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The Effect of Fenoldopam and Dopexamine on Cytokine and Endotoxin Release following On-Pump Coronary Artery Bypass Grafting: A Prospective Randomized Double-Blind Trial

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ABSTRACT

Background: Surgical trauma, exposure to an external circuit, and reduced organ perfusion contribute to the systemic inflammatory response following cardiopulmonary bypass (CPB). Reduced splanchnic perfusion causes disruption of the gastrointestinal mucosal barrier and the release of endotoxins. Fenoldopam (a new dopamine 1 receptor agonist) has been shown to be a specific renosplanchnic vasodilator in animal and human studies. We studied the effects of fenoldopam on the systemic inflammatory response and the release of endotoxins after CPB and compared the results with those for dopexamine.

Methods: Our prospective randomized study included 42 consecutive patients with good to moderate left ventricular function who were to undergo elective or inpatient coronary artery bypass grafting. We used closed envelope method to randomize patients to receive 0.2 μg/kg per minute of fenoldopam (n = 14), 2 μg/kg per minute of dopexamine (n = 14), or normal saline (n = 14). Patients received their respective treatments continuously from anesthesia induction until the end of the first 24 postoperative hours. Interleukin 1β (IL-1β), IL-6, IL-8, IL-10, IL-12, tumor necrosis factor α, complement 3a (C3a), C4a, C5a, and endotoxins were measured during the perioperative period. Repeated-measures analysis of variance was used to evaluate the results for the timed samples.

Results: There were no statistical differences between the groups with respect to pre- and intraoperative variables. Release of C3a was attenuated in the fenoldopam group (P = .002), and release of IL-6 and IL-8 was attenuated in the postoperative period in the fenoldopam group (P = .012 and .015, respectively). The other interleukins showed no uniform release in any of the 3 groups. There were no statistically significant differences in serum endotoxin elevation between the 3 groups.

Conclusion: A partial attenuation in the inflammatory response is possible with fenoldopam infusion. The elevation in serum endotoxin levels was not affected by dopexamine or fenoldopam infusion.

INTRODUCTION

Cardiopulmonary bypass (CPB) is indispensable for most open heart operations; however, an undesirable systemic inflammatory response is associated with CPB [Elgebaly 1994; Cremer 1996]. Many factors during CPB, such as surgical trauma, ischemia-reperfusion to the organs, changes in body temperature, and the release of endotoxins, induce a complex inflammatory response [Wan 1997]. This response involves complement activation, release of cytokines, leukocyte activation along with the expression of adhesion molecules, and the production of various substances, including oxygen free radicals, arachidonic acid metabolites, platelet activating factor, nitric oxide, and endothelins [Wan 1997]. This inflammatory response can contribute to postoperative morbidity that can lead to respiratory failure, renal dysfunction, altered liver function, bleeding disorders, neurologic dysfunction, and ultimately multiorgan failure.

Modifications to techniques and devices with an aim of reducing the deleterious effects of CPB have led to the common use of heparin-coated circuits, leukocyte filters, and ultrafiltration. Splanchnic hypoperfusion with the consequent release of endotoxins has been thought to be a key player in the expansion of the inflammatory response [Jansen 1992]. Dopamine analogs (dopexamine, dobutamine) have been studied [Lisbon 2003], because their differential effects on systemic and organ perfusion are believed to be protective. Studies that used such agents as milrinone and enoximone [Berendes 1997; Lisbon 2003] to augment splanchnic blood flow and then investigated the effects on the inflammatory response have shown mixed results. In an earlier study, the

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use of dopexamine at a dosage of 2 µg/kg per minute was shown to augment hepatic blood flow [Sharpe 1999].

Recently, fenoldopam, a benzazepine derivative used for treating systemic hypertension after cardiac surgery, has stimulated a lot of interest. It is a selective postsynaptic dopamine 1 (DA-1) receptor agonist with minimal α_2 receptor antagonistic activity and no significant affinity for the α_1, β_1, or β_2 receptor [Brodgen 1997]. Animal and human studies have shown that fenoldopam increases gastric mucosal perfusion with little alteration in the systemic mean arterial pressure [Gombotz 1998; Schwarte 2003; Morelli 2004]. We have described the hemodynamic effects of fenoldopam and dopexamine and their effect on hepatic function [Adluri 2009]. We hypothesized that fenoldopam would augment the splanchnic blood flow and hence reduce the postoperative inflammatory response. We therefore set out to study the effects of fenoldopam on the systemic inflammatory response and serum endotoxin release and to compare its effects with those of dopexamine.

METHODS

The approval of the local ethics committee was obtained. Medicines and Healthcare Products Regulatory Agency approval was obtained for the importation and use of fenoldopam in the UK. We obtained informed consent from the 42 consecutive patients included in the study who were to undergo either elective or inpatient coronary artery bypass grafting (CABG). Patients were randomized to receive 0.2 µg/kg per minute of fenoldopam (F group; n = 14), 2.0 µg/kg per minute of dopexamine (Dx group; n = 14), or normal saline (NS group; n = 14) from immediately after the induction of anesthesia until the end of the first 24 hours following surgery. Inclusion criteria were the following: first-time CABG, left ventricular ejection fraction ≥45%, and normal preoperative renal and hepatic functions. Patients who had a poor left ventricular function, required intravenous nitrate infusion for unstable angina, required an intra-aortic balloon pump either pre- or postoperatively, required multiple inotropes, or were to undergo emergency CABG were excluded from the study. We also excluded patients who were on steroid medications or drugs with the potential to interfere with the study, such as angiotensin-converting enzyme inhibitors. Calcium channel blockers were avoided on the day of surgery.

Anesthesia Protocol

General anesthesia was induced with fentanyl (15-20 µg/kg) and propofol (0.5 mg/kg) and was maintained with isoflurane at an end-tidal concentration of 0.5% to 1.0% and a propofol infusion rate of 2 to 3 mg/kg per hour. Muscle relaxation was achieved with 0.1 mg/kg pancuronium. Following intubation, an internal jugular central venous catheter and radial artery catheter were inserted to monitor central venous pressure and arterial pressure. Heparin (3.0 mg/kg) was administered to maintain the activated coagulation time at >480 seconds; heparin was reversed with protamine at the end of the operation.

Perfusion Protocol

The CPB circuit consisted of a hollow-fiber oxygenator (Jostra Quadrox oxygenator; Maquet Cardiovascular, Wayne, NJ, USA), a Stöckert S3 roller pump set (Sorin Group, Arvada, CO, USA), and a Quart (Jostra) filter (Maquet Cardiovascular). All patients were commenced on CPB by means of a 2-stage atrial cannula (Medtronic, Minneapolis, MN, USA) and an aortic cannula (DLP/Medtronic, Grand Rapids, MI, USA). The pump flow was set at 2.4 L/min per m^2 and reduced to 1.8 L/min per m^2 when the target core temperature (28°C) was achieved. Following the commencement of CPB and application of the aortic cross-clamp, antegrade intermittent cold blood cardioplegia (Harefield formula cardioplegia solution) was delivered at regular 20-minute intervals. An alpha-stat method was used to maintain the pH and acid-base status of the patient. During CPB, the mean arterial pressure was maintained at 55 to 70 mm Hg, and the hematocrit was maintained at 20% to 25%. Potential immune modulators such as steroids and aprotinin were not used.

Measurement of Inflammatory Cytokines

Peripheral arterial blood samples were obtained at the following times: sample 1, immediately after induction of anesthesia; sample 2, five minutes before CPB; samples 3 and 4, five and 30 minutes after the commencement of CPB, respectively; samples 5 and 6, before and 30 minutes after the administration of protamine sulfate, respectively; and samples 7 to 12, at 2, 4, 6, 8, 12, and 24 hours, respectively, after return of the patient to the intensive care unit.

Samples were centrifuged immediately (at 2000 rpm for 4 minutes) and stored frozen at –80°C in the laboratory to be analyzed later. We used the Human Inflammatory Cytokine Kit and the Human Anaphylatoxin CBA Kit (BD Biosciences, San Jose, CA, USA) with flow cytometry to measure interleukin 1β (IL-1β), IL-6, IL-8, IL-10, IL-12, tumor necrosis factor α (TNF-α), complement 3a (C3a), C4a, and C5a.

Principle of Measurement of Inflammatory Markers

The Human Anaphylatoxin CBA Kit has 3 populations of beads (with capture antibodies specific for the C3a, C4a, and C5a plasma proteins and their des-Arg forms), and the Human Inflammatory Cytokine Kit has 6 populations of beads (with capture antibodies specific for IL-8, IL-1β, IL-6, IL-10, TNF-α, and IL-12p70 proteins) with distinct fluorescence intensities. The beads were incubated with standards (purified from human plasma) or test samples (EDTA plasma or serum), washed, and then incubated with the phycoerythrin-conjugated detection antibodies to form sandwich complexes. We constructed standard curves for the given dilution of sample and used these curves to determine the range of detection (usually between 4 and 1000 pg/mL). Samples were treated with EDTA to prevent the activation of plasma proteases and with Futhan (FUT-175) to prevent cleavage of complement components. To 50 µL of mixed capture beads in an assay tube, we added 50 µL of serum for the test group. Controls were prepared by adding 50 µL of standard dilutions to the assay tubes. Wash buffer was added after 2 hours of incubation, and samples were centrifuged. Phycoerythrin

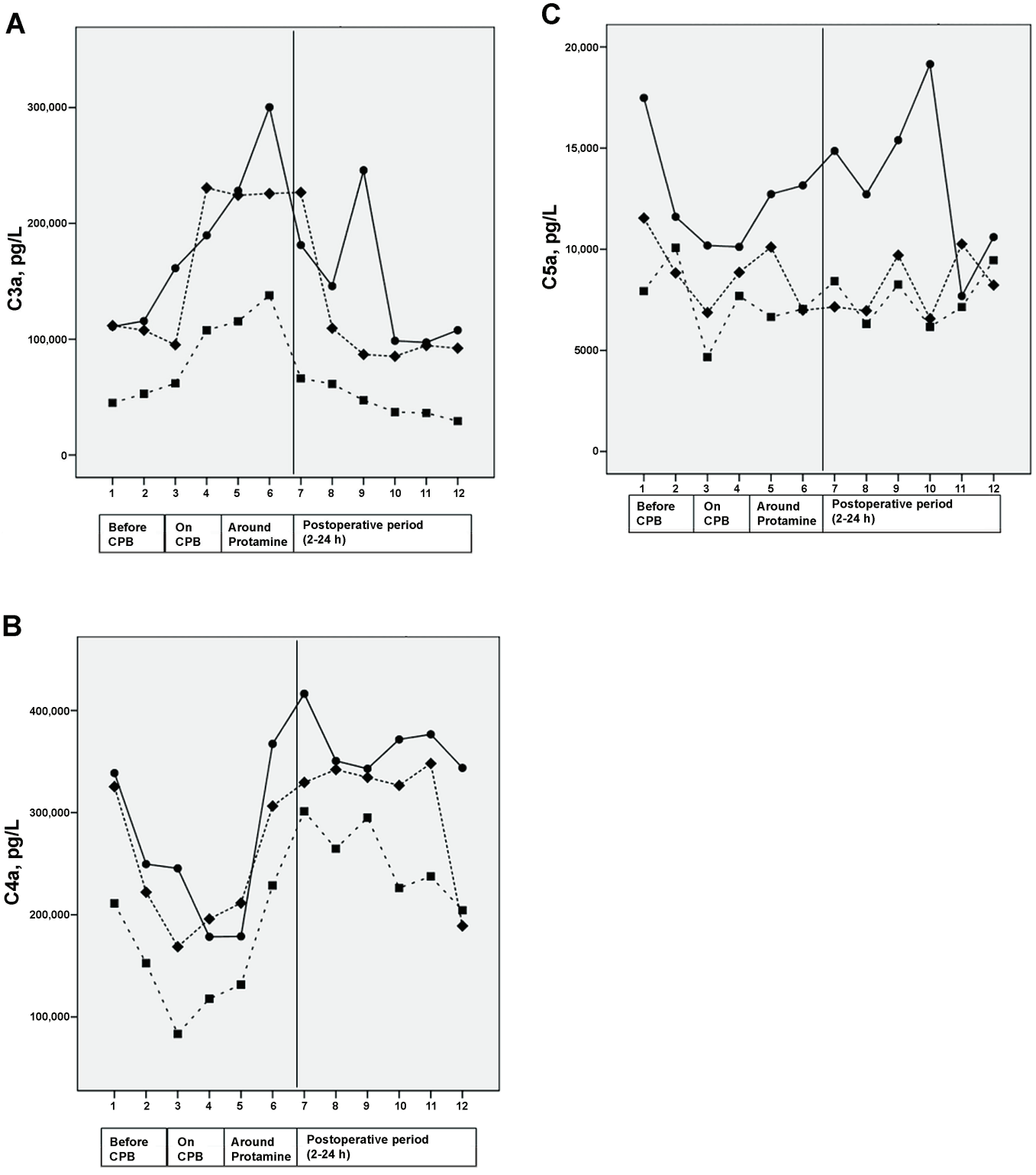

Figure 1. Trends in serum levels for complement 3a (C3a) (A), C4a (B), and C5a (C). Timing of samples: samples 1 and 2, before cardiopulmonary bypass (CPB); samples 3 and 4, during hypothermic CPB; samples 5 and 6, before and after protamine administration, respectively; samples 7 to 12, at 2, 4, 6, 8, 12, and 24 hours after CPB, respectively. Data for the fenoldopam group (closed squares), the dopexamine group (closed diamonds), and the normal saline group (closed circles) are presented as the mean for the respective time points.

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Table 1. Demographic Data*

	Normal Saline (n = 14)	Fenoldopam (n = 14)	Dopexamine (n = 14)
Age, y	65.5 ± 7.9	65.3 ± 4.5	63.67 ± 9.2
M:F ratio, n	10:4	9:5	12:2
Height, cm	168 ± 6.8	168.2 ± 6.3	170.6 ± 6.5
Weight, kg	77.1 ± 9	77.0 ± 8.7	80.0 ± 13.4
Body surface area, m^2	2.2 ± 0.19	2.03 ± 0.27	2.17 ± 0.30
No. of grafts	2.6 ± 0.5	2.5 ± 0.5	3.0 ± 0.1

*Data are presented as the mean ± SD.

detection reagent was added to the precipitate, and samples were incubated for 1 hour. A flow cytometer was then used to analyze the washed samples.

Measurement of Endotoxins

The timing of sample collection was as follows: sample 1, before CPB; samples 2 and 3, during hypothermic CPB; samples 4 and 5, around the time of protamine administration; samples 6 and 7, immediately postoperatively at 2-hour intervals.

Gram-negative bacterial endotoxin was measured with the Limulus Amebocyte Lysate (LAL) Kinetic-QCL assay (Lonza, Cambridge, UK). This method yields data as endotoxin units per milliliter, which reflects the biological activity of the bacterial endotoxins rather than as simple concentrations in plasma. Standard endotoxin was dissolved in pyrogen-free water, and serial dilutions were made. We then placed 100 µL of each standard and sample into duplicate wells of a 96-well plate and added 100 µL of the LAL/substrate reagent. The plate was placed in an incubating plate reader at 37°C and monitored colorimetrically over time (via WinKQCL software; Lonza) for the appearance of a yellow color. The software then converted the readings to endotoxin units.

Statistical Analysis

The current study forms part of a larger study to investigate the systemic and hemodynamic effects of fenoldopam and dopexamine. The sample-size calculations were based on a 2-sided α error of .05 and 80% power. A 40% increase in splanchnic blood flow was anticipated. On the basis of earlier studies, we calculated the sample size for a 3-sided study to be 14 patients per group, hence the total of 42 patients in this study.

All data were analyzed according to the intention-to-treat principle. Data were stored electronically and analyzed with SPSS software (version 15; SPSS, Chicago, IL, USA). Dichotomous data were compared with the 2-tailed χ^2 test. Repeated-measures analysis of variance was used to compare the groups with respect to cytokine release, and post hoc tests were performed by using the Bonferroni correction. Because 3 groups were compared for each factor, a P value of .017 (.05/3) was taken to indicate statistical significance. The unpaired Student t test was used in further statistical analyses of the groups with respect to mean serum levels at specific time points. Results are presented as the mean ± SD. We used the following formula [Taylor 1976] to correct for hemodilution: PCV-Corrected Cytokine Concentration = (Measured Cytokine Concentration × Preoperative Hematocrit)/(Hematocrit at Time of Sample), where PCV is the packed cell volume and the cytokine concentration is expressed in picograms per milliliter.

Table 2. Intraoperative and Postoperative Times in the 3 Groups*

	Normal Saline Group (n = 12)	Fenoldopam Group (n = 12)	Dopexamine Group (n = 12)	P
CPB time, min	51.2 ± 7.5	46.8 ± 9.8	53.8 ± 12.3	.598
Aortic cross-clamp time, min	26.7 ± 3.2	23.3 ± 6.2	29.4 ± 7.7	.435
Temperature, °C	28.6 ± 1.1	28.8 ± 1.1	28.8 ± 1	.614
Metaraminol, mg	1.8 ± 0.9	4.1 ± 4.4	2.2 ± 1.3	.0114
Heart rate difference, beats/min†	−1.5 ± 7.2	11.9 ± 13.5	18.4 ± 20.2	.007
MAP difference, mm Hg‡	−10.6 ± 14.4	−7.7 ± 19.9	2.6 ± 2.3	.699
Ventilation time, h	9.5 ± 4.4	8.3 ± 4.5	8.3 ± 5.2	.619
ICU stay, d	2.5 ± 0.7	2.4 ± 1.2	2.0 ± 0.0	.830
Hospital stay, d	7.0 ± 3.5	7.3 ± 2.9	6.7 ± 0.8	.843

*Data are presented as the mean ± SD. CPB indicates cardiopulmonary bypass; MAP, mean arterial pressure; ICU, intensive care unit.

†Difference in heart rate before and 30 minutes after commencing drug infusion.

‡Difference in MAP before and 30 minutes after commencing drug infusion.

RESULTS

There were no statistically significant differences between the 3 groups with regard to preoperative variables, risk factors, and intraoperative variables (Tables 1 and 2).

Systemic Inflammatory Response

Complement 3a. Serum concentrations of C3a started increasing immediately following the commencement of CPB and reached peak levels following release of the cross-clamp and the administration of protamine. In the control group (NS group), another increase occurred by 4 hours postoperatively. The trends in the Dx group followed a pattern similar to that of the NS group; however, there was a significant attenuation of complement activation in the F group (P = .002). A post hoc analysis (Bonferroni test) showed a significant reduction in the F group (versus NS group, P = .003; versus Dx group, P = .036) (Figure 1A). Serum C3a levels returned to preoperative levels in all groups by 24 hours following surgery.

Complement 4a. The serum levels of C4a, which represents the activation of the classical pathway, decreased

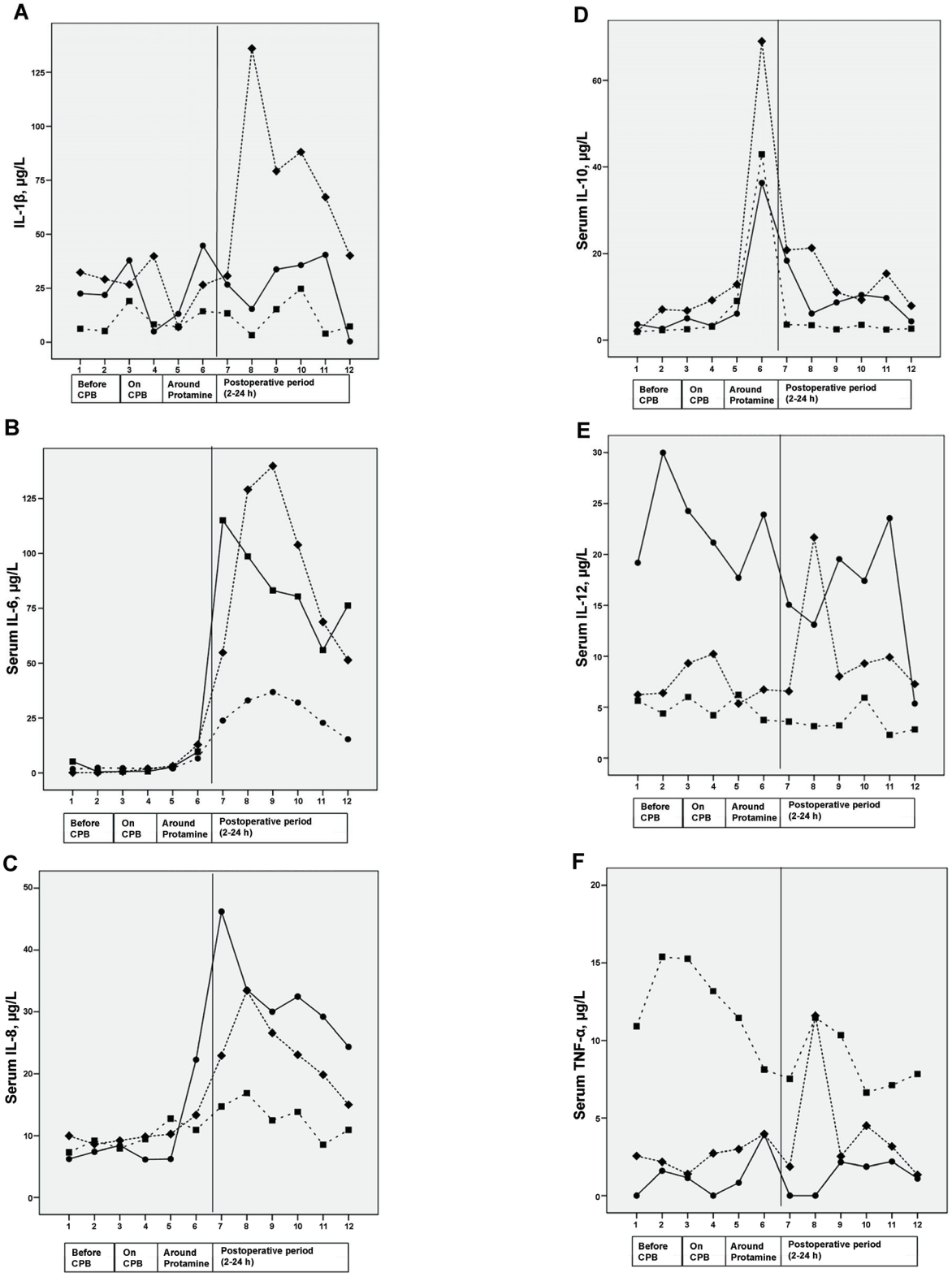

Figure 2. Trends in serum levels for interleukin 1β (IL-1β) (A), IL-6 (B), IL-8 (C), IL-10 (D), IL-12 (E), and tumor necrosis factor α (TNF-α) (F). Timing of samples: samples 1 and 2, before cardiopulmonary bypass (CPB); samples 3 and 4, during hypothermic CPB; samples 5 and 6, before and after protamine administration, respectively; samples 7 to 12, at 2, 4, 6, 8, 12, and 24 hours after CPB, respectively. Data for the fenoldopam group (closed squares), the dopexamine group (closed diamonds), and the normal saline group (closed circles) are presented as the mean for the respective time points.

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immediately after the start of CPB but reached peak levels after protamine administration. The Dx and NS groups were similar with respect to trends of increasing C4a levels, but serum C4a levels were lower at all time points in the F group than in the other 2 groups. This difference did not reach statistical significance, however (P = .349). Further analysis with the unpaired Student t test in a comparison of means at different times showed that the F and NS groups were significantly different at sample times 3 and 10 (P = .034 and .05, respectively; Figure 1B). In the NS and F groups, serum C4a levels reached preoperative levels by 24 hours, whereas in the Dx group they were lower than preoperative levels by this time point.

Complement 5a. C5a levels were reduced following the start of CPB in the NS and Dx groups but were increased in the F group just before the commencement of CPB. Serum C5a levels in the Dx and F groups were lower than in the NS group, but this difference was not statistically significant. At 8 hours postoperatively, however, serum C5a levels reached their maximum in the NS group, but they remained closer to preoperative levels in the F and Dx groups (Figure 1C). By 24 hours after the operation, C5a levels had reached preoperative levels in the F and Dx groups but were lower than the corresponding preoperative levels in the NS group.

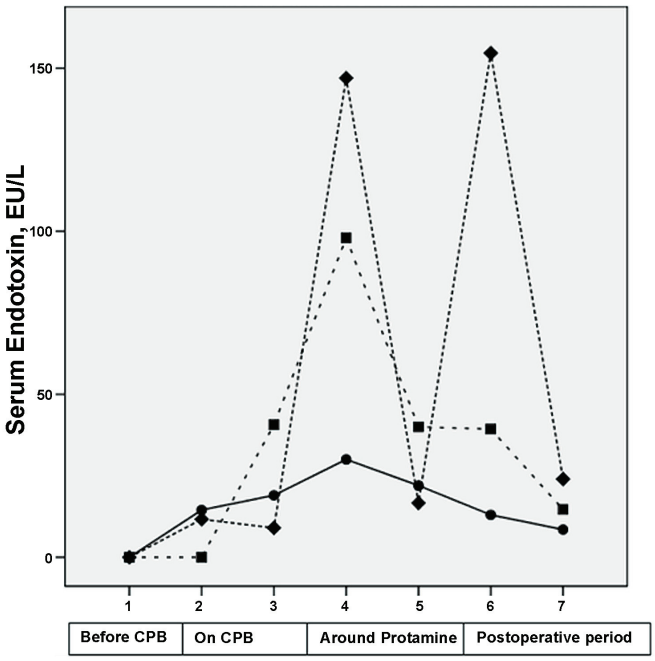

Figure 3. Changes in the serum endotoxin levels. Timing of samples: sample 1, before cardiopulmonary bypass (CPB); sample 2, during CPB; sample 4, after removal of the cross-clamp; sample 5, after protamine administration; samples 6 and 7, at 2-hour intervals after completion of the procedure. Data for the fenoldopam group (closed squares), the dopexamine group (closed diamonds), and the normal saline group (closed circles) are presented as the mean for the respective time points. EU indicates endotoxin units.

Cytokines

Interleukin 1β. Serum IL-1β levels increased following the commencement of CPB and after protamine administration; however, the maximum increase occurred in the Dx group at 4 hours postoperatively (Figure 2A). There was no statistically significant difference between the groups. Serum IL-1β levels returned to normal by 24 hours in all 3 groups (P = .105). There were significant differences between the F and DX groups at time points 9, 10, and 11 (P = .02).

Interleukin 6. Serum IL-6 levels remained normal preoperatively and intraoperatively but increased only 2 hours after protamine administration (Figure 2B). Serum IL-6 levels remained elevated after 24 hours in all 3 groups, but they were more so in the Dx and NS groups. IL-6 activation was attenuated in the F group, but an analysis of variance revealed that this trend did not reach statistical significance (P = .124). A comparison of the means at time points 9, 10, 11, and 12 showed significant differences (F versus NS, P = .012; versus Dx, P = .014).

Interleukin 8. The serum levels of IL-8 remained close to preoperative levels before and during CPB; however, after protamine administration the levels peaked by 2 hours in all 3 groups, with an attenuated response occurring in the F group (Figure 2C). This difference did not reach statistical significance, however (P = .085). A further analysis of the means at time points 9, 10, and 11 showed that the attenuation in IL-8 release in the F group was statistically significant (F versus NS, P = .015; versus DX, P = .021).

Interleukin 10. There was a marginal increase in serum IL-10 levels before and during CPB; however, the maximum increase occurred 30 minutes after protamine administration. The levels returned to normal postoperatively (Figure 2D). Serum IL-10 levels returned to normal earlier in the F group. Serum IL-10 levels reached preoperative levels by 24 hours postoperatively. There were no statistically significant differences between the groups at any of the time points (P = .210).

Interleukin 12. The serum IL-12 level was variable in all 3 groups. In the NS group, IL-12 levels increased 30 minutes following the commencement of CPB, after the administration of protamine, and at 4 to 6 hours after the completion of surgery (Figure 2E). In the Dx group, IL-12 levels increased during CPB and by 4 hours postoperatively, whereas in the F group IL-12 levels remained near normal through out the perioperative period. There were no statistically significant differences between the groups at any of the time points (P = .061).

Tumor Necrosis Factor α. The fact that only 10 patients showed elevated TNF-α levels precluded a meaningful analysis of the data. Two patients in the NS group, 3 in the DX group, and 5 in the F group had elevated TNF-α levels (Figure 2F).

Endotoxins

Serum endotoxin levels remained near preoperative levels in the 3 groups before and during CPB. Levels increased to a peak after protamine administration and in the first 2 hours after return of the patient to the intensive care unit

(Figure 3). The increase was more marked in the Dx and F groups than in the NS group. The differences between the groups did not reach statistical significance (P = .708), however, and the mean increase in endotoxin levels at different times was not statistically significant.

DISCUSSION

Cardiac surgery with CPB is associated with an inflammatory response, which contributes to postoperative morbidity and mortality. In an attempt to reduce this response, investigators have studied several anti-inflammatory strategies, such as the use of heparin-bonded circuits, leukocyte filters, epidural anesthesia [Bach 2002], and the use of such drugs as steroids, aprotinin, and dopamine analogs. The splanchnic hypoxia and subsequent release of endotoxins demonstrated in earlier studies [Jansen 1992] led investigators to believe that improving splanchnic perfusion might attenuate the inflammatory response. Dopamine analogs have been used for their specific action on dopamine DA-1 receptors, which leads renosplanchnic vasodilatation. Previous studies have failed to categorically demonstrate the beneficial effects of routine use of dopamine analogs in the setting of cardiac surgery [Lisbon 2003]. Fenoldopam has been shown in animal and human studies to specifically cause splanchnic vasodilatation, with little effect on systemic hemodynamics [Mathur 1999]. As part of our study, we previously evaluated the effects of fenoldopam and dopexamine on hepatic blood flow and systemic hemodynamics. We demonstrated that hepatic blood flow as measured by the disappearance of indocyanine green dye did not increase with fenoldopam [Adluri 2009]. Fenoldopam administration, however, does increase the cardiac index, reduces the systemic vascular resistance, and exerts a protective effect on preserving hepatic function [Adluri 2009]. The principle aim of the current study was to study whether fenoldopam and dopexamine are effective in reducing the inflammatory response after cardiac surgery.

Effects on the Complement System

The complement system is activated by the classical, alternative, and mannose-lectin (mannose-binding protein) pathways. The exposure of blood to extracorporeal circuits activates the alternative pathway, leading to the release of C3a and C5a [Chenoweth 1981], whereas the reversal of heparin anticoagulation with protamine activates the classical pathway, with an associated increased in C4a levels and a further increase in C3a levels [Chenoweth 1981]. The release of endotoxins in the circulation may be able to activate both the classical and alternative pathways [Jansen 1992]. Complement activation in turn causes histamine release from mast cells and basophils, increased vascular permeability, and stimulation of white blood cells to release oxygen free radicals and lysosomal enzymes [Wan 1997]. C3a is a potent stimulator of platelet aggregation, whereas C5a stimulates neutrophil aggregation and adherence to endothelial cells [Utley 1990]. Many groups of investigators have demonstrated an immediate increase in serum complement levels soon after the exposure of blood to the CPB circuit [Chenoweth 1981; Jansen 1992]. C3a levels increase during CPB and remain elevated after CPB, and the magnitude of such increases has been associated with the length of CPB. The clinical relevance of complement activation is still not known; however, some investigators have suggested that increased C3a levels predict postoperative morbidity, prolonged ventilation times, the incidence of lung injury, and the development of multiorgan failure [Kirklin 1983].

The results of our study confirm complement activation soon after the beginning of CPB, with a significant attenuation in C3a levels occurring in the F group. In our study group, C3a levels remained increased in the postoperative period, but the increase was not associated with clinically noticeable morbidity. C4a levels increased after protamine administration, an observation that is consistent with activation via the classical pathway. C4a activation was attenuated in the F group; however, the difference was not statistically significant. C5a activation via the alternative pathway usually occurs immediately after the exposure of blood to an artificial surface. Our results indicate that a significant increase in C5a levels occurred in the postoperative period, with an attenuated response occurring in both of the study groups. This difference between the groups was not statistically significant.

Our study showed that fenoldopam attenuated complement activation; however, this effect has to be independent of its splanchnic-sparing effect because complement activation follows immediately after the commencement of CPB, much before the occurrence of organ hypoperfusion. Hence, we propose that fenoldopam has some anti-inflammatory effects. Our study protocol does not allow us to differentiate such properties, however. Hence, further studies will be needed to evaluate the other effects of fenoldopam.

Cytokine Activation

The release of cytokines is known to be stimulated by numerous factors, such as ischemia-reperfusion, complement activation, endotoxin release, and the effects of other cytokines [Wan 1997]. Increased TNF-α levels have been demonstrated during and after CPB [Berendes 1997], although not in all studies [Wan 1997]. CPB has been more consistently associated with the production of IL-6 and IL-8 [Wan 1997]. The levels of these cytokines have been correlated with the duration of cardiac ischemia during CPB [Wan 1996]. TNF-α and IL-6 have been associated with cardiac dysfunction after CPB, although direct hemodynamic effects are doubtful [Wan 1997]. IL-8 is a potent chemoattractant for neutrophils and may play a role in lung injury associated with the pulmonary sequestration of leukocytes. The amount of IL-10, an anti-inflammatory cytokine, often is dependent on the amount of proinflammatory cytokine release [Wan 1997]. Few studies have investigated the release of IL-12, another anti-inflammatory cytokine, after cardiac surgery. The balance between the actions of pro- and anti-inflammatory cytokines determines the extent of the inflammatory response and the clinical outcome. The myocardium has been suggested as a possible source of such cytokines as TNF-α, IL-6, and IL-8 [Wan 1997], whereas the liver is thought to be the source of IL-10 [Wan 1997]. The release of endotoxins also contributes to the degree of the cytokine

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response, hence the importance of maintaining splanchnic perfusion during CPB.

In our study group, IL-1β, IL-6, and IL-8 increased in the postoperative period, with an attenuated response occurring in the F group. Statistical significance was perceivable only in the postoperative period, with little difference observed during CPB. The increase in serum IL-10 levels following the administration of protamine corresponds to the timing of proinflammatory cytokine release. The earlier return of IL-10 levels to normal in the F group corresponds to the attenuated release of proinflammatory cytokines. Serum IL-12 levels remained increased in the control group during most of the perioperative period, a result that corresponds to the increased complement and cytokine response in this group. Maximum levels were seen immediately after the commencement of CPB, after protamine administration, and by 8 to 12 hours after surgery. Cytokine levels returned to normal by 24 hours after surgery, with all time points corresponding to the release of different cytokines. IL-12 levels appeared to be lower in the F group because of the reduced release of proinflammatory cytokines. In our study group, TNF-α release was variable and limited to a few patients at a few time points. As has been suggested, TNF-α is thought to be released from the myocardium, and its release has been correlated with the duration of myocardial ischemia. In the current study, the cross-clamping time was short in most patients, which may account for the differential release of this cytokine.

Endotoxin is a powerful activator of the inflammatory cascade [Jansen 1992]. The release of endotoxins has been shown to occur after the release of the cross-clamp and the resumption of pulsatile flow. There are many possible sources of endotoxins, but the gut is probably the most important [Wan 1997]. Splanchnic hypoperfusion during CPB causes gut mucosal ischemia [Tao 1995] and increased intestinal permeability. Riddington et al [1996] demonstrated increased intestinal permeability and increased endotoxin levels during CPB but could not demonstrate a clear relationship between the 2 events. Similarly, Andersen et al [Wan 1997] demonstrated both an increase in endotoxin levels and a decrease in the gastric intramucosal pH but found no significant relationship between the 2 parameters. Ohri et al [1993] noted that gut permeability was related to the duration of CPB, but this observation was not supported by other studies. Some investigators have shown a positive correlation between the duration of CPB and the cross-clamp time on the one hand and the release of endotoxins on the other [Rocke 1987], but other researchers [Nilsson 1990] have not been able to confirm such a relationship. Jansen et al [1992] suggested that serum endotoxin levels were related to the degree of initial vasoconstriction, the duration of aortic cross-clamping, and the degree of the hypooncotic state during CPB. The presence of endotoxin is responsible for the activation of complement via the alternative pathway and for an increased release of cytokines, including TNF-α [Wan 1997]; however, no study thus far has been able to demonstrate a correlation between elevated endotoxins levels and clinical outcomes [Wan 1997].

In our study population, peak endotoxin levels were noted after protamine administration and in the postoperative period. Surprisingly, the elevation was larger in the F group. This conflicting result is difficult to explain and could be due to the use of vasoconstrictors during CPB because of the higher fenoldopam dose.

Fenoldopam has been shown to reduce systemic vascular resistance and increase cardiac output [Gombotz 1998], thereby improving the perfusion state. Studies that have examined the gastric mucosal effects of fenoldopam have had variable results [Gombotz 1998; Schwarte 2003; Morelli 2004]. Fenoldopam was found to increase gastric mucosal blood flow in septic patients but not to have a similar effect in patients undergoing cardiac surgery [Halpenny 2001]. Most studies have used fenoldopam in lower doses (0.01-0.1 μg/kg per minute) and did not demonstrate a systemic effect of the drug. The dose used in the present study was higher than in previous series. At the dose used in this study (2 μg/kg per minute), fenoldopam showed systemic effects, and its vasodilatory effect was noticeable and required administration of vasoconstrictors in most patients. This effect seems to have affected the results, such as in the release of endotoxins. Despite this drawback, however, the F group did show attenuation in the release of certain cytokines and in complement activation. The results of the study demonstrate that routine use of fenoldopam has a partial protective effect against the inflammatory response after cardiac surgery. Whether this effect is due to a specific gut-protective action or to a nonspecific effect of an improved perfusion state has been difficult to resolve with the current study protocol.

Limitations

For the power calculation, we anticipated a reduction in cytokine release of 40%, which is a large effect; hence, the study population was small, which could have had a bearing on the lack of statistical significance. The higher fenoldopam dose used in this study than in previous studies may have affected the results. The findings of the study are applicable only to low-risk patients undergoing cardiac surgery with hypothermic CPB. Further studies are needed to study the effects of fenoldopam in off-pump CABG and normothermic cardiac surgery procedures.

CONCLUSIONS

Fenoldopam affords partial protection against the inflammatory response after cardiac surgery. A balance must be drawn between the vasodilatory effects of fenoldopam and the benefits of higher doses. The partial attenuation of the inflammatory response seen in the current study could be due to a specific action on improved gut perfusion or to improved organ perfusion due to a higher cardiac index. Studies that use the gastric pH to demonstrate mucosal perfusion in different cardiac surgery situations may prove the specific effects of fenoldopam on splanchnic perfusion.

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