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Single Nucleotide Polymorphisms in the Beta-adrenergic Receptor Genes are Associated with Lung Allograft Utilization

Anil Sapru¹, Ludmila Pawlikowska¹, Kathleen D. Liu¹, Kiran K Khush², Lee Ann-Baxter-Lowe¹, Vanessa Hayden³, Rebecca L Menza⁴, Maureen Convery¹, Annie Poon¹, Megan Landeck³, Jonathan G Zaroff⁵, and Michael A. Matthay, MD¹ for the DOGMATIC study Investigators

¹ Departments of Pediatrics, Medicine, Surgery and Anesthesia and Perioperative Care and the Cardiovascular Research Institute, University of California, San Francisco, CA, United States ² Cardiovascular Medicine, Stanford University School Of Medicine, Palo Alto, CA, United States ³ California Transplant Donor Network, Oakland, CA, United States ⁴ Victoria University of Wellington, Graduate School of Nursing Midwifery and Health, Wellington, New Zealand ⁵ Department of Cardiology, Kaiser Permanente, San Francisco, CA, United States

Abstract

Background—Pulmonary edema and associated impaired oxygenation are a major reason for rejection of donor lung allografts offered for transplantation. Clearance of pulmonary edema can be up-regulated by stimulation of β adrenergic receptors (β AR). Single nucleotide polymorphisms (SNPs) in β AR genes have functional effects *in vitro* and *in vivo*. We hypothesized that SNPs in β AR genes would be associated with rates of utilization of donor lung allografts offered for transplantation.

Methods—951 organ donors were genotyped for 4 amino-acid coding SNPs in the β AR genes. Lung allograft utilization was compared among donors stratified by genotypes.

Results—Utilization of donor lung allografts was 55% vs. 35% ($p = 0.02$) among donors with GG vs. AA/AG genotypes of the Ser49Gly SNP, 39% vs. 32% ($p = 0.04$) with GG vs. AA/AG genotype of Gly16Arg SNP and 37% vs. 32% ($p = 0.1$) with CC vs. GC/GG genotype of the Arg389Gly SNP. In combined analysis, donors carrying 0–1 associated genotypes had a utilization rate of 33%, whereas donors carrying two or three associated genotypes had utilization rate of 44% and 58% respectively ($p=0.008$). There was a stepwise decrease in chest radiograph infiltrates and increase in the PaO₂/FiO₂ with increasing number of these associated genotypes.

Conclusions—Genetic variants in the β AR genes among organ donors are associated with higher rates of lung allograft utilization. The increased utilization may be related to increased clearance of pulmonary edema and improved oxygenation in donors with favorable genotypes and suggests β AR agonists may have a role in donor management.

Address for correspondence: Anil Sapru, MD, Department of Pediatrics Room M680 B, 505 Parnassus, San Francisco, CA 94143, anil.sapru@ucsf.edu.

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INTRODUCTION

The demand for donor lungs far exceeds the available supply and despite the use of extended donor criteria, the overall donor lung allograft utilization rate in the U.S. is only 15%^{1,2}. The most common reasons for failure to use donor lungs offered for transplantation are donor hypoxemia and/or infiltrates on chest radiographs. Pulmonary edema, a significant contributor to poor donor lung function, is associated with impaired donor oxygenation and infiltrates on chest radiograph³.

The clearance of pulmonary edema fluid from the distal airspaces is driven by the active transport of sodium and chloride across the alveolar epithelium⁴. Faster rates of alveolar epithelial fluid clearance lead to more rapid clinical resolution of pulmonary edema, improvements in oxygenation, shorter duration of mechanical ventilation and improved survival in patients with hydrostatic and increased permeability pulmonary edema⁵⁻⁷.

β-1 and β-2 adrenergic receptors⁸⁻¹⁰ are expressed on the surface of alveolar epithelial cells and respond to β adrenergic agonist stimulation with increased rates of alveolar fluid clearance¹¹. These effects have been demonstrated in the normal lung⁴, the acutely injured lung¹²⁻¹⁵ and models of hydrostatic pulmonary edema^{11,16-18}.

The physiology and genetics of β-adrenergic receptors have been well characterized in previous studies. A number of single nucleotide receptor polymorphisms (SNPs) in the genes for the β adrenergic receptor genes have demonstrated functional effects in both *in vitro* and *in vivo* studies^{8,19-23}. Specific β adrenergic receptor polymorphisms with known *in vitro* functional effects are associated with clinical phenotypes in asthma and heart failure^{19,22,24-28}. Some of these polymorphisms also appear to have an impact on lung fluid balance. In a study carried out among human volunteers, subjects carrying the GG genotype at the Arg16Gly polymorphism had less lung fluid accumulation compared to those with the AA genotype, following an isotonic fluid challenge²⁹. An association between SNPs in the β adrenergic genes and lung allograft utilization would reinforce the importance of β-adrenergic dependent mechanisms in clearance of pulmonary edema and might suggest a role for β-agonist use during donor management. Therefore, we hypothesized that specific SNPs in the β adrenergic genes with previously characterized functional effects would be associated with differing rates of donor lung utilization because of the potential effect of these polymorphisms on the rates of alveolar fluid clearance, pulmonary edema and oxygenation.

METHODS

Subjects

The study population was a cohort of consecutive organ donors managed by the California Transplant Donor Network (CTDN, Oakland, CA) from 2001–2005. Treating physicians at hospitals throughout the region identified potential brain dead organ donors and consent for organ donation and collection of biological materials was obtained from family members or next-of-kin. CTDN staff subsequently assumed management of the organ donor, and management was conducted according to protocols developed by CTDN, which include treatment with steroids, inhaled beta agonists (albuterol 2.5 mg every 4 hours), and loop diuretics in addition to mechanical ventilation. Study subjects had to have available stored DNA samples and consent for at least one organ to be donated. The Committee on Human Research at the University of California San Francisco approved this study.

Clinical Data

Upon assumption of donor management the CTDN staff collected comprehensive data on the donors including demographic variables, blood gases and chest radiographs. Chest radiographs were evaluated by radiologists and based on the radiologist's report, the coordinators assigned each lung a score from 0–3 with 0 signifying no infiltrates, 1 signifying minor infiltrates limited to one quadrant only, 2 signifying infiltrates involving more than one quadrant and 3 representing complete consolidation of the lung.

Polymorphism Selection and Genotyping

Four β -adrenergic receptor polymorphisms Arg389Gly (rs1801253), Ser49Gly (rs1801252), Gly16Arg (rs1042713), Gln27Glu (rs1042714) in the two β adrenergic receptor genes, previously reported to be functionally significant were chosen for analysis^{8,19–23}. Genomic DNA was isolated from blood or spleen of deceased donors using commercial kits (QIAmp DNA kits, Valencia, CA) at the Immunogenetics and Transplantation Laboratory at the University of California, San Francisco. Genotyping was carried out using the template-directed dye-terminator incorporation assay with fluorescence polarization detection (FP-TDI) method using the AcycloPrime-FP kit (Perkin-Elmer)³⁰; for the rs1801253 SNP, the TaqMan based allelic discrimination method³¹ was used (Applied Biosystems Assay ID: C_8898494_10). Investigators who performed the genotyping were blinded to the clinical information.

Data Analysis

The primary outcome variable was lung allograft utilization. Secondary outcome variables were the chest radiograph score and the PaO₂/FiO₂ ratio at the conclusion of donor management.

We assessed genotypic effects at single SNP loci using the chi-square test to compare the effect of genotypes on the rates of lung allograft utilization. In the univariate analysis of individual SNP genotypes, additive, dominant and recessive models were considered. Multivariable regression models were created to quantify the association between each polymorphism and the outcomes. SNPs individually associated with (Ser49Gly, Gly16Arg) or having a trend (Arg389Gly) towards increased lung allograft utilization were tested jointly to evaluate the potentially additive effects of genotypes on lung allograft utilization using non parametric trend tests. Statistical analyses were performed with Stata (version 9, StataCorp LP, College Station, TX). A p-value of less than 0.05 was considered statistically significant.

Finally, we conducted an exploratory analysis testing for haplotype effects. Haplotype frequencies for each gene were imputed from un-phased genotype data, within each self reported ethnic group, using Haploview (Broad Institute, Boston, MA). The association of the imputed haplotypes with the primary endpoint was assessed in a case control analysis using PLINK (Broad Institute, Boston, MA).

RESULTS

Subjects

A total of 951 organ donors out of a total of 1223 managed by the CTDN from 2001–2005 had stored DNA available for analysis and defined the study cohort. The clinical characteristics of the cohort are shown in Table 1.

Association of Clinical Characteristics with Lung Utilization

Out of a total of 951 potential donors, lungs allografts were used from 325 individuals, yielding an overall lung utilization rate of 34%. Both lungs were transplanted together from 216 (23%), both single lungs were transplanted from 47 (5%), only one single lung was transplanted from 44 (5%), and heart and lungs were transplanted enbloc from 18 (2%) donors.

The mean PaO₂/FiO₂ at the conclusion of donor management was 347 ± 129. Among donors that had a PaO₂/FiO₂ of ≥ 300 at the end of donor management, the lung allograft utilization was 51%, whereas among donors with PaO₂/FiO₂ of ≥ 400, the lung allograft utilization was 65% (p=0.001).

At the completion of donor management, the chest radiographs were reported as infiltrate-free (score =0) in 299 donors. The rate of successful lung allograft utilization among this group of donors was 64%. The chest radiograph score was 0 in 299 donors, 1 in 193 donors, and ≥ 2 in 338 donors, with an allograft utilization rate of 64%, 40%, and 17%, respectively (p=0.001).

Association of lung allograft utilization with beta-adrenergic receptor SNP genotype

The distribution of genotypes for the four adrenergic receptor polymorphisms is shown in Table 2. The GG genotype of the β1 Ser49Gly SNP (p= 0.03) and the GG genotype of the β2 Gly16Arg SNP (p=0.03) were associated with increased rates of lung allograft utilization. The CC genotype of the β1 Arg389Gly SNP showed a strong trend towards increased utilization, but this did not reach statistical significance (p=0.09). The rates of successful lung allograft utilization for donors stratified by genotypes and the results of multivariate regression analysis to adjust for potential confounding by age, gender race and cause of death are shown in Table 3.

Combined Analysis

We carried out a combined analysis of the first three polymorphisms that were individually associated with (Ser49Gly, Gly16Arg), or showed a strong trend (Arg389Gly) towards association with increased lung allograft utilization. Donors that carried 0–1 associated genotypes at the three loci had a lung allograft utilization rate of 33%, donors that carried two associated genotypes at the three loci had a lung allograft utilization of 44%, whereas the donors that carried all three associated genotypes at the three loci had a lung allograft utilization of 58% (p=0.009) (Figure 1). The association of increased allograft utilization persisted when analysis was limited to Caucasians only (p=0.05).

We also carried out a combined analysis of just the 2 SNPs (Ser49Gly and Gly16Arg) that had a statistically significant association with lung allograft utilization and found increasing lung allograft utilization with increasing number of favorable genotypes. The lung graft utilization was 32%, 40% and 58% in patients carrying none, one and two favorable genotypes respectively (p= 0.01).

After stratification by race and ethnicity, there was a minor variation in lung allograft utilization rates among the various ethnic groups, but there was a consistent stepwise increase in lung allograft utilization with increasing number of favorable genotypes in each racial ethnic subgroup suggesting that the beneficial effects of the favorable genotypes are consistent across all racial and ethnic subgroups.

In order to test for a relationship between oxygenation and genotypes, we compared the percentage of donors achieving a PaO₂/FiO₂ threshold of ≥ 400 at the conclusion of donor

management among donors stratified by the number of favorable genotypes. There was a stepwise increase in the percentage of donors who met the threshold of a $\text{PaO}_2/\text{FiO}_2 \geq 400$ with increasing number of associated genotypes ($p = 0.03$) (Figure 2), indicating that these genotypes were also associated with better oxygenation. We also compared oxygenation shortly after brain death at the time of first ABG on the assumption of management by CTDN to the last ABG at the conclusion of donor management and before organ harvest. The mean PF ratio among patients stratified by number of favorable genotypes was 306 ± 145 , 311 ± 135 and 367 ± 156 at the beginning of donor management and 342 ± 128 , 356 ± 128 and 443 ± 106 at the end of donor management respectively for donors carrying 0–1, 2 or 3 favorable genotypes. Therefore, during the donor management the mean PF ratio increased by 36, 45 and 76 respectively in patients carrying 0–1, 2 or 3 genotypes respectively. Similarly, the percent of donors reaching the threshold of $\text{PaO}_2/\text{FiO}_2$ ratio of ≥ 400 increased from 28% to 35%, 32% to 41% and 50 to 67% respectively among donors carrying 0–1, 2 or 3 favorable genotypes suggesting greater benefit on oxygenation during donor management with increasing number of favorable genotypes.

Finally, we compared the chest radiograph scores at the completion of donor management and prior to transplantation among donors stratified by the number of the associated genotypes. There was a decrease in the chest radiograph score with increasing number of associated genotypes ($p = 0.001$) (Figure 3) suggesting that these genotypes were associated with less extensive infiltrates and probably less pulmonary edema. A comparison of chest radiograph scores obtained at the beginning of donor management following declaration of brain death with radiographs obtained at the completion of donor management just before the end of organ harvest revealed that there was a greater decrease in the chest radiograph score (hence more clearance of infiltrates) with an increasing number of these genotypes. The change in mean radiograph scores was 0.1 (1.46 to 1.36), 0.19 (1.35 to 1.16) and 0.46 (1.27 to 0.8) among donors carrying 0–1, 2 or 3 associated genotypes respectively.

DISCUSSION

In this study of 951 potential organ donors, we found that the GG genotype of the Ser49Gly SNP in the $\beta 1$ adrenergic receptor gene, and the GG genotype of the Gly16Arg SNP in the $\beta 2$ adrenergic receptor gene are independently associated with increased lung allograft utilization from eligible donors. We also found that a combination of three favorable (associated with higher utilization) genotypes at three SNPs, the Ser49Gly SNP and Arg 389Gly SNP both in the $\beta 1$ adrenergic receptor gene, and the Gly16Arg SNP in the $\beta 2$ adrenergic receptor gene is associated with higher rates of lung allograft utilization with increasing number of genotypes in a stepwise manner. This increased utilization rate is also associated with improved oxygenation and decreased chest radiograph infiltrates with an increasing number of these genotypes.

In the present study, as has been reported previously, better oxygenation in the donor lungs was associated with increased allograft utilization. Improved oxygenation was probably related to less pulmonary edema in donors with the favorable genotypes, as suggested by the chest radiograph scores at the end of donor management. Recent data from Ware and colleagues suggests that clinical interpretation of chest radiographs can provide a reasonable assessment of the degree of pulmonary edema in donor lungs³². On comparison of the radiographs obtained at the beginning of assumption of donor management to radiographs obtained at the end of donor management, we further noted that not only did patients with the genotypes associated with utilization have fewer chest radiograph infiltrates at the end of donor management, but that during donor management there was a increasing improvement in chest radiographs among donors with the increasing number of the associated genotypes. On comparison of the PF ratio obtained shortly after brain death at the beginning of donor

management to the PF ratio at the end of donor management and prior to organ harvest, we observed that there was a greater improvement in the PF ratio with increasing number of favorable genotypes. It is possible that the improvement in oxygenation and the chest radiographs that occurred during donor management was a result of clearance of neurogenic edema that may have accompanied brain death.

Genetic variants in β adrenergic receptor genes have been demonstrated to have functional effects *in vitro* and *in vivo* studies. *In vitro* studies have revealed that β adrenergic receptor SNPs are associated with functional properties including higher basal and agonist-stimulated adenylate cyclase activity, greater agonist-promoted binding²¹, and greater agonist-promoted down-regulation^{20,25}. Clinical studies have demonstrated that β adrenergic receptor SNPs are associated with clinical phenotypes consistent with enhanced β adrenergic receptor stimulation. Mothers with the GG genotype of the Arg16Gly SNP in the β 2 adrenergic receptor received significantly less ephedrine than mothers with AA and AG genotypes during anesthesia for cesarean sections⁴³. These agonist β adrenergic effects are also reported in situations without the use of exogenous catecholamines. In a clinical study carried out on normal human volunteers, subjects with the GG genotype of the Arg16Gly SNP in the β 2 adrenergic receptor accumulated less lung water than individuals with the AA genotype, in response to a fluid challenge with isotonic saline²⁹. These results suggest that these specific β adrenergic receptor SNPs are associated with clinical phenotypes compatible with their β adrenergic agonist effects.

β adrenergic stimulation increases sodium transport across the alveolar epithelium by increasing intracellular cAMP, leading to an increased probability of opening of the apical sodium channel¹¹ and increased basolateral sodium extrusion by increasing Na⁺-K⁺-ATPase activity^{33–35}. This process can accelerate the rate of alveolar fluid clearance and reduce pulmonary edema in sheep, dogs, rats, mice and the *ex vivo* human lung^{11,36–38}. Importantly, these effects have been demonstrated in the normal lung⁴, the acutely injured lung^{12–15} and in models of hydrostatic pulmonary edema^{11,16,39}. In addition to direct effects on alveolar fluid reabsorption, β adrenergic receptor stimulation also has anti-inflammatory, endothelial and lung epithelial protective effects that may be beneficial in the brain dead organ donor^{40,41,42}.

The strengths of the current study include the relatively large cohort of donors, careful collection of clinical data, complete ascertainment of the primary outcome and the high rates of successful genotyping. The study also has some limitations. The cohort subjects were of diverse race and ethnicity. However, there was no change in our findings when we adjusted for race, and our results were consistent in stratified analyses in all major racial and ethnic groups. In addition the association of lung allograft utilization with favorable genotypes persisted when analysis was limited to just the Caucasian race. Finally there was no difference in lung utilization by race. Another limitation may be the lack of adjustment for the multiple SNPs tested. We did not correct the individual SNPs for multiple comparisons, since our *pre hoc* hypothesis was based on the biological plausibility of the SNPs studied. It is therefore unlikely that our results are due to a Type 1 error alone. However, as is true for all genetic epidemiology studies, these results need to be confirmed in a validation cohort.

Even though the Arg389Gly SNP individually did not have a statistically significant association with lung allograft utilization, we included it in the combined analysis based on the previously well-characterized functional effects of this SNP and the trend towards increased lung allograft utilization in our cohort. However, in analysis excluding this SNP, we found that increased lung allograft utilization with the increasing number of favorable genotypes still persisted in the model excluding this SNP.

In conclusion, two β adrenergic receptor SNPs were individually associated with increased lung allograft utilization from eligible donors, and a combination of three favorable genotypes in β adrenergic receptor SNPs was associated with higher rates of lung allograft utilization. The increased utilization is probably related to increased clearance of pulmonary edema and improved oxygenation in patients with the favorable genotypes. These results reinforce the importance of β -adrenergic dependent mechanisms in clearance of pulmonary edema and suggest that β -agonists may have a role during donor management in increasing lung donor utilization by improving oxygenation and the resolution of pulmonary edema.

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AS, JZ, KDL, KK, MAM conceived the study, participated in data collection, data analysis and writing the manuscript. RM, LAB, VH, ML, MC participated in data collection, data cleaning and revising the manuscript. LP and AP designed the assays carried out the genotyping and helped with writing the manuscript.

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Figure 1.

The percentage of lung utilization stratified by the number of associated genotypes. The height of the bar represents the percent lung allograft utilization for each group. There was an increase in the percentage of lungs utilized as the number of genotypes present increases. 33% for 0–1, 44% for 2, and 58% for 3 ($p=.009$).

Figure 2. Percentage of donors with PaO₂/FiO₂ > 400 stratified by the number of associated genotypes. The height of each bar represents the percent donors with PaO₂/FiO₂ values > 400 in each group. There is an increase in percentage of donors meeting the PaO₂/FiO₂ threshold values > 400 with an increase in number of genotypes (p=.03).

Figure 3.

Chest radiograph scores stratified by the number of associated genotypes. The height of each bar represents the mean value for each group. There was a significant decrease ($p=.001$) in the chest radiograph scores with an increase in the number of genotypes.

Table 1

Baseline characteristics of 951 organ donor

Donors (N)	951
Age in years (mean $\pm$ SD)	39 $\pm$ 18
Female (%)	40%
Race/Ethnicity (%)	
Caucasian	55%
African-American	10%
Hispanic	26%
Asian	9%
Other	1%
Cause of death (%)	
Anoxia	10%
Cerebrovascular Accident	48%
Head Trauma	41%
CNS Tumor	1%
Other	1%

Table 2

SNPs genotyped and their allele frequencies

SNP	dbSNP ID	Alleles	Minor Allele Frequencies	Minor Allele Frequencies		HW p value	Genotyped
				Overall	Blacks		
					Whites	Blacks	
61 Arg389Gly	rs1801253	C:G	0.24	0.26	0.32	1.00	0.68
61 Ser49Gly	rs1801252	A:G	0.17	0.11	0.25	0.58	0.15
62 Gly16Arg	rs1042713	G:A	0.40	0.38	0.42	1.00	0.10
62 Gln27Glu	rs1042714	C:G	0.31	0.40	0.19	0.35	1.00
							98.6%
							94.2%
							97.9%
							97.8%

Table 3

Lung allograft utilization by genotype

SNP	Genotypes	N	Allograft Utilization	p	Univariate OR	p	Multivariate* OR	p
81 Arg389Gly	CC	535	37%	0.09	1.3 (0.96–1.7)	0.09	1.24 (0.96–1.6)	0.10
	GG/GC	380	32%					
81 Ser49Gly	GG	31	55%	0.02	2.2 (1.1–4.6)	0.03	2.3 (1.1–4.8)	0.03
	AG/AA	841	35%					
82 Gly16Arg	GG	330	39%	0.03	1.3 (1.02–1.8)	0.03	1.4 (1.03–1.9)	0.03
	AA/AG	580	32%					
82 Gln27Glu	GG	809	36%	0.30	0.9 (0.8–1.1)	0.50	0.8 (0.5–1.3)	0.40
	CC/CG	99	31%					

OR=Odds ratio

* Multivariate model adjusted for age, gender, race and cause of death