

Comparison of Prosthetic Valve Hydrodynamic Function: Objective Testing using Statistical Multilevel Modeling

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Background and aim of the study: The performance of novel prosthetic heart valves is assessed using in-vitro hydrodynamic function tests. The study aim was to examine the problem of objective discrimination of hydrodynamic performance to determine significant differences between valve designs, and illustrate proposed methodology using data collected from five different polyurethane trileaflet valve designs.

Methods: Two engineering designs were manufactured with leaflets of the same polyurethane (GE, LE); design L was manufactured using three further leaflet materials of differing material modulus (LL, L4, L5). Six valves were made in each design, each tested at five flow rates in a standard hydrodynamic test rig, with five test replications for each valve. The data were analyzed using multilevel statistical modeling methods, allowing simultaneous comparison of multiple regression lines describing valve performance. The multilevel model is hierarchical in structure, in this case with two levels of data, describing individual valves at level 2 and test replicates at level 1. In all cases, the multilevel model uses the hydrodynamic function measure of interest, e.g. mean

pressure gradient or leakage, with logarithmic transformation as required as the dependent variable, Y . The independent variable, X , is, in all cases, the natural logarithm of the RMS flow measured through the valve.

Results: The two-design multilevel model enabled quantitative discrimination of designs GE and LE, showing that design GE had significantly better hydrodynamic function overall than design LE in this case (mean pressure gradient was estimated as 0.93 mmHg lower at low cardiac output, 14.74 mmHg lower at 9.6 l/min). The five-design multilevel model showed clearly the relatively poor hydrodynamic performance of designs L4 and L5 compared with others. The procedure was straightforward, and produced a statistical comparison among valve designs that is not easily achieved by other means.

Conclusion: This methodology provides a useful means of objective assessment of valve function for valve developers. Variance estimates provided by the analysis also provide a basis for quality control of valve production and testing.

The Journal of Heart Valve Disease 2004;13:467-477

The initial functional assessment of prosthetic heart valves in development uses hydrodynamic function testing to determine the ease of opening the valve and the efficiency of its closure. Valve comparisons are often made subjectively, by plotting a functional relationship (e.g. the variation of mean pressure gradient across the valve with flow through the valve). Objective testing that could define valve sets by parameter values and determine significant differences between the parameters of different designs would provide a useful tool for the valve developer.

The present study focuses on the problem of discriminating among hydrodynamic function behavior in a series of polyurethane valve design configurations using, initially, a simple comparison of two design variants, followed by a more complex comparison of five design variants.

One published report has been made of an attempt to characterize the pressure gradient/root mean square (RMS) flow curves obtained from hydrodynamic function testing of valves using statistical methods (1). In this case, the aim was to compare two different hydrodynamic function test rigs, and two mechanical valves of differing designs were used. Each valve was tested in each rig with three test replications, over four cardiac outputs. A logarithmic transformation allowed a straight-line fit to the data, and a multi-

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ple regression model was applied to show that the mean response was not significantly different between the two test rigs. These authors considered the use of regression coefficients to characterize valves. However, although the manufacture of mechanical valves is more precise than for other types of valve, it is questionable whether a single example of each of two different valves is sufficient for a valid comparison. The authors further made a presumption of similarity between the two sets of results, and the statistical modeling applied was probably inadequate to demonstrate any differences that otherwise might have been discovered. There seems to be no published example of a satisfactory statistical assessment of valve function enabling valve comparisons to be made with any degree of confidence over the whole range of physiological cardiac output.

A hierarchical or multilevel modeling approach has been used in the present study, enabling simultaneous comparison of the regression lines describing the hydrodynamic function of several valve designs, covering the whole cardiac output range of interest. The ability of the multilevel modeling approach to use *all* the information available for an individual valve (not only the intercept and slope parameters of a regression line fitted through the data points) should provide more power to detect differences among valve designs. The multilevel models used were originally developed for the analysis of hierarchical data in social sciences, for situations in which data could be grouped into categories (often, school classes) within which individuals (pupils) were more similar than between categories (2-4). In the same way, it is recognized that data from replicate tests on a given valve are likely to be more similar than data from tests on different valves. Previously, the application of such an approach has been impractical for the ordinary researcher, given the high level of computational skill required. In recent years, new software has become available, making the approach accessible for general use.

Materials and methods

Valves

Two valve designs were used, and these have been described in detail elsewhere (designs G (5-7) and L (8-9)). Briefly, the valves consisted of polyetheretherketone frames, coated with a thin layer of polyurethane. The leaflets were dip-coated onto the frames using a shaped former. The designs are similar 24 mm trileaflet valves with minor differences in leaflet geometry. Each valve design was manufactured into valves using the same polyurethane (Estane 58315, Noveon™ Europe BVBA), giving experimental designs, GE and LE, respectively. This material has been extensively

researched, and its properties and behavior in this application are well known (10,11). Design L was also manufactured using Lycra (DuPont), a polyetherurethane urea (11,12), as well as two members of a new family of biostable polyurethanes (Aortech Biomaterials, Sydney, Australia), based on a polydimethylsiloxane soft segment (9,13). These experimental designs were designated LL, L4 and L5, respectively. The valves and materials are described more fully in Table I.

Hydrodynamic function testing

Six valves were manufactured in each configuration, under the same conditions. The hydrodynamic function testing has been described in detail elsewhere (14,15). Briefly, valves were assessed over a range of five pulsatile flow rates, including 3.6, 4.9, 6.4, 8.0 and 9.6 l/min equivalent cardiac output, using combinations of pump frequency (beats per minute): pump displacement (ml) of 60:60, 70:70, 80:80, 80:100 and 80:120, respectively. Each valve was tested five times, and no test was repeated on the same day. All valves were tested under similar conditions in the mitral simulation position. A standard mechanical valve (23 mm tilting disk type) was placed into the aortic simulation position of the rig, which was operated at a mean aortic pressure of 95 mmHg. The pressure transducers were zeroed and calibrated at each test setting applied. A number of parameters of valve function were measured including:

- Root mean square (RMS) flow through the valve (ml/s)
- Mean pressure gradient across the open valve (mmHg)
- Regurgitant (reverse) flow through the closing valve (ml)
- Leakage flow through the closed valve (ml)
- Energy losses during forward flow (mJ)
- Energy losses during valve closing (mJ)
- Energy losses while the valve is closed (mJ)
- Maximum effective orifice area achieved by the valve (cm²)

Table I: Valve and polyurethane properties.

Design/leaflet material	Leaflet material modulus (MPa)	Valve leaflet thickness (µm)*
1. GE (Estane)	16.2	90.5 (88-93)
2. LE (Estane)	16.2	81 (79-83)
3. LL (Lycra)	8.5	93 (91-95)
4. L4 (EV3.34)	32.5	137 (134-140)
5. L5 (EV3.35)	63.6	112.5 (110-115)

*Values are mean (95% CI).

Energy loss was calculated by integrating (pressure difference \times flow) with respect to time, for each phase of valve operation, open, closing and closed. The effective orifice area was derived from the function $\text{RMS flow}/[\sqrt{(\text{mean pressure}) \times 51.6}]$ (15). All other measurements were made directly.

Statistical analysis

In the statistical models described, the dependent variable (Y) was the hydrodynamic function measure of interest, for example, mean pressure gradient or leakage, with logarithmic transformation as required. The independent variable (X) was, in all cases, the natural logarithm of the RMS flow measured through the valve. The multilevel software used was MLwiN version 1.10 (Multilevel Models Project, Institute of Education, University of London, UK). A manual that describes the statistical modeling and application of the software in detail (16) accompanied the software.

For each valve design configuration, six valves were each tested five times, with each test providing data at five separate flow rates, thereby providing 150 data points for each design configuration and 750 data points overall. The multilevel model was hierarchical in structure: the hydrodynamic function test data falls naturally into this format, enabling the influence of individual valves in each design to be examined at level 2 and that of the test replicates for each valve to be examined at level 1. The model included separate variance components for each of these levels. In addition, inter-design differences were included as fixed effects in the model. For all analyses, design GE was taken as the 'baseline' design against which all comparisons were made.

The form of a multi-level model for design GE on its

own is $Y = \beta_{01} + \beta_{11}X + \text{error}$, where the constant (intercept) parameter of design GE is represented by β_{01} and the slope parameter of design GE is represented by β_{11} . The error term represents the random effects and includes variance of the intercept due to valve variability (σ_{u0}^2) and to replicate variability within valve ($\sigma_{\epsilon 0}^2$), variance of the slope due to valve (σ_{u1}^2) and replicate variability within valve ($\sigma_{\epsilon 1}^2$). Covariance terms were also included in the original model, but were always non-significant, and will be omitted from further discussion. This multi-level model allows for different slopes as well as different intercepts for the various valves of the same basic design. This complexity of model is required in the present case, as the manufacture of these valves does not allow precise duplication of leaflet thickness from valve to valve. Figure 1a demonstrates one set of mean pressure gradient test data for each valve of design GE. Figure 1b demonstrates the logarithmic transformation of this raw data with linear fits for the data for each valve. It can be seen that there is substantial scatter among the regression lines and that the fits are not mutually parallel, so that there are likely to be significant variances associated with both the intercepts and the slopes of any regression model. These effects are increasingly pronounced for higher modulus leaflet materials and for thicker valve leaflets (9), particularly as flow rates increase. Similar, though generally lesser, effects may, in theory, be seen in the test iterations due, for example, to possible effects of valve orientation in the tester.

This basic model was extended to more than one design configuration by adding fixed parameters, introduced using dummy variables. In the simplest problem, for comparison of two designs, the dummy

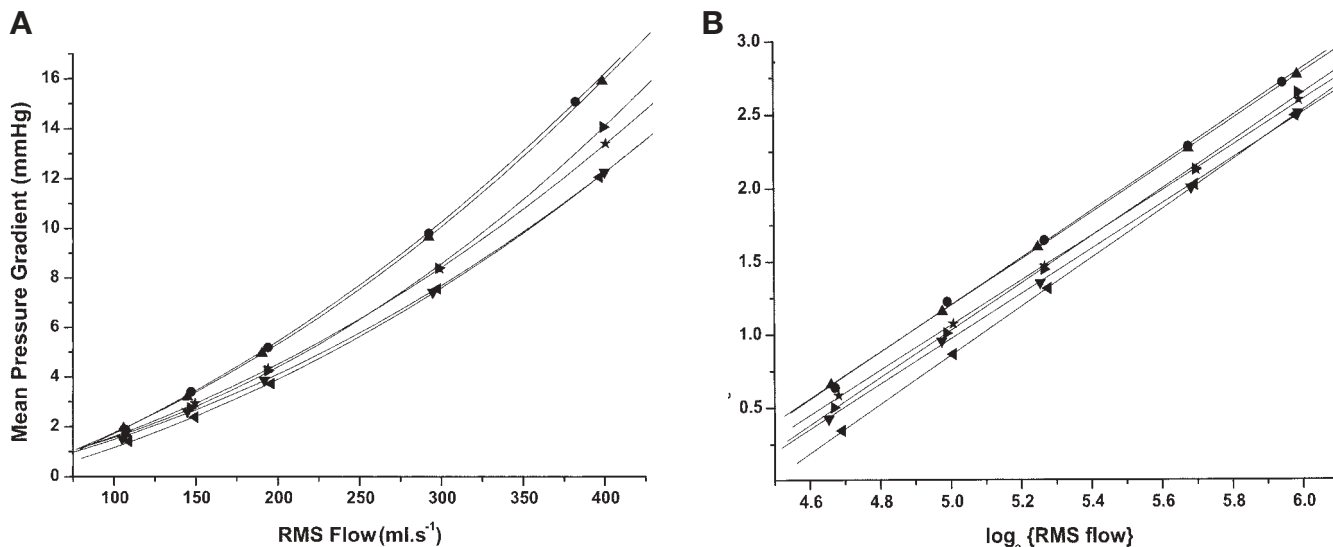


Figure 1: A) Mean pressure gradient versus RMS flow, plotted for a single test run for each individual valve of design GE. B) Data from curve (A) after logarithmic transformation with linear fits to individual valve data.

variable, $\delta = 1$, if design was LE and 0 if design was GE. This allowed the construction of a model of the form, $Y = \beta_{01} + \beta_{11}X + (\beta_{02} - \beta_{01})\delta + (\beta_{12} - \beta_{11})\delta X + error$ where the parameters of design GE are represented by β_{01} and β_{11} , as before; the same parameters for design LE are designated β_{02} and β_{12} , hence the difference in intercept between designs GE and LE is modeled directly and represented by $(\beta_{02} - \beta_{01})$, and the difference in slope between designs GE and LE by $(\beta_{12} - \beta_{11})$. These parameters constitute the *fixed* parameters of the model. A set of *random* parameters, making up the error term, was included as before.

In order to compare five designs, the model was expanded with the addition of four separate dummy variables to represent each of four design contrasts. The explicit formulation of these models that is discussed below involves contrasts between all the other designs and GE. The choice of GE as baseline design was based on prior knowledge of its excellent hydrodynamic function. In order to compare the four L designs one with another, it was also necessary to examine different sets of contrasts. Full details have been omitted in the interests of conciseness, but the final models that are plotted below exclude all non-significant contrasts among the designs.

The full multi-level model can be written in the form $Y = \beta_{01} + \beta_{11}X + (\beta_{0n} - \beta_{01})\delta_n + (\beta_{1n} - \beta_{11})\delta_n X + error$. Here, β_{01} and β_{11} are the intercept and slope parameters for the baseline design (design GE). The δ_n variables are dummy variables representing designs LE, LL, L4 and L5, respectively; coded as 1 if the specified design was present and 0 else. $(\beta_{0n} - \beta_{01})$ represents the increment on the intercept parameter for design n and, similarly, $(\beta_{1n} - \beta_{11})$ is the increment on the slope parameter for design n . The model includes the same set of random parameter as before.

It is unlikely that all these contrasts will be statistically significant. A possible model selection process is based on differences between the $\{-2(\log\text{likelihood})\}$ value generated by a series of nested models. This determines which fixed and random parameters are influential in the model. The χ^2 distribution was used to compare models using a significance level of 5% for parameter inclusion in the model. In all cases, the analysis began with the full model and sequentially removed all terms that were not significant to produce the final model. In those cases where designs other than the baseline design were not significantly different, the model was simplified by collapsing the relevant parameters for those designs to estimate a common fixed parameter. Model selection and testing issues are discussed in detail elsewhere (17).

A logarithmic data transformation was required for the following response variables: mean pressure gradient, regurgitant flow and energy losses during forward

flow, to achieve a plausible linear model. A satisfactory fit was achieved for leakage flow, energy losses during valve closing, energy losses when the valve is closed and maximum effective orifice area without transformation of the Y data. Normal probability plots of the residuals and plots of standardized residuals versus fitted values showed reasonable adherence to the usual assumptions of linearity, constant variance and normal errors, for all measures with the exception of $\log_e\{\text{mean pressure gradient}\}$. In this case, a slight deviation from normality was observed. This is likely to result from a positive correlation between residuals from the same test run, when the measured function, RMS flow, is used as the independent variable. However, the residuals distribution is symmetric and, given a reasonable number of observations, the Central Limit Theorem would justify the use of standard confidence intervals and tests, even in this case.

Results

The two design case

Estimates of the significant fixed and random parameters in the final models with their standard errors are listed in Table II. In all cases, the regression lines for designs GE and LE had slopes that were not significantly different, so a simplified model with parallel regression lines has been fitted. In this model, the mean effect of an increase in flow rate on valve behavior is the same for both designs. Thus, if one valve performs better than another at one flow rate, it will be better across all flow rates. In this case, for all the hydrodynamic function measures assessed, design GE had significantly better opening characteristics than design LE. Design GE had significantly lower leakage through the closed valve than design LE. Only variance terms associated with the intercepts of the regression lines were significant for these designs.

Variances related to slope were not significant in any case. The 95% confidence intervals (CI) for the model parameters were calculated via the software (roughly approximated by the estimate \pm twice its standard error). In this case, for $\log_e\{\text{mean pressure gradient}\}$, the intercepts for designs GE and LE are highly likely to lie in the intervals -6.659 ± 0.124 and -6.251 ± 0.136 , respectively. Thus, in terms of the untransformed *mean pressure gradient*, design GE had a significantly lower gradient than design LE over all tested cardiac outputs ($p < 0.001$) (estimated mean difference 0.93 mmHg at 3.6 l/min, rising to 14.74 mmHg at 9.6 l/min).

Neither the intercept nor the slope parameter estimate of the model for $\log_e\{\text{regurgitation}\}$ was significantly different for designs GE and LE, hence there was no difference between these designs in terms of their closing behavior.

In the case of *leakage* flow, the intercept parameter estimate for design GE was 6.213 ± 0.632 , and for design LE was 6.830 ± 0.406 . Mean leakage in design LE was significantly higher than in design GE at all given cardiac outputs (estimated mean difference at all flow rates 0.61 ml, 95% CI 0.21 to 1.02 ml; $p = 0.003$).

The intercept parameter estimate for $\log_e\{\text{energy loss during forward flow}\}$ was -5.424 ± 0.136 for design GE, and -5.005 ± 0.125 for design LE. Thus, during forward flow, the energy losses in design GE were significantly lower than those of design LE ($p < 0.001$) (estimated mean difference 8.77 mJ at 3.6 l/min and 206.48 mJ at 9.6 l/min).

Neither the intercept nor the slope parameter estimate of the model for *valve closing energy losses* was significantly different for designs GE and LE. When the valves were closed, the intercept parameter estimates for *closed energy losses* for designs GE and LE were 92.592 ± 9.244 and 99.817 ± 5.695 , respectively. The closed energy losses were significantly higher in design LE than in design GE (estimated mean difference 7.23 mJ at all flow rates, 95% CI 1.53 to 12.92 mJ; $p = 0.013$).

The *effective orifice area* at peak pressure and flow had intercept parameter estimates of -0.315 ± 0.105 for design GE, and -0.609 ± 0.095 for design LE. This maximum effective orifice area was significantly greater

for design GE than for design LE (estimated mean difference 0.29 cm^2 , 95% CI 0.20 to 0.39 cm^2 ; $p < 0.001$).

The five-design case

The significant fixed and random parameter estimates in the final model are listed in Table III. For all individual designs, the predicted hydrodynamic function measure for 3.6 l/min applied cardiac output, calculated from the fixed parameter estimates, is quoted throughout the following text to facilitate comparisons among designs. The fitted lines for all designs are plotted for four hydrodynamic function measures (Figs. 2-5) to demonstrate the relative rankings of each of the designs over the physiological range of cardiac outputs.

Considering $\log_e\{\text{mean pressure gradient}\}$, the slopes of designs GE, LE and LL were not significantly different, and were significantly greater than those of designs L4 and L5. The slope of design L4 was significantly greater than that of design L5. Design GE had the lowest intercept parameter estimate of all five designs. There was no significant difference between the intercept parameters of designs LE and LL, although they were different from the intercept parameter estimate for design GE. Hence, the final model provided a single estimate for a common intercept parameter for designs LE and LL. Design L5 had the

Table II: Parameter estimates (estimated standard errors) for comparison of designs GE and LE.

Parameter	Response variable						
	$\log_e\{\text{mean pressure gradient}\}$	$\log_e\{\text{regurgitation}\}$	Leakage	$\log_e\{\text{energy loss in forward flow}\}$	Energy loss, closing	Energy loss, closed	Maximum orifice area
β_{01} (intercept, design GE)	-6.659 (0.060)	1.234 (0.063)	6.213 (0.323)	-5.424 (0.069)	-24.193 (3.356)	92.592 (4.718)	-0.315 (0.053)
$(\beta_{02} - \beta_{01})$ (increment, design LE)	0.408 (0.063)	NS	0.617 (0.207)	0.419 (0.064)	NS	7.225 (2.906)	-0.294 (0.048)
β_1 (slope, common)	1.547 (0.008)	-0.045 (0.011)	-0.895 (0.054)	1.755 (0.010)	9.955 (0.618)	-11.776 (0.798)	0.396 (0.008)
σ_{i0}^2 (intercept variance due to valve)	0.012 (0.005)	0.008 (0.003)	0.121 (0.052)	0.012 (0.005)	4.764 (2.348)	23.636 (10.345)	0.007 (0.003)
σ_{e0}^2 (intercept variance due to replication)	0.004 (0.000)	0.008 (0.001)	0.195 (0.016)	0.007 (0.001)	25.503 (2.125)	42.558 (3.547)	0.004 (0.000)

NS: Parameter not significant when the model was fitted.

Table III: Parameter estimates (estimated standard errors) for comparison of five designs.

Parameter	Response variable						
	\log_e {mean pressure gradient}	\log_e {regurgitation}	Leakage	\log_e {energy loss in forward flow}	Energy loss, closing	Energy loss, closed	Maximum orifice area
β_{01} (intercept, design GE)	-6.633 (0.148)	1.057 (0.077)	6.165 (0.426)	-5.107 (0.148)	-26.069 (7.307)	101.147 (7.684)	-0.561 (0.069)
$(\beta_{02} - \beta_{01})$ (increment, design LE)	0.366 (0.054)	NS	NS	0.388 (0.060)	NS	NS	NS
$(\beta_{03} - \beta_{01})$ (increment, design LL)	0.366 (0.054)	NS	3.296 (0.550)	0.388 (0.060)	NS	NS	NS
$(\beta_{04} - \beta_{02})$ (increment, design L4)	1.741 (0.289)	NS	3.296 (0.550)	1.628 (0.287)	25.568 (3.914)	NS	-0.381 (0.044)
$(\beta_{05} - \beta_{01})$ (increment, design L5)	2.897 (0.289)	NS	3.296 (0.550)	2.676 (0.287)	33.852 (3.914)	NS	-0.675 (0.044)
β_{11} (slope, design GE)	1.544 (0.024)	-0.018 (0.013)	-0.830 (0.071)	1.697 (0.024)	10.562 (1.324)	-12.506 (1.260)	0.442 (0.013)
$(\beta_{12} - \beta_{11})$ (increment, design LE)	NS	NS	NS	NS	NS	NS	-0.052 (0.007)
$(\beta_{13} - \beta_{11})$ (increment, design LL)	NS	NS	-0.550 (0.099)	NS	NS	NS	-0.052 (0.007)
$(\beta_{14} - \beta_{12})$ (increment, design L4)	-0.215 (0.047)	0.082 (0.008)	-0.846 (0.093)	-0.190 (0.048)	NS	-4.121 (0.330)	NS
$(\beta_{15} - \beta_{11})$ (increment, design L5)	-0.346 (0.043)	0.103 (0.008)	-0.846 (0.093)	-0.300 (0.048)	NS	-4.121 (0.330)	NS
σ_{u0}^2 (intercept variance due to valve)	0.345 (0.096)	0.139 (0.046)	1.090 (0.570)	0.334 (0.094)	57.182 (17.812)	1454.931 (459.767)	0.118 (0.035)
σ_{u1}^2 (slope variance due to valve)	0.009 (0.003)	0.003 (0.001)	0.023 (0.016)	0.010 (0.003)	-	36.019 (12.239)	0.004 (0.001)
σ_{e0}^2 (intercept variance due to replicate)	0.222 (0.042)	0.212 (0.065)	2.659 (1.875)	0.114 (0.052)	294.062 (15.498)	62.060 (3.341)	0.099 (0.031)
σ_{e1}^2 (slope variance due to replication)	0.007 (0.001)	0.007 (0.002)	0.071 (0.065)	0.002 (0.002)	-	-	0.003 (0.001)

NS: Parameter not significant when the model was fitted.

highest intercept value, with the other designs in the order $L5 > L4 > LL$ and $LE > GE$.

In terms of assessment of valve design performance, design GE had the lowest mean pressure gradient at all flow rates of interest (1.87 mmHg at 3.6 l/min; Fig. 2). The increment on pressure gradient for designs LE and LL compared with design GE was 0.82 mmHg at 3.6 l/min. Design L4 had a relatively high pressure gradient at low flow rates (3.87 mmHg), but converged with designs LE and LL at higher flow. Design L5 had consistently higher pressure gradients at all flow rates (6.65 mmHg at 3.6 l/min).

In the case of *regurgitation*, the intercept parameter estimate was common for all designs. Designs GE, LE and LL also had common slope parameter estimates. The order of magnitude of slope estimates were design $L5 > L4 > GE, LE$ and LL . Of particular interest was the negative slope parameter estimate for designs GE, LE and LL, implying that the valve was less regurgitant as the flow rate rises. This was in contrast to designs L4 and L5 for which regurgitation increased slightly as the flow rate increased. The predicted regressions demonstrated the coincidence of designs GE, LE and LL (2.64 ml regurgitant volume at 3.6 l/min) and the almost constant amount of regurgitation over the flow rates of interest. The regurgitations of designs L4 (3.89 ml) and L5 (4.29 ml) were greatest (Fig. 3). Thus, in terms of regurgitation, there was little to choose among designs GE, LE and LL, and the performance of designs L4 and L5 was less good.

The slope parameter estimates for *leakage* were all negative, indicating increasingly efficient closure of all valves as flow rate increased. Designs L4 and L5 had the lowest, and common, slope parameter estimate. Designs GE and LE had the highest slope parameter

estimate in common, while design LL was intermediate. The intercept estimates for designs GE and LE were common. Designs LL, L4 and L5 had a separate, common intercept parameter estimate that was significantly higher than that of designs GE and LE. The predicted regression lines are shown in Figure 4. Considering 3.6 l/min, designs GE and LE had a predicted leakage of 2.26 ml, design LL had 2.98 ml leakage, and designs L4 and L5 each had a leakage of 1.58 ml. Design LL had the highest leakage at low flow rates, but closed more efficiently than designs GE and LE at high flow rates. Designs L4 and L5 had lower leakage at all flow rates, and the predicted regression line appeared to fall below zero at intermediate flow rates. Thus, in terms of leakage through the closed valve, designs L4 and L5 were the most efficient.

The model for *energy loss in forward flow* indicated the design ranking to be similar to that for mean pressure gradient. At 3.6 l/min, design GE had the lowest predicted energy losses in forward flow (17.62 mJ). Designs LE and LL did not differ significantly from each other, and had higher energy losses (25.97 mJ). Design L4 had significantly higher energy losses (36.74 mJ), and design L5 had the highest losses (62.48 mJ). Design GE was consistently lower than the other designs at all flow rates. Design L4 was higher than designs LE and LL at low flow rates, but converged at higher flow rates. Design L5 was highest at all flow rates.

The final model for *energy loss during valve closing* had a common slope parameter estimate for all designs. Designs GE, LE and LL had the lowest intercept parameter estimates. Design L5 had the highest intercept, and design L4 was intermediate. There were fewer differences among design configurations for this

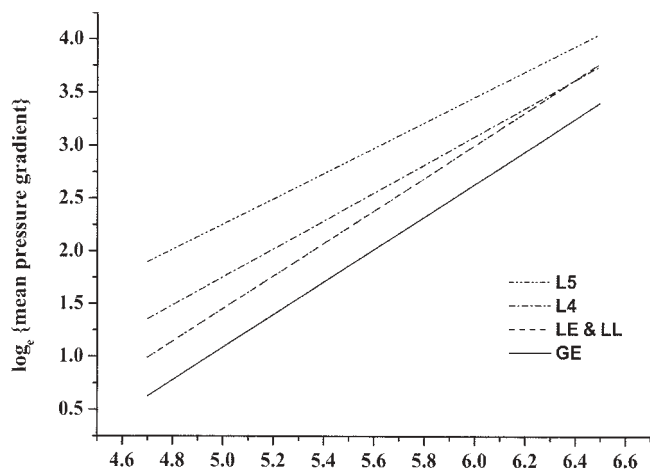


Figure 2: Predicted regression lines for all valve designs for $\log_e \{ \text{mean pressure gradient} \}$ regressed on $\log_e \{ \text{RMS flow} \}$.

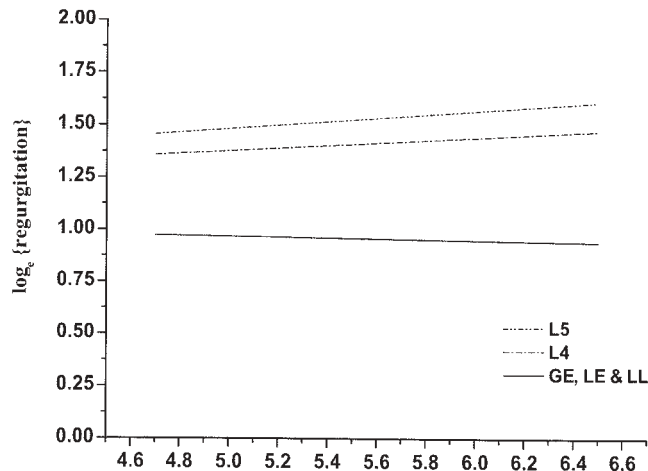


Figure 3: Predicted regression lines for all valve designs for $\log_e \{ \text{regurgitation} \}$ regressed on $\log_e \{ \text{RMS flow} \}$.

hydrodynamic function measure than for others examined. Designs GE, LE and LL could not be distinguished from each other (23.57 mJ at 3.6 l/min). The closing energy losses increased with flow rate and in parallel for all designs, with L4 and L5 having significantly higher losses than other designs (49.11 and 57.42 mJ, respectively, at 3.6 l/min).

The final model for *energy loss while the valve is closed* included a common intercept parameter for all designs, a common slope for designs GE, LE and LL, with a separate, common slope parameter for designs L4 and L5. In the flow region of interest, in spite of the common intercept of the model, designs GE, LE and LL had higher energy losses (42.37 mJ at 3.6 l/min) than designs L4 and L5 (23.00 mJ at 3.6 l/min). The predicted regression line for designs L4 and L5 extended below zero at higher flow rates, similar to the case for leakage flow.

The final model for *effective orifice area* of the valve included a common intercept parameter estimate for designs GE, LE and LL. Designs L4 and L5 had significantly lower intercept estimates, with design L5 significantly lower than design L4. Designs GE, L4 and L5 had a common slope parameter estimate, with a separate, common, slope parameter estimate for designs LE and LL that was significantly lower. The predicted regression lines demonstrated the relative orifice sizes expected from each design (Fig. 5). Design GE had consistently the largest orifice at all flow rates of interest (1.52 cm² at 3.6 l/min). Designs LE and LL had a slightly smaller orifice (1.27 cm²). Design L4 had a smaller orifice than these at low flow rates (1.13 cm²), but converged with designs LE and LL at high flow rates. Design L5 had the smallest orifice consistently at all flow rates (0.84 cm², at 3.6 l/min). It would be preferable that a valve should be capable of opening as wide

as possible; thus design GE, with the largest effective orifice, is significantly better in this respect than any other design.

Discussion

The application of multi-level modeling to the data under consideration has enabled a relatively complex data set to be analyzed in a straightforward manner, using all the data available for the analysis and without contradicting underlying model assumptions; this was in contrast to conventional methods of analyzing these types of data. The final result was a demonstration of differences among a variety of valve designs on which a high degree of reliance may be placed.

Certain hydrodynamic function measures were more sensitive to design-related influences than others. The least sensitive measures in this respect were regurgitation, leakage, closing and closed energy losses. The closing and closed valve energy losses demonstrated fewer differences among valves than did leakage and regurgitation. These measures are related to each other, with the energy losses being derived measures calculated by integration of flow and pressure during the closing and closed phases of valve function, respectively.

The most sensitive measures in demonstrating differences in valve hydrodynamic function were mean pressure gradient, energy losses during forward flow, and maximum effective orifice area attainable by the valve. Of these, maximum orifice area demonstrated fewer differences among design configurations than did mean pressure gradient or energy losses during forward flow.

The differences between designs GE and LE suggested that design G - a different engineering design from

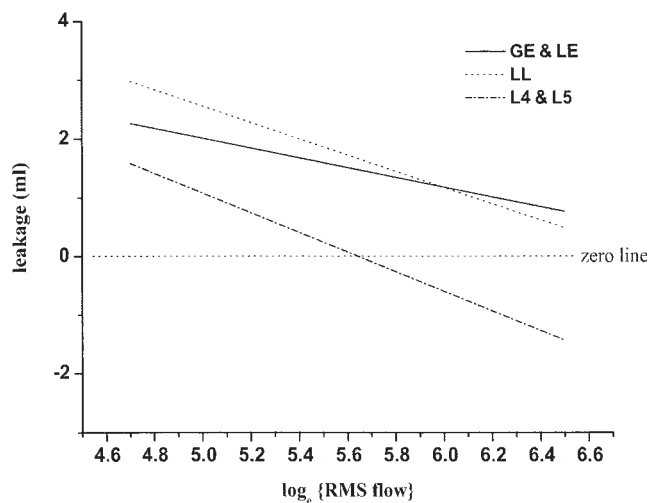


Figure 4: Predicted regression lines for all valve designs for leakage regressed on log_e {RMS flow}.

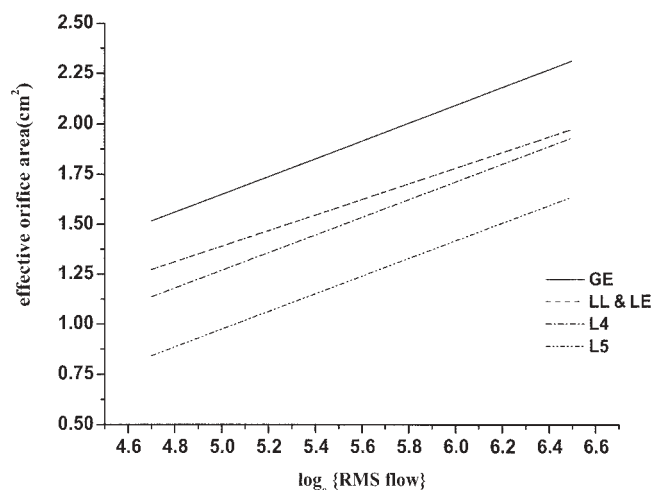


Figure 5: Predicted regression lines for all valve designs for effective orifice area regressed on log_e {RMS flow}.

design L, but made with leaflets of the same material - was the best design in terms of the opening that could be achieved by the valve to allow blood to flow. It might be expected that design LL would have had the best performance by this measure as this design had leaflets made of the lowest modulus material. Its leaflets, however, were slightly thicker (Table I) than those of design LE, which might explain its close similarity to design LE for most hydrodynamic function measures. Design LL had leaflets of similar thickness to design GE, which was manufactured using a slightly stiffer material, and this in turn reinforced the finding that design GE had a larger orifice area and better forward flow characteristics than the other designs.

Analyses of mean pressure gradient and energy losses during forward flow had similar abilities to discriminate among design performances. In terms of the intercept parameter estimate (a measure of how easy it is to open the valve at low flow rates), design GE had the lowest intercept and, hence, the best performance. Designs LL and LE were next best, followed by design L4 and, worst of all, design L5. Design GE had leaflets made from the same material as design LE, but the leaflets were slightly thicker, suggesting that a greater significance might be associated with the better performance. Further experimentation on the effects of leaflet thickness would be required to clarify this relationship. It is known for other valves, that the relationship between leaflet thickness and hydrodynamic function is not linear, particularly for low-modulus materials (9). Thus, it is uncertain, how much of the difference in this case may be attributed to differences in leaflet thickness. Design L4 had a lower intercept than design L5, in spite of its much thicker leaflets. In this case, the difference in modulus is likely to be the major influence on the intercept parameters. Indeed, previous research has suggested that there is a critical value of modulus, for designs L, below which acceptable hydrodynamic function can be achieved, and that this critical value lies between the modulus of material 4 and that of material 5 (9).

Overall, design GE had a significantly better hydrodynamic performance than any other design studied here. Designs LE and LL also performed fairly well. Designs L4 and L5 had the poorest hydrodynamic performances, with design L4 being significantly better than design L5. Design L4 may perform rather better than it appeared here, in fact, if the leaflet thicknesses were matched to those of the better designs, but this was not possible in the present study.

When comparing the two-design model with the five-design model, in most cases the differences between designs GE and LE were similar. However, in the case of leakage flow and energy loss when the valve was closed, the five-design model detected no

significant difference between these two designs in contrast to the two-design model. Considering these two measures in the five-design model, it was also notable that the regression lines for designs L4 and L5 progressed below zero within the flow range of interest. This suggests that there may be differences in behavior between these two designs and the other valve designs tested that affect the model, thereby introducing artifacts into the predictions for designs L4 and L5. Thus, in this case, an analysis of valve behavior for the three best valves (designs GE, LE and LL) may be best performed in a three-design model, omitting designs L4 and L5 from consideration. This decision would be determined by the needs of the researcher and the resolution required to determine significant differences for the hydrodynamic function measures of most interest. The model as formulated here is optimized for examining differences between design GE and any other design. If interest were mainly in differences between other pairs of designs, then it would be advisable to reformulate the model with an alternative baseline design.

Hydrodynamic function is an extremely important indicator of valve performance. If the hydrodynamic function is poor, then the valve will not open at low flow rates, and this may be critical for a patient with already poor cardiac function. However, it is also important that the valve is capable of being able to function for long periods (preferably in excess of 20 years) without failure of the leaflet material as a result of biodegradation or fatigue. In this respect, research findings have suggested that higher-modulus materials may provide an advantage in terms of durability (18). Thus, the materials used in designs L4 and L5 may provide advantages for long-term use over the lower-modulus materials, and their hydrodynamic function must be interpreted with this in mind. A design must be shown to have satisfactory - if not optimum - hydrodynamic function combined with the potential for long-term durability. In this respect, design L4 may be regarded as having satisfactory performance, particularly if a suitable leaflet thickness can be targeted.

The random parameter estimates (Tables II and III) provide measures of the amount of variability attributable to valve differences within the same design configuration at level 2 of the multi-level model, and to replicates within the same valve at level 1 of the model. The level 2 variance is an indicator of the reproducibility of the valve manufacturing process, while the level 1 variance is a measure of the reproducibility of the hydrodynamic function testing. These variances are estimates that yield some indication of quality control limits that can reasonably be set on the performance of individual valves within a group, and the amount of

variability during hydrodynamic function testing that can reasonably be attributed to testing differences rather than to valve-related differences. In the case of energy losses in closing and closed phases of valve function, modeling issues as discussed above may result in extreme variances. Ideally, quality control information would be derived from a one-design multilevel model, specifically for a design of interest. In the present study, only random parameters associated with the intercept parameter were significant and included in the model for all measures.

Of the five design variants examined here, two differing physical designs were used with a single material. All the valves were 24 mm - a typical mid-range size of valve. The design comparison is likely to be similar for all valve sizes, although a higher modulus material might be expected to perform relatively worse in smaller valve sizes. The mean leaflet thickness of Estane leaflets was similar for both valve designs, and these would be expected to produce similar hydrodynamic function. All other materials were tested in design L. The increasing material modulus - the major influence on the L designs - is likely to be associated with worsening hydrodynamic function, as the valve leaflets become harder to open with the stiffer materials. In theory, this may be compensated to some degree by reducing leaflet thickness. Lycra (material L) had a similar thickness distribution over the leaflets to Estane (material E) valves in design L, although even a small difference may be sufficient to influence hydrodynamic function. This should be compensated to some degree by the lower modulus of Lycra.

The higher moduli of materials EV3.34 and EV3.35 would tend to produce valves with relatively poor hydrodynamic function. It is uncertain as to which factor, modulus or thickness, would have the greatest influence on this. However, previous research has suggested that the extremely high modulus of EV3.35 cannot be adequately compensated by reducing leaflet thickness, at least in this design (9). Unfortunately, due to practical difficulties in working with limited quantities of two experimental polyurethane variants (materials EV3.34 and EV3.35), it was not possible to produce sets of valves which were more closely matched in leaflet thickness across design variants. However, this does not detract from the potential of the analytical methodology for comparing valve types.

In conclusion, multilevel modeling has enabled quantitative discrimination of different valve designs by any of several hydrodynamic function measures, and allowed a statistical assessment of their relative performances. The potential for developing quality control criteria for valve manufacture and testing has been demonstrated. Future development of the methodolo-

gy will include investigation of influential factors such as leaflet thickness.

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