ORIGINAL ARTICLE

Effects of fenoldopam infusion in complex cardiac surgical operations: a prospective, randomized, double-blind, placebo-controlled study

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ABSTRACT

Aim. Fenoldopam mesylate is a short-acting dopamine-1 agonist that has been suggested to be a possible reno-protective agent in patients undergoing cardiac surgery. The present study is a prospective, randomized, double-blind placebo controlled trial conducted to determine the effects of fenoldopam in a population of patients undergoing complex cardiac operations.

Methods. Eighty subjects undergoing complex cardiac operations with cardiopulmonary bypass (CPB) were enrolled in the study. Patients were randomly assigned either to the fenoldopam (0.1 μg · kg^{-1}· min^{-1}) or the placebo group. Fenoldopam infusion started at the onset of CPB and was maintained for the first twelve postoperative hours. CPB parameters and renal outcome data were collected.

Results. Patients in the fenoldopam group had higher oxygen delivery during CPB and a significantly lower perfusion pressure, although this parameter was still within the normal range. Blood lactate concentrations during CPB were similar in the two groups. Urine output during and after CPB did not differ between groups, nor did the renal function parameters. There was a significantly higher rate of acute kidney injury (AKI) in the placebo group (10% vs 0%). In the subgroup of patients requiring inotropic support for more than 48 hours, renal function parameters were significantly better, the peak arterial blood lactate was significantly lower, and the major morbidity rate was significantly lower (36% *vs* 100%) for patients who received fenoldopam.

Conclusion. Fenoldopam improves the quality of perfusion during CPB. In patients receiving catecholamines to treat a postoperative low cardiac output state, fenoldopam significantly improves renal function and prevents AKI and major morbidity. *(Minerva Anestesiol 2010;76:249-59)*

Key words: Cardiac surgical procedures - Cardiopulmonary bypass - Vasodilatation.

Acute kidney injury (AKI) following cardiac operations with cardiopulmonary bypass (CPB) are a common and life-threatening complications, with a reported incidence of 1% to 5%. When dialytic treatment is required, the mortality rate may reach 50%.[1-3] Various factors related to the conduction of CPB have been advocated as possible determinants of AKI. They include CPB duration,[1, 4, 5] a low perfusion pressure,[6] low pump flow,[6, 7] severe hemodilution,[7-10] and low oxygen delivery.[7]

Fenoldopam mesylate is a short-acting dopamine-1 agonist with antihypertensive properties. It appears to improve renal function in clinical situations of reduced blood flow [11, 12] by increasing renal blood flow to both the cortex and

medullary region. In cardiac surgery, it has been proposed as a reno-protective agent. Case reports and case series have provided encouraging results.[13, 14] In 2004, a large, non-randomized, propensity score-adjusted study [15] failed to identify a beneficial effect of fenoldopam in patients at high-risk for acute renal failure following cardiac surgery. However, the same study found that in the subgroup of patients with a low cardiac output state (LCOS) after cardiac operation, the use of fenoldopam significantly decreased the incidence of acute renal failure. Subsequently, a randomized controlled trial [16] found no effect of fenoldopam on the renal function of patients who had undergone cardiac surgery. However, other studies confirmed that fenoldopam may have a beneficial effect on renal function in patients undergoing cardiac surgery with CPB [17], and a recent meta-analysis [18] found that in cardiovascular patients undergoing operations, fenoldopam use resulted in a reduced rate of acute renal failure and mortality.

In light of this, the present level of knowledge with respect to the role of fenoldopam in reducing the renal risk associated with cardiac operations is inconsistent. The present study is a prospective, randomized, double-blind, placebo-controlled trial aimed to determine if the use of fenoldopam results in favorable changes in the quality of perfusion during CPB and to investigate whether the use of fenoldopam reduces renal morbidity following cardiac operations.

Material and methods

Study design

This single-center prospective, randomized, double-blind, placebo-controlled study was performed at a tertiary University Hospital. The study was approved by the local Ethics Committee and was registered in the Protocol Registration System Clinical Trial.Gov (registration number NCT00747331). The study was conducted according to the most recent amendments to the Declaration of Helsinki and in adherence to good clinical practice guidelines. Each patient provided written informed consent.

This study is reported according to the Revised Consolidated Standards of Reporting Trials (CONSORT) statement.[19]

Subject population

Patients who were scheduled for elective cardiac operations with CPB, who were age of 18 years or more, and who had a planned complex cardiac operation (coronary and valve operation; double/triple valve operation; ascending aorta operation) requiring a predictable CPB time of 90 minutes or more were included.

Exclusion criteria were the absence of written informed consent and the presence of a known allergy to fenoldopam. Preoperative chronic renal failure needing dialysis was not an exclusion criterion. However, patients in this condition were excluded from the renal function related outcome analyses (secondary endpoints).

Between September 25, 2008 and March 19, 2009, all patients received their operations in the same Hospital (IRCCS S. Donato Policlinic). All data were recorded using the Institutional Database. Additional data were recorded using a specific data collection form.

Operative details

Premedication included atropine sulphate (0.5 mg), promethazine (50 mg), and fentanyl (50 to 100 μg, according to the patient's weight). Anesthesia was induced by an intravenous infusion of remifentanil (starting dose 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and a midazolam bolus of 0.2 mg/kg. Cisatracurium besylate (0.2 mg/kg) was subsequently administered to allow for tracheal intubation. Subsequently, anesthesia was maintained with a continuous infusion of remifentanil (dose ranging from 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, titrated based on the hemodynamic response) and midazolam (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$).

CPB was conducted using either closed or open circuits, standard or phosphorylcholine-coated hollow-fiber oxygenators, and roller or centrifugal pumps, according to availability. Regardless of the circuit used, the priming volume was always minimized to 800-1 000 mL. CPB flow was settled at a value of 2.8 $L \cdot min^{-1} \cdot m^{-2}$. The lowest temperature on CPB was decided by the surgeon but was kept within a range of 28 °C - 34 °C. The CPB flow was adjusted to maintain a mean perfusion pressure in the range of 60-80 mmHg. If needed, systemic vasoconstrictor (norepinephrine)

or vasodilator (sodium nitroprusside) infusions were used to keep the perfusion pressure within range. In case of low urine output during CPB (<0.5 mL· kg $^{-1}$· h^{-1}), furosemide (10 mg) was administered intravenously.

Cold crystalloid or blood cardioplegia were used according to the surgeon's preference.

Interventions

Patients were randomly allocated to the study group (fenoldopam) or to the placebo group. The intervention consisted of an intravenous infusion of fenoldopam at the dose of 0.1 μg·kg^{-1}·min^{-1}, which was started immediately before the onset of CPB and lasted for twelve hours after the patient's arrival at the Intensive Care Unit (ICU). The infusion was limited to the intraoperative and early postoperative period because the primary endpoint was related to intraoperative variables. Patients in the placebo group received an intravenous infusion of saline solution at the same rate (mL/h) and during the same time period as the fenoldopam group.

No changes to our standard of care for the intraoperative or postoperative treatment were applied during the study period.

Objectives

The primary endpoint of this study was to assess if fenoldopam infusion during prolonged CPB resulted in changes to the adequacy of perfusion, as established by serial measurements of blood lactate (BL) concentration and oxygen delivery (DO_2) during CPB. Peak BL during the first 72 hours in the ICU were recorded. Additional data collected during CPB were pump flow, perfusion pressures, hemoglobin values, arterial oxygen tension, arterial carbon dioxide tension, arterial pH, arterial bicarbonate levels, and temperature.

Sampling times were defined as follows: T0: after induction of anesthesia, 30 minutes before going on CPB; T1: 10 minutes after the onset of CPB; T2-T6: on CPB, at time intervals of 20 minutes; T7: peak value in the ICU (in the first 72 hours after the operation).

Secondary endpoints were focused on renal function during and after CPB, with the following measurements:

1. Urine output during CPB and in the first 12 hours in the ICU;

2. changes in serum creatinine values (mg/dL) from baseline to the peak postoperative level and changes in the creatinine clearance (mL/min) calculated according to the Cockcroft-Gault equation from baseline to the lowest value within the first 72 hours after the operation;

3. incidence of AKI in the two groups, defined according to the RIFLE criteria [20] as a peak postoperative creatinine value higher than 2.0 mg/dL and double the baseline value, sustained for more than 24 hours within the first 72 postoperative hours.

Outcomes considered at the above points (2) and (3) were restricted to the first three days after the operation to select a time frame that could be affected by drug administration. AKI presenting at a later stage, as a complication of a chronic condition of multi-organ failure, was not considered within the secondary outcomes.

Other parameters considered in the analysis were hospital mortality (*i.e.*, within 30 days of hospital admission) and major morbidity (defined as the presence of at least one of the following conditions: AKI, stroke, mechanical ventilation > 48 hours, surgical re-exploration, and sternal wound infection).

The other data included in our standard data collection were recorded but were not considered as primary or secondary outcome measurements. Demographics, preoperative risk profile, and intraoperative data were collected for checking the homogeneity of the two groups. Acute renal failure risk was assessed using the score proposed by the Cleveland Clinic.[21]

Sample size

The study was powered based on the primary outcome (changes in BL concentration). In this study, the reference value for peak BL concentration during CPB was obtained from our recent study [22] in which patients who underwent a CPB longer than 90 minutes experienced a mean peak BL concentration of 2.1 mMol/L (standard deviation 1.2 mMol/L), with 34% of the patients demonstrating hyperlactatemia (>2 mMol/L). The experimental hypothesis was that patients treated with fenoldopam would have a lower peak BL

concentration during CPB (effect size -0.6 mMol/L, 40% of the variance) and that the rate of patients with hyperlactatemia would be reduced to 10%. With an alpha of 0.05 and power of 80%, the number of patients in each group was calculated as 38 for changes in peak BL concentration and 40 for changes in the rate of patients with hyperlactatemia.

Therefore, the number of patients to be studied was settled at 40 for each group (total patient population=80). An interim analysis was planned at 50% of the study (40 patients enrolled). A stopping rule was determined in the case that the interim analysis detected significant differences in mortality and/or major morbidity.

Randomization procedure

The random allocation sequence was generated using a computerized random generation program.

The randomization was generated in blocks of 20 patients. This procedure was performed by an external staff person working in the hospital pharmacy. Based on this process, sealed envelopes containing the allocation group were created and stored in the pharmacy.

The patients were evaluated for eligibility the day before the operation. If patients were eligible and agreed to participate in the study, they were enrolled. On the morning of the operation, the investigator(s) contacted the pharmacy, and the sealed envelope was opened and stored. The pharmacist prepared either drug or placebo according to the randomization sequence, using unlabeled 500 mL bottles. Fenoldopam bottles contained 250 mg of drug. The bottles were then sent to the operating theater, where the investigator prepared a 50 mL syringe of the drug or placebo that was used for continuous intravenous infusion during and after the operation, at an infusion rate corresponding to a dose of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of fenoldopam.

Blinding

The participants, those administering the drug, and those assessing the outcomes were blinded to group assignment.

Statistical methods

The analysis was conducted according to "intention to treat". The two groups were compared for homogeneity of preoperative and intraoperative data using a Student's t-test for continuous variables with a normal distribution, non-parametric tests for continuous variables that were not normally distributed, and a Pearson's chi-squared test for categorical variables.

Continuous outcome variables were investigated for between-groups differences using a Student's t-test for continuous variables with a normal distribution, non-parametric tests for continuous variables that were not normally distributed, and a Pearson's $\chi\sigma^2$ test with the Yates' correction or a Fisher exact test, when appropriate, for categorical variables.

The association between continuous variables was explored with linear or polynomial regression analyses. Two-sided tests were used throughout. When needed, adjustment analyses were applied.

A subgroup analysis was pre-planned for patients who developed LCOS after weaning from CPB. LCOS was defined as the need for inotropic support for more than 48 hours in the postoperative course and/or intra-aortic balloon pump use. This subgroup analysis was planned based on our previous observation that fenoldopam treatment was effective primarily in patients under LCOS.[15]

Additional analyses were considered in case significant differences in other parameters that were a part of our standard data collection but were not considered as primary or secondary outcome measurements, were found.

All data are presented as absolute numbers or means with standard deviation (SD). Statistical analyses were performed using a computerized statistical package (SPSS, Chicago, IL, USA).

Results

The flow of participants through each phase of the study is shown in Figure 1.

The two groups were homogeneous with respect to preoperative variables (Table I). Two patients with chronic renal failure under dialytic treatment in the fenoldopam group were excluded from the analysis of secondary endpoints related to changes in renal function and AKI incidence. Due to the

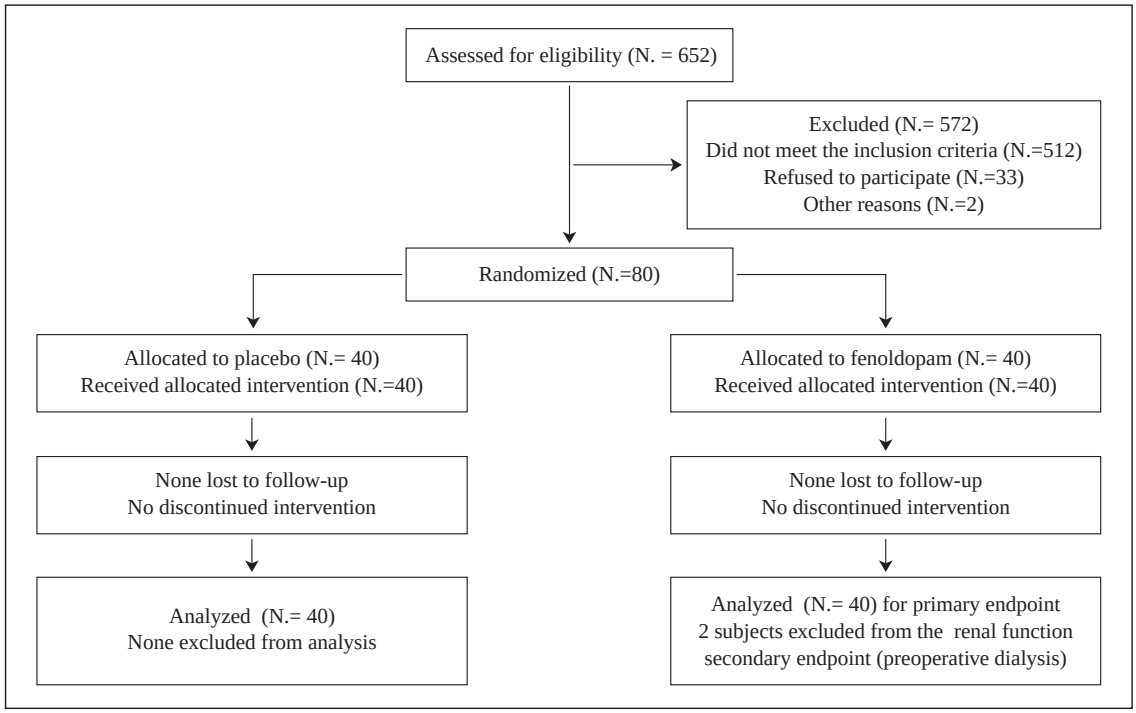

Figure 1.—Flow of participants through each stage of the study.

presence of these two patients, the standard deviation for preoperative creatinine was very large in the fenoldopam group. No between-group differences in the acute renal failure risk score were observed. Both patients under chronic dialysis survived the operation. Intraoperative variables did not significantly differ between the two groups, with the exception of the use of systemic vasodilators during CPB. Systemic vasodilators were utilized more frequently in the placebo group (10%) than in the fenoldopam group (0%).

Primary endpoint: perfusion and metabolic changes during CPB

During CPB, patients in the fenoldopam group had a significantly higher DO_2 than patients in the placebo group at times T3 through T5 (Figure 2). This difference disappeared at T6 (110 minutes), when only 25 patients in both groups were still on CPB. The lowest DO_2 on CPB was significantly lower in the placebo group (273±41 mL $\cdot$ $min^{-1} \cdot m^{-2}$) than in the fenoldopam group (292±41 mL $min^{-1} \cdot m^{-2}$) (P=0.048). No significant changes in hemoglobin concentration were detected during CPB, whereas the pump flow rate was significantly higher at times T2 through T5 (Figure 3). The mean perfusion pressure was significantly lower in the fenoldopam group for all sampling times, with the exception of T4 (Figure 4). No significant differences in BL concentration were detected during the observation period (Figure 5). Four patients in the placebo group and seven in the fenoldopam group had a peak BL value >2.0 mMol/L during CPB (P=0.330).

Secondary endpoints: outcome variables

No significant changes (Table II) were observed between the two groups with respect to the change in urine output during CPB and in the first 12 postoperative hours, the peak serum creatinine values or the creatinine clearance values. The incidence of AKI was significantly higher in the placebo group (10%) than in the fenoldopam group (0%).

There was a positive association between the lowest DO_2 during CPB and the lowest creatinine clearance in the ICU (P=0.04). However, when

TABLE I.— *Demographics, preoperative risk profile and operative data for the two groups.*

Variable	Placebo (N.=40)	Fenoldopam (N.=40)	P value
Pre-randomization data			
Age (years)	65±5	64±4.5	0.917
Male gender	28/40	29/40	0.805
Weight (kg)	79±7	79 1±7	0.880
Hematocrit (%)	39.1±4.4	36.8±9.3	0.158
Left ventricular ejection fraction	0.55±0.11	0.51±0.12	0.201
Unstable angina	1/40	0/40	0.314
Chronic obstructive pulmonary disease	1/40	2/40	0.556
Previous cerebrovascular accident	2/40	5/40	0.235
Diabetes, on medication	6/40	5/40	0.745
Serum creatinine value (mg/dL)	1.08±0.43	1.39±1.65	0.249
Creatinine clearance (mL/min)	84±38	80±41	0.661
Renal risk score*	2.9±1.6	3.1±1.6	0.628
Chronic dialysis	0/40	2/40	0.152
Logistic EuroSCORE	10.4±8.9	10.3±11.1	0.943
Redo operation	4/40	4/40	1.000
CABG and mitral valve procedure	5/40	4/40	0.723
CABG and aortic valve procedure	12/40	9/40	0.446
CABG and left ventricle restoration	4/40	4/40	1.000
Double/triple valve procedure	4/40	7/40	0.330
Aortic valve and ascending aorta	12/40	16/40	0.348
Others	3/40	1/40	0.305
Crystalloid/blood cardioplegia	2/38	5/35	0.235
Post-randomization data			
CPB duration (minutes)	114±35	111±35	0.693
Aortic cross-clamp time (minutes)	83±27	85±29	0.775
Use of systemic vasodilators	4/40	0/40	0.040
Use of systemic vasoconstrictors	0/40	1/40	0.314
Use of furosemide	11/40	8/38	0.507
Lowest hematocrit on CPB (%)	25.7 ±3.5	26.5±3.1	0.331
Lowest temperature on CPB (°C)	31.5±1.9	31.3±1.6	0.669

*Excluding patients under chronic dialysis; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass. Data are reported as mean±standard deviation of the mean or absolute numbers.

analyzed separately, this association was strongly confirmed in the placebo group (P=0.001) but not in the fenoldopam group (Figure 6).

Major morbidity and mortality rates were not significantly different between the two groups.

Allogeneic blood transfusion rate was the same (26 patients, 65%) in both groups.

We registered five (6%) postoperative deaths and no intraoperative deaths within the study group. One patient in the placebo group died on post-operative day 7 due to multi-organ failure in the setting of a LCOS treated with inotropic support and an intra-aortic balloon pump. Four patients in the fenoldopam group died. One patient died on postoperative day 12, after being re-operated on for an infectious endocarditis of the implanted mechanical mitral valve prosthesis and then developing multi-organ failure in the setting of a LCOS and severe sepsis. A second died on postoperative day 33 due to multi-organ failure caused by pneumonia and severe sepsis. A third died on postoperative day 5 due to mesenteric infarction in the setting of LCOS treated with inotropic support and an intra-aortic balloon pump. A fourth died on postoperative day 15 due to multi-organ failure secondary to pneumonia and severe sepsis in the setting of LCOS treated with inotropic support and an intra-aortic balloon pump. Considering the total postoperative outcome, two patients in the placebo group and four in the fenoldopam group required renal replacement therapy.

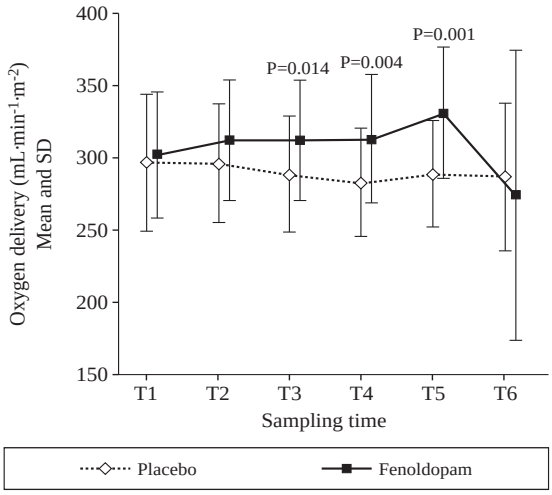

Figure 2.—Oxygen delivery during cardiopulmonary bypass in the two experimental groups. Data are reported as mean and standard deviation.

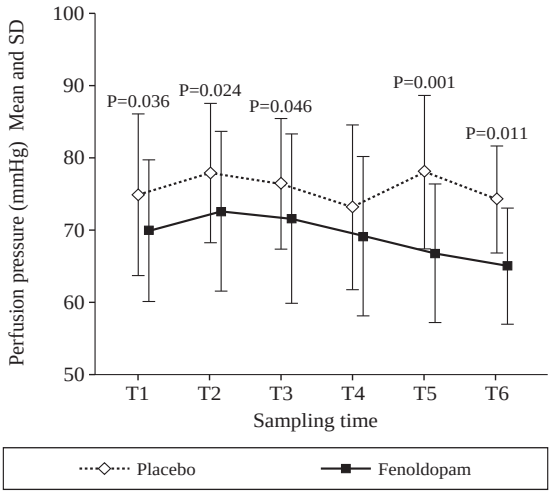

Figure 4.—Mean perfusion pressure during cardiopulmonary bypass in the two experimental groups. Data are reported as mean and standard deviation.

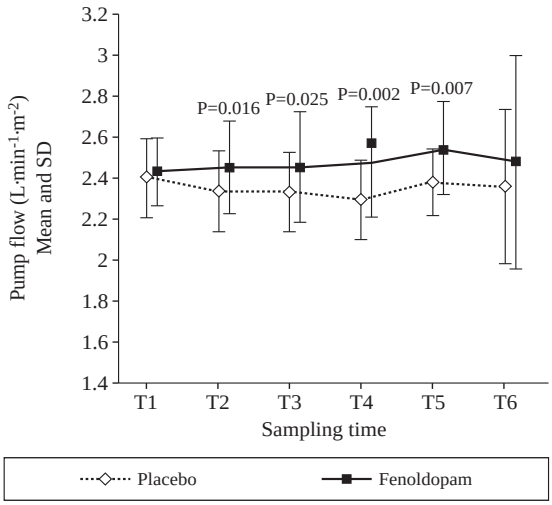

Figure 3.—Pump flow in the two experimental groups. Data are reported as mean and standard deviation.

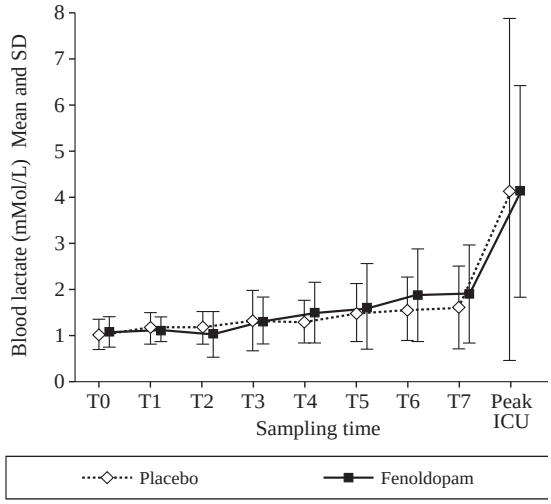

Figure 5.—Arterial blood lactate concentration during cardiopulmonary bypass and in the intensive care unit in the two experimental groups. ICU: intensive care unit. Data are reported as mean and standard deviation.

Subgroup analysis: patients with postoperative low cardiac output syndrome

Data for patients with LCOS (requiring inotropic support for more than 48 postoperative hours) are reported in Table 3. This subgroup comprised 17 patients (six in the placebo group and eleven in the fenoldopam group, P=0.172). The urine output during the first 12 postoperative hours was significantly higher in the fenoldopam group. The peak serum creatinine value and the serum creatinine increase were significantly higher in the placebo group. Additionally, the lowest creatinine clearance was significantly lower in the placebo group, and the creatinine clearance decrease was significantly more pronounced in the placebo group. All patients demonstrating AKI were found within this subgroup, and the rate of this was significantly higher in the placebo group.

The peak postoperative BL level was signifi-

TABLE II.— *Outcome data of the two groups (total population).*

Variable	Placebo (N.=40)	Fenoldopam (N.=40)	P value
Urine output during CPB (mL.kg-1.h-1)*	1.6±2.0	1.7±2.8	0.946
Urine output ICU (mL.kg-1.h-1)*	2.3±1.2	2.6±1.2	0.294
Peak creatinine value (mg/dL)*	1.4±0.9	1.3±0.6	0.521
Creatinine increase ratio (peak/baseline)*	1.3±0.9	1.1±0.2	0.306
Lowest creatinine clearance (mL/min)*	76±42	77±39	0.982
Creatinine clearance ratio (peak/baseline)*	0.91±0.25	0.91±0.19	0.995
Acute kidney injury*	4/40	0/38	0.045
Major morbidity	8/40	5/40	0.418
Operative mortality	1/40	4/40	0.139

Data are reported as mean±standard deviation of the mean or absolute numbers. *Excluding patients with preoperative chronic renal failure; CPB: cardiopulmonary bypass; ICU: intensive care unit.

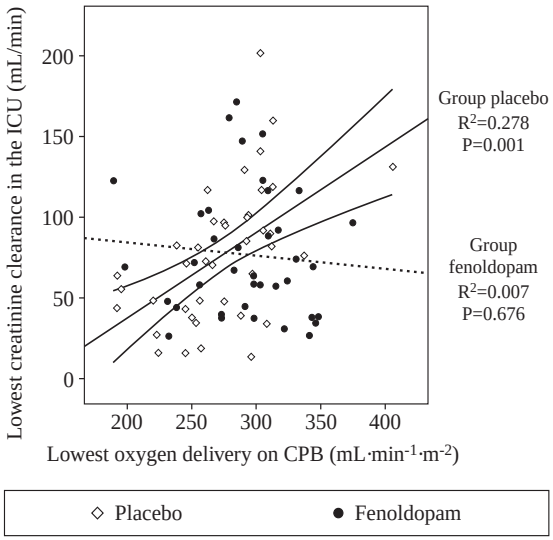

Figure 6.—Association between the lowest DO_2 during cardiopulmonary bypass and the lowest creatinine clearance during the intensive care unit stay. Solid lines: linear regression with 95% confidence interval for the placebo group. Dashed line: linear regression for the fenoldopam group. CPB: cardiopulmonary bypass; ICU: intensive care unit.

cantly higher in the placebo group. Major morbidity incidence was significantly higher in the placebo group (100%) than in the fenoldopam group (36%). No differences in mortality were observed.

Discussion

The key findings of our study are the use of fenoldopam during CPB is associated with a reduction in systemic resistance. This reduction may be effectively counteracted by increased pump flow, with a moderate reduction in perfusion pressure, and without the need for vasoconstrictive drugs. As a result, (1) the DO_2 during CPB was significantly increased by fenoldopam treatment, particularly after the first hour of CPB; (2) no effects on BL concentration during CPB were detected in patients receiving fenoldopam; (3) AKI rate in the first three days after the operation was significantly lower in fenoldopam-treated patients; and (4) in

TABLE III.—*Outcome data of the two groups (patients with postoperative low cardiac output).*

Variable	Placebo (N.=40)	Fenoldopam (N.=40)	P value
Urine output ICU (mL.kg-1.h-1)* – 12 hours	1.6±0.6	2.61±1.2	0.042
Peak creatinine value (mg/dL)	2.9±1.3	1.84±0.7	0.041
Creatinine increase ratio (peak/baseline)	2.6±1.4	1.35±0.2	0.007
Lowest creatinine clearance (mL/min)	34±22	56±41	0.166
Creatinine clearance ratio (peak(baseline)	0.47±0.22	0.76±0.14	0.005
Acute kidney injury	4/6	0/11	0.002
Peak blood lactate (mMol/L)	9.7±4.6	5.7±2.7	0.037
Major morbidity	6/6	4/11	0.011
Operative mortality	1/6	4/11	0.394

Data are reported as mean±standard deviation of the mean or absolute numbers. *Excluding patients with preoperative chronic renal failure; ICU: intensive care unit.

the subgroup of patients receiving inotropic drugs to treat LCOS immediately after the operation, fenoldopam treatment resulted in better kidney function and a reduced rate of AKI and major morbidity.

Indirect signs of renal perfusion (urine output) were not significantly different between the two groups. This finding is in agreement with Bove *et al*.[18] who compared low-dose fenoldopam with low dose dopamine.

Patients in the fenoldopam group demonstrated a higher DO_2 during CPB. A low DO_2 during CPB is associated with an increased rate of acute renal failure [7] and with increased BL production.[21] BL production during CPB was not significantly different between the two experimental groups in our study. However, the DO_2 was maintained above the previously identified critical threshold for hyperlactatemia in both groups,[22] and this could justify the lack of association between BL production and the DO_2.

The association between the lowest DO_2 during CPB and a deterioration of postoperative renal function (lowest creatinine clearance in the ICU), which has already been demonstrated by our group[7], was confirmed in this study. However, interestingly, this was true only in the placebo group. Our interpretation is that fenoldopam may have diverted blood perfusion and oxygen flow towards the renal vascular bed, therefore, limiting the deleterious effects of a low DO_2 during CPB.

With respect to the primary endpoint of the present study, we conclude that despite a higher DO_2, patients treated with fenoldopam did not demonstrate changes in urine output or BL production during CPB. However, this increased DO_2 may have limited early postoperative renal dysfunction. In fact, patients in the fenoldopam group had a significantly lower rate of AKI in the first 72 hours following the operation. This finding is in agreement with Barr *et al*.[17] who demonstrated, in a randomized controlled trial, that a fenoldopam dose of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ started at the beginning of the operation and continued for 48 hours afterwards preserved renal function in patients undergoing cardiac surgery.

In a previous study, we generated the hypothesis that fenoldopam treatment may be beneficial in patients receiving catecholamines for the treatment of postoperative LCOS. In a subgroup analysis of the present study, this hypothesis was confirmed. Patients experiencing LCOS and receiving fenoldopam in the first 12 postoperative hours demonstrated a significant improvement in all the renal function parameters considered, a significantly lower rate of AKI, a lower peak BL level, and a lower rate of major morbidity.

In the setting of cardiac surgery, AKI and acute renal failure are the consequence of postoperative LCOS in a large majority of cases. In a risk analysis for renal dysfunction following cardiac surgery, when one takes into consideration numerous postoperative factors, it appears that LCOS and the use of intra-aortic balloon pumps are always strongly associated with AKI/acute renal failure.[3, 23-25] In our study population, the four AKI events were all found within the LCOS group.

The mechanisms by which LCOS may lead to decreased blood flow to the splanchnic organs, namely to the kidney, are well known, and their analysis is beyond the purpose of the present study. It is, however, useful to recall the role of endogenous and exogenous catecholamines in the setting of LCOS and their action in determining peripheral and visceral vasoconstriction. In the setting of an endogenous and exogenous vasoconstrictive pattern, fenoldopam treatment exerted a protective effect on renal function. It is reasonable to hypothesize that the pre-renal vasodilating effect of fenoldopam [26, 27] may effectively counteract the splanchnic vasoconstriction generally considered to be a major determinant of acute renal failure. In fact, in patients not suffering from postoperative low cardiac output syndrome, fenoldopam treatment was not associated with any change in renal function after the operation.

The general interpretation of our results in the context of the current evidence is not in favor of the routine use of fenoldopam in cardiac surgery. Moreover, it should be considered that, although not significant, there was a trend towards a higher rate of LCOS and hospital mortality in the fenoldopam group. Our data confirm that, in the general population and in the absence of LCOS, fenoldopam treatment does not significantly change the outcome, as observed in a previous randomized controlled trial.[16] The results of this previous

randomized controlled trial are, however, difficult to compare with our findings — the fenoldopam dose was different (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the use of vasoconstrictors during CPB was more frequent in the fenoldopam group, and no subgroup analysis for patients needing inotropic support was presented. Similar studies using the same fenoldopam dose demonstrated a lower rate of AKI and renal replacement therapy in high-risk cardiac surgery patients treated with fenoldopam [28] and a lower rate of renal replacement therapy in patients with postoperative AKI.[29]

Conversely, our results have generated the hypothesis that patients at high risk for perioperative heart failure may benefit from fenoldopam treatment, thus confirming the results of a recent meta-analysis.[18] The risk stratification of our patient population is quite high, with a EuroSCORE around ten, thus, there is a high operation-related risk due to the complexity of the procedure.

There are two major limitations to the present study. The first is that despite the finding of a higher DO_2 in fenoldopam-treated patients, the primary endpoint regarding BL production changes was not achieved. We were able to find an indirect association between the use of fenoldopam, the lowest DO_2 on CPB, and the serum creatinine clearance during the ICU stay, but not with the other renal function-related variables. Therefore, the issue of CPB changes induced by fenoldopam as determinants of better renal outcomes needs further study. As a second limitation, we must admit that the most interesting findings came from a pre-planned subgroup analysis focused on LCOS patients. Although this analysis identified important differences between the two groups, the sample size of the analysis was small.

Conclusions

AKI is still a relatively frequent complication of cardiac surgery, with an incidence of about 2%[30] and standard diuretic treatment is ineffective in either preventing it or improving the outcome once it is established.[31] In this setting, alternative measures should be explored.

Our study suggests that the use of fenoldopam during prolonged CPB improves the quality of perfusion, without, however, changing the postoperative outcome. Conversely, there is evidence that, in patients suffering from postoperative LCOS, the use of fenoldopam along with the conventional treatment based on catecholamines and mechanical support may significantly limit the deterioration of renal function and avoid AKI. However, this improvement was not reflected in a lower mortality rate; thus, we cannot exclude that the beneficial effects observed may be limited to the early phases of peri-operative heart failure.

To better elucidate the role of fenoldopam during LCOS, a randomized controlled trial focused on this subgroup of patients is required.

References

1. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resources utilization. Ann Intern Med 1998;128:194-203.
2. Provenchere S, Plantefeve G, Hufnagel G, Vicaut E, De aumas C, Lecharny JB et al. Renal dysfunction after cardiac surgery with normothermic cardiopulmonary bypass: incidence, risk factors, and effect on clinical outcome. Anesth Analg 2003;96:1258-64.
3. Chertow GM, Lazarus JM, Christiansen CL, Cook EF, Hammermeister KE, Grover F et al. Preoperative renal risk stratification. Circulation 1997;95:878-84.
4. Llopart T, Lombardi R, Forselledo M, Andrade R. Acute renal failure in open heart surgery. Ren Fail 1997;19:319-23.
5. Wijeysundera DN, Karkouti K, Dupuis J-Y, Callum JL, Cheng D, Dupuis JY et al. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. JAMA 2007;297;1801-9.
6. Fischer UM, Weissenberger WK, Warters RD, Geissler HJ, Allen SJ, Mehlhorn U. Impact of cardiopulmonary bypass management on postcardiac surgery renal function. Perfusion 2002;7:401-6.
7. Ranucci M, Romitti F, Isgrò G, Cotza M, Brozzi S, Boncilli S et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg 2005;80:2213-20.
8. Fang WC, Helm RE, Krieger KH, Rosengart TK, DuBois WJ, Sason C et al. Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation 1997;96(Suppl II):194-9.
9. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? J Thorac Cardiovasc Surg 2003;125:1438-50.
10. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. Ann Thorac Surg 2003;76:784-92.
11. Poinsot G, Romand J-A, Favre H, Suter PM. Fenoldopam improves renal hemodynamics impaired by positive end-expiratory pressure. Anesthesiology 1993;79:680-4.
12. Shusterman NH, Elliot WJ, White WB. Fenoldopam but not nitroprusside improves renal function in severely hypertensive patients with impaired renal function. Am J Med 1993;95:161-8.

13. Garwood S, Swamidoss CP, Davis EA, Samson L, Hines RL. A case-series of low-dose fenoldopam in seventy cardiac surgical patients at increased risk of renal dysfunction. J Cardiothorac Vasc Anesth 2003;17:17-21.
14. Caimmi PP, Pagani L, Micalizzi E, Fiume C, Guani S, Bernardi M et al. Fenoldopam for renal protection in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2003;17:491-4.
15. Ranucci M, Soro G, Barzaghi N, Locatelli A, Giordano, Vavassori A et al. Fenoldopam prophylaxis of postoperative acute renal failure in high-risk cardiac surgery patients. Ann Thorac Surg 2004;78:1332-7.
16. Bove T, Landoni G, Calabrò MG, Aletti G, Marino G, Cerchierini E et al. Renoprotective action of fenoldopam in high-risk patients undergoing cardiac surgery: a prospective, double-blind, randomized clinical trial. Circulation 2005;111:3230-5.
17. Barr LF, Kolodner K. N-acetylcysteine and fenoldopam protect the renal function of patients with chronic renal insufficiency undergoing cardiac surgery. Crit Care Med 2008;36:1427-35.
18. Landoni G, Biondi-Zoccai GG, Marino G, Bove T, Fochi O, Maj G et al. Fenoldopam reduces the need for renal replacement therapy and in-hospital death in cardiovascular surgery: a meta-analysis. J Cardiothorac Vasc Anesth 2008;22:27-33.
19. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663-94.
20. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, the ADQI workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-R12.
21. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005;16:162-8.
22. Ranucci M, De Toffol B, Isgrò G, Romitti F, Conti D, Vicentini M. Hyperlactatemia during cardiopulmonary bypass: determinants and impact on postoperative outcome. Crit Care 2006;10:R167.
23. Ranucci M, Pavesi M, Mazza E, Bertucci C, Frigiola A, Menicanti L et al. Risk factors for renal dysfunction after coronary surgery: the role of cardiopulmonary bypass technique. Perfusion 1994;9:319-26.
24. Zanardo G, Michielon P, Paccagnella A, Rosi P, Calò M, Salandin V et al. Acute renal failure in the patients undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. J Thorac Cardiovasc Surg 1994;107:1489-95.
25. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998;104:343-8.
26. White WB, Halley SE. Comparative effects of intravenous administration of fenoldopam mesylate and sodium nitroprusside in patients with severe hypertension. Arch Intern Med 1989;149:870-4.
27. Elliott WJ, Weber RR, Nelson KS, Oliner CM, Fumo MT, Gretler DD et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. Circulation 1990;81:970-7.
28. Cogliati AA, Vellutini R, Nardini A, Urovi S, Hamdan M, Landoni G et al. Fenoldopam infusion for renal protection in high-risk cardiac surgery patients: a randomized clinical study. J Cardiothorac Vasc Anesth 2007;21:847-50.
29. Roasio A, Lobreglio R, Santin A, Landoni G, Verdecchia C. Fenoldopam reduces the incidence of renal replacement therapy after cardiac surgery. J Cardiothorac Vasc Anesth 2008;22:23-6.
30. Landoni G, Bove T, Crivellari M, Poli D, Fochi O, Marchetti C et al. Acute renal failure after isolated CABG surgery: six years of experience. Minerva Anestesiol 2007;73:559-65.
31. Karajala V, Mansour W, Kellum JA. Diuretics in acute kidney injury. Minerva Anestesiol 2009;75:251-7.

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