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Tyrosine and noradrenaline blood concentrations during CABG

The literature reports underline the importance of an issue concerning the effects of operation and anaesthesia on hormonal and amino acid balance of the organism (4-14). Moreover, it may seem that catecholaminemia observed during surgical procedures affects the amino acid balance, particularly amino acids which are the substrates for catecholamines. Such a commonly known relation is the tyrosine-noradrenaline axis. However, it is difficult to define explicitly the disorders of tyrosine balance during highly specialized procedures which undoubtedly include extracorporeal circulation operations. The multi-stage, complex character of such operations causes the changes in blood noradrenaline levels (4,13), which may result in disorders of the tyrosine--noradrenaline axis. These disorders may be important not only in the perioperative period but also immediately after the procedure.

The aim of the study was to evaluate the changes in blood tyrosine and noradrenaline levels in patients undergoing surgical revascularization of the myocardium with extracorporeal circulation.

MATERIAL AND METHODS

The study was conducted with the consent of the Committee of Bioethics, Medical University of Lublin (no KE-0254/244/2000) and enrolled the patients subjected to surgery for degree I and II of coronary disease (according to CCS). In the evening preceding the operation the patients were administered premedication consisting of oral lorazepam (Lorafen, Polfa, Pl.) in the dose of 2 mg and intramuscular promethasine (Biphergan, Polfa, Pl.) in the dose of 50 mg. One hour before anaesthesia all the patients were given oral 3 mg of lorazepam and intramuscularly 0.1 mg/kg body wt of morphine (Morphicum hydrochloricum, Polfa, Pl). All of them underwent general anaesthesia using fentanyl (Fentanyl, Polfa, Pl) in the dose of 0.01–0.02 mg/kg body wt., midazolam (Dormicum, Roche, Ch) – 0.05–0.1 mg/kg body wt. and etomidate (Hypnomidat, Janssen, G) – 0.1– 0.5 mg/kg body wt. Muscle relaxation was achieved using pancuronium in a bolus (from 0.08 to 0.1 mg/kg body wt.) (Pavulon, Organon-Teknika, F.) During the procedure anaesthesia was maintained by infusing the mixture of midazolam and fentanyl as well as fractionated doses of foran (Izofluran, Abbot, USA) administered by inhalation. During anaesthesia and surgery all the patients were subjected to IPPV (Intermittent Positive Pressure Ventilation) using the mixture of oxygen and air, 1:1 with the following ventilation parameters: tidal volume – 10 ml/kg body wt., respiration rate – 9/min., peak inspiratory pressure 0–25 cm H_2O. During aorto-coronary bypass grafting, circulation and ventilation were maintained by means of the S III lung-heart apparatus. Stockert. Priming was conducted using the Ringer solution (Ringer, Fresenius-Kabi, G)– 1000 ml, 6% solution of hydroxyethylated starch (HAES, Fresenius-Kabi, G) – 500 ml, 20% mannitol

(Mannitil, Fresenius-Kabi, G) – 250 ml, sodium hydrocarbonate (*Natrium bicarbonatum*, Polfarma, Pl)- 20 ml and heparine – 75 ml. Cardioplegia was prepared with 0.9% solution of salt supplemented with 3g of potassium chloride (*Kalium chloratum*, Polfa, Pl) and 20 ml of sodium hydroxycarbonate.

The patients were divided into two groups: group A – the patients not requiring catecholamine infusions, group B – the patients administered dobutamine in the dose adequate to the clinical picture (3–15 µg/kg $^{-1}$b.w. min.$^{-1}$). The patients requiring dopamine infusions were excluded from the study as it is well known that dobutamine is the substrate of the noradrenaline synthesis cycle.

The examinations were conducted at 5 stages: 1) after cannulation of the radial artery and before anaesthesia and operation, 2) during deep hypothermia, 3) after the operation before sending the patient to the Postoperative Intensive Care Unit, 4) on the first postoperative day, 5) on the second postoperative day. The blood for examinations was collected from the radial artery.

The determinations of noradrenaline and tyrosine levels in blood were performed using radioimmunoassays and biochemical tests. The results were statistically calculated by Wilcoxon and Mann-Whitney tests analyzing both inter-stage and inter-group relations. The correlation analysis of the changes in noradrenaline and tyrosine levels in the corresponding groups was carried out using the Spearman test.

RESULTS

The examinations were performed in 10 men aged 55–68 years. Seven patients had myocardial infarction within the past 3 years and nine were treated for concomitant arterial hypertension defined as 1° according to WHO classification. The mean time of surgery was 215 min±38 and of anaesthesia – 245 min.±46. In all the patients the aorta was compressed with typical clamps and the time of its closure was 43.21 min±11.5.The aorto-coronary anastomosis was carried out in superficial hypothermia and its mean value was 34.51^{0}C±.41. The disconnection of the lung-heart apparatus was uneventful and intra-aortic contrapulsation was not necessary.

In group A (five patients) the examinations revealed a statistically significant increase in noradrenaline levels at stage 4 and 5 ($p<0.05$). The changes in blood tyrosine levels in this group were observed at stage 4 ($p<0.05$) (Fig. 1 and 2).

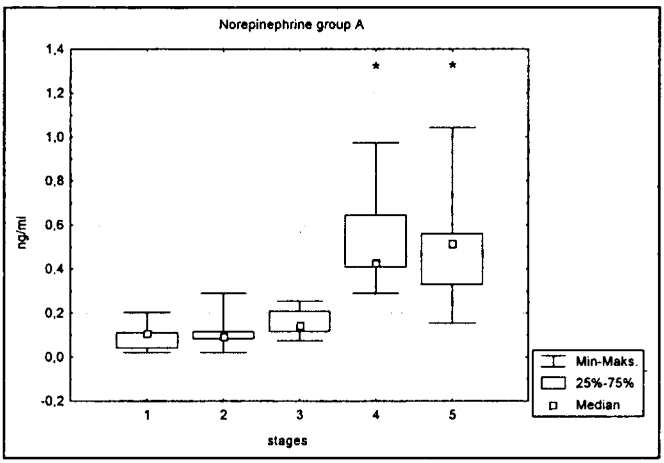

Fig. 1. Changes in blood noradrenaline levels in group A patients in the successive stages of examination

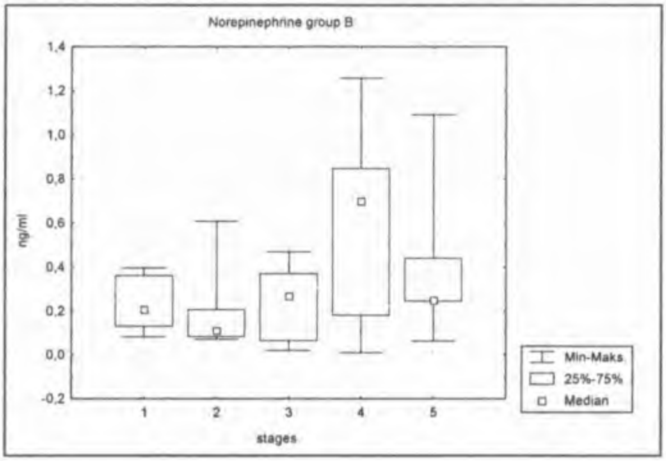

Fig. 2. Changes in blood noradrenaline levels in group B patients in the successive stages of examination

In group B (five patients) no blood noradrenaline and tyrosine changes were found (Fig. 3 and 4). The analysis of correlations of changes in blood noradrenaline and tyrosine levels showed a significant negative correlation of the examined parameters in group A ($p<0.05$).

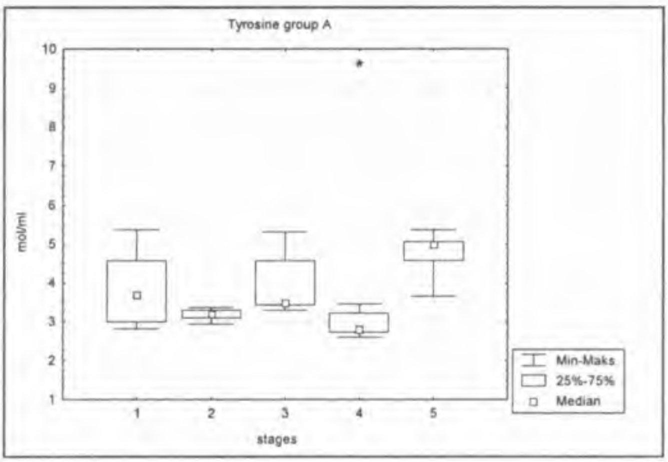

Fig. 3. Changes in blood tyrosine levels in group A patients in the successive stages of examination

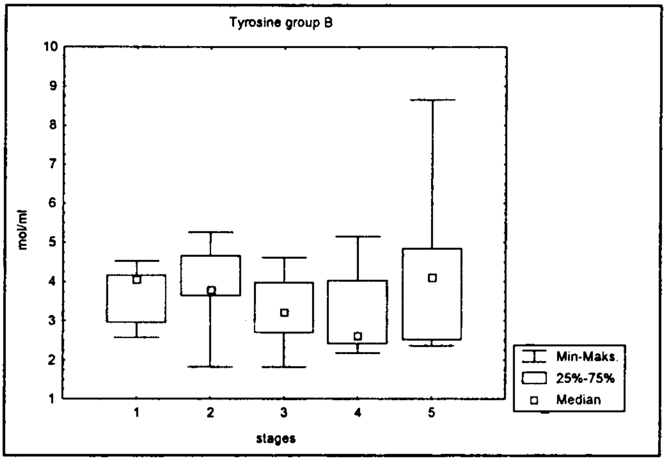

Fig. 4. Changes in blood tyrosine levels in group B patients in the successive stages of examination

DISCUSSION

An increase in blood catecholamines levels is a commonly known response of the organism to operative stress. Moreover, unfavourable effects of high noradrenaline levels are stressed, particularly in patients cardiologically compromised (13). The induction of general anesthesia causes a drop in stress hormone levels in blood resulting from decreased response to injury as well as inhibitory effects of analgesics in hormonal secretion; any intratracheal intubation causes their short-time increase (10,11). However, increased levels of catecholamines and accompanying tachycardia (7) result in unfavourable effects on the myocardium metabolism (4,13). Yoshida et al. (15) examining the changes in the ST segment demonstrated a strict relation between its elevation and the blood noradrenaline level. Due to these reasons many authors stress positive effects of high doses of opioids on the circulatory system(also used in our study) and their inhibitory action on hormonal secretion (2,4,7,16).

Moreover, blood noradrenaline levels are likely to be affected by intraoperative normovolemic hemodilution. Examining the changes in blood noradrenaline levels in rats, Estafanos et al. (6) demonstrated a strict correlation between its level and degree of haemovolemic hemodilution. According to them, an increase in blood dilution results in an increase in the normovolemic concentration which quickly becomes normal after haemodilution has been completed. However, the changes in levels of this hormone observed in our examinations do not confirm the above-mentioned relations. Moreover, it is difficult to define explicitly whether or to what extent the blood dilution used in our study affected the level of the examined parameter and therefore further detailed studies are needed to determine accurately the effects of intraoperative normovolemic hemodilution on the serum levels of noradrenaline in extracorporeal circulation.

Hypothermia and hypoxia also contribute to increased noradrenaline content in blood (9). Examining the response to operative stress in extracorporeal circulation, Lehot et al. (9) found higher intraoperative blood catecholamine levels and lower blood adrenaline and noradrenaline levels in patients undergoing surgery at temp.<28°C. However, the changes in blood noradrenaline levels observed in our study did not confirm the above-mentioned relations. It may be assumed that the use of high opioid doses was also of importance (7), although precise explanation of this difference requires further studies. Furthermore, postoperative temperature drop is worth discussing. An increase in noradrenaline levels resulting from this drop unfavourably affects the metabolism of the heart muscle and haemodynamic balance. Benedictin et al. (3), who analysed the relation between high blood noradrenaline levels and the rate of development of myocardial insufficiency and ischaemia observed the correlation between heart failure and levels of this hormone and thought that a high level of this catecholamine might be used as a prognostic factor. These observations confirmed also by Rundqvist et al. (12), however, were not confirmed by our findings as the patients did not show any features suggestive of postoperative heart muscle insufficiency, at least in the early postoperative period, although in the patients not requiring catecholamine infusions, the postoperative levels of noradrenaline were significantly higher.

The analysis of changes in blood tyrosine levels showed their variations on the first postoperative day in the group of patients not requiring catecholamine infusions. However, it is difficult to explain these changes explicitly. It seems that they are likely to result from the commonly known dependence between the degree of noradrenaline synthesis and tyrosine concentration. Such an explanation is favoured by negative correlation between the discussed parameters observed in our study. Furthermore, it may be assumed that an important role is also played by "inductive" effects of stress on the production of catecholamines (8, 14). In their study examining the changes in blood adrenaline and noradrenaline levels in patients after partial hepatectomy, Knopp et al. (8) observed significantly increased activity of tyrosine hydroxylase resulting from intensified synthesis of both catecholamines. Moreover, Adams and McMillan (1), studying the effects of stress and hypoxia on catecholamine synthesis found out increased activity of the above-mentioned enzyme in response to persistent hypoxia. Therefore, it may be thought that increased synthesis of noradrenaline is likely to cause a decrease in the blood levels of its substrate-tyrosine. On the other hand, the analysis of changes in amino acid levels during extracorporeal circulation carried out by Scrascia et al. (14) revealed an increase in fenylalanine and tyrosine during operations and in the early postoperative period, which was confirmed by our findings. Nevertheless, it seems that decreased level of this amino acid may have resulted from increased production of noradrenaline. A full explanation of the changes observed by us, however, requires further studies.

CONCLUSIONS

1. Revascularization of the myocardium with extracorporeal circulation results in a postoperative increase in blood noradrenaline levels and a decrease in blood tyrosine levels.
2. The procedure of extracorporeal circulation does not disturb the nora-drenaline-tyrosine relations.

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SUMMARY

The effects of extracorporeal circulation on the hormonal-metabolic balance are still the subject of numerous scientific studies. It seems that the procedure's complex character is likely not only to disturb hormonal homeostasis but also to affect the levels of their substrates. The aim of the study was to evaluate the changes in blood levels of noradrenaline and its substrate-tyrosine in patients undergoing surgical revascularization of the myocardium with extracorporeal circulation. The study involved 10 men operated on due to stable coronary disease. The patients were divided into two groups: A – not requiring catecholamine infusions and B – receiving dobutamine infusions. The study analysed the changes in noradrenaline and tyrosine levels at five stages of the surgical procedure and anaesthesia as well as in the early postoperative period. The analysis revealed an increase in the noradrenaline level on the first and second postoperative day and a decrease in the tyrosine level on the first postoperative day in group A. The procedures of revascularization of the myocardium with extracorporeal circulation result in increased noradrenaline and decreased tyrosine levels in blood in the postoperative period. It seems that extracorporeal circulation does not cause the disorders of noradrenaline-tyrosine relations.

Zmiany stężenia noradrenaliny i tyrozyny we krwi podczas chirurgicznej rewaskularyzacji mięśnia sercowego

Wpływ procedury krążenia pozaustrojowego na równowagę hormonalno-metaboliczną jest nadal tematem wielu badań naukowych. Wydaje się przy tym, że złożony charakter procedury może zaburzać nie tylko homeostazę hormonalną, lecz również może mieć wpływ na zmiany stężenia ich substratów. Celem pracy była ocena zmian stężenia noradrenaliny i jej substratu tyrozyny we krwi pacjentów poddanych chirurgicznej rewaskularyzacji mięśnia sercowego w krążeniu pozaustrojowym. Badaniami objęto 10 mężczyzn operowanych z powodu stabilnej choroby wieńcowej. Pacjentów podzielono na dwie grupy: A – niewymagających wlewu katecholamin i B – otrzymujących wlew dobutaminy. Analizie poddano zmiany stężeń noradrenaliny i tyrozyny w pięciu etapach operacji i znieczulenia oraz we wczesnym okresie pooperacyjnym. Analiza wykazała wzrost stężenia noradrenaliny w pierwszej i drugiej dobie pooperacyjnej w grupie A oraz spadek w tej grupie stężenia tyrozyny w pierwszej dobie pooperacyjnej. Na podstawie przeprowadzonych badań można uważać, że operacje rewaskularyzacji mięśnia sercowego w krążeniu pozaustrojowym powodują pooperacyjny wzrost stężenia noradrenaliny oraz spadek stężenia tyrozyny we krwi. Wydaje się także, że procedura krążenia pozaustrojowego nie zaburza zależności stężeń noradrenaliny–tyrozyny.