On-pump versus off-pump coronary artery bypass surgery in patients with preoperative anemia

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ABSTRACT

Objectives: The study objective was to evaluate the effects on early outcome and midterm survival of performing coronary artery bypass grafting with the off-pump technique in comparison with cardiopulmonary bypass (on-pump) in patients with preoperative anemia.

Methods: Consecutive adult anemic patients (preoperative hemoglobin <13.0 g/dL in men and <12.0 g/dL in women) resident in Puglia region who underwent isolated coronary artery bypass grafting between January 2011 and November 2013 were considered. Vital status was ascertained from the date of surgery to December 31, 2013. Odds ratio and hazard ratio (HR) were estimated. Propensity score methods were used to control for confounders.

Results: Of 939 anemic patients (234 female, aged 71 ± 9 years), 361 underwent operation with the off-pump technique and 578 underwent operation with the on-pump technique. Patients undergoing off-pump coronary artery bypass had a shorter intensive care unit length of stay, lower blood transfusion rate, and postoperative reduction in creatinine clearance. During a median follow-up of 18 months, 126 patients died: 46 in hospital (35 on-pump) and 80 after discharge (33 on-pump). In comparison with the off-pump technique, the on-pump technique had greater hospital mortality (odds ratio, 2.57; $P = .028$) and 30-day incidence of fatal events (HR, 2.67; $P = .026$). After a period without risk differences between groups (1-6 months; HR, 0.79; $P = .618$), a lower mortality in those undergoing the on-pump technique was detected (after 6 months HR, 0.35; $P = .014$). All results were confirmed in the 157 pairs of patients matched for propensity score, anemia grade, and surgery center.

Conclusions: In patients with low levels of preoperative hemoglobin, off-pump coronary artery bypass was associated with lower early morbidity and mortality but a greater risk of mortality during follow-up compared with on-pump coronary artery bypass. (J Thorac Cardiovasc Surg 2015;149:1018-26)

In anemic patients, the initial advantages of OPCAB are counterbalanced by worse survival during follow-up.

Central Message

Preoperative anemia is a risk factor for mortality and adverse outcome in patients undergoing coronary artery surgery. In anemic patients, OPCAB is associated with reduced operative mortality/morbidity; however, the initial advantages are counterbalanced by decreased survival during follow-up compared with on-pump surgery.

Perspective

The presented data impose 2 different considerations. First, the performance of CPB should be optimized to reduce short-term adverse events in anemic patients. The use of miniaturized CPB equipment, with reduced hemodilution and transfusion requirements, may lead to improved outcome. Second, OPCAB technique should provide documented complete and adequate myocardial revascularization to improve long-term survival.

See Editorial page 962.

Supplemental material is available online.

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Coronary artery bypass grafting (CABG) is a widely performed operation. It can be executed with the use of cardiopulmonary bypass (CPB) (on-pump) or off-pump coronary artery bypass (OPCAB), which has been developed to decrease perioperative complications related to the use of CPB.^{1,2} The optimal surgical strategy remains controversial without clear differences in early and long-term outcomes in randomized controlled trials.³⁻⁸ Recent observational and randomized studies have suggested that certain high-risk patient subgroups are more likely to benefit from an OPCAB approach, avoiding the deleterious effects of CPB.^{9,10} On the other hand, some studies have documented that the initial beneficial effects of OPCAB are counterbalanced by a worse survival during follow-up, probably because of a higher rate of incomplete revascularization or inaccurate anastomosis.^{11,12}

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CI	= confidence interval
CPB	= cardiopulmonary bypass
euroSCORE	= European System for Cardiac Operative Risk Evaluation
HR	= hazard ratio
ICU	= intensive care unit
OPCAB	= off-pump coronary artery bypass
OR	= odds ratio

Preoperative anemia is associated with a number of comorbidities, including advanced age, female gender, small body surface area, poor left ventricular ejection fraction, renal function impairment, congestive heart failure, unstable angina, and others,^{13,14} all of which are recognized risk factors for adverse outcome after cardiac surgery. Postoperative morbidity and mortality after cardiac surgery, specifically after CABG, are higher in anemic patients,¹³⁻¹⁶ and when preoperative anemia is added to risk classification scores, it improves their discrimination ability.¹⁷ Differences in postoperative outcomes between on-pump and OPCAB techniques have not been studied in patients with preoperative anemia. The aim of the present study was to compare in-hospital morbidity and short-term and midterm survival in patients with preoperative anemia undergoing on-pump coronary artery bypass or OPCAB surgery.

MATERIALS AND METHODS**Study Population**

Preoperative, intraoperative, and postoperative information on consecutive adult patients who underwent isolated CABG from January 1, 2011, to November 30, 2013, were gathered from the Puglia Regional Adult Cardiac Surgery Registry. The study is an initiative of the Health Regional Agency of Puglia region, which has been described.¹⁸ Briefly, by implementing an accurate database including prospectively clinical information and details on cardiac surgical procedures, the aims of the study were the evaluation of short- and long-term results of heart operations performed at the 7 adult cardiac surgery centers in the Puglia region (University of Bari–Policlinico Hospital Coordinating Centre, Anthea Hospital in Bari, Santa Maria Hospital in Bari, Villa Bianca Hospital in Bari, Villa Verde Hospital in Taranto, Vito Fazzi Hospital in Lecce, and Città di Lecce Hospital in Lecce). The study was conducted in accordance with the Declaration of Helsinki. According to institutional review board policy, it was determined that the research did not require informed consent. Hospital mortality risk prediction was carried out for each patient according to the European System for Cardiac Operative Risk Evaluation (euroSCORE) II model.¹⁹ Anemia was classified according to the preoperative hemoglobin level evaluated on the day of surgery. Patients with anemia according to the World Health Organization criteria were included.²⁰ Men with a hemoglobin level of 13.0 g/dL or greater and women with a hemoglobin level of 12.0 g/dL or greater were excluded. Anemia was classified as (1) mild if hemoglobin was 11.0 to 12.9 g/dL in men and 11.0 to 11.9 g/dL in women; (2) moderate if hemoglobin was 8.0 to 10.9 g/dL in both genders; or (3) severe if hemoglobin was less than 8.0 g/dL in both genders. Two of 7 cardiac surgery units of

region were excluded from the analysis because of systematic missing preoperative hemoglobin values.

Surgical Management

The conventional surgical approach was median sternotomy in most of the CABG procedures. Heparin was injected as a single bolus of 300 U/kg in on-pump procedures and 150 U/kg in OPCAB to obtain an activated clotting time of 400 and 300 seconds, respectively. An additional heparin bolus of 5000 units was injected if the activated clotting time decreased below these targets. After surgery, protamine sulfate was administered to neutralize heparin (1 mg protamine/100 U of heparin in on-pump procedures and 0.8 mg/100 U of heparin in OPCAB). CPB was established with aortic cannulation and right atrial cannulation with 2-stage cannula. Deep pericardial suture, heart stabilizer, intracoronary shunts, or snares were used to stabilize the heart and allow bloodless anastomoses according to the surgeon's preference. Patients with hemoglobin values less than 8 g/dL received transfusions after the induction of anesthesia. Indications for intraoperative homologous blood transfusion were hemoglobin less than 7 g/dL or hematocrit less than 0.21 to 0.22, and the postoperative cut-off was hemoglobin less than 8 g/dL or hematocrit less than 0.23 to 0.24.

End Point

The primary outcome was hospital mortality, defined as death occurring at any time after surgery during the hospital period in which the operation was performed. The secondary end point was hospital morbidity. The co-primary end point was midterm mortality. Vital status and dates of death to December 31, 2013, were obtained for resident in Puglia by linking regional Health Information System to the registry on the basis of an encrypted patient identifier. Follow-up was considered to be administratively censored on December 31, 2013, and was at least 1 month for all patients (maximum, 36 months).

Statistical Analysis

Data are shown as mean values $\pm$ standard deviation, and categorical variables are given as percentages. Because of the low number of patients with severe anemia, 2 anemia grades were analyzed: mild and moderate to severe. Intraoperative conversion from off-pump to on-pump CABG was analyzed according to the intention-to-treat principle based on the initial treatment assignment group (OPCAB). Preoperative patients' characteristics and individual risk factors were analyzed using a mixed model with centers fitted as random so that possible differences in data across surgical units could be considered. To control for selection bias as a result of nonrandom treatment assignment, the propensity analysis method was used to estimate the probability of being assigned to on-pump surgery.²¹ A multivariate mixed logistic regression model was developed including all risk factors and preoperative variables associated with the type of surgery. We matched participants, stratified by anemia grade, on the basis of closest propensity score (<0.15 in matched pairs). We used an automated matching procedure that for each OPCAB case selected 1 on-pump case that fulfilled the matching criterion. Patients were initially matched within the same cardiac surgeon, with the remaining patients who were matched by center.

In the entire sample, in-hospital mortality was analyzed by using mixed logistic regression analysis adjusting for linear predictor of propensity score.²¹ For the propensity analysis that required statistical methods appropriate for matched data, a conditional logistic regression model was used considering the pairs of selected patients. Odds ratios (ORs) for in-hospital mortality were estimated (on-pump vs OPCAB). The cumulative mortality curves, based on Kaplan–Meier analyses stratified by type of surgery, were compared with the Wilcoxon test. Survival analysis was performed by using Cox proportional hazards model with stratification by surgical center. Because of significant evidence against the proportional hazards assumption for the overall survival from surgery, we estimated separate hazard ratios (HRs) for each of the following time intervals

from the date of procedure: 0 to 30 days, 1 to 6 months, and more than 6 months. The first cut point (30 days) is one of the most frequently used definitions of operative mortality for analyses of short-term mortality after cardiac surgery. The second interval may be considered as the early postoperative period representative of the most seriously ill patients.²² We fitted 3 separate Cox regression models that were conditional on being alive at the beginning of each time interval. Confidence intervals (CIs) at the level of 95% were provided for OR and HR estimations. To evaluate whether anemia grade influenced mortality risk, each predictive model was also evaluated by including an interaction term. Statistical significance of the interaction between anemia grade and surgical technique in predicting mortality was tested using the likelihood ratio test by including the 2 variables and their cross-product term in the same multivariate model. The analyses were performed using STATA software, version 12 (Stata-Corp LP, College Station, Tex).

RESULTS

Study Population

A total of 2835 patients underwent CABG surgery; 35 patients (1.2%) with missing preoperative hemoglobin values were excluded. Of 2800 patients, 1013 (36.2%) had preoperative anemia. Anemia was significantly more frequent in OPCAB than on-pump surgery cases (41.9% vs 33.6%; $P < .001$). Seventy-four patients (7.3%) who were not residents of the Puglia region were excluded. The final study population included 939 patients (234 female, aged 71 ± 9 years); 361 underwent OPCAB, and 578 underwent on-pump. Anemia was mild in 651 patients (69.3%), moderate in 283 patients (30.1%), and severe in 5 patients (0.5%). Of 361 patients undergoing OPCAB, 244 (67.6%) had mild anemia, 113 (31.3%) had moderate anemia, and 4 (1.1%) had severe anemia. Among the 578 patients undergoing on-pump surgery, 407 (70.4%) had mild anemia, 170 (29.4%) had moderate anemia, and 1 (0.2%) had severe anemia. Intraoperative conversion from OPCAB to on-pump surgery occurred in 13 patients. Median sternotomy was the surgical approach in all on-pump procedures and in 355 (98.3%) OPCAB procedures. In the on-pump surgery group, cardioplegic solution was blood-based in 99.3% of procedures, cold in 59.7% of procedures, antegrade in 88.4% of procedures, and both antegrade-retrograde in 11.2% of procedures, with 81 ± 29 minutes and 49 ± 21 minutes for CPB and crossclamp duration, respectively. Table 1 shows the preoperative characteristics of patients according to CABG technique. In comparison with patients undergoing the on-pump technique, patients undergoing OPCAB were significantly older, with a greater prevalence of hyperlipidemia, renal impairment, extracardiac arteriopathy, previous percutaneous coronary intervention, lower preoperative hemoglobin, lower number of diseased vessels, and anastomoses performed.

Propensity Score Matching

Propensity score successfully matched 157 on-pump cases to 157 OPCAB cases (model details in Table

E1). The score performed well in balancing measured confounders: There was no significant difference between matched patients with regard to preoperative characteristics (Table 1) and in mean propensity score (0.53 vs 0.54).

Postoperative Outcome

Table 2 shows the postoperative outcome according to study groups. The total hospital length of stay was 10 ± 13 days versus 12 ± 11 days ($P < .001$) for OPCAB and on-pump surgery, respectively. In the entire sample adjusting for propensity score, OPCAB cases had a shorter stay in the intensive care unit (ICU) and a lower rate of postoperative red blood cell transfusions and postoperative creatinine clearance reduction. The total ICU length of stay was 2.9 ± 4.2 days in OPCAB cases and 3.4 ± 6.4 days in on-pump cases ($P = .004$). In the propensity-matched group, patients undergoing OPCAB had a shorter stay in the ICU and a lower rate of postoperative red blood cell transfusions.

Hospital Mortality

During hospital admission, 46 patients died (euroSCORE II 3.7%): 35 patients (6.1%, euroSCORE II 3.4%) in the on-pump group and 11 patients (3.1%, euroSCORE II 4.1%) in the OPCAB group. The estimated effect of the on-pump technique over in-hospital mortality was quantified by an unadjusted OR of 2.10 (95% CI, 1.03-4.28; $P = .042$) and 2.57 (95% CI, 1.11-6.01; $P = .028$) after correction for propensity score. The analysis corrected for anemia grade confirmed the greater mortality in the on-pump group compared with the OPCAB group (OR, 2.16; $P = .035$ and OR, 2.61; $P = .027$ for the model with anemia and the model with anemia and propensity score, respectively) without interaction between the surgical technique and the anemia grade (likelihood-ratio test for the interaction $P = .316$ and $P = .322$ for the model with anemia and the model with anemia and propensity score, respectively). In the matched group, in-hospital mortality was observed in 17 patients (5.4%). In comparison with OPCAB, a significantly greater incidence of fatal events was observed in the on-pump group (13 vs 4 deaths; 8.3% vs 2.6%) with an OR of 2.58 (95% CI, 1.13-14.2; $P = .032$). In-hospital mortality was greater, but not significant, in moderate-to-severe anemia than in mild anemia (6.3% vs 4.3%, $P = .200$ in the entire sample and 10.2% vs 7.4%, $P = .557$ in the matched group).

Overall Mortality

During a median period of 18 months, 80 fatal events were detected after the discharge: 33 in the on-pump group and 47 in the OPCAB group. A total of 126 patients died as a result of the surgery through December 31, 2013:

TABLE 1. Characteristics of patients according to coronary artery bypass grafting technique in the entire sample and in propensity-matched groups

	Entire sample		<i>P</i> value	Propensity matched		<i>P</i> value
	On-pump	OPCAB		On-pump	OPCAB	
	n = 578	n = 361		n = 157	n = 157	
Age (y)	70 ± 8	72 ± 9	.010	71 ± 8	71 ± 9	.784
Female gender	25.8%	23.5%	.419	27.4%	22.9%	.347
Body mass index (kg/m ²)	27.4 ± 4.1	27 ± 4.2	.100	27 ± 4.2	26.9 ± 4.1	.701
Hypertension	80.4%	85.3%	.696	82.2%	82.8%	.891
Hyperlipidemia	54.8%	62.3%	.035	59.9%	57.3%	.572
Current smoker	17.5%	12.5%	.235	19.7%	11.5%	.056
Atrial fibrillation	4.3%	5.0%	.781	6.4%	4.5%	.469
Renal impairment			<.001			.084
Creatinine clearance >85 mL/min	27.5%	15.8%		21.0%	17.2%	
Creatinine clearance 50-85 mL/min	50.7%	47.1%		57.3%	52.9%	
Creatinine clearance ≤50 mL/min	18.9%	31.0%		19.7%	24.2%	
On dialysis	2.9%	6.1%		1.9%	5.7%	
Extracardiac arteriopathy*	21.8%	31.0%	.010	21.0%	25.5%	.338
Neurologic dysfunction*	1.6%	1.7%	.494	1.3%	1.9%	.657
Previous cardiac surgery*	1.7%	1.4%	.082	4.5%	0.6%	.069
Bronchodilators or steroids for lung disease*	4.8%	8.3%	.957	8.3%	6.4%	.533
Critical preoperative state*	4.5%	3.6%	.548	4.5%	1.9%	.178
Diabetes			.073			.098
Only oral hypoglycemic agents	25.6%	15.8%		26.1%	16.6%	
On insulin	25.3%	33.8%		26.8%	32.5%	
NYHA class			.551			.223
I	34.8%	32.4%		33.1%	31.8%	
II	46.9%	49.6%		52.2%	45.9%	
III	17.6%	17.2%		14.6%	22.3%	
IV	0.7%	0.8%		0.0%	0.0%	
CCS class 4 angina	17.1%	15.5%	.593	18.5%	15.9%	.547
Left ventricular ejection fraction			.503			.759
>50%	47.6%	50.4%		46.5%	48.4%	
31%-50%	45.3%	44.3%		45.9%	45.9%	
≤30%	7.1%	5.3%		7.6%	5.7%	
Recent myocardial infarction within 90 d	41.9%	44.9%	.096	51.6%	42.0%	.085
Systolic pulmonary artery pressure			.800			.831
31-55 mm Hg	15.2%	13.0%		15.9%	15.3%	
>55 mm Hg	1.0%	1.7%		1.3%	0.6%	
Urgency*			.218			.507
Elective	64.0%	50.4%		57.3%	61.8%	
Urgent	32.5%	45.2%		36.3%	33.8%	
Emergency operation	3.5%	4.4%		6.4%	4.5%	
Previous percutaneous coronary intervention	17.8%	29.4%	.000	23.6%	24.2%	.884
Hemoglobin (g/dL)	11.4 ± 1.1	11.3 ± 1.2	.011	11.4 ± 1.2	11.3 ± 1.2	.149
Moderate-to-severe anemia	29.6%	32.4%	.153	31.2%	31.2%	—
Diseased vessel			<.001			.497
1	1.4%	14.4%		4.5%	3.2%	
2	15.7%	26.9%		28.7%	24.8%	
3	82.9%	58.7%		66.9%	72.0%	
Anastomoses/patient	3.0 ± 0.8	2.3 ± 1.2		2.8 ± 1.2	2.6 ± 0.9	
Anastomoses/patient			<.001			.566
1	1.4%	28.8%		5.1%	5.1%	
2	24.6%	35.2%		48.4%	49.7%	
≥3	74.0%	36.0%		46.5%	45.2%	

(Continued)

TABLE 1. Continued

	Entire sample		<i>P</i> value	Propensity matched		<i>P</i> value
	On-pump	OPCAB		On-pump	OPCAB	
	n = 578	n = 361		n = 157	n = 157	
Preoperative medications within 7 d						
ACE inhibitor/Sartans	63.5%	72.3%	.266	66.2%	74.5%	.077
Beta-blockers	62.5%	69.0%	.334	67.5%	72.6%	.303
Calcium antagonists	18.5%	22.7%	.054	13.4%	21.0%	.068
Statins	68.9%	75.9%	.776	74.5%	72.6%	.686
Aspirin	70.9%	82.0%	.453	75.2%	80.3%	.269
Ticlopidine or clopidogrel	28.4%	29.4%	.795	28.7%	26.8%	.706

Mean values $\pm$ standard deviation or percentage of patients. OPCAB, Off-pump coronary artery bypass; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; ACE, angiotensin-converting enzyme. *Variables definition according to euroSCORE II model.¹⁹ Creatinine clearance (mL/min) = [(140–age) $\times$ (body weight)]/72 $\times$ [serum creatinine (mg/dL)] $\times$ 0.85 (if female).

68 in the on-pump group and 58 in the OPCAB group. Cumulative mortality after the procedure by study groups in the whole population is shown in Figure 1, A, and in the propensity-matched group in Figure 1, B. After an initial lower risk, OPCAB surgery increased the cumulative mortality more than on-pump surgery (Figure 1). The Wilcoxon test for equality of overall survival (Figure 2, A and B) was not significant in both the entire population and the propensity-matched subgroup ($P = .432$ and $P = .491$, respectively). On Cox regression analysis including the type of surgery as the covariate, there was statistical evidence against the proportional hazards assumption ($P = .001$). Figure 2 shows cumulative mortality, by type of surgery, separately for the intervals 0 to 30 days, 1 to 6 months, and more than 6 months from the

procedure. During the first 30 days after the surgery (Figure 2, A and B), there was a significantly greater mortality for on-pump surgery than OPCAB surgery. In the interval from 1 to 6 months (Figure 2, C and D), there was a slightly, but not significant, lower incidence of events in the on-pump group than in the OPCAB group. Six months after surgery (Figure 2, E and F), survivors who underwent on-pump surgery demonstrated a significantly better outcome than patients who underwent OPCAB. Table 3 shows the results of Cox regression analyses according to the 3 intervals adjusting for propensity score and anemia grade. The analysis corrected for anemia grade confirmed that, compared with the OPCAB group, the on-pump group had greater mortality within 30 days from the surgery with a lower incidence of fatal events

TABLE 2. Postoperative outcome according to coronary artery bypass grafting technique in the entire sample and the propensity-matched groups

	Entire sample				Propensity matched		
	On-pump	OPCAB	<i>P</i> value	Adjusted	On-pump	OPCAB	<i>P</i> value
	n = 578	n = 361		<i>P</i> value	n = 157	n = 157	
ICU duration of stay >72 h	22.1%	18.0%	.051	.003	28.0%	17.8%	.026
Postoperative red blood cell	64.2%	58.4%	.001	.007	68.2%	55.4%	.020
Postoperative intra-aortic balloon pump	1.6%	0.8%	.287	.080	1.9%	0.0%	.250
Creatinine clearance reduction >50%	8.5%	7.7%	.020	.038	11.7%	7.5%	.167
Need for hemodialysis	5.2%	4.7%	.915	.889	4.5%	5.4%	.782
Atrial fibrillation	26.7%	24.7%	.061	.076	29.9%	23.6%	.206
Reexploration due to bleeding	3.0%	3.0%	.706	.766	3.8%	2.5%	.530
Gastric complications	1.0%	1.9%	.242	.427	1.3%	2.5%	.341
Confusion/delirium	2.3%	2.2%	.119	.095	3.2%	1.9%	.484
Stroke or TIA	0.9%	0.3%	.139	.355	2.5%	0.6%	.215
Reintubation	4.9%	3.6%	.454	.451	5.7%	3.2%	.292
Sepsis	1.4%	1.1%	.404	.787	1.9%	1.3%	.657
Overall stay >30 d	4.0%	2.5%	.723	.668	1.3%	0.6%	1.000
Hospital mortality	6.1%	3.0%	.027	.044	8.3%	2.5%	.032

Mean values $\pm$ standard deviation or percentage of patients. Adjusted P value at mixed logistic multivariate analysis correcting for propensity score. Creatinine clearance reduction calculated as the ratio between postoperative creatinine clearance at the creatinine peak and preoperative value. Sepsis was intended as evidence of infection and more than 1 of the following clinical findings (systemic inflammatory response syndrome criteria): body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/min, hyperventilation evidenced by respiratory rate >20 breaths/min, or partial pressure of arterial carbon dioxide <32 mm Hg, white blood cell count $>12,000$ cells/ μL or $<4000/\mu\text{L}$. OPCAB, Off-pump coronary artery bypass; ICU, intensive care unit; TIA, transient ischemic attack.

FIGURE 1. Overall cumulative mortality from cardiac surgery according to CABG technique in the entire sample (A) and the propensity-matched group (B). *OPCAB*, Off-pump coronary artery bypass; *CI*, confidence interval.

FIGURE 2. Cumulative mortality conditional on being alive at the beginning of each time interval according to CABG surgery in the entire sample (A, C, and E) and the propensity-matched group (B, D, and F). *OPCAB*, Off-pump coronary artery bypass.

TABLE 3. Cox model hazard ratios

	On-pump vs OPCAB		PH test	LRT
	HR	P value	P value	P value
Months after the surgery				
Up to 1	2.67 (1.13-6.32)	.026	.702	—
1-6	0.79 (0.32-1.96)	.618	.964	—
>6	0.35 (0.15-0.81)	.014	.324	—
Adjusted for anemia grade				
Months after the surgery				
Up to 1	2.64 (1.12-6.27)	.027	.635	.088
1-6	0.80 (0.32-1.97)	.627	.922	.547
>6	0.34 (0.15-0.79)	.013	.249	.879

HR with 95% CI adjusted for propensity score. LRT is for the interaction between anemia grade (moderate-to-severe vs mild) and surgical technique. OPCAB, Off-pump coronary artery bypass; PH, proportional hazards (test of Cox model); LRT, likelihood ratio test; HR, hazard ratio. Bold indicates significant *P* values.

after the first 6 months. No interaction was detected between the surgical technique and the anemia grade (likelihood-ratio test for the interaction was not significant in each analyzed interval) (Table 3). In the matched population, similar results were observed in the 3 intervals (Figure 2, B, D, and F) with HRs of 2.86 (1.03-7.93; *P* = .044) during the first 30 days, 1.08 (0.31-3.74; *P* = .902) from 1 to 6 months, and 0.18 (0.04-0.80; *P* = .024) 6 months after the surgery. Anemia grade was associated with overall mortality (*P* = .022 in the entire population and *P* = .003), with greater cumulative mortality in patients with moderate-to-severe anemia than in patients with mild anemia (24 months after the surgery, the estimated mortality was 19.3% vs 13.1% and 25.0% vs 10.3% in the matched group).

DISCUSSION

By using data on CABG procedures from a regional cardiac surgery registry, we found that the use of the OPCAB technique resulted in reduced rates of hospital mortality with a shorter ICU length of stay, lower red blood cell transfusion, and lower reduction in postoperative creatinine clearance compared with the on-pump technique. However, this initial benefit in mortality and morbidity was lost during follow-up with a greater number of deaths after hospital discharge in OPCAB cases.

The standard surgical approach for CABG includes the use of cardiac arrest coupled with CPB. The on-pump technique is associated with certain perioperative complications due to the use of CPB and manipulation of the ascending aorta: myocardial damage, cerebrovascular accidents, and potential neurocognitive, renal, and pulmonary dysfunction.^{1,2} To avoid these complications, the OPCAB technique was developed to perform surgery on the beating heart with the use of stabilizing devices.^{1,2} Currently, this technique is used in less than 1 in 5 patients who undergo surgical coronary revascularization

according to data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database regarding isolated primary CABG operations.²³ However, the percentage of CABG operations performed off-pump has steadily declined over the last years: The use of off-pump procedures peaked in 2002 (23%) and again in 2008 (21%), followed by a progressive decline in off-pump frequency to 17% by 2012.²³ In the Regional Cardiac Surgery Registry of Puglia, on approximately 4000 isolated CABG surgeries recorded from January 2011 to December 2013, approximately 1000 were OPCAB (27%), with a trend for reduction (from 29% in 2011 to 25% in 2013). The proportion of patients who underwent OPCAB selected in our population was high (37%) because of the high-risk profile of anemic patients for whom OPCAB was more frequently used than for nonanemic patients (42% vs 34%).

Several randomized controlled trials and registry data comparing on-pump and OPCAB have been published.^{3-8,24-26} Nevertheless, the 2 techniques generally have been considered similar for main short-term outcomes with large-scale prospective randomized studies that demonstrated the absence of superiority for mortality.^{7,8,27} OPCAB has been found to be associated with less bleeding, less renal dysfunction, a shorter length of hospital stay, and less neurocognitive dysfunction, with beneficial effects for patients at high risk for complications.^{1,2,9,10} However, none of the previous prospective or retrospective studies have specifically addressed the outcome of anemic patients.

In our evaluation, the incidence of hospital mortality is high, particularly for on-pump cases. This is in line with other reports: Boening and colleagues²⁸ reported 12.9% 30-day mortality in anemic patients undergoing on-pump CABG compared with 2.2% of nonanemic patients.²⁸ Anemia is characterized by a significant increase of major morbidity and is considered a risk factor for operative mortality and complications in adult cardiac operations.¹³⁻¹⁷ Anemia can be considered a marker for severe underlying diseases and is often associated with other concomitant comorbidities.¹⁴ Moreover, preoperative anemia is one of the major determinants of low hematocrit values during CPB, and low hematocrit during CPB is an independent predictor of adverse outcome after CPB surgery.²⁹ It is likely that anemic patients may experience (especially during CPB) inadequate oxygen delivery during the operation, triggering a dysoxia-related multiorgan dysfunction. In our cohort, OPCAB was more frequently used in patients with preoperative anemia than in those with normal preoperative hemoglobin values, confirming that the OPCAB technique is usually preferred in high-risk patients. Our results suggest that patients undergoing CABG surgery with a low preoperative hemoglobin

concentration have a lower hospital mortality rate if receiving the OPCAB technique, despite the fact that patients undergoing OPCAB had a greater risk profile than patients undergoing the on-pump procedure. However, to overcome the issue of different characteristics between groups, we performed a regression adjustment and propensity matching to compare groups of patients with the same preoperative and operative profile. The selection matching procedure, stratified by anemia grade and surgery center, performed well in balancing confounders between groups. Our results showed, irrespective of the adjustment method, a lower rate of hospital mortality (primary short-term end point) in the OPCAB group than in the on-pump group with reduced morbidity (secondary short-term end points). For anemic patients, we confirm data recently obtained from the Society of Thoracic Surgeons National Cardiac Database that compared OPCAB with on-pump CABG, and better early outcomes were observed for OPCAB correcting for preoperative risk (30 risk factors), center, and surgeon.³⁰ Moreover, procedures with a higher predicted risk of operative mortality had the largest apparent benefit, similar to our results in anemic patients.³⁰

Anemia could be corrected during and after the operation. Patients undergoing CPB more frequently received red blood cell transfusion than patients undergoing OPCAB. Unfortunately, our database does not allow specifying when transfusions occurred, but it is likely that a certain amount of transfusions were prescribed perioperatively to correct hemodilution caused by CPB. Transfusion of blood products is another recognized risk factor for adverse events after cardiac surgery.³¹ The pathophysiologic mechanism by which transfusions might harm has not been fully elucidated, but it is known that erythrocytes undergo irreversible morphologic and biochemical changes during storage. As a result, after transfusion, they can promote a proinflammatory state, impair tissue oxygen delivery, and exacerbate tissue oxidative stress. This in turn can contribute to organ dysfunction and explain, at least in part, the increased hospital mortality in on-pump cases.

Conversely, the initial advantage in mortality and morbidity observed in the short-term was lost during follow-up. Mortality after hospital discharge, particularly the first 6 months after the surgery, was significantly worse in the OPCAB group. We are unaware of the cause of death, but several previous reports have indicated decreased graft patency,¹¹ fewer grafts, and incomplete revascularization as a possible consequence of the OPCAB operation.¹² In a large registry, Hannan and colleagues²⁵ showed that the initial OPCAB benefit in mortality was lost during the 3-year follow-up, with a significantly greater need for repeated revascularization in these patients.²⁵

Study Limitations

The present multicenter study is subject to all the limitations of observational studies, although the statistical analyses aimed to control for confounding factors and to compare groups of patients with the same preoperative and operative profile. The association between surgical technique and postoperative outcome was confirmed in the matched subgroups, and differences in mortality between on-pump and OPCAB cases were also evaluated correcting for patients' anemia grade. No interaction was detected between surgical technique and anemia grade, but a greater sample size is required to better explore this relationship. Our study population included consecutive patients who underwent isolated CABG surgery in 5 of 7 centers of Puglia over 36 months with midterm mortality automatically available for residents in the region. The 74 excluded patients (postdischarge vital status unavailable for nonresident in Puglia region) confirmed general short-term results: no deaths in the 21 patients undergoing OPCAB and 3 deaths in the 53 patients undergoing on-pump surgery (0% and 6%, respectively).

CONCLUSIONS

In patients with preoperative anemia, OPCAB leads to better short-term results and on-pump CABG performs better in the midterm with fewer fatal events during follow-up.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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TABLE E1. Mixed logistic regression model: Predictors of on-pump surgery

	Coefficient ± SE	P value
Age (y)	−0.006 ± 0.012	.613
Hyperlipidemia	0.371 ± 0.214	.083
Renal impairment		
Creatinine clearance >85 mL/min	Reference	
Creatinine clearance 50-85 mL/min	−0.396 ± 0.268	.141
Creatinine clearance ≤50 mL/min	−0.861 ± 0.323	.008
On dialysis	−0.774 ± 0.512	.130
Extracardiac arteriopathy	−0.358 ± 0.215	.096
Previous percutaneous coronary intervention	−0.414 ± 0.221	.061
Hemoglobin (g/dL)	0.047 ± 0.083	.569
Diseased vessel		
1	Reference	
2	−0.425 ± 0.671	.527
3	−0.367 ± 0.671	.584
Anastomoses/patient		
1	Reference	
2	3.508 ± 0.578	<.001
≥3	5.391 ± 0.604	<.001

SE, Standard error.