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Tyrosine and dopamine blood concentrations during dobutamine infusion in patients undergoing extracorporeal circulation

The disorders of hormonal-metabolic equilibrium of the organism, especially during highly specialized procedures, such as extracorporeal circulation (ECC) are still the subject of many clinical studies (1,2,5). The complex character of ECC is not without an influence on homeostasis causing disorders of levels of individual blood parameters as well as changes in their interrelations. A special problem seems to be associated with variations of the substrate-product relation, which are important for the stress response of the substance. Its example is a well known tyrosine--dopamine system. It is commonly known that the basic catecholamine is formed from the endogenous amino acid – tyrosine with the help of tyrosine hydroxylase (TH). This reaction depends not only on the activity of the mentioned enzyme but also on the amount of circulating catecholamines and the treatment used (2,3).

Dobutamine is a substance exhibiting positive inotropic action, which is administered in continuous infusions to hemodynamically unstable patients. It may contribute to a decrease in endogenous catecholamine concentrations in blood (3), which seems to affect their production.

The aim of the study was to assess the relations between dopamine and tyrosine blood concentrations in patients undergoing myocardial revascularization who required dobutamine infusions.

MATERIAL AND METHODS

The study was approved by the Committee of Bioethics of the Medical University of Lublin (no. KE – 0254/244/2000) and included the patients operated on due to coronary disease I or II° (according to CCS).

Premedication administered in the evening preceding the operation consisted of oral lorazepam (Lorafen, Polfa, Pl) – in the dose of 2 mg and i.v. promethazine (Dophergan, Polfa, PL) in the dose of 50 mg. One hour before anaesthesia all of the patients received oral lorazepam (3 mg) and i. v. morphine (*Morphinum hydrochloricum*, Polfa, Pl). (0.1 mg/kg body wt). The general anaesthesia was induced with phentanyl (Fentanyl, Polfa, Pl) in the dose of 0.01–0.02 mg/kg body wt., midazolam (Dormicum, Roche) - 0.05–0.1 mg/kg body wt. and etomidate (Hypnomidat, Janssen, D) – 0.1–0.5 mg/kg body wt. Muscle relaxation was achieved using a single dose (0.08–0.1 mg/kg body wt) of pancuronium (Pavulon, Organon-Teknika, F). During the operation anaesthesia was maintained with the mixture of midazolam and phentanyl and fractionated doses of inhalatory forane (Izofluran, Abbot, USA). During the procedure and anaesthesia the patients were subjected to intermittent positive pressure ventilation (IPPV) using the mixture of oxygen and air (1:1) with the following ventilation parameters : tidal volume – 19 ml/kg body wt., respiration rate – 9/min, peak inspiratory pressure – 25 cm H_2O. During the implantation of aortic-coronary bypasses the circulation and ventilation were maintained using the heart-lung apparatus S III(Stockert). The following substances were used for priming: Ringer's solution (Ringer, Fresenius-Kabi, G) in the amount of 1000 ml, 6% solution of hydroxyethylated starch (HAES, Fresenius-Kabi, G) 500 ml, 20% mannitol (Mannitol, Fresenius-Kabi, G) 250 ml, sodium hydroxycarbonate (*natrium bicarbonatum*, Polfarma, Pl) – 20 ml and heparin in the dose of 75 ml. Cardioplegia was prepared with 0.9% salt solution supplemented with 3 g of potassium chloride (*kalium chloratum*, Polfa, PL) and 20 ml of sodium hydroxycarbonate.

The patients had their last meal 12 hours before the operation; immediately after the procedure they were transferred to the Postoperative Intensive Care Unit where they received a short infusion of 5% glucose-insulin solution.

The patients were divided into two groups: A – those not requiring dobutamine infusions and B – those requiring dobutamine infusions in the dose dependent on their clinical state. The changes in blood levels of dopamine and tyrosine and their relations were evaluated. The examinations were performed at 5 stages: 1) after the radial artery cannulation before initiation of anaesthesia and operation, 2) during deep hypothermia, 3) after the operation before transferring the patient to PICU, 4) on the first postoperative day, 5) on the second postoperative day.

The blood samples were collected from the radial artery and centrifuged (2500 r/min., temp. 0°C); and the obtained serum was frozen at -20°C. The determinations of tyrosine levels were performed after serum deproteinization with 6% solution of sulphosalicylic acid using liquid chromatography in the AAA-400 apparatus, INGOS, Prague.

The results were statistically analysed using the Wilcoxon and Mann-Whitney tests with regard to interstage and intergroup relations.

RESULTS

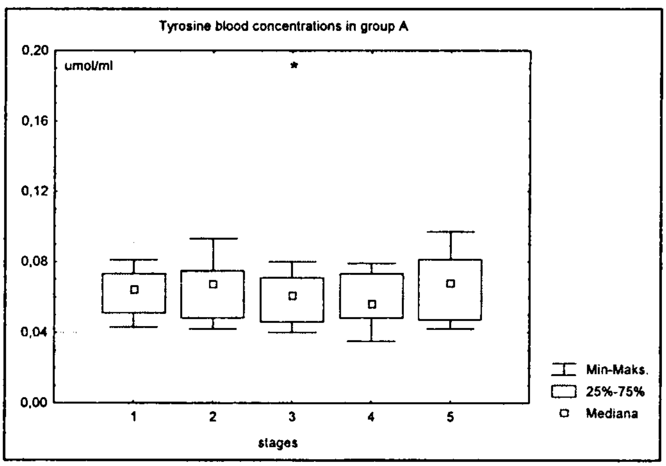

Fig. 1 Changes of tyrosine blood concentrations during each stages in group A

The examinations were performed in 20 men, aged 53–70 years (65.1±6.3). Seventeen had myocardial infarction during the last three years and 15 were treated due to concomitant arterial hypertension I° (according to WHO classification). None of the patients was treated because of systemic diseases or experienced sudden cardiac arrest. The mean time of operation was 210 min.±38 and of anaesthesia 245 min.± 41. In all the patients, the aorta was typically closed and the mean time of its closure was 41 min.±15.5. The aortic-coronary bypass was implanted in shallow hypothermia, whose mean value was 34.5°C±0.39. The discontinuation of the heart-lung apparatus was uneventful in all cases; moreover, the use of intraaortal contrapulsation was not required. In the examined group, five patients did not need catecholamine substitution (group A) while 15 patients received the dobutamine infusion (group B) in the third stage (3/15 ug/kg body wt – average 9.32±2.71).

The examinations revealed a significant decrease in blood tyrosine levels ($p<0.05$) in the third stage in group A (Fig. 1). There were no intergroup differences in the levels of that amino acid.

The blood levels of tyrosine dropped in group B ($p<0.05$) in the same stage (Fig. 2), in which significant intergroup differences were also observed.

No correlations between tyrosine and dopamine levels in blood were demonstrated.

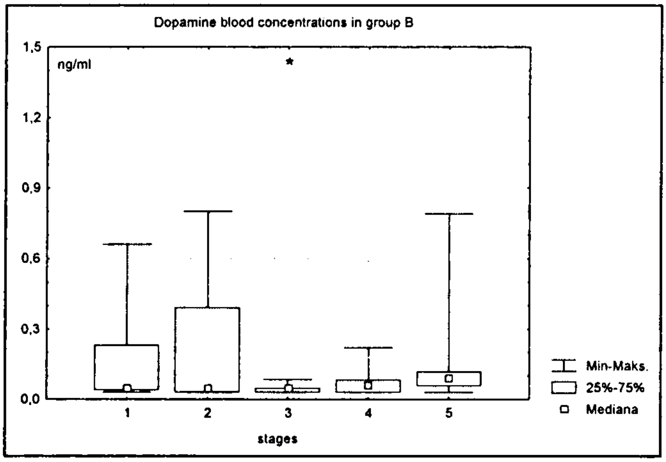

Fig. 2 Changes of dopamine blood concentrations during each stages in group B

DISCUSSION

The effects of ECC as well as intraoperative dobutamine infusion on tyrosine–dopamine relations and blood tyrosine levels are not explicitly defined. It may be assumed that hypercatecholemia accompanying this kind of procedure and inotropic treatment affect the levels of the examined parameters (2,3). Many authors also stress also an important influence of stress on the activity of TH – the enzyme acting directly on the tyrosine molecule, indispensable for the production cycle of catecholamines (5,9), which is likely to result in disorders of the balance discussed. It is well known that an increase in TH activity is reflected in variations of the level of the amino acid examined. Does, however, the operative procedure cause the tyrosine–dopamine relations and changes in levels of both mentioned above substances? Examining the blood tyrosine level in healthy persons and those subjected to gynaecological operations, Gomar et al. (6) found a significantly higher level of that amino acid in the operated group, which may suggest that stress situation affects the tyrosine level in blood serum. Furthermore, Knopp et al. (8) determining blood catecholamine levels in patients after partial hepatectomy observed a significant increase in TH activity, resulting from its increased synthesis. Likewise, Adams and McMillen (1), who studied the effects of stress and hypoxia on catecholamine synthesis, demonstrated increased activity of the enzyme in the question resulting from prolonged hypoxia. Hypercatecholemia, underlined by many researchers, which accompanies extracorporeal circulation procedures is also worth stressing (2,3,4). Thus it may be thought that ECC procedures cause changes in levels of both parameters studied.

It is difficult, however, to define explicitly what the effects of extracorporeal circulation itself are. Analyzing variations of blood amino acid levels in patients subjected to ECC procedures, S t r a s c i a et al. (10) observed significantly lower values of tyrosine at the end of the procedure, yet they did not clearly define the cause of those changes. On the other hand, the lack of tyrosine level changes observed by G o m a r a et al. (6) during procedures with high doses of phentanyl is worth pointing out. It should be added that analgesics markedly decrease the adrenergic response of the organism to stress, thus decreasing the blood levels of catecholamines (7). Therefore, it should be assumed that high doses of opioids used in our study limited the organism's response to operative stress and the changes observed were likely to result from the extracorporeal circulation procedure itself.

Discussing the changes in blood dopamine levels, its substantially lower level in patients receiving dobutamine is worth stressing. It is difficult to define clearly the causes of hormone variations. It seems that the use of inotropic substance decreases the dopamine secretion, which is confirmed by a significant intergroup difference in dopamine levels observed in our study, however it is impossible to define conclusively the effects of dobutamine on secretion and production of the catecholamine discussed and the issue requires further studies. The lack of blood tyrosine level changes in the group receiving dobutamine and its significant decrease in patients who did not receive inotropic substances are also worth stressing. All considered, it may be assumed that tyrosine levels are greatly dependent on the blood dopamine level, which seems to indicate intact tyrosine–dopamine relation.

CONCLUSIONS

1. The procedures of myocardial revascularization with extracorporeal circulation cause a decrease in blood tyrosine levels.
2. The intraoperative dobutamine infusion reduces the blood dopamine level.
3. The procedure of extracorporeal circulation does not disturb the substrate – product relation, i.e. the tyrosine–dopamine relation.

REFERENCES

1. A d a m s M.B., M c M i l l e n I.C.: Actions of hypoxia on catecholamines synthetic enzyme mRNA expression before and after development of adrenal innervation in the sheep fetus. J. Physiol., 529, 519, 2000.
2. D ą b r o w s k i W., R z e c k i Z., C z a j k o w s k i M., S t ą ż k a J., N e s t o r o w i c z A.: Wpływ śródoperacyjnej hemodilucji na stężenia endogennych amin katecholowych podczas rewaskularyzacji krążenia wieńcowego. Anest. Int. Ter., 36, 18, 2004.
3. D ą b r o w s k i W. et. al.: Wpływ infuzji dopaminy lub dobutaminy na stężenie endogennych amin katecholowych w warunkach krążenia pozaustrojowego. Anest. Int. Ter., 34, 35C, 2002.
4. D e s b o r o u g h t J. P. e t . a l .: Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block. Br. J. Anaesth., 64, 688, 1990.
5. E r d e m R. S. et. al.: Effect of exercise on mRNA expression of select adrenal medullary catecholamines biosynthetic enzymes. J. Appl. Physiol., 93, 463, 2002.
6. G o m a r C. et. al.: Tyrosine serum levels during anesthesia with high doses fentanyl. Acta Anaesthesiol. Belg., 34, 97, 1983.
7. G r u b e r E. M. et. al.: Stress response in infants undergoing cardiac surgery: a radomized study of fentanyl bolus, fentanyl infusion and fentanyl–midazolam infusion. Anesth. Analg., 92, 882, 2001.
8. K n o p p J. et. al.: Changes in plasma catecholamines and corticosterone levels and gene expression of key enzymes of catecholamines biosynthesis in partially hepatectomized. End Reg., 33, 145, 1999.

9. S a b b a n E. L., K v e t n a n s k y R.: Stress triggered activation of gene expression in catecholaminergic system: dynamics of transcriptional events. Trends Neurosci., 24, 91, 2001.
10. S t r a s c i a E. et. al.: Free amino acids in plasma and erytrocytes during and after cardiopulmonary by-pass in open heart surgery. Resuscitation, 4, 115, 1975.

SUMMARY

The disorders of hormonal-metabolic relationship of the organism, especially during highly specialized procedures, such as extracorporeal circulation (ECC) are still the subject of many clinical studies. The multi-stage, complex character of ECC causes the changes in blood dopamine levels, which may result in disorders of the tyrosine–dopamine axis. Moreover, the intraoperative treatment may result in changes of such relationship. The aim of the study was to assess the relations between dopamine and tyrosine blood concentrations in patients undergoing myocardial revascularization who required dobutamine infusions. 20 male patients aged 53 to 70 underwent CABG. The patients was divided into two groups: A – those not requiring dobutamine infusions and B- those requiring dobutamine infusions in the dose dependent on their clinical state. The changes in blood levels of dopamine and tyrosine and their relations were evaluated. The examinations were performed at 5 stages: 1) after the radial artery cannulation before initiation of anaesthesia and operation, 2) during deep hypothermia, 3) after the operation before transferring the patient to PICU, 4) on the first postoperative day, 5) on the second postoperative. The examinations revealed a significant decrease in blood tyrosine levels ($p<0.05$) in the third stage in group A. There were no intergroup differences in the levels of that amino acid. The blood levels of tyrosine dropped in group B ($p<0.05$) in the same stage, in which significant intergroup differences .were also observed. No correlations between tyrosine and dopamine levels in blood were demonstrated.

Wpływ infuzji dobutaminy na stężenia tyrozyny i dopaminy we krwi pacjentów poddanych zabiegom z zastosowaniem krążenia pozaustrojowego

Zaburzenia równowagi hormonalno-metabolicznej ustroju, zwłaszcza podczas wysoko wyspecjalizowanych i złożonych procedur, jaką bez wątpienia jest operacja z zastosowaniem krążenia pozaustrojowego, są nadal tematem wielu badań klinicznych. Szczególny problem wydają się przy tym stanowić wahania relacji substrat–produkt, jaką jest powszechnie znana zależność tyrozyna–dopamina. Nie bez znaczenia na wspomnianą równowagę ma również wpływ stosowanego śródoperacyjnie leczenia. Celem pracy była ocena zależności zmian stężenia dopaminy i tyrozyny we krwi pacjentów poddanych operacjom rewaskularyzacji mięśnia sercowego, u których zaszła konieczność zastosowania wlewu dobutaminy. Badania przeprowadzono u 20 mężczyzn w wieku od 53 do 70 lat (65,1 ± 6,3). Pacjentów podzielono na dwie grupy: A – niewymagający wlewu dobutaminy oraz B – wymagający wlewu dobutaminy w dawce zależnej od stanu klinicznego. Ocenie poddano zmiany stężenia dopaminy oraz tyrozyny we krwi, a także ich wzajemną zależność. Badania przeprowadzano w pięciu etapach: 1) po kaniulacji tętnicy promieniowej przed rozpoczęciem znieczulenia i operacji, 2) w trakcie najgłębszej hipotermii, 3) po zakończonej operacji przed oddaniem pacjenta na OIOP, 4) w pierwszej dobie pooperacyjnej, 5) w drugiej dobie pooperacyjnej. Przeprowadzone badania wykazały w trzecim etapie istotny spadek stężenia tyrozyny we krwi w grupie A oraz dopaminy w grupie B, w której zanotowano również znamienne różnice pomiędzy stężeniem dopaminy w obu grupach. Na podstawie przeprowadzonych badań stwierdzono, że operacje rewaskularyzacji mięśnia sercowego z zastosowaniem krążenia pozaustrojowego powodują spadek stężenia tyrozyny we krwi; śródoperacyjny wlew dobutaminy zmniejsza stężenie dopaminy we krwi oraz procedura krążenia pozaustrojowego nie zaburza relacji substrat–produkt, jaką jest zależność tyrozyna–dopamina.