Pigmentary Irregularities and Optic Disc Edema After Heart Transplantation

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Objectives: To determine the prevalence of chorioretinal lesions and optic disc edema after heart transplantation and to study potential associations.

Design and Patients: One hundred one patients who had undergone heart transplantation at one institution and 19 patients prior to heart transplantation underwent ophthalmological examination, including fundus photography. The prevalence of fundus lesions was then compared between the two groups.

Main Outcome Measure: With a standardized protocol, the presence of optic disc edema, chorioretinal hyperpigmentation and depigmentation, retinal hemorrhages, cotton-wool lesions, and arteriovenous nicking was graded on color transparencies.

Results: The prevalence of optic disc edema and hypo-

pigmentations was significantly higher among the transplant recipients than among the patients prior to heart transplantation (31% vs 5%, $P=.01$, and 55% vs 11%, $P<.001$, respectively). Hyperpigmentation was only present in patients after transplantation (15% vs 0%, $P=.06$). Heart transplant recipients showed an increased risk of hyperpigmentations after 2.5 years. Acute rejection episodes were not associated with posterior pole lesions.

Conclusion: Common posterior pole lesions after heart transplantation are optic disc edema and pigmentary changes. Although visual acuity does not seem severely impaired, further longitudinal study is necessary to evaluate the long-term significance of these lesions.

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ONLY CASE reports have described ocular complications after heart transplantation.¹⁻⁵ Most of them report opportunistic infections and development of ocular tumors, which are both complications of the immunosuppressive regimen after transplantation. Conversely, ocular lesions occurring after renal⁶⁻¹⁰ and bone marrow¹¹⁻¹⁶ transplantation have been studied more thoroughly. They may be divided into those involving either the anterior or the posterior segment. Anterior segment complications, such as corneal and conjunctival calcifications and subcapsular cataract, have been well described.^{7,9,11-14} Recent reports have mentioned pathological changes in the posterior segment: chorioretinopathy,¹⁷ optic disc edema,¹⁶ serous retinal detachment,¹⁸ and cotton-wool spots.¹⁹ The prevalence and pathogenesis of these lesions, however, remain a matter of speculation.

In this study we aimed to investi-

gate the prevalence of chorioretinal lesions in patients who had undergone heart transplantation, comparing these with a group of patients before transplantation, and to evaluate possible related factors.

RESULTS

Clinical characteristics and demographic data are shown in **Table 1**. Most heart transplant recipients had hypertension, whereas the waiting list patients were more likely to be hypotensive. The groups were comparable for other clinical features, excluding physical condition and medication. The immunosuppressive medication regimen of cardiac recipients consisted of cyclosporine (100%), prednisone (96%), and azathioprine (23%). Eighty-five patients (84%) were taking antihyperten-

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PATIENTS AND METHODS

CARDIAC RECIPIENTS

All cardiac recipients included in this report underwent heart transplantation at the University Hospital of Rotterdam (the Netherlands). Those studied attended the outpatient department of cardiology for a follow-up examination between March and June 1993 (n=115). Of these, 101 (88%) consented; an ongoing rejection episode was the main reason for nonresponse.

PATIENTS PRIOR TO HEART TRANSPLANTATION

The comparison group consisted of patients with end-stage cardiomyopathy who were on the waiting list for heart transplantation. Those eligible were visiting the cardiology clinic or outpatient department during the study period (n=29). Nineteen patients (66%) participated in the study. Most nonparticipants were in such poor physical condition that ophthalmological examination could not be carried out.

CLINICAL DATA AND DEFINITIONS

From the patients' records, we obtained information on clinical characteristics about indications for heart transplantation, acute rejection episodes, presence of hypertension, medication, and demographic background. We defined current patient data as those at the time of the ophthalmological examination. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater and/or a diastolic blood pressure of 95 mm Hg or greater and/or a history of hypertension with use of hypertensive medication at the time of the examination. The definition of a rejection episode was based on histological staging of repeated endomyocardial biopsy specimens according to the guidelines of the International Society for Heart and Lung Transplantation.^{20,21} To minimize rejections, all patients were treated prophylactically with a combination of cyclosporine and, in most cases, prednisone. Azathioprine was added to the maintenance immunosuppressive regimen in patients who had had recurrent rejection episodes, in patients who had developed diabetes mellitus (allowing discontinuation of prednisone), and in patients who had developed cyclosporine-related severe renal failure (allowing reduction of the dose of cyclosporine). Rejection episodes were treated

with pulsed high doses of methylprednisolone sodium succinate (1 g intravenously on 3 consecutive days) or with polyclonal or monoclonal anti-T-cell antibodies in ongoing or frequently recurring rejection episodes.

OPHTHALMOLOGICAL EVALUATION

Ophthalmological examination consisted of best corrected Snellen visual acuity and, after mydriasis, indirect ophthalmoscopy and fundus photography. Centered on the disc, stereoscopic 20° color photographs were taken, and centered on the macula, stereoscopic 50° color photographs were taken (Kodak Ektachrome 64 ASA, Kodak Eastwood, Rochester, NY; Topcon TRV-50VT fundus camera, Topcon Corp, Tokyo, Japan). Additional fundus transparencies were taken if any lesions were found outside these fields.

Posterior pole lesions were graded with a stereo viewer in a masked fashion by two graders using a standardized protocol. Optic disc edema was classified as grade 1, a swollen optic disc with an indistinct margin but maintenance of the physiological cup, or grade 2, a markedly swollen disc with obliteration of the physiological cup. In addition, late leakage on the fluorescein angiogram was obligatory for the classification of optic disc edema. Granules or clumps of gray or black pigment in or beneath the retina were classified as hyperpigmentation, while areas of diminished pigmentation were classified as hypopigmentation. Retinal hemorrhages, cotton-wool spots, hard exudates, and arteriovenous nicking were classified as such using an abbreviation of the modified Airlie House classification scheme.^{22,23}

ANGIOGRAPHY

Fluorescein angiography was performed in cases with optic disc edema and pigmentary irregularities. An indocyanine green videoangiogram was obtained in one case with severe visual loss and extensive pigmentary changes.

STATISTICAL METHODS

By using χ^2 analysis and Student's *t* test, the presence of the various posterior pole lesions and means of continuous variables were compared between the posttransplant patients and the patients before transplantation. Associations between age, rejection episodes, postoperative duration, and hyperpigmentation or optic disc edema were determined with logistic regression analysis.

sive medication, and the patients with diabetes mellitus were being treated with oral antidiabetic agents (14%). Medications of the waiting list patients included digoxin (63% [12/19]), angiotensin converting enzyme inhibitors (58% [11/19]), and diuretic agents (89% [17/19]). Three of the 19 patients were taking catecholamines and one was taking amiodarone.

Visual acuity was not significantly different between the two study groups. In the group after transplantation, 82% had a visual acuity (worse eye) of 20/20, compared with 74% of patients before transplantation (*P*=.3). In each group there was only one patient with a visual acuity (worse eye) of less than 2/20 (1% [1/101] vs 5% [1/19], *P*=.3).

Prevalence of chorioretinal lesions in at least one eye is shown in **Table 2**. Optic disc edema, hypopigmentations, and hyperpigmentations were the most common lesions after transplantation, and the prevalence of the first two differed significantly between the two patient groups. Sixty-eight percent (21/31) of posttransplant patients who had optic disc edema had bilateral optic disc edema (**Figure 1** and **Figure 2**). In patients in whom just one eye was involved, only grade 1 optic disc edema was present (**Figure 1**). Hyperpigmentation was present only in the posttransplant patients. Various patterns of hyperpigmentation were identified: one patient had wide, scattered zones of pigment epithelial disruption and clumping of yellow-orange pigment (**Figure 3**), three

Table 1. Demographic and Clinical Characteristics

Characteristic	Heart Transplant Recipients (n=101)	Waiting List Patients (n=19)	P
Gender, No. (%)			
M	78 (77)	16 (84)	.4
F	23 (23)	3 (16)	
Mean±SD age, y	49.6±10.7	51.5±8.0	
Age group, No. (%)			
15-30 y	6 (6)	0 (0)	.7
31-40 y	12 (12)	2 (11)	
41-50 y	21 (21)	4 (21)	
51-60 y	44 (44)	11 (58)	
≥61 y	18 (18)	2 (11)	
Heart disease, No. (%)			
Ischemic heart disease	58 (57)	14 (74)	.3
Cardiomyopathy	43 (43)	5 (26)	
Hypertension, No. (%)	98 (97)	0 (0)	<.001
Diabetes mellitus, No. (%)	14 (14)	1 (5)	.3

Figure 1. A cardiac recipient with grade 1 optic disc edema; note swollen optic disc with an indistinct margin but maintenance of the physiological cup. **Figure 2.** A cardiac recipient with grade 2 optic disc edema; note markedly swollen disc with obliteration of the physiological cup.**Table 2. Fundus Lesions in Heart Transplant Recipients (n=101) and Waiting List Patients (n=19)**

Lesion	Heart Transplant Recipients, No. (%)	Waiting List Patients, No. (%)	P
Optic disc edema			
Grade 1	28 (28)	1 (5)	.01
Grade 2	3 (3)	0 (0)	
Hyperpigmentation	15 (15)	0 (0)	.06
Hypopigmentation	56 (55)	2 (11)	<.001
Arteriovenous nicking	22 (22)	1 (5)	.08
Yellow pigment	6 (6)	0 (0)	.35
Cotton-wool spots	5 (5)	1 (5)	.65
Hemorrhages	5 (5)	0 (0)	.42
Venous branch occlusion	1 (1)	0 (0)	.84
Hard exudates	1 (1)	0 (0)	.84

patients had a diffuse mottled pattern of pigmentation (**Figure 4** and **Figure 5**), and several patients each had only focal hyperpigmentation or solitary pigmentations surrounded by a halo.

INDOCYANINE GREEN ANGIOGRAPHY

The macular areas of one cardiac recipient showed large zones of disruption and subretinal clumping of yellow-orange pigment. Indocyanine green angiography revealed small areas of nonfluorescence in the choroidal vasculature. These areas corresponded with the subretinal orange deposits (Figure 1).

ASSOCIATIONS WITH AGE, GRAFT REJECTION, AND TIME AFTER TRANSPLANTATION

We evaluated the associations between age, number of acute rejection episodes, time after transplantation, and optic disc edema and hyperpigmentations. Age was not significantly associated with these fundus changes. The number of rejection episodes ranged from zero to 10, with

an average of two rejections per recipient. The number of rejection episodes had no significant relationship with optic disc edema or with hyperpigmentations. The mean duration of the posttransplantation period was 3 years, ranging from 1 month to 7.5 years. Patients with a cardiac transplant for more than 2.5 years showed an increased risk of hyperpigmentations compared with patients with a transplant of shorter duration (odds ratio, 10.9; 95% confidence interval, 1.3 to 91.7). There was no association between time after transplantation and optic disc edema. Among patients with optic disc edema, the shortest time after transplantation was 4 months.

COMMENT

Searching the *Index Medicus* for 1987 through 1995 using the descriptors "heart transplantation" and "ocular complication," we found no report on the prevalence of fundus lesions in a population of cardiac recipients. Hence, we believe this is the first study to address this problem. We detected lesions of the posterior segment in 65 of the 101 patients with a heart transplant. Optic disc edema

Figure 3. Top, Fluorescein angiogram of a cardiac recipient with severe visual loss showing a leopard-skin appearance of multifocal areas of hyperfluorescence and hypofluorescence. Center, Red-free photographs of the same patient. Bottom, Indocyanine green video angiograms of the same patient showing parafoveal areas of hypoperfusion, indicating local ischemia of the choroidal vasculature.

and chorioretinal pigment alterations were the most common of these lesions, and they were significantly more frequent in heart transplant recipients than in a comparable group of patients before transplantation.

Response rates in the posttransplant patient group and the group prior to transplantation were 88% (n=101) and 66% (n=19), respectively. Ongoing rejection was the main reason for nonresponse among post-transplant patients. As the data show, we found no relation between fundus changes and rejection episodes. Frequency of fundus changes is therefore not likely to be different among nonresponding heart transplant recipients. Although exclusion of the most ill patients on the waiting list implies selection, the effect on the results is likely to be small, since all patients on the waiting list were in very poor physical condition prior to transplantation.

Figure 4. Fluorescein angiogram of a cardiac recipient showing a patternlike hypofluorescence within an area of mottled fluorescence.

Figure 5. Fluorescein angiogram of a cardiac recipient showing hypofluorescent spots and pinpoint hyperfluorescence corresponding with hyperpigmentation and hypopigmentation.

There are reports about optic disc edema occurring after other organ transplantations. Gass et al¹⁷ mentioned mild swelling of optic discs in one case after renal transplantation, while others^{15,16,19} have reported this in groups of patients after bone marrow transplantation. Bernauer et al¹⁹ concluded from their cases that the combination of cyclosporine and total body radiation was causing the optic disc edema. Our data show that radiation is not a prerequisite because radiation is not a pre-transplantation procedure in cardiac recipients. Avery et al¹⁶ ascribed optic disc edema to cyclosporine, arguing that it resolved after discontinuation of this medication. Our patients were taking cyclosporine continuously for life, the oral dose being regularly adjusted according to serum levels. Serum levels of cyclosporine differed only slightly between recipients; therefore, we considered time after transplantation to be a marker for cumulative dose of the immunosuppressive medication. The risk of optic disc edema did not increase with longer time. Thus, if medication is an associated factor, cumulative dose is unlikely to be important.

Hyperpigmentation occurred in 15% of cardiac recipients, hypopigmentation in 55%. Two authors have^{10,24} reported pigmentary irregularities after renal transplantation. Kopsa et al²⁴ compared fundus lesions before and after renal transplantation within the same patients, detecting pigmentary changes in 11 of 51 renal transplant recipients. Obermann and Chatterjee¹⁰ described depigmentation in the perimacular area and considered a possible viral cause. Although this cannot be ruled out, post-mortem histopathologic examination of one of our heart transplant recipients with pigmentary irregularities showed no signs of infection, only increased fibrosis of the choroidal vessels. This finding is rather nonspecific and can also be detected in hypertensive retinopathy.²⁵ Cyclosporine could be important in this process, because it is known to cause hypertension and is associated with arteriopathy.²⁶

We identified different patterns of pigmentation. Whether they all have a similar pathological cause is difficult to say. One patient developed severe visual loss associated with zones of disruption and coarse clumping of the pigment epithelium. This lesion closely resembled the posterior chorioretinopathy described by Gass et al¹⁷ in three patients after renal transplantation and in one patient after heart-lung transplantation. Gass and colleagues commented on an uncertain pathogenesis but hypothesized that localized intravascular coagulation affecting the posterior choroid might be a causal factor. The nonperfused areas of the choroid on the indocyanine green angiogram support this theory. Choroidal vascular occlusion may also be the cause of the focal hyperpigmentations surrounded by a halo. They resemble Elschnig spots, which are ischemic infarcts of the choroid.²⁷ Whatever causes these pigmentary changes, we found no relationship with acute rejection episodes. The risk did increase with longer time after transplantation, indicating that medication may play a role.

This cross-sectional study was mainly designed to investigate which chorioretinal lesions occur after heart transplantation; therefore, our ability to draw valid conclusions on possible causes is limited. Only prospective follow-up studies will provide more clues about time of onset, natural course, and etiology. We conclude that marked fundus changes are not as frequent as previous case reports suggest. Nevertheless, optic disc edema and pigmentary irregularities are common after heart transplantation. As the life expectancy of cardiac recipients increases, a study of the long-term ophthalmological effects of heart transplantation and the consequences of the immunosuppressive regimen may become indicated.

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