CARDIAC AND PULMONARY REPLACEMENT

REEVALUATING THE SIGNIFICANCE OF PULMONARY HYPERTENSION BEFORE CARDIAC TRANSPLANTATION: DETERMINATION OF OPTIMAL THRESHOLDS AND QUANTIFICATION OF THE EFFECT OF REVERSIBILITY ON PERIOPERATIVE MORTALITY

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Objectives: **Right-sided circulatory failure resulting from severe preoperative pulmonary hypertension is a source of mortality early after cardiac transplantation. We undertook the present study (1) to analyze the association of elevated pulmonary hemodynamic indices with 30-day mortality, (2) to define threshold ranges associated with an increase in 30-day mortality, and (3) to evaluate the effect of vasodilator reversibility on 30-day mortality.** *Methods:* **Preoperative hemodynamic profiles were evaluated in 476 patients who ultimately underwent cardiac transplantation. From these data, receiver-operating characteristic curves and stratum-specific likelihood ratios were generated to compare the efficacy of each hemodynamic index. A subset of patients with elevated hemodynamic profiles at baseline additionally underwent graded sodium nitroprusside infusion.** *Results:* **Analysis of receiver-operating characteristic curves demonstrated no statistically significant difference among the indices in their ability to predict 30-day mortality. Analysis of stratum-specific likelihood ratios demonstrated three risk strata that correlated with significant differences in 30-day mortality, with patients in the high-risk stratum having a 3.2 to 4.4 increase in odds of 30-day mortality when compared with patients in the low-risk stratum. Nitroprusside data demonstrated that although 30-day mortality was better in patients with reversible pulmonary hypertension than in those with fixed pulmonary hypertension, it was not comparable with that of patients without pulmonary hypertension at baseline.** *Conclusions:* **Candidates for cardiac transplantation may be categorized into three risk strata on the basis of their preoperative pulmonary hemodynamic profile; the association of this profile with 30-day mortality is not linear. Reversibility with nitroprusside appears to confer some improvement in the risk of 30-day mortality, but it may not eliminate the risk entirely. (J Thorac Cardiovasc Surg 1997;114:627-34)**

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Despite advances in perioperative management, right-sided circulatory failure remains a significant source of morbidity and mortality early after cardiac transplantation.[1-3] Previous investigators have suggested that severe pulmonary hypertension can result in right-sided circulatory failure because of a marked increase in afterload presented abruptly to the donor right ventricle.[4-7] Thus preoperative pulmonary hypertension currently is a relative con-

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traindication to cardiac transplantation at many centers worldwide.[8, 9]

Transplant physicians traditionally have placed great emphasis on calculated estimates of pulmonary hypertension (pulmonary vascular resistance [PVR], pulmonary vascular resistance index [PVRI] and transpulmonary gradient [TPG]) in the preoperative evaluation of candidates for cardiac transplantation. However, since the first reports documenting a relationship between an elevated PVR and the risk of death from acute right ventricular failure, substantial controversy has persisted regarding the power of individual hemodynamic indices to predict perioperative mortality accurately.[1-7] Some investigators have additionally suggested that patients may be subdivided on the basis of "fixed" or "reactive" components to their pulmonary hypertension, the relative proportions of which may be determined by the use of pulmonary vasodilator therapy such as sodium nitroprusside.[10]

Receiver-operating characteristic (ROC) curves have enjoyed increasing clinical application in the assessment of the predictive ability of a given test. This analysis is useful when a test result is represented on a continuous scale and more than one possible threshold value exists to define a positive and negative result.[11] The area under the ROC curve reflects an estimate of the overall accuracy of a given test over its entire range of values and thereby represents a means by which the discrimination of individual tests may be compared.[12] Stratum-specific likelihood ratios (SSLRs), derived from data with which ROC curves are constructed, may be used to determine threshold values that more precisely distinguish cohorts of patients with different outcomes.[13]

We retrospectively analyzed the preoperative cardiac catheterization data from patients undergoing transplantation at our institution between 1983 and 1994 to determine whether an association exists between individual elevated preoperative pulmonary hemodynamic indices and 30-day all-cause mortality. Second, using ROC curve analysis, we compared the relative ability of each individual index to predict perioperative mortality to determine whether any individual index is superior in its predictive ability. Third, from these ROC curves we derived SSLRs to delineate better threshold ranges that define an "elevated" preoperative hemodynamic profile. Last, we evaluated a subgroup of patients who underwent vasodilator "challenge" to compare the 30-day mortality of patients who had fixed pulmonary hypertension with that of both patients with reversible pulmonary hypertension and patients in the entire cohort who had no preoperative pulmonary hypertension.

Methods

Patient population. From April 1983 through June 1994, a total of 671 patients underwent heart transplant procedures at the Columbia-Presbyterian Medical Center. For 476 (70.9%) of these patients, complete preoperative hemodynamic data were available from which to evaluate the association between perioperative mortality and the calculated pulmonary hemodynamic indices PVR, PVRI, and TPG. All patients received cyclosporine-based immunosuppression (INN: ciclosporin), and 30-day all-cause mortality was used as the end point of the study. Presumed causes of death were obtained by a retrospective review of the clinical data by an investigator blinded to the preoperative hemodynamic assessment. Patients excluded from transplantation (and this cohort) on the basis of pulmonary hypertension were those with a fixed PVRI of 6.0 WU/m^2 or greater.

Cardiac catheterization. Right heart catheterization was performed with the use of a balloon-tipped flow-directed catheter. For those patients with multiple cardiac catheterization procedures, the values obtained closest to the time of transplantation were chosen for further analysis. Hemodynamic parameters including right atrial, pulmonary artery, and pulmonary capillary wedge pressures were obtained according to standard clinical methods. Body surface area was calculated from height and weight, cardiac output was measured by thermodilution with iced injection solution, cardiac index was calculated from cardiac output and body surface area, and pulmonary hemodynamic indices were calculated by means of the following equations:

$$\text{PVR (WU)} = \frac{(\text{PA mean} - \text{PCW})}{\text{CO}}$$

$$\text{PVRI (WU} \cdot \text{m}^2) = \frac{(\text{PA mean} - \text{PCW})}{\text{CI}} = \text{PVR} \cdot \text{BSA}$$

$$\text{TPG (mm Hg)} = \text{PA mean} - \text{PCW}$$

where PA is pulmonary artery pressure, PCW is pulmonary capillary wedge pressure, CO is cardiac output, CI is cardiac index, and BSA is body surface area.

Nitroprusside protocol. Complete catheterization data obtained before and after the standard graded administration of sodium nitroprusside were available for 119 patients with abnormal pulmonary hemodynamics (as defined by a PVR $\geq$ 2.5 WU or a systolic PA pressure $\geq$ 50 mm Hg). Intravenous nitroprusside therapy was begun at a dose of approximately 25 μg/min. Hemodynamic measurements were obtained at rest before the administration of nitroprusside and then were monitored at regular intervals. The dose of nitroprusside was increased rapidly until there was (1) a decrease in PVR below 2.0 WU, (2) a decrease in PA systolic pressure below 50 mm Hg, or (3) a decrease in mean blood pressure below 65 mm Hg.

Table I. *Demographic profile of the entire cohort and of 30-day survivors and nonsurvivors*

	Entire cohort (n = 476)	*Nonsurvivors (n = 47)*	*Survivors (n = 429)*	*p Value*
Sex				
Male	379 (79.6%)	35 (74.5%)	344 (82.0%)	NS*
Female	97 (20.4%)	12 (25.5%)	85 (19.8%)	
Age (mean ± SD)	47.8 ± 13.3	49.2 ± 12.9	47.6 ± 13.3	NS
Range	2.1-68.9	15.7-67.4	2.1-68.9	
Indication for transplantation				
Coronary artery disease	179 (37.6%)	13 (27.7%)	166 (38.7%)	NS
Idiopathic cardiomyopathy	252 (52.9%)	26 (55.3%)	266 (52.7%)	
Viral cardiomyopathy	17 (3.6%)	5 (10.6%)	12 (2.8%)	
Congenital heart disease	10 (2.1%)	3 (6.4%)	1 (0.2%)	
Other	18 (3.8%)	0 (0%)	24 (5.6%)	

NS, Not significant; *SD,* standard deviation.
*$p > 0.05$ for comparison of survivors versus nonsurvivors for the given parameter.

Table II. *Baseline hemodynamic data for the entire cohort and of 30-day survivors and nonsurvivors*

	Entire cohort (n = 476)	*Nonsurvivors (n = 47)*	*Survivors (n = 429)*	*p Value**	*Difference of mean*	*95% CI*
PA mean	31.5 ± 11.4	35.9 ± 10.3	31.0 ± 11.4	0.005	−4.9	−8.3-−1.4
PCW	20.9 ± 9.0	22.3 ± 8.0	20.7 ± 9.6	0.27	−1.6	−4.4-1.2
Cardiac output	4.0 ± 1.4	4.0 ± 1.4	3.9 ± 1.4	0.64	−0.1	−0.5-0.3
Calculated indices						
PVR	3.1 ± 2.1	3.8 ± 2.0	3.0 ± 2.1	0.010	−0.8	−1.4-−0.17
PVRI	5.5 ± 3.7	6.9 ± 3.5	3.4 ± 3.6	0.0001	−3.5	−4.6-−2.4
TPG	10.7 ± 5.9	13.5 ± 6.1	10.4 ± 5.8	0.0006	−3.1	−4.9-−1.3

PA, Pulmonary artery pressure; *PCW,* pulmonary capillary wedge pressure.
**p* Value reflects Student's *t* test for unpaired samples comparing survivors versus nonsurvivors.

Statistics

ROC curves. χ^2 Analysis and Student's *t* tests were used to compare categoric and continuous data from 30-day survivors and nonsurvivors, without adjustment for multiple comparisons. ROC curves were generated by plotting sensitivity on the ordinate and 1-specificity on the abscissa with the use of individual pulmonary hemodynamic indices for the prediction of 30-day mortality.[11, 12] Curves were generated with the use of data cut-points at regular intervals. The area under each ROC curve was derived from the Wilcoxon statistics.[11]

A logistic regression analysis was also performed with 30-day survival as the dependent variable and with PVR, PVRI, and TPG as independent variables. The score χ^2 statistic associated with each independent variable describes the relative strength of the relationship between each hemodynamic variable and 30-day survival; the variable with the highest score χ^2 would be selected for model inclusion in a stepwise regression. The overall strength of each model is best described by the c statistic, which is the probability that a patient with an elevated PVR (or PVRI or TPG) will have a greater predicted probability of 30-day mortality than a randomly selected patient with a less elevated PVR (or PVRI or TPG). This statistic is mathematically identical to the area under the ROC curve.

SSLRs. SSLRs and 95% confidence intervals were generated for 30-day all-cause mortality, for strata of PVR, PVRI, and TPG, with the use of regular increments specific to the indices (PVR: 1 WU increments; PVRI: 1 WU · m^2 increments; TPG: 1 mm Hg increments). SSLRs were defined with the use of the following formula[13]:

$$\text{SSLR} = \frac{\frac{\chi_{1g}}{\eta_1}}{\frac{\chi_{0g}}{\eta_0}}$$

where χ_{1g} = the number of persons who died at less than 30 days' follow-up after transplantation in the gth stratum of the given pulmonary hemodynamic index, η_1 = the total number of persons who died at less than 30 days' follow-up after transplantation, χ_{0g} = the number of persons who are alive at 30 days' follow-up or more after transplantation in the gth stratum of the given pulmonary hemodynamic index, η_0 = the total number of persons who are alive at 30 days' follow-up or more after transplantation, and where χ_{1g}/η_1 = the probability of being in the gth stratum of a given pulmonary hemodynamic index given that one has died at less than 30 days' follow-up after transplantation and χ_{0g}/η_0 = the probability of being

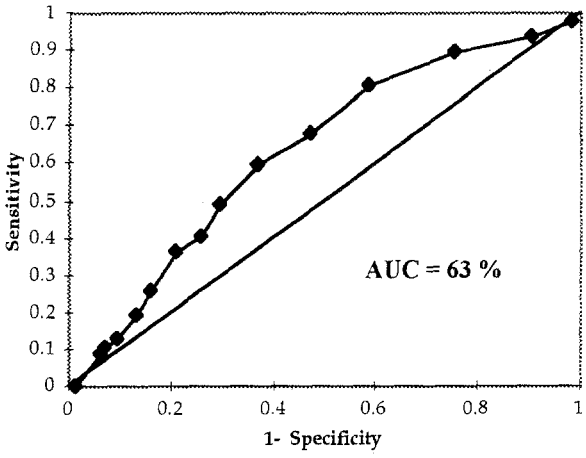

Fig. 1. ROC curves and the associated area under the curve *(AUC)* for PVR.

in the gth stratum of a given pulmonary hemodynamic index given that one is alive at 30 days' follow-up or more after transplantation.

Ninety-five percent confidence intervals were calculated as follows:

$$SSLR_u, SSLR_L = e^{lnSSLR \pm 1.96 \sqrt{Var(lnSSLR)}}$$

where

$$Var(lnSSLR) = \frac{1}{\chi_{1g} + 0.5} - \frac{1}{\eta_1 + 0.5} + \frac{1}{\chi_{0g} + 0.5} - \frac{1}{\eta_0 + 0.5}$$

By combining adjacent strata with statistically indistinct SSLRs (i.e., those with overlapping 95% confidence intervals), we determined threshold values for the three pulmonary hemodynamic indices. When only two statistically distinct strata could be formed, but the data suggested an intermediate risk strata, three strata were formed. Statistical significance was defined as a p value less than 0.05. Survival analysis and ROC curve area computations were performed with SAS (version 6.09) PROC LIFETEST and PROC NPAR1WAY (SAS Institute, Inc., Cary, N.C.). SSLRs were calculated with the use of a previously published macro for Microsoft Excel spreadsheets (Microsoft Corporation, Redmond, Wash.).[13] Thus, for patients with pulmonary hemodynamic indices in a given range, the SSLR represents the relative odds of death when compared with the whole cohort.

Results

Demographics. The demographic profile of the entire cohort and, separately, for 30-day survivors and nonsurvivors studied is depicted in Table I. No statistically significant differences were detected between survivors and nonsurvivors on the basis of age, sex, or indication for transplantation. Baseline hemodynamic data evaluated in the preoperative assessments of the cohorts are depicted in Table II. Forty-seven patients died during the 30-day perioperative period. Presumed causes of death for patients in this cohort are detailed in Table III.

Table III. *Presumed causes of 30-day mortality (n = 47)*

Cause	*No.*
Primary graft failure	13
Acute right-sided circulatory failure	8
Infection/sepsis	7
Rejection	6
Embolic episode	4
Multisystem organ failure	2
Hemorrhage	2
Other	5

ROC curves. The score χ^2 statistics associated with each hemodynamic variable were 5.29 for PVR ($p = 0.022$), 2.89 for PVRI ($p = 0.089$), and 12.10 for TPG ($p < 0.001$). ROC curves and the corresponding area under the curve for each of the three hemodynamic indices are shown in Figs. 1 to 3. ROC curves and the corresponding areas under the curve ± standard deviation for each of the three hemodynamic indices were 0.63 ± 0.04 (PVR), 0.62 ± 0.04 (PVRI), and 0.67 ± 0.05 (TPG). These areas were not statistically significantly different.

SSLRs. Data from SSLR analysis of the generated ROC curves are represented in Table IV. As shown, data for each pulmonary hemodynamic index could best be described as distributed over low, average, and high risk strata. SSLRs were significantly different for high versus low strata for PVR, PVRI, and TPG ($p < 0.05$).

Baseline strata. With the use of a χ^2 analysis and the aforementioned threshold ranges to define risk strata for the cohort, we reviewed the data from the entire cohort to evaluate their associations with 30-day mortality. These data are also represented in Table IV.

Nitroprusside challenge. With the use of the aforementioned risk strata for data evaluation, the subcohort of patients undergoing nitroprusside challenge was distributed into groups of patients who had pulmonary hemodynamic indices that were in the higher risk strata at baseline and either nonreversible (fixed) or reversible (reactive). *Reversibility* was defined differently for the purposes of two separate analyses (liberal and stringent criteria). For the *liberal* criteria (group B1), reversibility represented a decrease with nitroprusside therapy from

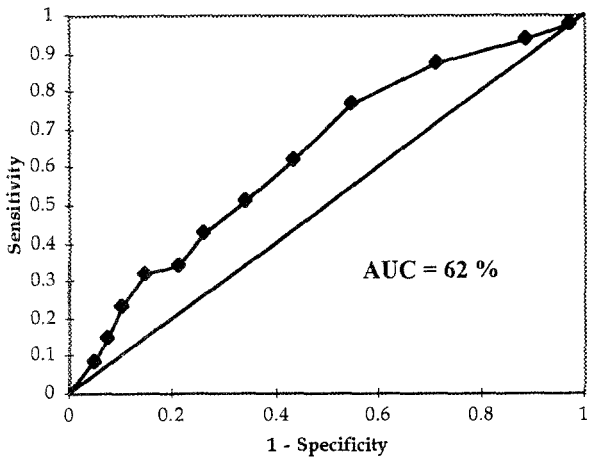

Fig. 2. ROC curves and the associated area under the curve *(AUC)* for the PVRI.

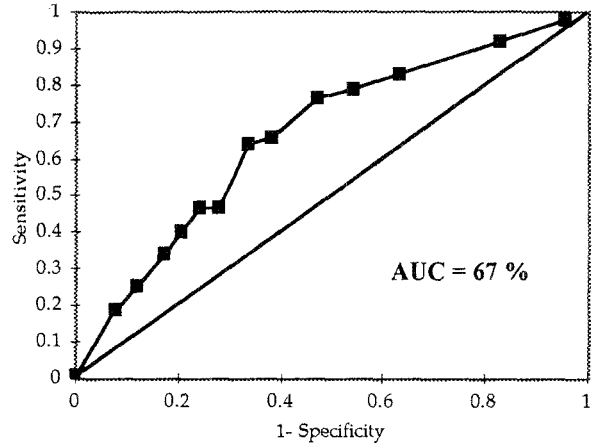

Fig. 3. ROC curves and the associated area under the curve *(AUC)* for the TPG.

the high or average risk strata at baseline to the low risk stratum. Those patients in the corresponding *fixed* category (group A1) had hemodynamic indices that remained at the high or average risk strata with the administration of nitroprusside.

With the use of stringent criteria (group B2), reversibility represented a decrease with nitroprusside therapy from the high risk stratum at baseline to the low risk stratum. Those patients in the corresponding fixed category (group A2) had either no significant change with nitroprusside therapy from the high risk stratum or had a reduction from the high to the average risk stratum only. These data are depicted in Tables V and VI.

Discussion

Right-sided circulatory failure and its associated morbidity remains a substantial source of perioperative mortality for recipients of cardiac transplants.[1-7] Because of this widely recognized association, extreme preoperative pulmonary hypertension (as evidenced by elevated pulmonary hemodynamic indices) has remained a contraindication to cardiac transplantation at many transplant centers worldwide. Despite this, significant controversy persists regarding which of the three major calculated indices (PVR, PVRI, or TPG) represents the most accurate predictor of perioperative mortality.

Proponents of the use of the TPG have suggested that the PVR (and thus the PVRI), in using cardiac output in its calculation, may be unreliable because of inherent inaccuracies in the measurement of cardiac output by thermodilution, particularly at low cardiac outputs.[14] The TPG, it is argued, is flow-independent and thus may better reflect resistance to flow across the pulmonary bed.[5] In contrast, others have argued that the gradient across the pulmonary bed itself is flow-dependent and thus requires that total flow (or cardiac output) be considered in its interpretation. Additionally, Addonizio and associates[15] have argued that the "indexed" PVR may more accurately estimate the degree of pulmonary resistance because it better accounts for variations in body size (especially important in the pediatric population).

ROC curves may be plotted as a graphic representation of the relationship between sensitivity and specificity (the true-positive rate and the false-positive rate). The area under the ROC curve, or the probability that a randomly selected patient with an abnormal result will have a greater predicted probability of a given outcome than a randomly selected patient with a normal result, may then be calculated to compare the overall discriminative accuracy of each hemodynamic index. Our data suggested that none of the indices was superior in its discrimination of perioperative mortality, a finding perhaps not surprising in that PVR and PVRI are derived from TPG.

With any test whose results are represented on a continuous scale, the clinician hopes to optimize both sensitivity and specificity. ROC curves graphically depict the relationship between the true- and false-positive rates and thus are an excellent method to determine the overall discriminative accuracy of a test measured on a continuous scale. SSLRs, derived

Table IV. *Data from SSLR evaluation of ROC curve analysis*

	Baseline strata		
	Low risk	*Average risk*	*High risk*
PVR			
Risk stratum range	<2 WU	2-3 WU	>3 WU
SSLR*	0.46 (0.26-0.83)	0.97 (0.55-1.71)	1.62 (1.24-2.10)
30-Day mortality	9/177 (5.1%)†	10/94 (10.6%)	28/158 (17.7%)
PVRI			
Risk stratum range	<4 WU · m^2	4-7 WU · m^2	>7 WU · m^2
SSLR*	0.52 (0.30-0.87)	1.18 (0.78-1.79)	1.64 (1.14-2.37)
30-Day mortality	11/194 (5.7%)†§	16/124 (12.9%)	20/111 (18.0%)
TPG			
Risk stratum range	<10 mm Hg	10-14 mm Hg	>14 mm Hg
SSLR*	0.44 (0.27-0.74)	1.28 (0.81-2.03)	1.95 (1.38-2.75)
30-Day mortality	11/226 (4.9%)†‡	14/100 (14.0%)	22/103 (21.4%)

*$p < 0.05$, for comparison of SSLRs in high risk with low risk baseline strata groups (PVR = 0.04, PVRI = 0.05, and TPG = 0.02); data represented as SSLR (95% confidence interval).

†$p < 0.01$, for comparison of 30-day mortality in high risk with low risk baseline strata groups (PVR = 0.002, PVRI = 0.004, and TPG = 0.0001) (difference of mean, 95% confidence interval): PVR (12.6, 5.9 to 19.4), PVRI (12.3, 4.5 to 20.2), and TPG (16.5, 8.1 to 24.9).

‡$p = 0.02$, for comparison of 30-day mortality in low risk with average risk baseline strata groups for TPG (difference of mean, 95% confidence interval): PVR (5.5, −1.5 to 12.6), PVRI (7.2, 0.5 to 14.0), and TPG (9.1, 1.8 to 16.5).

§$p = 0.06$, for comparison of 30-day mortality in low risk with average risk baseline strata groups for PVRI (difference of mean, 95% confidence interval): PVR (7.1, −1.5 to 15.7), PVRI (5.1, −4.1 to 14.4), and TPG (7.4, −3.1 to 17.8).

Table V. *Thirty-day mortality rates for patients with fixed and reactive pulmonary hypertension in the vasodilator subcohort and for patients without pulmonary hypertension in the entire cohort*

	*Group A1: Fixed pulmonary hypertension, nitroprusside cohort**	*Group B1: Reactive pulmonary hypertension, nitroprusside cohort†*	*Group C: No pulmonary hypertension, entire cohort*
PVR	13/72 (18.1%)	6/25 (17.1%)	9/177 (5.1%)
PVRI	11/61 (18.0%)	7/45 (15.5%)	11/194 (5.7%)
TPG	15/70 (21.4%)	4/27 (14.8%)	11/226 (4.9%)

Group A1 not significantly different ($p > 0.05$) from group B1 for all three indices (PVR = 0.92, PVRI = 0.98, and TPG = 0.74) (difference of mean, 95% confidence interval): PVR (−0.9, −16.2 to 14.4), PVRI (−2.5, −16.8 to 11.8), and TPG (−6.6, −23.1 to 9.9).

Group B1 versus group C (PVR, $p = 0.05$; PVRI, $p = 0.08$; and TPG = 0.14) (difference of mean, 95% confidence interval): PVR (−12.1, −25.0 to 0.8), PVRI (9.9, −1.2 to 21.0), and TPG (−9.9, −23.6 to 3.7).

Group A1 versus group C (PVR, $p = 0.01$; PVRI, $p = 0.02$; and TPG, $p = 0.0004$) (difference of mean, 95% confidence interval): PVR (−13.0, −3.5 to 22.4), PVRI (12.4, 2.2 to 22.5), and TPG (−16.6, −26.6 to −6.5).

*High or average risk stratum at baseline; with nitroprusside there was either no change or a reduction to average stratum.

†High or average risk stratum at baseline; with nitroprusside there was a reduction to low risk stratum.

from these curves, reflect a powerful means by which accurate thresholds for these tests may be elucidated. The ability to combine strata on the basis of statistically indistinct adjacent SSLRs in our analysis not only helped to define different risk strata for associated mortality (rather than one arbitrarily defined threshold point, as had been historically used), but further refuted the notion of a continuous association between pulmonary hemodynamic indices and postoperative mortality. Our evaluation revealed three risk strata that, when applied to the entire cohort data, were associated with differences in 30-day mortality.

Some have suggested that patients may be subdivided further into those with fixed or reactive components to their pulmonary hypertension, the relative proportions of which may be elucidated with the use of pulmonary vasodilator therapy such as sodium nitroprusside.[10] Those patients with a high degree of reactivity to their pulmonary hypertension with this vasodilator challenge may have a large reversible component and, it is postulated, may subsequently have a perioperative mortality comparable with patients who have no preoperative pulmonary hypertension. Conversely, those patients whose pulmonary hypertension responds less well may have a larger fixed component that may adversely affect their posttransplantation outcome.

Table VI. *Thirty-day mortality rates for patients with fixed and "reactive" pulmonary hypertension in the vasodilator subcohort and for patients without pulmonary hypertension in the entire cohort based on stringent criteria of reversibility*

	*Group A2: Fixed pulmonary hypertension, nitroprusside cohort**	*Group B2: Reactive pulmonary hypertension, nitroprusside cohort†*	*Group C: No pulmonary hypertension, entire cohort*
PVR	12/62 (19.4%)	3/22 (13.6%)	9/177 (5.1%)
PVRI	9/46 (19.6%)	4/19 (21.1%)	11/194 (5.7%)
TPG	11/48 (22.9%)	2/15 (13.3%)	11/226 (4.9%)

Group A2 not significantly different ($p > 0.05$) from group B2 for all three indices (PVR = 0.32, PVRI = 0.91, and TPG = 0.85) (difference of mean, 95% confidence interval): PVR (−5.7, −23.1 to 11.7), PVRI (1.5, −20.1 to 23.1), and TPG (−9.6, −30.5 to 11.3).

Group B2 not significantly different ($p = 0.05$) from group C for all three indices (PVR = 0.85, PVRI = 0.08, and TPG = 0.47) (difference of mean, 95% confidence interval): PVR (8.6, −6.1 to 23.3), PVRI (−13.9, −25.8 to 2.0), and TPG (−8.5, −25.9 to 9.0).

Group A2 versus group C (PVR, $p = 0.01$; PVRI, $p = 0.02$; and TPG, $p = 0.001$) (difference of mean, 95% confidence interval): PVR (14.3, 3.9 to 24.6), PVRI (−15.4, −34.0 to 3.2), and TPG (−18.0, −30.3 to −5.8).

*High risk stratum at baseline; with nitroprusside there was either no change or a reduction to average risk stratum.

†High risk stratum at baseline; with nitroprusside there was a reduction to low risk stratum.

To evaluate the effect of reversibility on postoperative outcome, we reviewed data from a subcohort receiving vasodilator challenge whose pulmonary hemodynamic profile placed them in the higher risk strata at baseline. Because our previous data analysis (see Table IV) demonstrated no statistically significant difference in 30-day mortality between patients in the high and average risk strata, we initially defined *reversibility* (liberal criteria) as a decrement from *either* high or average risk strata at baseline to the low risk stratum with vasodilator therapy.

The conclusions from this data evaluation are threefold. First, those patients in the nitroprusside cohort with fixed pulmonary hypertension (group A1) had a nearly fourfold increase in their incidence of mortality when compared with those patients in the entire cohort without preoperative pulmonary hypertension (group C). Second, those patients with reversible hypertension (group B1) appeared to have a relative reduction in their 30-day mortality when compared with those patients with fixed hypertension (group A1). Finally, those patients with reversible hypertension (group B1) still had a marked increase in mortality when compared with patients in the entire cohort without preoperative pulmonary hypertension (group C). These data suggested that any reduction in 30-day mortality associated with reversibility was mild; 30-day mortality for patients with reversible hypertension was more comparable with that of patients with fixed pulmonary hypertension than with that of patients without pulmonary hypertension.

To establish whether a subcohort of patients existed for whom reversibility with vasodilator therapy had a more substantial impact on 30-day mortality, we proposed a more stringent criterion to define reversibility: a decrement from only the high risk stratum at baseline to the low risk stratum with nitroprusside (see Table VI). The conclusions from this analysis were less clear; only those in the fixed category (group A2) had a mortality rate that was statistically different from that of patients with no pulmonary hypertension at baseline (group C). The lack of statistical significance between groups A2 and B2 and groups B2 and C may reflect the small sample size of those patients who met the stringent criteria of reversibility (group B2). Although the mortality rate of those in group B2 appeared better than that of patients with fixed hypertension (group A2), it was still substantially higher than that of patients without pulmonary hypertension at baseline (group C). The power of this final analysis will require a larger cohort of patients to confirm these findings.

Our findings suggest that transplant physicians must continue to monitor patients in the early postoperative period for complications related to right-sided circulatory failure *despite* preoperative reversibility of pulmonary hemodynamic indices. We encourage other transplant groups to report their experience regarding the prognostic significance of preoperative reversibility in the hopes that these difficult and contentious issues may be resolved.

Limitations. In this study, we chose to consider the association between increased preoperative pulmonary hemodynamic indices and all-cause 30-day mortality. In light of the underlying pathophysiologic relationship between pulmonary hypertension

and right-sided circulatory failure, it could be argued that only death resulting from right-sided circulatory failure should have been used as the outcome measure. Our decision to use all-cause 30-day mortality as the outcome was based on the following considerations. A retrospective determination of the cause of death is prone to error, particularly in the perioperative cardiac transplant setting. Right-sided circulatory failure may have contributed substantially to some patient deaths for which other causes were assigned retrospectively. For example, patients with right-sided circulatory failure were likely to have remained intubated and to have pulmonary artery catheters remain in place longer, rendering them more susceptible to potentially fatal pneumonia or line sepsis. Treatment of infections may have mandated a decrease in immunosuppression, placing such patients at increased risk for fatal allograft rejection.

Inasmuch as no firm quantitative definition of right-sided circulatory failure has been established, its diagnosis is essentially subjective. The use of 30-day all-cause mortality, an unequivocal end point, was preferable to dependence on a retrospective assignment of causes of death. Our inclusion of deaths that were unlikely to have resulted from right ventricular failure biases our results *against* finding the associations we did and thus strengthens the conclusions that can be drawn from these results.

This was a retrospective study spanning more than a decade of transplant recipients. Thus patient medications at the time of catheterization were not prospectively recorded and were not available for analysis. However, optimization of the medical regimen was routine before catheterization.

Last, the power of some analyses was limited by relatively small sample sizes. These analyses should be repeated prospectively in larger cohorts to confirm our results.

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