The Influence of Immunosuppression on Hypertension Following Cardiac Transplantation

KALP NAK1JNDEN SONR/i MEYDANA Gt.LEN HYPERTANSIYONDA IMMUNOSUPRESSJON'UN ETKISI

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SUMMARY

TJie results of 488 cardiac transplants which were performed between January 1980 and December 1987 at Harefield Hospital to define the factors associated with postoperative hypertension have been analyzed. Vie mean age of the recipients was 43.3 years (range 9 days to 68 years). TJie number of the male and female receipent was 413 and 75 respectively-

The main indications for transplantation were ischaemic heart disease and cardiomyopathy. The incidence of hypertension (Bp > 150:95 mm fig) in survivors has been analyzed.

Tlxe recepienls have been divided into three groups according to the immunosuppression used during the first postoperative months.
Group 1: Prednisone and azathioprine (f'red + Aza);
Group 2: Cyclosporin and azathioprine (CsA + Aza);
Group 3: Cyclosporin, azathioprine andpiednisone.

71te incidence of hypertension at one year in Group 1,2 and 3 were 39%, 49% and 58% respectively. Hypertension was evaluated by the life table method. Patients died without developing hypertension were removed from the analysis at the time of death.

There is an important incidence of hypertension in all three groups which increases %ith time after operation and a trend for an increased incidence in group 2 and 3 (p = 0.16 Breslow test statistic), ft is concluded that hypertension is an important long term problem after cardiac transplantation and its incidence is likely to be influenced by the immunosuppression used.

KeyWords: Cardiac transplantation, Immunosuppression. Hypertension

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ÖZET

Kalp naklinden sonra ortaya çıkan hypertansiyonda risk faktörlerini ortaya çıkarmak için, 1980 Ocak ile 1987 Aralık arasında kalp nakli yapılan 488 hasta ile ilgili sonuçlar bu çalışmada incelenmiştir. En küçük hasta 9 gün, en yaşlı hasta 68 yaşında olup. yaş ortalaması 43.2 idi. Hastaların 413'ü erkek, 75'i kadın idi.

Kalp nakli için endikasyonlar iskemik kalp hastalığı ve kardiyomiyopati idi. Hypertansiyon insidansını (Bp 150195 mmHg) yaşayan hastalarda araştırdık.

Postoperatif ilk ayda kullanılan immunosuppressive tedaviye göre hastalan üç gruba ayırdık.
Grup 1: Prednisone ve azathioprine (prediaza);
Grup 2: Cyclosporin ve azathioprine (CsA /aza);
Grup 3: Cyclosporin, azathioprine ve prednisone.

Bir yılda hypertansiyon insinadnsı Grup 1, 2 ve 3'de sırası ile %39, %49 ve %58 idi. Hipertansiyon ortaya çıkmadan ölen hastalar çalışmaya alınmamıştır.

Her üç grupta da hipertansiyon sıklığında zamanla orantılı olarak önemli bir artış vardı. Bu artış Grup 1 ve 2'de bariz idi (p = 0.16 Breslow test). Hipertansiyonun kalp naklinden sonra önemli bir problem olduğunu ve insidansının kullanılan immunosupresiftedavi şeklinden etkilendiği sonucuna varılmıştır.

Analılar Kelimeler: Kalp nakli, İmmünosuperfıon, hipertansiyon

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Cardiac transpantation has been used with increasing succcs for the patients with cnd-salge heart disease in many cardiac centers in the world. After introduction of a new immunosuppressive agent,

cyclosporinc-A (CsA), result of organ transplantalino has improved (1). However, there is some concern about its adverse effects including dose-related nephrotoxicity and systemic arterial hypertension (2).

The aim of this study was to evaluate the risk factors for posttransplant hypertension developing in associated with the use of CsA for immunosuppression by analyzing the number of 488 patients undergone cardiac transplantation.

MATERIAL AND METHOD

449 orthotopic, 35 heterotopic and 4 combined orthotopic + Heterotopic cardiac recipients have been reviewed between January 1980 and December 1987 in trems of immunosupprcsion on hypertension.

The mean age of the recipents was 43.2 years (range 9 days to 68 years). All recipients have been divided into three groups according to (he immunosuppression used during the fust postoperative months (Figure 3).

Group 1: Prednisone and azalhioprine (pred + aza);
Group 2: Cyclosporine and azalhioprine (CsA + aza);
Group 3: Cyclosporine, azalhioprine and prednisone.

Informations about the paliens were collected either notes of the patients of inlcrwiev with the transplant palienls in the patients clinic regarding to patients age, sex, previous personcl history of hyperL ision, family history of cardio-vascular disease, reason for cardiac transplantation and kidney function (urea and crealainine). Arterial pressure was measured either directly with an intra arterial catheter or indirectly with a sphygmomanometer. Hypertension was defined as blood pressure persistency over 150/95 mrnHg. The study was concluded at the end of June 1988, providing a minimum of 6 months and maximum of 7 years follow-up for all survivor patiens. Pre and postoperative renal function was assessed using the serum ccratinine value. The incidence of hypertension was evaluated using the actuial life-table method. Patients died without developing hypertension were removed from the analysis at the time of death.

Indications for Transplantation:
Ischacmic Heart Disease: 299
Cardiomyopathy and Specific Heart Muscle Disease: 163
Congenital Heart Disease: 13
Valvular Heart Disease: 11
Others: 2
Immunosuppressive Therapy: 2

Between January 1980 and September 1982,39 patients were transpanled using prednisone, azalhioprine and anlilihymocylc globulin for immunosuppression.

From September 1982 CsA was introduced in combination with azalhioprine avoiding the long-term effects use of oral steroids, including increased risk of infection, osteoporosis and hypertension together with adverse effects on glucose and lipid metabolism (3). However, steroids were temporarily added to the regimen or substituted for cyclosporin.

When patients experienced repealed or persistent episodes of rejection (3 or more positive biopsies within a period of one month) or a temporary impairment of renal function. A; (his condition, CsA is temporarily discontiuned and oral steroids introduced at a dose of 1 mg/kg/day, tapering by 2.5 mg/day to a maintenance dose of 15 mg/day which is continued until renal function recovers, CsA is reintroduced and a therapeutic plasma level achieved before discontinuing oral steroids. Triple therapy consisted of CsA, azalhioprine and low dose steroids (15 mg/day of prcdnisore).

CsA influence T-cell function and the addition of azathioprine which has an anli B-cell effect might be of particular value in preventing antibody-mediated rejection, CsA and azathioprine have a synergislic immunosuppressive effect. CsA (2-10 mg/kg) and azathioprine (1-2 mg/kg/day) are given peroperatively with anesthetic premedication and 1 g of mcthy/prcdnisolone is given inlraopcratively after releasing the aorlic clamp. After transplantation, the patients are maintained on CsA administered twice daily in doses varying between 2-40 mg/kg/day. Dose is adsted according to the trough plasma level (determined by radioimmunassay) and the patients renal function.

Azathioprine is given in doses varying between 1-2 mg/kg/day (depending on the White CountCell (WCC). The dose of CsA used has been progressively reduced. The aim was to maintain a level of 400-500 ng/ml during the fist month and 100-200 ng/ml subsequently. Aspirin and dipyridamole are used as antiplatelet agents.

Diagnosis of Rejection:

Clinical signs of cardiac failure (fluid retention and development of a third heart sound), Serial E C G to determine B C G voltage and to detect arrhythmias, Echocardiographic determination of systolic and diastolic left ventricular function and wall thickness, Endomyocardial biopsy (third day and then at weekly intervals for 3 months, 2 months intervals for 6 months and at 1 year).

The results have been analyzed both on the basis of intention to treat with conventional or cyclosporin based immunosuppression and on the basis of the drug therapy actually received during the first month following transplantation.

Treatment of Acute Rejection:

It is usually treated with pulse doses of intravenous methyl prednisolone (1 g daily for 3 days) or occasionally antithymocyte globulin or a combination of the 2 agents depending on the severity of rejection.

Repeated or persistent rejection (3 or more positive biopsies within a period of one month) receive a short course of oral steroid starling with a dose of 1 mg/kg/day. The steroids are tapered off at a rate of 2.5 mg/day until the prednisone is discontiuned.

RESULTS

The incidence of hypertension was higher in the cyclosporin group (Figure: 1). It was 49% at one year. The difference was even more marked when allowance was made for patients in the conventional immunosuppression (pred + aza) group who were 'ransferred to cyclosporin late after transplantation because of steroid side effects (Figure 2). The immunosuppression used in the first month also appeared to be releatcd to the incidence of hypertension with the highest incidence occuring in the group receiving triple therapy. It was 58% at one year (Figure 3). Older transplant recipients were more likely to develop hypertension (Figure 4), as were male recipients (Figure 5).

Although there was also a higher incidence of hypertension in patient with a positive family history of cardiovascular disease (myocardial infarction, cardiac failure, hypertension and stroke) (Figure 6). No corelalion was found between the CsA serum level and serum creatinine and hypertension.

DISCUSSION

The etiology of hypertension in the transplant patients is multifactorial and still unclear.

Hypertension is common in heart transplant patient treated with CsA and normotensive before transplant.

Intractable hypertension associated with CsA may adversely affect graft function either directly by prolonged pressure overload or indirectly by accelerating coronary artery atherosclerosis in the cardiac graft. The study of the renin angiolcnsin-aldosteron system should give more information about Ihe mechanism of hypertension, but the data reported in literature is limited and often contradictory while only 20% of cardiac transplant recipients treated with azathioprine and prednisone develop

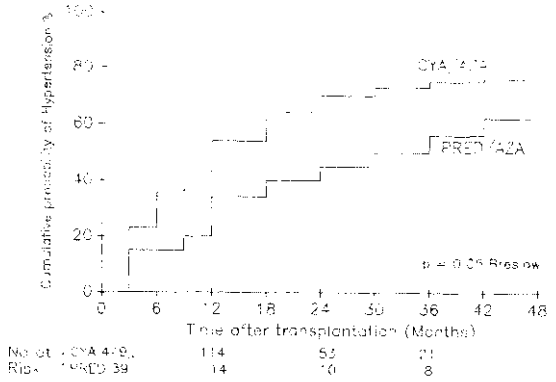


Figure 1. Hypertension after Heart Transplantation Influence of Immunosuppression AH patients.

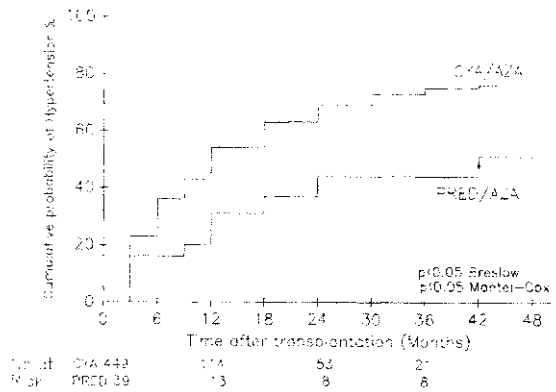


Figure 2. Hypertension after Heart Transplantation Influence of Immunosuppression Patients "crossing over" are censored.

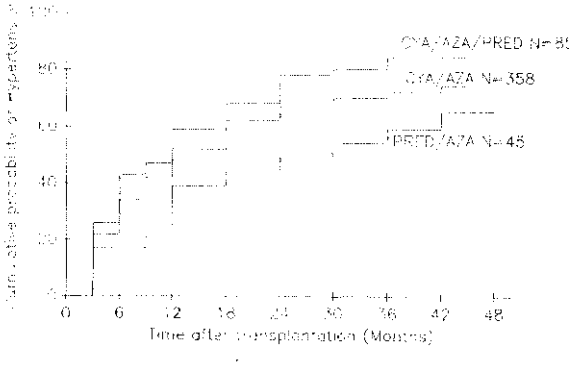


Figure3. Hypertension after Heart Transplantation Influence of Immunosuppression used in 1 st Month.

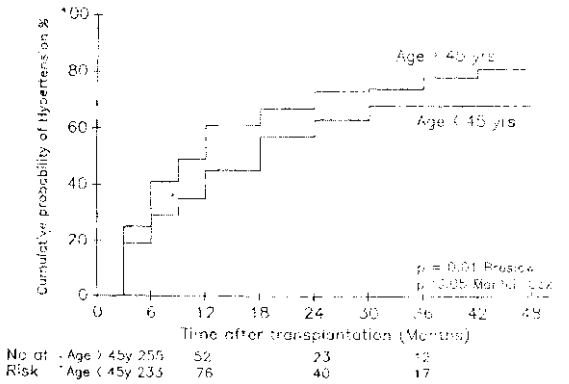


Figure 4. Hypertension after Heart Transplantation Influence of Recipient Age.

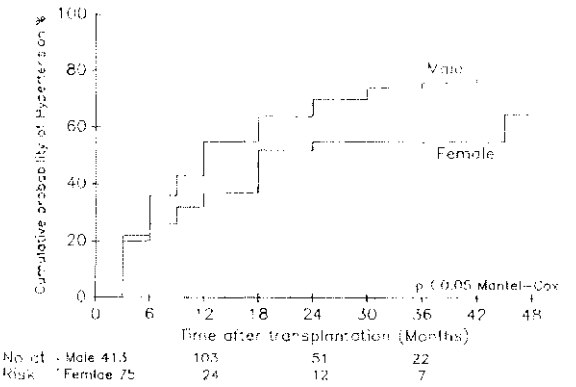
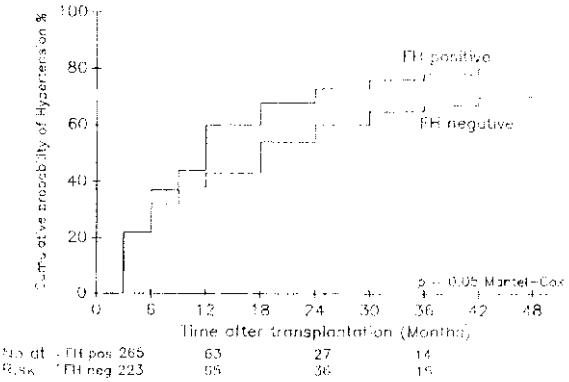


Figure 5. Hypertension alter Heart Transplantation Influence of recipient sex.



Figurée. Hypertension after Heart Transplantation Influence of recipient family history of CVD.

hypertension, 20% and 80% of CsA treated patients become hypertensive (4,5,6). Our studies showed that blood pressure was significantly higher in patients receiving CsA than in those receiving corticosteroids (Figure 1,2,3).

Thempson et al. (7) reported that posttransplant hypertension is associated with normalization of cardiac output, an abnormally elevated systemic vascular resistance and modest impairment of renal function and that postoperative peripheral renin activity and catecholamines levels were within normal limits. These observations do not support renin mechanism as an explanation fo the systemic hypertension. They also stated that the development of hypertension appeared to be independent of patient age, sex, weight or reason for transplantation and that the incidence of hypertension in the CsA group was hiphger than the azathioprine group. Joss et al. (8) suggested that impairment of renal function contributed to the development of hypertension but precise mechanism was not clear. In addition, steroids could contribute to the development of hypertension in the group o patients on CsA. When this high pressure untreated or unrecognized, it is likely to cause encephalopathy, seizures, hemorrhages and occasionally microangiopathic hemolytic anemia.

Tcxtor et al. (9) reported that plasma renin activity fell after CsA administiration and remained low during during accelerated phase hypertension

and lhat plasma levels t)l niorepinephi inc did not change during CsA therapy, but they stated that measurable serum creatinine elevations were evident in hypertensive CsA patients. However, we did not find any correlations between scrum ceralinine levels and hypertension at one year. They also indicated lhat typertensive effect of CsA may arise in normotensivc subjects withoud steroids, but why some patients develop hypertension under the same conditions while others do not, is not understood, whether familial or genetic factor predispose to those changes is an important questions, but we found a positive correlation between sex, age, positive family history of cardiovascular disease and hypertension (Figure 4,5,6). Whereas, some authors (10,11) reported that there was not correlation between sex, age, weight, reason for transplantation and hypertension in the CsA group.

Charpman et al. (10) stated lhat addition of prednisone clearly augmented thai the levels of blood pressure. This is in agreement wilh the results obtained (Figure 3). Thompson el al. (11) suggested that maintenance doses of steroids may also have contributed to some extent to the development of hypertension. Bertman el al. (12) suggested that postlransplant hypertension was associated with elevated scrum lipid levies and that incidence of hypertension was associated with elevated serum lipid levels and that incidence of hypertension was 52.7% al one year. They also stated that prednisone may cause elevation in blood pressure and that medications used to treat hypertension may have contributed to hyperlipidemia.

Bachy et al. (13) reported that age, sex, weight, corticosteroid dose, allograf function, the number of rejection episodes and length of follow-up were associated wilh postlransplant hypertension. However, Pollin et al. (14) stated that these factors were not related toh hypertensino in transplant recipient. Adu et al. (15) pointed out that Renin-Angiotensin system is not mechanism of high blood pressure and that Renin level is low in renal transplant patients treated with CsA. Steigerwalt et al. (6) reported that vascular responsiveness to transmural nerve stimulation is increased in the presence of CsA.

Transmural nerve stimulation results in the release of catecholamines from noradrenergic nerve terminals within the blood vessel and subsequent vasoconstriction of the postsynaptic blood vessels, CsA may contribute to an increased vascular resistance in transplant patients by increasing the release of norepinephrine from the peripheral nervous system. They have also reported that plasma renin activity and angiotensinogen II concentrations were normal levels, but aldosterone levels increased after cardiac transplantation. They concluded that CsA related hypcr'"nsion in cardiac transplant recipients is characterized by an expanded plasma volume and by the absence of major abnormalities in the renin/angiotensin systems and that CsA increases the sensitivity of vascular smooth muscle to contractile agents but the other hand, Rego et al. (16) pointed out that CsA, in a dose dependent manner, markedly affcects both the contractile and relaxatinon responses of the rat toracic aorla. Bantlc et al. (17) suggested that CsA suppreses the rein-angiolensin system in hypertensive transplant patients, the drug may be causing a low renin type of postlransplant hypertension that is quite paradox. Spratt et al. (18) stated that hpcrtension had been a significant problem, despite the use of low doses of CsA and the presence of normal serum ceralinine in many patients we also did not find any correlation between CsA doses and hypertension at one year. Jacquot et al. (10) reported lhat there was a positive correlation between scrum ceralinine level and blood pressure we did not find the same results at one year. Reeves et al. (20) suggested that esA may act directly on arterioles to raise peripheral vascular resistance and thai the mechanism for the hypertension may include sodium and water retention as a result of renal dysfunction from CsA, On the other hand, loss of the normal nocturnal decline in blood pressure and heart rate which is related to the denervated state of the transplanted heart may play an important role in blood pressure control. Bellet et al. (21) reported that pasma renin, angiotensine, aldosterone and converting enzyme activity were normal, but Baxter ct al. (22) and Halen et al. (23) suggested that a possible influence of CsA on the renin, angiotensin, aldosterone system and stimulation of renin release of production subsequent release of angiotensin 11 could be responsible for the hypertension. On the other hand, non transplanted patients treated with CsA for ocular conditions had usually high rates of hypertension. This is important because it appears such patients without evidence of nephrotoxicity as judged by scrum creatinine can develop CsA-releated hypcrtensin consisted of diuretics to

reduce excess intravascular volume, vasodilatators to reduce vasculcr tone and sympatholytic drugs to attenuate the effects **of** circulating catecholamines and the Sympathetic Nervous Systems. In spite of this approach, this hypertension has been resistant to treatment. Further studies are needed to define the mechanism of this new form of hypertension.

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