Orthotopic Heart Transplantation: Management and Results

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Summary. Between March 1989 and December 1991, 316 orthotopic heart transplantations (HTX) were performed at the Heart Center North Rhine-Westfalia (NRW), Bad Oeynhausen, in 311 patients (267 men, 44 women). Five patients required retransplantation. The age of the recipients ranged from 3 days to 73 years (mean: 51 years). There were 16 children under 18 years old. The age of the donors ranged from 0.5 to 61 years (mean: 38 years). The main indications for HTX were dilatative cardiomyopathy (DCM; n = 142), end-stage ischemic heart disease (IHD; n = 139), valvular disease (VD; n = 19), and congenital heart disease (CHD; n = 10). One woman was transplanted for acute myocarditis (Coxsackie). In 11 patients a ventricular assist device (VAD) was applied as a bridging for HTX. In 7 of these 11 patients HTX was performed; 6 patients survived. Immunosuppresive protocols were based on "double drug therapy" with cyclosporine and azathioprine. More than two-thirds of the patients have had no long-term corticosteroid treatment. Early mortality (<30 days) was 7.2% (n = 23). According to the primary diagnosis, patients with DCM had the lowest mortality, 1.3% (2/142), followed by IHD, 6.4% (9/139), VD 21% (4/19), and CHD 60% (6/10). The causes of death were multiorgan failure (n = 7), sepsis (n = 4), acute rejection (n = 3), bleeding (n = 3), acute respiratory distress syndrome (ARDS) (n = 1), right heart failure (n = 3), size-missmatch (n = 1), and stroke (n = 1). Two of five patients (40%) with re-HTX died in the early postoperative period. Late mortality was 11.7% (n = 37). The causes of death were infection (n = 25), rejection (n = 10), and cancer (n = 2). The majority of the survivors returned to a productive lifestyle. This impressive number of HTX with these satisfying results was made possible by (1) perfect organization, (2) the creation of new and extended donor criteria, (3) special immunosuppresive treatment ("double drug therapy" whenever possible).

Key Words: Orthotopic heart transplantation — Double drug therapy — Results

Introduction

Less than 25 years has passed since the first human-human heart transplantation; the world-wide experience now exceeds 16000 heart and 1600 heart-lung transplantations from more than 250 centers. More than 87% of all heart transplant procedures have taken place since 1984; 1217 in 1985, 2547 in 1987, 2809 in 1989, and 3033 in 1990 [1]. With the introduction of cyclosporine a decade ago, excellent results in heart transplantation (1-year survival rate 90%) have been achieved in a wide variety of patients [2,3]. On the other hand, with the growing number of recipients, the shortage of donor hearts has become a serious problem in the transplant program. The United Network for Organ Sharing (UNOS) estimates that only 1800 of the 50000 patients requiring hearts each year will receive them [4]. Extensive organization for the procurement of donor hearts with not only proper timing of donation but also preferable matching in donor-recipient weight ratio and in major histocompatibility antigens [5,6] will permit improved survival rates after transplantation. New strategies for increasing the donor heart pool must be pursued by accepting "critical" donors, i.e., donors who are more than 55 years old, who weigh less than 50% of the recipient's body weight [7], and those in whom ischemic time is up to 5 hours [8–10].

For some patients, a long wait for a donor heart can result in profound end-organ deterioration, which can jeopardize their status as viable transplant candidates. To allow such hopeless patients to survive, heart assist devices and artificial hearts have been applied, not only as bridging to transplant [11,12] but also for permanent use for many other end-stage heart disease patients in whom cardiac transplantation is contraindicated [4,13].

Patients and Methods

The Heart Center North Rhine-Westfalia, the Herzzentrum Nordrhein Westfalen (HZNRW), Bad Oeynhausen, Germany, where we are working, is located in the north-western part of Germany, 70 km from the industrial and university city of Hannover. This Heart Center, which was built in 1984 by a foundation of the state of North Rhine-Westfalia and

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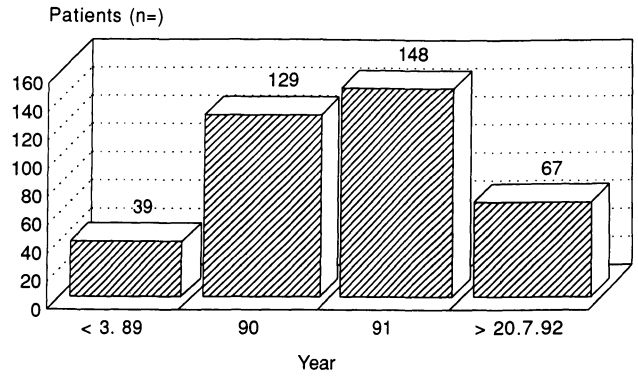

Fig. 1. Orthotopic heart transplantation between March 1989 and June 1992

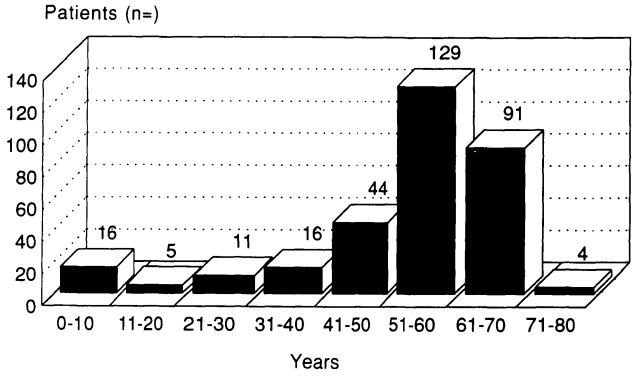

Fig. 2. Age distribution of recipients undergoing orthotopic heart transplantation. The mean age of recipients was 52.6 years

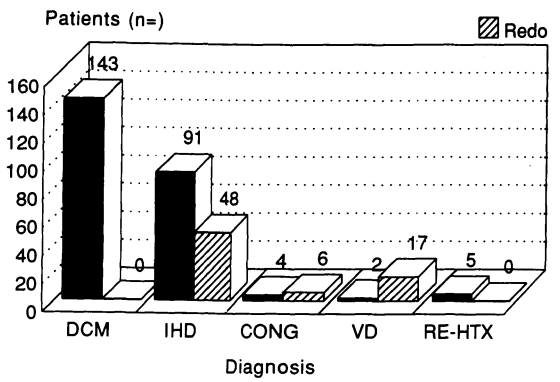

Fig. 3. Indications for orthotopic heart transplantation in children and adults. Recipients: Diagnosis + previous heart operation. *DCM*, dilative cardiomyopathy; *IHD*, ischemic heart disease; *CONG*, congenital heart disease; *VD*, valvular disease; *RE-HTX*, re-heart transplant

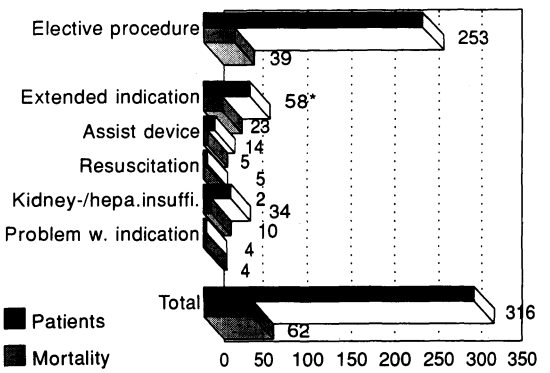

Fig. 4. Preoperative clinical condition in recipients undergoing orthotopic heart transplantation: 253 of the 311 patients (81.3%) were operated upon electively, whereas the rest of the patients (58; 18.7%) had to be transplanted in an unsuitable clinical condition. *Five of these 58 patients underwent re-transplantation due to graft failure

the German Government, has several institutes and clinical departments and has around 500 beds for patients.

From November 1984 to December 1991, over 15 000 open heart procedures were performed in our clinic. From March 1989, when we began the heart transplant program, to July 20, 1992, 383 orthotopic heart transplantations were performed in our clinic (39 patients in 1989; 129 in 1990; 148 in 1991; and 67 patients this year (to June 1992) (Fig. 1). Herein, we describe the clinical data for the 316 heart transplants performed in 311 patients operated upon up to December 1991.

Figure 2 shows the age distribution of recipients undergoing heart transplantation. The mean age of recipients was 52.6 years. The age range has been expanded to include infants and patients more than 70 years of age.

The indications for orthotopic heart transplantation in children and adults were dilatative cardiomyopathy in 143 patients (45.3%), ischemic heart disease in 139 (44.7%), valvular disease in 19 (6.1%), and congenital heart disease in 10 (3.2%). In 48 patients with ischemic heart disease, 17 patients with valvular disease, and 6 with congenital heart disease, one or several previous cardiac procedures had been carried out. In five patients, re-heart transplant (Re-HTX) was necessary due to graft failure or size-mismatch (Fig. 3).

The recipients undergoing heart transplantation were in varying clinical condition. Two hundred and fifty-three of the 311 patients (81.3%) were operated upon electively, whereas the rest of the patients (58; 18.7%) had to be transplanted in unsuitable clinical condition, that is, they had extended indications: 14 patients were transplanted under mechanical support

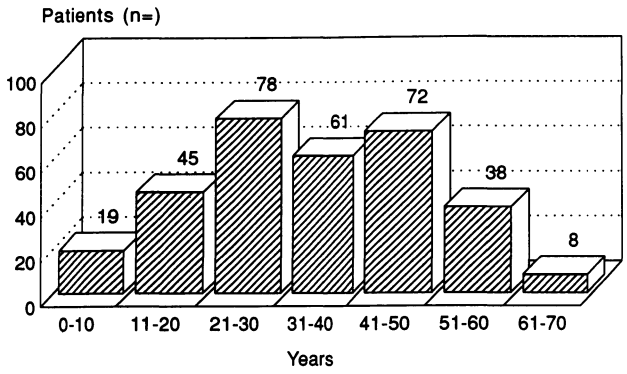

Fig. 5. Orthotopic heart transplantation: Age distribution of donors. The mean age of donors was 41 years (range 4 months to 67 years). Forty-six donors (14.6%) were more than 50 years old

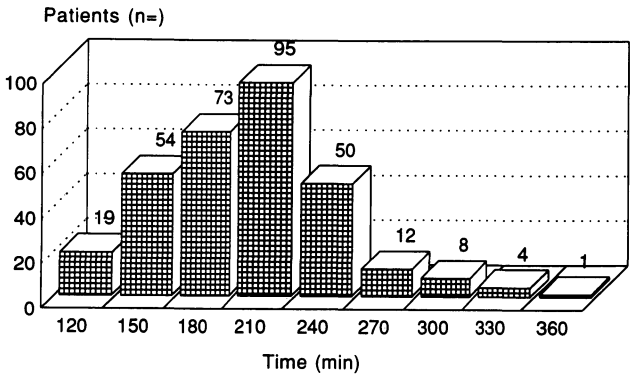

Fig. 6. Orthotopic heart transplantation: Ischemic time of donor heart. The mean ischemic time was 195 min (range, 120–360 min). One-fourth of the donor hearts had an ischemic time longer than 240 min

with a ventricular assist device; 3 underwent heart transplant under cardiopulmonary resuscitation; and 34 had renal or hepatic insufficiency. Five patients in this group underwent re-transplantation due to graft failure. The mortality in the patients who underwent elective heart transplantation was significantly lower than that in patients with extended indications. The mortality rate in the two groups was 15.4% and 36.5% ($P < 0.001$), respectively (Fig. 4).

Because of the growing shortage of donor hearts we have modified and extended our criteria in recent years. Donors over 50 years of age, those with serum sodium concentration over 170 mmol/l, those in need of inotropic drugs, and donors after resuscitation have been recognized as potential donor candidates ("critical donor") and selected as donors for individual recipients.

The age distribution of donors can be seen in Fig. 5. The mean age of donors was 41 years (range, 4 months to 67 years). Forty-six donors (14.6%) were more than 50 years old.

To ensure long-distance heart procurement, various organ preservation solutions, i.e., University of Wisconsin, St. Thomas, and Bretschneider HTK solution, are applied for clinical use [14]. Bretschneider HTK solution was used in all our donor hearts. The effectiveness of this solution is based upon a decrease of sodium and calcium ions, which ions are important in cell membrane depolarization and electromechanical coupling. The solution contains a slightly higher than normal potassium concentration and histidine as an important buffer [15]. The ischemic time of donor hearts ranged from 120 to 360 min, with the mean ischemic time being 195 min. One-fourth of the donor hearts had an ischemic time longer than 240 min (Fig. 6).

Table 1. Orthotopic heart transplantation immunosuppressive therapy protocol

Preoperative	Intraoperative
— Cyclosporine 4–6 mg/kg	— Methylprednisolone 1 g i.v.
— Azathioprine 4–5 mg/kg	
Early Postop.	Long-term
— Methylprednisolone 1 g over 3 days	— Cyclosporine 4–6 mg/kg
— Cyclosporine 4–6 mg/kg	— Azathioprine 0–2 mg/kg
— Azathioprine 1–4 mg/kg	

Heart Center NRW, Bad Oeynhausen

Our protocol for immunosuppressive therapy in recipients pre-, intra-, and postoperatively is shown in Table 1. In all recipients, 4–6 mg/kg cyclosporine and 4–5 mg/kg azathioprine are administered a few h before operation. Intraoperatively, 1 g methylprednisolone is substituted just before declamping of the aorta. In the early postoperative period, patients receive 1 g methylprednisolone over 3 days, besides cyclosporine and azathioprine. In the case of an uneventful postoperative course, the immunosuppressive protocol with the double drug administration is maintained and clinical examinations and pathology investigation by routine endocardial biopsies are carried out.

In the case of early acute graft rejection confirmed by endocardial biopsy, methylprednisolone is administered in addition to cyclosporine and azathioprine in patients with moderate rejection, and methylpredonisolone and rat ATG or OKT 3 is administered in those with severe rejection.

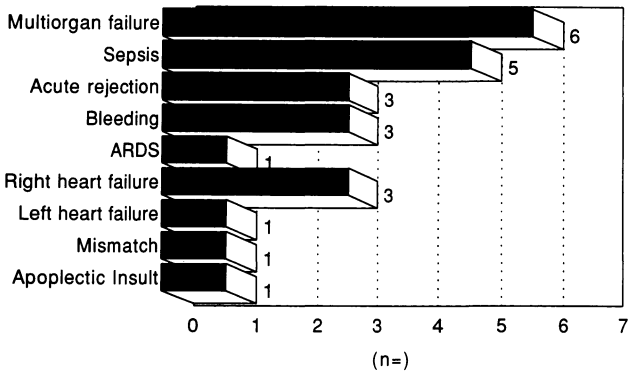

Fig. 7. Early mortality in our patients — causes of death. There were 24 deaths (mortality rate: 7.7%). *ARDS*, acute respiratory distress syndrome

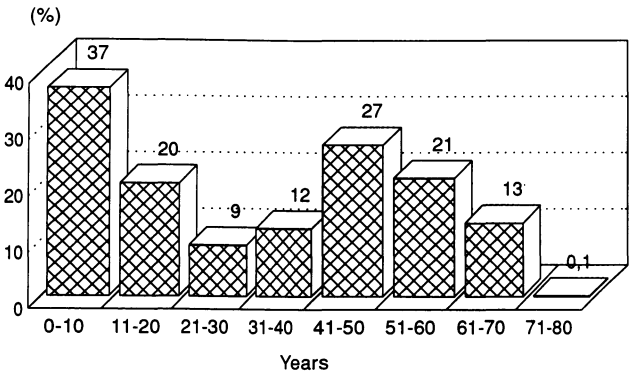

Fig. 10. The effect of recipient age on overall mortality after orthotopic heart transplantation

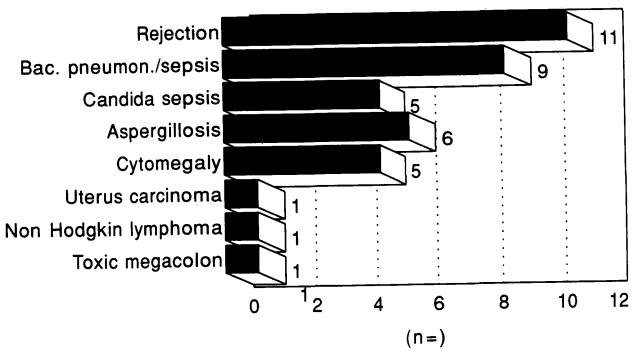

Fig. 8. Late mortality — causes of death. Rejection and infection were the predominant causes of late mortality. There were 38 deaths (overall mortality rate 12.2%)

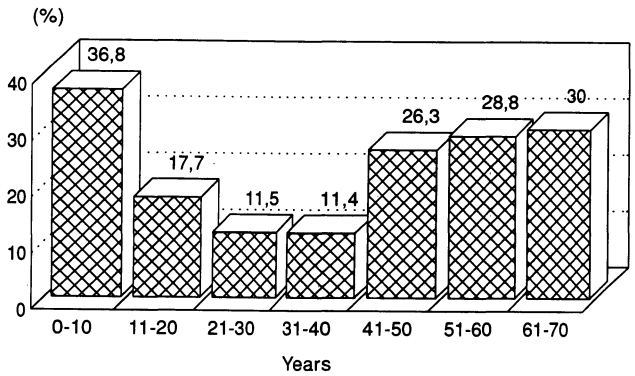

Fig. 11. The effect of donor age on overall mortality after heart orthotopic transplantation

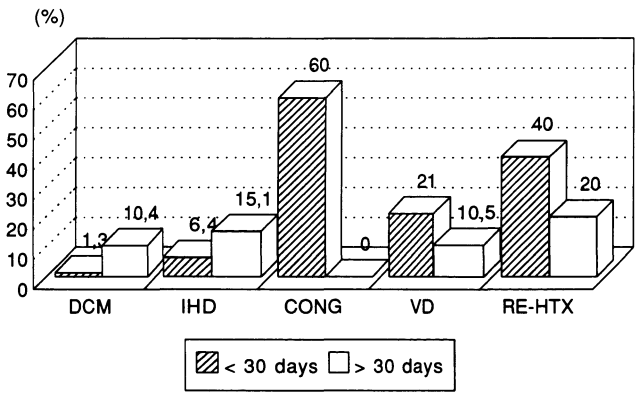

Fig. 9. The effect of indication for heart transplantation on early and late mortality. Dilative cardiomyopathy (*DCM*) has the lowest overall mortality, 11.8% followed by ischemic heart disease, (*IHD*) 21.5%, and valvular disease (*VD*), 31.5%

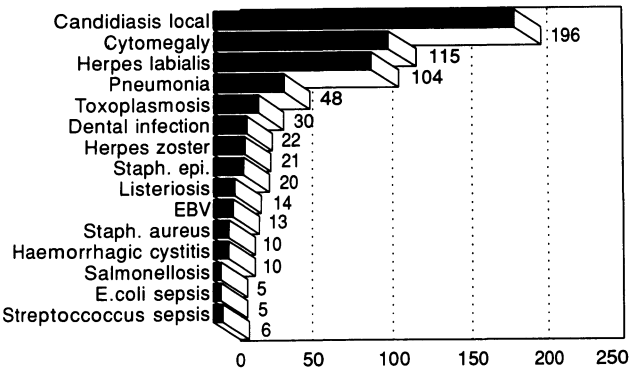

Fig. 12. Non-lethal complications caused by infection after heart transplantation. Local candidiasis (63%), and local infections with cytomegalovirus (37%), *Herpes labialis* (33%), and *Herpes zoster* (6.7%) were the common infections. *EBV*, Epstein-Barr virus

Results

Regarding early mortality in our patients, there were 24 deaths (mortality rate: 7.7%): 6 patients due to multi-organ failure; 5 due to sepsis; 3 due to acute rejection; 3 due to bleeding; 1 due to acute respiratory distress syndrome (ARDS); 3 due to right heart failure; 1 due to left heart failure; 1 due to size mismatch, and 1 due to apoplectic insult (Fig. 7). Rejection and infection were the predominant causes of late mortality. The overall mortality rate was 12.2% (38/311 patients). Bacterial and candida pneumonia, aspergillosis, and cytomegalo virus infection were the causes of fatal infection (Fig. 8).

The effect of indication for heart transplantation on early and late mortality is shown in Fig. 9. In early mortality, DCM had the lowest mortality rate, 1.3%, followed by IHD, 6.4%, and VD, 21%. The late mortality rate ranged from 0% in congenital heart disease, to 10.4% in DCM, 10.5% in VD, 15.1% in IHD, and 20% in re-heart transplantation.

The effect of recipient age on mortality after heart transplantation demonstrates that the mortality rate in infants and children (0–10 years) was higher than that in the elderly patient groups. The high mortality rate was mainly due to technical problems in complex congenital heart disease and to size mismatch in an infant (Fig. 10).

The effect of donor age on mortality after heart transplantation is shown in Fig. 11. Besides the high mortality in small children, the mortality rate increased in groups with donor hearts over 40 years of age.

Regarding non-lethal complications caused by infection after heart transplantation, the common infections were local, i.e., candidiasis (63%), and those due to cytomegalovirus (37%), *Herpes labialis* (33%), and *Herpes zoster* (6.7%). There were several serious infection complications due to pneumonia (15%) and sepsis (3.5%) of bacterial pathogenesis (Fig. 12).

Transitional cerebrovascular syndrome (81/311 patients; 26%) and arterial hypertension (69/311 patients; 22%) were the most common non-lethal complications not caused by infection. Drug-induced complications such as acute renal failure (46/311 patients; 15%), steroid diabetes (35/311 patients; 11%), and leucocytopenia (34/311 patients; 11%) were further causes of post-transplant complications.

Two hundred and forty-nine of the 311 patients are long-term survivors after orthotopic heart transplantation. In 160 of these long-term survivors (64%) double drug immunosuppressive therapy has been performed successfully after transplantation. In about one-third of patients, triple drug therapy is necessary due to recurrent graft rejection episodes.

Conclusions

Extensive national and international organization for the procurement of donor hearts will permit improved survival rates after transplantation. New strategies for increasing the donor heart pool must be pursued by accepting "critical" donors.

In agreement with the Harefield experiences in London [16] of "double drug" immunosuppression with azathioprine and cyclosporine, but without steroid maintenance and without ATG/OKT 3 prophylaxis, there have been only a few rejection-related deaths in the early and late post-operative period. The incidence of diabetes and hypertension is low with this immunosuppression protocol, so that we are encouraged to continue with this protocol for patients after orthotopic heart transplantation.

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Discussion

Dr. Hachida:
When we consider the selection of the recipient, renal failure is such a common complication in those candidates for transplantation; if you have any management or other considerations regarding this kind of candidate please tell us.

Dr. Minami:
Thank you very much for your important question. I have a few slides about that. It is difficult to define renal failure, but if you say plasma creatinine level over 1.5 mg/dl and urea level over 120 mg/dl, then we have seen renal failure in almost half of the 65 patients out of 102 patients who were operated on in 1991, excluding children. In most of these patients we have seen pre-renal failure and renal failure; 15 patients, just only one-third had normal renal function. I can show you something in detail of this subgroup. Seventy-five patients were treated with Lasix (frusemide), 2 with ethacrinamide and 22 with a combination of two drugs. In 34 patients with preoperative renal failure, administration of catecholamine was necessary. We have performed so-called hemofiltration in 27 patients only and the majority of the patients we could treat with diuretics. In no patient have we done dialysis; the level of creatinine after the operation is a little higher, and in both groups, the pre-renal and renal failure group, urea is also the same. Look at the postoperative complications. We have seen the pre-renal and renal failure group had almost same complication rate, a little bit higher in fact in the pre-renal failure, but we can treat such preoperative renal failure relatively safely.

Dr. McKeown:
I was again impressed with your results for what we might call marginal donors, and I wondered if you had any special methods of managing those situations? Did you use thyroid hormone T3 or did you use a warm reprefusion prior to removing the cross clamp?

Dr. Minami:
No we do not have any such special method. But we have very good organizations in Europe; as you know, we have three big organizations, one in the UK, one in France, and the Eurotransplant organization that we belong to. Therefore we have rather short ischemic time, even with long distance for donation. We do not have a special rewarming technique, reperfusion, or anything like that.

Dr. McKeown:
Do you routinely use isuprel or prostaglandin on the recipient?

Dr. Minami:
No, nothing.

Dr. Morita:
When I was at the University of Pittsburgh we extended our donor criteria also and we accepted donors over 40 years old. However, we used to ask the donor hospital to do a coronary angiogram. Is it the case for your donor criteria to do the coronary angiogram in your series?

Dr. Minami:
Yes, we have done coronary angiograms, bench coronary angiograms they are called only in two cases. Both donors had a history of cardiac episodes. One of them could be taken out as donor heart. The other one had so much sclerosis on the coronary artery, which we could not touch. Therefore, we did a coronary angiogram and it showed severe stenosis. Therefore, we left that.

Dr. Morita:
If my understanding is correct, you also accepted donors over 50 or 60 years old.

Dr. Minami:
Yes. Yes. Yes.

Dr. Morita:
Do you think the incidence of having to reject the patient at the donor site is increased with an older patient?

Dr. Minami:
It is very difficult to answer that. But I would like to answer your question, yes, because in general, the elderly donors have an unstable hemodynamic situation, so that they are sometimes not suitable for donation.

Dr. Nosé:
As a Japanese, I am particularly proud to have Dr. Minami perform such a wonderful job in Europe. It is proof that the idea that Japanese surgeons are not capable of heart transplantation is not the truth. I believe that what Dr. Minami has done is an extremely important stimulus for all the cardiac surgical colleagues in Japan. I would like to ask one question to Dr. Minami. I am interested in the extremely good long-term results in the babies. Everybody said that babies have an immunologically more forgiving status, almost in the same way as in liver tissue. Dr. Starzl and his group did xenotransplantation of the liver successfully. I was wondering, do you believe there is a possibility of heart transplantation from a small-size non-human primate? Such Non-human primates are more easily available in Japan, so this might be an excellent starting point for xenotransplantation.

Dr. Minami:
I agree with you completely. That is only my feeling or our feeling. Because children have very good long-term results, but there are only 18 cases so we cannot say definitely. About the xeno transplant of Dr. Iwaki in Pittsburgh, I have heard about it a few weeks ago. When the immunological problems are resolved, I find that it is an absolutely new step for transplantation surgery.

Dr. Pavie:
I am quite surprised that you have a very short ischemic time, even with long procurement. I want to make a comment. For the last 3 years in the case of long donor procurement, we use warm reperfusion and blood cardioplegia and we really improve the results in cases of long ischemic time with very old donors, as you do. I think it is an improvement, the blood conservation is very interesting for the heart, and especially for heart and lung; we have the same results in La Pitie hospital.