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The impact of early postoperative cyclosporine serum levels on the incidence of cardiac allograft rejection

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Abstract. The introduction of cyclosporine A (CyA) into the immunosuppressive therapy has significantly improved the results of heart transplantation (HTX). Its nephrotoxicity and hepatotoxicity, however, often limit the perioperative and postoperative use of this drug. The purpose of this retrospective study was to evaluate the effect of early postoperative CyA blood levels on the incidence of early as well as late cardiac rejection and patients' survival. Between October 1985 and June 1991, HTX was performed in 311 patients. Standard immunosuppression consisted of azathioprine (1–2 mg/kg), prednisolone (0.5 to 0.1 mg/kg) and CyA. Rabbit-antithymocyte-globulin (RATG – 1.5 mg/kg) was administered for the first 4 days postoperatively. Moderate rejection was treated with 3 × 500 mg methylprednisolone, severe rejection with RATG (1.5 mg/kg three times a day). Patients were excluded from this study because of a positive cross-matching, early death unrelated to rejection or alternate forms of immunosuppression ($n = 111$). Follow-up was complete in 200 patients (mean age 44 ± 11; 18 female, 182 male; 204233 patient days) with a total of 5380 biopsies. The cohort was divided into group I (no CyA for day 0 to 2; $n = 108$) and group II (CyA during day 0 to 2; $n = 92$) according to the onset of CyA therapy. In 101 patients (group A) the mean CyA blood level was less than 150 ng/ml from day 0 to 14 and in 99 patients more than 150 ng/ml (group B). On the 60th (365th) postoperative day the incidence of rejection per patient month for group I amounted to 0.84 (0.36) versus 0.93 (0.35) for group II, 0.84 (0.28) in group A and 0.93 (0.30) in group B with a survival of 94% (84%) in group I, 96% (87%) in group II, 92% (84%) in group A and 97% (89%) in group B. In conclusion, following HTX the onset of CyA therapy can be postponed and the respective early CyA target trough levels decreased (150 ng/ml) without disadvantages regarding the incidence of early and late rejection or patient survival. [Eur J Cardio-thorac Surg (1993) 7:257–262]

Key words: Heart transplantation – Cyclosporine – Allograft rejection – Renal failure

The inclusion of cyclosporine A (CyA) in the standard immunosuppressive protocol following organ transplantation has considerably reduced the frequency of rejection and early graft failure [11, 15, 20]. In addition, triple drug immunosuppression consisting of azathioprine, prednisone and CyA reduces the necessary dosages of prednisone (0.5 to 0.1 mg/kf per day) and azathioprine (1–2 mg/kg per day) and therefore also decreases the drug induced side effects [5, 8]. However, CyA is known to be potentially nephrotoxic [2, 22] and hepatotoxic, as well as having chronic side effects [6, 16] such as arterial hypertension, tremor, hirsutism and gingival hyperplasia [3, 19].

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At present many surgical centers add antilymphocyte globulins to the initial immunosuppressive therapy for the first 2–7 days following heart transplantation to prevent the development of acute or hyperacute rejection [4]. Methylprednisolone (2 mg/kg) is administered to prevent allergic reactions and hypersensitization as well as to add an additional, immediately effective, immunosuppressive agent. With this quadruple immunosuppression the incidence of acute cardiac rejection within the first week after transplantation is usually low [1, 10].

Potential candidates for cardiac transplantation are normally in end-stage heart failure with compromised hepatic and renal functions. The transplant procedure itself often has a negative impact on liver and kidney functions [13, 17]. Acute renal and hepatic failure are known complications of cardiovascular surgery and are associated with a high mortality [14]. Their occurrence may be independent of preoperative organ function. Re-

nal and hepatic functions may be further impaired with the addition of CyA in the early postoperative period [18], a dose-dependent phenomenon.

In the department of Thoracic and Cardiovascular Surgery at the Hannover Medical School heart transplantation has been performed since 1983. Within the last years it has become our standard practice to reduce or postpone the immediate postoperative cyclosporine therapy in selected patients with renal and/or hepatic dysfunction. It was the intention of this retrospective study to determine the impact of delayed or reduced CyA therapy on the early (less than 60 days postoperatively) and intermediate (less than 365 days postoperatively) incidence of acute cardiac allograft rejection.

Patients and methods

Between October 1985 and June 1991, 311 patients (41 female/270 male) received a total of 332 organs. Within the first 30 postoperative days 31 patients died of various non-rejection related causes and were excluded from the study population (4 female/27 male). Of the remaining 280 patients only those treated according to the following immunosuppressive protocol were included:

- Rabbit antithymocyte globulin i.v. 1.5 mg/kg qd for 3 days starting 6 h postoperatively
- Methylprednisolone i.v. 3 times 2 mg/kg q 12 h starting 5 h postoperatively
- Azathioprine 1–2 mg/kg qAM, tapered over months to a minimum of 0.75 mg/kg
- Prednisolone 0.25 mg/kg bid starting 36 h postoperatively and tapered every three days by 2.5 mg until a minimum of 5–7 mg/d was reached.

The dose of azathioprine was adjusted to maintain the absolute number of leukocytes between 3000 and 5000/ml. Eighty patients were excluded from the study due to variations in the immunosuppressive protocol (monoclonal anti – T cell antibodies instead of RATG, CyA without antibody administration, etc.) or due to a positive cross-match ($n=10$). At the time of transplantation the mean age of the remaining 200 patients (18 female/182 male) was 44 ± 11 years (range 10–63 years).

Due to the fact that for the first 4 years of the cardiac transplant program only polyspecific (including metabolites) CyA blood level measurements (RIA) had been available which were later replaced by specific (excluding metabolites) CyA (RIA) analysis, the following statistical analysis was performed separately for patients with polyspecific and specific blood CyA measurements, depending on the year of transplantation. Patients were subclassified into group I and II according to their CyA blood levels averaged for the first 2 days postoperatively. An additional subclassification was performed according to the measured CyA blood levels as a mean for the first 14 postoperative days (group A, group B; Table 1). The analysis included the rate of rejection, renal function on the 60th and on the 365th postoperative day, and survival.

Blood for the determination of specific CyA levels was drawn one hour before the morning application of the drug (trough levels). Cyclosporine A concentrations were measured in hemolyzed whole blood by radioimmunoassay (kit provided by Sandoz AG). Endomyocardial biopsies were obtained at weekly intervals for the first 2 months and then at intervals according to the results of previous biopsies as depicted in Table 2 [12]. For each biopsy, 5–7 endomyocardial specimens were obtained and all samples were evaluated by one and the same pathologist for the entire study population. Biopsy evaluation was performed according to the Hannover classification. Only biopsies with grade A3b or A4 were considered rejections requiring additional immunosuppressive therapy. Patients with moderate rejection (A3b) were treated with 500 mg methylprednisolone i.v. qd for 3 days, episodes of severe rejection (A4) were

Table 1. Classification criteria according to average CyA levels. In the first 84 patients transplanted between 1985 and 1988 CyA levels were measured as polyspecific CyA levels while later the remaining 116 patients were treated based on specific RIA CyA levels

Polyspecific CyA-levels:		
Number of patients = 84	Average CyA levels ± Standard deviation	
Group I mean day 0–2 =	< 51 ng/ml	(27 ± 22 ng/ml)
Group II mean day 0–2 =	> 50 ng/ml	(265 ± 73 ng/ml)
Group A mean day 0–14 =	< 401 ng/ml	(267 ± 156 ng/ml)
Group B mean day 0–14 =	> 400 ng/ml	(678 ± 178 ng/ml)
Specific CyA-levels:		
Number of patients = 116	Average CyA levels ± Standard deviation	
Group I mean day 0–2 =	0 ng/ml	(0 ± 0 ng/ml)
Group II mean day 0–2 =	> 0 ng/ml	(115 ± 123 ng/ml)
Group A mean day 0–14 =	< 151 ng/ml	(97 ± 56 ng/ml)
Group B mean day 0–14 =	> 150 ng/ml	(247 ± 98 ng/ml)

Table 2. Scheduled biopsy intervals in weeks based on the postoperative month. Hannover classification: 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; A5a = resolving rejection, recent and old myocytolysis; A5b = resolving rejection, old myocytolysis

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

Table 3. Incidence of rejection (RX) during the first 60 postoperative days

	Group I	Group II	Significance
RX/d	0.028 ± 0.01	0.031 ± 0.01	n.s.
RX/yr	1.8 ± 0.7	1.9 ± 0.6	n.s.
BY/yr	10 ± 2	9 ± 2	n.s.
RX/BX	18.9%	20.8%	n.s.
Patients	108	92	
	Group A	Group B	
RX/d	0.028 ± 0.01	0.031 ± 0.01	n.s.
RX/yr	1.7 ± 0.6	1.9 ± 0.7	n.s.
BX/yr	9 ± 2	8 ± 2	n.s.
RX/BX	18.6%	21.1%	n.s.
Patients	101	99	

RX/d = Rejections per day; RX/yr = Rejections per year; BX/yr = Biopsies per year; RX/BX = Rejections per biopsy

Table 4. Incidence of rejection (RX) during the first 365 postoperative days

	Group I	Group II	Significance
RX/d	0.0115±0.007	0.0117±0.007	n.s.
RX/yr	4.2±2.5	4.3±2.6	n.s.
BY/yr	26±6	25±7	n.s.
RX/BX	16%	17%	n.s.
Patients	108	92	
	Group A	Group B	
RX/d	0.00929±0.007	0.0011±0.009	n.s.
RX/yr	4.2±2.3	4.3±2.4	n.s.
BX/yr	27±8	25±7	n.s.
RX/BX	15.5%	17.2%	n.s.
Patients	101	99	

RX/d = Rejections per day; RX/yr = Rejections per year; BX/yr = Biopsies per year; RX/BX = Rejections per biopsy

Table 5. Patient survival

	Group I	Group II	Statistics
Survival at 1 year (%)	84%	87%	P = n.s.
Death due to rejection (% of total deaths)	20%	17%	P = n.s.
Number of patients	108	92	
	Group A	Group B	Statistics
Survival at 1 year (%)	84%	89%	P = n.s.
Death due to rejection (% of total deaths)	18%	16%	P = n.s.
Number of patients	101	99	

treated with rabbit antithymocyte globulin (i.v. 1.5 mg/kg qd) and methylprednisolone (125 mg qd) for 3 days each.

The cyclosporine application was either postponed or it was administered in reduced dosages in selected patients with postoperative renal impairment evidenced by either azotemia, oliguria or anuria. Hepatic dysfunction was documented by increased levels of SGOT and SGPT or increased ammonia, bilirubin, alkaline phosphatase or gamma glutamyl transferase levels. Patient evaluation included data obtained within the first 365 days posttransplantation. Variables such as cyclosporine blood levels, immunosuppressive drug dosages, biopsy results, renal function and patient survival were categorized and statistically analyzed.

The results were analyzed with the statistical software of the SPSS program. All calculations were performed separately for patients with polyspecific and specific CyA levels. As the results were not statistically different, for the purpose of simplification the two subgroups (polyspecific and specific CyA levels) were combined in the following Results, Figures and Tables. The incidence of rejection was averaged using the rate of rejection per postoperative day and compared between groups by unpaired Student's t-test for continuous variables. The statistics of the serum creatinine over time was carried out using multi-variate analysis (MANOVA). Actuarial events were calculated according to the Kaplan – Meier analysis. A $P<0.05$ was considered significant.

Results

The mean CyA level for each study group is shown in Table 1. The age of the patients in group I was 45±12 years, group II 44±11 years, group A 46±10 years and group B 43±13 years. The incidence of rejection per postoperative day (RX/d), postoperative year (RX/yr) and number of biopsies per year and patient (BX/yr) at 60 and 365 days postoperatively are listed Tables 3 and 4. The percentage of positive biopsies is calculated under RX/BX. Groups I and II had incidences of 1.8±0.7 and 1.9±0.6 rejections respectively for the first 60 days after transplantation. With an average of approximately one biopsy per week around 20% of the biopsies were positive. The incidence of rejection dropped in the following months after transplantation in all four groups. Within the first year the average rate of rejection was calculated to be around 4 to 5 rejections per patient per year. A group comparison shows no significant differences between groups I and II, and groups A and B.

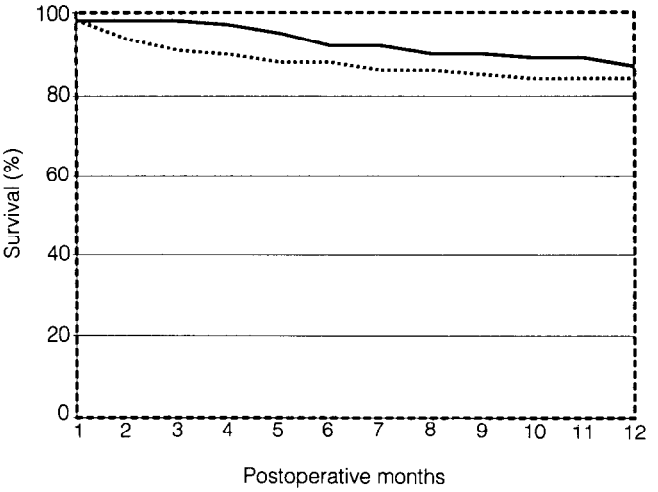

Fig. 1. Actuarial survival calculated according to the Kaplan-Meier equation for group A and B for the first year following transplantation. The differences in survival were not significant, ····· Group A, —— Group B

The actuarial patient survival for the first 365 days, as a comparison between groups A and B, is depicted in Fig. 1. The patient survival at 1 year was slightly, but not significantly, better in the group of patients with higher initial CyA levels (group B) when compared to group A (group A = 84%, group B = 89%; Table 5) with a higher mortality rate especially after the first 30 days following transplantation.

The distribution of biopsy results for the first 2 weeks is depicted in Fig. 2. After the first two biopsies around 14% of the histological samples were evaluated as being grade 3b, 4% grade A4 and beginning rejection was diagnosed as grade A2 in 20–35% and grade 3a in 20–25% of the biopsies. The differences among the four groups were not significant. The maximum, mean, and median observation period of each patient group were comparable (group I max: 2072 days, mean: 978 days SD: 621 days, median : 882 days; group II max: 2018 days, mean: 1046 days SD: 581 days, median: 1064 days; group A max: 2072 days, mean: 1056 days SD: 645 days, median: 1104 days: group B max: 1991 days, mean: 960 days SD: 555 days, median: 891 days).

Figure 3 shows the averaged creatinine levels of the patients in group A ($n=45$) and B ($n=54$) with impaired

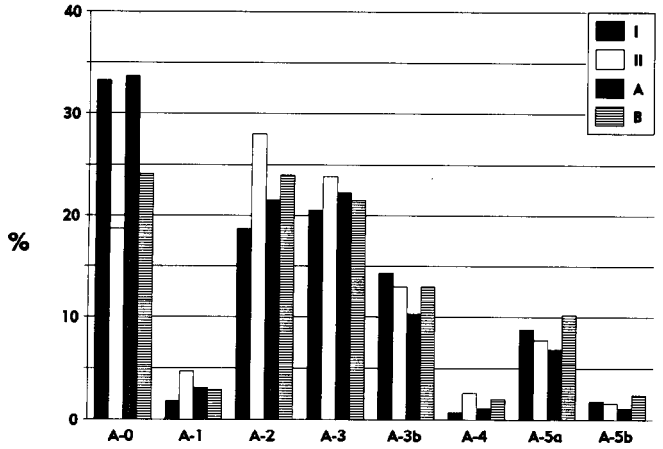

Fig. 2. Biopsy results at postoperatively day 14 of the first two biopsies per patient averaged for each group. There was no significant difference among the four groups

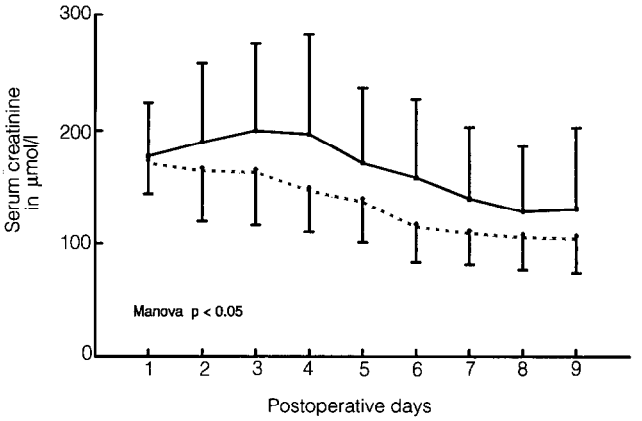

Fig. 3. Postoperative renal function (patients with impaired preoperative renal function). The course of the average serum creatinine is shown as a comparison between those patients in group A and B with intially (postoperative day 1) elevated serum creatinine levels (>150 µmol/l). In multi-variate analysis the differences between the two groups were significant with improved renal function in the group of patients treated with lower CyA levels, ····· Group A, —— Group B

kidney function immediately after transplantation (creatinine levels higher than 150 µmol/l on postoperative day 1) for the following 9 days. For patients with impaired renal function the delay or decrease of the CyA therapy improved renal function during the first 10 days after transplantation (MANOVA $P<0.05$; Fig. 3) as evidenced by the continuing fall in serum creatinine levels in group A from 170 µmol/l at day 1 to 105 µmol/l at day 9. In group B the serum creatinine levels first rose from 170 µmol/l to a peak level of 200 µmol/l at day 3 and then dropped to approximately 150 µmol/l by day 9.

Discussion

The introduction of CyA in the standard immunosuppression following organ transplantation has undoubtedly decreased the incidence of graft rejection and rejection-related mortality [21]. The associated adverse side effects, such as impairment of renal and hepatic functions, often limit its use in the early postoperative period [9]. At present there is a tendency to accept these side effects in order not to endanger the graft by early rejection, as renal or hepatic impairment is most often reversible. Due to the fact that many centers start immunosuppression with the addition of a fourth agent, antilymphocyte globulins, the necessity of early cyclosporine therapy is questionable, especially in patients with impaired renal or hepatic function.

Long-standing preoperative malperfusion and relatively high drug toxicity, especially in pre-heart transplant condidates, significantly impairs preoperative organ function. The activation of the renin-angiotensin system [3], increased hemolysis [2], a decrease in renal perfusion pressure and non-pulsatile perfusion during cardiopulmonary bypass [10] are some of the features of open heart surgery that could significantly contribute to further impairment of renal or hepatic function. At our institute the CyA therapy is delayed or the target CyA blood levels decreased for some patients with preoperative or intraoperative renal and/or hepatic compromise. This is especially true for patients with long-standing renal dysfunction (preoperative creatinine levels >200 µmol/l) or postoperative right heart failure. Serum creatinine, transaminases, alkaline phosphatase and bilirubin levels are monitored and CyA levels adjusted appropriately. Generally we have adapted to the standard CyA levels, suggested by Baldwin and Shumway [1], of specific CyA blood level measured by RIA of approximately 300 ng/ml for the first year after HTX, although we are aware that at present there is no hard evidence for the necessity of these high levels when compared to accepted standards in kidney and liver transplantation.

It was the intention of this retrospective study to evaluate the incidence of rejection as well as to calculate survival following HTX in relation to the early postoperative immunosuppressive regimen, especially in respect to the CyA serum levels. In order to analyze the impact of a single immunosuppressive drug in a multi-drug regimen, the majority of the surrounding factors had to be kept constant. Patients were therefore, excluded if there was a variation in the initial standard immunosuppressive drug therapy, such as the use of OKT3 instead of ATG. In addition, all patients with a positive cross-match of ABO mismatching were excluded. The remaining 200 patients were divided into groups according to immediate postoperative (groups I and II) and early postoperative (groups A and B) averaged CyA levels.

The initiation of CyA therapy with a priming dose a few hours before heart transplantation is suggested by many centers. The most important result of our study was that patients who had not received CyA during day 0 to day 2 after HTX did not have a higher rate of rejection during the first two biopsies, on day 6 and day 13, nor did they present with more rejection episodes for the first 60 days posttransplant. As a prerequisite for this benign postoperative course we feel that the simultaneous application of methylprednisolone, azathioprine and RATG is necessary. The 60-day survival in patients with

low CyA levels (group I) is slightly less when compared to group II. This finding can be explained by the fact that CyA therapy was predominantly delayed in patients with impaired multi-organ function. This group of transplant recipients typically has an increased early mortality, which may be completely independent of rejection. Therefore the higher mortality rate in this subgroup may not necessarily correlate with the omission of the CyA therapy during the first 2 postoperative days. Significantly reduced CyA blood levels for the first 2 weeks after HTX showed no impact on the rate of rejection within the first year. It therefore appears safe to reduce the postoperative immunosuppression to lower drug dosages, at least in respect to CyA therapy. Survival at 1 year was again slightly, but not significantly, better in the group with higher initial CyA levels. Survival after the entire observation period of about 3 years was quite similar (79% vs 83%).

This study, like any retrospective analysis, certainly suffers from the uncontrolled design of the investigation. Nevertheless it may be concluded that in patients with a standard immunosuppressive therapy consisting of prednisone and azathioprine in addition to RATG for the first 4 days, the onset of CyA therapy may be delayed or its dosage decreased with no effect on the incidence of rejection during the first 60 days or at 1 year after transplantation. This form of therapy may allow an early recovery of postoperative renal and hepatic function. Further prospective studies must verify these results and help determine the minimum CyA levels necessary to maintain a low incidence of rejection. The crucial question will be whether similar results could be obtained if the cytotoxic T-cell therapy is also omitted. This latter type of immunosuppression has been known to precipitate infectious complications, especially of viral origin. Current data of the registry of the ISHLT would indicate no benefit of anti-T cell antibody treatment when compared to triple drug immunosuppression alone. Whether this holds true for the high risk cases with low CyA induction immunosuppression, as described in this study, remains unknown. Here, also, prospective randomized trials are needed to define the specific role of each separate component of the triple drug treatment. Only then can it be clarified if omission of CyA therapy early postoperatively or application of the drug in significantly lower dosages requires supplementation by cytotoxic T-cell drugs. If this hypothesis could be rejected, induction immunosuppression could be substantially reduced without increasing the risk of subsequent rejection. This strategy should then result in a significant reduction of infectious complications, which represent one of the major risk factors of early death after cardiac allografting at present.

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Discussion

Dr. H. Huysmans (*Leiden, The Netherlands*). I would like to start with the first question. All your findings were not significant, which in itself seems hopeful and very helpful for our daily practice in dealing with transplant patients. Do you think the outcome might have been different if you had chosen a different cut off point of the cyclosporine levels?

Dr. Hausen: Yes, the lower you choose the cyclosporine levels, this is just an assumption, the higher the chance of rejection.

Dr. H. Huysmans (*Leiden, The Netherlands*). It would be very helpful to know what is the absolute minimum level you need in order to avoid rejections.

Dr. Hausen: Yes. I think that's something which you should determine prospectively.

Dr. Huysmans: Thank you.

Dr. R. A. Cichon (*Zabrze, Poland*). The first question would be: do you modify your protocol according to the positive cross-match test, for example? And if I understood well, the average number of biopsies for one patient within the first year is 26, right?

Dr. Hausen: Yes.

Dr. Cichon: Is there any reason to do the biopsies so often?

Dr. B. Hausen: To answer the first question, the patients with a positive cross-match are more vigorously immunosuppressed during the postoperative period. We would not lower cyclosporine levels, being afraid that acute or hyperacute rejection might occur. The second question: we are aware that we are doing a lot of biopsies in our patients, and there are two reasons for this. One reason is we don't trust non-invasive methods as much as we do the biopsies, and second, we want to be sure that everything is okay, and the more often you check, the better.

Dr. A. Gheissari (*Los Angeles, California, USA*). Based on your results, since there was no significant difference between those who had cyclosporine started preoperatively and those who did not, would you conclude that in general you can get away with starting cyclosporine late in all patients, not just the renal failure patients?

Dr. B. Hausen: Yes, by all means. You never know what's going to happen during the operation, what's going to happen to renal function particularly. So I think there is no advantage in giving cyclosporine beforehand, and the results show that you do not need to administer the preoperative dose and maybe even for the first 24 to 36 hours, if you give some form of antibodies. We're just testing the value of OKT3 versus rabbit ATG, and at least for rabbit ATG we can say you are safe for at least 4 days with only rabbit ATG by itself.

Dr. A. Gheissari (*Los Angeles, California, USA*). I think we corroborate your studies, because at the Los Angeles Heart Institute we have, in the past 3 years, used a routine of starting induction therapy with antithymocyte serum for the first 5 days and starting cyclosporine on the 4th day after transplantation in all patients, and we have had a mean rejection of two per year per patient in the first year after transplantation.

Dr. B. Hausen: I think you can't compare rate of rejections between centers. It's a very subjective evaluation of histological biopsies by the pathologists. This is a study of 5,400 biopsies for this one-year period, all of them evaluated by one and the same pathologist. If you give us your biopsies I'm sure we will have different results from our pathologists.

Dr. A. Varela (*Madrid, Spain*). I would like to ask you if your conclusions could be made in lung transplantation also?

Dr. B. Hausen: I can't give you an answer. We haven't evaluated it yet. Also, right now we're hesistant to give antibodies to lung transplants. So we have to rely on early cyclosporine levels to make sure we don't have rejections early.

Dr. H. Huysmans: (*Leiden, The Netherlands*). I have one last question. You did not give us the interrelationships between Groups I and II and Groups A and B. Did patients administered cyclosporine later also have lower levels or was there no connection between the two?

Dr. B. Hausen: I think around 70% of the patients in Group I were also in Group A, but in some we started later and were able to go right up to 300 micrograms very early. So their average level for the 14-day period was above 150 micrograms and that put them into Group B.