The Effects of Cardiopulmonary Bypass on Androgen Hormones in Coronary Artery Bypass Grafting Operations

KORONER ARTER BYPASS CERRAHİSİNDE KARDİYOPULMONER BYPASSIN ANDROJEN HORMONLAR ÜZERİNE ETKİSİ

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Summary

Objectives: The effects of testosterone on coronary vasomotor regulation and atherosclerotic coronary artery disease has been reported recently. For this purpose; we investigated alterations of serum androgen hormone's levels during and after cardiopulmonary bypass on the patients when undergone coronary artery bypass operations.

Methods: Serum luteinizing hormone, free testosterone and dihydroepiandrestenedione sulfate levels were evaluated on 20 male coronary artery bypass operations patients with cardiopulmonary bypass. Serum hormones levels were measured with chemicalimmunoassay five days before, just prior to anesthetic induction, at the weaning from cardiopulmonary bypass, first postoperative day and seventh postoperative day.

Results: Serum free testosterone level is decreased considerably at the weaning from cardiopulmonary bypass (from 4,54±1,2 to 1,78±0,8 ng/ml) and this decrease has progressed in the first postoperative day (to 1,56±0,9 ng/ml) ($p<0,01$). Consecutively; at seventh postoperative day, free testosterone level reached normal value (3,41±1,6 ng/ml) but not preoperative level ($p<0,05$). There is mildly alteration on serum DHEA-SO4 level, but there is only statistically significant decrese at seventh postoperative day compared to first postoperative day (from 173,3±79,9 to 138,1± 66,5 UI/dl) ($p<0,05$). Serum luteinizing hormone levels were decreased at the weaning from cardiopulmonary bypass (from 4,81±2,1 to 3,90±1,8 mIU/ml) ($p<0,05$) but it's level rapidly increased over preoperative values (to 5,48±2,5 mIU/ml)($p<0,05$).

Conclusion: Cardiopulmonary bypass effects serum LH, free testosterone and dihydroepiandrestenedione sulfate levels. The free testosterone level decreases considerably during and after cardiopulmonary bypass. The effects of testosterone on coronary vasomotor regulation during coronary artery surgery must be investigated in detail through further studies.

Key Words: Cardiopulmonary bypass, Androgen, testosterone, Cardiac surgery

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Özet

Amaç: Son zamanlarda testosteronun koroner vazomotor regülasyon ve atherosklerotik koroner arter hastalığı üzerine etkileri sıkça bildirilmektedir. Bu nedenle koroner arter bypass cerrahisi uygulanan hastalarda kardiyopulmoner bypass esnasında ve sonrasında serum androjen hormon düzeylerindeki değişimleri araştırdık.

Metod: Kardiyopulmoner bypass altında koroner arter bypass cerrahisi uygulanan yirmi erkek hastada serum luteinizan hormon serbest testosteron ve dihidroepiandrestenedion sülfat düzeyleri ölçüldü. Serum hormon düzeyleri kimyasal immü-noassay yöntemle operasyonda beş gün önce, anestezi indüksiyonundan hemen önce, kardiyopulmoner bypasstan çıkışta, ilk postoperatif gün ve postoperatif yedinci gün ölçüldü.

Sonuçlar: Serum serbest testosteron düzeyi kardiyopulmoner bypasstan çıkışta belirgin olarak düştü (4,54±1,2 den 1,78±0,8 ng/ml'ye) ve bu düşüş ilk postoperatif günde de devam etti (1,56±0,9 ng/ml'ye)($p<0,01$)). Takiben postoperatif yedinci günde serbest testosteron düzeyi normal değerine tekrar erişti (3,41±1,6 ng/ml) fakat hala preoperatif düzeyin altındaydı ($p<0,05$). Serum dihidroepiandrestenedion sülfat düzeyinde genelde hafif derecede bir değişiklik saptanrken, yalnızca postoperatif yedinci gündeki düşme postoperatif ilk gün ile karşılaştırıldığında istatistiksel olarak anlamlı bulundu (173,3±79,9'dan 138,1± 66,5 UI/dl'ye) ($p<0,05$). Serum luteinizan hormon düzeyi kardiyopulmoner bypasstan çıkışta düştü (4,81±2,1'den 3,90±1,8 mIU/ml'ye) fakat postoperatif birinci gün hızla artarak preoperatif değerine ulaştı (5,48±2,5 mIU/ml)($p<0,05$).

Tartışma: Kardiyopulmoner bypass serum luteinizan hormon serbest testosteron ve dihidroepiandrestenedion sülfat düzeylerini etkilemektedir. Serum testosteron düzeyi kardiyopulmoner bypass esnasında ve sonrasında belirgin ölçüde düşmektedir. Bu bilgiler ışığında, koroner arter cerrahisi esnasında testosteronun koroner vazomotor regülasyondaki etkilerinin detaylı olarak araştırılması gerekmektedir.

Anahtar Kelimeler: Kardiyopulmoner bypass, Androjen, Testosteron, Kalp cerrahisi

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Cardiopulmonary bypass (CPB) for the open heart surgery differs from other surgical procedures in that involves a period of extracorporeal circulation with circulatory bypass of the patient's heart and lungs. Very important haemodynamic, metabolic and endocrine changes occur during and after cardiopulmonary bypass (1-3). The purpose of this prospective study was to assess the effects of cardiopulmonary bypass on function of androgen hormones function especially testosterone; since alteration of androgen hormones through cardiopulmonary bypass has not been reported previously.

Testosterone;

Androgen hormones are dihydroepiandrestenedione (DHEA), dihydroepiandrestenedione sulfate (DHEA-SO4), androstenedione, testosterone and dihydrotestosterone (4). In term of quantitative standpoint, most important androgen is testosterone (4-5). In the blood, Testosterone exist in free (unbounded) state or as bound to serum proteins (4). Majority of plasma free testosterone can be measured and is a more direct measure of circulating biologically active testosterone than the total plasma level (4). Over %95 of testosterone is secreted by the testicular leydig cells; remainder is derived from the adrenals (4). DHEA-SO4 is secreted by adrenals and it is the precursor of testosterone (4-5). Testosterone leaves the circulation and rapidly traverses the cell membrane. In most androgenic target cell, testosterone is enzymatically converted to the more potent androgens derivatives; dihydrotestosterone and estrogen by the microsomal isoenzyme 5 ∝ reductaze (4-5). A variety of biological effects of androgens have been defined in males. They are essential for apropriate differentiation of the internal and external male genital system during fetal life (4-5). Androgens stimulate skeletal muscle growth and growth of larynx which result is deeping of the voice, hair growth as in male fenotype, erythropoiesis and social behavioral changes (4). It is suggested that androgen reseptors are present in cardiac myocytes, and both testosterone and DHEA may lead to hypertrophy of cardiac myocytes (6).

The hypothalamus syntesizes a gonadotrophin-releasing hormone (GnRH), and secretes it into the hypotalamopituitary portal blood. GnRH binds to the luteinizing hormone (LH) and to a less extent, FSH in to the general circulation from anterior pituitary gland. LH taken up by the leydig cells, where it binds to specific membrane receptors and leads to activation of adenyl cyclase and cAMP results in the secretion of androgens (4). When androgen levels increase in the plasma, LH releasing is decrease as well (4).

If testosterone deficiency develops after puberty, the patients may complain of decreased libido, impotence and low energy state (4). Serum LH level has greater variation than testosterone troughout a day. Testosterone ranged 3-10 ng/ml (10-35 nmol/L) in adult men (4-5).

Patients and Methods

Twenty consecutive male patients were evaluated for androgen hormones levels before, during and after cardiopulmonary bypass. None of the patients had sexual dysfunction and they all had normal secondary sex characters. Patient age ranged between 47-76 (mean 59,9±8,5) years and body weight 65-96 (mean 84±10) kg. None of the patients had received any preoperative medication that interfered with androgens or steroid metabolism. Haemodynamic status of the patients were similar. Ejection fractions of the all of them were higher from 50 percent and none of them had any other major system disorder or previous heart failure history.

Before the operation; all patients had a central venous catheter and arterial line inserted. The detailed haemodynamic and other monitorisation were carried out before, during and after the operation. The anesthetic procedure was standard in all patients. Cardiopulmonary bypass was instituted with ascending aortic root perfusion and right atrial drainage. After the patients were heparinised by bolus injection of 3 mg/kg of body weight, cardiopulmonary bypass circuit initiated with a roller pump and non-pulsatil flow technique. Cardiopulmonary bypass was maintained with a mean pressure of 60-80 mmHg and moderate

hypothermia (28-30 C). Pump prime solution was 1 liter of 0.9% sodium chlorid. Standart antegrade cold crystalloid cardioplegic agent and topical cardiac hypothermia applied in all patients. The patients who needed mechanical and pharmacologic inotropic support at the end of the bypass, were excluded from study. Arterial blood gases were analysed before, during and after CPB routinely.

The postoperative course was free of complications in all patients. During convalescense, all patients were haemodynamicaly stable and has not received any inotropic agent.

The effects of CPB on androgen hormone concentrations were determined by collection of blood samples for testosterone (T), dihydroepiandrestenedione sulfate (DHEA-SO4) and luteinizing hormone (LH) tests through an peripheral vein line at the following times; 5 days before the operation, just before the anesthetic induction, just after weaning the CPB, first and seventh postoperative days.

The serum free testosterone, DHEA-SO4 and luteinizing hormone measurements were analysed by chemicalimmunoassay (CIA) technique, using Immulite 2000 analyser. Referrence values in the author's laboratory were as follows;

Free Testosterone: 2,12–17,3 ng/ml DHEA-SO4: 80-560 Ug/dL Luteinizing Hormone: 0,8-7,6 mIU/ml

All hormones levels of three were compared with preoperatively 5 days before, preanesthesia, period of weaning CPB, postoperative first and seventh postoperative day.

All statistical analys were done one-sample test and paired-samples test and p value of < 0.05 was considered statistically significant. Data were presented as the mean and standard deviation.

Results

Mean ejection fraction of patients in the study, was 64,4±13 percent and the average cardiopulmonary bypass time was 97,2±28 minute. All patients had normal androgen and luteinizing hormone levels preoperatively. Just before the anesthetic induction at operation morning, androgen hormone levels changed slightly and were statistically not significant.

However; at the weaning period of CPB and first postoperative day, serum testosterone levels decreased significantly from 4,54±1,2 ng/ml to 1,78±0,8 and 1,56±0,9 ng/ml and this decline was statistically significant ($p<0,01$). On the seventh day, serum testosterone levels increased to 3,41±1,6 ng/ml and this difference was statistically significant ($p<0,01$). Change in the serum DHEA-SO4 levels were insignificantly for the first four periods. However serum DHEA-SO4 levels decreased from 173,3±79,9 Ug/dl to 138,1±66,5 at the seventh day ($p=0,048$). Serum LH level was 3,90±1,8 mIU/ml at weaning from CPB intraoperatively but this value increased rapidly to 5,48±2,5 mIU/ml at first postoperative day ($p<0,05$).

The results of the study were summarized in Table 1 and Figure 1.

Discussion

The effects of androgen hormones on cardiovascular system has not been studied in detail. In a similar manner; the effects of cardiovascular system disorder on androgen metabolism has been obscure too. Both of them need to detailed investigation. In a comprehensive study; relationship between prevalent ischemic heart disease and sex hormones was investigated; it demonstrated that persons with ischemic heart disease had significantly lower testosterone level than persons without ischemic heart disease (7). Importance of androgens on ischemic heart disease was investigated by several researchers; it was shown; decreasing exercise-induced ischemia by acute testosterone administration in men with ischemic heart disease (8-10). Studies on coronary vasomotor regulation showed that testosterone induces coronary artery dilatation and improves coronary blood flow (11-13). It explained that this relaxation mechanism is independent of endothelium and possible potassium channel modulation (11).

Table 1. Alteration of androgens and LH during open heart surgery

	Preoperative		Operative	Postoperative	
	5 days before	Preanesthesia	Post CPB	First day	Seventh day
LH	4.64±1.9	4.81±2.1	3.90±1.8	*5.48±2.5	4.92±2.0
Testosterone	4.79±1.7	4.54±1.2	*1.78±0.8	*1.56±0.9	*3.41±1.6
DHEA-SO_4	169.5±118.5	187.2±93.3	151.0±47.6	173.3±79.9	*138.1±66.5

LH; Luteinizing hormone: 0.8-7.6 mIU/ml
Testosterone: 2.12-17.3 ng/ml
DHEA-SO4; Dihydroepiandrostenedione sulfate: 80-560 Ug/dl
Post CPB; Weaning from cardiopulmonary bypass
Values; Mean ± Standard Deviation
* ; p <0.05

In literature; following cardiac surgery, several hormonal and metabolic changes were investigated lengthily. It has been reported that while growth hormone, glucose, insulin, c-peptid, lactate, glutamate, aspartate and total aminoasid levels show an increase, thyroid hormones, especially T3 decrease after CPB (14-18). And it has been demonstrated that cortisol, lactate, free faty acids, glucose increase, glucagon and growth hormone levels decrease following pediatric cardiac surgery (19). In adults, blood cortisol and adrenocorticotrophin (ACTH) metabolism has been investigated after cardiac surgery, and it was hypothesised that major surgical trauma causes inactivation of cortisol and cortisol to persist in high levels postoperatively (20-21). Another study; suggested that there were no effect of systemic intraoperative hypothermia on the acute phase and andocrine response to cardiac surgery except adrenaline (22).

In spite of these hormonal alterations; there has been lack of information on alterations of androgen hormones following cardiac surgery. For this reason; the effects of CPB on serum androgen hormones concentrations were investigated in this study.

In contrast to previously referred studies, at first period of our study; serum free testosterone, DHEA-SO4 and LH levels were normal range in men with coronary heart disease. Our study not supported the thesis of testosterone level is low in men with coronary heart disease.

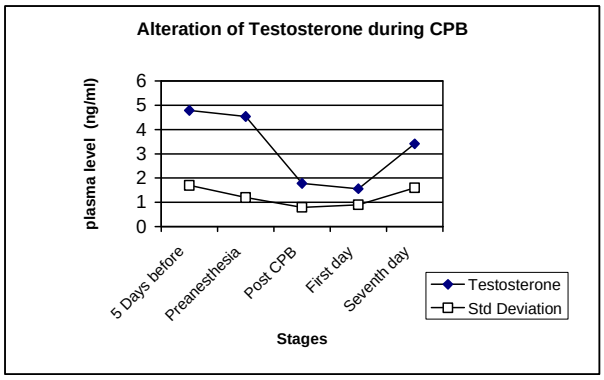

Figure 1. Alteration of testosterone levels before, during and after cardiopulmonary bypass.

The data in this prospective study, demonstrated a significant decrease in serum free testosterone concentration at CPB weaning period and on the first postoperative day, compared to preoperative values. Decrease in testosterone levels at CPB weaning period may be due to the remarkable haemodilution during cardiopulmonary bypass and early postoperative period. However, all hormones levels were still at very low concentration twentyfour hours later, in the first postoperative day when hemodilution in intravascular area is no more a problem. For this reason, it might be suggested that serum testosterone levels were decreased after CPB. After a week, serum testosterone level reaches to normal range. But there was a statistically significant difference between preoperative and postoperative values (p<0,05).

In first four periods; even thought there were an alteration on serum DHEA-SO4 level, this alteration was not statistically important. Serum DHEA-SO4 level has significantly decreased at seventh postoperative day when compared to preoperative and first postoperative day values (from 173,3±79,9 to 138,1±66,5 Ug/dl) (p=0,048). There is an increase in serum testosterone levels during the postoperative period. During this fast synthesis and secretion phase of testosterone, while plasma testosterone levels were increasing, it is supposed that DHEA-SO4 as a precursor of testosterone would utilised rapidly.

Serum LH levels have decreaed during operation, as compared to preoperative values. This decrease may be concerned with haemodilutional effects of cardiopulmonary bypass or hypoperfusion of pituitary gland during CPB. It has found that serum LH levels increased from 3,90±1,8 mIU/ml to 5,48±2,5 on the first postoperative day. There may be two explanations for this condition. The first; perfusion of pituitary gland improved rapidly at postoperative period or the second; there is a fast release of LH from pituitary gland in response to decrease in levels of serum testosterone.

As a result; cardiopulmonary bypass affects serum androgens and LH levels. Testosterone; the most important androgen derivative; decreases considerably during and after cardiopulmonary bypass, and increase progressively during postoperative period. This observation may have important clinical implications if considered with another clinical experiences regarding effects of testosterone on coronary vasomotor regulation. Additionally, further clinical studies are required with androgens, especially testosterone. Effect of acute testosterone administration on coronary arteries and cardiovascular haemodynamics must be investigated during and after cardiopulmonary bypass.

REFERENCES

1. Kirklin JW, Barratt-Boyes BG. Cardiac Surgery. Morphology, diagnostic criteria, natural history, techniques, results and indications. New York: Churchill Livingstone Inc, 1993:83-96.
2. Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Glenn's thoracic and cardiovascular surgery. Connecticut: Appleton and Lange, 1991:1405-7.
3. Kirklin JK, Kirklin JW. Cardiopulmonary bypass for cardiac surgery. In: Sabiston DC, Spencer FC, eds. Surgery of the chest. Philadelphia: WB Saunders company, 1990:1113-9.
4. Greenspan FS, Strewler GJ. Basic and clinical endocrinology. Massachusetts: Prentice-Hall International Inc, 1997:304,405-11.
5. Wilson JD, Foster DW, Kronenberg HM, Larsen PR. Williams textbook of endocrinology. Philadelphia: WB Saunders Company, 1998:819-57.
6. Marsh JD, Lehman MH, Ritchie RH, Gwathmey JK, Green GE, Schiebinger RJ. Androgen receptors mediate hypertrophy in cardiac myocytes. Circulations 1998;98(3):256-61.
7. Lichtenstein MJ, Yarnell JW, Elwood PC, Beswick AD, Sweetnam PM, Marks V. Sex hormones, insulin, lipids and prevalent ischemic heart disease. Am J Epidemiol 1987;126(4):647-57.
8. Rosano GM, Leonardo F, Pagnotta P, Pelliccia F, Panina G, Cerquetani E. Acute anti-ischemic effect of testosterone in men with coronary artery disease. Circulation 1999;99(13):1666-70.
9. Wu SZ, Weng XZ. Therapeutic effect of an androgenic preparation on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. Chin Med J 1993;106(6):415-8.
10. Webb CM, Adamson DL, de Ziegler D, Collins P. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. Am J Cardiol 1999;83(3):437-9.
11. Webb CM, McNeill JG, Hayward CS, de Zeigler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999;100(16):1690-6.
12. White CM, Ferraro–Borgida MJ, Moyna NM, McGill CC, Ahlberg AW, Thompson PD. The pharmacokinetics of intravenous testosterone in elderly men with coronary artery disease. J Clin Pharmacol 1998;38(9):792-7.
13. Hutchison SJ, Sudhir K, Chou TM, Chatterjee K. Sex hormones and vascular reactivity. Herz 1997;22(3):141-50.
14. Rumelin A, Nietgen G, Pirlich M, Thum P, Bischoff S, Schafers HJ. Postoperative pattern of various hormonal and metabolic variables. A pilot study in patients without complication following cardiac surgery. Curr Med Res Opin 1999;15(4):339-48.
15. Reinhardt W, Mocker V, Jockenhovel F, Olbricht T, Reinwein D, Mann K. Influence of coronary artery bypass surgery on thyroid hormone parameters. Horm Res 1997;47(1):1-8.
16. Malatinsky L, Vigas M, Jezova D, Jurcovicova J, Samel M, Vrsansky D. The effect of open heart surgery on growth hormone, cortisol and insulin levels in men. Hormone levels during open heart surgery. Resuscitation 1984;11(1-2):57-68.
17. Barta E, Kuzela L, Langer P, Tordova E. Effects of open heart surgery on thyroid hormone levels. Resuscitation 1980;8(4):233-41.

18.Keceligil HT, Kolbakir F, Adam B, Arikan A, Erk MK. Thyroid hormone alterations during and after cardiopulmonary bypass. Cardiovasc Surg 1996;4(5):617-22.

19.Buheitel G, Scharf J, Dorr HG, Ramsauer T, Schuderer E, Singer H. Follow-up of hormonal and metabolic parameters after heart operations in childhood. Monatsschr Kinderheilkd 1993;141(5):427-33.

20.Vogeser M, Felbinger TW, Roll W, Jakob K. Cortisol metabolism in the postoperative period after cardiac surgery. Exp Clin Endocrinol Diabetes 1999;107(8):539-46.

21.Roth-Isigkeit AK, Schmucker P. Postoperative dissociation of blood levels of cortisol and adrenocorticotropin after coronary artery bypass grafting surgery. Steroids 1997;62(11):695-9.

22.Taggart DP, Fraser W, Gray CE, Beastall G, Shenkin A, Wheatley DJ. The effects of systemic intraoperative hypotermia on the acute-phase and endocrine response to cardiac surgery. Thorac Cardiovasc Surg 1992;40(2):74-8.

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