Diminution de la durée de séjour hospitalier par la mise en place d'un protocole de récupération rapide (ERAS) après remplacement valvulaire aortique par mini-sternotomie

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Introduction

L'évolution de la chirurgie cardiaque, et de ses résultats postopératoires a été conditionnée en parallèle par l'évolution des techniques chirurgicales et de la prise en charge de médecine péri-opératoire.

En 1953, Pender définissait la mission de l'anesthésiste en chirurgie cardiaque comme étant d'assurer la survie et la sécurité du patient et non simplement de permettre une analgésie et des conditions opératoires adéquates[1].

La spécialité est marqué par des innovations techniques majeures : l'avènement de la circulation extracorporelle, l'utilisation d'une cardioplégie froide à visée cardioprotectrice, l'hypothermie profonde à visée neuroprotectrice[2,3,4], permettant d'intervenir sur un cœur ouvert et arrêté en minimisant les dommages myocardiques et cérébraux liés à l'ischémie.

Par ailleurs le développement de techniques de revascularisation myocardiques chirurgicales par Vindeberg, avec en 1967 le premier pontage aorto-coronarien permettent de soulever la problématique de la prise en charge péri-opératoire du patient coronarien sévère, et par la même occasion de mettre l'accent sur l'importance du maintien de la perfusion coronaire chez ces patients.

L'avènement de la circulation extra-corporelle pose le problème du maintien de conditions hémodynamiques peropératoires adéquates et c'est sur le maintien de ces conditions que la prise en charge anesthésique se concentre initialement[5].

L'anesthésie en tant que médecine per-opératoire.

Dans l'optique de permettre à l'anesthésiste de jouer un rôle diagnostique per-opératoire, lui permettant d'adapter rapidement les thérapeutiques (remplissage, transfusion, profondeur d'anesthésie), la surveillance péri-opératoire se complexifie, avec notamment l'usage du cathéter artériel pulmonaire (Swan-Ganz), qui permet de mesurer indirectement la pression atriale gauche et donne un indice objectif du statut volémique et de la fonction ventriculaire gauche du patient[6], dont l'utilisation est décrite en 1972 et qui fournit à l'anesthésiste un moyen de monitorer l'hémodynamique de façon plus précise[7], mais dont la pertinence est sujette à controverse[8,9]. Par ailleurs, l'apport de l'échographie transoesophagienne dans les années 1980, a permis d'élargir le rôle diagnostique de l'anesthésiste, dont la responsabilité ne se cantonne plus à évaluer l'état hémodynamique et respiratoire du patient, mais assiste le chirurgien cardiaque par une évaluation anatomique et fonctionnelle en temps réel[10,11,12].

Dans ce contexte où l'anesthésie en chirurgie cardiaque se donne comme mission principale le maintien de bonnes conditions hémodynamiques et d'une adéquation entre la perfusion coronaire et la consommation myocardique en oxygène, naît le concept d'anesthésie basée sur de hautes doses de morphiniques[13], qui permet de s'affranchir de la dépression myocardique liée aux agents hypnotiques et assurer ainsi la stabilité hémodynamique des patients les plus fragiles[14]. L'utilisation de hautes doses de morphine est également justifiée par l'intérêt d'une ventilation mécanique prolongée en postopératoire chez certains patients, pour lesquels la morphine permettait une tolérance convenable de l'intubation orotrachéale prolongée[14].

L'anesthésie comme médecine péri-opératoire.

L'anesthésie morphinique et les hautes doses de morphine en postopératoire sont nées du constat d'une mortalité postopératoire élevée chez des patients dont la pathologie avait été corrigée avec succès, et qui présentaient dans les heures ou jours suivant l'intervention une détresse respiratoire aiguë, soit par insuffisance cardiaque, soit d'origine pulmonaire.

Pour s'affranchir de la part des atteintes pulmonaires, une stratégie développée dans les années 1960 consista à maintenir les patients sous ventilation mécanique moyennant de hautes doses de morphine[13] (et c'est en observant la bonne tolérance hémodynamique de ces doses que l'idée d'anesthésie morphinique fut proposée).

Le maintien d'une ventilation mécanique en postopératoire semblait améliorer la survie chez les patients opérés d'un pontage aorto-coronarien[15,16,17], mais s'accompagnait d'un surrisque de complications infectieuses et respiratoires.

Dans les années 1990, le concept de « Fast Track » en chirurgie cardiaque naît de pressions économiques pour la réduction du séjour hospitalier[18,19]. Les suites opératoires sont satisfaisantes, mais il n'y a pas de réduction de la durée de séjour, ni des complications[20,21].

Au-delà du Fast Track : l'ERAS.

Les stratégies du « Fast Track » sont centrées sur l'extubation précoce, en réduisant les doses de morphiniques et en utilisant des molécules de demi-vie plus courte [21,22].

En 2008, un nouveau concept voit le jour en chirurgie digestive : l'ERAS (Enhanced Recovery After Surgery), dont le principe n'est plus de modifier un seul élément de la prise en charge (par exemple : extuber les patients en postopératoire précoce), mais de mettre en place un « bundle » d'actions concrètes dans le but de diminuer les complications et la durée de séjour hospitalier[23].

La notion d'ERAS s'étend rapidement aux chirurgies autres que digestive[24,25,26], avec des résultats favorables notamment sur la durée de séjour hospitalier, mais la chirurgie cardiaque reste pour l'instant en dehors de son champ d'application.

Néanmoins la pression financière pour la réduction des séjours hospitaliers et l'avènement de techniques moins invasives (TAVI) avec la publicité dont elles bénéficient auprès du public, redéfinissent les attentes des patients, des soignants et des responsables des structures sur ce que doivent être les suites opératoires d'une chirurgie cardiaque, et tout particulièrement d'un remplacement valvulaire aortique. L'amélioration des résultats péri-opératoires et la réduction de la durée de séjour étant les objectifs premiers de l'ERAS, son intérêt apparaît donc en chirurgie cardiaque sous l'effet de ces contraintes[22].

Dans ce contexte, notre étude s'est intéressée à l'effet de l'implémentation d'un tel protocole sur la durée de séjour et les suites opératoires de patients bénéficiant d'un remplacement valvulaire aortique par mini-sternotomie.

Reduced length of hospital stay for cardiac surgery implementing an optimized perioperative care: prospective evaluation of an Enhanced Recovery After Surgery Program designed for Mini-Invasive Aortic Valve Replacement.

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Running title:

Prospective evaluation of an ERAS program for mini-invasive cardiac surgery.

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Résumé

Les programmes de récupération rapide après chirurgie (ERAS) engendrent actuellement un intérêt certain. La littérature montre clairement une diminution des durées de séjours hospitaliers et une amélioration du devenir des patients. Cependant la plupart des études actuelles s'intéressent à la chirurgie colorectale et orthopédique.

Nous rapportons ici les résultats d'une étude monocentrique, prospective dans laquelle nous évaluons la faisabilité et l'efficacité de l'implémentation d'un programme ERAS dans les remplacements valvulaires aortiques par mini-sternotomie (MIAVR).

Méthodes : Les patients programmés pour bénéficier d'un MIAVR étaient suivis sur 2 périodes, avant (groupe MIAVR) et après implémentation d'un protocole ERAS spécifique (groupe MIAVR-ERAS). Nous recueillions les caractéristiques démographiques et cliniques des patients, leur compliance à chaque item du protocole ERAS, les scores de douleur, les complications et la consommation de morphiniques postopératoires, la durée de séjour hospitalier (qui constituait le critère de jugement principal).

Résultas: 23 patients ont été inclus dans chaque groupe. Les patients bénéficiant du protocole ERAS avaients des scores de douleur postopératoire moins élevés ($P = 0.03$), avaient tendance à être extubés plus rapidement ($P = 0.08$), et présentaient moins d'infections ($P = 0.06$). La médian de la durée de séjour hospitalier était respectivement de 10[9-13.5] et 7[6.5-8] jours dans les groupes MIAVR et MIAVR-ERAS ($P < 0.001$).

Conclusions: un parcours ERAS pour les patients programmés pour un MIAVR semble faisable et associé à une durée de séjour réduite, une tendance à la réduction de la consommation de morphiniques, ainsi que des complications postopératoires moins fréquentes.

Abstract

Background: There is presently a warm enthusiasm for enhanced recovery after surgery (ERAS) program. The literature clearly indicates that such program could shorten the hospital length of stay and could improve patient outcome. However, most of the studies conducted encompassed mainly colorectal and orthopedic surgeries. Thus, in an effort to provide more evidence to the literature, we have investigated prospectively the feasibility and clinical effectiveness of a dedicated ERAS program for mini-invasive Aortic Valve Replacements (MIAVR).

Methods: After ethic committee approval, data of consecutive patients scheduled for a MIAVR via a mini-sternotomy were collected prospectively during 2 time periods, before (MIAVR group) and after implementation of a dedicated ERAS pathway specifically designed for this procedure (MIAVR-ERAS group). Patients' demographics, patients' characteristics, compliance to the ERAS protocol, postoperative morphine consumption, postoperative pain scores, postoperative complications, hospital length of stay and hospital readmission rate were collected.

Results: There were 23 patients enrolled in each group. Patients enrolled in the new protocol had significantly lower postoperative pain scores ($P = 0.03$), a trend toward a shorter time to extubation ($P = 0.08$), as well as a trend toward less pulmonary infection ($P = 0.06$). The median hospital length of stay was 10[9-13.5] and 7[6.5-8] days in the traditional MIAVR group and in the MIAVR-ERAS group, respectively ($P < 0.001$).

Conclusions: An ERAS pathway planned for mini-invasive AVR seems feasible and associated with a shorter length of hospital stay and with a trend towards both less opioid consumption and less postoperative complications.

Introduction

Remarkable anaesthetic and surgical advancement have been achieved in the field of cardiac surgery within the last 3 decades[1, 2]. Although, cardiac fast-track protocols aiming to extubate cardiac patients after surgery at an early stage have been implemented successfully, postoperative morbidity continues to be frequent[1]. Moreover, mini-invasive cardiac surgical approaches have been described to reduce the surgical stress response, but few objective advantages have been demonstrated and equivalent postoperative outcomes have been reported when compare to traditional techniques[2]. The surgical stress response is considered as the principal and most frequent factor leading to postoperative morbidity[3]. To blunt this response causing a systemic release of stress hormones and inflammatory mediators Enhanced Recovery After Surgery (ERAS) program have been developed showing outstanding results[4]. The ERAS concept is based on a multidisciplinary approach, which aim to create a synergistic effect applying several evidence-based perioperative elements[5]. This strategy has been implemented effectively improving outcomes in colorectal, orthopaedic, urologic gynaecology and breast surgery[6]. Unfortunately, only few trials have assessed the effectiveness of an ERAS program for cardiac surgery[7-9]. In addition, most of these trials were retrospective and none have been conducted in a population undergoing a mini-invasive aortic valve replacement (MIAVR). Therefore, the objective of this trial was to determine prospectively the clinical effectiveness of an ERAS protocol specifically designed for MIAVR at a tertiary medical centre. We tested the hypothesis that adoption of an ERAS pathway for MIAVR reduces hospital length of stay (LOS) and improve outcomes when compared with traditional care.

Methods

This human research, prospective, observational, single-centre study was conducted in the Department of Cardiac Anaesthesia and Critical Care at the Bordeaux University Hospital (Service d'Anesthésie-Réanimation GH Sud, CHU Bordeaux, France) from September 2014 to November 2015. Before starting the study, the research protocol was approved by the Research Ethics Boards of the Bordeaux University Hospital on the 3rd of September 2014 (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France, Chairperson Prof R.I. GALPERINE Ethical Committee N° DC 2014/91). Agreement from the "Commission Nationale de l'Informatique et des Libertés" was also obtained before commencing the study (registration number 1791818 v 0).

Study Design

The present trial was a comparative effectiveness study using a 'before-after' approach, with a nonrandomized, pre-implementation and post-implementation of the ERAS protocol, data collection scheme. Thereby, this study follows the guidelines and the checklist of the STROBE statement[10]. Data collected before the implementation stage occurred from September 2014 to December 2014. During this period, data from patients undergoing aortic valve replacement via a mini-sternotomy following the traditional perioperative care of our institution were collected prospectively. Meanwhile, a multidisciplinary team has been formed inviting leaders of every discipline participating in the accelerated recovery program conception. Once the team was created several meetings were scheduled during which a team-based approach allowed agreeing on the

evidence-based medicine elements incorporating the final ERAS program specifically designed for aortic valve replacement via a mini-sternotomy (Table 1). To ensure both a good communication between every care providers and the adherence to the various elements encompassed in the program, the official implementation of the ERAS pathway started after a 4-month period allowing all the staff members to become familiar with such program. Data obtained once the ERAS protocol was fully implemented were collected from May to November 2015.

The Ethics Boards authorized a waiver of the written informed consent because data were collected according to the standard practice of care of our institution, which consists in applying evidence-based perioperative principles to patients[4]. Thus, the present trial involved minimal additional risk to the study participants. This study was not registered on a clinical trial registry.

Study participants

Patients were enrolled in the study if they were older than 18 years old and were scheduled to undergo an elective aortic valve replacement via a mini-sternotomy. Exclusion criteria included patients scheduled for an aortic valve replacement with a full sternotomy or scheduled for other cardiac surgeries than aortic valve replacement, patients who underwent a previous sternotomy, patients with dementia, patients presenting with endocarditis and patients with chronic renal failure.

Demographic and outcomes data collected before and after the implementation of the dedicated ERAS pathway designed for a MIAVR procedure were compared.

The preoperative data collected were: anthropomorphic data, NYHA functional status, additive EuroSCORE, medical history and preoperative left ventricular ejection fraction

estimation. The intraoperative data collected were: duration of surgery, cross-clamp time, duration of cardiopulmonary bypass (CPB), number of patients transfused with red blood cells and proportion of patients converted full sternotomy. Other data collected were: proportion of adhesion to each item of the ERAS pathway, consumption of morphine, time to first flatus, proportion of patients re-operated, proportion of patients that contracted an infection, proportion of patients that developed an acute myocardial infarction, proportion of patients that developed a stroke, proportion of patients that developed acute kidney injury (AKI) according to the KDIGO criteria[11], proportion of patients that required renal replacement therapy, proportion of patients reintubated for respiratory failure, length of Intensive Care Unit (ICU) stay, length of hospital stay, all-cause ICU readmission before hospital discharge, all-cause readmission rate at 30-day, hospital mortality rate and mortality rate at 30-day.

Study groups

Traditional MIAVR group

Pre-operative management:

Patients were fasted from mid-night on the day of surgery. No preoperative counseling was performed in this group. One hour prior to their arrival in the operating theatre, patients received 0.1 $mg.kg^{-1}$ of oral midazolam and 50 mg of hydroxyzine. In the operating room, patients were monitored with a two-channel electrocardiogram, a pulse oximeter, an arterial line and a bispectral index monitor to reach and maintain BIS values within 40 and 60.

Intraoperative anaesthesia management and surgical technique:

A total intravenous anaesthesia was administered using target-controlled infusion with either sufentanil or remifentanil for analgesia and propofol for hypnosis via a peripheral intravenous catheter. Injection of 0.15 $mg.kg^{-1}$ of cisatracurium was used to facilitate endotracheal tube insertion. Then a continuous infusion of cisatracurium was started at a rate of 0.10 $mg.kg^{-1}.hr^{-1}$ and stopped when steel cerclage wiring of the sternum was completed. After intubation, antibiotic prophylaxis was delivered. After the induction, a central venous line and a urinary catheter with a temperature sensor were inserted. If no contraindications were found, a bolus of 20 $mg.kg^{-1}$ followed by an infusion of 2 $mg.kg^{-1}.hr^{-1}$ of tranexamic acid was delivered until sternum closure. A Swan-Ganz catheter and a transesophageal echocardiographic (TEE) probe were inserted at the discretion of the attending anesthesiologist. Intraoperative fluid delivery was based on changes in hemodynamics (arterial blood pressure and heart rate) and urine output. Before initiating CPB patients received 300 $IU.kg^{-1}$ of heparin to achieve an activated clotting time longer than 420 seconds. The CPB technique was not standardized and was left at the discretion of the perfusionist. It consisted in using either a standard open bypass circuit comprising a hard-shell venous reservoir, a microporous membrane oxygenator and a roller pump or a minimal extracorporeal circulation circuit (MECC) (Maquet Cardiopulmonary, Hirlingen, Germany). No goal direct-direct therapy perfusion strategy was performed in this group. Priming varied at the discretion of the anesthesiologist in charge and ranged from 800 ml to 1300 ml of balanced crystalloid solution (PlasmaLyte, VIAFLO, BAXTER S.A.S, Guyancourt, France). Heparin was reversed with protamine after weaning from CPB to obtain an ACT value at +/- 10% of the baseline value. Postoperative analgesia was administrated during the sternum closure using morphine 0.2

$mg.kg^{-1}$, 1 g of acetaminophen and 0.3 $mg.kg^{-1}$ of nefopam when not contraindicated. In a surgical standpoint, an upper hemi-sternotomy was performed in a J-shaped fashion at the 4th intercostal space to replace the native aortic valve with a bioprosthesis stainless valve. Both, the arterial and the venous cannulation were carried out centrally through the main surgical site. At this point, anterograde cardioplegia was administered. After initiation of CPB, the body temperature was reduced to 35-36°C. The calcified aortic valve was removed as usual, taking great care in repairing every annular defect to avoid annular hematoma. The aorta was closed in a standard fashion. Before separation from CPB, blood was warmed to reach a body temperature of 36.5°C. At the end of the surgery, a pacing wire was placed on the right ventricle, and a small sized (16 Ch) chest tube was left next to the pacing wire. All patients were transferred intubated in ICU and were extubated following a traditional fast track cardiac recovery protocol[1].

Postoperative management:

Upon arrival in the ICU, sedation was stopped and endotracheal extubation was allowed within 6 hours from the end of the surgery, when patients met the modified Reyes' extubation criteria[12]. After extubation, patients were allowed to breath spontaneously through a facemask with 6 $l.min^{-1}$ of O_2. Postoperative acute pain was treated with Patient-Controlled Analgesia (PCA) morphine (containing 0.05 mg of droperidol for each mg of morphine), and nefopam 65 $\mu g.kg^{-1}.h^{-1}$ for the first 48 postoperative hours, or until discharge from ICU. Patients were reintubated when they experienced acute respiratory failure. After extubation, non-invasive ventilation (NIV) was prescribed at the discretion of the attending intensivist without any detailed protocol. When patients were discharged from ICU, ketoprofen 100 mg was prescribed twice a day with breakthrough tramadol

100 mg every 4 to 6 hours, as required. Removal of both pericardial and retrosternal chest drains occurred 48 hours after surgery and only if during the last 10 hours there were less than 10 ml of blood per hour drained. The central venous line and the bladder catheter were removed on POD 3 on the surgical floor. Patients were mobilized from bed to chair on POD 3 when the tubes and catheters were removed. Patients were offered a fluid meal on POD 3 and a solid meal on POD 4. Postoperative physical therapies, embracing breathing and coughing exercises were prescribed at the discretion of the intensivist in charge. Patients were eligible to be discharged to the surgical floor when the following criteria were met: nasal administration of O_2 with a flow lower than 3 $l.min^{-1}$ and a respiratory rate lower than 25 per min and higher than 10 per min with blood gas analysis showing a PaO_2 superior than 9 kPa and a $PaCO_2$ lower than 6.5 kPa; no evidence of myocardial ischemia, no on-going infarction nor unstable hemodynamic dysrhythmia, no catecholamine infusion, no major neurologic complication and a urinary output higher than 0.5 $ml.kg^{-1}.h^{-1}$.

MIAVR-ERAS group

The key supplementary perioperative ERAS elements implemented at the University hospital of Bordeaux are summed up in Table 1.

Pre-operative management:

On average, 4 to 5 weeks before the surgery, patients met with a surgeon (P.O), an anaesthetists, an intensivist, a nurse, a physiotherapist and a nutritionist. Every stakeholder explained what it would do perioperatively and what he expect his patient to do in order to involve and engage him adhering to the ERAS pathway. The physiotherapist thought how to perform postoperative respiratory exercises efficiently

and emphasized their importance in optimizing postoperative pulmonary function and in reducing the infection rate. The nutritionist assessed patients' nutritional status measuring the levels of serum blood albumin, prealbumin and C-reactive protein. A tailored diet was prescribed preoperatively if judged necessary, in order to enhance patients' muscle strength and allow effective postoperative respiratory exercises and early mobilization. Patients also received a booklet with preoperative instructions and details about the surgery and the postoperative course. In addition, the day before surgery patients were invited watching a dedicated video explaining their arrival in the OR (supplementary data). Neither benzodiazepines nor hydroxyzine were prescribed preoperatively. Pregabalin was the only premedication allowed on the evening before the surgery and on the morning of the surgery (75 mg for patients with a bodyweight below 70 kg and or 150 mg for patient above 69 kg).

Intraoperative anaesthesia management and surgical technique:

Patients were monitored in a standard fashion. A total intravenous anaesthesia was administered using target-controlled infusion with remifentanil for analgesia and propofol for hypnosis via a peripheral intravenous cannula inserted on the forearm. To facilitate endotracheal tube insertion, 1.2 $mg.kg^{-1}$ of rocuronium was administered with no subsequent continuous infusion. After intubation, an antibiotic prophylaxis was administered. After induction, a central venous line, a urinary catheter with a temperature sensor and a TEE probe were inserted. Insertion of a Swan-Ganz catheter was not part of the ERAS protocol. A preemptive multimodal analgesic strategy was implemented at induction and consisted in boluses of ketamine 0.5 $mg.kg^{-1}$, dexamethasone 0.15 $mg.kg^{-1}$ and magnesium 50 $mg.kg^{-1}$. Tranexamic acid was also administered in this group

respecting the same dosage and criteria described above in the MIAVR group. Patients were ventilated according to a multimodal protective lung ventilation management consisting in low tidal volumes (6 $ml.kg^{-1}$ of ideal bodyweight) associated with positive end-expiratory pressure (PEEP) of 5 cmH_2O and a fraction of inspired oxygen (FiO_2) never above 0.60. Ventilation was maintained during CPB with 3 $ml.kg^{-1}$ of ideal bodyweight, with a PEEP of 5 cmH_2O, and with a FiO_2 of 0.35. Recruitment maneuvers were performed immediately after endotracheal intubation and right after the aorta was unclamped. Maneuvers were discontinued if MAP dropped below 55 mmHg for more than 15 seconds. In this group, the protocol included the standardization of CPB using a MECC. A dose of 300 $IU.kg^{-1}$ of heparin was administered, aiming to reach an ACT of at least 360 seconds. During CPB, no goal direct-direct therapy perfusion strategy was performed but a normothermia approach was applied, the flow rate was set at on average at 2.4 $l.min^{-1}.m^{-2-1}$, blood perfusion pressure was maintained between 55 and 80 mmHg and patients received red blood cell units only when the hemoglobin level was below 7.2 $g.dl^{-1}$. Surgically wise, only one change occur which was the replacement of the native aortic valve with a rapid deployment bioprosthesis (INTUITY, Edwards Lifesciences, Irvine, CA, USA). During separation from CPB, de-airing was meticulously guided by TEE imaging and paravalvular leaks were ruled out also by TEE. In addition, TEE allowed hemodynamic assessment and goal-directed therapy (GDT) optimizing fluid filling. The GDT strategy consisted in delivering fluid challenge of 3 $ml.kg^{-1}$ of a balanced crystalloid (PlasmaLyte VIAFLO, BAXTER S.A.S, Guyancourt, France) until a steady stroke index was reached (the GDT protocol is described in Figure 1). This strategy was applied before and after CPB. After the last skin suture, the incision was

protected with skin glue (Dermabond© Ethicon). To limit discomfort and facilitate early mobilization two small drainage-tubes were inserted through little incisions made above the mini-sternotomy. No adhesive bandage was applied. After sternum closure, wound infiltration with a total of 20 mL of 0.75% ropivacaine was applied along with administration of a multimodal analgesia encompassing acetaminophen, 1 g, ketoprofen, 100 mg, nefopam, 0.3 $mg.kg^{-1}$ and morphine, 0.1 $mg.kg^{-1}$. Propofol and remifentanil were stopped when the skin glue was applied. Patients were extubated either on the operating table or in ICU as soon as the following criteria were met: bleeding < 50 mL after skin glue was applied, diuresis > 0.5 $mL.kg^{-1}.h^{-1}$, hemodynamic stability without doses of norepinephrine > 0,1 $\mu g.kg^{-1}.min^{-1}$, no uncontrolled arrhythmias, SpO_2 > 94% with an FiO_2 < 60%, $PaCO_2$ between 5 and 6.5 kPa, patient awake and responsive, body temperature > 36°C and train-of four ratio > 90% [4].

Postoperative management:

From patients' arrival in ICU to the morning after the surgery, prophylactic NIV was prescribed in patients with a body mass index above 28 $kg.m^{-2}$ and/or in patients with chronic obstructive pulmonary disease. NIV sessions were also prescribed when patients presented specific medical conditions previously described[4]. Once these conditions were restored, NIV sessions were deemed unnecessary. In case of acute respiratory failure, patients were rapidly reintubated. For the first 48 postoperative hours, or until discharge from ICU, pain was managed with both PCA morphine (with 0.05 mg of droperidol for each mg of morphine in the PCA solution), and nefopam 65 $\mu g.kg^{-1}.h^{-1}$ and pregabalin once a day for the first five postoperative days (75 mg for patients with a bodyweight below 70 kg and or 150 mg for patient above 69 kg). When patients were discharged

from ICU, ketoprofen 100 mg was prescribed twice a day with breakthrough tramadol 100 mg every 4 to 6 hours, as required. Four hours after extubation, patients were sitting on the chair from the moment they agreed to sit on a chair, they had a ratio of $PaO_2/FiO2$ > 250, O_2 saturation was >92%, MAP was > 60 mmHg with dose of norepinephrine below 0.1 $\mu g.kg^{-1}.min^{-1}$ without increment from the moment they were extubated. From the moment patients sat, they were invited to start incentive spirometry exercises and continuing such exercises until hospital discharge. From this same moment, we have applied the latest nonpharmacologic guidelines suggested to prevent postoperative delirium[13]. Five % dextrose in 0.45% NaCl was infused intravenously at a rate of $1m.kg^{-1}$ until the morning after the surgery via the central venous line. In ICU, volume status was assessed by transthoracic echocardiography. If urinary output was less than 0.5 $ml.kg^{-1}.hr^{-1}$ and associated with hypovolemia, a bolus of 5 $ml.kg^{-1}$ of Plasma-Lyte solution was infused. On the contrary, if urinary output was less than 0.5 $ml.kg^{-1}.hr^{-1}$ and associated with hypervolemia, diuretics were prescribed. Patients were given oral fluid and offered a fluid meal 6 hours after extubation and a solid meal on postoperative day (POD) 1 if tolerated. Surgical drains were removed as soon as the blood outflow was less than 100 mL in 8 hours or less than 50 ml for 5 consecutive hours. Urinary catheter and central venous line were removed on the morning after surgery if the urinary output was above 0.5 $ml.h^{-1}$ for 6 consecutive hours with no diuretic prescribed and no on-going infusion of vasoactive amines. Until POD 4, only a peripheral IV cannula was left in situ with transparent polyurethane dressing with no drip. Patients were discharged to the surgical floor as soon as they met the same criteria described in the MIAVR group. On POD 1, patients were encouraged walking in their bedroom along with the presence of a

physiotherapist. From POD 2, patients were invited walking in the corridor of the surgical ward along with a physiotherapist. From POD 3, patients were invited to climb flight of stairs twice a day along with a physiotherapist.

Hospital discharge

For both groups the criteria for hospital discharge were: presence of sinus rhythm or persistence of the same rhythm traced by the EKG preopeartively, absence of infection, no rise in body temperature, haemoglobin greater than 8 $g.dl^{-1}$, normal white blood cell count, normal serum creatinine and electrolytes, unremarkable chest X-ray, unremarkable EKG, unremarkable transthoracic echocardiography, as well as having recovered an adequate mobility according to the physiotherapist.

Outcome data

The primary outcome was postoperative hospital LOS, which was defined as the number of days spent in the hospital after surgery. Secondary outcomes were percentage of patients adhering to the protocol, number of patients extubated on the operating table, time to extubation after the last skin suture, reintubation for respiratory failure, postoperative pain scores, morphine consumption during the first two postoperative days, time to first flatus, postoperative infection, postoperative complication, all-cause ICU readmission, all-cause 30-day readmission, and intra-hospital death. Pain intensity was assessed using the Visual Analogue Scale (VAS) every 6 hours as long as patients were in ICU and then twice a day at rest and on coughing when transferred to the surgical ward. PCA morphine consumption was recorded every 6 hours as long as patients were in ICU.

Patients were diagnosed having in-hospital urinary tract infection and surgical site infection according to international guidelines[14, 15]. A postoperative bronchial congestion clinically significant requiring a treatment with antibiotics by the attending intensivist was considered as a bronchopulmonary infection.

Statistical analysis

The sample size was calculated to detect a reduction of patients LOS scheduled to undergo an aortic valve replacement via a mini-sternotomy. In our institution, the average hospital stay for patients undergoing an aortic valve replacement via a mini-sternotomy was on average 10 days. Twenty-three patients per group would be necessary to detect a 30% reduction of the LOS in the ERAS group with a type-1 error of 5% and a power of 80%. All data collected were inserted in a private computer database. Data were then transferred to the XLSTAT for analysis (Addinsoft, XLSTAT Version 2016.02.27444, Paris, France). Results are presented as mean standard deviation (SD) when normally distributed, as median and [interquartile range] for nonparametric data and as proportions (%) for categorical data. Student's t test, Mann- Whitney U test, and Fisher's exact test were used appropriately, according to their distribution and their scale. A *P*-value below 0.05 was considered statistically significant. Demographic and clinical variables were compared between the two groups. To control for the potential confounding effect all independent variables statistically significant in bivariate analysis were forced into a multivariable linear regression model to study the effect of such covariates on the primary endpoint.

Results

Twenty-three consecutive patients scheduled to undergo an aortic valve replacement via a mini-sternotomy were included in the "MIAVR traditional protocol of care" group and twenty-three consecutive patients were included in the "MIAVR-ERAS" group after a 4-month period of protocol implementation. The same surgeon (P.O.) performed all the mini-sternotomies. The cardiac anaesthesia and intensive care clinicians in charge of patients' during the study period remained unchanged. Patients' demographic and preoperative data were similar between the two groups except for a higher body mass index in the MIAVR group and more female in the MIAVR-ERAS group (Table 2). There was no significant difference in the mean surgical time, CPB time or aortic cross-clamp time between the two groups (Table 2).

Protocol compliance.

Each patient in the accelerated recovery pathway received counselling session with every stakeholder of the protocol and was able to watch the video describing the arrival in the OR. In contrast, no patient had counselling session in the traditional patient care protocol. Every patient in the traditional MIAVR group received a multimodal analgesia. However, only 3 out of the 8 agents integrating the multimodal analgesic ERAS protocol were used in the MIAVR group. The proportion of patient adhering to each items of the multimodal analgesia varied considerably (Table 3). Overall, adherence to the ERAS elements of the pathway were statistically more frequent in the MIAVR-ERAS group except for 5 out of the 19 items described in Table 3. Those five elements that did not reach a statistical difference between the two groups, were not consequent to poor protocol adherence but

because it was already part of the common practice of some anaesthetists before implementation of the ERAS protocol. Five out of 14 patients (36%) and 9 out of 13 (69%) received preventive postoperative NIV in the MIAVR and in the MIAVR-ERAS group, respectively. Despite, a two-fold higher number of patients receiving preventive NIV in the MIAVR-ERAS group compared to the MIAVR group, the difference between the two groups was not statistically different ($P = 0.180$).

Primary clinical outcome

Hospital LOS was significantly shorter in the MIAVR-ERAS group compared to the traditional MIAVR care group with 7 [6.5-8] days and 10 [9-13.5] days, respectively ($P <0.001$). In the model built to adjust for possible confounding factors we found that significant covariables were: patients with no postoperative infection (shorter stay, $P =0.002$) and patients adhering to the ERAS bundles adherence (shorter stay, $P = 0.005$) (table 5).

Secondary clinical outcome

Time to extubation was not significantly different between the two groups. However, it seems that there was a trend toward a faster extubation time in the MIAVR-group ($P = 0.083$). Thirteen patients (57%) were extubated on the operating table in the MIAVR-ERAS group. During the postoperative ICU stay, morphine consumption in the MIAVR group was 7 [3–12] mg compared with 2 [0-12] mg in the MIAVR-ERAS group, ($P = 0.090$) (Table 4). Although the highest median pain score in ICU was collected in the MIAVR-ERAS group ($P = 0.068$), the median average ICU pain was statistically greater in the MIAVR group ($P =0.030$) (table 4). No difference in the median pain score on the

surgical ward was detected between the two groups. Time to first flatus was significantly shorter in the MIAVR-ERAS group compared to the MIAVR group with a median of 1[1-1.5] day and 1[1-2] day, respectively (P = 0.035). One patient was converted to full sternotomy during the surgical procedure in the MIAVR group. Another patient in the MIAVR group was brought back to the OR during his ICU stay because of significant postoperative bleeding (2 $ml.kg^{-1}$ of blood for 2 consecutive hours with normal values of the coagulation profile). No acute myocardial infarction, no stroke, no renal replacement therapy nor reintubation for respiratory failure was reported in any of the groups. The postoperative overall infection rate were greater than two-fold in the old protocol of care with 39% in the MIAVR group compared with 17% in the MIAVR-ERAS group. However, no statistical difference was detected between the two groups (P = 0.098) (Table 4). Interestingly, taking into account only the pulmonary infection the difference between the two groups almost reached the statistical difference (P = 0.060). The other postoperative complication rates were similar between the two groups (Table 4). Intensive Care Unit LOS was significantly shorter in the MIAVR-ERAS group compared to the other group (P = 0.003). In the MIAVR group, 2 patients have been readmitted in ICU for respiratory failure secondary to cardiogenic pulmonary oedema that did not require re-intubation. Two patients in the MIAVR group developed AKI stage 1. In contrast, no patient has been readmitted in ICU in the MIAVR-ERAS group and none developed AKI. One patient died during the hospital stay in the MIAVR group (septic shock) and two patients were re-hospitalized before postoperative day 30 in the MIAVR group for drainage of a pericardial effusion. There was no 30-day mortality and no 30-day hospital re-admission in the MIAVR-ERAS group.

Discussion

To the best of our knowledge our trial is the first prospective investigation demonstrating that patients undergoing a MIAVR coupled with an ERAS pathway is feasible and could shorter both ICU LOS and hospital LOS. Although, the postoperative recovery program started the same day of the surgery with early mobilization, incentive spirometry and respiratory exercises, patients following the accelerated recovery program had less postoperative pain. Also, patients in the MIAVR-ERAS group followed a trend toward earlier extubation time as well as a trend toward less postoperative all-cause infections.

Fast track protocols in cardiac surgery aiming to extubate patients at an early stage postoperatively have been described since the early 1980's. The most recent meta-analysis including a total of 28 trial with more than 4400 patients, mostly low-risk patients undergoing Coronary Artery Bypass Graft (CABG) surgery, did not demonstrate better postoperative outcome, shorter ICU LOS nor hospital LOS[16]. In light of the strong data showing the benefit of ERAS programs for patient outcome for many surgeries[17], it could be advocated that the cardiac fast track protocol lacks postoperative advantages, because no dedicated multidisciplinary perioperative pathways have been implemented. Therefore, after the extubation, this period of 'therapeutic silence' that does not incorporate early physiotherapy, early oral nutrition, early mobilization and early tube/line removal might explain why these cardiac fast-track protocols have failed to show any postoperative potential patients' benefit[18]. It has to be underlined that implementation of an ERAS program for cardiac surgery is challenging considering the important heterogeneity of institutional practice and the unique sequence of the procedure

requiring a CPB with an aortic cross-clamping. However, recent trials suggest that such implementation is feasible and carries substantial postoperative advantages in terms of patient outcome[7, 8]. Based on our previous experience in cardiac surgery[4], the key to success in implementing ERAS elements was building the program with a trans-disciplinary participation. Every stakeholder suggested several elements to implement based on his experience within the institution and the evidence-based knowledge in his field. A crucial aspect was found to be the preoperative period that allows every stakeholder to set the ground for patients' psychophysical status optimization to start promptly and most importantly efficaciously the postoperative program (Table 1). Another fundamental feature of our protocol favouring an early postoperative recovery was to avoid benzodiazepine premedication, which could trigger delirium postoperatively[7]. Our preoperative anxiolytic strategy was rather based on counselling and pregabalin. Preoperative patient counselling and education with video material coupled with tailored patient communication seems to reduce anxiety and also improve outcome after cardiac surgery[19, 20]. On the other hand, pregabalin encompasses several advantages. First, it possess anxiolytic property[21] . Second, it seems that it could act as a sparing opiate agent reducing postoperative acute pain and chronic pain after cardiac surgery[22, 23]. Third, pregabalin has antiemetic properties[24], which is an essential facet to help starting efficiently and rapidly our postoperative protocol.

The backbone of the pathway established during the preoperative period was strengthened pharmacologically and surgically during the intraoperative phase. The intraoperative ERAS pharmacological strategy was based on a multimodal analgesia protocol. Our results are in line with a recent trial analysing specifically how such

strategy could help implementing the other ERAS elements such as ultrafast track extubation, reduced postoperative opiate consumption, shorter ICU stay as well as shorter hospital stay[8]. However, in their trial the average postoperative morphine consumption in the ERAS group was almost 15-fold higher than the average noted in our MIAVR-ERAS group. This noteworthy difference could be explained by our more extensive multimodal analgesia protocol but also by the association with a mini-invasive surgical technique. The later has been shown to decrease significantly postoperative pain[25]. In fact, mini-invasive abdominal surgery is considered as the cornerstone of ERAS pathway[26]. Nevertheless, how the minimally invasive cardiac surgical procedure could modulate the recovery process is still unknown[7]. Rapid deployment valves (Edwards INTUITY Elite) were implanted in the MIAVR group aiming to facilitate the technical gesture and to lower the CPB time known to be the major pro-inflammatory factor of this intervention[27]. Also, to lower the inflammatory cascade, particular intraoperative elements were incorporated in the present ERAS cardiac bundle. First, we used a MECC, which has been shown to be an independent predictor of early recover after CABG with less blood transfusion, shorter duration of inotropic support and less AKI[28]. Second, ventilation with small tidal volume was maintained during CPB. This strategy seems to reduce the inflammation preventing alveolar collapse, atelectasis, and hypoxemia[29]. Third, the procedure was performed under normothermic conditions. The latter does not reduce the inflammation per se but seems lowering the incidence of patient transfused[7]. In combination with our low transfusion threshold, it could be advocated that our strategy might reduce indirectly the pro-inflammatory state, the tissue oxidative stress and the coagulation cascade related to red blood cells transfusion[30]. However, no difference in the

number of patients with red blood cell transfusion was observed between the two groups. This absence of difference could be explained by the low sample size that was not powered to detect such variation. Another crucial element of our intraoperative ERAS bundle was the pre-emptive goal directed fluid therapy echo-guided. A meta-analysis reviewing suggests that such fluid management reduces postoperative morbidity and hospital LOS for patients undergoing cardiac procedure[31]. Finally, no intraoperative continuous infusion of muscle relaxant was delivered offering the advantage to avoid reversal agents administration known to potentially activate several threatening side effects[32].

Our findings suggest that the preoperative and intraoperative elements of our ERAS protocol offer appropriate conditions to start early mobilization, early feeding, and early physiotherapy compared to the standard protocol. As suggested by recent trial conducted in the cardiac setting[7-9], it is likely that the postoperative ERAS bundle established favoured the earlier ICU discharge, the earlier hospital discharge as well as the trend toward less postoperative infections. Early mobilization is a fundamental element for fast recovery[33]. A recent randomized control trial conducted in patients undergoing major abdominal cancer surgery suggests that mobilisation is an independent factor helping early functional capacity recovery[34]. On the other hand, our opioid-sparing approach in combination with early mobilisation and early hospital discharge might have helped diminishing both delirium and postoperative cognitive dysfunction, especially in our elderly population[35]. However, these parameters have not been studied in our trial and the impact of an ERAS program on these complications needs further investigations.

Our study presents several strengths. The major strength of our study is that our anaesthesia department is constituted of cardiac anaesthetists that also supervised the cardiac ICU. Therefore the same group of physicians guaranteed the standardization of the ERAS program from the OR to the ICU. This point was decisive because the primary assumption of an ERAS program is the standardization of the perioperative patient care. Also, the surgeon was the same for all surgeries, which is an important bias that was control in this trial. On the other hand, there were several limitations. The main limitation of our trial was that the present study is a nonrandomized-controlled trial and the ERAS bundles were implemented concomitantly. Thus, it is difficult to define which elements of the protocol were responsible for the positive outcome reported in the MIAVR-ERAS group. However, prospective auditing is considered to be more prone to demonstrate efficacy than randomized investigations, which are impossible to blind and claimed to be unethical[5]. Nevertheless, randomized clinical trials have been conducted in the cardiac setting[9]. Another limitation is that the Hawthorne effect[5] might have affected the time of discharge from both ICU and hospital in the MIAVR-ERAS group. However, the discharge criteria were the same between the two groups. Also, implementation and adherence to the present ERAS program encompassing many elements required an increased workload from all the stakeholders. Conversely, it is possible to claim that shorter ICU stay and shorter hospital stay could lower the cost related to the surgical procedure. Also, the lower incidence of postoperative complications found in the MIAVR-ERAS group could lower indirectly the cost related to the intervention. Despite not being strictly in line with the definition of a bronchopulmonary infection, our definition considered the present major public health issue represented by antibiotic

resistance[36]. Hence, whether the infection was documented or not, the necessity to use antibiotics was deemed clinically more relevant than the occurrence of a documented infection per se. Finally, the ERAS protocol studied in the present investigation has been refined according to new evidence and thanks to the organization set, as well as the experienced gain during this period. For instance, from 2017 our protocol has evolved. Preventive NIV as been replaced with prophylactic high-flow oxygen therapy with which is less invasive and seems to be as effective as NIV[37]. Furthermore, it is our intention to complement our protocol with new elements such as preoperative use of iron or rhEPO in anaemic patients, shorten the fasting time, allow carbohydrate beverage intake 2 hours before anaesthesia induction, implement a postoperative antiarrhythmic protocol and implement a goal direct perfusion strategy during CPB.

Conclusion

In conclusion, we showed a significant reduction in hospital length of stay after implementation of a dedicated cardiac enhanced recovery pathway for minimally invasive aortic valve replacement. The present study suggests that this type of protocol for such intervention is feasible and could enhance the benefit of this surgical approach sublimating patient outcome. As demonstrated in our trial optimized perioperative care achieved in the MIAVR-ERAS group seems to favour a low and well-controlled surgical stress consenting early postoperative recovery even in elderly patients. Therefore, in the future a MIAVR procedure associated with a dedicated ERAS protocol should be considered as a treatment option for high/intermediate risk patients considered in the grey zone between TAVI and surgery. As the anaesthetist is now considered a perioperative physician, he must be aware of the surgical innovations and play the role of a conductor orchestrating the harmonious integration of cardiac multidisciplinary evidence based strategies to obtain synergistic effects striving for the improvement of postoperative patient outcome.

Legend for Figure

Figure 1: Perioperative goal-direct fluid therapy protocol implemented in the MIAVR-ERAS pathway.

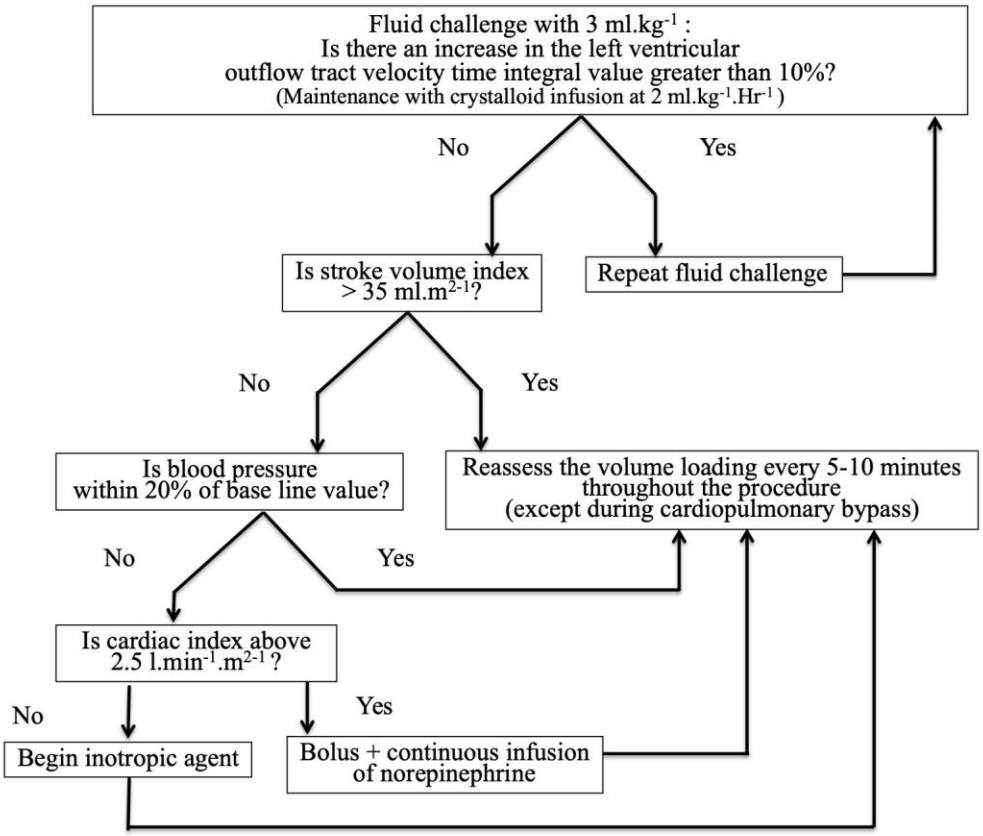

Table 1: Bordeaux University Hospital MIAVR-ERAS protocol

	MIAVR (n=23)	MIAVR-ERAS protocol (n=23)
Preoperative		
Counseling/Education	Absent	a - Meeting with a nurse: screening for tobacco use, comorbidities and explaining the pathway and our expectation regarding patients' involvement and engagement b - Meeting with a physiotherapist: explanation and training how the respiratory exercises are done properly, c - Meeting with a nutritionist: screening for malnutrition (with albumine, pre-albumine and C-reactive protein) and prescription of a diet if deemed necessary d - Booklet describing every step of the protocol to reduce anxiety and stress related to the surgery e - Video describing the patients arrival in the OR reduce anxiety and stress related to the surgery*
Premedication	Benzodiazepines or hydroxyzine	No premedication allowed except for pregabalin the night before and on the morning of surgery if no contraindication
Intraoperative		
Multimodal analgesia	Physician's discretion	Protocol associating dexamethasone, acetaminophen, ketoprofen, nefopam, morphine, magnesium, ketamine, pregabalin
Surgical wound infiltration	No	20 mL of Ropivacaïne 0.75%
Insertion of a pulmonary artery catheter	Physician's discretion	Exclusion of its usage
Surgical Technique	Mini-sternotomy aortic replacement with bioprosthesis stainless valves	Mini-sternotomy aortic replacement with of rapid deployment valves
Type of CPB	No standardization	Minimal Extra Corporeal Circulation
Intraoperative ventilation strategy	No standardization	Protective lung ventilation intraoperatively based on the predicted body weight and during CPB
Intraoperative fluid therapy	Management based on changes in hemodynamics (arterial blood pressure and heart rate) and urine output	Goal directed therapy TEE- guided *
Transfusion threshold	Physician's discretion	Only when hemoglobin is below 7.2g.dl^{-1} during CPB
Postoperative		

Extubation criteria	Fast track criteria	As soon as the ultrafastrack extubation criteria were met**
Non pharmacologic strategies to reduce postoperative delirium	Absent	Application of the best practice statement from the American Geriatric society***
Mobilization	Mobilization on postoperative-day 3.	Mobilization on chair on the same day after surgery
Tubes removal	No protocol, urinary catheter and central venous line usually left at discharge from ICU. Chest tube removed at physician's discretion.	Urinary catheter and central venous line removed at discharge from ICU. Chest tubes removed when collecting less than 100 mL of blood in 8 hrs. No routine chest X-ray after drain removal.

*: See Figure 1

: Zaouter C, Imbault J, Labrousse L, et al. Association of Robotic Totally Endoscopic Coronary Artery Bypass Graft Surgery Associated With a Preliminary Cardiac Enhanced Recovery After Surgery Program: A Retrospective Analysis. *Journal of cardiothoracic and vascular anesthesia* 2015; **29: 1489-97

***: American Geriatrics Society Expert Panel on Postoperative Delirium in Older A. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. *Journal of the American College of Surgeons* 2015; **220**: 136-48 e1

Table 2: Patients' characteristics and intraoperative data of interest.

	MIAVR(n=23)	MIAVR-ERAS(n=23	P-Value
Patients' characteristics			
Age, year	73(*68-82*)	80(*74-82*)	0.156
Female gender, n(*%*)	7(*30*)	14(*61*)	0.038
Body Mass Index, $kg.m^{-2}$	28(*26-32*)	26 (*23-27*)	0.022
NYHA functional status I or II, n(*%*)	17(*74*)	18(*78*)	0.808
Additive EuroSCORE	6(*4-10*)	8(*6-11*)	0.410
History of stroke, n(*%*)	1(*4*)	2(*9*)	0.550
PVD, n(*%*)	3(*13.0*)	2(*9*)	0.636
COPD, n(*%*)	4(*17*)	2(*9*)	0.381
Diabetes, n(*%*)	7(*30*)	5(*22*)	0.502
Hypercholesterolemia, n(*%*)	9(*39*)	13(*56*)	0.238
Arterial hypertension, n(*%*)	18(*78*)	20(*87*)	0.437
History of smoking, n(*%*)	5(*22*)	7(*30*)	0.502
LVEF, %	60(*50-65*)	60(*58-70*)	0.224
Intraoperative Data			
Duration of anesthesia, (min)	240(*227-277*)	240(*225-260*)	0.494
Cross clamp time, (min)	53(*47-60*)	51(*48-55*)	0.275
CPB time, (min)	80(*73-90*)	81(*75-85*)	0.667
Number of patients transfused with RBC, n(*%*)	11(*48*)	13(*56*)	0.554

Data are expressed as mean± (Standard Deviation) or median (*interquartile* range) or n (% of patients). The p-value refers to comparison between groups (pre AVRERAS versus AVRERAS). All tests of significance were 2-tailed, and results of comparisons were considered statistically significant when the p-value was ≤ 0.05.

Abbreviations: MIAVR: mini invasive aortic valve replacement; MIAVR-ERAS : mini invasive aortic valve replacement - enhanced recovery after surgery; NYHA : New York Heart Association; PVD: perivascular disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; CPB : cardiopulmonary bypass; RBC : red blood cells.

Table 3: Protocol compliance

	MIAVR(n=23)	MIAVR-ERAS(n=23)	P-Value
Counseling			
Counseling with all the stakeholders, n(%)	0	23(*100*)	*<0.001*
Patients that watched a video describing their arrival in the OR, n(%)	0	23(*100*)	*<0.001*
Multimodal analgesic protocol compliance			
Patients that received pregabalin perioperatively, n(%)	2(8.7)	21(*91*)	*<0.001*
Patients that received remifentanil intraoperatively, n(%)	12(*52*)	17(*74*)	0.221
Patients that received magnesium intraoperatively, n(%)	0	23(*100*)	*<0.001*
Patients that received ketamine intraoperatively, n(%)	3(*13*)	10(*43*)	*0.020*
Patients that received dexamethasone intraoperatively, n(%)	2(*9*)	8(*35*)	*0.032*
Patients that received ketoprofen, n(%)	12(*52*)	15(*65*)	0.369
Patients that received nefopam, n(%)	17(*74*)	22(*96*)	*0.04*
Patients that received acetaminophen, n(%)	23(*100*)	23(*100*)	1
Patients that received wound infiltration with ropivacaine, n(%)	0	23(*100*)	*<0.001*
Other elements compliance			
Patients who underwent the CPB with a MECC circuit, n(%)	15(*65*)	16(*70*)	0.753
Patients transfused only when Hb level < 7.2 $g.dL^{-1}$during CPB, n (%)	3(13)	10(*43*)	*0.020*
Patients ventilated during CPB, n(%)	23(*100*)	23(*100*)	1
Patients following a GDT protocol for fluid therapy, n(%)	0	10(*43*)	*0.020*
Patients mobilized on chair on POD 0, n(%)	0	11(*48*)	*<0.001*
Patients that received their first postoperative meal on POD 0, n(%)	0	7(*30*)	*0.004*
Patients that had their transurethral catheter removed on POD 1, n(%)	0	22(96)	*<0.001*
Patients that had their central venous line removed on POD 1, n(%)	1(*4*)	17(*74*)	*<0.001*

Data are presented as frequency (proportion).
The *P*-value refers to comparison between groups (MIAVR versus MIAVR-ERAS).
All tests of significance were 2-tailed, and results of comparisons were considered statistically significant when the *P*-value was ≤ 0.05.
Abbreviations: MIAVR: mini-invasive aortic valve replacement; MIAVR-ERAS: mini-invasive aortic valve replacement - enhanced recovery after surgery; CPB : cardiopulmonary bypass; MECC : minimal extracorporeal circulation circuit; NIV : non invasive ventilation; GDT : goal directed therapy; POD : postoperative day

Table 4: Patient outcome of interest

	MIAVR (n=23)	MIAVR-ERAS (n=23)	p -value
Postoperative opioid consumption and pain scores			
Total postoperative morphine (mg)	7 (3-12)	2 (0-12)	0.090
Highest ICU pain score	4 (2-6)	5 (3-6)	0.680
Average ICU pain score	2 (2-3)	1.4 (0-2)	0.030
Average surgical ward pain score	0.5 (0-1)	0.5 (0-1)	0.320
Postoperative complications			
Overall infections, n(%)	9(39)	4(17)	0.098
UTI	1(4)	1(4)	1
SSI	1(4)	1(4)	1
Pulmonary infection	7(30)	2(9)	0.060
Stroke, n(%)			
Reintubation for respiratory failure, n(%)	0 (0)	0 (0)	1
New onset of atrial fibrillation, n(%)	6(26)	9(39)	0.345
ICU Readmission, n(%)	2(9)	0	0.148
Hospital readmission within 30-day of surgery, n(%)	2(9)	0	0.148
Number of patients developing AKI, n(%)	2(9)	0	0.148
Length of stay in ICU and Hospital			
ICU length of stay (hours)	28(25-47)	24(24-28)	0.003
Hospital length of stay (days)	10(9-13)	7(6-8)	<0.001

Data are presented as median and interquartile range (IQR : 25th – 75th percentiles).
The p-value refers to comparisons between groups (MIAVR versus MIAVR-ERAS), and a difference between the two groups is said to be statistically significant when the p- value is under .05.
Abbreviations: MIAVR: mini-invasive aortic valve replacement ; MIAVR-ERAS : mini-invasive aortic valve replacement - enhanced recovery after surgery; ICU : intensive care unit ; UTI : urinary tract infection; SSI : surgical site infection;

Table 5: Multivariate linear regression on Hospital Length of Stay

	Value	Std err	T test	*P*- value	CI (95%)
Age	0.044	0.169	0.263	0.795	-0.305; 0.394
Patient with infection	0.448	0.177	2.526	0.019	0.081; 0.814
Body Mass Index	-0.100	0.177	-0.566	0.577	-0.466; 0.265
Female gender	0.003	0.156	0.019	0.985	-0.321; 0.326
ERAS bundles adherence	-0.637	0.204	-3.116	0.005	-1.060; -0.214
Early mobilization	-0.200	-0.203	-0.984	0.331	-0.612; 0.212
Early urethral catheter removal	0.330	0.226	1.456	0.159	-0.138; 0.798

Data are presented as Value of the regression coefficient, Standard Error (Std err) of the regression equation, T test of the linear regression model, and the probability (*P*-value) that a linear relation exists between the studied variable and the Hospital Length of Stay.
The relation is said to be significant between the independent variable and the Hospital Length of Stay when the *P*-value is under 0.05.
Abbreviations: MIAVR-ERAS; Mini-invasive Aortic Valve Replacement - Enhanced Recovery After Surgery.

Discussion

Jusqu'à maintenant, la chirurgie cardiaque ne bénéficiait pas d'étude prospective évaluant l'intérêt d'un protocole ERAS. Pourtant les incitations à la réduction des durées de séjour d'un côté et, d'autre part, l'efficacité des protocoles ERAS dans les chirurgies autres que cardiaque pour réduire ces durées font apparaître l'intérêt de l'évaluation de tels protocoles, notamment pour le remplacement valvulaire aortique qui subit la concurrence de techniques moins invasives (TAVI).

Cette contradiction s'explique par une expérience du « Fast Track » en chirurgie cardiaque dans les années 1990, centrée sur l'extubation précoce, sans effet démontré sur les durées de séjour ou les complications[21].

Les principes de l'ERAS vont au-delà des concepts de « Fast Track » : il s'agit d'optimiser chaque élément du péri-opératoire en même temps, l'ensemble des actions entreprises constituant un « bundle », et c'est l'implémentation de tout le protocole et non d'un élément en particulier (comme l'extubation précoce) qui est censé réaliser un bénéfice sur les suites opératoires[22].

Bien qu'aucun consensus n'existe encore sur les composants d'un protocole ERAS en chirurgie cardiaque, ses aspects peuvent être inférés des expériences du « Fast Track » et de l'ERAS dans les autres chirurgies. Se répartissant en trois périodes (pré-opératoire, per-opératoire, post-opératoire), ils concernent : l'analgésie, la prévention des nausées-vomissements post-opératoires (NVPO), l'apport hydrique péri-opératoire, la stratégie

transfusionnelle, la prévention du syndrome confusionnel, la mobilisation précoce[22], la reprise précoce d'une alimentation orale.

La prévention du syndrome confusionnel.

Le syndrome confusionnel postopératoire est associé à une morbi-mortalité accrue[27]. Les facteurs modifiables associés au syndrome confusionnel sont : la durée de la circulation extra-corporelle, la profondeur de l'hypothermie, la dose administrée de FENTANYL en per-opératoire et probablement l'utilisation de sédatifs de longue durée d'action où d'anticholinergiques[22].

Notre protocole s'attache à prévenir la survenue d'une confusion par des actions à chaque étape :

- En préopératoire dans le groupe ERAS, la prise en charge de l'anxiété s'appuie sur l'information (vidéo décrivant le parcours patient au bloc opératoire, explications sur le déroulement de chaque moment de la prise en charge), la réassurance et une anxiolyse utilisant la PREGABALINE à la place des benzodiazépines et de l'HYDROXYZINE qui étaient utilisés traditionnellement.
- En peropératoire : mini-CEC et normothermie d'une part et réduction des doses d'opioïdes (mini-sternotomie et analgésie multimodale) d'autre part.
- En postopératoire : tendance à la réduction des besoins morphiniques, mobilisation précoce, reprise précoce d'une alimentation orale.

Nous avons appliqué dans le groupe ERAS les recommandations de l'American Geriatric Society pour la prévention non pharmacologique du syndrome confusionnel post-

opératoire.

Le schéma de l'étude n'étant pas destiné à rechercher une différence dans la survenue d'une confusion, nous ne pouvons pas nous prononcer sur l'efficacité de ces mesures sur la réalisation de cet objectif. L'implémentation de ces mesures est malgré tout justifié par les résultats obtenus sur la durée de séjour et par leur effet possible sur les facteurs de risque décrits dans la littérature.

L'analgésie.

Un mauvais contrôle de la douleur postopératoire peut avoir un effet défavorable sur les suites opératoires, notamment sur la survenue d'une ischémie myocardique[27]. Par ailleurs des doses élevées d'opioïdes retardent l'extubation[28], sont associées à des complications digestives[29] et à l'augmentation des durées de séjour[30,31].

Notre stratégie est de proposer une analgésie multimodale permettant d'une part un meilleur contrôle de la douleur, avec un score de douleur médian plus bas en postopératoire chez les patients du groupe ERAS, d'autre part une tendance à l'épargne morphinique (statistiquement non significative par manque de puissance).

Nous associons :

- La PREGABALINE en prémédication et pendant 5 jours en post-opératoire, qui permet de diminuer les besoins morphiniques[32]
- REMIFENTANIL per-opératoire
- KETAMINE, DEXAMETHASONE, MAGNESIUM, KETOPROFENE, PARACETAMOL, NEFOPAM et MORPHINE débutés en per-opératoire.
- Une infiltration de la cicatrice opératoire à la ROPIVACAINE.

Cette analgésie multimodale est associée à une technique chirurgicale mini-invasive (abord par mini-sternotomie) moins douloureuse que la sternotomie médiane[33].

La prévention des NVPO.

Les nausées et vomissements post-opératoires peuvent être responsables de stimulation adrénergique, d'un retard à la reprise de l'alimentation et à la mobilisation. D'une part, nous utilisons la DEXAMETHASONE et le DROPERIDOL en prévention, ainsi que la PREGABALINE qui semble montrer une réduction de leur incidence[34], d'autre part, l'analgésie multimodale et la technique mini-invasive permettent probablement une réduction de la consommation de morphiniques.

La stratégie transfusionnelle.

Un seuil transfusionnel bas, et le maintien d'une normothermie permettent probablement de diminuer les besoins transfusionnels[35], malgré l'absence d'effet retrouvé dans notre étude, probablement par manque de puissance.

Si la réduction des besoins transfusionnels se confirme, l'activation de la cascade pro-inflammatoire liée au stress chirurgical serait probablement moindre[36].

L'apport hydrique péri-opératoire.

La maîtrise de l'hydratation per-opératoire est indispensable à la conception d'un protocole ERAS. La littérature indique une supériorité des stratégies de « Goal Directed Therapy » (GDT) : leur implémentation en chirurgie cardiaque permet possiblement à elle seule de réduire les complications post-opératoires et la durée de séjour[37].

Notre protocole d'hydratation per-opératoire est représenté par la Figure 1. Nous ne retrouvons pas de différence dans les volumes apportés avant et après l'implémentation du protocole ERAS, du fait d'équipes déjà sensibilisées à l'optimisation volémique et à la lutte contre la surcharge.

Le contrôle thermique :

Malgré une littérature qui n'offre pas de recommandation sur l'objectif de température centrale en per-opératoire de chirurgie cardiaque[38], nous avons choisi de maintenir les patients en normothermie. La littérature n'offre pas de consensus en faveur de cette stratégie[39]. Cependant, nous considérons, que par une réduction des besoins transfusionnels[40] nous réduisons la cascade inflammatoire liée à la transfusion et par là le stress chirurgical.

La mobilisation précoce.

La mobilisation précoce des patients de réanimation à un effet bénéfique sur leur devenir[41]. Peu de données existent sur les patients de chirurgie cardiaque, elles semblent néanmoins favorables à une mobilisation précoce[42]. Nous avons choisi de mobiliser les patients au fauteuil, dès que possible à partir de la sixième heure post-opératoire.

Pour favoriser leur mobilité, nous avons procédé à un retrait aussi précoce que possible des cathéters, drains et sondes vésicales (Tableau 1 et Tableau 3).

Autres interventions.

Nous proposons une reprise précoce d'une alimentation orale (dès le premier jour post-

opératoire) en adaptant les recommandations pour l'ERAS en chirurgie digestive[43]. Il est établi que chez ces patients un délai à la reprise d'une alimentation orale est associé à des suites opératoires défavorables.

Dans le groupe ERAS, nous avons proposé une VNI préventive aux patients avec un indice de masse corporelle supérieur à 28 $kg.m^{-2}$, ou avec des antécédents respiratoires dans un but de réduction des complications respiratoires[44].

Notons comme points forts de notre étude une prise en charge des patients par la même équipe d'anesthésie-réanimation cardiaque en pré, per et post-opératoire. Cette continuité permet une standardisation homogène de la prise en charge du patient durant tout son parcours, sans laquelle un protocole ERAS ne peut être implémenté.

Par ailleurs, le fait que toutes les interventions soient réalisées par le même chirurgien permet de s'affranchir d'un biais potentiel.

Une limite de notre étude est son caractère non randomisé, sans aveugle avec une implémentation d'un paquet d'interventions « en bloc », qui ne permet pas de discriminer lesquelles de ces interventions sont efficaces. Nous pensons toutefois que le principe même de l'ERAS nécessite l'implémentation d'un faisceau d'actions pour être efficace et, comme l'expérience de l'extubation en postopératoire immédiat des pontages aorto-coronariens dans les années 1990 l'a montré, il est probable qu'on ne retrouve pas un effet franc si on s'intéresse à chaque élément du protocole de façon séparée. De plus, compte tenu de la complexité d'un protocole ERAS, une étude randomisée en aveugle est difficilement envisageable, et l'audit prospectif semble la forme d'évaluation la plus adaptée pour détecter une efficacité de protocoles de ce type[45]. Du fait même de

l'absence d'un élément central clair responsable des effets bénéfiques de l'ERAS il a été suggéré que la surveillance accrue liée à l'inclusion dans une étude observationnelle pouvait être responsable des bénéfices observés (effet Hawthorne). Une façon de limiter cet effet est de définir clairement les paramètres réalisant les critères de jugement et de s'y tenir. Dans notre protocole, les patients étaient sortants d'hospitalisation sur la base de critères objectifs identiques entres les 2 groupes.

Notons par ailleurs, qu'outre la réduction des durées de séjour, le groupe ERAS voit l'incidence des complications infectieuses diminuer. Ces deux bénéfices, en plus de marquer une évolution plus favorable pour le patient, seront possiblement assortis d'une baisse des coûts.

Pour finir, l'implémentation d'un protocole ERAS est un processus dynamique. Les différents éléments du bundle sont adaptés en continu, selon les données de la littérature, et selon un processus d'audit régulier des pratiques et des résultats[22]. Notre protocole est sujet à évolutions, notamment le remplacement de la VNI préventive par de l'Optiflow, sur la base d'une meilleure tolérance avec une efficacité similaire[46], l'implémentation d'une stratégie d'épargne transfusionnelle recourant à la supplémentation martiale et à l'EPO pré-opératoire, et un protocole de Goal Directed Therapy pour la gestion de la circultation extra-corporelle[47].

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