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Impact of Classic and Paradoxical Low Flow on Survival After Aortic Valve Replacement for Severe Aortic Stenosis

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ABSTRACT

BACKGROUND Low flow (LF) can occur with reduced (classic) or preserved (paradoxical) left ventricular ejection fraction (LVEF).

OBJECTIVES The objective of this study was to compare outcomes of patients with low ejection fraction (LEF), paradoxical low flow (PLF), and normal flow (NF) after aortic valve replacement (AVR).

METHODS We examined 1,154 patients with severe aortic stenosis (AS) who underwent AVR with or without coronary artery bypass grafting.

RESULTS Among these patients, 206 (18%) had LEF as defined by LVEF of <50%; 319 (28%) had PLF as defined by LVEF of ≥50% but stroke volume indexed to body surface area (SVi) of ≤35 ml · m^{-2}; and 629 (54%) had NF, as defined by LVEF of ≥50% and SVi of >35 ml · m^2. Aortic valve area was lower in low flow/LVEF groups (LEF: 0.71 ± 0.20 cm^2 and PLF: 0.65 ± 0.23 cm^2 vs. NF: 0.77 ± 0.18 cm^2; $p < 0.001$). The 30-day mortality was higher ($p < 0.001$) in LEF and PLF groups than in the NF group (6.3% and 6.3% vs. 1.8%, respectively). SVi and PLF group were independent predictors of operative mortality (odds ratio [OR]: 1.18, $p < 0.05$; and OR: 2.97, $p = 0.004$; respectively). At 5 years after AVR, overall survival was 72 ± 4% in LEF group, 81 ± 2% in PLF group, and 85 ± 2% in NF group ($p < 0.0001$).

CONCLUSIONS Patients with LEF or PLF AS have a higher operative risk, but pre-operative risk score accounted only for LEF and lower LVEF. Patients with LEF had the worst survival outcome, whereas patients with PLF and normal flow had similar survival rates after AVR. As a major predictor of perioperative mortality, SVi should be integrated in AS patients' pre-operative evaluation. (J Am Coll Cardiol 2015;65:645–53) © 2015 by the American College of Cardiology Foundation.

Low flow in aortic stenosis (AS) can occur with reduced or preserved left ventricular ejection fraction (LVEF), which are named classic and paradoxical low flow, respectively. Because the transvalvular pressure gradient is highly flow dependent, these clinical conditions are often associated with low gradient, which adds complexity to the assessment of stenosis severity and therapeutic decision making. According to current American College of Cardiology/American Heart Association (ACC/AHA) guidelines (1), aortic valve replacement (AVR) should be considered (Class I or IIa) in symptomatic patients with low ejection fraction (LEF) or paradoxical low flow (PLF), low-gradient AS, if the presence of severe stenosis can be confirmed. Low flow, as documented by reduced stroke volume index (SVi), has been shown to be an independent predictor of mortality following transcatheter aortic valve replacement, regardless of LVEF (2,3), but little is known about the impact of flow status after surgical AVR (4–6). Thus, the primary objective of this study was to compare the outcomes of patients with LEF, PLF, and normal flow (NF) after AVR. The secondary objective was to

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

CABG = coronary artery bypass graft

LEF = low ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

NF = normal flow

NYHA = New York Heart Association

PLF = paradoxical low flow

SVi = stroke volume index

compare perioperative outcomes among patients with LEF, PLF, and NF AS.

METHODS

STUDY POPULATION. Among 1,984 consecutive patients who underwent AVR with or without coronary artery bypass graft (CABG) as their first open-heart surgery in our institution between 2002 and 2010, we included 1,154 patients with calcific severe AS (as defined by a mean gradient ≥40 mm Hg, a peak aortic jet velocity ≥4 m · s^{1}, an aortic valve area ≤1.0 cm^2, or an indexed aortic valve area ≤0.6 cm^2 · m^{-2}) (Figure 1). Data were prospectively collected and stored in an electronic database.

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Patients for whom primary indication for AVR was aortic insufficiency or CABG and patients with an incomplete echocardiographic evaluation in the 3 months before AVR were excluded.

ECHOCARDIOGRAPHY. Doppler echocardiographic measurements included LV dimensions according to recommendations of the American Society of Echocardiography: LVEF calculated by the biplane Simpson method, the peak aortic jet velocity, the peak and mean transvalvular pressure gradients obtained with the use of the modified Bernoulli equation, and the aortic valve area obtained with the use of the standard continuity equation (7). Doppler echocardiographic measurement of LV outflow tract stroke volume was corroborated by the 2-dimensional (2D) volumetric method.

Our population was divided into 3 groups depending on the values of LVEF and SVi: the NF group, defined as LVEF ≥50% and SVi >35 ml · m^{-2}; the PLF group, defined as LVEF ≥50% and SVi ≤35 ml · m^{-2}; and the LEF group, defined as LVEF <50%.

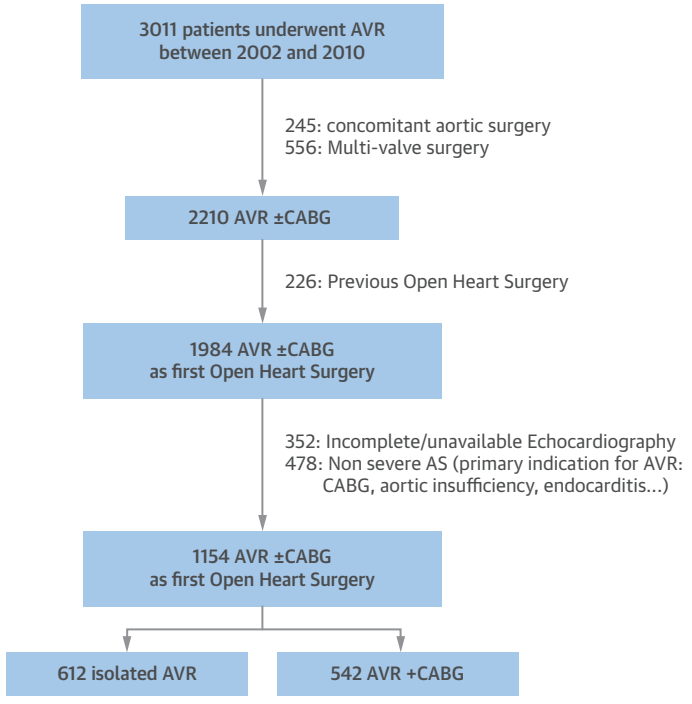
CORONARY ANGIOGRAPHY. All patients underwent coronary angiography as part of the pre-operative evaluation. The severity of coronary artery disease was assessed by angiographic Duke myocardial jeopardy score, which expresses how many of the 6 coronary arterial segments are jeopardized by significant (>70% estimated luminal area reduction) stenoses (8). Two points are added to the score for each jeopardized segment.

STUDY ENDPOINTS. Primary endpoints for this study were 30-day mortality and long-term mortality. Secondary endpoints were: 1) perioperative major cardiovascular nonfatal events consisting of atrial fibrillation/flutter, ventricular tachycardia/fibrillation, cardiac arrest, low output syndrome, acute cardiac failure, intra-aortic balloon pump application, multiorgan failure and ischemic event; 2) perioperative noncardiac, nonfatal events consisting of respiratory intubation (intubation time period longer than 48 h and reintubation), renal (hemodialysis/filtration and increase in blood level rate of creatinine higher than 100 μmol · l^{-1}), and neurological (stroke and transient ischemic accident) events; 3) length of time of vasotrope/inotrope use; 4) intensive care unit length of stay; and 5) hospital length of stay.

Perioperative events and deaths were prospectively collected. Late mortality data were retrospectively obtained from Quebec Institute of Statistics. To maximize the interrogation of the central Quebec Institute of Statistics database, a list with multiple demographics (including first and last names, dates of birth, and social security numbers) and a delay of 1 year between interrogation and closing follow-up dates were used.

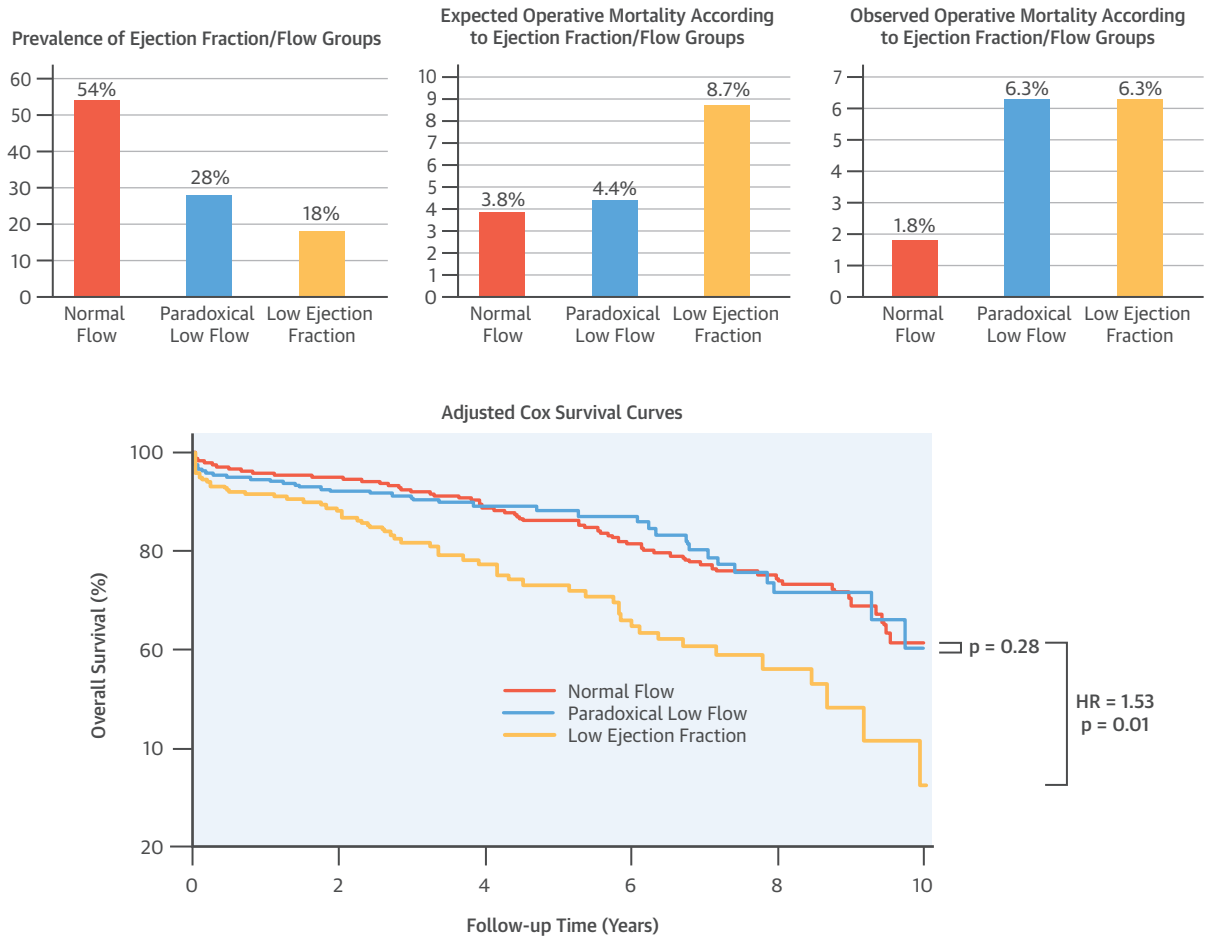
STATISTICAL ANALYSIS. Results are mean ± SD or percentages. For continuous variables, differences between groups were analyzed with the use of 1-way ANOVA, followed by the Tukey post-hoc test for

FIGURE 1 Study Flow Chart



AVR = aortic valve replacement; AS = aortic stenosis; CABG = coronary artery bypass graft.

CENTRAL ILLUSTRATION **Impact of Flow and Ejection Fraction After Aortic Valve Replacement**



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Prevalence for patient groups, 30-day mortality, and overall survival in normal flow **(red line)**, paradoxical low flow **(blue line)**, and low ejection fraction **(orange line)** patients. Survival is shown by Cox survival curves adjusted for age, female sex, New York Heart Association functional class III or IV, atrial fibrillation, chronic kidney failure, diabetes, coronary artery disease, chronic obstructive pulmonary disease, left ventricular mass index, and mean gradient.

intergroup comparisons. The chi-square or the Fisher exact test was used to compare categorical variables as appropriate. The association between periprocedural (30-day) mortality and risk factors was examined by logistic regression analysis and are presented as odds ratio (OR, 95% confidence interval [CI], and p value). Multivariate analysis of periprocedural mortality was analysed by stepwise backward models. Effects of the clinical and Doppler echocardiographic variables on overall survival were assessed using Cox proportional hazard models and are presented as hazard ratios (HR, 95% CI, and p value). A p value of <0.05 was considered statistically significant. All variables with a p value of <0.05 in univariate analysis were entered in multivariate models. All variables in the Cox models verified the proportional hazards assumption on the basis of inspection of trends in the Schoenfeld residuals (all $p > 0.15$). Statistical analyses were performed with JMP version 9.1 and SPSS version 20.0 software (IBM, Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. Among the 1,154 patients included in the study, 629 (54%) were in the NF

TABLE 1 Baseline Characteristics

	NF Group (n = 629; 54%)	PLF Group (n = 319; 28%)	LEF Group (n = 206; 18%)	p Value
Clinical data				
Age, yrs	69 ± 10	70 ± 10	71 ± 10	0.19
Females	239 (38)*	132 (41)*	53 (26)†‡	0.0007
Body surface area, m^2	1.81 ± 0.20*†	1.84 ± 0.23‡	1.85 ± 0.21‡	0.005
Systolic blood pressure, mm Hg	130 ± 21*	127 ± 19	123 ± 19‡	0.001
Diastolic blood pressure, mm Hg	70 ± 10†	73 ± 11*‡	71 ± 10†	0.0002
Heart rate, beat/min	65 ± 11*†	72 ± 13‡	73 ± 15‡	<0.0001
NYHA functional class III-IV	221 (35)*†	143 (45)*‡	109 (53)†‡	<0.0001
Hypertension	439 (70)	225 (71)	141 (68)	0.88
Diabetes	163 (26)*	100 (31)	77 (37)‡	0.006
COPD	80 (13)*	48 (15)*	60 (29)†‡	<0.0001
CAD	298 (47)*	162 (51)*	144 (70)†‡	<0.0001
Myocardial Duke jeopardy score	1.56 ± 2.97*	1.82 ± 3.21*	3.39 ± 4.21†‡	<0.0001
Previous myocardial infarction	97 (16)*	58 (18)*	82 (40)†‡	<0.0001
Chronic kidney disease	41 (7)*	26 (8)*	38 (18)†‡	<0.0001
Parsonnet risk score, %	3.8 ± 3.6*	4.4 ± 4.3*	8.7 ± 10.9†‡	<0.0001
Echocardiographic data				
LV end diastolic diameter, cm	4.71 ± 0.58*†	4.57 ± 0.56*‡	5.35 ± 0.83†‡	<0.0001
LV end diastolic volume, ml	105 ± 31*†	98 ± 28*‡	143 ± 51†‡	<0.0001
Relative wall thickness ratio	0.52 ± 0.11*†	0.54 ± 0.13*‡	0.46 ± 0.12†‡	<0.0001
LV mass index, $g \cdot m^{-2}$	122 ± 34*†	115 ± 33*‡	146 ± 45†‡	<0.0001
Peak aortic jet velocity, $m \cdot s^{-1}$	4.3 ± 0.7*†	4.0 ± 0.8*‡	3.7 ± 0.8†‡	<0.0001
Mean gradient, mm Hg	45 ± 15*†	42 ± 17*‡	36 ± 16†‡	<0.0001
Aortic valve area, cm^2	0.77 ± 0.18*†	0.65 ± 0.23*‡	0.71 ± 0.20†‡	<0.0001
Indexed aortic valve area, $cm^2 \cdot m^{-2}$	0.43 ± 0.09*†	0.35 ± 0.13*‡	0.38 ± 0.10†‡	<0.0001
Stroke volume, ml	77 ± 15*†	56 ± 10*‡	59 ± 16†‡	<0.0001
Stroke volume index, $ml \cdot m^{-2}$	43 ± 7*†	30 ± 4*‡	32 ± 8†‡	<0.0001
LV ejection fraction, %	65 ± 8*†	62 ± 7*‡	35 ± 9†‡	<0.0001

Values are mean ± SD or n (%). *Different from LEF. †Different from PLF. ‡Different from NF.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LEF = low ejection fraction; LV = left ventricular; NF = normal flow; NYHA = New York Heart Association; PLF = paradoxical low flow.

group, 319 (28%) were in the PLF group, and 206 (18%) were in the LEF group (Central Illustration). Age was similar among the 3 groups. Patients in the LEF group were more often male; had more incidence of chronic obstructive pulmonary disease, chronic kidney disease, coronary artery disease, previous myocardial infarction, and a more severe burden of coronary artery disease (as documented by the Duke myocardial jeopardy score) and thus a higher surgical risk as estimated by the Parsonnet score (9) than the 2 other groups (Table 1, Central Illustration). Baseline clinical data were similar between PLF and NF groups, and accordingly, the risk of operative death predicted by the Parsonnet score was equivalent in both the PLF and NF patients. With regard to echocardiographic data, PLF patients had more pronounced LV concentric remodeling (smaller LV cavity size and higher relative wall thickness) and, a priori, more severe AS (with a smaller aortic valve area and comparable mean gradient) and lower LVEF while remaining in the normal range than NF patients. As expected, PLF patients had a lower stroke volume and SVi than NF patients, comparable to that of LEF patients, even if LVEF was preserved (Table 1).

PREDICTORS OF 30-DAY MORTALITY. Forty-four patients (3.8%) died within 30 days following AVR. These deaths occurred for 13 patients (6.3%) in the LEF group, 20 patients (6.3%) in the PLF group, and 11 patients (1.8%) in the NF group ($p < 0.0001$) (Central Illustration, Table 2). When observed 30-day mortality was compared with predicted 30-day mortality, the Parsonnet risk score explained the excess of mortality in LEF patients but not in PLF patients (Figure 2).

In univariate analysis, variables associated with increased risk of 30-day mortality were older age ($p = 0.007$), female sex ($p = 0.002$), New York Heart Association (NYHA) functional class III and IV ($p < 0.0001$), diabetes ($p = 0.004$), coronary artery disease ($p = 0.01$), Duke myocardial jeopardy score ($p = 0.0003$), previous myocardial infarction ($p = 0.005$), chronic obstructive pulmonary disease ($p = 0.03$), chronic kidney disease ($p = 0.02$), Parsonnet score ($p < 0.0001$), smaller aortic valve area ($p = 0.05$), lower mean gradient ($p = 0.04$), lower peak aortic jet velocity ($p = 0.03$), lower SVi ($p = 0.0003$), lower LVEF ($p = 0.003$), LEF group ($p < 0.001$), and PLF group ($p < 0.0001$) (Table 3).

After adjustment for age, sex, Parsonnet risk score, NYHA functional class III to IV, and Duke myocardial jeopardy score, PLF group remained an independent predictor of 30-day mortality (OR: 2.97; 95% CI: 1.40 to 6.60; $p = 0.004$) whereas LEF did not ($p = 0.28$) (Table 3, Model 1). When entering SVi and LVEF as continuous variables in place of flow groups into the multivariate model, SVi (OR: 1.18; 95% CI: 1.01 to 1.36 per 5 $ml \cdot m^{-2}$ decrease; $p = 0.05$) was an independent predictor of 30-day mortality whereas LVEF was not ($p = 0.82$) (Table 3, Model 2).

Among the 206 LEF patients, 71 had a normal flow (SVi >35 ml/m^2). In this LEF subset, the operative mortality rates of low flow versus normal flow were similar (OR: 1.81; 95% CI: 0.48 to 6.81; $p = 0.36$).

PERIOPERATIVE EVENTS. With regard to perioperative cardiovascular events, low output syndrome and the use of intra-aortic balloon pump were more frequent in the low flow and LEF groups than in the NF group (all $p < 0.0001$). Accordingly, the length of use of vasopressor or inotrope and the occurrence of intubation longer than 48 h were higher in the low flow and LEF groups (Table 2). Acute cardiac decompensation and multiorgan failure followed the same trend but did not reach statistical significance

in the PLF group. When we compared patients experiencing at least one cardiac event among acute ischemic events, cardiac arrest, low output syndrome, acute cardiac failure, intra-aortic balloon pump use, and multiorgan failure, incidence of this composite event was higher ($p < 0.0001$) in LEF and PLF groups than in the NF group (Table 2). Noncardiac events and cardiac enzyme levels were similar among groups (all $p > 0.07$). Patients with LEF had slightly but significant longer hospital length of stay ($p = 0.04$) than NF patients (Table 2). Prolonged use of inotropic support was significantly elevated in the LEF and PLF groups than in NF patients.

PREDICTORS OF MID-TERM SURVIVAL. During a follow-up of 4.1 ± 3.0 years, there were 241 deaths (21%). Five-year survival rates were lower ($p < 0.0001$) in LEF and PLF groups than in the NF group (72 ± 4% and 81 ± 2% vs. 85 ± 2%, respectively) (Figure 3). In univariate analysis, significant preoperative predictors of mortality were older age ($p < 0.0001$), NYHA functional class III or IV ($p < 0.0001$), atrial fibrillation ($p = 0.0006$), chronic kidney failure ($p < 0.0001$), diabetes ($p = 0.001$), coronary artery disease ($p = 0.0004$), Duke myocardial jeopardy score ($p = 0.0004$), chronic obstructive pulmonary disease ($p = 0.0001$), higher LV mass index ($p = 0.02$), lower peak aortic jet velocity ($p = 0.005$), lower mean gradient ($p = 0.003$), lower SVi ($p < 0.0001$), lower LVEF ($p < 0.0001$), LEF group ($p < 0.0001$), and PLF group ($p = 0.03$) (Table 4). The factors independently associated with increased risk of mortality were older age ($p < 0.0001$), NYHA functional class III or IV ($p = 0.005$), chronic kidney failure ($p = 0.002$), Duke myocardial jeopardy score ($p = 0.03$), diabetes ($p = 0.02$), and LEF group ($p = 0.01$) or lower LVEF ($p = 0.02$) (Table 4, Central Illustration). PLF group or SVi did not remain associated with mid-term mortality in the multivariate analysis ($p = 0.11$ and $p = 0.12$, respectively) (Central Illustration).

In all models, mean gradient could be replaced by peak aortic jet velocity or aortic valve area without impact on the results. Similar to mean gradient, peak aortic jet velocity or aortic valve area were not independently associated with mortality (all $p > 0.81$ or $p > 0.26$, respectively). Among patients with LEF, low flow (e.g., SVi ≤35 ml · m^{-2}) and low gradient (<40 mm Hg or ≤20 mm Hg) were not independent predictors of higher mortality (all $p \geq 0.13$).

If the analysis was restricted to patients who underwent an isolated AVR or an AVR and CABG, the results were similar with an independent impact of LEF group or LVEF on long-term mortality (all $p < 0.05$), and there was no independent association between PLF group or SVi and mid-term mortality (all $p > 0.27$) (Online Appendix).

TABLE 2 Perioperative Data, Death, and Nonfatal Events

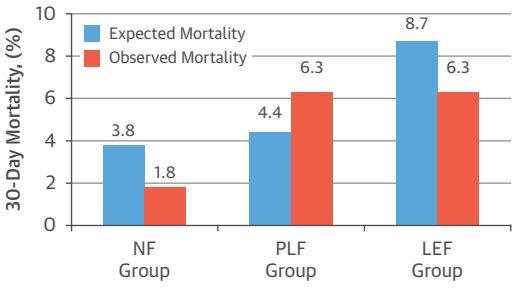
Perioperative Data	Normal Flow Group	Paradoxical Low Flow Group	Low Ejection Fraction Group	p Value
Intraoperative data				
Concomitant coronary artery bypass graft	278 (44)*‡	150 (47)*‡	114 (55)†‡	0.004
Clamp time, min	78 ± 29	81 ± 33	81 ± 35	0.42
Bypass time, min	104 ± 37	106 ± 43	109 ± 48	0.19
Event				
30-day mortality	11 (1.8)*†	20 (6.3)‡	13 (6.3)‡	0.0003
Cardiovascular events				
Atrial fibrillation/flutter	296 (47)	167 (52)	111 (54)	0.13
Ventricular arrhythmia	32 (5.1)	13 (4.1)	13 (6.3)	0.52
Acute ischemic event	1 (0.2)	1 (0.3)	1 (0.5)	0.73
Cardiac arrest	10 (1.6)	6 (1.9)	3 (1.5)	0.92
Low output syndrome	29 (5)*†	31 (10)*‡	32 (16)†‡	<0.0001
Acute cardiac failure	8 (1.3)	6 (1.9)	7 (3.4)	0.18
Intra-aortic balloon pump	8 (0.8)*†	9 (2.8)*‡	17 (8.3)†‡	<0.0001
Multi-organ failure	4 (0.6)	5 (1.6)	4 (1.9)	0.21
Composite cardiac events (except for arrhythmias)§	41 (7)*†	38 (12)*‡	44 (21)†‡	<0.0001
Respiratory events				
Intubation >48 h	21 (3.3)*†	22 (6.9)‡	15 (7.3)‡	0.01
Reintubation	23 (3.7)†	23 (7.2)‡	10 (4.9)	0.05
Neurologic events				
Stroke/transient ischemic attack	13 (2.1)	15 (4.7)	8 (3.9)	0.07
Renal events				
Hemodialysis/filtration	14 (2.2)	7 (2.2)	10 (4.9)	0.15
Increase in creatinine >100 μmol · l^{-1}	49 (7.8)	15 (4.7)	16 (7.8)	0.16
Laboratory data				
Peak troponin I, μg · l^{-1}	52 ± 71	36 ± 38	56 ± 77	0.17
Peak troponin T, μg · l^{-1}	0.81 ± 087	0.83 ± 1.65	0.85 ± 0.94	0.93
Peak CKMB, μg · m^{-1} l	46 ± 61	40 ± 42	45 ± 56	0.29
Length of hospital stay/medications				
Hospitalization, days	8.8 ± 8.7*	9.8 ± 9.4	10.4 ± 9.4‡	0.04
Intensive care unit, h	59 ± 130	64 ± 129	68 ± 93	0.60
Vasotrope/inotrope use, h	15 ± 17*†	20 ± 23*‡	28 ± 27†‡	<0.0001

Values are n (%) or mean ± SD. *Different from low ejection fraction group. †Different from paradoxical low flow group. ‡Different from normal flow group. §Composite event was calculated by at least one of the following: acute ischemic event, cardiac arrest, low output syndrome, acute cardiac failure, intra-aortic balloon pump, or multiorgan failure.

DISCUSSION

There are 3 main findings of this study. 1) Patients with LEF and PLF have increased 30-day mortality compared to NF patients. 2) The 30-day mortality excess observed in LEF patients was entirely captured by the operative risk score. On the other hand, PLF remained independently associated with increased risk of 30-day mortality, even after adjustment for operative risk score. 3) Beyond 30 days, the mortality

FIGURE 2 Predicted Score and Observed 30-Day Mortality



Predicted (Parsonnet) score and observed 30-day mortality in normal flow, paradoxical low flow, and low ejection fraction patients.

risk continued to be higher in LEF than in NF patients but was similar in PLF and NF patients (**Central Illustration**).

It is well known that low LVEF is a powerful independent predictor of mortality after AVR, and this factor was therefore included in the calculation of operative risk scores (9–11). Thus, it is not surprising that LVEF and LEF group were not found to be independent predictors of 30-day mortality after adjustment for operative risk score (e.g., Parsonnet risk score). LVEF also was found to be a powerful independent predictor of mid-term mortality in this study, as well as in previous studies in AS patients undergoing AVR (12,13). Low preoperative LVEF may reflect a more advanced stage of myocardial fibrosis and dysfunction (14,15). Hence, a substantial proportion of patients with LEF may have irreversible myocardial impairment and may thus not improve their LV function and symptoms following successful AVR, thereby explaining the continued mortality excess observed in this subset during the late postoperative phase. Additional imaging biomarkers, such as LV flow reserve, assessed by dobutamine stress echocardiography or extent of myocardial fibrosis assessed by late gadolinium enhancement or T1-weighted mapping cardiac magnetic resonance could be helpful in improving patient risk stratification and selection for AVR in this challenging subset of patients (14–17). Conversely, reduced SVi and PLF groups were independently associated with 30-day mortality but not with late mortality (**Central Illustration**). Although several of the features of PLF (e.g., pronounced LV concentric remodeling and/or hypertrophy, moderate to severe diastolic dysfunction, decreased longitudinal strain, and reduced SVi) are associated with increased operative mortality, they often improve within the weeks or months following a successful surgical or transcatheter AVR (18–22). This may explain the fact that PLF has no impact on late postoperative mortality. Low pre-procedural SVi has been shown to be an independent predictor of procedural and/or 2-year mortality after transcatheter AVR, whereas low LVEF was not (2,3). Discrepancies between these results and those of the present study regarding the impact on late mortality could be explained by differences in the type of procedure (e.g., transcatheter versus surgical AVR), baseline risk profile of the study population, and follow-up duration (2 vs. 4 years). Interestingly, a post-hoc analysis of the PARTNER-I (Placement of

TABLE 3 Univariate and Multivariate Predictors of 30-Day Mortality

		Univariable Analysis			Model 1			Model 2		
Predictor	**Increment**	**Odds Ratio**	**95% CI**	**p Value**	**Odds Ratio**	**95% CI**	**p Value**	**Odds Ratio**	**95% CI**	**p Value**
Age	1 yr	1.05	1.02–1.09	0.007	–	–	0.49	–	–	0.44
Sex	Female	**2.58**	**1.41–4.84**	**0.002**	**2.81**	**1.42–5.73**	**0.003**	**2.82**	**1.41–4.78**	**0.004**
Parsonnet risk score	1 point	**1.08**	**1.05–1.11**	**<0.0001**	**1.05**	**1.01–1.09**	**0.002**	**1.04**	**1.01–1.08**	**0.003**
NYHA functional class III to IV	Yes	**3.91**	**2.04–8.00**	**<0.0001**	**3.13**	**1.58–6.59**	**0.0009**	**2.96**	**1.48–6.26**	**0.002**
Myocardial Duke jeopardy score	1 point increase	**1.14**	**1.06–1.22**	**0.0003**	**1.10**	**1.01–120**	**0.03**	**1.10**	**1.01–1.20**	**0.03**
Mean gradient	5 mm Hg increase	0.90	0.80–0.99	0.04	–	–	0.26	–	–	0.34
SVi	5 ml · m^{-2} decrease	**1.43**	**1.18–1.74**	**0.0003**	**–**	**–**	**–**	**1.18**	**1.01–1.36**	**0.05**
LVEF	5% decrease	1.16	1.05–1.27	0.003	–	–	–	–	–	0.82
Groups				0.0003			0.02			
NF	Referent	–	–	–	–	–	–	–	–	–
LEF		3.78	1.67–8.75	0.002	–	–	0.28	–	–	–
PLF		**3.76**	**1.81–8.22**	**0.0004**	**2.97**	**1.40–6.60**	**0.004**	–	–	–

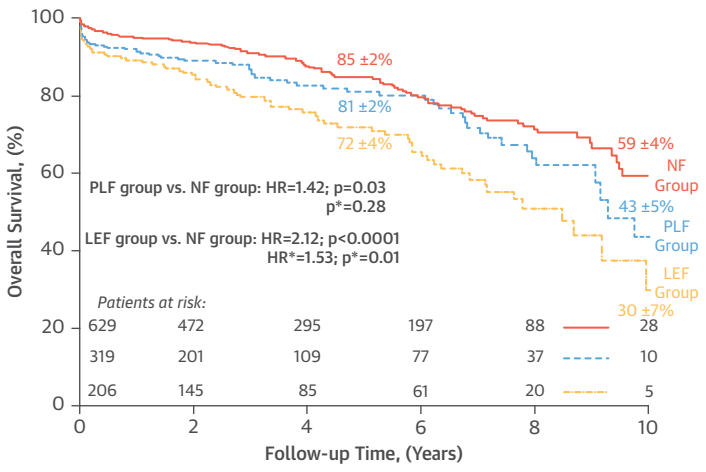
Bold variables are the independent predictors of mortality (i.e., statistically significant in multivariable analysis).
CI = confidence interval; LVEF = left ventricular ejection fraction; SVi = stroke volume index; other abbreviations as in Table 1.

Aortic Transcatheter Valves) trial (3) revealed that PLF is associated with increased mortality following both types of procedures, but 1-year survival was significantly better with transcatheter AVR than with surgical AVR. This early survival benefit associated with transcatheter AVR in patients with PLF may be, at least in part, due to the better hemodynamics and lower incidence of severe prosthesis-patient mismatch achieved by this procedure than surgical AVR (23,24), as well as to its less invasive nature. These findings suggest that transcatheter AVR may be superior to surgical AVR in this particular subset of patients, but more data are needed to further support this hypothesis.

Low pre-procedural mean gradient also has been associated with increased mortality after surgical (11) or transcatheter AVR (25,26). However, recent studies revealed that this association was, in large part, explained by the presence of low flow (2,3). Accordingly, in the present study, association between low mean gradient or low peak aortic jet velocity and mortality was no longer significant after adjustment for SVi and LVEF.

STUDY LIMITATIONS. The most important limitation of this study is the small number of operative deaths that may not allow identification of all independent predictors of operative mortality. Accordingly, due to the important differences in baseline characteristics among groups, especially between LEF and the other groups, we cannot exclude the possibility of residual

FIGURE 3 Kaplan-Meier Curves of Overall Survival



Kaplan-Meier curves of overall survival in normal flow **(red solid line)**, paradoxical low flow **(blue dot line)**, and low ejection fraction **(orange dash-dot line)** patients. *Adjusted for age, female sex, New York Heart Association functional class III or IV, atrial fibrillation, chronic kidney failure, diabetes, coronary artery disease, chronic obstructive pulmonary disease, LV mass index, and mean gradient. LV = left ventricular; HR = hazard ratio.

TABLE 4 Univariate and Multivariate Analysis of Overall Survival

	Univariate Analysis			Multivariate Analysis					
				Model 1			Model 2		
Factor	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Age, yrs	**1.04**	**1.03–1.06**	**<0.0001**	**1.04**	**1.02–1.06**	**<0.0001**	**1.04**	**1.02–1.06**	**<0.0001**
Female	–	–	0.19	–	–	0.35	–	–	0.35
NYHA functional class III to IV	**2.03**	**1.57–2.64**	**<0.0001**	**1.51**	**1.13–2.02**	**0.005**	**1.50**	**1.12–2.01**	**0.006**
Atrial fibrillation	1.88	1.33–2.59	0.0006	–	–	0.20	–	–	0.24
Chronic kidney failure	**1.98**	**1.42–2.70**	**<0.0001**	**1.78**	**1.23–2.51**	**0.002**	**1.80**	**1.24–2.54**	**0.002**
Diabetes	**1.55**	**1.18–2.01**	**0.001**	**1.44**	**1.07–1.92**	**0.02**	**1.42**	**1.06–1.90**	**0.02**
Coronary artery disease	1.61	1.24–2.12	0.0004	–	–	–	–	–	–
Duke Myocardial Jeopardy Score	**1.06**	**1.03–1.09**	**0.0004**	**1.04**	**1.01–1.08**	**0.03**	**1.04**	**1.01–1.07**	**0.04**
COPD	1.82	1.35–2.41	0.0001	–	–	0.15	–	–	0.13
Concomitant CABG	–	–	0.31	–	–	–	–	–	–
LV mass index, 10 g · m^{-2} · kg	1.04	1.01–1.08	0.02	–	–	0.17	–	–	0.16
Peak aortic jet velocity, m · s^{-1} increase	0.79	0.66–0.93	0.005	–	–	–	–	–	–
Mean gradient, 5 mm Hg increase	0.93	0.90–0.98	0.003	–	–	0.46	–	–	0.50
Stroke volume index, 5 ml · m^{-2} decrease	1.18	1.09–1.27	<0.0001	–	–	–	–	–	0.12
LVEF, 5% decrease	**1.11**	**1.06–1.15**	**<0.0001**	–	–	–	**2.24**	**1.13–4.38**	**0.02**
Groups			**<0.0001**			**0.03**	–	–	–
NF	Reference			Reference			–	–	–
LEF	**2.12**	**1.56–2.87**	**<0.0001**	**1.52**	**1.09–2.11**	**0.01**	–	–	–
PLF	1.42	1.04–1.93	0.03	–	–	0.11	–	–	–

Bold variables are the independent predictors of mortality (i.e. statistically significant in multivariable analysis).
CABG = coronary arteries bypass graft; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

confounding in the logistic regression and Cox models. Our results need to be confirmed in larger, prospective studies.

Despite the fact that data were prospectively collected, they were retrospectively analyzed. However, our design, routine clinical practice, and interrogation of the central Quebec Institute of Statistics database limited enrollment and follow-up bias.

Data for myocardial strain or dobutamine stress echocardiography were not available in this cohort despite their potentially great interest.

CONCLUSIONS

In this series of patients with severe AS who underwent AVR, patients with PLF or LEF AS had higher operative risk. However, the association between LEF and lower LVEF with operative mortality was no longer significant after adjustment for operative risk score, whereas PLF or low SVi remained independent predictors of mortality even after adjustment for risk score. LEF and lower LVEF were independent predictors of mid-term mortality, whereas PLF or low SVi were not. Consideration of SVi may be useful to enhance operative risk stratification prior to AVR and improve decision making between surgical and transcatheter AVR. Further studies are needed to determine whether outcomes of patients with PLF are better with transcatheter AVR or surgical AVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Low transvalvular flow occurs in 15% to 35% of patients with aortic valve stenosis regardless of LVEF. Low flow is associated with increased mortality early AVR surgery, even in patients with preserved EF, but is not predictive of later postoperative mortality.

COMPETENCY IN PATIENT CARE: Stroke volume index should be considered in addition to LVEF in assessment of early and long-term mortality risks associated with AVR surgery.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the relative advantages and disadvantages of transcatheter and surgical AVR in patients with low flow aortic stenosis stratified according to LVEF.

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KEY WORDS aortic stenosis, low ejection fraction, low flow, survival

APPENDIX For supplemental material including figures and tables, please see the online version of this article.