by anaerobic metabolism improving its efficiency, ketoglutarate that improves ATP production during reperfusion, tryptophan a cell membrane stabilizer and protector and mannitol, which like in Del Nido solution lowers cellular oedema and acts as a free radical scavenger (40,41).

Composition of Custodiol© Cardioplegia:

No blood added
9µmol/L of Potassium
30 µmol/L of Mannitol
15µmol/L of Sodium
198µmol/L of Histidine
1 µmol/L of Ketoglutarate
2 µmol/L of Tryptophan
7.02 – 7.20pH

Figure 4 Composition of Custodiol© cardioplegia (40)

The main concerns with Custodiol© are the hyponatremia, oedema and acidosis related to the administration of a high volume hyponatraemic solution and the increased incidence of ventricular fibrillation that some studies have shown without reaching statistical significance (40). Custodiol components are cleared mainly via the kidney.

Custodiol© is also approved by the U.S. Food and Drug Administration (FDA) for its use as an organ preservation agent for heart, kidney and liver in the transplantation process, as well as its indication for myocardial protection during cardiac surgery (42).

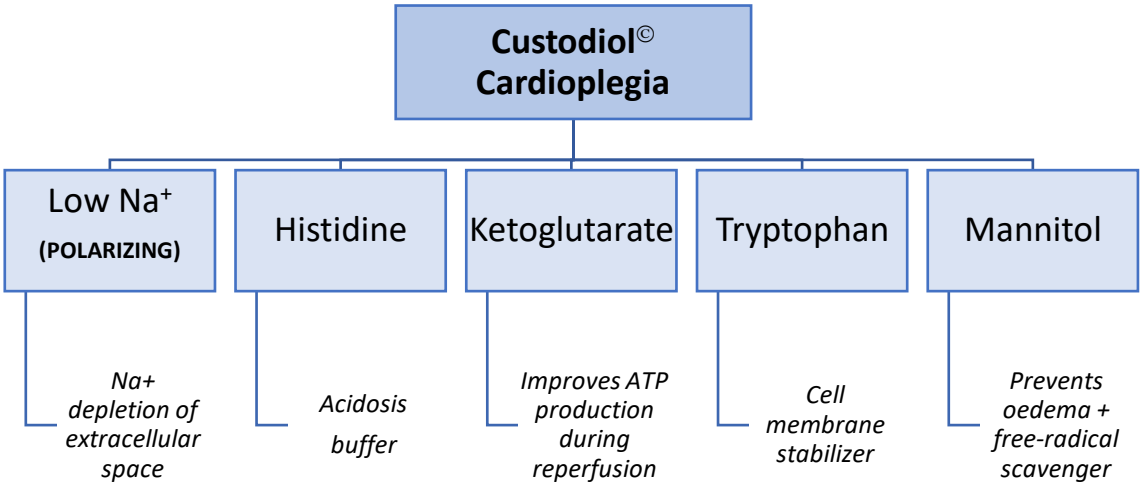

Figure 5 Custodiol© cardioplegia components and function

Taking into account the actual evidence, *Siddiqi et al.* proposed the following algorithm for cardioplegia selection in 2018 (43):

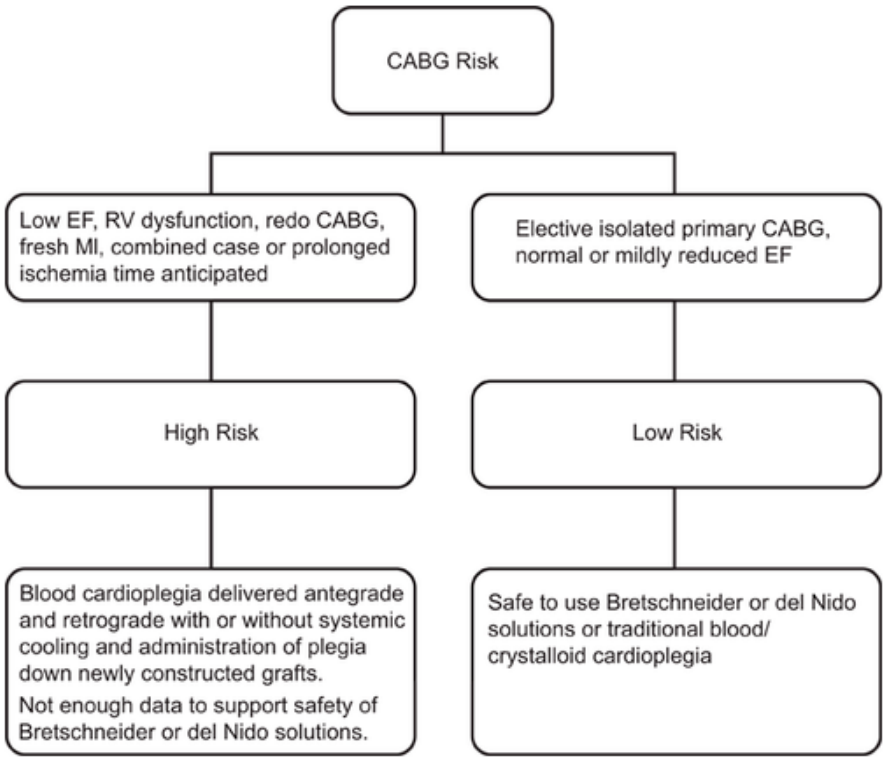

Figure 6: Proposed algorithm of Custodiol© and Del Nido cardioplegia selection in high-risk versus low-risk cardiopulmonary artery bypass graft surgery (43).

Low Cardiac Output Syndrome (LCOS)

The LCOS can be defined as a postoperative complication in cardiac surgery due to a decrease in the cardiac output resulting in a mismatched oxygen delivery and metabolic demand. It differs from the concept of Acute Heart Failure as it a different origin and presentation. The Spanish Society of Intensive Care Medicine, Critical Care and Coronary Units (SEMICYUC in Spanish) elaborated a consensus guidelines that define the LCOS in postoperative period of heart surgery:

- CI <2.2L/min/m^2 without the presence of relative hypovolemia, related to both left and right heart-failure, with or without pulmonary congestion and regular or low blood pressure.
- Presence of compatible clinic when the cardiac output is not monitored: oliguria (diuresis <0.5mL/kg/h), central venous saturation <60% (with normal arterial saturation) and lactate >3mmol/L and patients that need sustained ionotropic agents or Intra-aortic Balloon Pump (IABP) when leaving the operation room in order to maintain a hemodynamically stable situation.
- Lastly, Cardiogenic Shock (CS) corresponds to the most critical condition under the LCOS spectrum. It is defined by CI < 2L/min/m^2, systolic blood pressure <90mmHg, without relative hypovolemia and presence of oliguria (44).

LCOS is one of the most common and serious complications in the postoperative of cardiac surgery. It is associated with increased morbidity, long-term mortality and increased resource utilization (45,46). Its incidence is estimated to range between 3% and 45% according to different studies and surgeries (44), with a mortality rate that can be as high as 20% (47).

Conditions affecting the heart function after heart surgery can be attributed to the surgery itself or to the comorbidities and underlying disease of the patient. In this case, LCOS due to the surgical procedure typically occur up to 18 hours and tend to peak between 4 to 6 hours after the moment of reperfusion (48–50)

Due to the severity of the condition, inotropic agents or mechanical circulatory support (such as IABP or ECMO) are required to improve the patients hemodynamic situation.

The most common consequences of LCOS are acute renal failure, atrial fibrillation, neurologic and pulmonary complications (47).

From a pathophysiological point of view, LCOS can occur due to left ventricle systolic disfunction (LVSD), left ventricle diastolic disfunction (LVDD) or right ventricle systolic dysfunction (RVSD):

- LVSD and RVSD can occur due to a pressure overload, volume overload or decrease in contractility.
- LVDD can occur due to a severe tachycardia or a decrease in myocardial compliance and relaxation.
- All of these situations can coexist and all reflect as a diminished CI and venous oxygen saturation (SvO_2) (47,51)

The treatment of LCOS is geared towards increasing oxygen delivery and preventing organ failure by using hemodynamic support measures. The first steps should be to optimize the fluids, acid-base management, electrolytes and optimization of ventilation support. It is also important to identify the underlying cause of LCOS (graft disfunction, valvular incompetence, pericardial tamponade…) as soon as possible. If the situation is not solved, it is important to select the adequate strategy according to CI and mean arterial pressure (MAP):

- MAP <60 and CI >2 -> Use of vasopressors (norepinephrine and vasopressin).
- MAP >60 and CI<2 -> Use of inotropic agents (dobutamine, dopamine, epinephrine, levosimendan).
- MAP>60 and CI>2 -> Intra-Aortic Balloon Pump (IABP), ventricular assist device, extracorporeal membrane oxygenation. (47,52)

JUSTIFICATION

As the current theorical evidence has been referenced in the introduction, the optimal cardioplegia strategy is one of the main focuses in the field of cardiac surgery research. In the last five years there has been an increase in the usage of single-dose cardioplegic solutions, mainly Del Nido and Custodiol©, and some institutions use it as their main cardioplegic agent during heart surgery. However, we are lacking strong evidence that supports its usage and safety in high-risk patients and with specific groups of patients, such as individuals suffering of chronic kidney disease.

Moreover, current studies mainly focus on cardiac enzyme increase which can be a misleading target, as heart surgery involves manipulation of the heart increasing the enzymes per se. One of the other main targets that cannot be reliable is myocardial infarction after CABG which is the Type 5 Myocardial Infarction according to the European Society of Cardiology (53). First of all, this is a highly discussed definition and there is no consensus among the scientific community regarding its validity, secondly it can be extremely difficult to identify the patients suffering myocardial infarction, and thirdly a study published in 2019 by *Sef et al.* found that graft disfunction affected up to 72% of the patients that suffered postoperative myocardial infarction after CABG (54). This shows that the most of Type 5 Myocardial Infarctions can be attributed to a complication of the surgery itself, not the cardioprotection strategy, and a reliable randomized trial assessing the myocardial infarction excluding graft disfunction would require large resources and a very high population sample.

Lastly, there are no prospective quality studies comparing Custodiol© and Del Nido solutions in adult individuals, which are the most prominently used single dose solutions in medical practice today. The only prospective randomized trial that we have found was published in 2019 by *Talwar et al.* but it only included pediatric patients under 12 years old undergoing any type of open heart surgery. However, the study found that the Del Nido cardioplegia was superior regarding preservation of CI, duration of mechanical ventilation, intensive care unit and hospital stay, lower inotropic scores and less troponin-I release (55).

According to this, the aim of this study is to contribute with new evidence by choosing more feasible variables. The main endpoint of the study is to asses spontaneous return to sinus rhythm in both groups. As cardioplegia shuts down the action potential that creates both electrical activity and contraction of the heart, a higher spontaneous return to sinus rhythm can reflect a better cardioprotective strategy. As a study published in 2018 by *Ad et al.* comparing Del Nido cardioplegia against whole blood cardioplegia, found that the Del Nido group presented a higher return to spontaneous sinus rhythm (97.7%) than the blood cardioplegia group (81.6%) (26).

Taking into account that Custodiol© has not shown significant differences to blood cardioplegia regarding spontaneous sinus rhythm return, the superiority of Del Nido should be expected. Our hypothesis is that this difference is related to the presence of Lidocaine in the solution, a class IB antiarrhythmic. Furthermore, the higher incidence showed in some studies of VF in Custodiol© (30) might indicate that it does interfere at a higher degree with the action potential generation, and provide a less effective restore of the heart regular electrical activity.

Our secondary outcomes are, first of all, LCOS incidence the first 24 hours after reperfusion in both groups The 24 hours mark has been chosen as LCOS related to surgery factors has been found to occur most likely in the first 18 hours after reperfusion (48–50). By targeting LCOS as a secondary outcome, one of the most common and serious complications related to CABG, we can analyze which cardioplegic solution affects less contractility and cardiac output.

Secondly, the need for defibrillation the first 24 hours after reperfusion in both groups can show the effects on electric conduction and pacemaker function of the myocardium. The 24-hour mark has been chosen in order to detect the immediate consequences of reperfusion.

Lastly, the mortality after 30 days can be used as an indicator of the systemic effect of the cardioprotective strategy itself and its impact on the recovery of the patient. The

30-day mark has been chosen as it is the benchmark in heart surgery for short-term mortality.

The exclusion of patients with severe chronic kidney disease and acute kidney failure from this study is important in three ways:

- First of all, chronic kidney disease (CKD) has consistently been linked with increased mortality after heart surgery, which increases with the severity of the condition (56,57), therefore the inclusion of patients with end-stage kidney failure or severe chronic kidney disease could be harmful for them.
- In patients with severe and end-stage CKD the clearance of the cardioplegia solution when removing the aortic cross-clamp might be compromised as the solutions are cleared mainly through the kidney, resulting in increased complications and biasing the results of the study, not favoring an equal comparison of the two solutions. Therefore, we have decided to exclude patients in GFR stages G4 and G5 (ANNEX 4) as they can classified as suffering from a severely decreased GFR.
- Lastly, the aim of the study is to establish that the use of Del Nido and Custodiol© is safe in this particular group of both low-risk and high-risk patients, paving the ground for future trials assessing its use in other specific groups of individuals.

Taking all of this into account, the comparison in a randomized prospective study of these two cardioplegic solutions can provide capital and much needed evidence regarding what we consider today as standards in cardioplegia, and also cementing the pathway for further studies to be carried regarding the safety and adequation of this cardioplegic solutions in other specific groups of patients.

HYPOTHESIS

The patients undergoing a cardioprotection strategy with Del Nido cardioplegia will have a higher spontaneous return to sinus rhythm than the group with Custodiol© cardioplegia.

OBJECTIVES

MAIN OBJECTIVE

- To assess the relation between the cardioprotection strategy and spontaneous return to sinus rhythm after reperfusion in patients undergoing CABG surgery.

SECONDARY OBJECTIVES

- To assess the relation between the cardioprotection strategy and the incidence of Low Cardiac Output Syndrome the first 24 hours after reperfusion in patients undergoing CABG surgery.
- To assess the relation between the cardioprotection strategy and the need for defibrillation in the first 24 hours after reperfusion in patients undergoing CABG surgery.
- To assess the relation between the cardioprotection strategy and the mortality rate after 30 days in patients undergoing CABG surgery.

METHODOLOGY

Study design

Taking into account that the aim of the study is to compare two pharmacological strategies, the best possible design is a prospective, randomized, double-blinded clinical trial.

The study will be carried out in the Dr. Josep Trueta University Hospital of Girona by the Anesthesiology and Reanimation team.

Study Population

All patients over 18 years old undergoing Coronary Artery Bypass Graft surgery in the Dr. Josep Trueta University Hospital of Girona during the study period.

Inclusion criteria

- Patients willing to sign the written informed consent document and able to understand it.
- Patients undergoing isolated Coronary Artery Bypass Graft surgery or associated with other types of heart surgery.
- Patients over 18 years old.

Exclusion criteria

- Patients with acute kidney failure at the moment of the surgery or the anesthesiology preoperatory assessment.
- Patients diagnosed with Chronic Kidney Disease classified as GFR Stages G4 and G5 (ANNEX 4) at the moment of the anesthesiology preoperatory assessment.
- Patients dependent on hemodialysis at the moment of the surgery or the anesthesiology preoperatory assessment.
- Patients with an implanted peacemaker.

Sample size

Taking into account the aforementioned study of 2018 by *Ad et al.* (26) we will use as a reference the proportion of patients treated with Del Nido cardioplegia that spontaneously returned to sinus rhythm in their study. Considering also that Custodiol© cardioplegia has been proved non-inferior in low-risk patients than blood cardioplegia, a similar proportion of patients should achieve spontaneous return to sinus rhythm. However, the increased incidence of ventricular fibrillation observed might make this number lower, so we are taking the following numbers as a reference to calculate the necessary sample size:

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 62 subjects receiving Del Nido solution and 62 subjects receiving Custodiol© solution are necessary to recognize as statistically significant a relative risk greater than or equal to 1.22, considering a difference equal or greater than 20% as clinically significant. A proportion in the non-exposed group has been estimated to be 0.8. A drop-out rate and loss to follow-up of 2% has been estimated.

This calculations have been made using the Sample size and power calculator of the Institut Hospital del Mar d'Investigacions Mèdiques developed by Jaume Marrugat.

Sample selection

A non-probabilistic consecutive sample method will be followed in the Hospital Universitari Dr. Josep Trueta of Girona in order to recruit the necessary patients stated in the previous section that meet the inclusion and none of the exclusion criteria, who will be handed the information sheet and offered to enroll in the study by asking their consent.

Estimated time of recruitment

Taking into account that 124 patients will be needed in order to reach statistical significance, and that between 90 and 110 CABG surgeries are performed in the Hospital Universitari Dr. Josep Trueta of Girona each year, we estimate that about 18 months will be needed in order to find the necessary sample, taking into account that some patients

might refuse to participate in the study and some others would not be fitting the study criteria.

Randomizing and masking

In order to avoid a confusion bias a randomization will take place using the software SPSS. This software will assign the patient to the Del Nido or Custodiol© group randomly. The randomization will be made by the pharmacy staff not directly involved in the study at least 24 hours before the surgery using the software SPSS. Investigators will be unaware of the assigned intervention until the study completion as the solution will be administered by the perfusionist and surgery team.

The study will be a double-blinded randomized trial, as we will externalize the randomization process to the pharmacy staff that are not involved in the study, therefore the anesthesiologist that collects the data will not know what intervention has been assigned to each patient.

STUDY VARIABLES

These are the variables that will be analyzed in this study. It should be noted that all of them are dichotomic qualitative nominal variables.

Independent variable -> The use of a cardioprotection strategy with Del Nido or Custodiol© cardioplegia.

The solution dosage and delivery methods are detailed in the data collection and procedures section of the protocol.

Primary outcome

Dependent variable -> Spontaneous return to sinus rhythm after cross-clamp removal and reperfusion.

Sinus rhythm will be defined by the following criteria:

- Regular rhythm at a rate of between 60 to 100bpm.
- Presence of P waves that are followed by a QRS complex at a 1:1 rate.
- A PR interval of between 120 and 200ms.

Secondary outcomes

Defibrillation

Number of patients that need defibrillation the first 24h after the moment of aortic cross-clamp removal and reperfusion.

The need of defibrillation will be defined by the presence of a shockable rhythm which include:

- Ventricular fibrillation
- Ventricular tachycardia without pulse.

Low Cardiac Output Syndrome

Number of patients that present LCOS the first 24h after the moment of aortic cross-clamp removal and reperfusion.

The presence of LCOS will be defined by the SEMICYUC criteria (44):

- CI <2.2L/min/m^2 without the presence of relative hypovolemia, related to both left and right heart-failure, with or without pulmonary congestion and regular or low blood pressure.
- Presence of compatible clinic when the cardiac output is not monitored: oliguria (diuresis <0.5mL/kg/h), central venous saturation <60% (with normal arterial saturation) and lactate >3mmol/L and patients that need sustained ionotropic agents or Intra-aortic Ballon Pump (IABP) when leaving the operation room in order to maintain a hemodynamically stable situation.
- Cardiogenic Shock (CS) corresponds to the most critical condition under the LCOS spectrum. It is defined by CI < 2L/min/m^2, systolic blood pressure <90mmHg, without relative hypovolemia and presence of oliguria

30-day mortality

Number of patients discharged as deceased 30 days after the surgery.

Covariates

The following covariates have been chosen in order to describe the sample and asses the correct randomization of both groups:

Covariate	Type	Measure instrument	Categories or values
Age	Continuous quantitative variable	Clinical examination	18 – 65 66 - 99
Gender	Dichotomous nominal qualitative variable	Clinical examination	Male Female
Surgery type	Nominal qualitative variable	Clinical examination	Isolated CABG CABG + Valve surgery CABG + Aortic surgery
Number of grafts	Discrete quantitative variable	Clinical examination	1 graft 2 grafts 3 grafts 4 grafts
Re-do CABG	Dichotomous nominal qualitative variable	Clinical examination	Yes No
EuroSCORE Risk Stratification (ANNEX 3)	Discrete quantitative variable + Ordinal qualitative variable	Clinical examination	Low risk (0-2) Intermediate risk (3-5) High risk (5-45)
Cardioplegia delivery	Nominal qualitative variable	Clinical examination	Anterograde Retrograde

			Selective
CKD GFR stage (ANNEX 4)	Ordinal qualitative variable	Clinical examination	No CKD Stage I Stage II Stage III A Stage III B
Post-operatory Unit	Nominal qualitative variable	Clinical examination	UCO UCI REA

Table 3 List of covariates

It is also important to note the following aspects of each covariate.

- As the **age** increases, so does the risk of complications and mortality (58), so it is important to check that both groups have a similar mean age in order to be comparable. We will also classify the patients into the categories stated in the table above using the 65 years old as an arbitrary reference to classify patients according to their age.
- **Gender** has been chosen as being a female has been identified as a risk factor for increased mortality when submitted to heart surgery (58).
- **Surgery type** has been chosen to avoid the confusion risk associated with more complex surgeries resulting in increased complications. Higher CPB and total surgery time is related to an increased risk of postoperative complications and mortality.
- **Number of grafts** has been chosen as a higher number of grafts imply more CPB and total surgery time, thus increasing the possible complications. The mean number of grafts in each group would be calculated in order to verify that the groups are comparable.
- **Re-do CABG** has been chosen as a covariate as patients that are re-operated from heart surgery have an increased risk of postoperative complications and mortality (58).
- The **EuroSCORE** additive score (ANNEX 3) has been chosen as the tool to predict mortality and stratify patients according to its risk as EuroSCORE is the most used

score to estimate mortality in heart surgery. The logistic variant of EuroSCORE is designed to better estimate mortality in higher risk patients, but both the additive and logistic model do overestimate mortality, so the additive model has been chosen due to its simplicity (59). The EuroSCORE II model was not chosen as there is a current debate regarding its superiority and estimation capabilities compared to the regular EuroSCORE form which is derived (60). The STS score was not chosen either, as it is primarily used in the US and it is validated in an American cohort, that can differ from our patient sample. As EuroSCORE was based in an European cohort of patients it might better estimate mortality in our patient sample.

- As per the **EuroSCORE** variable we will use it both as a qualitative variable, calculating the proportion of patients assigned to each risk category (low, intermediate and high) in order to then stratify the results latter, but we will also calculate the mean score in each group using the score as a quantitative variable to verify that both groups are comparable.
- The **cardioplegia delivery** method will be taken into account in order to determine if different delivery methods result into differences regarding our primary and secondary endpoints. It is important to note that cardioplegia will be delivered anterogradely as per study protocol unless the surgery team decide that there are anatomical difficulties that justify retrograde or selective delivery.
- We used the **CKD GFR** classification in order to identify patients with severe chronic kidney disease and to avoid the risk of confusion related to problems with the clearance of the cardioplegic solution rather than its effect. Moreover, we will stratify our groups and outcomes into the different GFR categories.
- Lastly, we took into account the **post-operative critical care unit** into which the patient was admitted to, as in our hospital these patients can be admitted into three different units: the critical care unit (UCI), the coronary unit (UCO) or the reanimation unit (REA). We will take this into consideration in order to identify if there are any significant differences between the patients managed by intensivists, cardiologists and anesthesiologists taking into account our outcomes.

DATA COLLECTION AND PROCEDURES

1. Anesthesiology pre-operatory visit:

Following the regular pre-operatory visit and assessment that all patients that are eligible for surgery undergo in our hospital, patients scheduled for CABG will be identified. Once the physician can confirm they meet the inclusion criteria and none of the exclusion criteria the patients will be informed about the study, handed the information sheet and asked to sign the informed consent.

If the patient gives his consent, their data would be entered in the data base by one of the investigators. The patient will be assigned an identification number in the database in order to preserve their personal data. The patient's gender, age, surgery type scheduled, if the patient is a re-do CABG, EuroSCORE score and risk group and CKD GFR stage will be compiled in the data collection sheet.

2. Surgery and intervention:

The randomization will be done by the pharmacy staff, which will then prepare the cardioplegic solution assigned to the patient and deliver it to the operation room.. During the surgery, once the patient is on CPB and the aortic cross-clamped is placed, the assigned cardioplegic solution will be administered according to the randomization by the heart surgeon and perfusionist. The anesthesiologist will not know which strategy is being used.

The Del Nido cardioplegia will be administered anterogradely when the aortic cross-clamp is in place. The total dose will be 20mL/kg up to a maximum of 1000mL in patients larger than 50kg. The cardioplegic solution will be administered in a single-dose in a period of 1-4 minutes at a rate of 250-450mL/min at a pressure of 150mmHg. The solution will be delivered at 4ºC.

In case of expected cross-clamp of over 120 minutes or spontaneous electric activity, a second dose consisting of half the initial dose will be administered following the same parameters as before.

The Custodiol© cardioplegia will be administered anterogradely when the aortic cross-clamp is in place. The total dose will be 25mL/kg. The cardioplegic solution will be administered in a single-dose in a period of 6-8 minutes at a pressure of 150mmHg. The solution will be delivered at 4ºC.

In case of expected cross-clamp of over 180 minutes or spontaneous electric activity, a second dose at a dosage of 25mL/kg will be administered in a period of 2-3 minutes following the same parameters as before.

In case of severe aortic insufficiency, the cardioplegic delivery method will be retrograde or selective according to the criteria and level of expertise of the surgeon with both techniques. In case of retrograde delivery, the cardioplegic solution will be delivered at a pressure of 40mmHg.

When the aortic cross-clamp is removed and the reperfusion starts, the anesthesiologist will be monitoring the cardiac electrical activity with the Nihon Kohden Lifescope G7 monitor and will assess if there is spontaneous return to sinus rhythm or not. The presence or absence of spontaneous rhythm according to our stablished criteria will be compiled on the data collection sheet. The delivery method of the solution and number of grafts performed will also be compiled on the data collection sheet. The patient will also be monitored by trans-esophageal echography during the surgery in order to identify spontaneous heart contraction.

3. Admission to post-operative critical care unit:

Once the surgery is completed, the patient will be admitted into a post-operative critical care unit as per hospital protocol and availability of beds and resources. The patient will be admitted to the Intensive Care Unit (UCI), Coronary Care Unit (UCO) or Anesthesiology Reanimation Unit (REA). There, the patient's heart rhythm will be monitored at all times with the Nihon Kohden Lifescope G5 monitor and the cardiac index will be monitored using the Edwards Vigileo monitor.

4. Post-operatory data collection and follow up:

The principal investigator will collect the data regarding the post-operatory period through the centralized medical record software of the hospital (SAP) plus the specific software used in the critical care units (Centricity™) according to the following timing:

- 24h after the aortic cross-clamp removal and reperfusion, the principal investigator will check through the Centricity™ software if the patient has presented arrhythmias requiring defibrillation (ventricular tachycardia without pulse and ventricular fibrillation).
- In patients with Implanted Cardioverter Defibrillator (ICD) the Centricity™ application would be checked for the presence of VT without pulse and VF.
- 24 hours after the aortic cross-clamp removal and reperfusion, the principal investigator will check through the Centricity™ software if the patient has met the criteria of LCOS.
- 30 days after the aortic cross-clamp removal and reperfusion, the principal investigator will check through the SAP software if the patient has been discharged as deceased.

All this information will be collected through the data collection sheet and registered in the study data base. All the adverse effects experimented by the patient will be codified and treated according to the MedDRA system.

STATISTICAL ANALYSIS

Descriptive analysis

The first step would be to conduct a descriptive analysis of our sample stratifying the groups through the covariates in order to verify that the randomization has resulted in equal and comparable groups.

The following variables will be analyzed according to their nature (qualitative or quantitative). For quantitative variables means, medians and standard deviations will be used. Qualitative variables will be described using frequency tables, with absolute and relative frequencies.

Age -> The mean and median and standard deviation age of the patients included in each group will be calculated. We will also calculate the proportion of patients in the group of 18– 65 years old and 66 - 99 years old.

Gender -> The proportion of men and women assigned to each group will be calculated.

Surgery type -> The proportion of each surgery type in the two groups will be calculated.

Number of grafts -> The mean, median and standard deviation number of grafts performed in each group will be calculated.

Re-do CABG -> The proportion of patient submitted to re-do CABG in each group will be calculated.

Delivery -> The proportion of patients that received anterograde, retrograde and selective cardioplegia delivery in each group will be calculated.

EuroSCORE -> The mean, median and standard deviation score in each group of patients will be calculated. The proportion of patients assigned to low, intermediate or high risk in each group will also be calculated.

CKD GFR stage -> The proportion of patients in each stage of CKD CFR in each group will be calculated.

Post-operatory unit -> The proportion of patients admitted to UCI, UCO and REA in each group will be calculated.

Bivariate analysis

The primary outcome of the study will be analyzed comparing the proportion of patients that presented a spontaneous return to sinus rhythm after cross-clamp removal in each group calculating the relative risk with its confidence interval at 95%. To contrast all the qualitative outcomes we will use a X^2 test. Results will be considered statistically significant at a value of $p<0.05$.

The secondary outcomes will be analyzed using the following criteria:

- Comparing the proportion of patients that present LCOS the first 24 hours after cross-clamp removal in each group calculating the relative risk with its confidence interval at 95%.
- Comparing the proportion of patients that needed defibrillation the first 24 hours after cross-clamp removal in each group calculating the relative risk with its confidence interval at 95%.
- Comparing the proportion of patients deceases after 30 days calculating the relative risk with its confidence interval at 95%.

To contrast all the qualitative outcomes we will also use a X^2 test. Results will be considered statistically significant at a value of $p<0.05$.

Multivariate analysis

In order to avoid confusion and extract further information from our data, we will perform a subgroup analysis of our primary and secondary outcomes stratifying the results by the aforementioned covariates contrasted in a multiple logistic regression model. The variables used will be:

- Age group
- Gender
- Surgery type
- Re-Do CABG
- EuroSCORE risk category
- CKD GFR stage
- Post-operatory unit

We will not be stratifying the patients according to delivery method as a different delivery method to anterograde delivery will only be performed for anatomical difficulties such as severe aortic insufficiency, so we are not expecting to have enough patients to have statistically significant results. Furthermore, we do not expect the delivery method to affect our outcomes.

We will not be stratifying the patients by number of grafts performed or EuroSCORE numerical score, as this two covariates have been defined solely to perform a descriptive analysis and grant the comparability of the groups.

STUDY LIMITATIONS

First of all, the following aspects have been taken into consideration as for **internal validity**:

Patient selection:

In our study there might be a certain risk of selection bias regarding the risk and complexity of the patients treated and available in our hospital, as the more complex patients with higher risk scores might be derived to bigger hospitals in Barcelona with bigger teams and more specialized infrastructure. This might result in patients with lower risks and better outcomes. We considered solving this problem by making our study a multicentric trial, but the technical difficulty of the data collection, statistical analysis and therefore costs would have risen exponentially. We considered a more feasible alternative to conduct a stratification of patients according to EuroSCORE, number of grafts performed in the surgery and if the patient is a re-do CABG.

Data collection:

In this section we considered the possible risk of two forms of information bias, specifically detection and realization bias, which are closely related. Taking into account that our study is double-blinded regarding both the patient and the investigator who will collect the data we believe that the risk of these two bias is minimal. Furthermore, we have avoided any subjective outcome by defining pure objective outcomes with strict criteria and validated external scores.

Sample size:

Regarding our sample size, it has been calculated in order to obtain statistical significance regarding our primary outcome and the differences we consider to have clinical significance. We would also like to analyze our results through a stratification for covariates to extract further conclusions. Nevertheless, our sample might not be big enough to have statistically significant results in some covariates such as patients with CABG associated with valve surgery or heart root surgery, as they are far less frequent surgeries, patients that are admitted to REA as a post-operatory critical care unit after

heart surgery, and patients with higher EuroSCORE risks or re-do CABG as they are more likely to be derived to bigger more specialized hospitals.

Confounding factors:

We consider our study to have a very low risk of presenting a confusion bias as it is submitted to randomization performed by software and externalized of the investigation team, thus theoretically granting that the groups are comparable and equal. However, in order to assess that this randomization has been effective, we have established the covariates that we consider could have an impact on the results and that could serve as indicators of a proper and effective randomization. We will perform a stratification of each group according to our covariates to ensure that the confusion is kept to a minimum.

Loss of patients:

Our estimation is that the loss of patients due to intra-operatory mortality, withdrawal of the study and loss of follow-up would be minimal, as our study implies a short follow-up time of 30 days after the surgery. We do not require an active involvement of the patient and all the data we need should be compiled as part of the regular medical assistance of the patient. Moreover, we have accounted for a 2% loss of patients when calculating the necessary sample size, so the risk of encountering an attrition bias is practically null.

Lastly, regarding **external validity** and the ability of the results to be extrapolated to other populations and groups of patients we have considered the following topics:

Sample characteristics:

Taking into account that all of our patients will be from the same area of Girona, these might present different characteristics than those of the USA or northern Europe, as similar difficulties have been found when estimating cardiovascular risk with the REGICOR study in different foreign populations. However, CABG patients are of the highest risk and comorbidities all over the world, presenting similar characteristics, thus minimizing regional effect.

ETHICAL AND LEGAL ASPECTS

It is important to note that this study will be validated by many organizations and structures in order to assess its ethically feasible. First of all, the study will be drafted according to the World Medical Association *Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects of June 1964,* more specifically its October 2013 revision, therefore respecting the following principles:

- The principle of **autonomy** would not be in conflict as every patient will be handed an information sheet and will have to sign an informed consent document in order to be drafted for this study. Furthermore, the intervention carried out in our study regarding the selection of the cardioplegic solution used in CABG surgery does not normally involve the patient, and it is selected by the surgery team according to their expertise.
- The principle of **nonmaleficence** would be respected as the two solutions used in the study have already been approved by the competent authorities for this specific use, therefore granting security for the patient and that no harm will be inflicted to the patients.
- The principle of **beneficence** would also not be in conflict as this study has the wellbeing of the patient and the bettering of society in mind, as its main goal is to discern the solution that causes less complications and systemic impact on the patient.
- Lastly, the principle of **justice** could be challenged taking into account that we are excluding patients with acute kidney failure, CKD grade G4, G5 or in dialysis from the study, and arguably are left out of the intervention not respecting the principle However, the exclusion of these patients has been decided in order to protect them from possible adverse effects of the solution itself for their own wellbeing and in order to avoid a conflict with the nonmaleficence principle.

To further ensure the ethical feasibility of this study, it will be presented to the Clinical Research Ethics Committee (CEIC) of the Hospital Universitari Dr. Josep Trueta de Girona. Any input and contributions from said committee will be introduced in the study. Once the CEIC approves the study, permission will be asked to the direction of the center

in order to carry out the study. Finally, the study will need to be authorized by the AEMPS, as it involves the administration and comparison of drugs

As this study needs personal and sensitive data from the patients, it will be carried under the guidelines stablished in the *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de derechos digitales (BOE núm. 294, de 6 de diciembre de 2018)* and the *Real decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos,* which will ensure the confidentiality and proper treatment of the patient data. In order to further ensure this mandate, the personal information of the patient will be randomized with a numeric code and only the investigators will have access to it in case of needing it. Moreover, all the information will be stored in an anonymous database.

The study will also comply with the regulations established in the *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos (BOE núm. 307, de 24 de diciembre de 2015)* and the *Ley 14/2007 de 3 de julio, de investigación biomédica (BOE núm. 159, de 4 de julio de 2007)* by which studies regarding invasive procedures are regulated.

Lastly, taking into account that the drugs being used in this study are authorized and used according to the terms of said authorization there would be no need for additional insurance policy, as the center civil liability policies should cover any legal trouble derived from the investigation.

WORK PLAN AND RESEARCH TEAM

Research team

The research team will be formed by:

- The principal investigator who will coordinate the project, help with the data collection, conduct the initial bibliographical research, and interpret the statistical analysis.
- The other 2 physicians of the department of Anesthesiology and Reanimation who perform heart surgery. Their duties will consist on collecting data and helping on the trial drafting.
- A qualified statistician who will perform the statistical analysis of the collected data.
- A computer science expert who will elaborate the data base, the data collection form and the randomization application.

Work plan and chronogram

Stage 0: Protocol design (2 months)

1. Conduction of bibliographic research by the principal investigator. Summarization of the current state of the art practice in the field and identifying the current evidence on the proposed interventions. *2 weeks*
2. Proposal of the project to the Anesthesiology and Reanimation and Heart Surgery teams. *2 days*
3. Protocol elaboration by the principal investigator with the help of the other collaborating investigators. *4 weeks*
4. Secure of the necessary funding. *1 month*
5. Development of the database, data collection sheet and randomization application by the computer science expert. *1 week*
6. Adaptation and preparation of the necessary paperwork for the ethical committee approval. *1 week*

Stage I: Ethical and legal approval (3 months)

1. Presentation of the study protocol to CEIC for ethical approval and implementation of the necessary *1 month*

2. Proposal and authorization of the hospital direction. *1 week*
3. Authorization of the *AEMPS 2 months*
4. Registration of the study into the *Registro Español de estudíos clínicos* (REec). *1 week*

Stage II: Data collection (18 months)

1. Brief formation of the participating investigators that would be collecting data in order to standardize the criteria. *1 day*
2. Data collection *18 months*

Stage III: Statistical analysis (1 month)

1. Descriptive analysis *1 week*
2. Bivariate analysis *1 week*
3. Multivariate analysis *1 week*
4. Creation of graphics and tables. *1 week*

Stage IV: Interpretation and discussion of the results (1 month)

Stage V: Drafting of the results and publication (1 month)

Stage VI: Publication of the study, presentation and dissemination in congresses (3 months

	2020		2021								2022									2023			
Stages:	*NOV*	*DEC*	*JAN*	*FEB*	*MAR*	*APR - DEC*					*JAN - OCT*							*NOV*	*DEC*	*JAN*	*FEB*	*MAR*	*APR*
STAGE 0:																							
Bibliographic research																							
Proposal to anaesthesiology and heart surgery team																							
Protocol elaboration																							
Secure of funding																							
Database development																							
Adaptation to CEIC																							
STAGE I:																							
CEIC approval																							
Hospital direction approval																							
AEMPs authorization																							
REec registration																							
STAGE II:																							
Formation																							
Data collection																							
STAGE III:																							
Statistical analysis																							
STAGE IV:																							
Interpretation and discussion of the results																							
STAGE V:																							
Drafting of the results																							
STAGE VI:																							
Publication																							
Dissemination and presentation in congresses																							

Table 4 Chronogram

BUDGET

Staff:

- The research team will be part of the medical staff of the Hospital Universitari Dr. Josep Trueta of Girona, therefore there would be no cost associated to it.
- A qualified statistician will have to be hired in order to perform the statistical analysis of all the data collected. We estimate that approximately 50 hours of work will be needed in order to properly analyze all the data, at a cost of 50€/hour.
- A qualified computer scientist specialized in data management will have to be hired in order to construct a data base, data collection sheet and randomization application. We estimate that approximately 40 hours of work will be needed in order to construct all the necessary computer technology structures at a cost of 30€/hour.
- An external expert will have to be hired in order to validate and asses the quality of the data collected. We estimate approximately that this would cost 150€ per patient for 126 patients enrolled in the study.

Material:

- We estimate that a total of 100 information sheets would be needed to be printed (65 in Catalan and 35 in Spanish) and 100 informed consents (65 in Catalan and 35 in Spanish) at a cost of 0.06€ each.
- Custodiol© and Del Nido solutions cost approximately 170€ per 1000mL and 40€ per 1000mL respectively. However, there is no need to pay for the cardioplegic solutions as they would be supplied by the hospital. As it was aforementioned before, both solutions are indicated and approved by the competent authorities regarding the use taking place on this study.
- There is also no need to pay for any medical equipment, as all the interventions and variables of this study can be extracted from the regular medical practice.

Insurance:

- In this case, there is no need to take on any extra insurance policy as all the interventions and drugs used in this study are approved and authorized for its usage and are part of the regular medical practice, therefore all the activities conducted on study are covered under the insurance policy of the hospital.

Fees:

- Authorization of a clinical trial with authorized and registered drugs in Spain by AEMPs at a cost of 114.55€.
- Publishing the study in a journal at a cost of approximately 2500€.
- Presenting the study in a national congress at a cost of approximately 500€.

All the expenses detailed above are summarized in the following table:

	Item	Cost per unit Cost per hour	Quantity	Total
STAFF	Statistician	50€/hour	50 hours	2500€
	Computer scientist	30€/hour	40 hours	1200€
	Research team	-	-	0€
	Data validation and quality	150€/patient	124 patients	18600€
MATERIAL	Printing	0.06€/unit	200	12€
	Drugs	48€/1L 170€/1L	124L	0€
	Equipment	-	-	0€
INSURANCE	Insurance	-	-	0€
FEES	AEMPs authorization	114.55€	1	114.55€
	Publication	2500€	1	2500€
	Congress	500€	1	500€
			TOTAL	**25426.55€**

FEASIBILITY

We consider this study to be feasible and easy to conduct taking into account the following points:

- First of all, the two interventions taking place in this study are part of regular medical practice and do not mean additional interventional procedures to the patient neither do need the active involvement of the patient.
- All the necessary data needed for the study can be extracted through medical equipment that is already being used either in the operation room or the postoperative critical care unit.
- There is no need for a long follow-up period, as the interval we are interested in and where we will extract our data is comprised between the surgery and the first 30 days.
- We can obtain all the necessary sample in one single third-level hospital, with the surgery being conducted by one single heart surgery and anesthesiology team in a reasonable space of time.
- The design of the study, being a prospective double-blinded randomized clinical trial, allows for a minimization in the risk of biases and both high internal and external validity.
- All this factors contribute into a low necessary budget taking into account it is a randomized prospective clinical trial, making it easier to secure funding.

The main feasibility concern about our study is the approximate time needed to conduct it being almost 3 years due to the necessary sample that we need. Because of the limited number of patients that undergo cardiac surgery in our center, there would be approximately a 18 month sample collection. This might difficult the conduction of the study, but could be solved by turning the study into a multicentric trial.

PROJECT IMPACT AND FUTURE PERSPECTIVES

The subject of cardioprotection and cardioplegia has been in discussion since the first attempts at achieving elective heart arrest by *Melrose et al.* at it in the 1950s. Numerous techniques have been developed, and countless of variables to each solution are in use nowadays. However, the irruption of single-dose cardioplegic solutions in adults in the regular medical practice about 5 years ago in the form of Custodiol© and Del Nido cardioplegia aroused a new debate and opened a new window in cardioplegia use and investigation.

Taking into account that these two solutions are being used both in North-America and Europe without extensive evidence on its usage in different types of patient profiles, and that there are no proper prospective randomized trials comparing the two solutions in equal conditions in adults, we believe that the results of this study could bring new light into the subject and cement new evidence on which to conduct further investigation in the topic.

If our hypothesis is correct, and Del Nido cardioplegia is in fact superior regarding spontaneous rhythm return, defibrillation need, LCOS and 30-day mortality we could be talking of a new gold standard regarding elective heart arrest in CABG surgery. Furthermore, the results of this study can arouse new questions to be answered in future investigations:

- Is Del Nido cardioplegia also superior to other cardioplegic strategies regarding myocardial damage and post-operatory myocardial infarction in both low and high risk patients?
- Is Del Nido cardioplegia more cost-effective than blood cardioplegia?
- Could a modified Custodiol© solution with the addition of Lidocaine be equal or superior to Del Nido cardioplegia?

To sum it up, the questions and hypothesis proposed in this study represent the next step in cardioplegic and cardioprotection management in heart surgery, and its outcomes could signify new evidence and a rethinking of current practice.

CONFLICTS OF INTEREST

The author of this study declares no conflict of interest.

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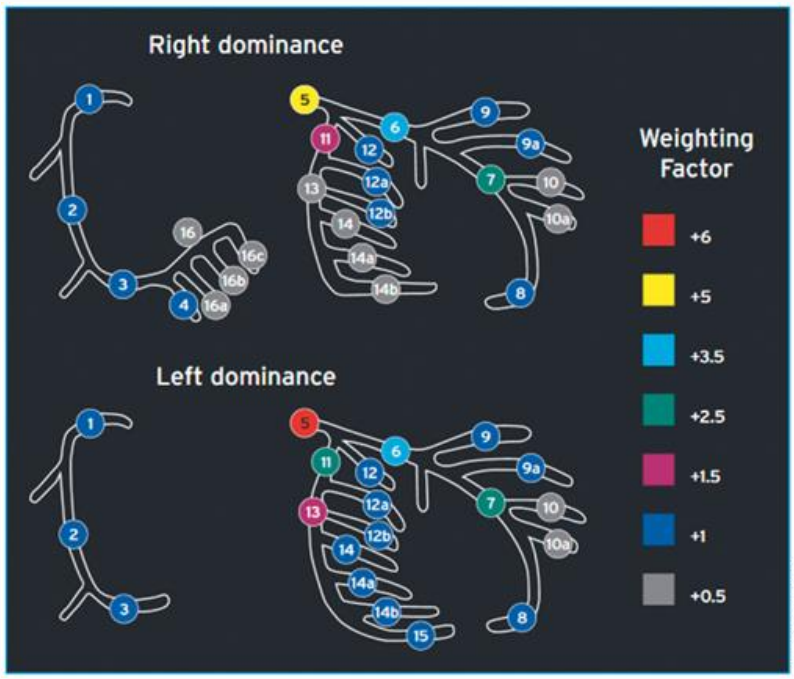
ANNEXES

ANNEX 1: ESC/EACTS REVASCULARIZATION RECOMMENDATIONS

Recommendations according to extent of CAD	CABG		PCI	
	Class[a]	Level[b]	Class[a]	Level[b]
One-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,101,139–144]	I	A	I	A
Two-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,70,73]	I	B	I	C
Left main CAD				
Left main disease with low SYNTAX score (0 - 22).[69,121,122,124,145–148]	I	A	I	A
Left main disease with intermediate SYNTAX score (23 - 32).[69,121,122,124,145–148]	I	A	IIa	A
Left main disease with high SYNTAX score (≥33).[c] [69,121,122,124,146–148]	I	A	III	B
Three-vessel CAD without diabetes mellitus				
Three-vessel disease with low SYNTAX score (0 - 22).[102,105,121,123,124,135,149]	I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,149]	I	A	III	A
Three-vessel CAD with diabetes mellitus				
Three-vessel disease with low SYNTAX score 0–22.[102,105,121,123,124,135,150–157]	I	A	IIb	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,150–157]	I	A	III	A

Recommendations for the type of revascularization in patients with stable coronary artery disease with suitable coronary anatomy for both procedures and low predicted surgical mortality (10)

ANNEX 2: SYNTAX SCORE

Steps	Variable assessed	Description
Step 1	Dominance	The weight of individual coronary segments varies according to coronary artery dominance (right or left). Co-dominance does not exist as an option in the SYNTAX score.
Step 2	Coronary segment	The diseased coronary segment directly affects the score as each coronary segment is assigned a weight depending on its location, ranging from 0.5 (i.e. the posterolateral branch) to 6 (i.e. left main in case of left dominance). 
Step 3	Diameter stenosis	The score of each diseased coronary segment is multiplied by two in case of a stenosis 50–99% and by five in case of total occlusion. In case of total occlusion, additional points will be added as follows: Age >3 months or unknown +1 Blunt stump +1 Bridging +1 First segment visible distally +1 per non-visible segment Side branch at the occlusion

		+1 if <1.5 mm diameter +1 if both <1.5 mm and ≥1.5 mm diameter +0 if ≥1.5 mm diameter (i.e. bifurcation lesion)
Step 4	Trifurcation lesion	The presence of a trifurcation lesion adds additional points based on the number of diseased segments: • 1 segment +3 • 2 segments +4 • 3 segments +5 • 4 segments +6
Step 5	Bifurcation lesion	The presence of a bifurcation lesion adds additional points based on the type of bifurcation according to the Medina classification: Medina 1,0,0–0,1,0–1,1,0 +1 Medina 1,1,1–0,0,1–1,0,1–0,1,1 +2 Moreover, the presence of a bifurcation angle <70° adds one additional point
Step 6	Aorto-ostial lesion	The presence of aorto-ostial lesion segments adds one additional point
Step 7	Severe tortuosity	The presence of severe tortuosity proximal of the diseased segment adds two additional points
Step 8	Lesion length	Lesion length >20 mm adds one additional point
Step 9	Calcificatio n	The presence of heavy calcification adds two additional points
Step 10	Thrombus	The presence of thrombus adds one additional point
Step 11	Diffuse disease/ small vessels	The presence of diffusely diseased and narrowed segments distal to the lesion (i.e. when at least 75% of the length of the segment distal to the lesion has a vessel diameter <2 mm) adds one point per segment number

SYNTAX score algorithm (10)

ANNEX 3: EUROSCORE

Patient-related factors		*Score*
Age	(Per 5 years or part thereof over 60 years)	**1**
Sex	Female	**1**
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for lung disease	**1**
Extracardiac arteriopathy	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	**2**
Neurological dysfunction disease	Severely affecting ambulation or day-to-day functioning	**2**
Previous cardiac surgery	Requiring opening of the pericardium	**3**
Serum creatinine	>200m micromol/L preoperatively	**2**
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	**3**
Critical preoperative state	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intra-aortic balloon counter-pulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)	**3**
Cardiac-related factors		*Score*
Unstable angina	Rest angina requiring iv nitrates until arrival in the anaesthetic room	**2**

LV dysfunction	Moderate or LVEF30-50%	**1**
	poor or LVEF <30	**3**
Recent myocardial infarct	(<90 days)	**2**
Pulmonary hypertension	Systolic PA pressure>60 mmHg	**2**

Operation-related factors		***Score***
Emergency	Carried out on referral before the beginning of the next working day	***2***
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	***2***
Surgery on thoracic aorta	For disorder of ascending, arch or descending aorta	***3***
Postinfarct septal rupture		***4***

EuroSCORE score ítems (58)

Risk categories:

Low risk -> 0 – 2

Intermediate risk -> 3 - 5

High risk -> 5 - 45

ANNEX 4: CHRONIC KIDNEY DISEASE STAGING

				Albuminuria categories		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Stages	**G1**	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Key to Figure:
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst.
Green: Low Risk (if no other markers of kidney disease, no CKD)
Yellow: Moderately Increased Risk
Orange: High Risk
Red: Very High Risk
Deep Red: Highest Risk

Chronic Kindey Disease GFR and ACR categories (61)

ANNEX 5: INFORMATION SHEET

FULL D'INFORMACIÓ PER AL PACIENT:

ESTUDI:

Investigador principal: Albert Calvo Porcel (albert17calvo@gmail.com)

Centre: Hospital Universitari de Girona Dr. Josep Trueta

Benvolgut/da,

Ens posem en contacte amb vostè per convidar-lo/la a participar al estudi d'investigació mèdica que es realitzarà pel servei de Anestesiologia i Reanimació de l'Hospital Universitari de Girona Dr. Josep Trueta.

La participació en aquest estudi és totalment voluntària i sense ànim de lucre, el fet de rebutjar la participació en el mateix no suposarà cap canvi en la relació assistencial amb el seu metge ni en el seu tractament i seguiment.

Descripció i objectiu de l'estudi:

Aquest estudi està dirigit a pacients que com vostè seran sotmesos a una cirurgia de Bypass Coronari en el nostre hospital i que no pateixen d'insuficiència renal en el moment de la valoració preoperatòria.

L'objectiu és determinar quina d'aquestes dues solucions que s'utilitzen per posar el seu cor en parada durant la cirurgia és millor a l'hora de reanimar el seu cor i que aquest recuperi de forma espontània el ritme sinusal.

D'aquesta informació se'n poden beneficiar molts pacients com vostè, evitant possibles complicacions postoperatòries en el futur.

Activitats de l'estudi:

Si vostè accepta participar en aquest estudi simplement rebrà una de les dues solucions de manera aleatoritzada i es recolliran les dades referents a la seva cirurgia i període postoperatori per professionals del servei d'Anestesiologia i Reanimació.

No serà necessària que participi de forma activa en l'estudi ni que se li realitzi cap intervenció o prova complementaria extraordinària, ja que es tracta de procediments i dades recollides de forma estàndard i seran extretes de la seva història clínica i del sistema informàtic de l'àrea de crítics postoperatoris en la que sigui ingressat.

Els únics riscs i molèsties que vostè pot experimentar són els efectes secundaris i complicacions derivades de les pròpies solucions, que estan aprovades i indicades per l'Agencia Europea del

Medicament (EMA) i l'Agencia Espanyola de Medicaments i Productes Sanitaris (AEMPS) pel seu ús en cirurgies com a la que vostè s'ha de sotmetre, i formen part de la pràctica clínica habitual. En cas que vostè es negui a participar en l'estudi no se li assignarà aleatòriament una de les dues solucions i se li administrarà la solució cardioplegica més adequada a vostè seguint els protocols de l'hospital i científics actuals i a discreció de l'equip quirúrgic.

Aspectes legals:

L'estudi ha estat aprovat pel Comitè d'Ètica d'Investigació Clínica (CEIC) de l'Hospital Universitari de Girona Dr. Josep Trueta.

Les dades obtingudes dels pacients seran estrictament confidencials. El tractament, comunicació i cessió de les dades de caràcter personal de tots els pacients participants s'ajustarà a la *Llei Orgànica 3/2018, de 5 de Desembre, de Protecció de Dades Personals i garantia de Drets Digitals*. D'acord amb aquesta llei vostè podrà exercir el seu dret al accés, modificació, oposició i cancel·lació d'aquestes dades. Tota la informació obtinguda amb finalitats de recerca serà guardada en una base de dades i anonimitzada mitjançant un codi numèric. Només el personal investigador podrà relacionar les dades amb la seva persona. En cap cas el seu nom apareixerà en la publicació dels resultats.

Aquest estudi està cobert sota la pòlissa d'assegurança de l'Hospital Universitari de Girona Dr. Josep Trueta.

Per participar en aquest estudi vostè no rebrà cap compensació econòmica ni li suposarà cap despesa.

Canvi d'opinió:

La participació és totalment voluntària i tots els participants poden expressar la seva voluntat d'abandonar l'estudi en qualsevol moment sense necessitat de donar cap explicació.

Més informació:

Si vostè te alguna pregunta o desitja conèixer més informació sobre l'estudi en qüestió li pot preguntar al professional que li ha entregat, pot enviar un correu electrònic al investigador principal a traves de albert17calvo@gmail.com o es pot adreçar al telèfon de secretària del Servei d'Anestesiologia i Reanimació al 972 940 226 i preguntar per l'investigador principal.

HOJA DE INFORMACIÓN PARA EL PACIENTE

ESTUDIO:

Investigador principal: Albert Calvo Porcel (albert17calvo@gmail.com)

Centro: Hospital Universitario de Girona Dr. Josep Trueta

Apreciado/a:

Nos ponemos en contacto con usted para invitarlo/a a participar en el estudio de investigación medica que se llevara a cabo por el servicio de Anestesiología y Reanimación del Hospital Universitario de Girona Dr. Josep Trueta.

La participación en dicho estudio es totalmente voluntaria y sin animo de lucro. En caso de rechazar la participación en el mismo en ningún caso supondrá un cambio en la relación asistencial con su medico ni en su tratamiento y seguimiento.

Descripción y objetivo del estudio:

Este estudio esta dirigido a pacientes que como usted serán sometidos a una cirugía de Bypass Coronario en nuestro hospital y que no sufren insuficiencia renal en el momento de la valoración preoperatoria.

El objetivo es determinar cual de las dos soluciones en estudio (Del Nido y Custodiol) que se utilizan para poner su corazón en parada durante la cirugía es mejor a la hora de reanimar su corazón y que este recupere de forma espontanea el ritmo sinusal.

De esta información se pueden beneficiar muchos pacientes como usted, evitando posibles complicaciones postoperatorias en el futuro.

Actividades del estudio:

Si usted acepta participar en este estudio simplemente recibirá una de las dos soluciones de manera aleatorizada y se recogerán los datos referentes a su cirugía y período postoperatorio por parte de profesionales del servicio de Anestesiología y Reanimación.

No será necesario que participe de forma activa en el estudio ni que se le someta a ninguna intervención o prueba complementaria extraordinaria, ya que se trata de procedimientos i datos recogidos de forma estándar que serán extraídos de su historia clínica y del sistema informático del área de críticos postoperatorios en la que usted sea ingresado.

Los únicos riesgos y molestias que usted puede experimentar son los efectos secundarios y complicaciones derivados de las propias soluciones, que están aprobadas y indicadas por parte de la Agencia Europea del Medicamento (EMA) i la Agencia Española de Medicamentos y

Productos Sanitaros (AEMPS) para su uso en cirugías como a la que usted se va a someter, y que forman parte de la práctica clínica habitual.

En el caso que usted se niegue a participar en el estudio se le administrará la solución cardioplegica más adecuada a su caso siguiendo los protocoles del hospital y científicos actuales a discreción del equipo quirúrgico.

Aspectos legales:

El estudio ha sido aprobado por el Comité de Ética de Investigación Clínica (CEIC) del Hospital Universitario de Girona Dr. Josep Trueta.

Los datos obtenidos de los pacientes serán estrictamente confidenciales. El tratamiento, comunicación y cesión de los datos de carácter personal de todos los pacientes participantes se ajustara a la *Ley Orgánica 3/2018, del 5 de diciembre, de Protección de Datos Personales i garantía de Derechos Digitales*. De acuerdo con esta ley usted podrá ejercer su derecho al acceso, modificación, oposición y cancelación de estos datos. Toda la información obtenida con finalidades de investigación será guardada en una base de datos y anonimizada mediante un código numérico. Tan solo el personal investigador podrá relacionar los datos con su persona.. En ningún caso su nombre aparecerá en la publicación de los resultados.

Este estudio está cubierto bajo la póliza aseguradora del Hospital Universitario de Girona Dr. Josep Trueta.

Por participar en este estudio usted no recibirá ningún tipo de compensación económica. Así mismo tampoco le supondrá ningún gasto.

Cambio de opinión:

La participación es totalmente voluntaria y todos los participantes pueden expresar su voluntad de abandonar el estudio en cualquier momento sin necesidad de ofrecer ninguna explicación.

Más información:

Si usted tiene alguna pregunta o desea conocer más información acerca del estudio se puede dirigir al profesional que le ha entregado este documento, puede enviar un correo electrónico al investigador principal a albert17calvo@gmail.com o se puede dirigir al teléfono de secretaria del Servicio de Anestesiología y Reanimación al 972 940 226 i preguntar por el investigador principal.

ANNEX 6: INFORMED CONSENT

CONSENTIMENT INFORMT

Títol del estudi:

Jo, _____, amb DNI/NIF _____, accepto voluntàriament participar en aquest estudio i manifesto:
- Que he estat degudament informat/da pel Dr./Dra. _____ havent entès tota la informació que he pogut llegit en la fulla d'informació i que me han explicat, havent comptant amb l'opció de realitzar totes les preguntes que he cregut convenients.
- Que puc negar-me a participar en aquest estudio sense la necessitat de donar cap explicació i sense que això tingui conseqüències en la meva relació assistencial.
- Que les dades que faciliti seran utilitzades únicament amb finalitats d'investigació mèdica, que seran completament confidencials i en compliment amb les lleis vigents.
- Que la meva participació es totalment voluntària i que podré revocar el consentiment prèviament firmat en qualsevol moment sense que això comporti cap conseqüència negativa al meu tractament ni seguiment.

Firma del pacient:

Firma del responsable/investigador/a:

Lloc i data: _____, _____ de _____ del 20____.

REVOCACIÓ DEL CONSENTIMIENT INFORMAT

Jo, _____, amb DNI/NIF _____ revoco el consentiment informat prèviament firmat per la participació en aquest estudi especificat en aquest mateix documento.

Firma del pacient:

Firma del responsable/investigador/a:

Lloc i data: _____, _____ de _____ del 20____.

CONSENTIMIENTO INFORMADO

Título del estudio:

Yo, _____, con DNI/NIF _____, acepto voluntariamente participar en este estudio y manifiesto:
- Que he estado debidamente informado/a por el Dr./Dra. _____ habiendo entendido toda la información que he podido leer en la hoja de información y que me han explicado, habiendo contado con la opción de realizar todas las preguntas que he creído convenientes:
- Que puedo negarme a participar en este estudio sin la necesidad de ofrecer ninguna explicación y sin que ello tenga consecuencias en mi relación asistencial.
- Que los datos que dé serán utilizados únicamente con finalidad de investigación médica, que serán completamente confidenciales y de acuerdo con las leyes vigentes.
- Que mi participación es totalmente voluntaria y que podre revocar el consentimiento previamente firmado en cualquier momento sin que esto conlleve ninguna consecuencia negativa a mi tratamiento ni seguimiento.

Firma del paciente

Firma del responsable/investigador/a

Lugar y fecha: _____, _____ de _____ del 20____.

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____, con DNI/NIF _____, revoco el consentimiento informado previamente firmado para la participación en este estudio especificado en este mismo documento.

Firma del paciente

Firma del responsable/investigador/a

Lugar y fecha: _____, _____ de _____ del 20____.

ANNEX 7: DATA COLLECTION SHEET

Dades preoperatòries:

Numero de pacient: _____.

Cirurgia prevista:_____.

Data de la cirurgia: ___/___/202__.

Cirurgians:_____.

Anestesista:_____.

Edat:_____

Gènere: Home ☐ Dona ☐

EuroSCORE: Puntuació:_____

Risc: Alt ☐ Intermig ☐ Baix ☐

Insuficiència renal: No ☐

Grau I ☐

Grau II ☐

Grau IIIa ☐

Grau IIIb ☐

Grau IIIc ☐

Re-operat Bypass: Si ☐ No ☐

Dades intraoperatòries:

Hora inici cirurgia:____:____h.

Hora repermeabilització:____:____h

Hora final cirurgia:____:____h

Nombre de bypassos:_____.

Retorn a ritme sinusal: Si ☐ No ☐

Administració cardioplegia: Anterograda ☐ Retrograda ☐ Selectiva ☐

Dades postoperatòries:

Unitat post-operatòria: UCI ☐ UCO ☐ REA ☐

Síndrome Baix Gast Cardíac (24h): Si ☐ No ☐

Desfibril·lació (24h): Si ☐ No ☐

Èxitus (30 dies): Si ☐ No ☐

Altres complicacions:

_____

_____

_____

_____

_____