Effects of different cardioplegic solutions on nitric oxide release from coronary vasculature in diabetic patients undergoing coronary artery bypass surgery

İki değişik kardiyoplejik solüsyonun koroner arter baypas cerrahisi geçiren diyabetik hastalarda koroner yataktan salınan nitrik oksit seviyelerine etkileri

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ABSTRACT

Objective: The aim of this study was to compare the effects of two different cardioplegic solutions on nitric oxide (NO) release from coronary vasculature in patients with type II diabetes mellitus undergoing coronary artery bypass grafting (CABG) surgery.

Methods: Forty patients undergoing elective CABG surgery were randomized to be given crystalloid (Group 1) or blood (Group 2) cardioplegia. Aortic and coronary sinus blood samples were taken at three different time periods and the release of NO from the coronary vasculature was determined by measuring its stable end-products, nitrite and nitrate. The difference between the aortic and coronary sinus concentrations of nitrite and nitrate represents the amount of NO released by coronary vascular bed.

Results: Before application of aortic cross-clamp, at T1 period, the levels of nitrite/nitrate from the coronary vasculature were similar in both groups (6.53±1.21 µM vs 6.07±1.24 µM , p> 0.05). However after the removal of cross-clamp, a significant decrease in NO was observed in Group 1 as compared with Group 2 (4.21±0.73 µM vs 4.92±1.02 µM, p< 0.01) . This decrease persisted at T3 period, after 30 minutes of reperfusion in group 1 being significantly different from group 2 (3.86±0.49 vs 4.37±0.72 µM, p<0.05).

Conclusion: This study has shown that in patients with type II diabetes mellitus crystalloid cardioplegia causes a decrease in the release of NO from coronary vascular bed during aortic cross-clamp and reperfusion period whereas more physiologic blood cardioplegia did not. Our findings indicate that blood cardioplegia protects endothelial function better than crystalloid cardioplegia in diabetic patients. *(Anadolu Kardiyol Derg 2006; 6: 347-51)*

Key words: Diabetes mellitus, cardiopulmonary bypass, nitric oxide

ÖZET

Amaç: Bu çalışmada kan ve kristalloid kardiyoplejinin tip II diyabeti olan hastalarda koroner yataktan salınan nitrik oksit (NO) düzeylerine etkilerini karşılaştırmayı amaçladık.

Yöntemler: Kırk hasta iki gruba ayrılarak Grup 1'de kristalloid; Grup 2'de kan kardiyoplejisi kullanılmıştır. Aort ve koroner sinüs kanları 3 farklı zamanda alınmış ve NO seviyelerindeki fark koroner yataktan salınan NO olarak kabul edilmiştir. Ayrıca indüksiyon öncesi ve kardiyopulmoner baypastan çıktıktan 15 dakika sonra hemodinamik ölçüm yapılmıştır.

Bulgular: Aortik kros klempten önce iki grup arasında farka rastlanmazken, kros klempin alınmasını takiben Grup 1'in NO seviyeleri anlamlı olarak düşük bulunmuştur (4.21±0.73 µM; 4.92±1.02 µM, p< 0.01). Bu düşüşün reperfüzyonun 30. dakikasında da sebat ettiği gözlenmiştir (3.86±0.49 µM; 4.37±0.72 µM, p<0.05). Kardiyak indeks Grup 2'deki hastalarda daha yüksek bulunmakla birlikte istatistiksel olarak anlamlı değildir.

Sonuçlar: Bu çalışmada tip II diyabeti olan hastalarda kristalloid kardiyoplejinin koroner yataktan salınan NO seviyelerini düşürdüğü bu düşüşün reperfüzyon döneminde de devam ettiği görülmüştür. Öte yandan daha fizyolojik olan kan kardiyoplejisinin bu etkiyi yapmadığı ve bu gruptaki hastalarda kardiyak indeksin daha yüksek olduğu gözlenmiştir. Bu bulguların ışığında, diyabetli hastalarda kan kardiyoplejisinin zaten disfonksiyonu olan endoteli daha iyi koruduğunu düşünmekteyiz. *(Anadolu Kardiyol Derg 2006; 6: 347-51)*

Anahtar kelimeler: Diyabet, kardiyopulmoner baypas, nitrik oksit

Introduction

Although it is being used commonly, cardiopulmonary bypass (CPB) is not an innocent technique. The contact of blood cells with the non-physiologic surfaces activates many inflammatory pathways and inflammatory cells in the body. As a consequence of this wide-spread activation, a clinical picture of " Whole Body Inflammatory Response Syndrome" develops with characteristic fluid retention, coagulation dysfunction and multiple organ dysfunction.

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In addition to CPB itself, application of aortic cross-clamp to create a bloodless surgical field, results in myocardial ischemia-reperfusion injury and causes myocardial contractile dysfunction at the end of operation. Despite vigorous use of a variety of myocardial protection methods, ischemia-reperfusion injury still can be seen. Ischemia- reperfusion injury is an end-point of variety of reasons including reactivation of local and systemic inflammatory mediators (1, 2) and endothelial dysfunction (3). It has been known, that patient with diabetes have higher risk of perioperative complications and mortality compared to those with no history of diabetes following cardiac surgery (4). Altered endothelial responses and release of endothelial substances in this patient population may play a role. Ischemia and reperfusion of the myocardium and the endothelium triggers the release of endothelin and nitric oxide (NO), important mediators of vascular tone. In diabetic patients the metabolism and production of this substances are altered (5, 6).

Nitric oxide, basally released by vascular endothelial cells, is generated by the enzyme nitric oxide synthase (NOS). Nitric oxide inhibits neutrophil and platelet accumulation (7), ameliorates 'no-reflow' phenomenon (8) and reduces infarct size (9). However, the release and metabolism of NO in diabetic patients and how it may be affected by the cardioplegic solutions are unclear.

In this study, we aimed to compare two different cardioplegic solutions with respect to NO release from coronary vascular bed in patients with type II diabetes mellitus.

Methods

This study has performed in Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center between the dates of January 2003-March 2003. After the study protocol has been approved by the local ethics committee, written informed consent was obtained from 40 American Society of Anesthesiologists (ASA) physical status II-III male patients with a history of type II diabetes, aged 50 to 70 years, undergoing elective coronary artery bypass graft surgery for two and three vessel coronary artery disease, with no history of peripheral vascular disease, hypertension and prostate hypertrophy. Patients with ejection fraction of less than 40%, those patients who used acetyl salicylic acid in the last 7 days before the surgery, and smokers were excluded from the study.

Forty patients scheduled for elective coronary artery surgery were randomized into either the cold crystalloid cardioplegia group (Group 1; n= 20) or the cold blood cardioplegia group (Group 2; n=20). In both groups the myocardium was protected by intermittent antegrade (every 20 min) and continuous retrograde cold (4-6°C) cardioplegia. Premedication was standardized and consisted of oral diazepam 0.15 $mg.kg^{-1}$ one night before surgery and intramuscular midazolam 0.07 $mg.kg^{-1}$ and scopolamine 0.01 $mg.kg^{-1}$ 1 h before surgery.

All patients had insertion of a pulmonary artery catheter (right internal jugular vein) to evaluate hemodynamics. In addition, continuous electrocardiogram, invasive blood pressure (radial artery, non-dominant side), end-tidal carbon dioxide and oxyhemoglobin saturation were monitored throughout surgery.

Anesthesia was induced with intravenous fentanyl (20 $\mu g.kg^{-1}$) and propofol (2 mg. kg^{1}). Muscle relaxation was provided with pancuronium (0.1 $mg.kg^{-1}$). Anesthetic maintenance was ensured with fentanyl infusion 0.3-1.0 $\mu g.\ kg^{-1}.min^{-1}$, propofol (1 $mg.kg^{-1}.\ h^{-1}$), and isoflurane (0.4-1.0%) until the initiation of CPB. During CPB, fentanyl was infused at 0.1 $\mu g.\ kg^{-1}.min^{-1}$, and propofol was infused at 0.5 $mg.kg^{-1}.h^{-1}$. After completion of CPB fentanyl and propofol dosages were increased to previous levels. Intermittent positive pressure ventilation (IPPV) with 10 $ml.kg^{-1}$ tidal volume at 12 $breaths.min^{-1}$ respiratory rate, and 100% oxygen (F_1O_2 =1.0) was used before the initiation and after completion of CPB. No vasodilators were used in any of the patients in the study. All patients received short-acting insulin as a continuous infusion for 24 hours starting with anesthesia induction. The rate of insulin infusion was adjusted according to the following formula:

Units per hour: Plasma glucose ($mg.dL^{-1}$)/ 150.

Blood glucose levels were monitored periodically and they were kept between 120-180 $mg.dL^{-1}$.

All patients were treated with the same operative technique by the same surgical team. Anticoagulation was achieved by administration of sodium heparin (200 $U.kg^{-1}$).

Cardiac arrest was provided by the use of cold crystalloid cardioplegia (PLEGISOL;ABBOTT LABORATORIES North Chıcago-IL 60064, USA) in Group 1 and hyperkalemic cold blood cardioplegia in Group 2, 10 $ml.kg^{-1}$ as the initial dose (1 L Blood, 20 mEq K^{+}, 16 mEq HCO_{-3}, 7.364 $mg.L^{-1}$ citrate, 16 m Mol.L-1 Mg^{++} and 1 $gr.L^{-1}$ glucose). Both crystalloid and blood cardioplegia were given by infusion bag manually. Antegrade cold induction cardioplegia infusion was not allowed to become greater than 100 mm/Hg and retrograde infusion was not continued with pressure exceeding 40 mm/Hg due to risk of myocardial edema. The cardioplegia infusion rates of antegrade and retrograde cardioplegia were 200 ml/min and 100 ml/min respectively.

During cross-clamp period, in every 20 minutes retrograde cardioplegia was repeated ($5ml.kg^{-1}$). Patients were cooled to rectal temperature of 28 ^{0}C. In all patients complete revascularization was performed. All patients had a left internal mammary artery graft to the left anterior descending coronary artery. The remainder of the bypass grafts used a reversed saphenous vein for conduit. After re-warming (rectal temperature of 36.5 ^{0}C) patients were weaned from CPB.

Before anesthesia induction, we recorded baseline measurements of hemodynamic parameters.

Arterial and coronary sinus blood were drawn simultaneously for blood gas analysis and determination of arterio-coronary sinus nitrite/nitrate concentration difference which represents the amount of NO released from coronary vascular bed were done at;

T1 : after institution of CPB and hypothermia, before the application of aortic cross clamp

T2 : immediately after cross-clamp removal

T3 : following the proximal anastomoses and 30 min of reperfusion.

At 15 min after weaning from CPB we repeated measurements of all hemodynamic parameters.

Blood samples drawn at each point of observation were centrifuged at 4000 rpm for 5 min and serums were refrigerated at -70 ^{0}C. Total NO level was determined as the total amount of nitrite plus nitrate, the stable end-products of NO, since NO is rapidly oxidized to nitrite and nitrate (9).Before the measurement,

again serums were centrifuged at high speed and supernatants were studied for nitrite/ nitrate according to Griess method at 540 nanometer spectrophotometrically (10).

SPSS (Statistical Package for Social Sciences for Windows version 10.0 Chicago, IL, USA program was used for statistical analysis. All data are presented as mean± standard deviation (SD). Parametric variables were analyzed using Student's t- test for independent samples and non-parametric variables were analyzed by using Mann Whitney U test. Intragroup comparisons were performed by using Wilcoxon test.

Intragroup changes were assessed by analyses of variances (ANOVA) for repeated measurements. A p value of 0.05 or less was considered to be statistically significant.

Results

Patients in both groups possessed similar cardiovascular disease profiles. Preoperative and peroperative characteristics are shown in Table 1. There were no significant differences between the groups with respect to age, weight, height, cross-clamp time, CPB time or perioperative therapy. Additionally, hemodynamic parameters were comparable between groups at baseline.

Table 1. Demographic and peroperative variables

Characteristic	Group 1	Group 2	P
Age,years	61.10±5.68	59.50±5.84	NS
Weight, kg	81.10±3.71	81.70±3.58	NS
Height, cm	168.00.8±1.73	169.00±1.68	NS
Vessels bypassed, n	2.60±0.50	2.50±0.51	NS
EF, %	50.45±5.97	50.10±6.60	NS
Cross-clamp time, min	48.05±8.35	50.15±10.06	NS
CPB time, min	74.90±8.48	73.10±6.60	NS
ICU stay, hr	20.05±2.81	18.70±2.71	NS
Hospital stay, days	5.90±0.96	6.15±0.93	NS
Chest tube drainage, ml	799.50±121.58	767.50±130.78	NS

CPB- cardiopulmonary bypass, ICU- intensive care unit, NS- nonsignificant

Table 2. Intraoperative nitrite/nitrate levels

Amount of nitrite/nitrate	Group 1	Group 2	P
Aorta at T1, µmol/lt	32.69±6.07	30.35±6.22	NS
Coronary sinus at T1, µmol/lt	39.23±7.28	36.42±7.46	NS
Difference at T1, µmol/lt	6.53±1.21	6.07±1.24	NS
Aorta at T2, µmol/lt	21.07±3.68	24.61±5.12	0.02
Coronary sinus at T2, µmol/lt	25.28±4.41	29.53±6.14	0.02
Difference at T2, µmol/lt	4.21±0.73#	4.92±1.02#	0.01
Aorta at T3, µmol/lt	19.34±2.49	21.89±3.60	0.01
Coronary sinus at T3, µmol/lt	23.21±2.99	26.27±4.32	0.01
Difference at T3, µmol/lt	3.86±0.49#*	4.37±0.72#*	0.05

#compared to baseline (T1) p < 0.01
*p=0.01 - differences are significant ANOVA for repeated measurements for changes through T1 to T3
CPB- cardiopulmonary bypass, NS- nonsignificant
T1: After institution of CPB and hypothermia, before the application of aortic cross clamp
T2: Immediately after cross-clamp removal
T3: Following the proximal anastomoses and 30 min of reperfusion

The changes in the nitrite/nitrate levels in aortic and coronary sinus blood and the difference between the two, which represents the release of NO from the coronary vasculature, are shown in Table 2. Before application of aortic cross-clamp, at T1 period, the nitrite/nitrate levels were similar in both groups (6.53±1.21 µM vs 6.07±1.24 µM, p>0.05). A significant decrease in nitrite/nitrate concentration was observed in group 1, immediately after the removal of aortic cross-clamp (4.21±0.73 µM vs 4.92±1.02µM, p<0.01) as compared with group 2. This decrease persisted at T3 period, after 30 minutes of reperfusion in group 1 being significantly different from group 2 (3.86±0.49 µM vs 4.37±0.72 µM, p<0.05).

Patients receiving crystalloid cardioplegia (Group 1) displayed a significant decrease in NO production at T2 and T3 periods when compared to baseline T1 period (ANOVA, p= 0.01), however, patients receiving blood cardioplegia did not (Table 2).

Hemodynamic parameters measured 15 minutes after weaning from bypass showed no differences between the two study groups (Table 3). However, cardiac index (CI) CI tended to be higher and systemic vascular resistance (SVR) was lower in Group 2. Atrial fibrillation developed in 3 (15%) patients in Group 1 and in 2 (10%) patients in Group 2 during their hospital stay. None of the patients had a stroke or any major neurological event. No patient died in the hospital. There were no serious adverse drug events. Blood glucose levels remained within the same range throughout the surgery in both groups of patients (Table 4)

Table 3. Hemodynamic parameters before anesthesia induction and 15 minutes after weaning from CPB

Parameter	Group 1	Group 2	P
CVP_{before}, mmHg	4.40±0.99	4.55±1.19	NS
CVP_{after}, mmHg	3.90±0.78	3.80±0.61	NS
MAP_{before}, mmHg	65.30±4.07	65.75±4.55	NS
MAP_{after}, mmHg	63.20±2.98	63.15±2.64	NS
CI_{before}, $L.min^{-1}.m^2$	2.25±0.18	2.29±0.16	NS
CIafter, $L.min^{-1}.m^2$	2.18±0.11	2.23±0.13	NS
$PCWP_{before}$, mmHg	9.35±1.72	8.55±1.39	NS
$PCWP_{after}$, mmHg	7.15±1.04	6.90±0.78	NS
HR_{before}, bpm	79.05±6.14	78.05±5.97	NS
HR_{after}, bpm	83.70±5.50	81.75±5.60	NS
SVR_{before}, $dyn.sn.cm^{-5}$	1143.34±130.72	1123.75±84.45	NS
SVR_{after}, $dyn.sn.cm^{-5}$	1144.28±85.54	1114.01±66.07	NS

CI- cardiac index, CPB- cardiopulmonary bypass, CVP- central venous pressure, HR- heart rate, MAP- mean arterial pressure, NS- nonsignificant, PCWP- pulmonary capillary wedge pressure, SVR- systemic vascular resistance

Table 4. Blood glucose levels

Parameter	Group 1	Group 2	P
Blood glucose at T_1,$mg.dL^{-1}$	176.4±9.5	174.6±8.9	NS
Blood glucose at T_2, $mg.dL^{-1}$	175.5±5.6	171.7±6.7	NS
Blood glucose at T_3, $mg.dL^{-1}$	178.6±5.3	174.9±5.7	NS

T_1: After institution of CPB and hypothermia, before the application of aortic cross clamp
T_2: Immediately after cross-clamp removal
T_3: Following the proximal anastomoses and 30 min of reperfusion
CPB- cardiopulmonary bypass, NS- nonsignificant

Discussion

Nitric oxide has been accepted as one of the vasoactive mediators implicated in cardiovascular and diabetic pathophysiology. The effect of different cardioplegic solutions on NO release from the coronary vasculature during cardiopulmonary bypass in patients with type II diabetes has not been characterized. In the present study, the levels of NO released from the coronary vasculature before cardioplegic arrest and after reperfusion were compared between two groups of diabetic patients receiving different cardioplegic solutions. This study has shown that in patients with type II diabetes mellitus, crystalloid cardioplegia decreased the release of NO from coronary vasculature during aortic cross-clamp and reperfusion period whereas more physiologic blood cardioplegia did not.

The production and metabolism of NO is altered in diabetic patients according to some studies (5). However NO metabolism in diabetics during cardiac surgery involving cardiopulmonary bypass is still not clearly defined. Matata et.al (11) showed increased production of NO in diabetic patients during cardiopulmonary bypass but in that study they measured the amount of NO from the peripheral blood not from the coronary effluent, suggesting that the source of the increase in NO production is not the heart. On the other hand Sharma et.al (12) have shown elevated levels of endothelin-1 (ET-1) but no change in NO levels in the coronary effluent in patients with diabetes. Different from our study Sharma cooled the patients to 30 °C and used warm blood cardioplegia after the last distal anastomosis. These factors may decrease the impact of ischemia-reperfusion on endothelial injury and therefore they did not experience the decrease as in our study.

Nitric oxide, basally released by vascular endothelial cells, is an important determinant of vascular tone and vascular patency. It accounts for vasodilation. However, the role of NO in global myocardial ischemia and reperfusion is controversial. In literature some studies have shown its cardioprotective effects whereas others indicated that increased myocardial NO release induced by ischemia may contribute to reperfusion injury (13). Potential cardioprotective effects include inhibition of neutrophil and thrombocyte accumulation, inhibition of release of mediators from neutrophils (14), attenuation of 'no-reflow- phenomenon' (15). Thus, diminished NO release by the coronary vascular endothelium may play an important role in the pathogenesis of myocardial ischemia-reperfusion injury (16). In acute ischemia, restoration of blood supply and reduction of metabolic demand are the protection mechanisms and increased levels of NO have been shown to support these mechanisms (17). However, it is also possible to find studies reporting the deleterious affects of increased NO levels on myocardial performance after ischemic arrest (13, 18-20). Nitric oxide is synthesized from L-arginine by NOS. In the presence of oxygen-derived free radicals NO was metabolized to peroxynitrite (OONO-) which is toxic for vascular endothelium. Thus, the increase in NO levels in the hypoxic medium and in the presence of oxygen-derived free radicals in the same environment may explain the conflicting results in the literature (21).

The effect of CPB on the endothelial injury in diabetic patients has not been thoroughly studied. However it is now well-known that in diabetic patients ET-1 levels significantly rises after myocardial revascularization (12, 22). Interestingly in the non-diabetic population CABG causes no changes in plasma profiles of ET-1 (23, 24). Endothelin, produced by the vascular endothelium, is also an important mediator of vascular tone. In the coronary vasculature, ET-1 mediated vasoconstriction may be detrimental and would favor increased coronary vascular resistance, impaired tissue perfusion and exacerbation of the reperfusion injury. Verma et.al (25) reported that diabetic coronary microvessels respond to bypass and reperfusion with greater endothelin-1- mediated vasoconstriction and diminished NO-mediated vasodilatation and these effects were attenuated by endothelin antagonism. Coronary artery surgery, by its nature, involves ischemia and reperfusion. Thus, an increased ET-1 levels associated with altered endothelial dysfunction in diabetic patients may be associated with negative outcomes. Although the release of ET-1 during CPB in diabetic population has been studied, the effect of CPB and cardioplegic solutions on NO production in the same patient population is not clear. Our data show that, during cardioplegic arrest provided by crystalloid cardioplegia the release of NO from the coronary vasculature decreased significantly compared to blood cardioplegia. This decrease is persistent and become even more pronounced during reperfusion period. Our findings are in agreement with the results of previous studies (26, 27). One mechanism is that, NO release decreases during cross-clamp period due to the depletion of L-arginine, the substrate for NO synthesis in Group 1, since crystalloid cardioplegic solutions do not contain L-arginine, whereas blood cardioplegia does. The other possible mechanism to explain the decrease in NO production during cross-clamp period is that, the endothelial damage is caused by crystalloid hyperkalemic cardioplegic solutions per se (28). Blood cardioplegia, in this point of view, appears to carry a number of advantages over crystalloid cardioplegia. Its oxygen carrying capacity, pH-buffering ability and oxygen radical scavengers in the erythrocytes limit the ischemia-reperfusion injury during cross-clamp period. The third mechanism is the temperature difference between the cardioplegic solutions. The administration of cold (4 °C) crystalloid cardioplegic solution might have decreased the myocardial temperature resulting in depression in the activity of NOS. On the other hand, blood cardioplegia is always warmer than crystalloid cardioplegia. Since NO synthesis is affected by temperature, this point is one of the limiting factors in the present study (29).

After 30 minutes of reperfusion, the level of NO release from coronary vessels continued to decrease although during this period the myocardium was perfused with blood. This suggests that the coronary endothelial dysfunction persisted during reperfusion period and is in agreement with our and other authors' results on impairment of endothelial functions following cardioplegic arrest (30, 31).

However, despite the decrease in NO levels we did not observe any difference in hemodynamic parameters or clinical picture of patients after CPB . This may result from the our inclusion criteria of enrollment of patients with EF > 40 %. The relatively preserved ventricular function might have compensated the otherwise negative outcome of decreased NO levels. Further studies including patients with lower EF are required to determine the impact of ventricular function on negative effects of decreased NO levels. On the other hand, although not significant, SVR measurements performed after weaning from CPB were found to

be lower and CI were found to be higher in patients receiving blood cardioplegia. This finding is parallel with higher levels of nitrite/nitrate levels in this group since NO is one of the potent vasodilators.

In conclusion, the present study, showed that the level of NO release from coronary vasculature decreased during cardioplegic arrest and this decrease persisted during reperfusion period in patients receiving crystalloid cardioplegia as compared to blood cardioplegia in patients with type II diabetes. Our data suggest that crystalloid cardioplegia induced myocardial arrest may lead to endothelial dysfunction which results in limited recovery during early reperfusion as proved by decreased NO levels. We believe our findings have important implications for diabetic patients since cardiac surgery carries high risks of morbidity and mortality for this patient population. Thus, to decrease the perioperative complications and clear the mechanisms and pathways resulting in negative outcome and to determine the significance of what we know today, further investigations are warranted.

References

1. Giomarelli P, Scoletta S, Barrelli E, Biagioli B. Myocardial and lung injury after cardiopulmonary bypass: role of interleukin (IL)-10. Ann Thorac Surg 2003; 76 : 117-23.
2. Massoudy P, Zahler S, Becker BF, Braun SL, Barankay A, Meisner H. Evidence for inflammatory responses of the lungs during coronary artery bypass grafting with cardiopulmonary bypass. Chest 200; 119: 31-6.
3. Mentzer RM, Jahania MS, Lasley RD. Myocardial protection. In:Lawrence HC, Edmunds HL, editors. Cardiac Surgery in the Adult. 2nd edition. New York: Mc Graw Hill Companies; 2003. p 413-38.
4. Cohen Y, Raz I, Merin G, Mozes B. Comparison of factors associated with 30- day mortality after coronary artery bypass grafting in patients with and without diabetes mellitus. Am J Cardiol 1998; 81: 7-11.
5. Catalano M, Garzaniga G, Perilli E, Jun T, Scandale G, Andreoni S, et al. Basic nitric oxide is not reduced in patients with non-insulin dependent diabetes mellitus. Vascular Med 1997; 2: 302-5.
6. Matata BM, Galinanes G. Cardiopulmonary bypass exacerbates oxidative stress but does not increase proinflammatory cytokines release in patients with diabetes compared with patients without diabetes: regulatory effects of exogenous nitric oxide. J Thorac Cardiovasc Surg 2000; 120:1-11.
7. Moncada S, Palmer RMJ, Higgs EA. Nitric oxide:physiology, pathophysiolgy and pharmacology. Pharmacol Rev 1991; 43: 109-42.
8. Pearson PJ, Lin PJ, Schaff HV. Global myocardial ischemia and reperfusion impair endothelium-dependent relaxations to aggregating platelets in the canine coronary artery. A possible cause of vasospasm after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1992; 103: 1147-54.
9. Wennmalm A, Benthin G, Peterson A.S. Dependence of the metabolism of nitric oxide (NO) in healthy human whole blood on the oxygen of its red cell haemoglobin. Br J Pharmacol 1992; 106: 507.
10. Tracey WR, Tse J, Carter G. Lipopolysaccharide-induced changes in plasma nitrite and nitrate concentrations in rats and mice: pharmacological evaluation of nitric oxide synthase inhibitors. J Pharmacol Exp Ther 1995; 27: 1011-5.
11. Matata B, Galinanaes M. Effect of diabetes on nitric oxide metabolism during cardiac surgery. Diabetes 2001; 50; 2603-10.
12. Sharma AC, Fogelson BG, Nawas SI, Vigneswaran WT, Sam AD 2nd, Alden KJ, et al . Elevated coronary endothelin-1 but not nitric oxide in diabetics during CABG. Ann Thorac Surg 1999; 67: 1659-63.
13. Selke FW, Boyle EM, Verrier ED. The pathophysiology of vasomotor dysfunction. AnnThorac Surg 1997; 64; 9-15.
14. L üscher TF, Yang Z, Tschudi M, von Segesser L, Stulz P, Boulanger C, et al. Interaction between endothelin-1 and endothelium derived relaxing factor in human arteries and veins. Circ Res 1990; 66: 1088-94.
15. Dignan RJ, Yeh T, Dyke CM, Lee KF, Lutz 3 rd Ha, Ding M, et al. Reactivity of gastroepiploic and internal mammary arteries. Relevance to coronary artery bypass grafting. J Thorac Cardiovasc Surg 1992; 103: 116-23.
16. Lefer DJ, Nakanishi K, Johnson WE, Vinten- Johansen J. Antineutrophil and myocardial protection actions of a novel nitric oxide donor after acute myocardial ischemia and reperfusion in dogs. Circulation 1993; 88: 237-50.
17. Selke FW, Shafique T, Scoen FJ, Weintraub RM. Impaired endothelium-dependent coronary microvascular relaxation after cold potassium cardioplegia and reperfusion. J Thorac Cardiovasc Surg 1993; 55: 977-81.
18. Mehlhorn U, Bloch W, Krahwinkel A, LaRose K, Geissler H, Hekmat K, et al. Activation of myocardial constitutive nitric oxide synthase during coronary artery surgery. Europ J Cardiothorac Surg 2000; 17: 305-11.
19. Nonami Y. The role of nitric oxide in cardiac ischemia-reperfusion injury. Jpn Circ J. 1997; 61: 119-32.
20. Brady AJ, Warren JB, Poole WP, Williams TJ, Harding SE. Nitric oxide attenuates cardiac myocyte contraction. Am J Physiol 1993; 265: 176-82.
21. Nakano T, Tearato H, Asagoshi K, Masaoka A, Mukta M, Ohyama Y, et al. J Biochem 2003; 278: 25264-72.
22. Fogelson BG, Nawas S I, Vigneswaran VT, Ferguson JL, Law WR,Sharma AC. Diabetic patients produce an increase in coronary sinus endothelin 1 after coronary artery bypass grafting. Diabetes 1998; 47: 1161-3.
23. Mair P, Mair J, Waldenberger F, Furtwaengler W, Balogh D, Puschendorf B. Coronary sinus endothelin-1 concentrations after cardioplegic arrest. Coron Artery Dis 1995; 6: 533-7.
24. Hasdai D, Erez E, Gil-Ad I, Raani E, Sclarovsky S, Barak Y, et al. Is the heart a source for elevated circulating endothelin levels during aortacoronary bypass grafting surgery in human beings? Cardiovasc Surg 1996; 112: 531-6.
25. Verma S, Maitland A, Weisel RD, Fedak PW, Li SH, Mickle DA, et al. Increased endothelin-1 production in diabetic patients after cardioplegic arrest and reperfusion impairs coronary vascular reactivity: reversal by means of endothelin antagonism. J Thorac Cardiovasc Surg 2002; 6: 1031-4.
26. Tarr FI, Sasvari M, Dudas G, Kroo M, Somogyi A, Tomcsanyi I. Quantitative measurement of endothelium derived nitric oxide production of the internal mammary artery bypass graft during extracorporeal circulation. Euro J Cardiothorac Surg 2001; 19: 653-6.
27. Gohra H, Fujimura Y, Hamano K, Noda H, Katoh T, Zempo N, et al. Nitric oxide release from coronary vasculature before, during, and following cardioplegic arrest. World J Surg 1999; 23: 1249-53.
28. Keller MW, Geddes L, Spotnitz W, Kaul S, Duling BR. Microcirculatory dysfunction following perfusion with hyperkalemic, hypothermic, cardioplegic solutons and blood reperfusion: effects of adenosine. Circulation 1991; 84: 2485-8.
29. Ruvolo G, Speziale G, Greco E, Tritapepe L, Mollace V, Nistico G, et al. Nitric oxide release during hypothermic versus normothermic cardiopulmonary bypass. Eur J Cardiothorac Surg 1995; 9: 651-4.
30. Gohra H, Tsuboi H, Sasaki G, Minami Y, Hamano K, Katoh T, et al. Effect of cardioplegic arrest and reperfusion on coronary reserve and autoregulation. Ann Thorac Surg 1996; 62: 744-6.
31. Selke FW, Shafique T, Scoen FJ, Weintraub RM. Impaired endothelium-dependent coronary microvascular relaxation after cold potassium cardioplegia and reperfusion. J Thorac Cardiovasc Surg 1993; 55: 977-81.