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Coronary artery bypass surgery without cardioplegia: hospital results in 8515 patients[†]

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Abstract

OBJECTIVES: Cardioplegic myocardial protection is used in most cardiac surgical procedures. However, other alternatives have proved useful. We analysed the perioperative results in a large series of patients undergoing coronary artery bypass (CABG) using cardiopulmonary bypass (CPB) and non-cardioplegic methods.

METHODS: From January 1992 to October 2013, 8515 consecutive patients underwent isolated CABG with CPB without cardioplegia, under hypothermic ventricular fibrillation and/or an empty beating heart. The mean age was 61.9 ± 9.5 years, 12.4% were women, 26.3% diabetic, 64% hypertensive; and 9.6% had peripheral vascular disease, 7.8% cerebrovascular disease and 54.3% previous acute myocardial infarction (AMI). One-third of patients were in Canadian Cardiovascular Society Class III/IV. Three-vessel disease was present in 76.5% of the cases and 10.9% had moderate/severe left ventricle (LV) dysfunction (ejection fraction <40%). A multivariate analysis was made of risk factors associated to in-hospital mortality and three major morbidity complications [cerebrovascular accident, mediastinitis and acute kidney injury (AKI)], as well as for prolonged hospital stay.

RESULTS: The mean CPB time was 58.2 ± 20.7 min. The mean number of grafts per patient was 2.7 ± 0.8 (arterial: 1.2 ± 0.5). The left internal thoracic artery (ITA) was used in 99.4% of patients and both ITAs in 23.1%. The in-hospital mortality rate was 0.7% (61 patients), inotropic support was required in 6.6% and mechanical support in 0.8, and 2.0% were re-explored for bleeding and 1.3% for sternal complications (mediastinitis, 0.8%). AKI, the majority transient, occurred in 1595 patients (18.9%). The incidence rates of stroke/transient ischemic attack (TIA) and acute myocardial infarction (AMI) were 2.6 and 2.5%, respectively, and atrial fibrillation/flutter occurred in 22.6% of cases. Age, LV dysfunction, non-elective surgery, previous cardiac surgery, peripheral vascular disease and CPB time were independent risk factors for mortality and major morbidity. The mean hospital stay was 7.2 ± 5.7 days.

CONCLUSIONS: Isolated CABG with CPB using non-cardioplegic methods proved very safe, with low mortality and morbidity. These methods are simple and expeditious and remain as very useful alternative techniques of myocardial preservation.

Keywords: Coronary artery bypass grafting • Myocardial protection • Non-cardioplegic techniques • Hypothermic ventricular fibrillation • On-pump heart beating • Outcomes

INTRODUCTION

During the early years of myocardial revascularization (CABG), various techniques were used for preservation of the myocardium. Methods that involved ventricular fibrillation with varying degrees of hypothermia and either aortic or local vessel occlusion (or both) were routinely used. But from the late 1970s, most surgeons have started to turn to cardioplegic techniques.

The enthusiasm for cardioplegic methods has made many surgeons unaware of modifications made in the older techniques that have resulted in continuously improved operative results. Still today, a respectable minority of surgeons and institutions are using or have returned to non-cardioplegic methods for myocardial protection. We had routinely used cardioplegia during CABG until the early 1990s. Since then, and after having assisted with a demonstration in a foreign department, we started using intermittent aortic cross-clamping, initially and moderate-hypothermic ventricular fibrillation, without clamping, in virtually all cases after 1992. This occurred after a preliminary comparative study of cardioplegia versus non-cardioplegia showed advantages of the latter, in our hands [1].

In the current study, we aimed at evaluating the perioperative results in a large cohort of patients undergoing isolated CABG

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with cardiopulmonary bypass (CPB) using non-cardioplegic methods at a single centre during the last two decades.

MATERIALS AND METHODS

Population, study design and definitions

We have performed a retrospective study of patients undergoing CABG under CPB from January 1992 to October 2013. Only patients undergoing isolated first operations and reoperations were included. Patients undergoing off-pump surgery or who had CABG combined with heart valve repair or replacement, resection of ventricular aneurysm or other surgical procedures were excluded.

The records of 8515 consecutive patients were identified and retrieved for analysis from our institutional prospective CABG registry. This group represents 94.8% of all patients undergoing isolated CABG during this time period (5.2% had incomplete records). Data had been registered prospectively on a standardized written chart by the involved surgeon and validated and inputted into a computerized database by the first author. Data collection and storage were supervised by the project coordinator (Manuel J. Antunes) for consistency, and aggregate outputs were periodically cross-checked against an independent clinical database.

The study included the following preoperative, operative and postoperative variables:

(i) Preoperative: age, body mass index, gender, hypertension, recent smoking, peripheral vascular disease, cerebrovascular disease, baseline serum creatinine, renal impairment, chronic obstructive pulmonary disease, cardiomegaly, previous myocardial infarction, recent myocardial infarction, unstable angina, Canadian Cardiovascular Society (CCS) class, non-elective surgery, previous percutaneous coronary intervention, previous cardiac surgery, left ventricular ejection fraction, left ventricular dysfunction, left main disease and extent of coronary disease (one-, two- or three-vessel). Definitions of these variables are presented in Table 1.

(ii) Operative: number and type of grafts, number of periods and time of aortic cross-clamp, use of coronary endarterectomy and CPB times.

(iii) Postoperative: In-hospital mortality and the following postoperative morbidity complications: inotropic support, mechanical support, cerebrovascular accident, mediastinitis, myocardial infarction, acute kidney injury (AKI), respiratory failure, reoperation for bleeding, atrial arrhythmias and length of hospital stay. The definitions of these events are presented in Table 2.

All these variables were analysed as events occurring from the date of the surgery to the date of discharge from the hospital, with the exception of mortality and mediastinitis, which were analysed as events occurring from surgery to discharge or after discharge, within 30 days of the procedure.

AKI was defined according to the consensus definitions established by the Acute Kidney Injury Network [2] using serum creatinine criteria. The highest serum creatinine level within 2 days preceding the surgery was taken as the preoperative creatinine level. Postoperative renal function was assessed using the serum level of creatinine daily for the first 3 days postoperatively, on postoperative day 5, before discharge and whenever clinically indicated. AKI was defined according to the Acute Kidney Injury Network criteria: increase of serum creatinine ≥0.3 mg/dl or increase ≥150–200% from baseline. Creatinine clearance was calculated using the Cockcroft–Gault formula.

Table 1: Definition of preoperative variables

Hypertension	Blood pressure exceeding 140/90 mmHg, or a history of high blood pressure or the need of antihypertensive medications
Recent smoking	Up to less than 4 weeks of surgery
Cardiomegaly	Cardiothoracic ratio >0.50 on a chest X-ray film
Diabetes mellitus	History of the disease and the patient currently receiving treatment with either oral medications or insulin
Anaemia	Haematocrit ≤34%
Chronic pulmonary disease	Patient requires pharmacological therapy for the treatment of chronic pulmonary compromise, or patient has a FEV_1 <75% of the predicted value
Cerebrovascular disease	Unresponsive coma >24 h, CVA or TIA
Previous cardiac surgery	Requiring opening of the pericardium
Recent myocardial infarction	Myocardial infarction within 30 days
Unstable angina	Rest angina requiring i.v. nitrates until arrival in the anaesthetic room
Left ventricular dysfunction	Ejection fraction <40%
Renal dysfunction	Creatinine clearance <90 ml/min (classified into three groups: MDRD1, 60–90 ml/min; MDRD2 – 30–59 ml/min; MDRD3, <30 ml/min)
Intra-aortic balloon pump	Preoperative intra-aortic balloon pump for haemodynamic reasons
Non-elective surgery	Urgent or emergent surgery

CVA: cerebrovascular accident; MDRD: modification of diet in renal disease; TIA: transient ischemic attack.

Preoperative and operative data

The baseline characteristics of the population are detailed in Table 3. The mean age was 61.9 ± 9.5 years, but 63.5 ± 9.6 years in the last decade (range 23–85 years; 11.5% <50 years), and 12.4% were female. More than a quarter (26.3%) of the patients were diabetic, 64% were hypertensive, 9.6% had peripheral vascular disease and 7.8% had cerebrovascular disease. A previous myocardial infarction was recorded in 54.3% of the patients, 9.3% of which had occurred within the 30 days preceding surgery. Renal impairment was present to some degree in the majority (80.1%) of patients, previous cardiac surgery had been performed in 1.3 and 33.4% were in CCS Class III/IV. Three-vessel disease was present in 76.5% of the cases, and 10.9% had moderate/severe left ventricular dysfunction (ejection fraction <40%). Emergency surgery was performed in 4.3% of the cases. All other operations were performed electively within a few days of referral (no waiting list).

Operative data are resumed in Table 3. The internal thoracic artery (ITA), which was the only type of arterial graft used in this population, was used in almost all patients (n = 8474; 99.5%). The rate of use of left ITA, right ITA and bilateral ITA use was, respectively, 99.4, 23.3 and 23.1%. Arterial grafts were used almost exclusively for the territories of the left anterior descending and circumflex arteries. The mean number of arterial anastomoses was

Table 2: Definition of outcome end-points

In-hospital mortality	Death occurring from index surgery to discharge or 30 days, whichever is longer
Inotropic support	Use of one or more inotropic drugs, for any length of time
Mechanical support	Use of intra-aortic balloon pump or ventricular (left, right or both) assistance (roller pumps, centrifugal pumps or extracorporeal membrane oxygenation) or both
Cerebrovascular accident (CVA)	Any neurological deficit of abrupt onset caused by disturbance in blood supply to the brain, lasting less (transient ischaemic attack) or more than 24 h (stroke)
Mediastinitis	At least one of the following: (i) an organism isolated from the culture of mediastinal tissue or fluid; (ii) evidence of mediastinitis seen during operation; (iii) one of the following conditions: chest pain, sternal instability or fever (>38°C), in combination with purulent discharge from the mediastinum that requires surgical intervention
Myocardial infarction	At least one of the following: (i) CK-MB (or CK if MB not available) ≥ 5 times the upper limit of normal; (ii) development of new Q-waves in two or more contiguous ECG leads
Acute kidney injury (AKI)	From the acute kidney injury network—serum creatinine criteria—which differentiates AKI into three stages: Stage (1) increase in serum creatinine of 0.3 mg/dl or increase to 150–200% from baseline; Stage (2) increase in serum creatinine to >200–300% from baseline; Stage (3) serum creatinine increase to >300% from baseline, serum creatinine 4.0 mg/dl, with acute increase of 0.5 mg/dl or any dialysis.
Respiratory failure	Indicate whether the patient had pulmonary insufficiency requiring postoperative ventilator support for >48 h or tracheostomy, or both
Atrial arrhythmias	New atrial fibrillation/flutter requiring treatment
Prolonged hospital stay	Days from index surgery to discharge >14 days

Table 3: Preoperative patient cohort characteristics and operative data

	Study population (*n* = 8515)[a]
Age (years)	61.9 ± 9.5
Body mass index (kg/m^2)	26.2 ± 3.1
Female	1053 (12.4%)
Hypertension	5448 (64.0%)
Diabetes mellitus	2243 (26.3%)
Recent smoking	918 (10.8%)
Peripheral vascular disease	816 (9.6%)
Cerebrovascular disease	661 (7.8%)
Baseline serum creatinine (mg/dl)	1.0 ± 0.6
Renal impairment	
On dialysis (regardless of serum creatinine level)	68 (0.8%)
Moderately impaired (CC: 50–85 ml/min)	5296 (62.2%)
Severely impaired (CC: <50 ml/min) off dialysis	1456 (17.1%)
Chronic pulmonary disease	262 (3.1%)
Cardiomegaly	857 (10.1%)
Previous myocardial infarction	4617 (54.2%)
Recent myocardial infarction	791 (9.3%)
Unstable angina	617 (7.2%)
Angina class III/IV, CCS	2843 (33.4%)
Previous cardiac surgery	110 (1.3%)
Previous PCI	612 (7.2%)
Left main disease	1998 (23.5%)
Non-elective surgery	361 (4.3%)
LV ejection fraction (%)	
>60	5444 (63.9%)
40–60	2142 (25.2%)
30–39	684 (8.0%)
<30	245 (2.9%)
Extent of vessel disease	
1–2 vessel	2003 (23.5%)
3 vessel	6512 (76.5%)
Operative data	
No. of distal anastomoses per patient	
Arterial	1.24 ± 0.45
Venous	1.51 ± 0.80
Total	2.76 ± 0.79
LITA use	8462 (99.4%)
RITA use	1981 (23.3%)
BITA use	1969 (23.1%)
Coronary endarterectomy	362 (4.3%)
CPB (min)	58.2 ± 20.7
Aortic cross-clamp time/patient (min)[b]	7.0 ± 5.2
Aortic cross-clamp time/no. of periods of cross-clamping (min)[b]	2.6 ± 2.1

BITA: bilateral internal thoracic artery; CC: creatinine clearance; CCS: Canadian Cardiovascular Society; CPB: cardiopulmonary bypass; LITA: left internal thoracic artery; LV: left ventricle; PCI: percutaneous coronary intervention; RITA: right internal thoracic artery; SD: standard deviation.
[a]Values are mean ± SD or *n* (%).
[b]Population: 913 patients in whom the aorta was cross-clamped at least once.

1.2 per patient. In addition, a mean of 1.5 venous anastomoses per patient were constructed. Hence, the average of the distal anastomoses was 2.7 per patient. Coronary endarterectomy was performed in 362 patients (4.3%), 313 (3.7%) to the right and 49 (0.6%) to the left coronary system.

Decision-making and procedures

In the last decade, decision-making and patient information in the elective setting followed the lines now recommended in the *ESC/EJCTS* guidelines on myocardial revascularization [3]. Institutional protocols were developed to implement the appropriate revascularization strategy at PCI centres without on-site surgery, and patients for whom decision-making was complex were discussed in inter-disciplinary discussion meetings and included decisions on hybrid intervention. Indications for revascularization, timing of surgery and procedural aspects followed contemporary guidelines and successive updates, especially with regard to the type of revascularization and graft material.

Surgical technique

CPB was conducted with non-pulsatile flow and mild hypothermia (30–32°C), and the systemic perfusion pressure was electively maintained at 55–65 mmHg. A left ventricular vent was always used, introduced through the right superior pulmonary vein and left atrium. Topical cooling was not used routinely.

The method predominantly used for the construction of the distal anastomoses was hypothermic ventricular fibrillation. In the majority of the patients (n = 7480; 89.3%) the aorta was not cross-clamped at any time. In the remaining patients, the aorta was cross-clamped at least once, mostly in the first 10 years of this series, with the only purpose of obtaining a drier field for a better exposure of the anastomotic and/or endarterectomy site. In recent years, aortic cross-clamping was not used in more than 98% of the patients (Fig. 1).

The empty beating heart method, without fibrillation, was frequently used in combination with ventricular fibrillation. Initially in this experience, a brief application of a direct electrical current was used to initiate ventricular fibrillation, but after a few years, grafting was initiated with the heart beating and ventricular fibrillation occurred spontaneously in about two thirds of the patients, as the heart cooled down or with manipulation.

Generally, the anastomoses to the right coronary artery or its branches on the inferior surface of the heart were constructed first, followed by the anastomoses to the branches of the circumflex system. Bypasses to the anterior descending artery and its diagonal branches were performed last. However, in the cases with ongoing ischaemia, the coronary artery branch likely to be involved was grafted first, immediately followed by the respective proximal anastomosis.

Control of the residual and/or collateral blood flow was obtained with the use of coronary occluders and/or a soft jet of carbon dioxide, or, rarely, with intravascular shunts. Occasionally, we would also slow down the pump flow transiently or, ultimately, cross-clamp the aorta.

Proximal anastomoses were performed last with a single period of side-clamping of the ascending aorta. When significant atherosclerotic disease of the ascending aorta was present, as assessed by visual inspection and palpation of the site of proximal vein graft anastomoses (if they had not been identified preoperatively), side-clamping was not used and the proximal anastomoses were performed as an open method during short periods of very low pump flow, as described in detail in a previous report [4].

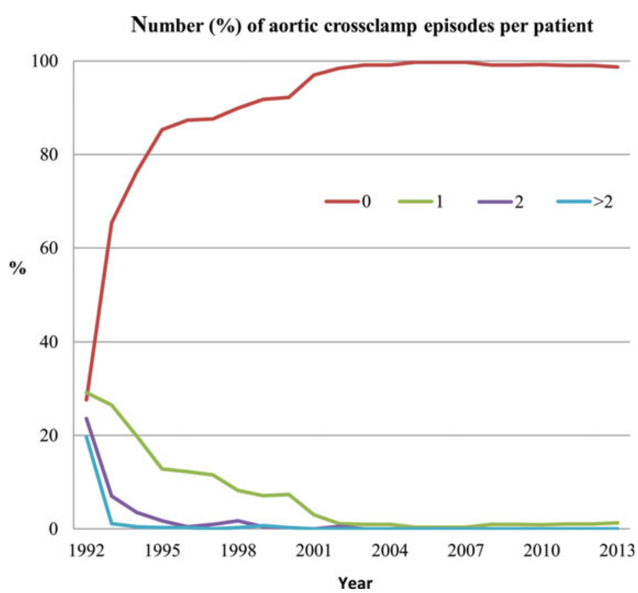

Figure 1: Percentage of patients undergoing isolated CABG without and with periods of aortic cross-clamping, per year. CABG: coronary artery bypass grafting.

A bloodless prime was used in more than 95% of the cases, whenever the preoperative haematocrit was greater than 35%, and blood was not administered unless that parameter fell below 20–25% during CPB. Collected mediastinal blood shed during the first 6 postoperative hours was reinfused.

Statistical analysis

Categorical variables are reported as frequency and percentage and continuous variables as mean ± standard deviation or median (interquartile range), as appropriate.

More than 50 preoperative and operative patient variables were available in the database, of which 23 potential risk factors were chosen, based on univariate screening, clinical knowledge and previous research. The risk factors selected for analysis are listed and defined in Table 1.

The entire database was initially used to develop the predictive logistic models. Univariate screening of all model eligible risk factors was performed using unpaired Student's t-test or the Mann–Whitney U-test for numeric variables, and the χ^2 test or Fisher's exact test for categorical variables. Variables with a P-value of <0.2 by univariate analysis were used for further analysis.

A multivariate stepwise logistic regression analysis was then performed for each of five dependent groups: in-hospital mortality (A); postoperative major morbidity complications: cerebrovascular accident (B), AKI (C), mediastinitis (D); and prolonged hospital stay (E), as defined in Table 2.

Because of the relatively small effective sample size of some events (mediastinitis), a P-value of less than 0.1 was selected for variable retention in the final regression model. Bootstrap analysis was used in combination with logistic regression analysis to select the final set of risk factors included in the model. In the bootstrap procedure, 200 samples of 8515 patients (the same number of observations as the original database) were sampled with replacement. A stepwise logistic regression analysis was applied to every bootstrap sample. If the predictors occurred in more than 50% of the bootstrap models, they were judged to be reliable and were retained in the final model.

The risk-prediction model was validated internally by randomly drawing 200 samples, each containing 100% of the total number of subjects. The risk-prediction model was applied to each sample to calculate an individual sample area under the receiver operating characteristic (ROC) curve and then the mean and standard error of the mean, with 95% confidence intervals (95% CIs), for all 200 ROC values.

Data were analysed using IBM SPSS Statistics for Windows, Version 20.0. software (IBM Corp., Armonk, NY, USA).

RESULTS

Postoperative outcomes are presented in Table 4. The overall in-hospital mortality rate was 0.72% (n = 61). The interval between surgery and death ranged from 1 to 127 days [median: 6; interquartile range (IQR): 14], and ten of the deaths (16.4%) occurred beyond 30 days. The cause of death was identified for 60 of the 61 deaths. Of these, 38 (62.3%) were attributed to heart failure, i.e. to cardiac cause, 9 (14.8%) to neurological causes, 5 (8.2%) to

Table 4: Perioperative outcomes

	Study population (*n* = 8515)[a]
In-hospital mortality	61 (0.7%)
Perioperative morbidity	
Inotropic support	562 (6.6%)
<12 h	196 (2.3%)
12–24 h	193 (2.3%)
>24 h	173 (2.0%)
Mechanical support	64 (0.8%)
IABP	14 (0.2%)
VAD	34 (0.4%)
IABP plus VAD	16 (0.2%)
Cerebrovascular accident	223 (2.6%)
Mediastinitis	69 (0.8%)
Myocardial infarction	212 (2.5%)
Acute kidney injury[b]	
No AKI	6851 (81.1%)
AKI stage 1	1258 (78.8%)
AKI stage 2	253 (15.9%)
AKI stage 3	85 (5.3%)
Respiratory failure	45 (0.5%)
Reoperation for bleeding/cardiac tamponade	170 (2.0%)
Atrial arrhythmias	1924 (22.6%)
Length of hospital stay (alive), days (mean ± SD)	7.2 ± 5.7
Prolonged hospital stay (>14 days)	215 (2.5%)

IABP: intra-aortic balloon pump; VAD: ventricular assist device; SD: standard deviation.
[a]Values are expressed as *n* (%) or mean ± SD.
[b]*n* = 8447 (68 patients on preoperative dialysis were excluded).

haemorrhage, 3 (4.9%) to dysrhythmia and 3 (4.9%) to respiratory failure, pulmonary embolism and aortic dissection, one each. One cause of death remained unknown.

Five hundred and sixty-two patients (6.6%) required inotropic support but for longer than 24 h in only 2.0%. In addition, mechanical support (intra-aortic balloon pump, extracorporeal membrane oxygenation and/or other methods) was used in 64 patients (0.8%). Two hundred and twenty-three patients (2.6%) had a cerebrovascular accident (CVA) (stroke or TIA), with recovery in about half. Two hundred and twelve patients (2.5%) had electrocardiogram (ECG) and/or biochemical criteria of perioperative myocardial infarction.

The incidence rate of AKI was 18.9% (78.8% Stage 1, 15.9% Stage 2 and 5.3% Stage 3), but new renal replacement therapy was required in only 60 patients (0.7%). Atrial arrhythmias, the majority being atrial fibrillation, occurred in 1924 patients (22.6%).

One hundred and seventy patients (2.0%) required reoperation because of haemorrhage and/or cardiac tamponade, and 112 patients (1.3%) were reoperated for sternal wound complications, including 69 (0.8%) with the diagnosis of mediastinitis.

The mean hospital stay was 7.2 ± 5.7 days (median = 7 days) and, in general, patients were discharged to their home. Two hundred and fifteen patients (2.5%) had a prolonged hospital stay (>14 days).

Risk factors for increased mortality and major morbidity

The results of the logistic regression risk models for in-hospital mortality, for postoperative major morbidity complications (cerebrovascular accident, AKI and mediastinitis) and for prolonged hospital stay are summarized in Table 5. Age, LV dysfunction, non-elective surgery, previous cardiac surgery, peripheral vascular disease and CPB time were independent risk factors for mortality and major morbidity. In addition, female sex, non-elective surgery, known cerebrovascular disease and number of episodes of aortic cross-clamping were risk factors for postoperative stroke; recent smoking, bilateral internal thoracic artery (BITA) use, angina CCS Class III or IV and cardiomegaly for mediastinitis; abnormal creatinine clearance for AKI; and BITA use, peripheral vascular disease, chronic pulmonary disease and angina CCS Class III or IV for prolonged hospital stay. The risk model performance metrics are indicated in Table 6.

DISCUSSION

Non-cardioplegic techniques were used in the earliest days of coronary surgery, but most surgeons now use one of several forms of cardioplegia as an adjunct to CPB during coronary artery revascularization. There is no doubt that cardioplegia affords good protection of the myocardium, as demonstrated unequivocally by an endless number of reports dealing with its numerous variations.

However, this does not mean that non-cardioplegic methods, which are still used by many, result in lesser protection. We and others have demonstrated the safety and efficacy of these methods in primary and reoperative CABG, as well in higher risk patients [1, 5–7]. In fact, a recent meta-analysis, based on 13 studies, of which eight were randomized prospective trials, showed that intermittent ischaemic arrest provides equal or better protection in comparison with cardioplegic techniques [8]. Other studies that compared cardioplegic techniques with the on-pump beating heart technique showed that the latter provides better myocardial protection and early results, particularly in the setting of acute myocardial infarction [9, 10].

Among the advantages claimed for the non-cardioplegic methods are the more expeditious surgery, less haemodilution resulting in lesser usage of blood and blood products and, most importantly, the continuous 'natural' irrigation of the myocardium throughout the entire surgery (when aortic cross-clamping is not used). On the other hand, because of the constantly perfused myocardium, a technically more demanding distal anastomosis could be expected. In fact, retraction of the heart for exposure of lateral and posterior wall coronary arteries may be more difficult and a more bloody operative field is predictable, although not significantly different from that seen with the continuous blood cardioplegic techniques. But, in our experience, the empty heart permits adequate manipulation and easy access to all segments of the arteries to be bypassed.

Mortality is the most commonly studied outcome and is one of the indicators most frequently used to assess efficiency and quality of health care provided to patients submitted to all kinds of cardiac procedures, including myocardial revascularization. In this series, the global in-hospital mortality rate was 0.72%. This rate is generally lower than those published in the international literature for identical patient groups and using the same definition for reporting this event [11, 12]. However, although in-hospital mortality represents one of the most widely reported metrics to assess death after CABG, this is a short time period for the early risk, which extends up to 2–3 months [13].

Next to operative mortality, cerebrovascular accidents, especially stroke, are one of the most dreaded complications following CABG, not only for the devastating consequences to the patients and their families, but also for the vastly increased cost of

Table 5: Logistic regression risk models for in-hospital mortality (A); postoperative major morbidity complications: cerebrovascular accident (B), acute kidney injury (C), mediastinitis (D) and for prolonged hospital stay (E)

Model	Risk factor	Coefficient	*P*-value	Odds ratio	95% CI (OR)	
A	Age (per 1 year increase)	0.051	0.001	1.053	1.021	1.086
	LV dysfunction	0.881	0.004	2.414	1.324	4.400
	Non-elective surgery	1.252	0.001	3.496	1.686	7.250
	Previous cardiac surgery	1.687	0.002	5.405	1.865	15.666
	Peripheral vascular disease	1.295	<0.001	3.651	2.126	6.269
	CPB time (per 1 min increase)	0.009	0.004	1.009	1.003	1.015
	Constant	−9.350				
B	Age (per 1 year increase)	0.032	<0.001	1.033	1.016	1.049
	LV dysfunction	0.460	0.016	1.584	1.088	2.307
	No. periods of aortic cross-clamping	0.238	0.042	1.268	1.008	1.595
	CPB time (per 1 min increase)	0.005	0.022	1.005	1.001	1.010
	Non-elective surgery	0.550	0.037	1.733	1.033	2.907
	Female sex	0.556	0.002	1.743	1.234	2.462
	Cerebrovascular disease	1.020	<0.001	2.774	1.955	3.936
	Constant	−6.356				
C	Recent smoking	0.663	0.026	1.940	1.082	3.478
	BITA use	1.471	<0.001	4.356	2.679	7.081
	Angina CCS Class III or IV	0.538	0.029	1.712	1.056	2.776
	Cardiomegaly	1.031	0.001	2.805	1.565	5.025
	Constant	−5.837				
D	Peripheral vascular disease	0.227	0.026	1.255	1.027	1.533
	Cerebrovascular disease	0.303	0.008	1.353	1.082	1.693
	Cardiomegaly	0.325	0.001	1.384	1.141	1.679
	CPB time (per 1 min increase)	0.013	<0.001	1.013	1.009	1.017
	Angina CCS Class III or IV	0.174	0.012	1.190	1.040	1.362
	Non-elective surgery	0.733	<0.001	2.082	1.544	2.808
	Creatinine clearance groups_MDRD		<0.001			
	Creatinine clearance group MDRD1	−0.054	0.472	0.948	0.818	1.097
	Creatinine clearance group MDRD2	0.210	0.020	1.233	1.033	1.472
	Creatinine clearance group MDRD3	0.836	<0.001	2.308	1.548	3.441
	Constant	−2.411				
E	Age (per 1 year increase)	0.029	0.001	1.030	1.012	1.047
	LV dysfunction	0.738	<0.001	2.093	1.515	2.891
	No. of periods of aortic cross-clamping	0.353	<0.001	1.423	1.179	1.717
	CPB time (per 1 min increase)	0.005	0.029	1.005	1.001	1.010
	BITA use	0.791	<0.001	2.206	1.559	3.121
	Peripheral vascular disease	0.573	0.001	1.774	1.275	2.468
	Chronic pulmonary disease	0.839	0.002	2.315	1.379	3.886
	Angina CCS Class III or IV	0.394	0.003	1.483	1.141	1.927
	Constant	−6.343				

Table 6: Risk model performance metrics

	AUC (95% CI)	H-L test	H-L test *P*-value
Final mortality model	0.754 (0.688, 0.819)	7.530	0.481
Final CVA model	0.667 (0.629, 0.705)	3.962	0.861
Final mediastinitis model	0.741 (0.681, 0.801)	2.072	0.558
Final AKI model	0.602 (0.584, 0.619)	19.529	0.062
Final PLOS model	0.680 (0.643, 0.717)	4.768	0.782

AKI: acute kidney injury; CVA: cerebrovascular accident; H-L: Hosmer–Lemeshow; PLOS: prolonged hospital stay.

hospitalization and subsequent care. Additionally, it partially offsets the benefits of CABG over other forms of treatment, i.e. medical therapy and percutaneous revascularization procedures. In this series, the incidence rate of cerebrovascular accident was 2.6%, which is comparable with the incidence rates for isolated CABG coming from some studies [14, 15] but higher than the 1.6% reported by others [16, 17]. Most episodes were, however, transient, with recovery in ∼50% of the cases.

There is a consensus that the principal source of cerebral macroemboli is the ascending aorta. By potentially reducing the embolic consequences of manipulation of the aorta, fibrillatory arrest without aortic cross-clamping may decrease the incidence of cerebrovascular accidents in CABG. In a previously published study, we found that the number of periods of aortic cross-clamping was an independent risk factor for CVA (odds ratio of 1.3 per each episode of cross-clamping) [16]. Because of our early awareness of this fact, reinforced by the results of that study, we have progressively reduced the number of periods of cross-clamping, which have been consistently avoided since 2003 in more than 98% of the patients (Fig. 1). This is, probably, one of the causes of the decreasing incidence of CVA over time (Fig. 2).

Despite improvements in surgical, anaesthetic and perioperative care for cardiac surgery patients, AKI still remains a common postoperative complication [17]. The incidence of AKI depends critically on the manner in which it is defined. In this study, we

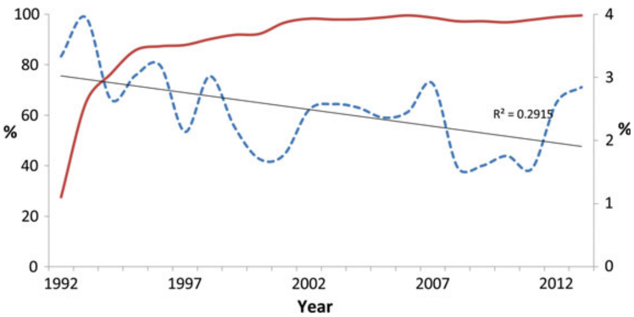

Figure 2: Inverse relationship observed between the performance of surgery without aortic cross-clamping (continuous line, left *Y*-axis) and the incidence of CVA over time (dashed line, right *Y*-axis). Continuous line, left *Y*-axis: percentage of cases without aortic cross-clamping; Dashed line, right *Y*-axis: incidence of CVA. CVA: cerebrovascular accident.

have used the strict Acute Kidney Injury Network criteria, which is widely accepted, and its utility in predicting the prognostic impact of AKI on in-hospital and long-term mortality has been evaluated in the cardiac surgical population [17, 18]. In our series, the incidence rate of AKI was only 19%. Of these, 79% had Stage I injury, which is a mild form and does not require renal replacement therapy. These findings are consistent with those of other studies, such as that by Li *et al.* who reported an incidence rate of AKI following elective CABG of 19.8% [18].

Mediastinitis is a severe complication of CABG and is associated with increased morbidity, mortality and cost. The incidence rate of this complication is usually reported between 0.4 and 4%, and was 0.8% (69 patients) in this series, a value that falls among the lowest commonly reported [19, 20], which may be related to faster surgery and less haemodilatation.

Adequate myocardial protection is an important issue regarding the safety and efficacy of these methods, but is difficult to evaluate. In this study, the incidence of use of inotropic (6.6%) or mechanical support (0.8%) and of myocardial infarction (2.5%) was low and compare favourably with those reported by others. We believe that, although not specific, these results constitute good clinical indicators of the safety and efficacy of non-cardioplegic methods in terms of myocardial protection. Finally, the low incidence rates of other causes of morbidity, as well as the mean duration of hospital stay (7.2 ± 5.7 days), also constitute good clinical indicators for a relatively smooth perioperative period and, presumably, are also an index of good myocardial protection.

In this study, we identified and confirmed the usual risk factors for mortality and major morbidity including age, LV dysfunction, non-elective surgery, previous cardiac surgery, peripheral vascular disease and CPB time. Not surprisingly, recent smoking and use of BITA were independent predictors of mediastinitis; abnormal creatinine clearance of AKI; and peripheral vascular disease, chronic pulmonary disease and angina CCS Class III or IV of prolonged hospital stay. BITA use also came up as a predictor of prolonged hospitalization, but this may have been influenced by its impact in the incidence of mediastinitis. Knowledge of the influence of these risk factors, most of which can be modulated, may help improve the results.

Limitations of the study

We recognise some limitations in this study, which may affect its conclusions. Although in-hospital mortality represents one of the most widely reported metrics to assess results after CABG, this is too short an interval for the evaluation of early results; consequently, the results reported in this work could be underestimated. In addition, the definition used to report the occurrence of MI is too narrow for accurate diagnosis of this event.

The impact of this technique on the quality of the anastomoses evaluated by long-term mortality, myocardial infarction and need for reintervention remains unknown in this series of patients due to the lack of angiographic follow-up.

Because of the historical component of this study, no international risk scoring system was used (the EuroSCORE was introduced only in 1999). However, it is our feeling, based on recent calculations using EuroSCORE II, that our patients in this unselected population have an average risk.

CONCLUSION

The results in this series demonstrate that non-cardioplegic methods afford good perioperative results, with low mortality and morbidity, in patients undergoing isolated CABG with CPB. They are simple and expeditious and remain very useful alternative techniques of myocardial preservation, and should be known to every surgeon who performs coronary surgery. In our experience, they are superior to cardioplegia. Our belief is so strong that in composite procedures, especially in associated valve surgery, the myocardial revascularization component is performed without cross-clamping, either before or after the valve surgery, which is performed under cardioplegia.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

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***Dr P. Sergeant** (Leuven, Belgium):* The authors present a study of a very large cohort of patients, 8515, covering a 20-year interval. The surgical procedure is CABG performed with CPB and without cardioplegia, most frequently using ventricular fibrillation. The authors present very respectable low hospital mortality.

The study population has an average age of 62 years and a very low female/male gender ratio. No international risk scoring system has been used in this manuscript, with all their limitations, and we're not going to discuss the limitations of the scoring systems, but it does not really allow for comparisons of risk profile. So based on a crude analysis that I was able to perform based on the data submitted, I have the impression it's a rather low-risk profile that is identified, with an average age of 61 years as just one example of one variable.

Arterial grafting using both internal artery grafts was very extensive, and I have to congratulate the authors for that, with up to 23% of the patients having both internal arteries constructed for grafting.

We identified in the manuscript a high use of 6.6% of inotropic support, not abnormal for this kind of surgical approach, even in the presence of short perfusion times at moderate hypothermia.

We were somewhat disappointed by the 5% of patients excluded due to missing files. I know some of these were also off-pump patients, but that's the only thing I could get out of the manuscript 'excluded due to missing files' in this prospective study. It's a prospective study and at the same time we're missing 5%.

In fact, we're also disappointed by the total absence of data after discharge from the primary hospital. As written down by Manuel in the manuscript, there is, of course, a whole lack of information of the early risk. So no data were reported even about the patients discharged home or to another hospital. So I'm not convinced that this manuscript presents early results. It doesn't even present in-hospital mortality or the whole time interval of the hospital mortality.

We have identified in these, as stated repeatedly, the low in-hospital mortality for as far as it is cited, but also the, very honestly, extremely high stroke rate of 2.6% for a rather low stroke risk population. I mean, there are very few patients in cardiac massage or in catastrophic situations.

I very much enjoyed the graphic that has been presented here also depicting the reduction over time of aortic clamping. I must say in my first reading of the manuscript I missed that the graphic showed aortic cross-clamping, so I thought it was clamping. So an in-depth reading of the manuscript identified that I had misread this. But that was well depicted here, that the graphic concerned also the total cross-clamping, so not the side clamping. So it's definitely no depiction of no-touch aortic technique and that has to be related to the 2.6% stroke risk.

I understand very well that stroke is a multifactorial issue and that total aortic clamping is just one element to reduce the stroke rate.

It is clear that several other elements play a role as there are cannulation, decannulation, side clamping of the aorta, the sandblasting effect of the perfusion on the walls, possibly low mean pressures during extracorporeal circulation, and the anticoagulation regimen after surgery. So there are whole numbers of elements that induce stroke.

I therefore have one single question to Prof Antunes: Do you believe that there is a future for surgical therapy when we have 2.6% stroke rate, when possible alternative either surgical techniques or interventional strategies can avoid this high stroke rate?

Dr Antunes: The first point that you raised is the rather low-risk profile. We do have that information in the database, but we didn't put it in here because we didn't think that it was really important. We don't want to compare our series with some others. It was rather an indication of the technique we used. It is, however, a totally unselected population because that includes 100% of the patients operated on during that period, there are no exclusions.

You made a reference of some missing files. There are no missing files. But when we reviewed the data, we found that the data was not complete for all patients. So, we decided not to include every patient that missed one of the data that should have been inserted. We thought with a greater than 8000 population that was a sure sample for doing this analysis.

In Portugal, virtually no patients are discharged to other wards or to other hospitals; the patients are discharged home only when they are well. That's why some patients died in hospital after up to 127 days. So this is total perioperative events that we are reporting. And we are quite sure that, again, if one patient did not have that information, we did not include it in the series.

The stroke rate is indeed one worry of ours. I don't want to compare this with off-clamp coronary surgery which was specifically designed to avoid the stroke. I must already say, however, that this includes minor and major stroke. That is, all types of neurological events that we could identify clinically. Most of the patients, of course, recovered from it.

Now, if I believe that this is a technique still valid today, I can only say that we took the care 20 years ago, of comparing our results, my personal results, with this technique in the first 100 patients with those of 100 patients before, and at that time it was better. And we still believe that 0.7% mortality for a total population of 8500 patients can stand comparison with any other method that are used, but I don't want to play the game, this is not a competition.

***Dr J. Puskas** (New York, New York, USA):* Just following on Dr Sergeant's comment regarding stroke, he identified numerous of the many factors that go into stroke in a perioperative period. He did not touch upon something that struck me about your technique, and that is, the introduction of a vent into the left atrium in a beating heart. If I heard your comments correctly, 90% of these patients did not have a clamp on the aorta.

Dr Antunes: Not a cross-clamp, that is correct.

Dr Puskas: Not a cross-clamp. And many were beating, some fibrillated, but you did not intentionally use an electric fibrillator to create fibrillation before introducing a vent into the left side of the atrium. I personally am very nervous about any violation of the left side of the heart in a situation where the heart can beat. Because even though the aorta is pressurized by the heart-lung machine, a little AI will fill the ventricle and it can eject, and it can eject air that one can inadvertently introduce into the left atrium. So I wonder if that might explain your relatively higher stroke rate and yet a relatively low mortality. Perhaps the strokes were due to air and the patients recovered and didn't die.

Dr Antunes: Well, that's a possibility, but I don't think so because the heart is filled up when we introduce the LV vent and that's done in the same way as we do for any other procedures on the left side of the heart, namely, aortic valve replacement.

We are careful that we don't introduce the vent without making sure that the heart is full, so that the air doesn't go in but rather comes out immediately on that. But again, it's a consideration.

Of course, we acknowledge some of the flaws in the paper identified in here and, if the paper passes the first evaluation for acceptance in the Journal, we will introduce some of the data that was requested by the discussants.