The effects of intra-operative amiodarone loading on the systemic inflammatory response syndrome induced by cardiopulmonary bypass

Kardiyopulmoner baypasın indüklediği sistemik inflamatuvar yanıt sendromunda intraoperatif amiodaron yüklemesinin etkisi

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ABSTRACT

Objective: Cardiopulmonary bypass (CPB) leads to systemic inflammatory response syndrome (SIRS). In vitro studies showed that amiodarone blocked cytokine production. The aim of this study was to evaluate the effect of intra-operative amiodarone loading on SIRS.

Methods: This prospective randomized study included 24 patients who underwent on-pump coronary artery surgery. The patients were classified into control (n=12) and amiodarone (n=12) groups. Plasma levels of the pro-inflammatory (C-reactive protein - CRP, interleukin-6 - IL-6) and the anti-inflammatory markers (interleukin-10 - IL-10) were measured before the induction of anesthesia, 5 minutes after aortic declamping, after protamine administration and 24 hours after the CPB. The myocardial lactate production was calculated before CPB and 5 minutes after aortic declamping. Statistical analyses were performed using Mann-Whitney U, Fischer's exact and ANOVA tests.

Results: In both groups, the IL-6 levels significantly increased after declamping (91.18±16.27 pg/ml and 86.37±14.66 pg/ml, p<0.01) and reached peak values after infusion of protamine (329.07±32.24 pg/ml and 354.31±29.61 pg/ml, p<0.01). The highest values of IL-10 were detected after infusion of protamine in the control and amiodarone groups (265.58±85.63 pg/ml, p<0.01 and 287.44±65.26 pg/ml, p<0.01). Amiodarone did not have any significant effect on release of cytokines. The CRP levels were significantly elevated in both groups at 24th hour after CPB, but no significant difference was found between the groups. Compared with pre-CPB values, lactate production increased significantly in two groups after aortic declamping. However there was no significant difference between the groups.

Conclusions: The results indicate that intraoperative loading of amiodarone, which is used for atrial fibrillation prophylaxis, does not seem to alter inflammatory response during CPB. *(Anadolu Kardiyol Derg 2009; 9: 318-24)*

Key words: Amiodarone, cardiopulmonary bypass, inflammatory response, C-reactive protein, interleukin, coronary artery surgery

ÖZET

Amaç: Kardiyopulmoner baypas (KPB) sistemik inflamatuvar yanıt sendromuna (SIYS) yol açmaktadır. *In vitro* çalışmalarda amiodaronun sitokin üretimini bloke ettiği gösterilmiştir. Bu çalışmanın amacı intraoperatif amiodaron yüklemesinin KPB'ın indüklediği SIYS'da etkisini değerlendirmektir.

Yöntemler: Bu prospektif, randomize çalışmaya pompa eşliğinde koroner arter baypas cerrahisi uygulanan 24 hasta alındı. Hastalar kontrol (n=12) ve amiodaron (n=12) olarak 2 alt gruba ayrıldı. Proinflamatuvar (C-reaktif protein - CRP, interlökin -6 - IL-6) ve antiinflamatuvar (interlökin-10, IL-10) belirteçlerin plazma düzeyleri anestezi indüksiyonu öncesi, aortik kros klempin alınması sonrası 5. dakikada, protamin sonrası ve postoperatif 24. saatte ölçüldü. Miyokardiyal laktat üretimi KPB öncesi ve aortik klempin alınması sonrası 5. dakikada hesaplandı. İstatistiksel analizlerde Mann-Whitney U, Fischer's exact ve ANOVA testleri kullanıldı.

Bulgular: Her 2 grupta IL-6 seviyeleri aortik kros klemp kaldırıldıktan sonra belirgin arttı (91.18±16.27 pg/ml ve 86.37±14.66 pg/ml, p<0.01) ve protamin sonrası doruk değere ulaştı. (329.07±32.24 pg/ml ve 354.31±29.61 pg/ml, p<0.01) Kontrol ve amiodaron gruplarında en yüksek IL-10 değerleri protamin infüzyonu sonrası elde edildi (265.58±85.63 pg/ml, p<0.01 ve 287.44±65.26 pg/ml, p<0.01). Amiodaron tedavisinin sitokin salınımında herhangi bir etkisi yoktu. C-reaktif protein düzeyleri KPB sonrası 24. saatte belirgin olarak yükseldi ancak gruplar arasında fark bulunamadı. Pre-KPB değerleriyle karşılaştırıldığında her 2 grupta miyokardiyal laktat üretiminde belirgin artış saptandı. Bununla beraber gruplar arasında fark yoktu.

Sonuç: Bu sonuçlar atriyal fibrilasyon proflaksisi için kullanılan intraoperatif amiodaron yüklemesinin KPB sırasında oluşan immün yanıtı değiştirmediği gösterilmiştir *(Anadolu Kardiyol Derg 2009; 9: 318-24)*

Anahtar kelimeler: Amiodaron, kardiyopulmoner baypas, inflamatuvar yanıt, C-reaktif protein, interlökin, koroner arter cerrahisi

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Introduction

Cardiopulmonary bypass (CPB) provokes a systemic inflammatory response syndrome (SIRS) that may contribute to the development of postoperative morbidity and mortality (1). The contact of blood with artificial surfaces, the ischemia-reperfusion (I/R) process, and the operative trauma are possible causes of SIRS (2). Cardiopulmonary bypass activates the complement system leading to granulocyte activation that causes to the release of reactive oxygen species. In addition, CPB also triggers a systemic cytokine release such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) (3). The increase of pro-inflammatory cytokines augments the release of surface adhesive molecules from neutrophils and endothelium, thus increasing neutrophil-endothelium adherence. IL-6, being an acute phase reactant like C-reactive protein (CRP), is responsible for the neutrophil-mediated damage (4). The development of SIRS may lead to the pulmonary, renal, gastrointestinal, central nervous system and myocardial dysfunction (2). Interleukin-10 is a potent anti-inflammatory cytokine, which acts by inhibiting the synthesis of IL-1 in the activated macrophages and reduces neutrophil adhesion to the endothelial cells (5). The severity of SIRS is determined by the balance between the pro-inflammatory and anti-inflammatory cytokines (2).

Cardiopulmonary bypass and aorta cross-clamping induce myocardial hypoxia-ischemia, and transport the lactate out of the myocytes. The myocardial lactate production is associated negatively with the cardiac performance recovery during the CPB (6). In patients undergoing CPB, abnormal septal motion and a temporary decline in the left ventricular wall movements also have been documented (7). In order to minimize the impact of SIRS on cardiac surgical patients, a number of different strategies, including new pharmacologic agents, CPB circuits and components (i.e. heparin coated system, leukocyte filters), and procedures avoiding CPB (off-pump technique) have been employed (1, 2).

Currently, amiodarone, a class III antiarrhythmic agent, is frequently being used prophylactically in order to reduce the incidence of postoperative arrhythmias following the coronary artery bypass grafting (CABG) (8). In *in vitro* studies, amiodarone treatment has been shown to inhibit the release of TNF-α and IL-6 from the peripheral mononuclear cells stimulated with lipopolysaccharides (9). In amiodarone-induced lung damage, cell-mediated immune mechanisms are well-recognized and this clinical picture is considered to be similar to hypersensitivity pneumonia (10). Therefore, it is not precisely known whether amiodarone use has proinflammatory or antiinflammatory effects. The effects of amiodarone, which is used intensely during cardiac surgery, on the systemic inflammation induced by CPB have not been sufficiently studied. With this regard, only one study has yet been published, reporting that amiodarone initiated in the preoperative period and maintained in the intra-

operative and postoperative periods has a tendency of increasing the pro-inflammatory mediators (11).

The aim of this prospective study was to investigate the effects of an intraoperative loading dose of 150 mg amiodarone on CPB-induced systemic inflammatory response.

Methods

After obtaining Ethical Committee approval and informed consent, 24 patients from both sexes, aged between 40 and 70, who would undergo CABG with CPB for coronary artery disease, were enrolled in this study. The study had a double-blind, prospective and randomised (closed enveloped) design. Exclusion criteria were history of thyroid disease/operation, chronic obstructive lung disease, acute or chronic renal failure, chronic antiarrhythmic drug use, emergency operations, reoperation, additional procedures to CABG, age over 70 years, heart rate <60/min, ejection fraction (EF) <30%, acute infection, and chronic administration of an antiinflammatory treatment.

The patients were randomized as follows: control group (n=12) and amiodarone group, (n=12). Subjects in the control group received 100 ml of normal saline, while the patients in amiodarone group were administered 150 mg amiodarone (Cordarone IV, Sanofi, Turkey) diluted in 100 ml of normal saline, intravenously over 10 minutes after the induction of anesthesia.

All the patients were premedicated with midazolam (0.1 mg/kg). Induction and maintenance of anesthesia was achieved with fentanyl and midazolam, while pancuronium was used for muscle relaxation. An intra-arterial catheter was placed in the right radial artery, and a pulmonary artery catheter was inserted into the right jugular vein. A median sternotomy was performed in every case and the grafting materials were harvested simultaneously. Cardiopulmonary bypass was instituted using ascending aortic cannulation and two stage venous cannulation in the right atrium. Aortic root and coronary sinus cannulations were also made in order to administer cardioplegic solutions. Cardiopulmonary bypass was performed using a roller pump (Stockert, Germany), hollow-fiber membrane oxygenator (Dideco, Italy), and an extracorporeal circuit line set. A non-pulsatile flow of 2.4 L/min/m^2 and mild hypothermia (32-34°C) were used. During CPB, the mean arterial pressure was kept above 60 mmHg, while the hematocrit level was maintained between 20% and 25%. Heparin was given at the dose of 3 mg/kg and activated clotting time was kept above 450 second. Cardiac arrest was established initially with antegrade warm hyperkalemic blood cardioplegia (with a blood-to-crystalloid ratio of 4:1), then ante-and retrograde cold and terminal "hot shot" blood cardioplegia were administered for myocardial protection. Distal anastomoses were performed with 7/0 polypropylene running sutures, Then, the aortic cross clamp was removed and the proximal anastomosis to the aorta were completed during rewarming period. At the termination of CPB, heparin was neutralized with protamine sulfate. In the postoperative period, none of the patients received amiodarone.

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Heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and thermodilution cardiac index (CI) were recorded as follows: before anesthesia induction, after administration of protamine, and at the 24th postoperative hour.

Blood samples were taken from the arterial line at the following times: before anesthesia induction, 5 minutes after aortic declamping, after protamine administration, and at the 24th hour after the CPB. The blood samples (5 ml) obtained for plasma IL-6 and IL-10 levels were centrifuged at 5000 rpm for 10 minutes and stored at -80°C until the day of assessment. The plasma interleukin levels were evaluated by the enzyme linked immunosorbent assay (ELISA) kits (Medgenix, Biosource International, Camarillo, USA). The CRP concentrations were measured using a high sensitivity immunonephelometry technique (BN II Analyzer, Dade Behring, Marburg, Germany).

Simultaneous samples of radial artery and coronary sinus blood were obtained for determination of myocardial lactate content before CPB and at the 5th minute after aortic declamping. The lactate concentration was measured using a blood gas analyzer (Nova Stat Profile Phox L, Nova Biomedical Waltham, MA, USA) and the myocardial lactate production was calculated as: (coronary sinus lactate - arterial lactate) / arterial lactate X 100.

Statistical analysis

All statistical analyses were performed using the SPSS 15.0 statistical software (SPSS Inc, Chicago, IL). The data were expressed as mean ± standard deviation. Normality of data distribution was tested by Shapiro-Wilk method. For comparison of the demographical and clinical data, Mann-Whitney U test and Fischer's exact tests were used. For comparison of the changes in the hemodynamic and biochemical parameters in the groups, repeated measurement ANOVA test was utilized. Tukey test was used as a post hoc analysis for multi-comparison of significant results. A p value of <0.05 was considered as statistically significant.

Results

The clinical profile and operative data are shown in Table 1. The two groups were comparable with respect to the all measured variables. In both groups, there was no mortality and serious postoperative complications. Cardiopulmonary bypass, aortic cross clamp and intubation times were similar between groups. Amiodarone administration did not induce any difference in the durations of the mechanical ventilation and in the length of stay in the intensive care unit.

The principal hemodynamic parameters are summarized in Table 2. There was no significant difference between two groups in hemodynamic variables. Even though MAP in both groups decreased after protamine administration and 24th postoperative hour, this decrement was not significant. There was no statistically significant decrease in the CI after the protamine administration in both groups. The MPAP and PCWP were much higher in the groups after CPB but no statistically significant difference was found during the repeated-measures.

We could not detect statistically significant differences in IL-6 concentrations between the two groups at any time point (Table 3). Both groups had elevated IL-6 levels after aortic declamping (91.18 ± 16.27 pg/ml and 86.37 ± 14.66 pg/ml, $p<0.01$), and reached a peak after infusion of protamine (329.07 ± 32.24 pg/ml and 354.31 ± 29.61 pg/ml, $p<0.01$). At 24th hour after CPB, IL-6 levels significantly decreased in both groups, but still remained above pre-induction levels ($p<0.01$).

Before induction IL-10 levels were similar in both groups, and increased following aortic declamping (Table 3). Compared with pre-induction values, the highest values of IL-10 were detected after infusion of protamine in control and amiodarone (265.58 ± 85.63 pg/ml, $p<0.01$ and 287.44 ± 65.26 pg/ml, $p<0.01$) groups. However, analysis of these increments revealed no statistically significant difference between groups.

Table 1. Demographic features and clinical characteristics of patients

Parameters	Control group (n=12)	Amiodarone group (n=12)	p
Age, years	65.73±6.82	64.18±9.80	NS
Gender, Male/Female, n	10/5	9/6	NS
Body surface area, m^2	1.76±0.13	1.72±0.13	NS
Preoperatif LVEF, %	47.40±4.28	51.34±6.17	NS
EuroScore, points	4.62±1.93	4.51±2.09	NS
Bypass grafts per patient, n	3.13±0.91	3.40±0.69	NS
Cross-clamp time, min	73.53±22.52	74.90±16.57	NS
Duration of CPB, min	107.86±52.25	102.66±24.35	NS
Intubation time, hours	8.64±3.91	9.13±4.05	NS
Length of stay ICU, days	1.7±0.2	1.6±0.2	NS
Length of stay hospital, days	7.83±2.03	8.22±2.49	NS

Data are expressed as mean ± standard deviation and proportion.

Mann Whitney U test and Fischer exact tests

CPB - cardiopulmonary bypass, ICU - intensive care unit, LVEF - left ventricular ejection fraction, NS – not significant

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Table 2. Perioperative and postoperative hemodynamic data

Variables	Before induction	After protamine	24 hours postoperative	F	*p
HR, beat per minute					
Control group	79.46±18.76	86.35±16.84	81.84±13.17	3.264	>0.05
Amiodarone	76.22±12.53	82.54±16.75	80.44±10.59	2.964	>0.05
MAP, mmHg					
Control group	93.73±12.83	86.35±14.34	82.84±10.88	2.549	>0.05
Amiodarone	91.90±13.26	85.63±14.38	79.44±12.11	2.153	>0.05
MPAP, mmHg					
Control group	14.30±6.23	18.21±6.39	18.15±6.03	2.789	>0.05
Amiodarone	18.11±5.99	20.00±6.22	21.77±4.29	2.415	>0.05
PCWP, mmHg					
Control group	7.53±3.66	7.78±2.93	8.40±2.99	2.156	>0.05
Amiodarone	8.63±2.33	10.18±3.70	10.72±2.83	3.056	>0.05
CI, l/min/m^2					
Control group	2.64±0.53	2.49±0.35	2.68±0.40	1.986	>0.05
Amiodarone	2.75±0.63	2.48±0.40	2.84±0.52	1.988	>0.05

Data are expressed as mean ± standard deviation
*Repeated measurement ANOVA and posthoc Tukey tests
CI - cardiac index, HR - heart rate, MAP - mean arterial pressure, MPAP - mean pulmonary artery pressure, PCWP - pulmonary capillary wedge pressure

Table 3. IL-6, IL-10 and CRP levels at different stages of cardiopulmonary bypass in control and amiodarone group

Variables	Before induction	After aortic declamping	After protamine	24 hours after CPB	F	p
IL-6, pg/ml						
Control group	13.99±6.65£	86.37±14.66¥	354.31±9.61€	45.72±17.35*	772	<0.01
Amiodarone group	12.68±9.26£	91.18±16.27¥	329.07±2.24€	52.09±4.40*	842.642	<0.01
IL-10, pg/ml						
Control group	26.64±5.59&	278.57±49.05	287.44±65.26	24.99±6.84&	89.808	<0.01
Amiodarone group	21.02±9.80&	240.44±41.76	265.58±85.63	22.44±8.13&	190.957	<0.01
CRP, mg/l						
Control group	2.94±0.52	2.94±1.08	3.39±1.30	105.13±0.57*	289.614	<0.01
Amiodarone group	3.41±0.59	3.76±0.89	3.58±0.96	99.25±19.27*	296.738	<0.01

Data are expressed as mean ± standard deviation
Repeated measurement ANOVA and post hoc Tukey tests for comparison of variables between groups:
*p< 0.01 24 vs before induction, after aortic declamping and after protamine
&p<0.01 vs after aortic declamping and after protamine
£p<0.01 vs after aortic declamping, after protamine and 24 hours after CPB
¥p<0.01 vs before induction, after protamine and 24 hours after CPB
€p<0.01 vs before induction, after aortic declamping and 24 hours after CPB
CPB - cardiopulmonary bypass, CRP - C-reactive protein, IL-6 - interleukin 6, IL-10 - interleukin 10

C-reactive protein levels were identical in both groups preoperatively (Table 3). The levels of CRP did not change after aortic declamping and protamine infusion in both groups, while they were significantly elevated at the 24th hour after CPB (99.25±19.27 mg/l, p<0.01 and 105.13±20.57 mg/l, p=0.01 in the control and amiodarone-treated patients, respectively).

However, there were no significant differences between the two groups at 24th hour after CPB.

The pre-CPB values for lactate production were similar in both groups (Fig. 1). Compared with the pre-CPB, lactate production increased significantly at the 5th minute after aortic declamping in control group (from 11.27% to 19.03%, p=0.006) and amiodarone

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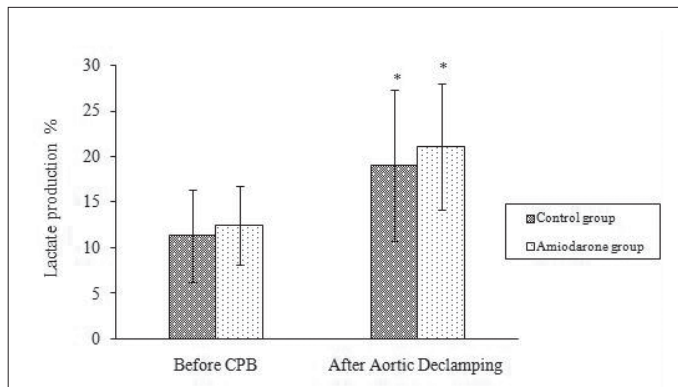
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Figure 1. Lactate production (%) in control and amiodarone groups
* p<0.05 before cardiopulmonary bypass vs after aortic declamping in both groups
CPB - cardiopulmonary bypass

group (from 12.45% to 21.04%, p=0.004). There was no statistically significant difference between the two groups.

Discussion

In this study, we evaluated whether or not amiodarone decreases inflammatory response during coronary artery surgery with CPB. In all enrolled patients, the IL-6 and IL-10 levels increased following release of the aortic cross clamp, but then decreased at 24th hour after CPB. Furthermore, CRP remarkably exhibited an increment at 24th hour after CPB. However, IL-6, IL-10 and CRP levels in the patients received amiodarone were similar to those in control subjects.

The pump-induced shear stress, activation of the coagulation system as a result of contact of blood with foreign surfaces, hypothermia, I/R injury, and endotoxemia are all possible causes of SIRS (2). The complex process of SIRS includes activation of polymorphonuclear leukocytes, monocytes, and complement system as well as the release of the mediators consisting of the cytokines such as IL-6, TNF-α, and IL-10, adhesion molecules including vascular cell adhesion molecule (VCAM-1), and chemokines i.e. elastase (12). The interaction between the leukocytes and endothelium, mediated by the listed factors, may lead to myocardial depression, multiple-organ dysfunction syndrome (MODS), coagulopathy, intravascular thrombosis and/ or death (2). The CPB-induced inflammatory response is assessed by measuring the plasma levels of inflammatory mediators IL-6 (13), IL-10 (4), CRP (14), and lactate (15).

The cytokines are comprised of low-molecular weight polypeptides that function like intercellular communication molecules and play key roles in the inflammatory reactions (13). The IL-6, a member of this group, is known as the proinflammatory cytokine, and plays a significant role in acute phase response. It contributes to the hemodynamic instability and myocardial injury following CPB particularly via acting in neutrophil-mediated ischemia/reperfusion injury (4). Synthesized by endothelial cells and leukocytes, the plasma levels of IL-6 begin to increase following cross clamping, reach a peak at the 6th hour following CPB, and remain high for 24 hours (16). This situation indicates that not only CPB but also reperfusion of the

heart and lungs also stimulate the SIRS.

Like IL-6, CRP is known to be a strong index of acute phase response (14). It is released from the liver particularly in response to interleukins such as IL-6, and its release increases following CPB accompanying the increase in IL-6; however, as its half-life is 19 hours, it peaks by the 2nd-3rd days and remains high for a longer period (17). In accordance with the previous studies, the IL-6 levels in our study were observed to raise following aortic declamping, reached a peak value after protamine administration, and decrease at the end of 24th hour after CPB. On the other hand, we found close to normal CRP levels following protamine infusion, which rose significantly at 24th hour after CPB.

Interleukin-10 is a potent antiinflammatory cytokine that reduces neutrophil adhesion to active endothelial cells (5). It may be protective against the myocardial damage of I/R that develops following aortic declamping (4). It can directly inhibit the release of proinflammatory cytokines such as IL-6, TNF-α, and IL-8. Production of IL-10 has been shown to correlate with IL-6 and IL-8, suggesting that pro- and anti-inflammatory cytokines are increased in order to their balance during CPB (2,4). In our study, the IL-10 levels were found to reach their peak values following the protamine administration.

Under normal conditions, the myocardial lactate uptake is high and lactate is a substrate preferred in the heart. Lactate production results from cellular metabolism of pyruvate into lactate under anaerobic condition (18). Splanchnic hypoperfusion during CPB related to the production of endogenous vasoactive mediators was proposed as an important event in the generation of lactate. Systemic microvascular control may become disordered in CPB resulting in peripheral arteriovenous shunting and a rise in lactate levels despite an apparently adequate oxygen supply. The myocardial lactate production rate has a negative correlation with cardiac index recovery. The changes in myocardial metabolism are evaluated via assessment of the net myocardial lactate production rate during or following the surgery. Wu et al. (7) have demonstrated that lactate production rises to approximately 40% during CPB, and begins to return to normal values following declamping. In this study, we observed that lactate production increases significantly in both groups following aortic declamping as compared to values prior to CPB.

A number of different strategies, including new CPB circuits and components, surgical techniques, and some pharmacologic agents such as glucocorticoids, complement inhibitors and aprotinin have been employed in attempt to minimize the impact of SIRS on CPB (1,10,12,16).

Amiodarone which carries the characteristics of all antiarrhythmic drugs, is a drug that has been included in Cardiopulmonary Resuscitation and Emergency Cardiovascular Care guidelines since the year 2000 (8,19). In cardiac surgery, it is used for preoperative oral administration for prophylaxis of atrial fibrillation, as well as being administered as intraoperative loading (8).

By *in vitro* studies, amiodarone has been proven to inhibit TNF-α and IL-6 production in peripheral blood mononuclear

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cells stimulated by lipopolysaccharides (9). In patients with congestive heart failure, amiodarone administration has been reported to have beneficial effects on left ventricular ejection (42). Singh et al (20) have reported that patients with non-ischemic cardiomyopathies have lower mortality rates when treated with amiodarone. It is thought that this recovery obtained with amiodarone treatment in patients with heart failure may be induced by not only the hemodynamic but also the immunomodulatory properties of the drug (21). The role of ion channels in T-lymphocyte activation and proliferation is known, and cytokine production can be inhibited by specific K^+-channel blockers such as vesnarinone (9). The inhibitor effect of amiodarone on cytokine release may be related to inhibition of the inward flow through the K^+-rectifier channels.

The IL-6 has been reported to activate myocyte cell surface marker of CD54, and to facilitate adhesion and oxidative radical-mediated injury by activated lymphocyte in the myocardium (21). It has been shown previously that IL-6 exerts negative inotropic effects mediated by myocardial nitric oxide synthase in mammal hearts (22). Also, the increments in IL-6 levels observed during heart surgery may have a role in reduced postoperative cardiac performance (23). We found reductions in cardiac indices in both groups following CPB. However, unlike the increments in IL-6, these reductions were not significant.

In animal experiments, amiodarone treatment has been shown to suppress TNF-α synthesis in bone marrow macrophages and monocytes, but to increase it in alveolar macrophages (23). In a clinical study conducted by Oral et al (24), amiodarone treatment at the same dosage was found not to alter the TNF-α level in dilated cardiomyopathy patients, but to increase them in cases of ischemic cardiomyopathy. This situation might be attributed to TNF-α expression in vascular smooth muscle and endothelial cells beside mononuclear cells, cardiac myocytes and macrophages in heart failure, which in turn would increase TNF-α release as a consequence of disruption in endothelial functions in ischemic patients.

Amiodarone use may be accompanied by thyro-, hepato-, reno- and particularly pulmonotoxicity. However, the precise mechanism underlying the development of toxic effects is unknown. Lung injury may be a direct effect of amiodarone (from the release of active iodide species), be due to the immunologic effects of the drug, or to a free radical effect (25). Likewise, increased numbers of natural killer and T-cells have been reported in bronchoalveolar fluids of animals with amiodarone induced pulmonary toxicity (10). Risk factors for the development of acute amiodarone lung toxicity include exposure to high oxygen concentrations such as the lungs of patients undergoing cardiac surgery and preexisting lung diseases (25). In our study, we found no statistically significant difference between the amiodarone treated group and controls regarding pro- and antiinflammatory parameters. This might be due to the rather low number of patients in the study groups, lack of postoperative infusion, or exclusion of patients with preexisting pulmonary pathologies. Although studies (21, 23, 24) regarding the immunomodulatory effects of amiodarone have been conducted, it possible effects on CPB-induced inflammation are not well-documented. The only study on this subject is performed by Karth et al (11), in which amiodarone was preoperatively administered for 7 days at a dose of 600 mg/day p.o., followed by intravenous infusion (45 mg/h) for 48 hours after start of surgery. They have demonstrated that amiodarone administration did not influence the TNF-α, IL-6, IL-10 and CRP levels but increased the levels of other inflammatory mediators, namely fibrinogen and monocyte chemoattractant protein I (MCP-1). Unlike Karth et al, our study did not involve the assessment of fibrinogen and MCP-I, which are rarely measured proinflammatory parameters. In agreement with the Karth et al., we did not observe any significant change in the measured inflammatory parameters (IL-6, IL-10 and CRP). Considering these, it is clear from Karth et al study that even 7-daypreoperative administration of amiodarone did not cause any change in proinflammatory parameters measured in line with our study. This provides further explanations to our findings, but these results, on the other hand, do not rule out the possible proinflammatory actions of amiodarone on other inflammatory pathways that are mediated by fibrinogen and MCP-I. Therefore, we cannot conclude on whether amiodarone has proinflammatory effects on CPB-induced inflammatory response or not.

Study limitations

The major limitation of the study is the low number of patients. Single loading dose of amiodarone and its use only at the intraoperative period systematically are the other limitations of the study.

Conclusion

The inflammatory response induced by CPB is multifactorial involving several pathways. It may not be possible to completely inhibit the proinflammatory cascade by blocking a single pathway. In our study, amiodarone was administered as a single intraoperative loading dose (150 mg for 10 minutes, i.v), and was not continued at the postoperative period. Therefore, further dose and time-dependent comprehensive studies are required for a conclusive statement on this topic.

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