Lung transplantation in older patients?

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Objective: Age 65 years and older is generally considered a contraindication to lung transplantation. Our group has offered lung transplantation to select patients 65 years of age and older who lack other comorbid conditions. We sought to define the short- and medium-term outcome of lung transplantation in patients aged 65 years and older.

Methods: We reviewed the records of our lung transplant recipients from March 2000 to September 2006. During this interval, 50 patients were 65 years or older at the time of transplantation. Fifty patients younger than 65 years were matched to the older cohort by means of propensity analysis. The demographics and perioperative and postoperative characteristics and survival of the 2 groups were compared.

Results: Older patients were more likely to receive single-lung transplantation (older group: 76% vs younger group: 16%, $P < .05$) and nonstandard donor lungs (older group: 46% vs younger group: 28%, $P = .06$). The composite in-hospital morbidity rate was similar in the older and younger groups. There was no significant difference in the early oxygenation parameters, incidence of acute cellular rejection, or incidence of bronchiolitis obliterans syndrome between the 2 groups. The early survival of the older patients was 95.7% compared with 95.9% in the younger cohort ($P = .73$). The 1-year survival of the 2 groups was also similar (older group: 79.7% vs younger group: 91.2%, $P = .16$). The 3-year survival of the older and younger recipients was 73.6% and 74.2%, respectively ($P = .64$). There were 8 deaths in the older recipient group during the 1-month to 1-year posttransplantation interval, predominantly because of infections.

Conclusions: Lung transplantation can be performed in patients older than 65 years with acceptable clinical outcomes. The “increased” mortality of older patients between 1 month and 1 year after transplantation, predominantly from infectious causes, might be due to immunosenescence of older patients. This finding warrants adjustments in the immunosuppression protocol of older patients undergoing lung transplantation. The effect of offering lung transplantation to older patients on donor lung availability deserves further investigation.

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Withholding life-saving therapies from a certain cohort of patients because of their advanced age is not considered acceptable in the Western world. Yet in the field of organ transplantation, it is common practice to exclude older recipients. The rationale for such practice includes limited donor supply and lower survival of older patients after transplantation. In fact, the consensus guidelines for selection of lung transplant recipients recommends an upper age limit of 65 years for single-lung transplantation and 60 years for double-lung transplantation.¹ Advanced recipient age has also emerged as an independent predictor of death after

Abbreviations and Acronyms

ATG	= anti-thymocyte globulin
BOS	= bronchiolitis obliterans syndrome
CMV	= cytomegalovirus
CPB	= cardiopulmonary bypass
F _{IO₂}	= fraction of inspired oxygen
IPF	= interstitial pulmonary fibrosis
ISHLT	= International Society for Heart and Lung Transplantation
LAS	= Lung Allocation Score
P _{aO₂}	= partial pressure of oxygen in arterial blood
UCLA	= University of California Los Angeles
UNOS	= United Network for Organ Sharing

lung transplantation in the International Society for Heart and Lung Transplantation (ISHLT) registry.²

Despite these strong arguments, several reports in the past decade have demonstrated that older recipients can undergo kidney, liver, and heart transplantation and be treated with immunosuppressive therapy with acceptable outcomes.³⁻⁶ In 1993, Snell and colleagues⁷ reviewed their lung transplantation experience in elderly patients; the survival of 5 patients older than 60 years was similar to that of the younger cohort. More recently, Smith and associates⁸ reported their lung transplantation experience with 16 patients older than 65 years. The survival of this cohort was similar to that of a contemporaneous younger group. Although advanced age remains a contraindication in many transplantation centers, a survey of active US lung transplantation programs showed that 24% of programs do not consider age of greater than 60 years a contraindication to bilateral lung transplantation. In the case of single-lung transplantation, approximately 20% of active programs did not consider age of 65 years or older to be an absolute contraindication.⁹

Starting in 1999, we have not used advanced age as an absolute contraindication in the selection of lung transplant recipients. We have offered lung transplantation to select older patients (>65 years) who lack other comorbid conditions. The purpose of this report is to compare the outcome of lung transplantation in older recipients with that in a matched younger cohort. The primary end points were 30-day, 1-year, and 3-year survival. The secondary end points included early oxygenation parameters, composite in-hospital morbidity rates, and the incidence of acute rejection and bronchiolitis obliterans syndrome (BOS).

Materials and Methods**Study Design**

This study was reviewed and approved by the University of California Los Angeles (UCLA) Institutional Review Board. We retrospectively analyzed the records of all patients who underwent lung transplantation at the UCLA Medical Center from March 1, 2000,

through September 30, 2006. During this interval, 50 transplantations were performed on 48 patients 65 years of age or older (range, 65–72 years; older group) at the time of transplantation. For comparison purposes, we matched each older patient with a recipient younger than 65 years (younger group) by means of propensity score analysis using the criteria of diagnosis, date of transplantation, and Lung Allocation Score (LAS).¹⁰ LAS was available for all transplant recipients after the institution of the new allocation system in May 2005. For patients undergoing transplantation before May 2005, LAS was tabulated after chart review by using the United Network for Organ Sharing (UNOS) Web site LAS calculator (http://www.unos.org/resources/frm_LAS-Calculator). If diagnostic tests had been performed more than 6 months before transplantation, they were used as up-to-date information for the LAS calculation.

Donor and recipient characteristics, operative variables, and posttransplantation characteristics were compiled for both the older recipients and their matched younger cohorts.

Recipient Selection Criteria

Lung transplant recipients younger than 65 years were selected according to the “International guidelines for the selection of lung transplant candidates.”¹ Since 1999, we have offered lung transplantation to a select group of patients aged 65 years and older. Relative contraindications for listing patients aged 65 years and older were body mass index of less than 18 or greater than 30, presence of obstructive coronary artery disease, presence of peripheral or cerebrovascular disease, renal insufficiency (creatinine clearance, <50 mL/min), and debilitation. All recipients were informed of the nonstandard donor lung program and consented.

Clinical Management Protocol

Single-lung transplantation was performed according to the standard techniques.¹¹ Cardiopulmonary bypass (CPB) was used only as dictated by the recipient's hemodynamics. All double-lung transplantations were performed during CPB. All patients (single- and double-lung transplant recipients) except one received modified reperfusion after transplantation. The details of this technique have been previously reported.¹²

All lung transplant recipients received induction immunosuppressive therapy. In older patients we used basiliximab (Novartis, East Hanover, NJ), whereas in the younger cohort we favored rabbit anti-thymocyte globulin (ATG) as the induction agent (Genzyme, Cambridge, Mass). The induction therapy was followed with tacrolimus, mycophenolate mofetil, and a steroid regimen. All patients underwent surveillance biopsies at weeks 1, 4, 8, 12, and 24 and as clinically indicated. All recipients were treated with broad antimicrobial therapy during the first posttransplantation week. Oral trimethoprim-sulfamethoxazole was administered biweekly for prophylaxis against *Pneumocystis carinii* infections. Cytomegalovirus (CMV)-positive recipients received intravenous ganciclovir (Roche, Nutley, NJ) during hospitalization and were transitioned to valganciclovir (Roche, Nutley, NJ) for the first year or longer if inflicted with CMV infection. CMV-negative recipients who received a CMV-positive donor were also treated with CytoGam (CSL Behring, King of Prussia, Pa). The latter group also received acyclovir (GlaxoSmithKline, Bridgewater, NJ) for herpes simplex viral prophylaxis. Pulmonary function tests were performed at least once every 3 months and at each clinic visit.

Definition of Terms

Recipient diagnoses were divided into 3 categories: obstructive pulmonary disease, restrictive pulmonary disease, and other. Obstructive pulmonary diseases included emphysema and α_1 -antitrypsin deficiency. Restrictive lung diseases included interstitial pulmonary fibrosis (IPF), usual interstitial pneumonia, nonspecific interstitial pneumonia, allergic alveolitis, scleroderma, rheumatoid arthritis, polymyositis, and sarcoidosis. Other end-stage lung diseases included bronchiectasis, cystic fibrosis, IgA deficiency, lymphangioleiomyomatosis, primary pulmonary hypertension, and granulomatous lung disease.

Nonstandard donor lungs were defined as follows: presence of lobar infiltrate on chest roentgenographic analysis (atelectasis was ruled out by means of preoperative and intraoperative treatment/assessment), hypoxemia (partial pressure of oxygen in arterial blood [P_{aO_2}] of <300 on a fraction of inspired oxygen [FiO_2] of 1.0 and a peak end-expiratory pressure of 5), age of donor greater than 55 years, and a smoking history of greater than 20 pack-years.¹³ Allograft ischemic time was defined as the time of donor aorta crossclamping to the time of lung reperfusion. In double-lung transplantation the reperfusion of both lungs was done after implantation of the second lung.

Blood gases were assessed at 6, 24, 48, and 72 hours after arrival in the intensive care unit. The P_{aO_2}/F_{iO_2} oxygenation parameters were collected on all recipients. The worst blood gas value within 6 hours of the specified time point was used to determine the P_{aO_2}/F_{iO_2} ratio. The in-hospital complications that were collected include atrial fibrillation requiring antiarrhythmic therapy, wound complication requiring surgical intervention, renal failure requiring dialysis, pulmonary embolus, gastrointestinal bleeding requiring diagnostic endoscopy, and cerebrovascular accident (transient or permanent neurologic deficit and consistent radiographic findings). To allow comparison, a composite in-hospital morbidity index was calculated for each group.

Acute cellular rejection was diagnosed by means of transbronchial lung biopsy and graded according to the ISHLT guidelines: grade 0 (no rejection), grade A1 (minimal), grade A2 (mild), grade A3 (moderate), and grade A4 (severe).¹⁴ BOS was assessed on a 5-stage scale, as defined by a modification of the ISHLT consensus statement.¹⁵ We defined the baseline as an average of the 2 best spirometric values obtained in the first 6 months after transplantation. If significant decreases in spirometric function were noted, then the patient's clinical record was evaluated to ensure no confounding factors, such as infection, acute rejection, airway complications, or underlying disease recurrence, were apparent. Biopsies for diagnosis of BOS were not routinely performed.

We had complete follow-up on all patients in this study. Cause of death was obtained either from the death note in the medical record or by means of autopsy report.

Statistical Analysis

Actuarial survival rates and freedom from BOS rates were plotted as Kaplan–Meier estimates and compared by using Cox regression models with robust variance estimators accounting for matched patient pairs. The χ^2 or Fisher exact tests were used, as appropriate, to test whether associations existed between groups for categorical variables. Continuous characteristics were compared by using the Student *t* test. The Wilcoxon rank sum test was used to compare medians

Figure 1. Lung transplantations performed at the UCLA Medical Center (2000–2006).

between groups. The data were presented as means and SDs of the mean, unless indicated otherwise. All analyses were performed with Stata software (version 9.0; StataCorp, College Station, Tex).

Results

From March 2000 through September 2006, 214 patients underwent 217 lung transplantations at UCLA. Fifty (23%) of 217 of lung transplantations were performed in patients aged 65 years and older. The number and percentage of transplantations performed in patients older than 65 years increased over this study period (Figure 1). Before 2003, 7 (14%) of 50 of the total transplantations were performed in patients 65 years and older. Since 2003, 43 (25.7%) of 167 transplantations were performed in older patients.

Donor Information

The donor characteristics for recipients in the older group and their matched cohorts are presented in Table 1. The median donor age, donor sex, cause of death, and donor oxygenation parameters were similar when the older recipient group and the younger matched cohort were compared. Forty-six percent of donor lungs for the older recipients were classified as nonstandard lungs compared with 28% of donor lungs in the younger group ($P = .06$). Older donors were preferentially allocated to the older recipients. Sixty-one percent of older recipients of nonstandard lungs received lungs from donors older than 55 years compared with 29% of their matched younger cohorts. This difference reached statistical significance ($P < .05$).

Recipient and Perioperative Characteristics

The recipient demographics and perioperative characteristics are presented in Tables 2 and 3, respectively. As expected, there was a difference in the median age of the 2 groups. The oldest patient to undergo lung transplantation during this period was 72 years old. There was no statistical difference in recipient sex, incidence of diabetes mellitus, preoperative mean pulmonary artery pressure, and waiting time between the 2 groups. As expected, the diagnoses and LASs were similar in both groups because the control younger recipients were matched to the older recipients based on

TABLE 1. Clinical characteristics of lung transplant donors for the older and younger recipient groups

	Older	Younger
Median donor age (%)	36 (11–74)	36 (14–68)
Sex (% male)	58	66
Cause of death		
Atraumatic brain injury	42	44
Traumatic head injury	34	46
Other traumatic injuries	4	2
Other	20	8
Pao ₂ /Fio ₂ (mm Hg)		
Best	386 ± 91	405 ± 85
Worst	352 ± 93	345 ± 66
Nonstandard donor lungs (%)	46	28
Reason for nonstandard lungs*		
Radiographic infiltrate	17	14
Donor Age >55 y†	61	29
Pao ₂ /Fio ₂ <300	39	43
Presence of purulent secretions	30	36
Smoking history >20 pack-years†	4	36

One pack-year is defined as 1 pack of cigarettes smoked per day for 1 year. Pao₂, Partial pressure of oxygen in arterial blood; Fio₂, fraction of inspired oxygen. *Subclassification of the reason for nonstandard lung transplants is reported as a percentage of the number of total nonstandard lungs in each cohort. The total percentages exceed 100% because many donor lungs had several nonstandard criteria. †*P* < .05 when older and younger groups were compared.

these criteria. It is notable that the median waiting time for both groups was less than 3 months. Analysis of our data before and after implementation of the new allocation system in May 2005 revealed that the median waiting time for our transplantation population has decreased: before May 2005, the median waiting time was 107 days, whereas after May 2005, the median waiting time was 47 days (*P* < .05).

Older recipients were preferentially treated with single-lung transplantation (Table 3). Seventy-six percent of older recipients received single-lung transplants compared with

TABLE 2. Demographics of older lung transplant recipients and their matched younger cohort

	Older	Younger
Median age (y)*	66 (65–72)	58 (33–64)
Sex (% male)	60	54
Diagnosis (%)		
Restrictive disease	58	58
Obstructive disease	36	36
Other	6	6
LAS score	39.9 ± 7.8	38.9 ± 7.2
DM (%)	16	8
Preoperative MPAP (mm Hg)	25.2 ± 8.8	27.4 ± 9.3
Waitlist time (d)	63 (3–298)	78 (1–703)

LAS, Lung Allocation Score; DM, diabetes mellitus; MPAP, mean pulmonary artery pressure. *P < .05 when older and younger groups were compared.

TABLE 3. Perioperative characteristics of older lung transplant recipients and their matched younger cohort

	Older	Younger
Double-lung transplantations (%)*	24	84
CPB		
Done on CPB (%)*	34	84
CPB time (min)	183 ± 50	214 ± 69
Allograft ischemic time (min)		
Single-lung transplantations	263 ± 50	295 ± 59
Double-lung transplantations	346 ± 88	367 ± 60
Concomitant cardiac procedures (%)	16	26
Reoperation (%)	4	4
Median ventilator time (h)	27 (11–435)	30 (13–159)
Median intensive care unit stay (d)	4 (2–182)	6 (2–56)
Median hospital stay (d)	14 (8–277)	14 (7–98)
Induction therapy (%)		
Rabbit ATG*	33	76
IL-2R antibody*	67	24
Composite in-hospital morbidity rate (%)	34	30
Atrial fibrillation	22	28
Wound complication	4	2
ARF requiring dialysis	6	8
Pulmonary embolus	0	4
GI bleed	6	2
CVA	0	0
Acute cellular rejection (episodes/patient-y)	0.22	0.16

Grade A3 and greater acute cellular rejection was defined as episodes per patient-year. CPB, Cardiopulmonary bypass; ATG, anti-thymocyte globulin; IL-2R, interleukin 2 receptor; ARF, acute renal failure; GI, gastrointestinal; CVA, cerebrovascular accident. *P < .05 when older and younger groups were compared.

16% of younger recipients (*P* < .05). The rationale for offering double-lung transplantation to the remaining 24% of the older recipients included severe pulmonary hypertension or infectious lung diseases. As expected, more lung transplantations in younger patients were performed during CPB (because the greater percentage received double-lung transplants). The duration of CPB (for those recipients whose procedures were performed during CPB), the allograft ischemic time, and the percentage of patients requiring concomitant cardiac procedures were similar in both groups.

There were no intraoperative deaths. The median durations of mechanical ventilation, intensive care unit stay, and hospital stay were also similar between the older group and the matched younger cohorts. As noted in the Materials and Methods section, the 2 groups were treated with different induction therapy protocols; the older recipients are treated with the anti-interleukin 2 receptor antibody, whereas most of the younger recipients received rabbit ATG.

The oxygenation parameters at 24, 48, and 72 hours were similar in the older versus younger recipient groups (Figure 2). Notably, the composite in-hospital morbidity rate was also similar in both groups (Table 3); the older recipients

Figure 2. Postoperative partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) ratio in lung transplant recipients aged 65 years and older and their matched younger cohort.

did not have higher in-hospital complication rates. The incidence of acute rejection (grade A3 or higher) during the study period was also similar in both groups (Table 3).

The presence of BOS was defined as a 20% or greater decrease in the forced expiratory volume in 1 second from baseline value. Nearly one third of older recipients were given diagnoses of BOS by the end of the first posttransplantation year compared with 16.1% of the younger cohort (Figure 3). After 12 months, the prevalence of BOS in the older cohort reached a plateau, whereas it increased in the younger cohort. Overall, there was no statistically significant difference in the prevalence of BOS between patients older than 65 years versus those younger than 65 years. Furthermore, we could not detect a difference in survival from the time of diagnosis of BOS in older patients who received single-

Figure 3. Freedom from bronchiolitis obliterans syndrome (BOS) after lung transplantation in the older and younger recipient groups. Patients were considered to have BOS if there was a greater than 20% decrease from baseline forced expiratory volume in 1 second values (ie, stage I or greater BOS on the basis of ISHLT criteria).

Figure 4. Kaplan–Meier survival curves for lung transplant recipients aged 65 years of age and older and their matched younger cohort. There was no significant difference between the 2 survival curves.

lung transplants versus the younger patients who received double-lung transplants (likely because of a small number of index cases in both groups).

The median follow-up period for the older and younger groups was 15 and 19 months, respectively ($P = .54$). The early (in-hospital, 30 days, or both) survival in the older group was 95.7%, and it was 95.9% in the younger matched cohort ($P = .73$, Figure 4). The 1-year survival in the older group was 79.7%, with 8 deaths during the 1-month to 1-year posttransplantation interval. The 1-year survival in the control cohort (<65 years) was 91.2%, with 3 deaths during the 1-month to 1-year posttransplantation period. There was not a statistically significant difference in the 1-year survival of the 2 groups ($P = .16$). The causes of death in the older group included infections ($n = 6$), cardiovascular issues ($n = 1$), and BOS ($n = 1$, Table 4). The 3 deaths in the younger group during this interval were due to infections ($n = 2$) and unknown causes ($n = 1$). None of the deaths in the single-lung transplant recipients could be attributed to the remaining native lung. The survival curve of the older group reached a plateau at 18 months and has been stable up to 3 years. The 3-year survival of the older recipients was 73.6%, whereas that of the younger matched group was 74.2% ($P = .64$).

TABLE 4. Causes of death from 30 days to 1 year after transplantation in the older and younger recipient groups

	Older	Younger
Causes of death (30 d–1 y)		
Infection	6	2
BOS	1	0
Cardiovascular	1	0
Unknown	0	1
Total	8	3

Six of 8 deaths in the older group were attributed to infectious causes.

Discussion

This study demonstrates that lung transplantation can be performed in select patients older than 65 years with acceptable short- and medium-term survival. The morbidities associated with this procedure (composite in-hospital morbidities, incidence of acute cellular rejection, and BOS) were also similar between the older and younger groups.

These observations are predicated on several programmatic guidelines that deserve special emphasis. First, the older recipients were selected by using strict previously noted criteria. We ensured that older recipients were otherwise healthy candidates, with at most 1 relative contraindication.

Second, we favor single-lung transplantation in older recipients. Older recipients have been known to have better outcomes with single-lung transplantation compared with double-lung transplantation.^{16,17}

Third, the immunosuppression regimen was tailored in older recipients. The findings of this study need to be analyzed within the context of the above caveats. The similarity of clinical outcomes in the older versus younger recipients in our experience might be due to our clinical management protocols (donor and recipient selection and management), small sample size in this study, or both.

Nonstandard donor lungs were preferentially allocated to older recipients. Use of nonstandard donor lungs is associated with higher perioperative mortality.¹⁸ The similar early outcome of the older and younger groups, despite this allocation bias, might be due to (1) the small number of patients in both groups (type II error) or (2) bias in the selection of “quality” nonstandard donor lungs when needed for single-lung transplantations in older recipients, or (3) higher perioperative mortality of double-lung transplantation¹⁷ in the younger group might balance the early perioperative mortality in the older group because of nonstandard donor lung dysfunction.

Despite the similarities of the early- and medium-term survival of the older group and the matched younger cohort, there were 8 deaths in the older group in the 1-month to 1-year period after lung transplantation. The majority of these deaths were attributed to infectious causes. Although our immunosuppression regimen was tailored in the older recipient group (interleukin 2 receptor blockade instead of rabbit ATG for induction therapy), it remains a possibility that overimmunosuppression in the older recipients might have contributed to life-threatening infections. Immunosenescence is a well-recognized entity in older individuals.^{19,20} Potential mechanisms of age-based differences in posttransplantation immune response include replicative senescence, thymic involution, degeneration of the T-cell repertoire, alterations in T-suppressor activity, altered cytokine profiles, and reduced perforin production.^{21,22} Moreover, several studies have shown that the incidence of acute cellular rejection in elderly recipients of kidney, liver, heart, and lung transplants are lower compared with that seen in younger recipients.⁴⁻⁷ In

this study the incidence of acute cellular rejection was similar in the elderly group and the matched younger cohort.

Based on the findings of this study, it is reasonable to alter/reduce the immunosuppression regimen in older lung transplant recipients. A reduction in the dose of calcineurin inhibitors can lead to a reduction in the renal side effects; adjustments in the dose of steroids can also decrease the associated metabolic complications. The potential benefits of such adjustments, provided that the incidence of acute rejection and BOS do not increase, are significant. A more robust recipient immune system can combat infections more vigorously.

This study does not support widespread application of lung transplantation to older recipients. In fact, larger databases, such as UNOS/ISHLT registry, might be the only reasonable basis on which to change the current guidelines. In a recent report 42 older lung transplant recipients were matched to a younger cohort, and their survival was compared. The medium-term and long-term survival of the older recipients was significantly lower, even after adjustment for the older group's expected higher age-related mortality.²³ Another important issue in offering lung transplantation to older recipients is the effect on donor supply. Given the limited donor pool, expanding the recipient pool by offering lung transplantation to older recipients will ultimately deprive a younger recipient of a potential donor organ. One might address this ethical dilemma by (1) informing all older recipients about a nonstandard donor pool program preoperatively and (2) preferential offering of nonstandard donor lungs to older recipients. Despite the adoption of these policies, more than half of our older recipients received donor lungs from the standard pool. A consensus on the definition of the nonstandard donor and recipients and UNOS adoption of a policy of allocating nonstandard donor organs to nonstandard recipients might be a solution to this ethical dilemma. Until then, the effect of lung transplantation in older recipients on the donor pool and other younger patients on the waiting list is an important question and deserves further study.

This study has several limitations. First, this is a retrospective case-control analysis with all the inherent limitations of such a study.

Second, the index older cases were matched to the younger recipients based on their diagnoses, severity of disease (by using LAS as surrogate marker), and the era of transplantation. Another factor that is known to affect short-term outcome after lung transplantation is the type of transplantation.^{16,17} We did not match for the type of transplantation (single vs double) because there were insufficient double-lung transplant recipients in the older group and single-lung transplant recipients in the younger group. The findings of this study might not be applicable when comparing the outcome of the type of transplantation in older versus younger recipients.

Third, another limitation of this study is the relatively small number of cases in both groups, thus requiring larger differences in clinical outcomes to detect statistically significant differences (type II error).

Fourth, although strict criteria were used in the selection of both the older and younger recipients, the final approval for lung transplantation was dependant on the decision of the multidisciplinary lung transplant selection committee. There might be inherent bias against selection of older patients based on overall clinical fitness and extent of comorbidities.

Fifth, another limitation of this study is the short follow-up time. Longer follow-up analyses are needed to assess the safety and clinical outcome of lung transplantation in older recipients.

Finally, this study only compares the survival of older and younger lung transplant recipients. Lung transplantation might not only affect survival but also the quality of life. We have no objective information on the quality of life after lung transplantation in the older or younger recipients as part of this study. The real effect of lung transplantation can only be assessed when survival and quality-of-life data are analyzed together.

In summary, lung transplantation can be performed safely and with comparable short-term and medium-term survival in selected patients older than 65 years.

Posttransplantation-related infections represent the major cause of early mortality that might require adjustments in immunosuppression protocols. Multidisciplinary consensus is needed to determine the ethical standards in offering lung transplantation to the elderly given the critically short supply of donor organs.

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Discussion

Dr John C. Wain (*Boston, Mass*). I appreciate the chance to discuss the article. Certainly I think the results are quite good, and Drs Bastani and Ardehali and their colleagues are to be congratulated on having not only completed this study but also their superlative results in terms of operative and perioperative morbidity and mortality looking in a retrospective fashion at patients older than 65 years of age. I think it is important to recognize that age greater than 65 years is actually a pretty narrow window; it is just 65 to 72 years of age as the maximum. Therefore we still have a question out there about even older patients. That being said, though, the results still stand for themselves in terms of the operative and perioperative morbidity and mortality.

Before I get to specific questions, I would like to say that the study also seems to validate 2 other things that are emerging concepts, if you will, at least about lung transplantation in the United States. The first is that the LAS system works. As I think you found in your manuscript, the time waiting at a busy transplantation center was reduced from 107 days to 47 days. Therefore the LAS is clearly an improvement.

The second is that ischemic times do not matter so much in the modern era of lung transplantation, and I think that that is an interesting observation, certainly one that seems to be growing and that probably relates to standardized procurement and preservation and the techniques of implantation.

But to return to the main thrust of the article, there were 3 conclusions I think they tried to stress. One is that lung transplantation in older patients is safe, the second is that older patients die most commonly from infectious causes, and the third is that nonstandard lungs can be used safely for older patients. About the first point, with which I would tend to agree, that the right selection of recipients allows you to have a successful transplantation, I am curious because in fact this is a comparison of single-lung transplantations in older patients versus double-lung transplantations in younger patients, and therefore we get into how you decide someone received a single-lung transplant versus a double-lung transplant for the same disease because your groups were matched based on their initial diagnosis. Therefore my question is as follows: in terms of selecting the older patient for a transplantation procedure, which by default in your case would be a single-lung transplantation procedure, are there other things, other specifics, such as right ventricular end-diastolic pressure, ejection fraction, or body mass index, that allow you to more accurately identify the older patient that you would see as a potential candidate for transplantation?

Dr Bastani. With regard to your question about more precisely defining our patient population of 65 years and older, we did not have enough older patients in the double-lung transplant group to be able to make an adequate comparison. We did, however, have a list of relative contraindications for the patients 65 years and older, some of which were body mass index of less than 18 and greater than 30, debilitation, and acute renal failure defined by creatinine clearance. In general, our lung transplantation committee made an effort not to list patients who had 2 or more of these relative contraindications.

Dr Wain. Were those the only relative contraindications? Was there anything else, such as osteoporosis or bad social history or any of those other things, that were in the mix?

Dr Bastani. By listing debilitation as one of the relative contraindications, we have the ability to introduce some subjectivity, and yes, osteoarthritis and other characteristics could preclude patients from receiving a lung transplant.

Dr Wain. The other question I have is this: How do you decide that a 63-year-old patient with IPF, for example, received a double-lung transplant and a 65-year-old patient with IPF receives a single-lung transplant? Is there anything else other than their absolute age that goes into your decision-making process that lets you decide that the patient should receive a single- or a double-lung transplant in the same relative age range?

Dr Bastani. At this time, despite our focus on a population of patients 65 years and older, there is no absolute contraindication on upper age limit with respect to single- versus double-lung transplantation. If our lung transplantation committee deems a patient to be clinically fit, despite advanced age of 65 years and older, he or she might be a potential candidate for lung transplantation, including double-lung transplantation.

Dr Wain. With regard to the second point about older patients dying more of infection, I guess in looking at it I would say that your data really say that your older patients just die more in that first

year. I say that because it looked like 6 of 8, or 75%, of the older group of patients died of infectious causes in the first year, and although the number of younger patients dying was much smaller, 2 of 3 died of those infectious causes. Therefore the first question is as follows: Was there any specific type of infectious cause that the patients in either group died of, and then, as an aside to that, was there a difference between the infectious causes in the 2 groups?

Dr Bastani. Five of the 6 patients in the older group died of infection of bacterial cause, and the other patient died of infection of fungal cause. There were no patients in this group who died of infectious cause secondary to a viral source. In the younger group both of the patients died of infection of bacterial cause.

Dr Wain. Therefore you had bacterial infections in both groups.

Dr Bastani. Yes.

Dr Wain. Then along those lines, akin to the single- versus double-lung transplantation, you have 2 different immunosuppressive protocols. Was there any suggestion or thought that the difference in induction immunosuppression might somehow relate to the likelihood of infection or death in the first year? Do you have any other experience to draw on using the interleukin 2 receptor blocker that would suggest that is not as good, for instance, as the rabbit ATG or vice versa?

Dr Bastani. We did not specifically look at that and compare those 2 groups, although we did initially have a bias for selecting interleukin 2 receptor antibody induction therapy for older patients and vice versa for the younger patients, but we did not specifically look at that.

Dr Wain. And why did you come to that bias, or what was the rationale behind that?

Dr Bastani. Because older patients are more susceptible to immunosenescence, our group selects for interleukin 2 receptor antibody induction therapy for the older group because of its more specific and less broadly immunosuppressive action.

Dr Wain. That is perfectly fine. To the last point in the study, that nonstandard lungs are okay or safe in older patients, I guess I would say that might be a little bit overstated. I say that because, having looked at that table of your donor characteristics, although there was clearly a preponderance of lungs from older donors in your older age group, functionally the lungs seemed much the same in terms of their overall PO_2 , and in fact, there was a little trend for a preponderance of donors who had a significant smoking history in the younger group compared with the older group. Recognizing that elastic fibers deteriorate as you get older and that sort of thing, if I needed a lung transplantation, I personally would want a lung from a 60-year-old marathon runner instead of a 48-year-old individual who smoked a lot. I just wondered if there are any other parameters, smoking, for instance, that you look at more critically than, say, age, which is a crude marker at best, in terms of trying to select donor lungs for older patients or patients who you might consider at higher risk.

Dr Bastani. We were surprised by our findings that a larger proportion of the patients in the younger group received lungs from smokers. We did look at other parameters. One of the parameters was donor age greater than 55 years. There were also other parameters that we examined. Other studies demonstrate smoking history to be a significant predictor as well. I am not certain whether this finding will be predictive of a negative outcome in our younger patients, but we did examine other nonstandard donor lung parameters.

I should note that a larger number of the patients in the older group had multiple criteria that met the nonstandard donor lung parameters compared with the younger patients, who had a single-criterion parameter.

Dr Wain. I have 1 final question about selecting donor lungs. Is there anything that you can think of or anything that you routinely do that is a little more precise than just donor age or smoking history or, you know, what the chest radiograph looks like? Do you do any routine chest computed tomographic scanning or routine bronchoalveolar lavage or something like that that would give us a better sense of the kind of true anatomic and inflammatory state of the donor lung than just what the PO_2 is at some little snapshot in time or the donor's age?

Dr Bastani. At our institution, we routinely perform bronchoscopies on all donor lungs, and if, for example, there is any question of whether there is an infiltrate on chest radiography or there are any significant findings on bronchoscopy, we do perform chest computed tomographic scanning on those patients; however, we do not routinely perform chest computed tomographic scanning on all donors.

Dr Wain. Again, congratulations, and thanks very much for letting me see the manuscript ahead of time.

Dr Yoshiya Toyoda (Pittsburgh, Pa). Congratulations on your excellent presentation and outcome.

I would like to make a comment. Over the last year and a few months, I have done 66 lung transplantations, and of these, 18 patients, about 25%, were age 65 years and older, including an 81-year-old man for whom I did a left single-lung transplantation for his IPF and moderate pulmonary hypertension. Fortunately, 30-day survival has been 100%, but I lost 2 patients, one from *Pseudomonas*-induced pneumonia and the other from sepsis. Therefore I agree with your conclusion. Probably these older patients should be managed with less immunosuppression.

Dr Bastani. Thank you.

Dr Walter Klepetko (Vienna, Austria). I enjoyed your article very much, and I want to congratulate you on these very good outcome data.

One thing was surprising to me and struck me a bit. You showed us an approximate freedom from BOS of only 50% after 1 or 1½ years. This is somewhat low compared with data that we recently have heard in which several multicenter studies have shown freedom from BOS after 3 years in the range of 75% to 80%. Do you think that at least in the cohort of your older patients that this is the price you are paying now when you are using lungs that are

not so ideal on the one hand and on the other hand potentially have altered your immunosuppressive regimen in a way that BOS might likely occur more frequently?

Dr Bastani. We were surprised by the pattern in which patients demonstrated the incidence of BOS, particularly the older patients, in whom there was a steady decrease in the incidence of BOS-free survival, and then that leveled off. BOS was one of the secondary end points that we examined. One explanation for differences in our data compared with those of the multicenter study you just eluded to might be in our definition of BOS; we defined BOS as a 20% or greater decrease in forced expiratory volume in 1 second. We did not routinely treat all patients with BOS or perform biopsies on all patients with BOS.

Dr Klepetko. I have one question regarding your acceptance criteria. You had obstructive cardiovascular disease as an exclusion criteria. How did you handle patients in whom the obstructive disease was already fixed, let us say, having a history of a bypass operation 2 years before or a stent application with no further obstructions there at the time of their evaluation?

Dr Bastani. Patients with prior history of percutaneous transluminal coronary angioplasty or bypass operation to correct obstructive coronary artery disease who were deemed to be free of coronary artery disease, as assessed by means of left heart catheterization, at the time of presentation to the lung transplantation committee were not excluded from consideration for lung transplantation.

Dr Shaf Keshavjee (Toronto, Ontario, Canada). I really enjoyed your presentation.

We actually have an article that was just published this week (*Am J Transplant.* 2007;7:1271-7) in which we compared outcomes of lung transplantation in older and younger patients, and even with age-adjusted mortality, we did find a higher risk of death over time after lung transplantation in patients older than 60 years versus those younger than 50 years. When you compare at a specific age cutoff, such as older than 65 versus less than 65 years, there is not much of a difference between a 64-year-old and a 66-year-old. Did you look at your data with a wider age spread to see whether you have an age difference?

Dr Bastani. We did not examine our subset of populations, for example, 60 to 64 years, to determine whether survival was similar to that seen in those older than 65 years or maybe those younger than 60 years, but certainly that is something that I think we need to go back and look at to see whether we need to redefine our parameters.