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Perioperative Use of Dobutamine in Cardiac Surgery and Adverse Cardiac Outcome

Propensity-adjusted Analyses

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Background: **Catecholamines, mainly dobutamine, are often administered without institutional guidelines or prespecified algorithms in cardiac surgery. The current study assessed the consequences on clinical outcome of catecholamines simply based on the clinical judgment of the anesthesiologists after cardiopulmonary bypass in adult cardiac surgery.**

Methods: **Consecutive patients were enrolled in a nonrandomized cohort study. Factors associated with perioperative use of catecholamines and with outcomes were recorded prospectively to conduct bias adjustment, including propensity scores. Major cardiac morbidity (*i.e.*, ventricular arrhythmia, use of an intraaortic balloon pump and postoperative myocardial infarction) and all-cause intrahospital mortality were the primary and secondary endpoints, respectively. Results are expressed as odds ratio (OR) [95% confidence interval].**

Results: **During the study, 84 of 657 patients (13%) received catecholamines, most often dobutamine (76 of 84, 90%). A higher incidence of both major cardiac morbidity (30 *vs.* 9%; $P < 0.001$; OR, 4.2 [2.5–7.3]) and all-cause intrahospital mortality (8 *vs.* 1%; $P < 0.001$; OR, 12.9 [3.7–45.2]) was observed in the catecholamine group compared with the control group. After adjusting for channeling bias and confounding factors, catecholamine administration remained significantly associated with major cardiac morbidity after propensity score stratification (OR, 2.1 [1.0–4.4]; $P < 0.05$), propensity score covariance analysis (OR, 2.3 [1.0–5.0]; $P < 0.05$), marginal structural models (OR, 1.8 [1.3–2.5]; $P < 0.001$), and propensity score matching (OR, 3.0 [1.2–7.3]; $P < 0.02$), but not with all-cause intrahospital mortality.**

Conclusions: **These results suggest that dobutamine should only be administered when the benefit is judged to outweigh the risks.**

LOW cardiac output syndrome commonly occurs after cardiac surgery with cardiopulmonary bypass (CPB) and often requires inotropic support to achieve an adequate hemodynamic status.[1] Despite a wide range of available positive inotropic agents, no consensus exists regarding the treatment of low cardiac output syndrome.[2] Some evidence supports the popularity of dobutamine, particularly in comparison with dopamine.[3,4] Nevertheless, tachycardia is more likely to occur with dobutamine,[5] and a significant increase in heart rate is the dominant method of increasing cardiac output with dobutamine in post-CPB patients.[6] The expected benefits of dobutamine could thus be counteracted by myocardial oxygen imbalance after CPB in cardiac surgical patients.[1,7]

Factors related to use of positive inotropic drugs, such as older age, decreased left ventricular function, emergency and/or redo surgery, combined surgery, or longer durations of CPB, have been well identified in coronary and valve surgery patients.[8–10] Independently of the patient, identity of the attending anesthesiologist has been also reported as a strong predictor of inotropic support in a multivariate model analysis.[9] Cardiac monitoring has proved to be an important tool to guide inotropic use after cardiac surgery.[11] Despite this, the results of a recent French multicenter trial showed that catecholamine (mainly dobutamine) administration was simply based on mean arterial pressure value in more than 80% of patients.[12] Moreover, no institutional guidelines or prespecified algorithms were used in 91% of cardiac centers.[12] Taken together, these data suggest an important variability in prescribing post-CPB inotropic agents among cardiac anesthesiologists and a possible inappropriate use of dobutamine for many patients. Indeed, the simple clinical judgment of anesthesiologists may not always reflect the right judgment.[13]

The appropriate use of catecholamines has been considered in carefully designed studies[8–10] as a marker of severity after cardiac surgery, because patients who require myocardial stimulation are at greater risk than patients who do not. Consequently, the impact of inappropriate use of catecholamines is difficult to assess in

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routine clinical practice, the patients with catecholamines being considered as more sick. In terms of clinical outcome, a recent systematic literature review has been unable to find any data relating to the effects of dobutamine and other catecholamines on major clinical outcome or survival in the cardiac surgical setting.[2]

We hypothesized that an adverse postoperative outcome would occur more frequently when use of catecholamines is simply based on the clinical judgment of the cardiac anesthesiologists. The current prospective risk-adjusted observational study was therefore designed to estimate the influence of perioperative catecholamines administration on both major cardiac morbidity and mortality after elective adult cardiac surgery with CPB.

Materials and Methods

Patient Population

Consecutive adult patients undergoing cardiac surgery with CPB were enrolled from January 2003 to December 2004 at the Saint-Martin Hospital (Caen, France). The study was prospective, open-labeled, nonrandomized, and observational and was conducted under the auspices of a large quality assurance project evaluating clinical practices in cardiac surgery approved by all staff members of the Department of Anesthesiology. Preoperative patient characteristics as well as intraoperative variables were collected prospectively into a database for later analysis. The study was approved by an institutional review board (Comité Consultatif pour la Protection des Personnes se prêtant à la Recherche Biomédicale Pitié-Salpêtrière, Paris, France). Because data were collected during routine care of patients which conformed to standard procedures currently used in our institution, authorization was granted to waive written informed consent. Inclusion criteria were elective coronary artery bypass grafting, aortic or mitral valve replacement, and combined surgery (coronary artery bypass grafting plus aortic or mitral valve replacement). Patients with high risk of postoperative cardiac morbidity and mortality (emergency surgery [<24 h], reoperative procedures, recent history [<4 weeks] of acute myocardial infarction and abnormal preoperative values of cardiac troponin I [>0.6 ng/ml]) were excluded from the study.

Inotrope Management

Neither institutional guidelines nor prespecified algorithms dictating inotropic support during separation from CPB were used in our hospital. Consequently, the perioperative use of catecholamines for difficult weaning from CPB was left to the discretion of each attending anesthesiologist.

Perioperative Management

All patients were premedicated with oral lorazepam (2.5 mg the evening before surgery and on the morning of surgery). β-Blocking agents and statins were given until the day of surgery in chronically treated patients. Standardized total intravenous anesthesia (target control propofol infusion, remifentanil and pancuronium bromide) and monitoring techniques (five-lead electrocardiogram with computerized analysis of ST segment, invasive arterial blood pressure, and central venous pressure) were used in all patients and complied with routine practice in our hospital.[14,15] The use of pulmonary artery catheter and/or transesophageal echocardiography was left to the discretion of each attending anesthesiologist. Antifibrinolytic therapy, either tranexamic acid (15 mg/kg twice) or aprotinin (2×10^6 KIU before CPB, 2×10^6 KIU in prime, and 500,000 KIU/h during surgery), was routinely administered. CPB was performed under normothermia (>35.5°C) in all types of surgery, and myocardial protection was achieved by intermittent anterograde or combined (anterograde plus retrograde) warm blood cardioplegia, as previously described.[14,15] Boluses of ephedrine and/or phenylephrine were intraoperatively given as necessary to maintain mean arterial pressure between 50 and 80 mmHg. The heart was defibrillated after aortic unclamping if sinus rhythm did not resume spontaneously. No calcium was used at termination of CPB. All patients were admitted postoperatively into the cardiac intensive care unit (ICU) for at least 48 h and were assessed for tracheal extubation within 1–8 h of arrival in the ICU. The decision to terminate catecholamine infusions was left to the attending physician who took care of the patients in the ICU. Standard postoperative care included blood glucose control (<8 mM), intravenous heparin (200 U/kg) in patients with valve disease, and aspirin (300 mg, oral or intravenous) associated to low-molecular-weight heparin (nadroparin, 2,850 U Anti-Xa, subcutaneous; Fraxiparine®; Sanofi-Synthelabo, Paris, France) in patients with coronary artery disease, beginning 6 h after surgery in the absence of significant mediastinal bleeding (>50 ml/h). β-Blocking agents and statins were given as soon as possible postoperatively in chronically treated patients. Postoperative care was delivered by anesthesiologists in the ICU and by cardiac surgeons in the ward.

Clinical Outcome

Patients were divided into two groups according to the perioperative administration of at least one catecholamine within 48 h after CPB (catecholamine group) or not (control group). The patients who received delayed postoperative catecholamines (>48 h) for secondary complications occurring in ICU were excluded from the analysis. To analyze the in-hospital outcome, the following postoperative variables were recorded: time of extubation, duration of hospitalization and stay in the ICU, Simplified Acute Physiologic Score,[16] total chest drainage, postoperative renal dysfunction, serum cardiac troponin I level 24 h after surgery, cardiac complications,

and in-hospital mortality. Cardiac complications included new atrial fibrillation or flutter, sustained ventricular arrhythmias necessitating treatment, requirement of an intraaortic balloon pump in the ICU, and postoperative myocardial infarction. Diagnostic criteria for postoperative myocardial infarction were the appearance of new Q waves of more than 0.04 s in duration and 1 mm deep or a reduction in R waves of more than 25% in at least two continuous leads of the same vascular territory, as previously described.[14,15] Daily 12-lead electrocardiogram recordings were assessed by two experienced physicians blinded to the clinical and biochemical information. Postoperative renal dysfunction was defined as an increase of 30% or greater in preoperative to maximum postoperative serum creatinine level within 7 days after surgery.[17]

Endpoints

Major cardiac morbidity and overall mortality were chosen as study endpoints. The primary endpoint was major cardiac morbidity, defined as one of the following: (1) any postoperative sustained ventricular arrhythmia necessitating treatment, (2) the need for an intraaortic balloon pump in the ICU, or (3) postoperative myocardial infarction as defined above and previously.[14,15] The secondary endpoint was overall mortality, defined as death at any time during the stay in the hospital. Causes of death were recorded and classified as cardiac (heart failure, myocardial infarction, ventricular arrhythmia) or noncardiac (hemorrhage, respiratory failure, sepsis, or other causes). Sudden death was considered as death from a cardiac cause.

Statistical Analysis

According to a preliminary study in our institution, we made the hypothesis that the primary endpoint occurred in less than 10% of patients without catecholamines and more than 30% of patients with catecholamines, and we estimated that 15% of patients undergoing conventional cardiac surgery needed perioperative catecholamines. Assuming an α risk of 0.05 and a β risk of 0.10, we determined that at least 667 patients should be analyzed in the study (NQuery Advisor 3.0; Statistical Solutions Ltd., Cork, Ireland).

Data are expressed as mean $\pm$ SD, or median [95% confidence interval] for nonnormally distributed variables, or number and percentage. Differences between patients reaching or not reaching the endpoints and receiving or not receiving catecholamines were compared using chi-square or Fisher exact tests for categorical variables and two-tailed, unpaired *t* test or Wilcoxon rank sum test for continuous variables, as appropriate.

The association between an adverse postoperative outcome and the administration of catecholamines was evaluated by the odds ratio (OR) and its 95% confidence interval. Because the study was not randomized, the patients receiving perioperative catecholamines could not have the same risk of postoperative adverse outcome as those who did not. Therefore, potential indication or "channelling" biases were adjusted for by developing a propensity score[18] for receiving catecholamines. A stepwise logistic regression analysis was performed to select baseline variables that were associated with the use of catecholamines. Variables were entered into the model at a cutoff *P* value of 0.50. Consequently, clinically relevant but not significant factors were also included to derive a full nonparsimonious model. Using these selected variables, a propensity score was estimated by maximum likelihood logistic regression analysis. Calibration of the final logistic model was assessed using the Hosmer-Lemeshow statistic.[19]

We performed four different methods described in detail by Austin *et al.*[20] to avoid channelling bias. These were stratification, regression, weighting, and matching on the propensity score. Each of these methods included the catecholamine group as well as variables associated with the endpoint as explanatory cofactors to also avoid confounding bias not associated with the use of catecholamines and partial confusion bias associated with quartile stratification. First, the endpoint probability was modeled in a nonconditional logistic regression analysis, adjusting for propensity score quartiles. We chose quartiles instead of quintiles because the latter yielded to strata without patient in one group.[21] Second, we used the estimated propensity score as a covariate in a multivariate nonconditional logistic regression model. Third, we used the concept of marginal structural models,[22] also known as inverse probability of weighted treatment. Fourth, we performed a one-to-many greedy five- to one-digit technique to match two controls (control group) by one case (catecholamine group). "Greedy five-to one-digit match" means that the cases were first matched to controls on five digits of the propensity score. For those that did not match, cases were then matched to controls on four digits of the propensity score. This continued down to a one-digit match on propensity score for those that remained unmatched. If a one-digit match was not possible, the case remained unmatched and was not included in the matched case–control analysis. In this matched sample, baseline characteristics included in the propensity score were compared between cases and controls by paired tests. Because *P* values could be influenced by sample size, we complemented the use of statistical testing by the standardized difference. The probability of endpoint was modeled in a conditional logistic regression analysis including the catecholamine group as explanatory factor.

A *P* value of less than 0.05 was considered significant, and all *P* values were two-tailed. Statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC).

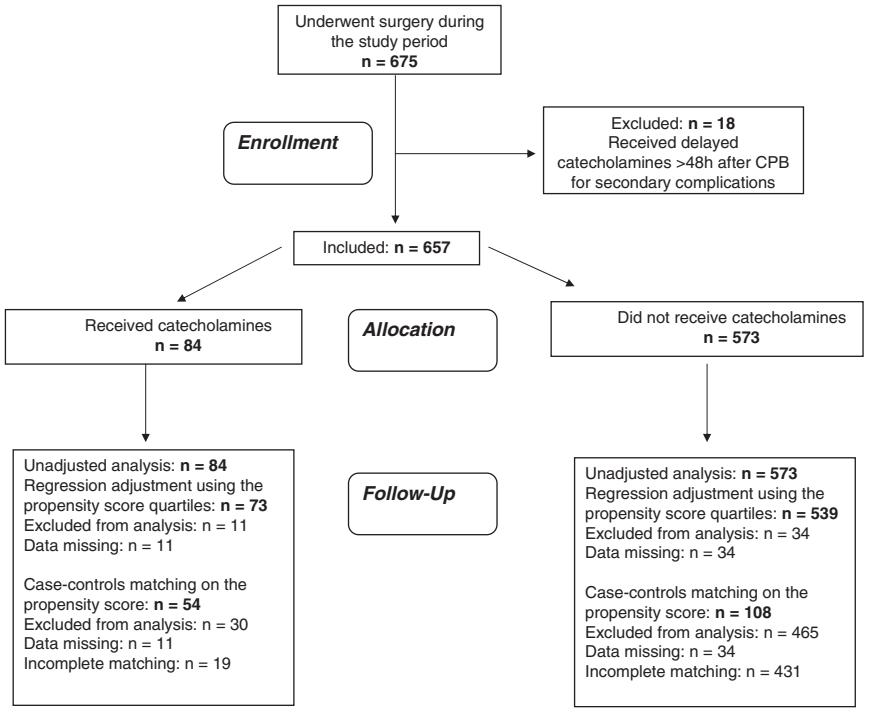

Fig. 1. The study flow chart. CPB = cardiopulmonary bypass.

Results

Baseline Characteristics and Postoperative Outcome

Six hundred fifty-seven consecutive patients fulfilled inclusion criteria and were enrolled prospectively into the study (fig. 1). Among them, 84 patients (13%) received catecholamines intraoperatively and/or during the first postoperative hours (day 0) and were assigned to the catecholamine group. A low dose of dobutamine ($<10\ \mu g \cdot kg^{-1} \cdot min^{-1}$) for a short postoperative period and remaining nearly unchanged throughout the duration of administration was used in 75 (89%) of these patients (table 1). Baseline characteristics and postoperative outcome of the cohort are shown in table 2. As expected, some of the variables are significantly different between groups (table 2). No patient required an intraaortic balloon pump during the ICU stay. Eleven patients (2%) died before discharge from hospital. Among them, 7 (1%) were from cardiac causes and 4 (0.6%) were from noncardiac causes.

Table 1. Characteristics of Perioperative Administration of Catecholamines in 84 Patients Undergoing Conventional Cardiac Surgery with Cardiopulmonary Bypass

Number of catecholamines	
1	73 (87)
≥2	11 (13)
First-line catecholamine	
Dobutamine	75 (89)
Dopamine	6 (7)
Norepinephrine	3 (4)*
Dobutamine dose, $\mu g \cdot kg^{-1} \cdot min^{-1}$	
Initial	4.8 ± 2.3
Maximal	6.0 ± 3.4
Duration of administration, h	31 [8–54]

Values are expressed as number (%), mean ± SD, or median [95% confidence interval].

* One patient who received norepinephrine as a first-line catecholamine also received dobutamine as a second-line catecholamine.

Propensity Analysis

The 11 variables associated with the use of catecholamines at $P < 0.5$ and included in all propensity score models are shown in table 3. The concordance index (c index) was 0.82 and the Hosmer-Lemeshow test was not significant ($P = 0.30$), indicating a strong ability to differentiate between patients receiving or not receiving catecholamines and good calibration, respectively. Our propensity score (which reflected the probability that a patient would receive catecholamines) ranged from 0.007 to 0.981 in the catecholamine group and from 0.003 to 0.724 in the control group. Figure 2 depicts the distribution of the propensity score by quartiles as a function of catecholamine treatment.

Using greedy matching, none were matched on five or four digits, 24 patients were matched on three digits, 48 patients were matched on two digits, and 36 patients were matched on one digit. None of the variables associated with the use of catecholamines in the overall cohort differed significantly between treated cases and controls after matching on the propensity score, as shown in table 3.

Table 2. Baseline Characteristics and Postoperative Outcome of Patients Undergoing Conventional Cardiac Surgery without and with Perioperative Administration of Catecholamines

Variable	Control Group, n = 573	Catecholamine Group, n = 84	*P* Value
Age, yr	73 ± 8	74 ± 7	0.47
Men/women	367/206 (64/36)	54/30 (64/36)	0.97
Body mass index, kg/m^2	26.8 ± 4.0	26.4 ± 4.0	0.47
EuroSCORE[23]	5.0 [4.8–5.2]	6.0 [5.5–6.5]	0.03
Diabetes mellitus	94 (16)	18 (21)	0.25
COPD	50 (9)	16 (19)	0.003
Hypertension	381 (66)	55 (65)	0.85
Stroke	30 (5)	4 (5)	0.85
Left ventricular ejection fraction, %	66 ± 11	58 ± 14	<0.001
Serum creatinine, μm	99 ± 37	100 ± 25	0.39
Creatinine clearance, ml/min	62 ± 20	58 ± 19	0.18
Preoperative medications			
Nitrates	199 (35)	28 (33)	0.80
Calcium blockers	145 (25)	18 (21)	0.44
β-Blockers	231 (40)	33 (39)	0.85
RAS inhibitors	217 (38)	33 (39)	0.80
Diuretics	178 (31)	50 (60)	<0.001
Surgery			
CABG	202 (35)	19 (23)	0.06
Valve replacement	190 (33)	30 (36)	
Combined	181 (32)	35 (42)	
Cardiopulmonary bypass time, min	107 ± 29	120 ± 35	<0.001
Aortic cross clamping time, min	69 ± 25	75 ± 28	0.04
Postoperative period			
Time of extubation, h	7 [6–8]	8 [1–15]	<0.001
Duration of stay in ICU, days	3 [3–3]	4 [3–5]	<0.001
Hospital discharge, days	8 [8–8]	8 [6–9]	<0.001
SAPS II score	30 [29–30]	32 [30–34]	<0.001
Total chest drainage, ml	624 ± 290	791 ± 456	0.002
Postoperative cTnI level, ng/ml	7.4 [4.6–10.2]	13.3 [1.7–24.9]	<0.001
Atrial fibrillation or flutter	182 (32)	39 (46)	0.008
Myocardial infarction	23 (4)	7 (8)	0.08
Ventricular arrhythmia	39 (7)	22 (26)	<0.001
Postoperative renal dysfunction	68 (12)	20 (24)	0.002
Major cardiac morbidity*	52 (9)	25 (30)	<0.001
In-hospital mortality	4 (1)	7 (8)	<0.001

Values are expressed as mean ± SD, number (%), or median [95% confidence interval].

* Defined as ventricular arrhythmia and/or need for intraaortic balloon pump in the intensive care unit (ICU) and/or postoperative myocardial infarction (see Materials and Methods).

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; cTnI = cardiac troponin I 24 h after surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; RAS = renin–angiotensin system; SAPS = Simplified Acute Physiologic Score.[16]

Potential Confounding Factors

The following variables were associated with outcomes and served as potential cofactors in all multivariate analyses: (1) the number of catecholamines, European System for Cardiac Operative Risk Evaluation,[23] combined surgery, preoperative use of diuretics, cardiopulmonary bypass time, Simplified Acute Physiologic Score,[16] preoperative left ventricular ejection fraction, aortic cross clamping time, postoperative serum cardiac troponin I level, postoperative serum creatinine level, and renal dysfunction for major cardiac morbidity; (2) combined surgery and postoperative serum cardiac troponin I level for global in-hospital mortality.

Endpoints

The incidence of major cardiac morbidity was 25 in 84 (30%) *versus* 52 in 573 (9%) in the catecholamine and control groups, respectively (OR, 4.2 [2.5–7.3]; $P < 0.001$). After controlling for other risk factors, the perioperative use of catecholamines was associated with increased major cardiac morbidity, regardless of the propensity score method used, as indicated in table 4. Separate analysis of myocardial infarction and ventricular arrhythmia showed that the use of catecholamines was significantly associated with ventricular arrhythmia (propensity score matching: OR, 3.1 [1.3–7.5]; $P < 0.02$) and not significantly associated with postoperative myocardial infarction (propensity score matching: OR, 2.3 [0.5–10.4]; $P = 0.3$).

The incidence of all-cause intrahospital mortality was 7 in 84 (8%) *versus* 4 in 573 (1%) in the catecholamine and control groups, respectively (OR, 12.9 [3.7–45.2]; $P < 0.001$). After adjusting for the propensity score, the administration of perioperative catecholamines was not

Table 3. Comparison of Variables Predicting the Use of Catecholamines and Included in the Propensity Score before and after Matching

	Before Matching			After Matching		
Propensity Score Variable	Catecholamine Group, n = 84	Control Group, n = 573	*P* Value (*d**)	Catecholamine Group, n = 54	Control Group, n = 108	*P* Value (*d**)
Preoperative diuretics	50 (60)	178 (31)	<0.001 (94)	28 (52)	53 (49)	0.73 (6)
Postoperative renal dysfunction	20 (24)	68 (12)	0.002 (100)	10 (17)	18 (17)	0.76 (0)
Chronic obstructive pulmonary disease	16 (19)	50 (9)	0.003 (111)	6 (11)	15 (17)	0.59 (35)
EuroSCORE[23]	5.8 ± 2.5	5.2 ± 2.3	0.03 (12)	5.4 ± 2.4	5.3 ± 2.4	0.79 (2)
Left ventricular ejection fraction, %	58 ± 14	66 ± 11	<0.001 (12)	61 ± 12	62 ± 11	0.54 (2)
SAPS II	34 ± 10	29 ± 6	<0.001 (16)	32 ± 6	31 ± 5	0.58 (3)
Postoperative serum creatinine, μm	121 ± 50	112 ± 53	<0.16 (7)	111 ± 41	111 ± 28	0.97 (0)
Time of extubation, h	15 ± 32	8 ± 15	<0.001 (21)	11 ± 34	9 ± 6	0.74 (6)
Aortic cross clamping time, min	75 ± 28	69 ± 25	0.04 (8)	72 ± 27	69 ± 27	0.52 (4)
Cardiopulmonary bypass time, min	120 ± 35	107 ± 29	<0.001 (12)	112 ± 30	111 ± 32	0.99 (1)
Preoperative cTnI level, ng/ml	0.09 ± 0.20	0.04 ± 0.13	<0.3 (25)	0.09 ± 0.20	0.06 ± 0.16	0.47 (14)

Values are expressed as mean ± SD or number (%).

* *d*: Standardized difference defined as $d = \frac{100 \times |\bar{x}_{\text{catecholamine}} - \bar{x}_{\text{control}}|}{\sqrt{\frac{s^2_{\text{catecholamine}} + s^2_{\text{control}}}{2}}}$, where $\bar{x}_{\text{catecholamine}}$ and $\bar{x}_{\text{control}}$ are the mean of the variable between the catecholamine group and the control group, and s^2 is the variance.

cTnI = cardiac troponin I; EuroSCORE = European System for Cardiac Operative Risk Evaluation; SAPS = Simplified Acute Physiologic Score.[16]

significantly associated with the risk of intrahospital mortality (table 4). Similarly, the propensity score–matched subgroup analysis (n = 162) did not identify a significant association between catecholamines and in-hospital mortality (adjusted OR, 2.0 [0.1–32.0]; $P = 0.63$). The relatively low number of events in one group corrupted the validity of other propensity score methods.

Sensitivity Analyses

We conducted additional analyses using similar models as indicated in table 4 after exclusion of patients (n = 8) who received any other catecholamine than dobutamine. We observed similar results on major cardiac morbidity (OR, 2.3 [1.1–5.1]; $P < 0.04$ in the covariate adjustment analysis and OR, 3.0 [1.2–7.3]; $P < 0.02$ in the propensity score matching analysis).

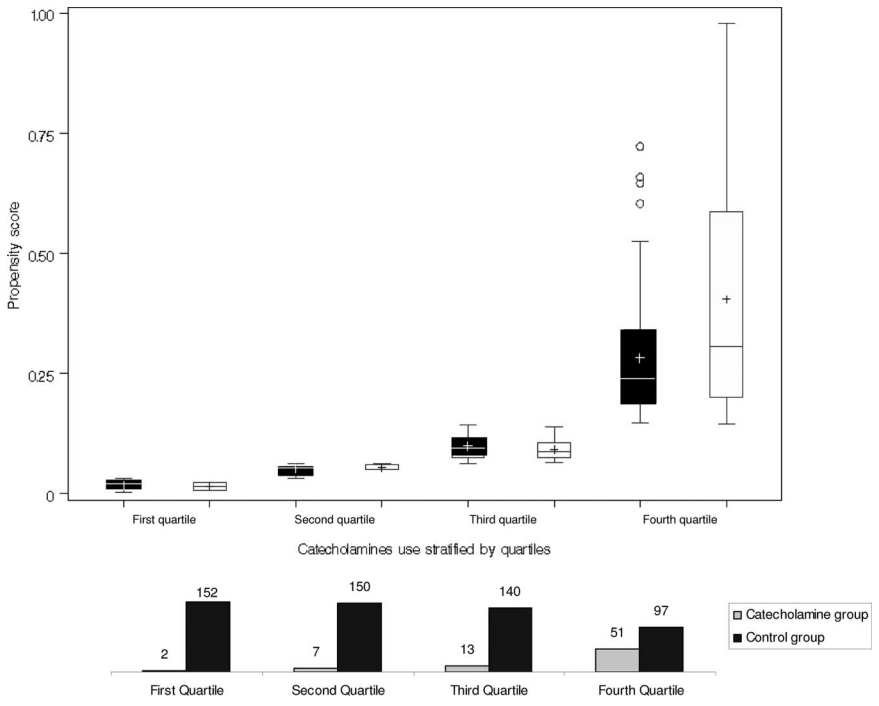

Fig. 2. Comparison of propensity scores for the use of catecholamines by group and quartiles. The figure contains eight box plots. The *lower* and *upper ends* of each box denote the 25th and 75th percentiles, respectively. The *solid horizontal line* through each shaded box denotes the median of the distribution, and the *cross* denotes the mean. The *vertical solid black lines* (whiskers) reach out to 1.5 × the interquartile range. The *circles* above the whiskers denote individual extreme observations. The *bars* represent the number of subjects included in each quartile.

Table 4. Catecholamines: Crude and Adjusted Effects for Major Cardiac Morbidity and Global In-hospital Mortality Endpoints

Method	Odds Ratio	95% Confidence Interval	*P* Value
Major cardiac morbidity			
Crude	4.2	[2.5–7.3]	<0.001
Stratifying on PS quartiles*	2.1	[1.0–4.4]	<0.05
Covariate adjustment using PS†	2.3	[1.0–5.0]	<0.05
Marginal structural models‡	1.8	[1.3–2.5]	<0.001
PS matching	3.0	[1.2–7.3]	<0.02
In-hospital mortality			
Crude	12.9	[3.7–45.2]	<0.001
Stratifying on PS quartiles	—	—	—
Covariate adjustment using PS§	2.7	[0.4–20.5]	0.33
Marginal structural models	—	—	—
PS matching	2.0	[0.1–32.0]	0.63

* Model adjusted for higher cardiac troponin I level 24 h after surgery ($P < 0.001$) and longer cardiopulmonary bypass time ($P < 0.001$). † Model adjusted for higher cardiac troponin I level 24 h after surgery ($P < 0.001$), combined surgery ($P < 0.04$) and higher propensity score (PS) ($P < 0.15$). ‡ Model adjusted for higher cardiac troponin I level 24 h after surgery ($P < 0.001$), combined surgery ($P < 0.001$), longer aortic cross clamping time ($P < 0.009$), and lower left ventricular ejection fraction ($P < 0.001$). § Model adjusted for higher PS ($P < 0.01$).

We also conducted additional analysis using similar model as indicated in table 4 after exclusion of patients (n = 5) who received catecholamines and had a propensity score above 0.7238 corresponding to the highest propensity score in the control group. Again, we observed similar results on major cardiac morbidity (OR, 2.2 [1.0–4.7]; $P < 0.05$ in the covariate adjustment analysis).

Discussion

The main finding of the current study is that the perioperative use of dobutamine, simply based on the clinical judgment of the attending anesthesiologist, is associated with increased postoperative major cardiac morbidity of patients undergoing cardiac surgery with CPB.

In daily clinical practice, inotropic agents are normally administered to the patients whose condition is serious. In the current observational study, clinicians controlled the treatment that was assigned and catecholamines were administered at the entire discretion of the attending anesthesiologist. Consequently, differences in other covariates that could have influenced postoperative outcome and led to biased estimates of catecholamines side effects cannot be excluded.[24] This major drawback has been partly offset by use of propensity analysis, a complex statistical technique that can reduce some of the potential for bias resulting from lack of randomization.[25] In contrast to traditional regression, the validity of propensity score analysis based on stratification does not rely on a goodness-of-fit test (Hosmer-Lemeshow statistic) or discrimination of the propensity score model (c index), but whether it allows sufficient overlapping of the propensity score within stratified groups.[20,26] We acknowledge that our stratification strategy has possible limitations because we were not able to construct quintiles. Moreover, the examination of the fourth propensity score quartile suggests potential differences between groups. Residual confounding effect could then remain. Another requirement to validate propensity score analysis based on matching[20,26] is to balance confounders in the matched sample. The latter was clearly verified in the current study. Moreover, the four different adjustment methods resulted in similar conclusions regarding major cardiac morbidity with similar effect size, increasing the internal validity of our results. Notably, matching on the propensity score has been shown to be the least biased marginal OR estimation in Monte Carlo simulations.[27] Nevertheless, propensity analysis can only adjust for observed and known confounders and does not protect against bias from unknown confounders.[28] Regarding mortality, the OR was reduced by 84% after propensity score matching, demonstrating a notable channeling bias in the crude analysis that our models were able to remove.

Dobutamine is most often the first-line catecholamine administered at the exclusion of institutional guidelines and without continuous or discontinuous cardiac output monitoring in French cardiac surgical centers.[12] The current results are in accord with these findings: A low dose of dobutamine for a short postoperative period and remaining nearly unchanged throughout the duration of administration was used in 89% of cases, without prespecified algorithms or cardiac output monitoring. The use of dobutamine as a first-line drug for hemodynamic instability suggests that myocardial stunning and ventricular dysfunction were considered by clinicians as the main causes of hypotension. Hypovolemia and isolated vascular dysfunction, however, are more often responsible for post-CPB hypotension than myocardial dysfunction.[1,29] A more frequent preoperative use of diuretics and an increase in postoperative mediastinal bleeding in patients receiving catecholamines in our study could suggest that a masked hypovolemia contributed to hy-

potension and administration of dobutamine, pointing out the role of cardiac monitoring to guide inotropic use.[11] Twenty-six studies investigating the effects of dobutamine in cardiac surgical patients were identified in a recent systematic literature review.[2] Most of them found that administration of dobutamine produced a dose-dependent rise in cardiac output, mainly by increasing heart rate.[5,6,30–32] An increase in incidence of both arrhythmias and postoperative myocardial infarction was also observed,[31,33] highlighting the potential risks associated with dobutamine infusion in post-CPB patients. As suggested by the current study, clinical manifestations of myocardial reperfusion injury could be worsened by the inappropriate use of dobutamine and other catecholamines, leading to adverse postoperative outcome.

Some remarks must be included to indicate the limitations of the current study. First, the administration of catecholamines was not randomized, and thus we demonstrate an association but cannot prove causality. Second, the study was conducted in a single center. However, the management of catecholamines in our institution was not different from that used in a large majority of French cardiac surgical centers.[12] Third, we only included patients with a low postoperative risk. Consequently, the low postoperative myocardial infarction and mortality rate precluded any powerful analysis regarding these outcomes. Fourth, we only evaluated short-term clinical outcome and thus cannot draw any conclusions on detrimental long-term effects of perioperative administration of catecholamines in the cardiac surgical setting. Fifth, we mainly focused on dobutamine administration, because use of other inotropic agents was unusual in our cohort of patients. Thus, we acknowledge that the current study is underpowered to evaluate any other catecholamine with respect to mortality and morbidity. Additional data are required before any conclusion can be drawn about other catecholamines currently used in the cardiac surgical setting. Last, some important variables, such as statin use, were not recorded in our database at the time we performed the study and consequently were not controlled for analysis. This is another limitation of the current study, even if early continuation of statin therapy was the rule in our clinical routine practice.[34]

In conclusion, the perioperative use of dobutamine simply based on the clinical judgment of the attending anesthesiologists in low-risk patients undergoing elective cardiac surgery with CPB is associated with adverse postoperative cardiac outcome. A better assessment of the risk/benefit ratio of dobutamine administration is mandatory in cardiac surgery to avoid its inappropriate use and limit its potential deleterious effects.

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