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The influence of extracorporeal circulation procedure on somatostatin–somatotropin axis

Disorders of the hypothalamic-hypophyseal axis during various medical procedures have been studied and clinically observed for many years. The recent papers stress the importance of this issue concerning the changes in hormonal balance during operations and anaesthesia as well as in the early postoperative period (2, 3). Moreover, much attention is focused on hormonal variations occurring during extremely complex operative procedures such as with extracorporeal circulation (3). The multi-step character of these operations as well as catecholamine infusions required affect hormonal balance and hypothalamic-hypophyseal relations.

The aim of the present study was to analyze the changes and relations of somatostatin and somatotropin blood levels in patients subjected to surgical myocardium revascularisation with extracorporeal circulation.

MATERIAL AND METHODS

The study, approved by the Bioethical Committee of the Medical University of Lublin (KE-0254/244/2000) and with informed consent given by the patients, involved male patients subjected to coronary artery bypass grafting (CABG) due to stable coronary disease of I or II degree according to the Canadian CCS. All the patients were qualified for planned surgical treatment.

In the evening proceeding the surgical procedure patients received the same premedication consisting of lorazepam and prometazine. One hour before anaesthesia all the patients received lorazepam and morphine. The patients were subjected to general anaesthesia using fentanyl, midazolam and etomidat; muscle relaxation was induced using pankuronium. Conduction of anaesthesia was performed by means of continuous venous infusion with fentanyl and midazolam and inhaled doses of foran.

The patients were divided into 3 groups: group A – the patients who did not require catecholamine infusions; group B – the patients receiving dopamine in the dose adjusted to their clinical condition (5–15 ugkg $^{-1}$b.w. min.$^{-1}$); group C – the patients receiving dobutamine in the dose adjusted to their clinical condition.(3–15 ugkg^{-1} b.w. min.$^{-1}$). The examinations were carried out at 5 stages: 1) after cannulation of the radial artery prior to anaesthesia and surgery, 2) during deep hypothermia, 3) after the procedure but before transporting the patient to the postoperative ICU, 4) the morning of first postoperative day, 5) the morning of second postoperative day.

The concentrations of somatotropin (GH) and somatostatin (SMS) in blood were determined using radioimmunological methods. Statistical analysis were performed by using the Wilcoxson test and Mann-Whitney U-test for nonparametric data. The relations between somatostatin and somatotropin and between the hormones levels and catecholamine doses were analysed by Spearman's rank correlation test.

RESULTS

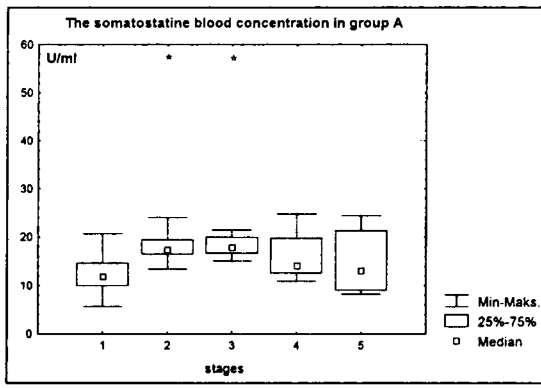
Table 1.

		Stages	Min	Max	Median	P Level
Somatostatin	Group A	1	5.63	20.68	9.93	
		2	16.1	24.05	23.58	0.028424
		3	15.1	21.5	19.4	0.016611
		4	12.15	24.75	12.48	0.09261
		5	8.55	24.43	8.95	0.721279
	Group B	1	6.73	20.98	11.83	
		2	16.3	27.98	21.3	0.011724
		3	11	21.35	11	0.0357
		4	8.33	19.6	14.68	0.123495
		5	8.43	53	17.22	0.0357
	Group C	1	2.35	18.33	11.3	
		2	14.25	20.03	17.2	0.027999
		3	18.73	34.6	24.25	0,017966
		4	12.23	34	17.3	0.017966
		5	12.68	22.68	22.08	0.027999
Somatotropin	Group A	1	0,1	1.7	0.2	
		2	0.2	14.9	2.4	0.006914
		3	0.3	30.2	2.3	0.006914
		4	0.2	7.5	1.35	0.01252
		5	0.2	7.1	1.3	0.109755
	Group B	1	0.3	2.8	1.25	
		2	0.3	5.2	1.4	0.025069
		3	1.5	16.8	1.7	0.017296
		4	0.3	5.5	1.95	0.068713
		5	0.6	3.6	0.6	0.207588
	Group C	1	0.2	2.3	1.25	
		2	1.4	14.7	6.3	0.017966
		3	11	56.4	16.1	0.017966
		4	1.7	19	5.2	0.027999
		5	1.4	3.3	2.7	0.017966

The studies included 25 men, aged 53–65. Twenty of them had myocardial infarction within 3 last years and 23 were treated for arterial hypertension (1° – according to WHO scale). None of the patients was earlier treated for endocrinological, neurological or other systemic diseases or was subjected to any resuscitation procedures due to cardiac arrest. In all the patients the extracorporeal circulation was uneventfully discontinued and the use of contrapulsation was not required. Ten patients did not require pharmacological support of hemodynamic balance (group A). Eight were subjected to continuous dopamine infusions (group B) in the doses adjusted to their clinical condition and seventh dobutamine infusion (group C). None of the patients required reoperation or changes of catecholamines in the O day. All the patients were extubated on the first postoperative day and further catecholamine treatment was not necessary.

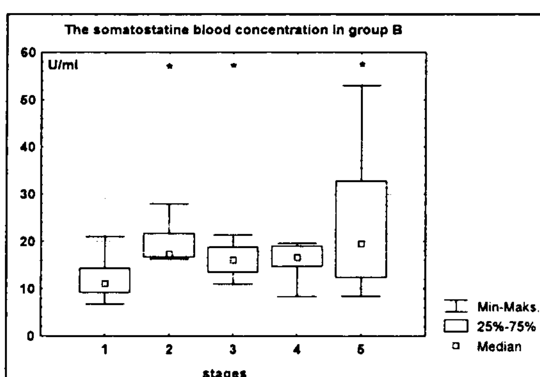
The blood SMS concentrations in group A (Fig.1.) showed a significant increase in the second and third stage ($p<0.05$). A statistically significant increase ($p<0.05$) was also observed in group B. In both groups the values of this parameter were similar (Table 1), however in group B increased values were also noted in the fifth stage. In group C a significant SMS increase was observed from second to fifth stage (Fig. 3.) but the concentration value of the hormone in this stage was the highest one (Table 1).

The intergroup analysis of blood SMS concentrations revealed significant differences between group A and C as well as between group B and C only in the third stage ($p < 0.01$) (Table 2).



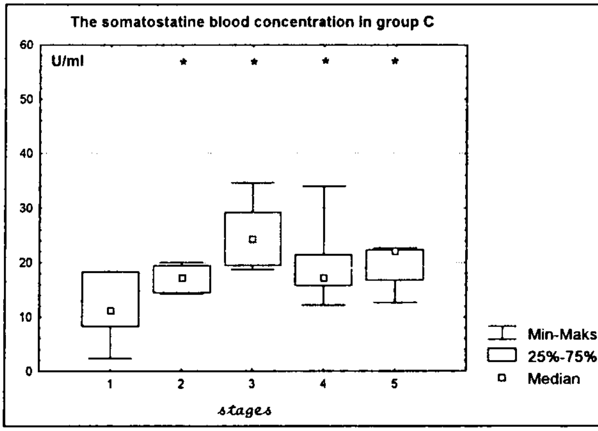
* $p < 0.05$

Fig. 1



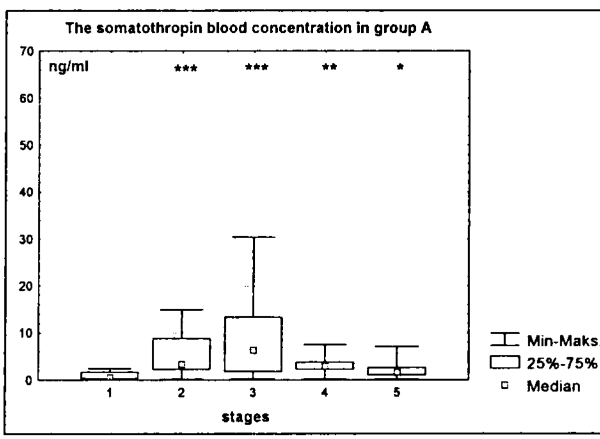
* $p < 0.05$

Fig. 2



* p < 0.05

Fig. 3



* p < 0.05, ** p < 0.01, *** p < 0.001

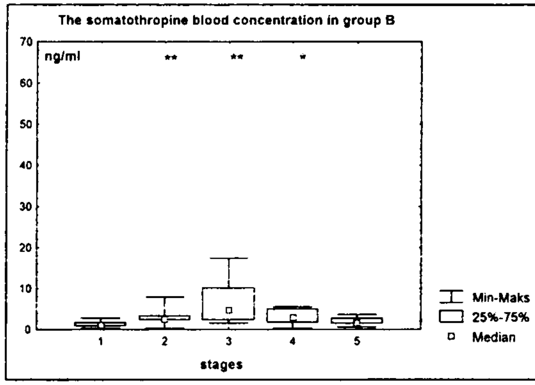
Fig.4

The blood concentrations of GH in group A (Fig. 4) were significantly increased in the second, third ($p<0.001$), fourth ($p<0.01$) and fifth stage ($p < 0,05$) and the highest values were observed in the third stage (Table 3). In group B significantly increased concentrations of this hormone were noted in the second, third ($p < 0.01$) and fourth stage ($p<0.05$) (Fig. 5). In group C a significant increase in blood GH ($p<0.01$, $p < 0.001$) was observed from the second stage and continued throughout all the remaining stages (Fig. 6).

The intergroup analysis of blood somatotropin concentrations showed significant differences between group A and C in the third and fifth stage ($p<0.05$) and between group B and C in the third stage ($p<0.01$). The highest blood GH concentrations were noted after the surgical procedure in group C (Table 1).

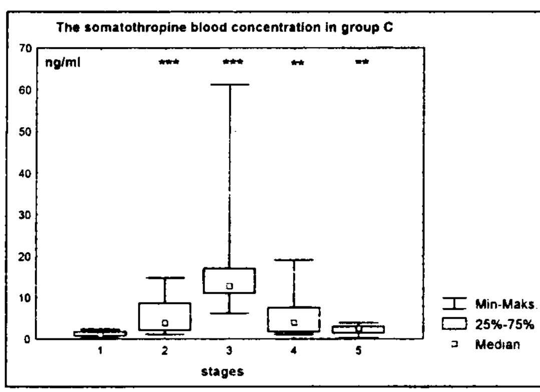
Table 2

	Groups	Stages	Sum of rang		U	p
			group 1	group 2		
Somatostatin	A:B	01:01	99	72	36	0.761826
		02:02	91	80	36	0.761826
		03:03	110	61	25	0.203071
		04:04	88	83	33	0.572604
		05:05	80	91	25	0.203071
	A:C	01:01	96	57	29	0.600884
		02:02	90	63	35	1.037742
		03:03	64.5	88.5	9.5	0.009667
		04:04	77	76	22	0.229535
		05:05	74	79	19	0.133073
	B:C	01:01	66	54	26	0.866511
		02:02	69	51	23	0.612587
		03:03	41	79	5	0.005905
		04:04	18.55	63	21	0.463403
		05:05	63	57	27	0.955089
Somatotropin	A:B	01:01	74.5	96.5	19,5	0.067599
		02:02	107	64	28	0.315417
		03:03	100	71	35	0.696467
		04:04	100	71	35	0.696467
		05:05	83	88	28	0.315417
	A:C	01:01	73.5	79.5	18.5	0.108803
		02:02	83.5	69.5	28.5	0.536199
		03:03	69	84	14	0.043089
		04:04	80	73	25	0.363842
		05:05	66.5	86.5	11.5	0.018511
	B:C	01:01	66	54	26	0.866511
		02:02	48.5	71.5	12.5	0.072106
		03:03	40	80	4	0.00373
		04:04	54.5	65.5	18.5	0.280963
		05:05	50.5	69.5	14.5	0.120591



* $p < 0.05$ ** $p < 0.01$

Fig. 5



** $p < 0.01$ *** $p < 0.001$

Fig. 6

No correlation was observed between the variations in blood somatostatin and somatotropin concentrations.

DISCUSSION

Disorders of the hypothalamic-hypophyseal axis are typical responses to stress conditions: undoubtedly both anaesthesia and surgical procedures with extracorporeal circulation belong to such conditions (1-3). However, the changes in blood SMS concentrations during extracorporeal circulation have not been well documented yet. Moreover, the reports published so far have stressed the complexity of responses of hypothalamic cells responsible for secretion of somatostatin (3, 4). An increase in the concentration of this hormone unquestionably depends on blood GH concentrations and this mechanism is known as hypothalamic-hypophyseal feedback. Thus it can be assumed that an increase in blood SMS concentrations observed in out studies was a response to increased blood GH concentrations. Moreover, hypercatecholinaemia observed in all stress conditions is relevant as high epinephrine and norepinephrine concentrations in blood stimulate the secretion of SMS (7). Furthermore, SMS may have favourable and protective effects on the function of the alimentary tract resulting in decreased secretion of digestive juices and reduced metabolism of gastric and intestinal mucosal. This limits the risk of potential injuries to the alimentary tract walls, which is often stressed by many authors (4, 5). Recently, the protective effects of SMS in hypoperfusion conditions have been questioned and unfavourable effects of high catecholamine concentrations on the intestinal mucosa indicated (9).

The increased blood concentrations of SMS observed in our studies seem to support the relations described in the literature (1, 2). Higher blood SMS concentrations throughout the studies in patients receiving dobutamine may be explained by higher concentrations of GH, which seems to confirm the normal, undisturbed character of reactions of the above-mentioned feedback. However, increased concentrations of this hormone on the second postoperative day are difficult to explain. It is likely that they result from a decrease in blood dopamine concentrations (3) and release of SMS collected in the prepyloric gastric cells to the circulation (9). Moreover, the protective, "substitutive" effects of dopamine on the alimentary mucosa may also be relevant. The studies performed by Thoren et al. (16) revealed worse visceral perfusion in patients receiving dobutamine compared to those receiving dopamine, which may explain higher blood SMS concentrations in the former group and the above mentioned increase in this hormone after discontinuation of dopamine infusion.

It should be also noted that the values of SMS concentrations in patients receiving dopamine were similar to those observed in patients without catecholamine infusions. On this basis it can be assumed that changes in blood SMS concentrations in extracorporeal circulation are "more physiological" during the infusion of dopamine than of dobutamine (3).

The increased blood concentrations of GH, called by some authors "the convalescence hormone" is a typical reaction to surgery (1-3). The anabolic character of somatotropin and its beneficial effects on mineral and electrolyte metabolism cause its increase in all stressful conditions (2, 12).

The influence of anaesthesia on the concentration of GH is also important although it seems that its type does not result in significant differences of hormone variations. Describing physiology and pathophysiology of somatotropin, Giustina and Veldhuis (7) indicate stimulating effects of opioids on the growth hormone secretion. According to them, these effects are caused by the stimulation of secretion of the hypothalamic hormone releasing somatotropin and by the inhibition of somatotropin activities. Rauhala et al. (15), studying the influence of opioids on the growth hormone secretion in rats in hypothermia did not observe its increased blood concentrations, which, according to them, resulted from the inhibiting effects of hypothermia on the opioid-dependent, regulating mechanisms described by Giustina and Veldhuis (7). Thus, it can be supposed that the intraoperative increase in blood somatotropin levels observed in our studies did not result from high opioid doses used, but the operative procedure itself.

The effects of temperature variations on the secretion of the hormone discussed is well known (8, 10, 14). Radomski et al. (14) in their studies on the effects of temperature changes on blood concentrations of stress hormones, demonstrated a significant, value-independent increase in the concentration of GH. Others documented the effects of intraoperative, therapeutic hypothermia on the changes of growth hormone concentrations in blood of the examined patients (10). Analysing the differences in blood somatotropin changes in patients operated on in normothermia and hypothermia < 28°C, Lehot et al. (8) observed markedly lower values of the growth hormone in those subjected to operations with low temperatures. However, these studies do not cover the postoperative period and do not define the time needed to normalize the growth hormone concentrations.

The increased blood GH concentrations observed by us during surgical procedures and anaesthesia are confirmed in the available literature, although some authors describe significant changes only at the end of hypothermia or even after the procedure (8). The highest GH values are found after the operations yet, in contrast to some other reports, in our studies increased values were also observed in the direct postoperative period (17). Higher blood GH concentrations in patients receiving dobutamine are difficult to explain.

The direct influence of dobutamine on the production and release of somatotropin is not fully known and requires further investigations. The recent reports also stress beneficial, inotropically-positive effects of the growth hormone on the heart, which is relevant to the proper course of the postoperative period (11). The increased ventricular ejection fraction, stronger myocardial contractions and decreased end-diastolic pressure of the left ventricle observed by many authors may be an alternative for the treatment of heart insufficiency (6, 13).

CONCLUSIONS

1. CABG results in increased blood levels of somatostatin and somatotropin.
2. The procedures of myocardial revascularization performed with extracorporeal circulation and shallow hypothermia do not substantially interfere with hypothalamic-hypophyseal feedback reactions.

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SUMMARY

Disorders of the hypothalamic-hypophyseal axis particularly during CABG procedure are still unknow. The somatostatin – somatotropin relation may get loose by many factors during CABG. The aim of the study was to analyze the changes and relations of somatostatin and somatotropin blood levels in patients subjected to surgical myocardium revascularisation with extracorporeal circulation. 25 male patients aged 53 to 65 underwent CABG. The patients were divided into 3 groups: A – the patients who did not require catecholamine infusions; B – the patients receiving dopamine and C – the patients receiving dobutamine. The somatostatin and somatotropin concentrations were measured in five stages: 1) after cannulation of the radial artery prior to anaesthesia and surgery; 2) during deep hypothermia; 3) after the procedure but before transporting the patient to the postoperative ICU; 4) the morning of the first postoperative day; 5) the morning of the second postoperative day. The radioimmunological methods were used for somatostatin and somatotropin measurements. The somatostatin and somatotropin increased during procedure and early postoperative day, however, the biggest changes were observed in group C. The study showed that the CABG procedures in extracorporeal circulation and shallow hypothermia do not substantially interfere with hypothalamic-hypophyseal feedback reactions.

Wpływ zabiegów z zastosowaniem krążenia pozaustrojowego na oś somatostatyna – somatotropina

Zaburzenia hormonalne zachodzące w warunkach krążenia pozaustrojowego są nadal tematem wielu dyskusji i badań naukowych. Szczególnie interesujące wydają się przy tym zmiany zależności międzyhormonalnych, do jakich można zaliczyć relację somatostatyna–somatotropina. Celem pracy była ocena wpływu procedury krążenia pozaustrojowego na wzajemną relację somatostatyny–somatotropiny we krwi pacjentów poddanych chirurgicznej rewaskularyzacji mięśnia sercowego. Do badań zakwalifikowano 25 pacjentów w wieku od 53 do 65 lat operowanych planowo w znieczuleniu ogólnym z powodu stabilnej choroby wieńcowej. Pacjentów podzielono na trzy grupy badawcze: A – niewymagających wlewu amin katecholowych podczas całego okresu badawczego, B – otrzymujących dożylny wlew dopaminy, C – otrzymujących dożylny wlew dobutaminy w dawce zależnej od stanu klinicznego. Zmiany stężenia somatostatyny i somatotropiny badano w pięciu etapach operacji i znieczulenia: 1) po kaniulacji tętnicy promieniowej przed indukcją anestezji, 2) w trakcie najgłębszej hipotermii, 3) po zakończonej operacji przed przekazaniem pacjenta do OIOP, 4) rano w pierwszej dobie pooperacyjnej, 5) rano w drugiej dobie pooperacyjnej. Do oznaczenia stężeń somatostatyny i somatotropiny zastosowano metody radioimmunologiczne. Zanotowano wzrost stężenia somatostatyny i somatotropiny we krwi zarówno podczas operacji, jak i we wczesnym okresie po jej zakończeniu, przy czym największe zmiany obserwowano w grupie C. Przez cały okres badawczy nie zanotowano istotnych zaburzeń osi somatostatyna–somatotropina .