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ORIGINAL ARTICLE

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Treatment of recurrent rejection in heart transplantation: cytolytic therapy or bolus steroids?

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Abstract *Objectives.* The treatment of recurrent rejection in heart transplant recipients has been a controversial issue for many years. The intent of this retrospective study was to perform a risk-benefit analysis between treatment strategies with bolus steroids only versus anti-thymocyte globulins (RATG; 1.5 mg/kg q 4 days).
Methods. Between 1986 and 1993, 69 of 425 patients (17 male, 52 female; mean age 44 ± 11 years) who had more than one rejection/patient per month (rej/pt per mo) in the first 3 postoperative months were defined as recurrent rejectors.
Results. Repetitive methylprednisolone bolus therapy (70 mg/kg q 3 days) was given in 27 patients (group M; 1.4 ± 0.2 rej/pt per mo) and RATG therapy for one of the rejection episodes of the 42 remaining patients (group A; 1.5 ± 0.2 rej/pt per mo). The quality of triple drug immunosuppression in the two study groups was comparable. The rejection-free interval (RFI) following RATG treatment in group A was 21.6 ± 10 days and 22 ± 11 in group M. In group M, 3 of 27 patients (11%) had a rejection treatment-related infection (2 bacterial; 1 viral) versus 6 of the 42 patients of group A (14.2%; bacterial 1, viral 5). During postoperative months 3–24, 0.15 ± 0.12 rej/pat per mo were observed in group M and 0.21 ± 0.13 rej/pat per mo in group A (n.s.). In this 21-month period cytolytic therapy for rejection was initiated in 8 of the remaining 21 patients of group M (38%) and 15 of the remaining 37 patients of group A (40.5%). The absolute survival and the individual causes of death were not affected by the type of initial treatment of recurrent rejection. The actuarial freedom of graft atherosclerosis is comparable in the two groups with 78% in group A versus 79% in group M free of graft atherosclerosis at 3 years postoperatively.
Conclusions. A comparison of cytolytic therapy versus repeated applications of bolus steroids for treatment of recurrent rejection reveals no significant difference in the long-term patient outcome with respect to the incidence of future rejection episodes and survival. [Eur J Cardiothorac Surg (1996) 10:905–911]

Key words Heart transplantation · Rejection · Anti-thymoglobulin · Methylprednisolone

Introduction

Graft rejection is a normal event following organ transplantation [2]. Traditionally, in heart transplantation the administration of pulsed intravenous corticosteroids represents the standard form of rejection treatment [18]. In a certain subset of patients repeated episodes of rejection may require a more thorough level of immunosuppression. In these patients cytolytic antibodies are commonly recommended for treatment [9]. A recently published article by Wagner et al. on the use of OKT-3 for rescue therapy in cases of steroid-resistant acute rejection has shown a high rebound rate of severe rejection [17]. There are as yet no exact data available regarding the efficacy of polyclonal cytolytic antibodies versus simply repeating intravenous bolus steroids in the early postoperative period for patients with multiple rejection episodes. We have in the past chosen a variable approach to this problem. A number of patients received corticosteroids in repeated doses while, as in some instances, patients received cytolytic antibodies primarily based on the preference of the individual surgeon involved.

The goal of this retrospective analysis was to compare the efficacy of rejection treatment in the early postoperative period using either pulsed intravenous methylprednisolone or polyclonal T-cell antibodies in patients undergoing multiple rejection episodes following heart transplantation.

Material and methods

This retrospective analysis included only patients defined as recurrent rejectors based on the following inclusion criteria:

- a minimum postoperative follow-up of at least 100 days
- continuous follow-up within one transplant center
- more than three rejection episodes within the first 3 postoperative months
- induction therapy with polyclonal rabbit anti-thymocyte globulin.

Of the 425 patients who received a cardiac allograft at the Hannover Medical School between April 1986 and October 1993, 69 patients met these inclusion criteria.

Immunosuppression

All patients received an intraoperative bolus of 500 mg methylprednisolone at the time of aortic cross-clamp removal during the operative transplant procedure. Postoperative induction immunosuppression was started with polyclonal antithymocyte globulins (rabbit ATG (Ch. Biber, Palo Alto, California) 1.5 mg/kg for 4 days, intravenously). Methylprednisolone was added at a dose of 125 mg every 12 h for a total of three doses followed by oral prednisolone at 0.5 mg/kg per day. The latter drug was tapered to 15 mg/day for the first 3 months postoperatively and finally to 5–10 mg/day for the remaining time period. Azathioprine was started on postoperative day 2 with 1–2 mg/kg and the dose was adjusted for a minimal white blood cell count of $3.5–5.0 \cdot 10^9$/l not to exceed 3 mg/kg per day.

Maintenance oral cyclosporine (CsA) therapy was commenced on day 2 depending on renal function, with target specific CsA through levels for the first year of 250–300 μg/l, for the second year 150–200 μg/l and then 100–150 μg/ml. Dosage adjustments were executed according to creatinine levels, where maximal creatinine levels of 120–150 μmol/l were considered acceptable.

Detection and grading of acute rejection

Detection and monitoring of acute rejection were accomplished by transvenous endomyocardial biopsies [3] graded according to the Hannover classification (Table 1) [13]. During the 1st months post-transplantation the minimal interval between positive biopsies following a rejection was 1 week and this interval was lengthened with increasing duration of the postoperative course and is depicted in Table 2 [12]. By the end of the 1st year the average follow-up interval was 4 weeks. Treatment was instituted in patients with moderate or severe rejection (grade 3b, grade 4). For this study only treated rejections were included in the analysis.

Rejection therapy

The primary form of rejection treatment in all patients consisted of pulsed methylprednisolone therapy (70–100 mg/kg per day for 3 consecutive days). The success of this form of treatment was controlled a week later by endomyocardial biopsy and echocardiographic evaluation of ventricular performance. Repetitive treatment for ongoing acute rejection was defined as treatment of an acute rejection within 7 days of a previous rejection treatment. All rejection treatment was accompanied by the administration of anti-cytomegalovirus (CMV) globulins as well as prophylactic antibiotic therapy with a first generation cephalosporine (Cefazolin) for 3 days.

Other prophylactic measures

All patients received trimethoprim-sulphamethoxazole (Bactrim, Roche, Basel Switzerland) and acyclovir for the 1st year postoperatively as prophylactic agents against pneumocystis and herpes simplex virus infection, respectively.

Cytomegalovirus seronegative recipients received seronegative blood products and were treated for 7 days with anti-CMV immunoglobulin (Cytoglobin; Cutter-Tropon, Frankfurt Germany) for passive immunization. Prophylactic perioperative antimicrobial therapy consisted of cefazoline.

Patient groups

The study population consisting of 69 patients with more than three rejection episodes during the first 90 days post-transplantation was subdivided into two groups according to the type of rejection thera-

Table 1 The Hannover classification for evaluation of cardiac biopsies

A0	=	no rejection
A1	=	minor rejection
A2	=	mild rejection
A3a	=	mild-to-moderate rejection, no treatment required
A3b	=	moderate rejection, treatment required
A4	=	severe rejection, treatment required
R1	=	resolving rejection, recent and old myocytolysis
R2	=	resolving rejection, old myocytolysis

Table 2 Scheduled biopsy intervals in weeks. Recommended interval depends on results of previous biopsy (*left column*) and postoperative month (*top line*)

Months	2	4	6	8	10	12	14	16	18	20	22	24	>24
	Interval between biopsies in weeks												
A-0	4	4	4	4	5	6	6	8	10	12	12	12	12
A-1	2	3	4	4	5	6	6	8	10	12	12	12	12
A-2	2	3	3	3	4	4	4	6	8	10	10	12	12
A-3a	1	1	2	2	2	2	2	4	4	4	4	4	4
A-3b	1	1	2	2	2	2	2	4	4	4	4	4	4
A-4	1	1	2	2	2	2	2	2	2	2	2	2	2
R-1	1	1	2	2	2	3	6	8	8	8	10	10	10
R-2	2	3	4	4	5	6	8	8	10	12	12	12	12

Table 3 General group characteristics in respect to age, sex, preoperative diagnosis and length of follow-up. Data displayed as mean ± standard deviation or percent of study population

	Group M	Group A	Statistics
No.	27	42	
Age (years)	44 ± 12	43 ± 9	n.s.
Sex (M/F)	6/21	10/32	n.s.
Preoperative diagnosis – Ischemic	34%	38%	n.s.
Cardiomyopathy – Dilative cardiomyopathy – Other heart disease	61% 5%	58% 4%	
Follow-up (days)	1479 ± 863	1695 ± 901	n.s.
Total HLA mismatch	4.45	4.96	n.s.
HLA-DR mismatch	1.45	1.58	n.s.

py performed during the initial 3 postoperative months. Group M (methylprednisolone; $n=27$) included patients with more than one rejection per patient month and rejection treatment using only methylprednisolone. The patients in group A (RATG; $n=42$) received rabbit antithymocyte globulin (1.5 mg/kg for 3 days; C. Biber, Palo Alto, California) for one of the rejection episodes during the first 3 months postoperatively.

Evaluation of transplant vasculopathy

The incidence of transplant vasculopathy was evaluated by annual coronary arteriograms and the histopathologic examination of deceased patients. Vasodilation was standardized by administration of isonitroglycerine (0.2 g) into the coronaries during the procedure. The angiograms were analyzed visually and were compared side-by-side (consensus of two observers) with special attention to the presence of minimal coronary vascular changes in all branches of the vascular tree. Coronary artery disease was defined as any narrowing of the coronary vessels. Two main patterns were distinguished: changes of the epicardial vessels and changes in the tertiary branches. Mild disease was characterized by less than 30% narrowing in one to two arteries. Moderate disease was defined as stenosis of 30–60% in any coronary artery or if three major vessels were involved. Any stenosis greater than or equal to 60% was defined as severe. Coronary alterations were categorized according to the description of Gao et al. as focal stenosis, diffuse concentric narrowing or abrupt ending of the terminal branches [10].

Statistical analysis

Patient data were analyzed with the Statistical Program of Social Sciences (SPSSWIN 6.0, Birmingham U.K.). Continuous data were expressed as the mean ± standard deviation and were compared by a two-tailed unpaired t test. The log-rank test was used for freedom of re-rejection analysis. Non-linear data were evaluated with the chi-square test or Fisher's exact test. A probability value of less than 0.05 was considered significant.

Results

The general group characteristics of group M (methylprednisolone treatment) and group A (RATG treatment) are outlined in Table 3. There was no statistical difference regarding age, sex, preoperative diagnosis and follow-up period. A retrospective HLA typing showed a similar number of HLA-mismatches, including DR mismatches, in the two groups. Rejection surveillance was accomplished with an average of 27 ± 12 biopsies per patient during the 1st year (bx/pt per year) in group M and 31 ± 14 bx/pt per year in group A (n.s.). The frequency of routine biopsies was 15 ± 11 bx/pt per year in group M and 16 ± 13 bx/pt per year during the 2nd postoperative year in group A.

The incidence of rejection per patient and month during the first 3 postoperative months was 1.38 ± 0.14 in group M and 1.5 ± 0.22 in group A (n.s.). In both groups the majority of biopsy results showed evidence of either mild-to-moderate (A-2/A3a) or resolving rejection (R-1/R-2) in the same proportion. In group A cytolytic therapy with RATG was instituted an average of 1.27 ± 0.58 times per patient within the first 3 months. The RATG treatment occurred on average at postoperative day 50 ± 26, which corresponds to the second rejection treatment in 40%, third rejection treatment in 30% and fourth rejection treatment in the remaining 30% of group A patients. Group A patients received an average of 6.2 ± 2.3 g of methylprednisolone compared to 7.5 ± 2.6 g in group M patients ($P<0.02$). The rejection-free interval following methylprednisolone treatment was 22 ± 12 days in group M versus 21 ± 11 days in group A after methylprednisolone treatment (n.s.). In group A the RATG treatment resulted in a

Table 4 Standard triple drug immunosuppression for the listed time periods. Cyclosporine oral dose in mg/d divided into two doses. Specific cyclosporine whole blood trough level in µg/l measured by radioimmunoassay

(Postoperative days 0–100)

	Group M	Group A	Statistics
Cyclosporine dose (mg/d)	374 ± 129	406 ± 127	P = n.s.
Specific cyclosporine level (µg/l)	239 ± 140	254 ± 141	P = n.s.
Oral prednisone (mg/d)	17.3 ± 7.7	18.2 ± 8.6	P = n.s.
Azathioprine (mg/d)	175 ± 55	188 ± 64	P = n.s.
White cell count (in 1000/µl)	3.4 ± 3.5	4.1 ± 3.7	P = n.s.

(Postoperative days 360–720)

	Group M	Group A	Statistics
Cyclosporine dose (mg/d)	301 ± 105	326 ± 144	P = n.s.
Specific cyclosporine level (µg/l)	220 ± 125	228 ± 115	P = n.s.
Oral prednisolone (mg/d)	11.2 ± 6	13 ± 7	P = n.s.
Azathioprine (mg/d)	125 ± 88	118 ± 78	P = n.s.
White cell count (in 1000/µl)	2.9 ± 4.1	3.2 ± 3.8	P = n.s.

rejection-free interval of 16 ± 9 days (n.s.). Repetitive treatment for ongoing rejection within an 8-day interval was necessary in 17 patients of group A (40.4%) and in 16 of the 27 group M patients (59.3%).

In group M, 3 of 27 patients (11%) had a rejection treatment-related infection (2 bacterial; 1 viral). Infections related to RATG treatment were observed in 6 of the 42 patients of group A (14.2%; bacterial 1, viral 5). The quality of triple drug immunosuppression in the two study groups during the first 3 postoperative months is depicted in Table 4, and was not statistically different. In group M one patient died of a late septic complication. Multi-organ failure related to cardiac insufficiency post-rejection was the cause of death in one patient of group A.

The analysis of the incidence of graft rejection after the first 3 postoperative months for a time interval of 21 months (reveals 0.15 ± 0.12 rej/pat per month in group M and 0.21 ± 0.13 rej/pat per month in group A (n.s.). In this 21-month period cytolytic therapy for rejection was initiated in 8 of the remaining 21 patients of group M (38%) and 15 of the remaining 37 patients of group A (40.5%). The average incidence of rejection over this time period is outlined in Fig. 1. A log-rank analysis for the freedom from the first re-rejection after postoperative day 90 is depicted in Fig. 2. The freedom from re-rejection was not statistically different between the two study groups. The quality of the standard triple drug immunosuppression was comparable as depicted in Table 4.

The incidence of rejection remained similar for the follow-up beyond the 2nd postoperative year. For the remaining patients, the mean follow-up was 2356 ± 556 days in group M and 2416 ± 673 days in group A, and their aver-

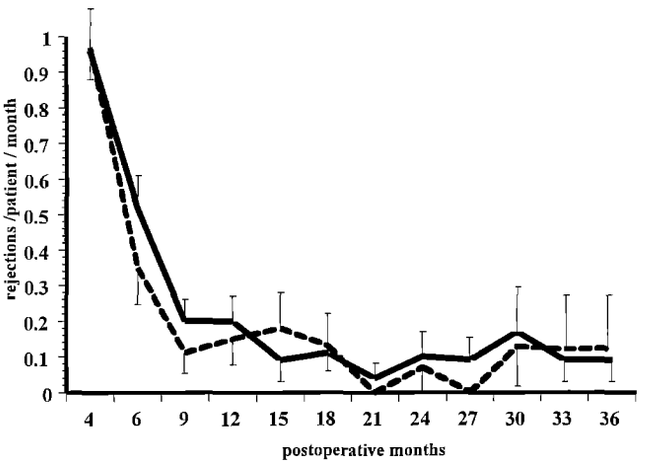

Fig. 1 Incidence of rejection during the time period starting postoperative months 4–36. Results depicted as rejections per patient and month (– – – Group M, —— Group A)

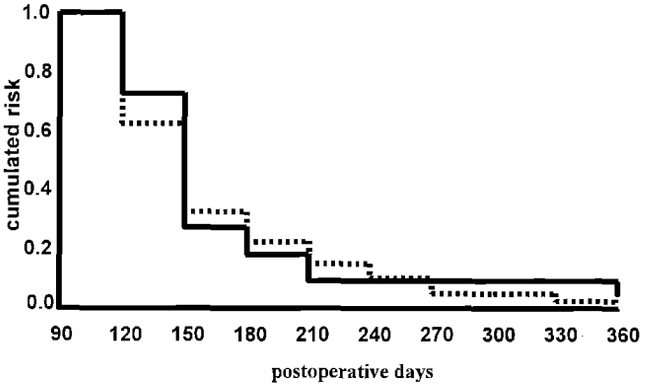

Fig. 2 Freedom from the first re-rejection after postoperative day 90 (– – – Group A, —— Group M)

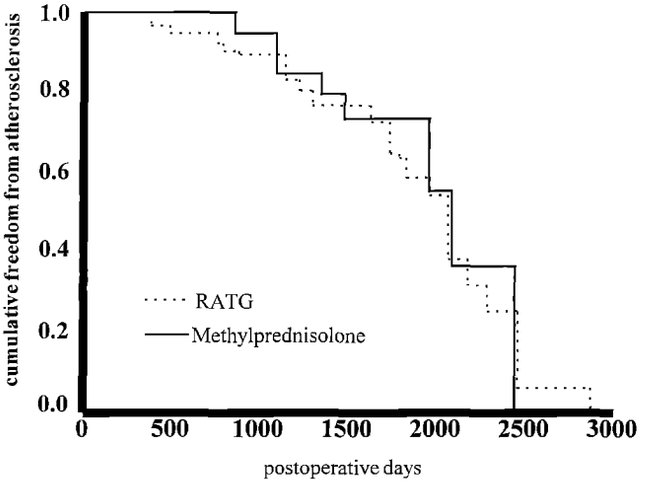

Fig. 3 Actuarial freedom from graft atherosclerosis based on the Kaplan-Meier method. No significant differences between the two groups

age rate of rejection per patient and month was 0.03 ± 0.01 rej/pt per month and 0.036 ± 0.01 rej/pt per month, respectively (n.s.).

The absolute survival and the individual causes of death were not affected by the type of initial treatment of recurrent rejection. In group M two patients died of chronic rejection with histologic evidence of graft atherosclerosis, one patient died of advanced lymphoproliferative disease and, finally, one patient died of a massive cerebral infarct. In group A six patients died of chronic rejection, two due to lymphoproliferative disease and two due to cerebral infarcts. In group M lymphoproliferative disease was present in five patients (4 skin tumors; 19%) while nine patients (21%) in group A had evidence of neoplasia. The latter included seven solid and two skin tumors.

The actuarial freedom from graft atherosclerosis for the total follow-up period is show in in Fig. 3. In the log-rank statistical analysis there was no significant difference in respect to actuarial freedom of graft atherosclerosis between the two study groups.

Discussion

Graft rejection is one of the major causes of early and late postoperative morbidity and mortality following heart transplantation. In addition, multiple rejection episodes may predispose to the development of graft atherosclerosis [5]. With the introduction of triple drug immunosuppression, the overall frequency and particularly the severity of graft rejection has decreased markedly [1]. Unfortunately, however, a significant number of heart transplant recipients still suffer from multiple rejection episodes, especially during the early postoperative period. Major treatment strategies for this subgroup of patients vary largely between individual centers but mainly consist of either pulsed steroids and/or monoclonal or polyclonal T-cell antibodies [11, 15, 17]. The purpose of this retrospective study was to evaluate the usefulness of polyclonal antibodies in this context.

For definition of the study population an analysis was made of the individual frequency of rejection episodes in our heart transplant population of 425 patients in the last 8 years. Based on the average frequency of rejection episodes in the first 3 postoperative months, patients in the upper 25 percentile were defined as recurrent rejectors and comprised the study population, with more than one rejection per patient and month. The results of this retrospective analysis showed a similar freedom from re-rejection, patient survival and freedom from graft atheroslerosis. The occurrence of lymphoproliferative disease was similar in the two groups. The incidence of bacterial, fungal or viral infection was also not influenced by the use of either steroids or RATG. The addition of RATG, therefore, did not improve the overall patient outcome.

Intravenous methylprednisolone bolus therapy has been the most widely used form of treatment for cardiac rejection. Miller et al. have shown that a single course of bolus steroids is successful in reversing rejection in 88% percent of heart transplant recipients [16]. An additional course of steroids eliminated any evidence of histologic rejection in another 7% of the patients. The Loyola experience on the use of the monoclonal antibody OKT-3 for this type of therapy has shown that cytolytic therapy may be beneficial in terms of reversing the acute rejection episodes, however this type of treatment did not diminish the recurrence of acute rejection in the further postoperative period [6]. These results were underlined by Wagner et al. [17].

Cytolytic therapy has many definite disadvantages. Couetil and others have found evidence for a correlation between the use of RATG and the development of malignant tumors [8, 14] following heart transplantation. The use of cytolytic therapy may significantly increase the risk for CMV infection post-transplantation [7]. Recent publications stress the importance of certain T-cell subpopulations for the development and maintenance of graft tolerance in the recipient [4]. A complete eradication of the entire complex of different T-lymphocytes [19] would also delete those important for graft tolerance and thus possibly promote future rejection. A more selective antibody therapy against certain T-cell subpopulations would perhaps be more beneficial. Rejection treatment with T-cell antibodies requires inpatient treatment while heart transplant recipients receiving methylprednisolone treatment for rejection can be treated on an ambulatory basis.

Graft surveillance with endomyocardial biopsies is widely accepted and its overall value is dependent on the frequency of biopsies performed. In this study the patients analyzed have been very closely monitored with more than 25 biopsies, on average, during the 1st postoperative year. During the initial and most critical time period post-transplantation weekly biopsies allow for an extraordinary tight surveillance. All biopsies have been exclusively evaluated by one pathologist avoiding inter-observer variability. The probability of overlooking a significant number of rejection episodes in this analysis, therefore, seems quite unlikely.

The limitations of this analysis include a possible bias in the selection of treatment strategies for individual patients, the inadequate correlation to potential rejection-related hemodynamic compromise and, finally, the general restrictions of a retrospective analysis. Nevertheless, one can conclude that the effect of anti-rejection treatment with RATG in this study was very similar to those of previous studies with OKT-3 [6, 17]. The use of cytolytic therapy with rabbit antithymocyte globulins does not reduce the incidence of future rejection episodes when compared to repeated applications of bolus steroids. Cytolytic therapy remains an excellent alternative form of treatment for rejection with hemodynamic compromise after failure of intravenous methylprednisolone therapy. Perhaps due to the

limited number of patients involved, the data of this study have failed to show a negative impact of cytolytic therapy on the incidence of viral, bacterial or fungal infection as well as the development of lymphoproliferative disorders. Nevertheless cytolytic treatment has the greater inherent potential for these life-threatening complications. This makes a careful indication for the use of T-cell antibodies necessary in this context.

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Discussion

Dr. M. Yacoub (*London, U.K.*): Thank you. This is a very interesting paper. So you don't think cytolytic therapy holds the promise of inducing specific immune tolerance, and do you think – if you used some other form of cytolytic therapy, like monoclonal antibodies, specifically something like anti-CD4 – you could have achieved a better result?

Dr. Hausen: I have no experience with anti-CD4. However, we have used OKT3 and the results were similar; however, the number of patients is not large enough for us to present the data.

There are two thinks. First of all, with OKT3 we see a higher incidence of CMV infection. That is very disturbing for us, as we think that there is an impact of CMV infection on graft atherosclerosis in the long term. Secondly, I think it is too simple to just get rid of T-cells for graft rejection. I think we have good T-cells and we have bad T-cells, and we're getting rid of all of them, including those that could induce tolerance in the long term. Therefore, I think these crude methods of treatment of rejection are becoming obsolete.

Dr. Yacoub: But all forms of immunosuppression are crude and non-specific so far.

Dr. Hausen: That is true.

Dr. Yacoub: What about lymphoproliferative disease, was it more common in the cytolytic therapy or the OKT3? You were specifically looking at polyclonal rabbit ATG, weren't you?

Dr. Hausen: Yes. There were four patients in the RATG group that had lymphoproliferative disease and two in the methylprednisolone group that had never received RATG. This was not statistically significant, but we all know from the literature that it may have an impact: another argument against a monoclonal or polyclonal antibody, I think.

Dr. Yacoub: Four and two, the numbers were equal. I mean what is the incidence if you take it in percentage?

Dr. Hausen: I can't tell you.

Dr. Jacoub: Because it could be a trend. We know that statistics can be misleading.

Dr. Hausen: Yes.

Dr. Yacoub: One more question?
(No response.)

Dr. Yacoub: I think you have convinced them. Thank you very much.

Forthcoming meetings and events

1996

October 15–17, 1996 – Kyoto, Japan
49th Annual Meeting of the Japanese Association for Thoracic Surgery
Information: Prof. Shigeki Hitomi,
Tel. +8 17 57 51 38 34,
Fax +8 17 57 51 46 47

October 20–23, 1996 – Tel Aviv, Israel
9th Annual Meeting of the Mediterranean Association of Cardiology & Cardiac Surgery
P.O. Box 50006, Tel Aviv 61500, Israel
Information: Prof. B. A. Vidner, President, Local Organizing Committee, Tel Aviv, Israel. Tel. +9 72 35 14 00 14,
Fax +9 72 35 17 56 74/5 14 00 77

October 25, 1996 – Zeist, The Netherlands
One-day Symposium on "Surgery of the Proximal Thoracic Aorta and the Carotid Arteries. Current Concepts and Controversies", Golden Tulip Hotel FIGI, Zeist, The Netherlands
Information: Congress Office Tonnc Verdonck, P.O. Box 113, 5660 AC Geldrop, The Netherlands. Tel. +3 14 02 85 22 12,
Fax +3 14 02 85 19 66

October 28–29, 1996 – London, UK
International Workshop on Intrathoracic Staging, Royal Brompton Hospital, London, UK
Information: C. Ratcliffe, Thoracic Surgery, Royal Bromptom Hospital, Sydney St., London SW3 6NP
Tel. +44 17 13 51 85 67,
Fax +44 17 13 51 85 55

October 28 – November 1, 1996 – San Francisco, CA, USA
American College of Chest Physicians
Information: 3300 Dundee Rd., Northbrook, IL 60062, United States
Tel. +1 70 84 98 14 00,
Fax +1 70 84 98 54 60

November 1–2, 1996 – Birmingham, England
Birmingham Aortic Surgery Symposium
Information: L. R: Associates,
PO Box 4663, Birmingham, B13 2RH, England
Tel. and Fax +44 12 80 84 81 43

November 9–13, 1996 – Crete, Greece
2nd International Congress on Lung Cancer
Information: Hellenic Society against Lung Cancer, Metaxa Cancer Hospital,
51 Botassi Street, GR-18537 Piräus, Greece
Tel. +30 14 28 50 00
Fax +30 14 53 89 53

November 11–14, 1996 – New Orleans, LA, USA
American Heart Association
Information: 7320 Greenville Ave., Dallas, TX 75231
Tel. +1 21 43 73 63 00,
Fax +1 21 43 73 34 06

December 4–7, 1996 – Rio Mar, Puerto Rico
8th Cardiac & General Thoracic Surgery: Update.
Information: American College of Chest Physicians, 3300 Dundee Road, Northbrook, IL 60062, USA
Tel. +1 84 74 98 14 00,
Fax +1 84 74 98 54 60

December 14, 1996 – Berlin, Germany
Symposium on "Organ Preservation in Heart Transplantation – Theory, Clinical Use and Legal Issues", Deutsches Herzzentrum, Berlin
Information: Dr. M. Loebe, Deutsches Herzzentrum, Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany
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1997

January 27–29, 1997 – San Diego, USA
The 33rd Annual Meeting of The Society of Thoracic Surgeons
Information: 401 N. Michigan Ave., Chicago, IL 60611-4267, USA
Tel. +1 31 26 44 66 10,
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February 13–15, 1997 – San Diego, California, USA
Pathophysiology & techniques of Cardiopulmonary bypass: The 17th Annual San Diego Cardiothoracic Surgery Symposium, San Diego Marriott Hotel & Marina, San Diego, CA, USA
Information: C. R. E. F., P.O. Box 23220, San Diego, CA 92193, USA,
Fax 0 01 61 95 41-14 47,
Email: 742241, 1523@compuserve.com