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A NEW EPITOPE-BASED HLA-DPB MATCHING APPROACH FOR CADAVER KIDNEY RETRANSPLANTS

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Background. **Several years ago a significant impact of matching for HLA-DPB1 alleles on the survival of cadaver kidney retransplants was shown. Here we report the results of a new approach, based on matching for HLA-DPB1 epitopes.**

Methods. **The analysis is based on 1,478 patients who received a cadaver kidney retransplant between 1988 and 1998. DNA methodology (polymerase chain reaction, sequence-specific oligonucleotides) was used to perform HLA-DPB1 typing. Epitope matching was facilitated with the aid of sequence databases and computer calculations.**

Results. **Matching for the HLA-DP epitopes A, B, E, and F, corresponding to the homonymous hypervariable regions of the second exon of the DPB1 gene, seems to have a greater influence on graft survival than matching for the epitopes C and D. Within a group of 529 retransplants with exactly one allelic HLA-DPB1 mismatch, a significantly better graft outcome was observed when less than two epitope mismatches were found, compared with the group with more than three epitope mismatches (at 2 years: 77.8% vs. 65.8%, $P=0.0112$). Importantly, patients with two DPB1 allele mismatches who had less than or equal to two epitope mismatches exhibited a significantly better graft outcome than recipients who had one HLA-DPB1 allelic mismatch but more than three epitope mismatches (at 2 years: 77.1% vs. 65.8%, $P=0.0488$).**

Conclusions. **The findings indicate that the impact of HLA-DPB1 matching on the outcome of kidney retransplants is a result of the predominant immunogenicity of certain epitopes of the HLA-DP molecule. Matching for immunogenic HLA-DPB1 epitopes seems**

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to be functionally more relevant than classical matching at the allelic level.

The discovery of the HLA-DP antigens was based upon the ability of these molecules to initiate a mixed lymphocyte culture response in restimulation experiments of previously primed T cells (*1*). The HLA-DP α and β chains of the DP molecule are encoded by the MHC genes HLA-DPA1 and -DPB1, respectively (*2*). With currently more than 100 described alleles, the HLA-DPB1 gene features a distinctive polymorphism that concentrates on six hypervariable regions within the second exon encoding for the β1 domain. Each HLA-DPB1 allele is characterized by a specific combination of the sequences in these six hypervariable regions (*3*) (Table 1).

Contrary to incompatibilities for HLA-A, -B, and -DR, mismatches for HLA-DPB1 have no influence on the outcome of first kidney transplants. However, they have a significant impact on retransplants, which is probably caused by the stimulation of a secondary allogeneic proliferative and cytotoxic response, as previously suggested (*5*).

Previous analyses regarding HLA-DPB1 compatibility were performed by classical matching methods, counting the number of "mismatches," that is, DPB1 alleles present in the kidney donor but absent in the recipient. Because the initiation of the immune response against the transplant is primed by antigenic determinants (epitopes) on the HLA molecules of the graft, it seemed logical to analyze whether matching for DPB1 epitopes may have an impact on transplant outcome. Such epitope-based matching approaches have been proposed for MHC class I specificities [eg, HLA-Matchmaker (*6*)].

MATERIALS AND METHODS

A total of 1,478 kidney retransplants from cadaver donors were retrospectively typed for HLA-DPB1 by DNA methods. HLA-DPB1 typings were performed between 1988 and 1998 within the framework of the DNA typing project of the Collaborative Transplant Study (*7*). Samples (peripheral blood, buffy coat, or donor spleen tissue) were collected at 112 participating centers and shipped on dry ice to the study center in Heidelberg. Routine methods were used to extract DNA (*8*,*9*). A modified polymerase chain reaction–sequence-specific oligonucleotide method (*10*) and a commercial kit (Innolipa, Abbott, Wiesbaden, Germany) were used for HLA-DPB typing. All typings were performed at the HLA laboratory of the University of Heidelberg.

Each HLA-DPB1 allele is characterized by a specific combination of sequence motives of the six hypervariable regions. Each region is encoding for a certain epitope variant on the HLA-DP molecule. Table 2 shows the codons that are encoding for the six polymorphic regions (epitopes). Table 3 shows all epitope variants that were detectable for the polymorphic regions A to F, whereby each amino acid sequence encoded by this regions represents a possible epitope.

On the basis of well-defined amino acid sequences (*4*), it was possible to assign zero to two mismatches for each epitope of each donor-recipient pair. Table 4 shows an example of two different donor-recipient pairs with the number of conventional mismatches (CMM) at the allelic level and the number of epitope mismatches (EMM). For example, when considering the amino acid sequences of epitope A of the homozygous donor D1 (LFQGR, LFQGR) in combination with recipient R1 (VHQLR, VYQLR), there is one EMM. Interestingly, although donor D2 and recipient R2 have two mismatches at the allelic level, the sum of mismatches at the epitope level is only one (Table 4).

TABLE 1. Amino acid sequences of the HLA-DPB1 β1 domain (HLA-DPB1*0101 to DPB1*1501)

Alleles	Codons/amino acid sequences 1 *	10 *	20 *	30 *	40 *	50 *	60 *	70 *	80 *	90 *
DPB1*01011	RATPENYVYQ	GRQECYAFNG	TQRFLERYIY	NREEYARFDS	DVGEFRAVTE	LGRPAAEYWN	SQKDILEEKR	AVPDRVCRHN	YELDEAFTLQ	
DPB1*01012	*****---	----------	----------	----------	----------	----------	----------	----------	----------	
DPB1*02012	------LF-	----------	----------	---FV-----	----------	---DE-----	------E-	----M-----	---GGPM--	
DPB1*02013	*****--LF-	----------	----------	---FV-----	----------	---DE-----	------E-	----M-----	---GGPM--	
DPB1*02014	*****--LF-	----------	----------	---FV-----	----------	---DE-----	------E-	----M-----	---GGPM--	
DPB1*0202	*****--LF-	----------	----------	---LV-----	----------	----E-----	------E-	----M-----	---GGPM--	
DPB1*03011	--------	L---------	----------	---FV-----	----------	---DED----	---L------	----------	----------	
DPB1*03012	*****---	L---------	----------	---FV-----	----------	---DED----	---L------	----------	----------	
DPB1*0401	------LF-	----------	----------	---F------	----------	----------	----------	----M-----	---GGPM--	
DPB1*0402	------LF-	----------	----------	---FV-----	----------	---DE-----	----------	----M-----	---GGPM--	
DPB1*0501	*****--LF-	----------	----------	---LV-----	----------	----E-----	----------	----M-----	----------	
DPB1*0601	******---	L---------	----------	---FV-----	----------	---DED----	---L---E-	----M-----	----------	
DPB1*0801	*******LF-	----------	----------	---FV-----	----------	---DE-----	------E-	----------	----------	
DPB1*0901	*****---H-	L---------	----------	---FV-----	----------	---DED----	------E-	----------	----------	
DPB1*1001	*****---H-	L---------	----------	---FV-----	----------	---DE-----	------E-	----------	----------	
DPB1*11011	******---	L---------	----------	--Q-------	----------	----------	---L---R-	----M-----	----------	
DPB1*11012	******---	L---------	----------	--Q-------	----------	----------	---L---R-	----M-----	----------	
DPB1*1301	******---	L---------	----------	----------	----------	----------	------E-	----I-----	----------	
DPB1*1401	*****---H-	L---------	----------	---FV-----	----------	---DED----	---L------	----------	----------	
DPB1*1501	******---	----------	----------	--Q-------	----------	----------	---L---R-	----M-----	---VGPM--	

-, Consensus sequences; *, unknown sequences (4).

TABLE 2. HLA-DPB1 hypervariable regions and their corresponding codons

DPB1 region	Codons
A	8, 9, 11, 12
B	33, 35, 36
C	55, 56, 57
D	65, 66, 69
E	72, 73, 76
F	84, 85, 86, 87

TABLE 3. HLA-DPB1 epitopes

DPB1 region	Possible epitopes
A	VYQGR, LFQGR, VYQLR, VHQLR, VDQLR, LFQGL
B	EEYA, EEFV, EEFA, QEYA, EELV
C	AAE, DEE, EAE, DED, DEV, EEE
D	ILEEK, ILEEE, LLEEK, LLEEE, FLEEE, NLEEK, LLEER, FLEEK
E	VPDRV, VPDRM, VPDRI, LPDRM, VLDRV
F	DEAV, GGPM, VGPM

Clinical follow-up data were recorded after transplantation at 3, 6, 12, and 24 months. Graft survival rates for the first 2 years after transplantation were calculated according to the method of Kaplan and Meier (*11*). Patient death was counted as graft failure. Statistical significance was estimated using the log-rank test or weighted regression. Multifactorial analyses were performed using the Cox regression model (*12*) in combination with the likelihood ratio test (*13*). The relevance of the new factor EMM was assessed with respect to established classical factors (donor and recipient age; HLA mismatches at the A, B, and DR loci; cold ischemia time; year of transplantation; number of retransplants; geographical region; donor and recipient gender). To check the validity of the proportional hazards assumption for Cox modeling, we used a special procedure that evaluates the necessity for replacing the classical constant coefficients in the Cox model by time-dependent regression coefficients (*14*).

RESULTS

At first, the influence of each polymorphic region was investigated separately. Matching for epitopes located in regions A, B, E, and F, respectively, had an influence on graft outcome, whereas matching for epitopes in regions C and D showed no effect. As typical examples, Figure 1 shows the effect of matching for epitopes located in regions B and C.

Table 5 shows 2-year graft survival rates for HLA-DPB1 epitope-matched and -mismatched transplants in each of the six polymorphic regions. Although a statistically significant effect of EMM is evident only at region F, there is a positive tendency for regions B and E and to a lesser extent for region A.

A mismatched HLA molecule consists of several epitopes that exert a collective influence on the recipient's immune response (*15*). In the subsequent analysis steps, we therefore considered the regions A, B, E, and F together. For each epitope, a donor and recipient may have zero, one, or two EMM. Therefore, when considering the epitopes in regions A, B, E, and F together, the total number of EMM can range from zero to eight. We separated the transplants into two groups, one group with less than two EMM and another with more than 3 EMM. Figure 2 shows graft survival rates for the two groups. A significantly better graft outcome was observed for the group with less than two EMM compared with the group having more than three EMM (at 2 years: $77.0\pm1.5\%$ vs. $65.1\pm2.9\%$, $P<0.0001$).

To exclude the possibility that a high number of EMM may be automatically associated with disparity for two HLA-DPB1 alleles, and to stratify for the impact of allelic matching, only patients with one DPB1 allele mismatch were analyzed in the following step. The impact of epitope matching could be verified (Fig. 3). The group of patients with less than two EMM had a significantly better graft outcome than the group with more than three EMM (at 2 years: $77.8\pm2.0\%$ vs. $65.8\pm5.0\%$, $P<0.0112$). In the multivariate proportional hazards model, the presence of more than three EMM was an independent risk factor (relative risk=1.80; 95% confidence interval, 1.40, 2.33], $P<0.0001$), in addition to the classical HLA-DR mismatch factor (relative risk=1.62, 95% confidence interval, 1.26, 2.07; $P<0.0001$).

In a further analysis step, classical matching and epitope matching were combined. At first, patients with one or two classical allelic mismatches were compared. The group with one mismatch showed a significantly better graft outcome

TABLE 4. Epitope mismatches within the hypervariable regions A, B, C, D, E, and F

	Alleles	A	B	C	D	E	F
Donor 1 (D1)	Allele 1: DPB1*0401	LFQGR	EEFA	AAE	ILEEK	VPDRM	GGPM
	Allele 2: DPB1*0401	LFQGR	EEFA	AAE	ILEEK	VPDRM	GGPM
Recipient 2 (R2)	Allele 1: DPB1*1401	VHQLR	EEFV	DED	LLEEK	VPDRV	DEAV
	Allele 2: DPB1*0601	VYQLR	EEFV	DED	LLEEE	VPDRM	DEAV
MM (R1)	CMM: 1	1	1	1	1	0	1
	EMM: 5						
Donor 2 (D2)	Allele 1: DPB1*0401	LFQGR	EEFA	AAE	ILEEK	VPDRM	GGPM
	Allele 2: DPB1*0402	LFQGR	EEFV	DEE	ILEEK	VPDRM	GGPM
Recipient 2 (R2)	Allele 1: DPB1*2301	LFQGR	EEFV	AAE	ILEEK	VPDRM	GGPM
	Allele 2: DPB1*2401	LFQGR	EEFA	EAE	ILEEK	VPDRM	GGPM
MM (R2)	CMM: 2	0	0	1	0	0	0
	EMM: 1						

CMM, conventional mismatches; EMM, epitope mismatches.

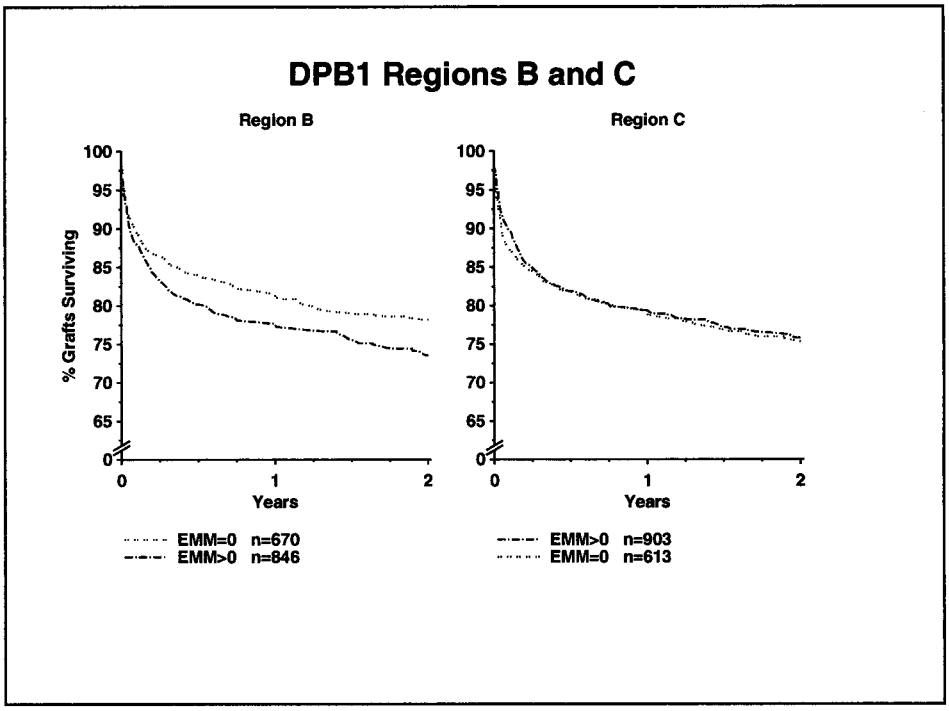

FIGURE 1. Effect of epitope mismatches (EMM) at DPB1 regions B and C on graft survival.

TABLE 5. DPB1 epitope histocompatibility and grafts surviving

	Epitopes					
	A	B	C	D	E	F
EMM = 0	76.4 (n=850)	77.7 (n=630)	74.5 (n=579)	75.2 (n=686)	76.5 (n=1004)	77.4 (n=949)
EMM >0	73.7 (n=602)	73.4 (n=822)	75.8 (n=873)	75.4 (n=766)	72.4 (n=448)	71.3 (n=503)
P value	0.196	0.063	0.556	0.986	0.065	0.010

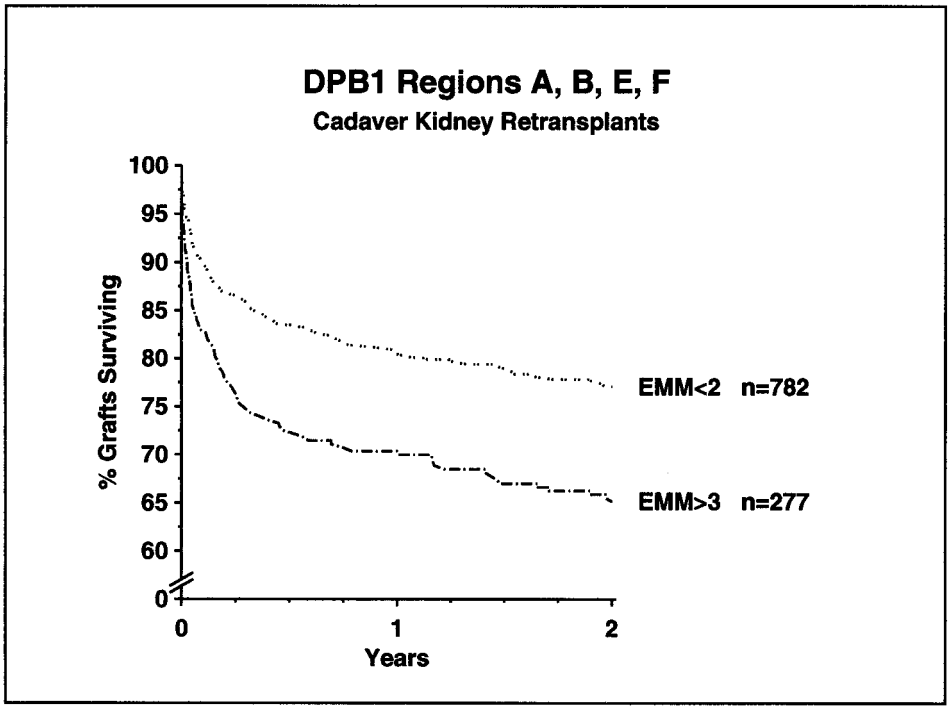

FIGURE 2. Graft survival in relation to number of EMM.

than the group with two mismatches (at 2 years: 76.4±1.5% vs. 71.8±2.0%, $P<0.048$; Fig. 4, left). Subsequently, the two groups were refined as follows: from the group of transplants with one classical allele mismatch, those having more than three EMM were compared with the group of transplants with two classical allele mismatches but no more than two

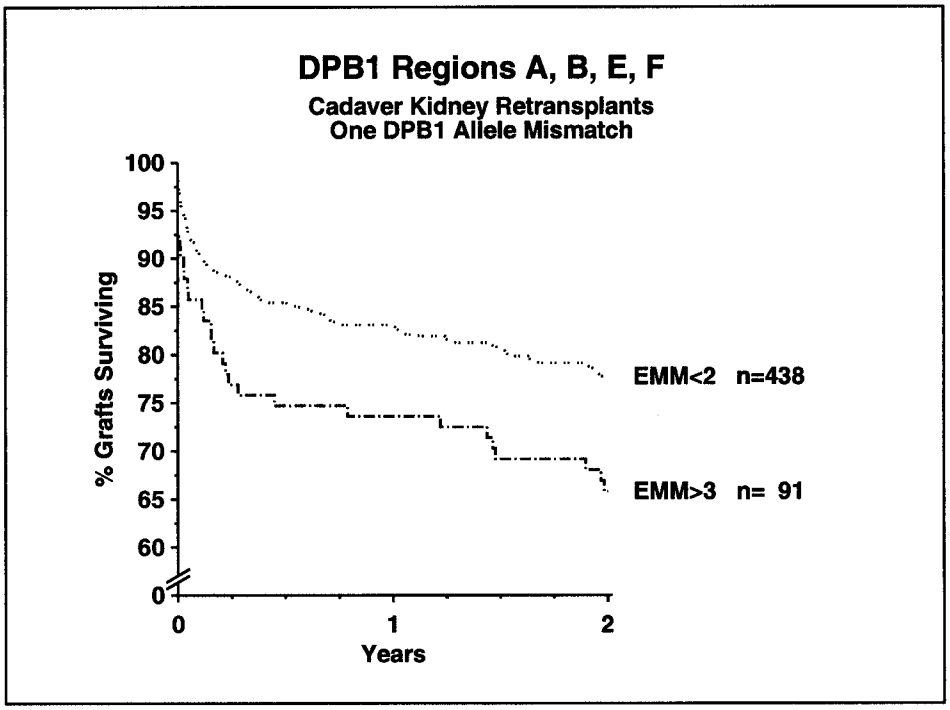

FIGURE 3. **Influence on graft survival of EMM at DPB1 regions A, B, E, and F in transplants with one allelic mismatch.**

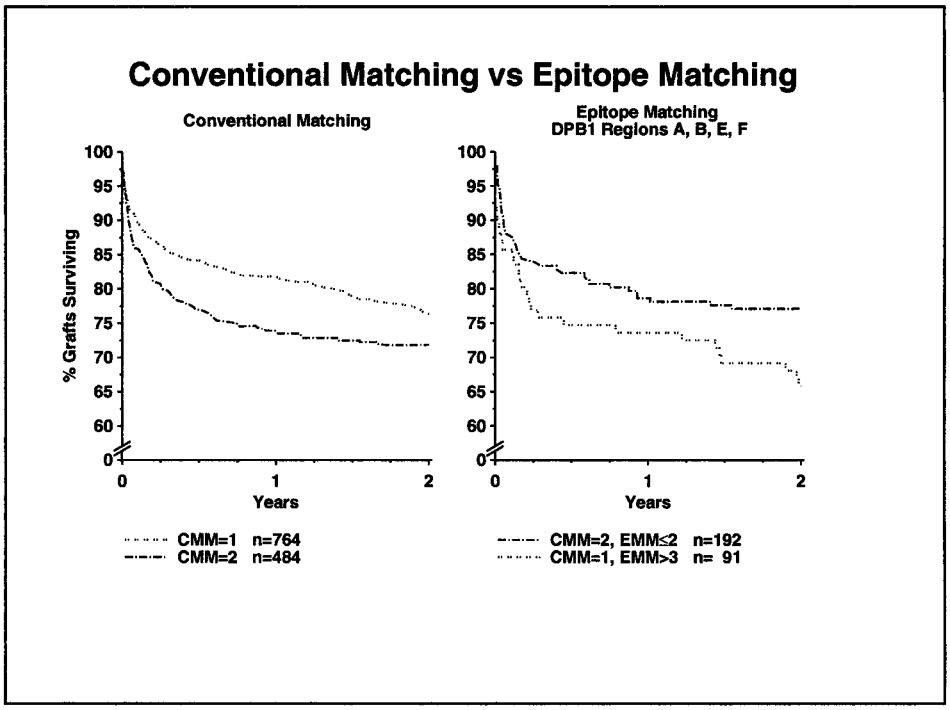

FIGURE 4. **Conventional allelic level matching (left) and epitope level matching (right).**

EMM. The three-EMM group showed a significantly lower graft survival than the two-EMM group (at 2 years: 65.8±5.0% vs. 77.1±3.0%, $P<0.049$; Fig. 4, right). Because patients within the three-EMM group had fewer classical allelic mismatches, this analysis demonstrates that EMM are of greater biological significance than conventional mismatches.

DISCUSSION

HLA-DPB is an MHC class II molecule that is known to influence the survival of kidney retransplants (*5*). Therefore, this locus should be integrated in the allocation algorithms of organ exchange organizations for patients awaiting a repeated transplantation. Based on our analyses, we suggest that it would be even more beneficial to match for HLA-DPB1 at the epitope level than at the allelic level.

Although the linkage disequilibrium between HLA-DPB1 and HLA-DR is weak, we included mismatches for HLA-DR in the multivariate Cox regression model to exclude the possibility that graft outcome of patients with a higher number of EMM would indirectly reflect mismatches at the HLA-DR-

locus. This approach established EMM as an independent prognostic factor.

The results of this study show that high resolution DPB1 typing allows precise matching at the epitope level, suggesting that the allocation of cadaver kidneys to retransplant patients would benefit from this molecular-based approach. DPB1 typing by polymerase chain reaction–sequence-specific oligonucleotides can be completed within 3 hr from bleeding and could therefore be easily implemented in the routine donor typing procedure. The epitope matching approach might also be applicable to the HLA-A, -B, and -DR loci. Conceivably, high-resolution typing and epitope matching at these loci may be important for kidney transplantation and existing organ allocation models could be suitably enhanced.

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THE ROLE OF SELF-EXPANDABLE METALLIC STENTS FOR THE TREATMENT OF AIRWAY COMPLICATIONS AFTER LUNG TRANSPLANTATION

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Background. **Airway complications continue to be an important source of morbidity and mortality after lung transplantation (LTx). Different approaches have been used for their nonsurgical management. We describe our experience using self-expandable metallic stents (SEMSs) in patients with airway complications post-LTx.**

Methods. **We present a retrospective analysis of stent related-data of all the LTx patients who received SEMSs to treat postoperative airway complications.**

Results. **Between January 1992 and December 2001, 36 of 253 patients (14.2%) developed post-LTx airway complications involving 40 of 348 anastomoses (11.5%). A total of 15 SEMSs were placed in 12 patients (mean age 47.3±9.6 years) for tracheobronchomalacia, stenosis, and anastomotic dehiscence, including one patient referred from an outside hospital. Mean follow-up was 20.1±19.5 months (range 1.2–58 months). Patency and symptom improvement were achieved in 11 of 12 patients. Stenting of the airway led to successful weaning of two patients who were on prolonged mechanical ventilation. Suture dehiscence was effectively managed in two patients who were not candidates for surgical repair. Overall, the complication rate was 0.040 complications per patient per month (total number of complications and total number of months using the stent). Bacterial bronchitis (four patients) and ob-**

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