The Use of Multi-level Modelling to Investigate the Hydrodynamic Function of Polyurethane Prosthetic Heart Valves

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Abstract

This thesis applies multi-level statistical modelling methods, which have been developed and mainly used for analysis of educational and sociological data, to a new type of data analysis problem. There are many engineering problems that have a multi-level structure, which cannot be easily analysed by conventional methods. The particular problem investigated here is the statistical comparison of prosthetic valve hydrodynamic function data. Such data has, until now, been presented in a subjective way, with selection of valves for demonstration of the desired behaviour. Few attempts have been made at objective analysis of such data.

The data presented here derive from experimental polyurethane valve designs. Of these, two design configurations have the same leaflet polyurethane material and different physical valve designs. The other design configurations use one of the physical engineering valve designs, but fabricate the leaflets out of one of four different polyurethane materials. Data were collected for seven different measures of hydrodynamic function, over a series of five different applied flow rates.

The first section of the thesis examines random regression analysis of the data using summary measures to compare two designs. Data were transformed as required to approximate assumptions of normality and equal variance using a natural logarithmic transformation. It was possible to discriminate the two designs on the basis of several hydrodynamic function measures. However, the data were pooled from iterative testing into individual valve regressions (n = 6 for each design), so information about the test reproducibility was lost. The data from each individual valve regression parameter estimate was pooled to provide a mean value to represent each design. Thus information about valve-to-valve reproducibility was lost. Correlation of residuals from the same test run means that the assumption of

independence that underlies ordinary regression analysis is not likely to be valid in this case. The first two designs had common regression slopes, but this is unlikely to be the case for all design configurations and would create problems with the random regression method. The data structure, therefore, has a hierarchical nature with test iterations nested within individual valves, and individual valves being members of specific design configuration groups. This data structure suggests that a multi-level modelling approach might provide useful insights, by permitting the simultaneous comparison of the regression lines, accounting for both “different intercepts” and “different slopes”, as well as the data hierarchy. The ability of the multi-level modelling approach to use all the information available for a valve should give more power to detect differences between valve types.

The multi-level approach is described with reference to various applications of the methodology. The method is then applied first to a single valve design, followed by comparison of the two designs used for the random regression approach initially investigated. The multi-level approach increased the power of discrimination compared with the random regression approach, so that more hydrodynamic function measures demonstrated significant differences between designs. The precision of estimation of the variances was improved in the two-design model compared with the single design model, probably as a result of the greater numbers of valves available for analysis. The analysis was then extended to include five different design configurations. The analysis was also modelled to include different slope parameters as well as different intercept parameters, with design included as a fixed parameter in the model. The outcome of the multi-level modelling is described for each hydrodynamic function measure investigated. The most important measures of valve performance (mean pressure gradient across the open valve, energy losses during forward flow and maximum effective valve orifice area) were capable of successful discrimination among all the valve designs. Variance estimates were also obtained that would enable an estimate of the acceptable degree of variation allowed for any valve within a design or for the repeatability associated with the hydrodynamic function testing itself. These estimates are likely to be underestimated in the present study due to small numbers of valves available, but still provide a useful indicator of variability. Some measures were affected by profound differences in valve design response to the function testing. In particular, regurgitation, leakage, energy losses while the valve is closing and while the valve is closed. In these cases, two designs, L4 and L5, were made from materials of much higher modulus than the other designs, and also had somewhat thicker leaflets. These factors, in combination, produced valves, which had a different pattern of response to the function testing for these specific measures. In these cases, separation of the designs might improve the modelling, with the three similar designs (GE, LE and LL) included in a separate model. The modelling might be further improved by the inclusion of influential covariates, for example material modulus or leaflet thickness.

In conclusion, multi-level modelling has been successfully applied in a novel scientific arena, to an engineering problem. The method has enabled discrimination of different valve designs by any of several hydrodynamic function measures and allowed a statistical assessment of their relative performances.

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Chapter 1: Introduction

Experimental work on prosthetic heart valves has been increasing over the last fifty years. There are large numbers of people throughout the world who require replacement of a heart valve due to disease or congenital abnormality, involving primarily the aortic or mitral valves. Today there are several types of valve available for clinical implantation. These include mechanical valves manufactured from materials such as titanium and pyrolytic carbon, or porcine aortic or bovine pericardial valves derived from animal sources or human grafts. All these various types of valve suffer different problems and none is the ideal valve to implant in all clinical circumstances. In general terms, mechanical types of valve are very durable but can be relatively damaging to the blood. Patients in receipt of mechanical valves must also be maintained on anticoagulant therapy, which has its own hazards, including spontaneous bleeding episodes or, if insufficient, thromboembolic events. Bioprosthetic valves are kinder to the blood although more susceptible to relatively early failure (Giddens et al, 1993; Chu et al, 1984).

Most of the differences between these two types of valve are design- and material-related. The mechanical valves are manufactured from materials such as titanium and pyrolytic carbon. These materials are very durable, but inflexible. The designs are of two main types, either a generally circular tilting disc, or a bileaflet design with semi-lunar leaflets. Both designs result in the leaflets opening directly in the blood flow field, with mechanical hinges. The interference with the blood flow field, with rigid materials and high velocity jets occurring in the flow field, causes significant blood trauma, which must be controlled by anticoagulants. The bioprosthetic valves are usually manufactured from a porcine aortic valve or from a material such as bovine pericardium. In both cases the valve design imitates some features of the native human aortic valve i.e. the trileaflet structure, with a central flow orifice. The leaflet materials are also relatively soft and flexible, producing low shear stress and minimal interference with blood flow. They do not, generally, require the use of long-term anticoagulants. However, they are subject to relatively early failure due to primary tissue failure of the leaflet material, or failure secondary to calcification and tissue overgrowth of the leaflets causing stenosis of the valve. These types of bioprosthetic valve failure are accelerated in younger patients, and these valves are generally reserved for use in elderly patients.

This present situation is not ideal. In certain situations, the use of a mechanical valve is undesirable, but there may be no satisfactory alternative, particularly if the patient is young. In many countries, it may be possible to carry out the primary surgical procedure, but there may be inadequate facilities to ensure safe follow-up to administer and monitor medications. There has been much interest in developing a better option than the currently available types of valve prosthesis.

The use of polyurethanes has been under investigation for this application for several years (Herold et al, 1987; Hilbert, et al, 1987; Jansen & Reul, 1992; Bernacca et al, 1995; Mackay et al, 1996a; Mackay et al, 1996b; Bernacca et al, 1997a). The advantage of these materials is the possibility of combining the best qualities of the two major types of commercially-available valve. This is due to the possibilities of chemical engineering of the polyurethane to achieve a particular material behaviour, the removal of biological variation inherent in animal-derived valves, and the retention of the flow characteristics of the bioprosthetic valve designs.

The assessment of prosthetic heart valves in development requires a number of widely recognised procedures including fatigue testing of valves to determine durability, blood compatibility testing, and valve function testing. This last is the first stage of functional screening once a whole valve has been made and consists of a standard set of hydrodynamic function tests that examine the ease of opening of the valve and the efficiency of its closure. Clinically, it is desirable for an open valve to display the lowest possible mean pressure gradient with the highest possible flow through the valve, particularly at low cardiac output. Hydrodynamic function testing can discriminate well among differing valve designs, but has, until now, been used in a purely subjective way to describe one design as "better" than another, on the basis of the position of lines on a graph, representing a functional relationship, such as the variation of mean pressure gradient across the open valve with flow through the valve. This subjectivity is undesirable, particularly as such discrimination is often made on the basis of only one or two selected valve tests and may not represent either the typical performance of a valve design or a true difference between valve designs. There is one published instance of an attempt to characterise the pressure gradient/RMS flow curves obtained from hydrodynamic function testing of valves (Barbaro et al, 1997). 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. After applying a logarithmic transformation to the data, a multiple regression model was fitted.There was no significant effect of choice of test rig within this model. These authors considered the use of regression coefficients to characterise valves. However, although the manufacture of mechanical valves is more precise than other types of valve, it is questionable whether two different valves are sufficient to validate their findings. They further made a presumption of similarity between the two sets of results and the statistical modelling applied was probably inadequate to demonstrate any "true" differences that might have been otherwise 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.

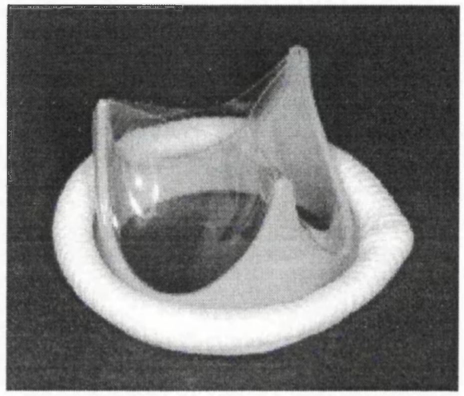
There is a need for objective testing of a valve design in terms of its hydrodynamic performance, so that each design may be described in terms that define not only whether it is better than another design, but also how great that improvement is. The current study focuses on the problems of discriminating hydrodynamic function behaviour in a series of polyurethane valve designs, using, initially, two design variants. The study is later expanded to include two different valve designs and four polyurethane materials.

Chapter 2: Polyurethane Prosthetic Heart Valve Assessment

Polyurethane valves have been under development for many years, and several research groups have produced designs that have excellent hydrodynamic function and good long-term durability as assessed by *in vitro* laboratory fatigue testing (Jansen & Reul, 1992; Bernacca et al, 1997a). There have, however, been problems when the valves have been implanted into large animal environments, due to biodegradation of the polymer structure. This has resulted in a lack of further development of such types of valve into the clinical environment to date. This situation is in the process of changing, as there are now polyurethane variants available which have altered chemistry with proven biostability in long-term implant situations (Rhodes et al, 1999; Gunatillake et al, 2000; Martin et al, 2000). This has revived interest in polyurethane valve development and focussed research effort on the necessity of discriminating among various similar polymer formulations in terms of various aspects of their function when manufactured into a prosthetic heart valve (O'Connor et al, 2000; Bernacca et al, 2000; 2001).

The great majority of polyurethane valves that have been researched use a variation of a three-leaflet design, similar to the natural aortic valve (Figure 2.1). This design has an open central orifice, which ensures the possibility of good flow characteristics, with no obstacle to blood flow within the flow field. The secondary advantage of this design is the lower likelihood of causing damage to the blood cells. A potential consequence is the possibility of using such valves without long-term anticoagulants and hence improving the quality of life of the recipient.

Figure 2.1 Typical Polyurethane Valve

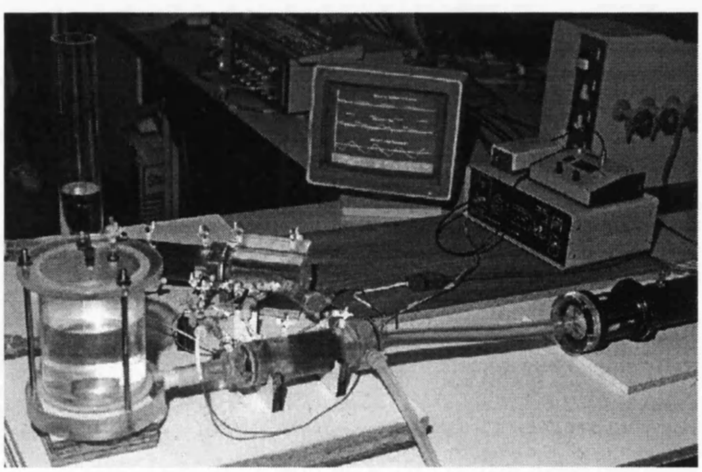


2.1: Hydrodynamic Function Testing

The primary method of assessing flow characteristics of a valve is by *in vitro* testing using a rig, which emulates the left side of the heart with built-in compliance to mimic the effects of the patient's peripheral circulation. The rig is designed with a "mitral" and an "aortic" valve position (Figure 2.2).

Figure 2.2 Overview of Hydrodynamic Function Test Rig

(aortic position in foreground, mitral position behind)



Different valve test centres use similar types of rig, based around the same type of fluid pumping system. The data are generated from the input of a series of 5 equivalent cardiac outputs applied to a valve mounted in a pulsatile flow simulator. These cardiac outputs are generated by a computer-controlled sinewave input to a pump, by controlling the frequency and displacement of the pump piston. The test fluid is saline. Valve function is assessed by measurement of the flow of fluid through the valve and the pressure gradient across the valve, using flow and differential pressure transducers. The data are collected using a computer programme designed for the purpose, as the flow and pressure waveforms throughout the valve functional cycle. A number of parameters of valve function are then calculated including:

- Root Mean Square flow through the valve,
- mean pressure gradient across the open valve,
- regurgitant flow through the closing valve,
- leakage flow through the closed valve,
- energy losses during forward flow,
- energy losses during valve closing,
- energy losses while the valve is closed and
- the maximum effective orifice area achieved by the valve.

All these parameters are assessed over the range of five applied flow rates, (3.6, 4.9, 6.4, 8.0 and 9.6 $l.min^{-1}$ equivalent cardiac output) for every valve, using frequencies of 60, 70 or 80 beats per minute with pump displacements delivering 60, 70, 80, 100 or 120ml in fixed combinations for each equivalent cardiac output. This provides a range of flow input that is approximately equivalent to physiological flow ranges and forms that would be expected in valve recipients. Data is acquired over between 20 and 40 functional valve cycles, dependent on flow rate, and an averaged pressure and flow waveform is calculated by the data processing software. Pressure difference and RMS flow are measured from the start of forward pressure to the end of forward pressure. Regurgitant flow is measured from the end of forward pressure to the end of forward flow. Leakage flow is measured from the end of forward flow to the start of forward pressure. Energy losses are calculated by integrating the pressure difference x flow, with respect to time. Effective orifice area at maximum is calculated as Peak Forward Flow/{√(Peak Forward Pressure) * 51.6}.

All valves are tested under similar conditions in the mitral simulation position. A standard mechanical valve is placed into the aortic simulation position of the rig and the rig is operated at a mean aortic pressure of 95mmHg. The pressure transducers are zeroed and calibrated at each test setting applied.

2.2: Factors Influencing Hydrodynamic Test Results

There are a number of mechanisms introducing random error into the results. These include errors in the response of the pressure transducers and the flow probe, the initial calibration of the system, as well as operator variation in defining start and end points within the dataset critical to the data calculation. These random errors would be expected to conform to a normal distribution. They are important when comparing data generated from different sources and for the setting of quality control parameters in valve testing. These sources of error are assessed in this study by multiple repetitions of testing on each individual valve.

Serious errors are obvious as soon as the data are calculated, e.g. introducing the wrong pump frequency or displacement, and the test should then be repeated.

There are several valve-related factors which influence the test results, many of which specifically apply to polyurethane-type valves. The first of these is the specific design of the valve. Even within a tri-leaflet design, there are many possible variations with a wide range of possible effects on hydrodynamic function. For example, a short free edge length will not permit the valve orifice to open as widely as a longer free edge length. The design must also take account of the specific material properties. In the first instance, this effectively means the Young's modulus of the material, i.e. how stiff the material is. A low modulus material is more flexible than a higher modulus material and, therefore, easier to open as a valve leaflet material, in most design conformations. A low modulus material may also be capable of producing a valve with a larger orifice, as the material may be able to open wider by stretching slightly. From the point of view of hydrodynamic function, it may be desirable to utilise a low modulus material, but other considerations, such as long-term durability, may result in a higher modulus material being preferred (O'Connor et al, 2000). Higher modulus materials, while being more difficult to open, may allow faster closure (Bernacca et al, 2000; 2001). The thickness of the valve leaflets also has a major influence on the hydrodynamic test results, with thicker leaflets producing much higher transvalvular pressure gradients and energy losses (Bernacca et al, 1997b, Bernacca et al, 2000; 2001).

The consistency of valve manufacture is also important in minimising variability in valve testing. Valve leaflets are dip-coated onto a frame from a polymer solution, and the valve is dried overnight in an oven under a controlled nitrogen atmosphere. It is important that the dipping and drying conditions are carefully controlled in order to produce leaflets of uniform thickness distributions. If, for instance, the drying valve is not positioned accurately into the oven, the resulting valve may have leaflets of differing thickness. This may also result from dipping into an inadequately mixed polymer solution.

Once the valve leaflets have dried, the valve is removed from the former and the leaflets cut to form the free edge of the valve. This cutting step introduces some variability into the precise length of the leaflets, from base to free edge. Again, valves are checked and those with obvious flaws rejected. There may, however, be sufficient variation remaining among valves to account for part of the difference in performance among valves of the same design and material, particularly in terms of regurgitant and leakage flow, and hence energy losses during closing and when the valve is closed. This arises from potential differences in the degree of closure possible for an individual valve, as well as the time taken during the valve cycle to reach full closure.

Leaflet thickness is mapped over 16 specified points on each leaflet. If the three leaflets do not have similar thickness distributions, the valve is rejected. If such a valve, with heterogeneous leaflet thicknesses, were tested hydrodynamically, it would be likely to demonstrate inefficient opening, with perhaps only two leaflets opening at low flow rates. In all valves of this type the thickness distribution over the valve leaflets is not uniform. The leaflets tend to be slightly thicker towards the leaflet-frame junction. This differential thickness is more apparent the thicker the leaflet is. Localised thickening of the leaflet, depending on its position, may affect the hydrodynamic function of the valve. For example, localised thickening close to the commissural region of the valve may prevent full opening of the valve compared with a valve that has thinner leaflets in this region. This in turn would produce higher pressure gradients, reduced flow through the valve, and reduced effective orifice area. Different valve designs will also produce somewhat different leaflet thicknesses and thickness distributions due to geometry effects influencing polymer run-off during valve drying.

2.3: What Does the Valve Development Scientist Want to Know from Hydrodynamic Function Testing?

The first item of information required is the ability to discriminate effectively among valves made of the same materials in the same way. This is a critical quality control function, which enables the rejection of valves that do not fall within a specified parameter set. In order to perform this function it is necessary to be able to define a parameter set that describes a particular valve design formulation.

Second, it must be possible to decide whether one valve design is better than another or whether a single design performs better when made using one material rather than another. Again, it is necessary to define a parameter set that describes the valves of interest.

Once this degree of objective discrimination is feasible, then investigation of the influence of other factors such as leaflet thickness and thickness distribution becomes possible.

The availability of objective assessment of valve hydrodynamic function would avoid the present situation in which valve performance is subjectively assessed by simple observation of graphical data. A limited portion of such data are generally selected for demonstration, due to the confusion created by plotting too many data on a single graph, and the viewer/reader may be easily influenced by selection of particular examples of valves, which demonstrate the effect desired by the researcher. Objective testing that used all available valve data, defining valve sets by parameter values, would avoid such subjective assessment and provide an invaluable tool for the valve developer.

2.4: The Valve Data Available for Analysis

There is a practical consideration that must be addressed when collecting hydrodynamic test data. The testing itself is relatively time-consuming, with five separate tests necessary for the simplest set of data for a single valve. Answers are required quickly so that design variations may be rejected or accepted for further evaluation. This sets a practical limit on the amount of testing that it is feasible to perform in order to evaluate any valve design.

A preliminary study was carried out to evaluate the degree of discrimination possible over a specified number of test repetitions of a single valve. For this testing, two valve designs were used (design GE and design LE). These were similar trileaflet designs with minor differences in leaflet geometry. Each design was manufactured into valves using a single polyurethane (Estane 58315, BF Goodrich) of relatively low Young's modulus. This material has been extensively researched and its properties and behaviour in this application are well known (Bernacca et al, 1995; 1997a; 2001). Six valves were manufactured in each design, under the same conditions, in parallel, to produce two sets of valves with similar leaflet thickness distributions. Each valve was tested ten times. No valve was tested more than once on any one day.

Further testing was performed using engineering design L, with six valves manufactured in each of three further polyurethane materials of differing composition and modulus properties. The four materials used for valve manufacture have different mechanical properties. In particular there is a wide range of material stiffness. The materials are described in Table 2.1, below.

Table 2.1: Valve Leaflet Properties

Design	Polyurethane	Modulus (MPa)	Mean (95%CI) Valve Leaflet Thickness (μm)
GE	Estane	16.2	88-93
LE	Estane	16.2	79-83
LL	Lycra	8.5	91-95
L4	EV3.34	32.5	134-140
L5	EV3.35	63.6	110-115

Of the five design variants, two differing physical designs are used with a single material. The mean leaflet thickness is similar for each valve group, and these would be expected to produce similar hydrodynamic function. Design G, however, has slightly better opening characteristics than design L. All other materials were tested in design L. The increasing modulus 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 altering the leaflet thickness. Lycra has a similar thickness distribution over the leaflets to the Estane valves, although the increase compared with design L in Estane may be sufficient to affect hydrodynamic function. This should be compensated to some degree by the lower modulus of Lycra compared with Estane.

The higher moduli of 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 (Bernacca et al, 2000; 2001). Unfortunately, due to practical difficulties in working with limited quantities of two experimental polyurethane variants (EV3.34 and EV3.35), it was not possible to produce sets of valves more closely matched in leaflet thickness across design variants. This does not detract from the potential of the analytical methodology for comparing valve types.

Testing in this phase was repeated five times for each valve, again with no valve being tested more than once in any one day. These data were compared with the first five test repetitions available on the first two data valve data sets. Selection of the first five data sets was made in consideration of the possibility of functional changes in the material performance with repeated testing. It is known that polyurethanes have time-dependent properties such that, in long-term fatigue testing, for instance, the modulus of the material drops slightly, as well as a tendency for the material to plasticise in solution. The consequence of this behaviour is an increased material flexibility. This effect is likely to be small over a small number of flexions of the valve leaflets; however, it may vary according to the material used, so that selection of a specified set of data repetitions is preferred, rather than a randomised selection among all the tests performed.

Chapter 3: Regression Analysis of Hydrodynamic Function Data

The two valve designs (G and L), both with Estane leaflets, as described in Chapter 2, were initially evaluated using a linear regression analysis for ten iterations of the tests on each valve. The amount of testing required to complete ten iterations is impractical for routine use, therefore the analysis was repeated using five iterations to determine whether sufficient discrimination could be achieved with fewer iterations on each valve.

It is known that over a continuous cycling period, polyurethane valve leaflets accommodate to the applied stress. It has also been shown that a polyurethane material demonstrates a fall in Young's modulus, during hysteresis testing applied at similar stress conditions to a functioning heart valve. This fall in modulus may be detected over a relatively small number of cycles, depending on the material (O'Connor et al, 2000). There is, therefore, the possibility that the hydrodynamic function of a valve may alter with increasing cycling, hence it was decided to select the first five iterations of each valve data set for the second analysis.

3.1 Regression Analysis by least squares

The application of a least squares regression analysis to the data from an individual valve should permit the description of the valve properties by an intercept and slope. Valve designs may then be compared by analysing intercepts and slopes for samples of valves of the different types.

The initial model is of the form

$$Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i$$

where the Y_i correspond to the hydrodynamic test parameter data (e.g. mean pressure gradient) and the X_i to the RMS flow data, β_0 is the intercept on the y-axis, β_1 is the slope of the line and ε_i are the amounts by which Y_i deviates from the population regression line. β_0 and β_1 can only be determined exactly using all possible occurrences of Y and X, hence estimates of these parameters, b_o and b_1 respectively, are determined from the sample data for the valve.

There are good experimental reasons for using the measured function, RMS flow, as the independent variable. We could use the assigned cardiac output applied by the pump, but this is not the flow that is directly delivered to the valve. Various factors influence the flow at the valve, both valve- and test rig-related. The RMS flow varies slightly with valve design, but more so with the test position used for the rig (here the mitral test position was used, but the aortic position may also be used and, in some circumstances will be preferred). The use of RMS flow as the independent variable gives a better picture of the real differences among valves tested than would the use of the applied flow. The conventional display of hydrodynamic function data, for these reasons, uses RMS flow as the "x" co-ordinate on graphs displaying the relationship with e.g. mean pressure gradient. The use of the RMS flow as the independent variable is acceptable from the statistical point-of-view as its variance is always very small compared with the variance of the dependent variable, although this does have some implications for the interpretation of the data that will be discussed later. For example, the residuals within a test run are likely to be positively correlated, violating the assumption of independent errors.

The initial analytical series involved 2 valve designs tested in the same material. There were 10 iterations of the test for each valve and a total of 6 valves of each type tested, initially, giving n = 60 datasets for each valve type. The second analytical series used the first five test iterations of the 2 valve designs denoted above, giving n = 30 datasets for each valve type. The aim of this second analytical procedure was to ensure that the amount of testing for future valves could be reduced without undue loss of statistical power.

The Ordinary Least Squares (OLS) estimators for the slope, β_1, and intercept, β_0, are

$$b_1 = S_{xy}/S_{xx} = \frac{(\sum X_i Y_i - n\bar{X}\bar{Y})}{(\sum X_i^2 - n\bar{X}^2)}$$

and

$$b_0 = \bar{Y} - b_1 \bar{X}$$

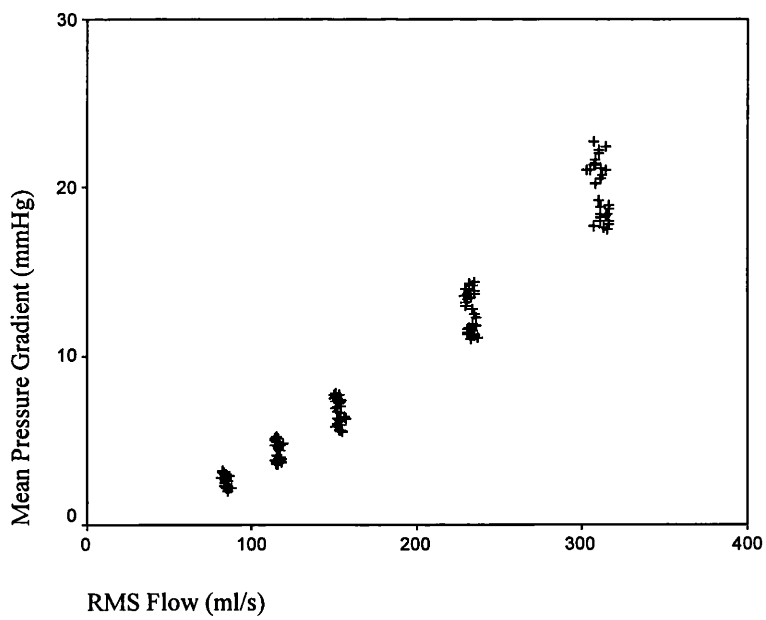
These estimators rest on the assumptions that $\varepsilon_1, \varepsilon_2 \ldots\ldots \varepsilon_n$ are independent and identically distributed random variables, each with mean 0 and variance, σ^2(>0). Standard methods of inference within the model assume additionally that each $\varepsilon_i \sim N(0,\sigma^2)$. However, it is the case that, even when these assumptions are not rigorously met, any least squares estimator is better than any other unbiased linear estimator, sinceit will produce an unbiased estimate with minimum variance (Silvey, 1975). In this situation, however, the estimated standard errors associated with the estimated regression parameters may not be correct.

All regression analyses were performed using Minitab for Windows version 12. All the regression data are tabulated in Appendix 1. Tables 3.1-3.7 contain data for ten iterations on each valve; tables 3.8-3.14 contain data for five iterations on each valve.

3.2 Data handling

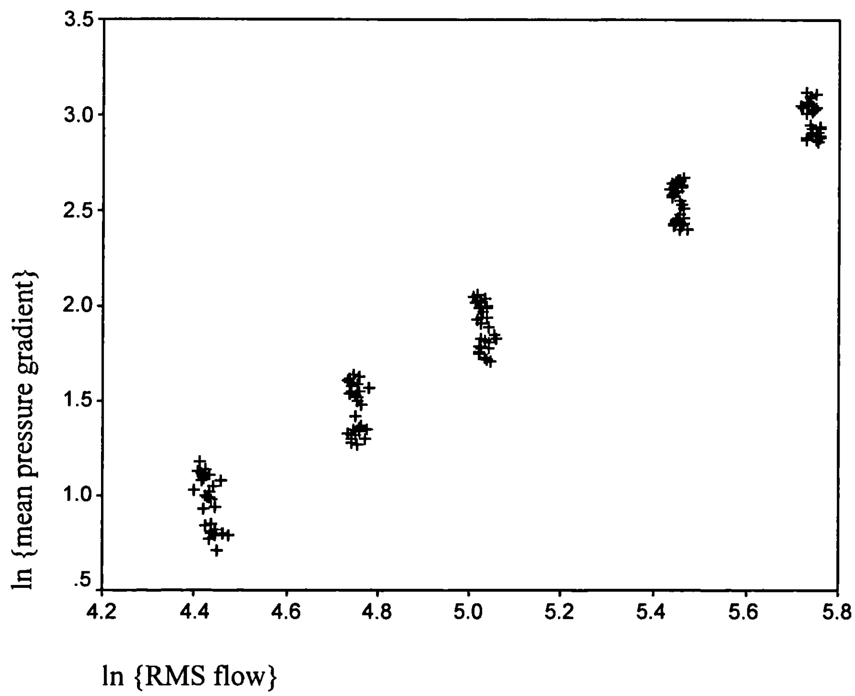
The mean pressure gradient vs RMS flow plot is non-linear (figure 3.1). The simplest analytical approach to attempt to deal with this is to transform the data to achieve linearity, prior to applying a least squares regression analysis to the data. The data also demonstrate a non-constant variance or heteroscedasticity, violating one assumption of the model above. Data transformation may also improve the variance homogeneity. Data were analysed for each valve individually.

Figure 3.1 Mean Pressure Gradient vs RMS Flow, showing non-linearity and heteroscedasticity



Various transformations were applied to the data, including reciprocal, square root and square transformations. However, the best fit was obtained with a logarithmic transform. A simple linear regression analysis, using the model described above, was applied to the log-transformed data: $X_i = \log_e$ RMS flow; $Y_i = \log_e$ {mean pressure gradient}. The fit appeared linear, although there was substantial deviation from the assumption of equal variance, notably at the lowest equivalent cardiac output (figure 3.2).

Figure 3.2 Natural logarithmic transform of Mean Pressure Gradient vs RMS Flow: regression is linear, some heteroscedasticity remains



A plot of the standardised residuals *vs* the fitted values (figure 3.3) indicated an improvement in the assumption of equal variances. The S-shaped curvature of the normal probability plot of the residuals (figure 3.4) suggests a degree of under-dispersion of the data. This may be caused by positive correlation between residuals from the same test run, when the measured function, RMS flow, is used as the independent variable. This can produce a residual plot with short tails, as seen here. Hence Normality does not hold for this measure, although the residuals distribution is symmetric. Given the symmetry of the distribution and a reasonable number of observations, the Central Limit Theorem would justify the use of standard confidence intervals and tests.

Figure 3.3 Plot of Standardised Residuals vs Fitted Values for log transformed Mean Pressure Gradient Data

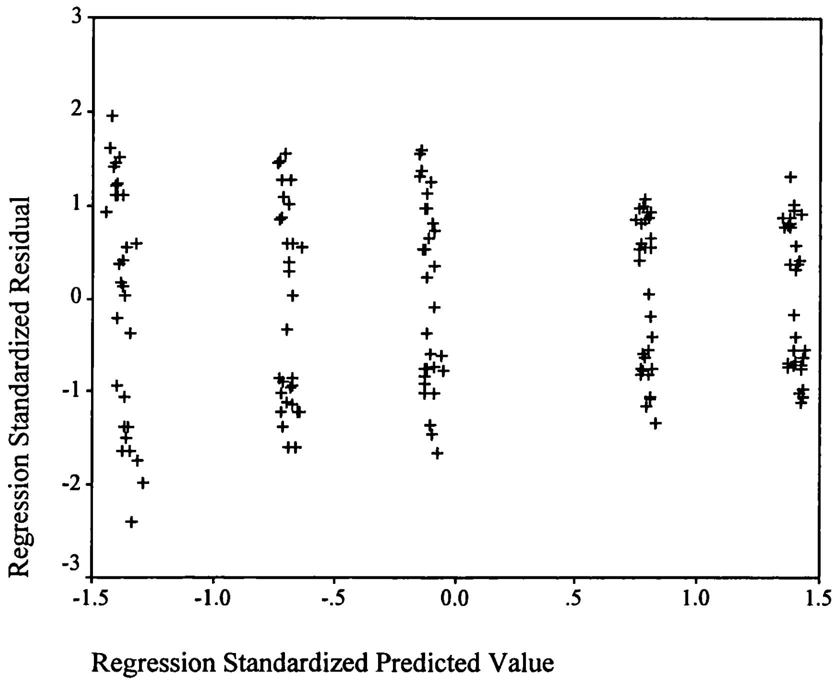
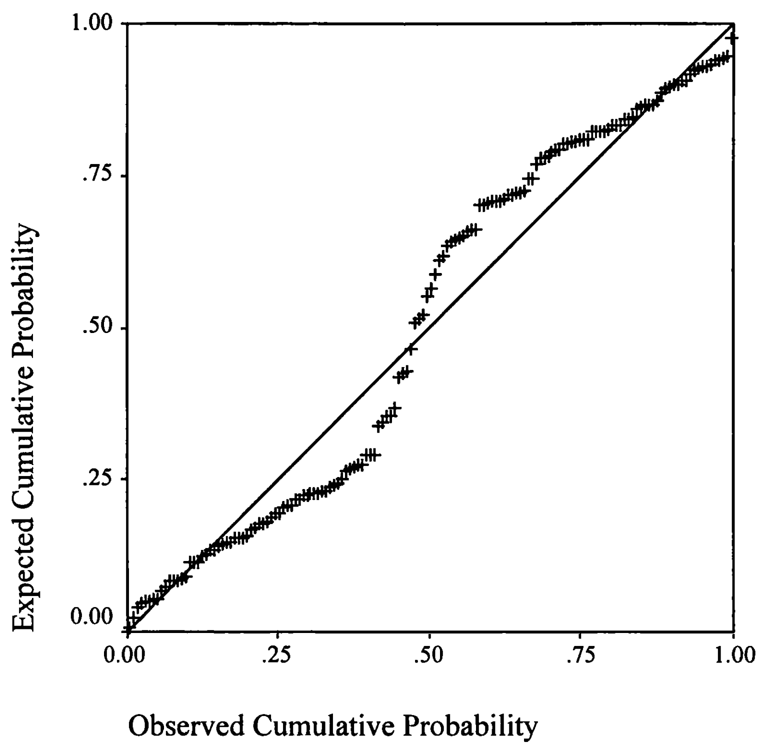


Figure 3.4 Normal Probability Plot of Standardised Residuals for log transformed mean pressure gradient data



A similar logarithmic data transformation was also required for the variables regurgitant flow and energy losses during forward flow, in order to achieve a plausible linear model: in these cases the normal probability plot was acceptable, with no evidence of serious deviation from normality and little evidence of under-dispersion of the data. 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.

It was clear, however, that the assumption of constant variance did not generally hold for these data. The principal cause of unequal variances is likely to be the relatively low signal:noise ratio in the differential pressure transducer at low cardiac output when the measured differential pressure is low, and the largest variance tends to be in the data for a cardiac output of $3.6 l.min^{-1}$. There is also a tendency to increased variance at the highest cardiac outputs, probably due to increased "noise" in the valve leaflet motion at high fluid throughput. A differential weighting according to applied cardiac output would allow greater weight to be placed on the data with the lowest variance, when estimating the regression parameters. Weighted Least Squares is a modification of Ordinary Least Squares that can improve estimation when error variances are not uniform or errors are correlated (Silvey, 1975).

Weighted Least Squares (WLS) Regression is more easily explained using matrix notation (Draper & Smith,1998). Thus the basic model described above may be written as

$$\underset{\sim}{Y} = X \underset{\sim}{\beta} + \underset{\sim}{\varepsilon} \quad where \quad E(\underset{\sim}{\varepsilon}) = 0, \quad V(\underset{\sim}{\varepsilon}) = \sigma^2 I \quad and \quad \underset{\sim}{\varepsilon} \sim \underset{\sim}{N}(0, \sigma^2 I)$$

The vector $\underset{\sim}{b}$ is the estimator of the vector $\underset{\sim}{\beta}$ and contains the two parameter estimators, b_0 and b_1. In this case, the least squares estimators are given by

$$\underset{\sim}{b} = \begin{bmatrix} b_0 \\ b_1 \end{bmatrix} = (X^{'}X)^{-1}X^{'}\underset{\sim}{Y}, \qquad \text{and the fitted values are} \qquad \underset{\sim}{\hat{Y}} = X\underset{\sim}{b} \quad .$$

Weighted Least Squares is used in situations in which $V(\varepsilon) \neq \sigma^2 I$, but is diagonal with unequal diagonal elements, so that Ordinary Least Squares (OLS) is no longer optimal. It is necessary to transform the original model, in order to find a new model that satisfies the assumptions of OLS, i.e. that the variance matrix V is equal to $I\sigma^2$ and that the errors approximate a Normal distribution, $\sim N(0, I\sigma^2)$. Matrix theory shows that it is possible to find a nonsingular, symmetric matrix, P, such that $P'P = PP = P^2 = V$. Now, let the random vector, $\underset{\sim}{f} = P^{-1}\underset{\sim}{\varepsilon}$, with $E(\underset{\sim}{f}) = 0$. Then $E(\underset{\sim}{f}\underset{\sim}{f}^{'}) = V(\underset{\sim}{f})$, where the expectation is distinct for every term in the square n x n matrix $\underset{\sim}{f}\underset{\sim}{f}^{'}$. It follows that $V(\underset{\sim}{f}) = E(\underset{\sim}{f}\underset{\sim}{f}^{'}) = E(P^{-1}\underset{\sim}{\varepsilon}\underset{\sim}{\varepsilon}^{'}P^{-1})$, since $(P^{-1})' = P^{-1}$. By rearrangement, this becomes $P^{-1}E(\underset{\sim}{\varepsilon}\underset{\sim}{\varepsilon}^{'})P^{-1} = P^{-1}PPP^{-1}\sigma^2 = I\sigma^2$. It also follows that $\underset{\sim}{f} \sim N(\underset{\sim}{0}, I\sigma^2)$ since the elements of $\underset{\sim}{f}$ are linear combinations of $\underset{\sim}{\varepsilon}$, which is itself assumed to be normally distributed.

We now return to the original matrix-format model, $\underset{\sim}{Y} = X\underset{\sim}{\beta} + \underset{\sim}{\varepsilon}$, and multiply throughout by the matrix P^{-1} to give $P^{-1}Y = P^{-1}X\beta + P^{-1}\underset{\sim}{\varepsilon}$. OLS theory can now be applied, since $E(P^{-1}\underset{\sim}{\varepsilon}) = E(\underset{\sim}{f}) = \underset{\sim}{0}$, and $V(\underset{\sim}{f}) = I\sigma^2$.

Estimates of the weights required for each valve were acquired by inversion of the variance estimates (s_{ei}^2, $i = 1,2\ldots5$) for each cardiac output, followed by normalisation by the largest inverted variance (Draper & Smith), giving estimated weights, $\hat{w}_i$. These weights are entered into the matrix P^{-1}, and OLS applied as before. In this case, the matrix of parameter estimators, $\underset{\sim}{b} = (X^{'}V^{-1}X)^{-1}X^{'}V^{-1}\underset{\sim}{Y}$, and the residuals are given by $P^{-1}(\underset{\sim}{Y} - \underset{\sim}{\hat{Y}})$. Even in situations in which

$V(\underset{\sim}{f}) \neq I\sigma^2$, the OLS estimators of $\underset{\sim}{\beta}$ are unbiased (as are the WLS estimators). The WLS estimators should, however, be more precise than the OLS estimators.

Weights were calculated for each individual valve, at each cardiac output, for each measured hydrodynamic parameter, for both ten and five replications of the tests. Weighting derived as described was applied to the data. The analysis was repeated giving a weighted least squares regression. In the majority of cases, this procedure gave satisfactory behaviour of the normal probability plots and the residual *vs* fitted value plots. In a few cases, a quadratic fit model seemed to give a marginally better fit to the data,

$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 X_i^2 + \varepsilon_i$$

with parameter estimates b_0, b_1 and b_2 derived in a similar way to that described above in section 3.1.

The quadratic fit was also applied in the cases of leakage flow, energy losses during valve closing and energy losses when the valve is closed. A weighted quadratic fit was further applied to the datasets using five replications only.

In several cases, large standardised residuals were observed. The data were re-examined, but no errors were detected in the data collection. The data were not regarded as experimentally unusual and were therefore retained in the statistical analysis. Adjusted R^2 values are given as measures of the goodness of fit of the regressions. R^2 is defined as the Residual Sum of Squares (RSS) divided by the corrected Total Sum of Squares (cTSS), subtracted from 1. The adjusted R^2 is defined as

$$1 - \frac{(RSS)/(n-p)}{(cTSS)/(n-1)} = 1 - (1 - R^2)\left[\frac{(n-1)}{(n-p)}\right]$$

, where n is the number of observations and p is the number of parameters to be estimated.

Means of regression parameters were compared between the two designs, using a t-test (SPSS v9.0 for Windows, SPSS Inc.)

3.3 Regression analysis of valve hydrodynamic parameters

In general, for all measures of hydrodynamic function, there was no apparent improvement in the goodness of fit (R^2) or precision (standard error) of parameter estimation gained from the weighted regression analysis compared with the unweighted analysis. This finding is contrary to expectations and may be an artefact of the relatively small numbers of valves and replications available for analysis. It may be that the sources of variation among the different valves are not identical thus influencing the effects of weighting in some individual valves. In addition, the estimated standard errors obtained from the ordinary least squares regression will not be correct, since the model does not match the true variance function, so this could also explain the apparent lack of improvement in precision using the weighted analysis.

3.3.1 Mean pressure gradient

The regression data for ten (Table 3.1) and five (Table 3.8) replications of each valve test are tabulated in Appendix 1. For design GE (valves designated g1-g6) and design LE (designated l1-l6), the mean values (standard deviation) for the intercepts and gradients of the six regression lines are tabulated below (Table 3.15).

Table 3.15 Regression parameter estimates for each valve design ($\log_e$ {mpg} regressed on $\log_e$ {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_1 unweighted	b_0 weighted	b_1 weighted
GE	10	-6.33 (0.25)	1.55 (0.04)	-6.42 (0.28)	1.57 (0.05)
	5	-6.32 (0.34)	1.55 (0.06)	-6.46 (0.28)	1.58 (0.04)
LE	10	-5.93 (0.33)	1.55 (0.04)	-5.92 (0.37)	1.55 (0.05)
	5	-5.85 (0.28)	1.54 (0.04)	-5.90 (0.33)	1.55 (0.04)

There was no significant difference on average, between the gradients of the regression lines for the two designs, whether 10 or 5 replications were considered. Over ten replications, the difference between the mean unweighted intercepts for the two valve designs was significant ($p = 0.035$). The difference between the mean intercepts of the two designs was even more significant after weighting the regression fit ($p = 0.025$).

The differences between the two designs were similar when only five replications of the data were considered. The mean unweighted and weighted intercept parameters of the regression fit were, again, significantly different between the two designs ($p = 0.026$ and $p = 0.011$, respectively).

In all cases, the intercept for design GE was significantly lower, on average, than for design LE. This implies that design GE has better valve opening characteristics than design LE, over the whole range of applied cardiac outputs. A lower mean pressure gradient (and hence a lower $\log_e$ {mean pressure gradient}) across the open valve indicates that less force is required to open the valve leaflets and/or that the open valve orifice is relatively large.

The regression fit was good, with the adjusted R^2 being greater than 98.6 in all cases, regardless of weighting.

3.3.2 Regurgitant flow

The regression data for ten (Table 3.2), and five (Table 3.9) replications of each valve test are tabulated in Appendix 1. The mean values (standard deviation) for the intercepts and gradients of the six regression lines are tabulated below (Table 3.16).

Table 3.16 Regression parameter estimates for each valve design ($\log_e$ {regurgitant flow} regressed on $\log_e$ {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_1 unweighted	b_0 weighted	b_1 weighted
GE	10	1.16 (0.19)	-0.02 (0.02)	1.19 (0.16)	-0.03 (0.01)
	5	1.19 (0.21)	-0.03 (0.03)	1.21 (0.16)	-0.03 (0.02)
LE	10	1.12 (0.20)	-0.02 (0.03)	1.11 (0.25)	-0.03 (0.04)
	5	1.16 (0.17)	-0.04 (0.03)	1.11 (0.24)	-0.04 (0.05)

Several of the b_1 estimates (the gradients of the regression lines) were not significantly different from zero. Otherwise there was a slight trend towards a decreasing slope with increasing cardiac output. There was no significant difference on average, between the gradients of the regression lines for the two designs. There was no significant difference on average between the intercepts for the two designs, whether an unweighted or weighted model was used. The increased number of replications did not affect the comparison of the two designs.

The regression fit was extremely variable, with the adjusted R^2 ranging from -4.2 to 44.6 in the unweighted model, and from –4.3 to 53.2 in the weighted model, for 5 replications.

The experimental measurement of flow is less precise than the measurement of differential pressure due to the peculiarities of the individual transducer designs. The actual regurgitant flow volume is small (generally less than 5ml) and the measuring system is not capable of distinguishing small differences in flow volume. The measuring difficulties are likely to exceed any real differences between these two particular valve designs, given the design similarity and the common leaflet material.

3.3.3 Leakage flow

The regression data for ten (Table 3.3) and five (Table 3.10) replications of each valve test are tabulated in Appendix 1. The mean values (standard deviation) for the intercepts and gradients of the six regression lines are tabulated below (Table 3.17).

Several of the b_1 estimates (the gradient of the regression lines) were not significantly different from zero. Otherwise there was a slight trend towards a decreasing slope with increasing cardiac output. There was no significant difference on average, between the gradients of the regression lines for the two designs.

Table 3.17 Regression parameter estimates for each valve design (leakage flow regressed on $\log_e$ {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_1 unweighted	b_0 weighted	b_1 weighted
GE	10	4.06 (0.71)	-0.69 (0.10)	3.85 (0.95)	-0.65 (0.15)
	5	4.24 (0.83)	-0.73 (0.12)	3.85 (1.34)	-0.66 (0.21)
LE	10	4.84 (0.25)	-0.75 (0.04)	4.84 (0.35)	-0.76 (0.06)
	5	4.83 (0.43)	-0.74 (0.11)	4.49 (0.78)	-0.69 (0.14)

There was no significant difference between the intercepts of the two designs, whether an unweighted or weighted model was used. The increased number of replications did not affect the comparison of the two designs.

The regression fit was extremely variable, with the adjusted R^2 ranging from 32.8 to 79.5 in the unweighted model, and from 5.9 to 85.5 in the weighted model, for 5 replications.

An unweighted quadratic model was applied to these data for both 10 and 5 replications. The fit, as judged by the adjusted R^2, was improved, to range from 47.4 to 88.9 for the individual regressions with 5 replications. There was little practical difference in the conclusions to be drawn from the unweighted quadratic fit and a weighted quadratic fit. The weighted fit should provide more precise estimates, but any benefit may be concealed here because of the small numbers of valves available for testing and the small numbers of replicate analyses made. A difference could be detected between the two designs using the quadratic fit. Again, mean parameter values (Table 3.18) were compared using a t-test.

The differences between the two designs were significant for each mean parameter estimate, b_0, b_1 and b_2, with p = 0.002, p = 0.004, p = 0.004, respectively for ten replications. Differences for five replications were not significant.

Table 3.18 Regression parameter estimates for each valve design - quadratic fit (leakage flow regressed on $\log_e$ {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_0 weighted	b_1 unweighted	b_1 weighted	b_2 unweighted	b_2 weighted
GE	10	22.16 (3.15)	-	-7.84 (1.29)	-	0.70 (0.13)	-
	5	24.56 (7.25)	25.75 (7.50)	-8.74 (3.02)	-9.23 (3.10)	0.79 (0.30)	0.83 (0.31)
LE	10	28.96 (1.62)	-	-10.30 (0.66)	-	0.94 (0.06)	-
	5	29.94 (2.54)	31.32 (8.02)	-9.02 (3.75)	-11.23 (3.23)	0.98 (0.10)	1.03 (0.32)

Similar considerations apply to the measurement of leakage flow through the closed valve as to regurgitant flow (see section 3.3.2, above). The measurement of leakage flow has an added complication, however, in that it is highly dependent on the accuracy of cutting the leaflets. It can be seen from the tabulated data above that the standard deviations of the mean parameter estimates for design GE are greater than those for design LE. Leaflet cutting is a skilled task, originally performed by hand, and later with the aid of a manually rotated dermatome blade. This latter development has improved the consistency of the cutting process, but there remains considerable variability that can be attributed to this process, particularly affecting the leakage flow. If, for example, the leaflets are cut a little low, then a flow path becomes available when the valve is closed, for backwards flow through the closed valve, and leakage flow increases. Minor differences in valve design may also affect the ease with which leaflet cutting can be achieved. It is likely that the increased variability associated with design GE is associated with the leaflet cutting procedure. Commonly, the variation in cutting noticeably affects one leaflet on a valve more than the remaining two leaflets. A consequence of this is likely to be a sensitivity of the measured leakage flow to the orientation of the valve in the test rig, and this sensitivity is likely to be greater for more leaky valves. Therefore, while it is apparent that in the current comparison, five replicates are insufficient to provide a significant separation of the two designs, it is likely that an improved leaflet cutting technique currently in development, would reduce the variance associated with this measurement and offer the possibility of separating the designs with fewer replications.

3.3.4 Energy Losses during Forward Flow

The regression data for ten (Table 3.4) and five (Table 3.11) replications of each valve test are tabulated in Appendix 1. The mean values (standard deviation) for the intercepts and gradients of the six regression lines are tabulated below (Table 3.19).

There was no significant difference on average, between the mean gradients of the regression lines of the two designs, whether a weighted or unweighted model was applied.

Over ten replications, the difference between the mean unweighted intercepts was significant ($p = 0.029$). There was little practical difference in the conclusions to be drawn comparing the unweighted and weighted fits: as before, the weighted fit should provide more precise estimates, but any benefit may be concealed here because of the small numbers of valves available for testing and the small numbers of replicate analyses made. The differences between the two designs were similar when only five replications of the data were considered. The intercept estimates of the unweighted regression model were, again, significantly different between the two designs ($p = 0.021$).

Table 3.19 Regression parameter estimates for each valve design

(log_e {energy losses during forward flow} regressed on log_e {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_1 unweighted	b_0 weighted	b_1 weighted
GE	10	-5.27 (0.21)	1.55 (0.03)	-4.86 (0.21)	1.68 (0.04)
	5	-5.28 (0.30)	1.76 (0.05)	-4.92 (0.35)	1.69 (0.06)
LE	10	-4.84 (0.35)	1.55 (0.06)	-4.41 (0.36)	1.68 (0.05)
	5	-4.83 (0.26)	1.76 (0.04)	-4.67 (0.65)	1.73 (0.12)

The regression fit was good, with the adjusted R^2 being greater than 98.7 for five replications, considering unweighted data. Design GE with significantly lower intercept estimates is, again, defined as the better valve design in terms of this hydrodynamic function measure.

3.3.5 Energy Losses during Valve Closing

The regression data for ten (Table 3.5) and five (Table 3.12) replications of each valve test are tabulated in Appendix 1. The mean values (standard deviation) for the intercepts and gradients of the six regression lines are tabulated below (Table 3.20).

Over ten replications, there were no significant differences on average, between the slope or intercept estimates of the two designs. As before, there was no difference in outcome using a weighted regression model.

Table 3.20 Regression parameter estimates for each valve design (energy losses during valve closing regressed on $\log_e$ {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_1 unweighted	b_0 weighted	b_1 weighted
GE	10	-10.35 (5.36)	9.03 (1.45)	-11.87 (12.31)	9.17 (2.85)
	5	-9.32 (6.57)	8.78 (1.59)	-11.46 (11.02)	9.21 (2.36)
LE	10	-9.95 (4.01)	8.53 (0.92)	-10.13 (4.11)	8.46 (1.07)
	5	-7.11 (5.59)	8.05 (1.23)	-8.14 (6.00)	8.23 (1.38)

Similar results arose from consideration of five replications of the data. Several intercept parameters were themselves not significant, although the adjusted R^2 was greater than 59.4 for all valves, considering five replications. Considering ten replications, however, there appears to be an anomalous dataset (11), which produced an individual R^2 of 4.3. Weighting the data did not affect the outcome of the analysis. A quadratic fit on ten replications produced an improvement (as expected) in R^2, but did not enable separation between the two designs. Considering five replications, the unweighted quadratic fit appeared to separate the two designs on the basis of the average values of b_0 (p = 0.006), and the parameter estimates b_1 (p = 0.008) and b_2 (p = 0.010).

A similar consideration of sources of error applies to the calculation of energy losses during valve closing as for regurgitant flow (see 3.3.2 above).

3.3.6 Energy Losses when Valve is Closed

The regression data for ten (Table 3.6) and five (Table 3.13) replications of each valve test are tabulated in Appendix 1. The mean values (standard deviation) for the intercepts and gradients of the six regression lines are tabulated below (Table 3.21).

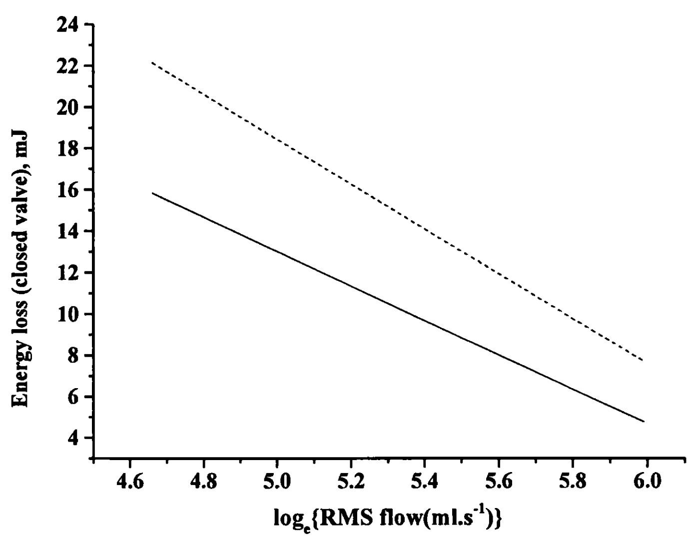
Table 3.21 Regression parameter estimates for each valve design (energy losses when valve is closed regressed on $\log_e$ {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_1 unweighted	b_0 weighted	b_1 weighted
GE	10	54.62 (9.41)	-8.32 (1.41)	54.04 (11.44)	-8.23 (1.87)
	5	56.74 (10.33)	-8.79 (1.60)	51.59 (16.90)	-7.85 (2.71)
LE	10	72.58 (8.96)	-10.83 (1.10)	71.37 (12.85)	-10.62 (1.86)
	5	74.37 (4.43)	-11.09 (0.75)	73.61 (10.07)	-11.09 (1.54)

Over ten replications, there were significant differences between both the slopes (p = 0.006) and the intercepts (p = 0.007) of the two designs. As before, there was no difference in outcome using a weighted regression model.

Similar results arose from consideration of five replications of the data (p = 0.003, p = 0.010, respectively for unweighted data). The adjusted R^2 was quite variable ranging from as low as 29.3 to 78.9 for unweighted data. A quadratic fit produced a small improvement (as expected) in R^2, and confirmed that there was a significant separation, on average, between the two designs. The two regression lines are plotted for 5 replications of each design (figure 3.5). It may be clearly seen from the plots that design GE has significantly lower energy losses when the valve is closed than design LE at all relevant cardiac outputs.

Figure 3.5 Regression lines plotted for energy loss when valve is closed vs $\log_e$ {RMS flow} for design GE (solid line) and design LE (dotted line), 5 replicates of each valve.



The energy losses while the valve is closed are subject to similar sources of variability as the regurgitant and leakage flows. However, the leakage flow is relatively small and moderated somewhat by the more accurate pressure measurement in the calculation of the energy losses (even although the valve is closed and the pressure averages zero, there is some pressure fluctuation which contributes to the calculation). This may explain the improved discrimination between the two designs using the closed valve energy losses as compared with the leakage flow data.

3.3.7 Effective Orifice Area at Maxima

The regression data for ten (Table 3.7) and five (Table 3.14) replications of each valve test are tabulated in Appendix 1. The mean values (standard deviation) for the intercepts and gradients of the six regression lines are tabulated below (Table 3.22).

Table 3.22 Regression parameter estimates for each valve design (effective orifice area at maxima regressed on $\log_e$ {RMS flow}, sample mean (s.d.))

design	replicates	b_0 unweighted	b_1 unweighted	b_0 weighted	b_1 weighted
GE	10	-0.18 (0.12)	0.32 (0.03)	-0.14 (0.10)	0.31 (0.02)
	5	-0.19 (0.16)	0.32 (0.04)	-0.15 (0.12)	0.31 (0.02)
LE	10	-0.32 (0.11)	0.30 (0.01)	-0.33 (0.11)	0.30 (0.02)
	5	-0.32 (0.10)	0.29 (0.02)	-0.34 (0.16)	0.30 (0.03)

Over ten replications, there was no significant difference on average, between the slopes of the two designs, whether a weighted or unweighted model was used. Similar results were obtained using five replications.

Differences between the intercepts of the two designs did not quite reach significance using unweighted data ($p = 0.051$). Using a weighted regression model improved the discrimination of the intercepts of the two designs ($p = 0.011$).

Similar discrimination of the intercepts was achieved considering five replications of the data ($p = 0.107$ for the unweighted model; $p = 0.036$ for the weighted model). The adjusted R^2 was greater than 82.0 in all cases.

The results imply a difference between the two valve designs, with respect to the orifice area achieved at maximum pressure and forward flow, with design GE having a larger flow orifice than design LE. The larger orifice allows a greater volumetric flow through the valve and is preferable to a smaller valve orifice.

3.4 Summary

The two valve designs were analysed using linear regression analysis, applied to each valve individually, over 10 or 5 iterations of the test. No significant differences were detected between the mean slopes of the regressions, with the exception of the hydrodynamic function measure, energy losses when the valve is closed. Significant differences between the two designs were detected for mean pressure gradient, energy loss during forward flow, energy loss when the valve is closed and effective orifice area at both 10 and 5 iterations of the test, for the mean intercepts of the regressions. For these hydrodynamic parameters, therefore, and with at least 6 valves of each design, it seems that 5 iterations of the test data are sufficient. The variability associated with regurgitation and energy loss through the closing valve suggests that these may be hydrodynamic parameters of the valve function with very low discriminating power between designs. Leakage through the closed valve provided inconsistent discrimination, and was only capable of detecting a statistically significant difference between the two designs using a quadratic regression model: discrimination here may be improved, however, by improvements in the valve manufacturing process to improve consistency in the leaflet trimming procedure.

The data examined here were pooled from the iterative tests into individual valve regressions. Thus the information about the reproducibility of the testing procedure was lost. The data for each regression parameter estimator for each valve was pooled to provide a mean value to represent each design. Thus information about individual valve variability within each design was lost. The two designs addressed here had similar regression slope behaviour, but this is unlikely to be the case for all designs studied, so that a further complication of a mixed regression model may be encountered where intercept and slope parameters may or may not be similar.

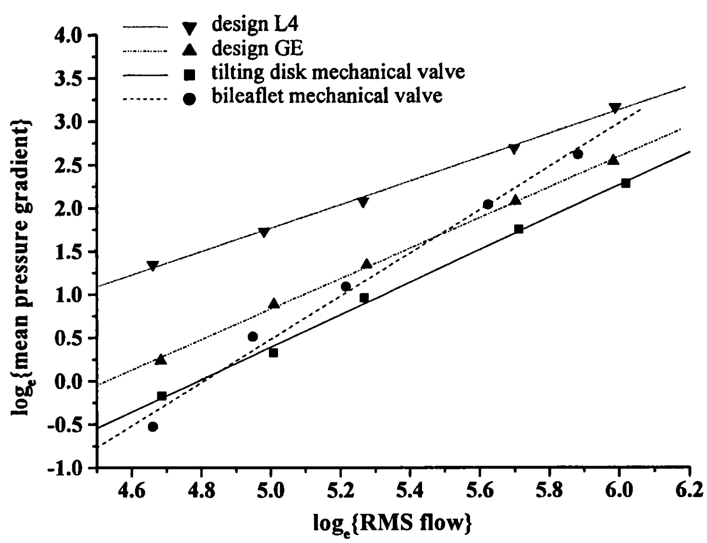
In general, valve design GE has a significantly better hydrodynamic performance than valve design LE.

Chapter 4: Evaluation of the Linear Regression Approach

Linear regression analysis has the value of enabling a specific mathematical description of the behaviour of a specific valve or set of valves. Thus any specific valve design may be described in terms of its hydrodynamic function by the average intercept and slope estimates of the regression line obtained from a specified measure of the hydrodynamic function at a series of applied flow rates, across a sample of individual valves. It is apparent from the data that there are differences between the two valve designs already considered that seem to be greater than differences among valves of a single design or among repeated analyses of a single valve. However, random regression analysis does not easily allow these differences to be quantified in terms of their statistical significance.

The data presented here provide 5 serial outcome measures for each hydrodynamic function measure calculated, for each individual valve. The data could have been compared at each applied cardiac output, but there are serious problems with such an approach (Matthews et al, 1990). In scientific terms, any variation in performance between valves over cardiac output is not observed effectively. It is fundamental to the evaluation of a valve that its performance over the whole range of cardiac outputs of interest can be compared with other valves. In statistical terms, the serially collected data will not be independent of each other so that the value at the lowest cardiac output influences subsequent measures at higher cardiac outputs. Such a statistical evaluation may be performed at any single cardiac output using analysis of variance for comparison of multiple valves. This approach would suffice for conditions in which the designs being compared were of "different intercept" but "same slope", such as seems to be the case for the first two designs compared for most hydrodynamic function measures, in which the leaflet material is the same in each valve type, but the engineering design of the valves is slightly different. However, it is unsuitable for situations that will arise in which the designs produce "different slopes" as well as "different intercepts". This is likely to be the case when comparing, for instance, a mechanical or bioprosthetic valve with the polyurethane valves under development (figure 4.1).

Figure 4.1 Comparison of $\log_e$\{mean pressure gradient\} vs $\log_e$\{RMS flow\} for a for 4 different types of valve: a tilting disk mechanical valve; a bileaflet mechanical valve, a GE design valve and an L4 design valve (all valves are within the nominal size range 23-5mm)



In this situation, the relative performance of individual valves varies over the range of cardiac outputs. Such a comparison becomes important for validation of the design in terms of its performance in competition with existing, commercially available valves.

It is also likely to be the case when materials of higher modulus are used in a similar engineering design or for substantially different engineering designs for the valve (see figure 4.1, design GE compared with design L4).

In both these cases, the performance of the valve is likely to vary depending on the applied flow rate and one valve may perform well at one extreme flow condition, but be relatively poor at the other extreme of flow. While it is important that the valve will open easily and fully at low flow rates, it is also important that it perform well at higher flow rates, when the valve recipient would be more physically active, in order to maintain a good quality of life. There may be a trade-off between good performance at low flow and the maintenance of performance as demand on the heart increases. The analysis of variation approach would require to be applied to each flow rate under consideration and viewed as a series of responses, considered as a whole. This is a clumsy and inelegant approach, and it is no longer feasible to assess the designs in a straightforward, simply defined way. This approach is also statistically flawed, as the data are not independent since they derive from the same subject. There is a further problem with this approach to the analysis in that the applied cardiac output itself does not transfer precisely to flow rate through each individual valve. The actual flow through the valve is measured as RMS flow and varies according to the properties of an individual valve. The variation in flow for an individual valve at any specified cardiac output is relatively small compared with the hydrodynamic function measure of interest (e.g. energy loss during forward flow), but the differences between applied and measured flow rates indicate that a regression approach is preferred whereby the whole range of data available for an individual valve is considered to represent the valve performance.

The data in Chapter 3 have, effectively, been analysed using a two-stage process. The first stage calculates an appropriate summary measure of the data (in this case, the regression parameter estimates for each individual valve for the selected hydrodynamic function measure regressed on the measured $\log_e$ {RMS flow}). The second stage compares the summary measures using simple statistical tests (in this case a t-test). This method is recommended to overcome some of the problems associated with the first analytical approach described above (Matthews et al, 1990), as this approach does utilise the whole range over which the serial measurements are collected. However, the situation in the present study raises further questions. In this case, the parameter estimates b_0 and b_1 tend to be negatively correlated. This creates difficulties in comparing valve designs for which the slopes of the regressions are significantly different. In this case the model must be extended to allow statistical inference about $(\beta_{0i} + \beta_{1i}x) - (\beta_{0j} + \beta_{1j}x)$ for some value x, for any valve types i and j.

The ideal situation would permit the simultaneous assessment of a series of valve designs, allowing these to be ranked in terms of their performance, highlighting those design combinations which are significant improvements over existing valves and other design options. The data available have restrictions associated with the difficulty of obtaining large numbers of valves to test and with the time required to actually perform the valve hydrodynamic testing. Hence the polyurethane valve dataset has repeated values on the valves, limited to five iterations for practical reasons. For manufacturing reasons, the numbers of valves available for any single design, in any specific size, does not exceed six. Consideration of existing commercial valves is even more difficult as often only one or two valves may be available due to the high cost of acquiring clinical quality valves.

These methods do not allow the straightforward assessment of the variance associated with each major source of variability. The variability associated with different valves of similar design is "lost" within the overall variance associated with the parameter estimates obtained by averaging the data for 6 valves, as is the variability associated with replications of each individual valve. In this context, variance has a straightforward interpretation in quality assurance terms. Variation from test run to test run in the same valve is introduced by the hydrodynamic test rig and knowledge of this allows a check on the rig function itself, which shows up as variability in test results among valves of the same design. There is significant variability in the valve manufacturing process. It is important to be able to describe the amount of this variability and, if possible, to achieve measurable improvements in the process control.

The data structure, therefore, has a hierarchical nature with test iterations nested within individual valves, and individual valves being members of specific design configuration groups. This data structure suggests that a multi-level modelling approach might provide useful insights, by permitting the simultaneous comparison of the regression lines, accounting for both "different intercepts" and "different slopes", as well as the data hierarchy. The ability of the multi-level modelling appro92h to use all the information available for a valve (not just $\hat{\beta}_0, \hat{\beta}_1$) should give more power to detect differences between valve types. A further potential advantage of multi-level modelling methods is their ability to handle unbalanced datasets. The data available for this study had no missing data. This may not always be the case, however, as for designs with extremely good hydrodynamic performance, when the material is very flexible and the flow rate is low, it becomes very difficult to separate the differential pressure across the valve from zero under these conditions and the test software cannot always provide a valid data point. This potential missing data problem increases for better valve designs, and complicates conventional analytical methods, which depend on the assumption of a balanced dataset. Technically, multi-level modelling requires that data be "missing at random", which is not entirely true for these data. However, this is unlikely to seriously affect estimation of the parameters, although it may affect their standard errors (Omar et al, 1999; Goldstein, 1999; Browne & Draper 2000).

Chapter 5: A Multi-level Modelling Approach to the Analysis

This chapter describes the principles of multi-level modelling, its applications and how it might apply to the present dataset.

5.1 General principles of multi-level modelling

Multi-level modelling was originally developed for the analysis of hierarchical data in social sciences, for situations in which data could be grouped into categories within which individuals were more similar than between categories, and thus data was not entirely independent, as the groupings influenced the behaviour of the individuals within the groups.

"*Multilevel modelling, also known as hierarchical regression, generalizes ordinary regression modelling to distinguish multiple levels of information in a model*" (Greenland, 2000). This definition summarises the purpose of multilevel modelling. The application of such an approach has, in the past, been impractical for the ordinary researcher, given the high level of computational skill and power required. In recent years, however, new software has become available to tackle the problem, making the approach more readily available for general use.

In social sciences these methods have been extensively used for the analysis of pupil performance in an educational context (Goldstein, 1999). In such cases, the individual pupil may be grouped within a class/teacher and within a school, i.e. pupil nested within class/teacher, nested within school. In situations where such groupings were ignored, and conventional multiple regression analysis techniques employed, "false" significances were attributed to individual pupil performances according to teaching styles. Such differences disappeared when the data were re-analysed using multilevel techniques, accounting for the group effects within the hierarchy. This type of significance finding is a recognised problem of aggregation of data from several hierarchical levels, in effect because individuals within a group should provide less information to the analysis, because of the within group influences, than do completely independent individuals. Thus, the sample size that is utilised for significance testing is too high and should more reasonably be that of the higher group level rather than the number of individuals, and the resultant standard error estimates are too low, producing spurious significances. The statistical power of the analysis is reduced (Hox, 1995). Multilevel modelling considers the influences of each level of the hierarchy on the performance of the individuals, for instance whether the influence of the teacher or the school is greater than individual pupil variations over time. Such techniques allow the researcher to obtain statistically efficient estimators of regression coefficients, as well as, by considering the grouping of the data, allowing the calculation of more accurate standard errors, confidence intervals and statistical significance tests. Multilevel modelling also allows the relative ranking of members of each level of the group hierarchy in a straightforward way (Goldstein, 1999).

5.2 Applications of multilevel modelling

The main area of application has been, as already suggested, in the area of social sciences (Hox, 1995; Goldstein,1999), especially within the analysis of educational attainment. Most other published applications involve a philosophically similar type of data configuration. There are, currently, no available published instances of application of these statistical methods to an engineering problem. Greenland (2000) has drawn attention to the fact that multilevel modelling is widely used in social sciences, but that it is neither understood well nor generally used in health sciences. He makes no reference to its use elsewhere.

Armstrong *et al* have applied multilevel modelling methods to the analysis of the effects of gender, growth and maturity on peak oxygen uptake (1999) and short-term power output (2000) of young people. They used the multilevel software package, MLwiN, to perform the analysis. The hierarchy was defined as repeated measure occasions (level 1) grouped within individual subjects (level 2). Multilevel modelling was the preferred method of analysis, given its ability to describe, in addition to the mean population response, the variation about the mean at both levels of the data hierarchy. Specifically, at level 2, each individual is permitted to have his/her own growth rate, varying randomly about the population response, and, at level 1, variation in the individual response is observed. A further advantage of this method is that a complete dataset is not required, in that the number of observations per individual may vary, as well as the longitudinal spacing of the measurements. The use of multilevel modelling allowed the underlying mean response to be described, while, at the same time, demonstrating the considerable variation in individual growth rates. Influences of age, gender and maturity on peak oxygen uptake were detected by the multilevel modelling approach, which may have been masked in previous studies by inappropriate statistical analysis methods or failure to consider the influence of all possible covariates.

A second area of research has used multilevel modelling techniques to investigate discard rates in commercial fishing and the variables that influence these (Tamsett & Janacek, 1999a, Tamsett *et al*, 1999b). This model was described in two ways. The first was a three-level model, with level 1 as discarding rate among trips within a level 2 described by a combination of type of fishing gear, port, season and area fished, within level 3, the year of study (1999a). The second model allocated level 1 as the discarding rate among hauls within level 2 trips, within a combined level 3, including vessel, port, fishing gear, season, area and mesh (1999b). The analysis was further refined by stratifying the combined levels in each case, as the datasets were too small to allow all parameters to be estimated. The stratification was also used to suppress bias in the estimates, caused by non-random sampling. This research used the software package MLn, an earlier version of MLwiN, referred to above. A major disadvantage of this software version was its inability to apply weighting to the model. There was variation in both the discard rate and the variance of the discard rate with catch size. It was, therefore, desirable to compensate for the variation in catch sizes by weighting, in order to suppress bias in the estimates. The data analysis in these studies was complicated by large variances and hence poor precision of the estimates of discarding. The authors have further work to do to determine optimum sampling conditions to improve the quality of the data available for this type of analysis: however, multilevel modelling is obviously an appropriate methodology to apply to the problem.

The multilevel approach has also been applied in veterinary medicine to investigate lamb growth (Lancelot *et al*, 2000). In this case, the study investigated the effects of a worming treatment given to ewes on the growth of young lambs, pre-weaning. The authors focus on the use of graphical methods to investigate the influence of various factors on growth curves of lambs and, hence to support the choice of model definition for the multilevel model. The model was defined at three levels: level 1, the lowest level, was village; level 2 was herd and level 3 was individual lamb. Models were fitted using restricted maximum likelihood, although a specific software solution was not specified. The use of the multilevel approach, in this case, identified a significant effect related to the worming treatment that had been missed by an earlier study using a cross-sectional ANOVA.

The multilevel modelling approach, using MLn, has been applied to demographic research, for example to investigate fertility among women in Bangladesh (Abdullah Khan, 1997). This was a three-level model, with mothers at level 1, nested within a regional blocking group at level 2, nested within regions at level 3. The data were further divided into four cohorts, encompassing two age groups and urban or rural living. A series of eight explanatory variables was also considered for inclusion in the model. The likelihood ratio statistic was used to determine the inclusion or exclusion of variables into the model and variance components analysis was used to determine the relative influences of the different levels of the model. The study found that almost all the variance was accounted for at level 1, the individual mothers. One conclusion, in this situation, was that a single level type of analysis was appropriate, although in the rural cohorts there was some variance associated with the level 2 blocks, possibly related to the proximity of a block to an urban area. Thus, the single level analysis probably would not produce a misleading result overall, but without the multilevel modelling the influence of location in some situations would have been missed.

Clinical trials of drugs, especially when repeated measures over time are investigated, are often situations in which multilevel modelling could usefully be applied. One such study compares methods of analysis of repeated measures, considering asthma treatments in children (Omar *et al*, 1999). The data considered are a baseline measurement and four post-randomisation measurements for each child. Treatments included one of two drugs or a placebo. Baseline covariates of age, height and centre were also available. As is common with clinical trial data, the amount of missing data increased with time throughout the study. The study considered unweighted and weighted summary statistics, repeated measures

ANOVA, marginal models based on generalized estimating equations and multilevel models using MLn software, and focussed on the value of these methods to the medical statistician. The advantage of the summary statistic methods, used in Chapter 3 and discussed in Chapter 4, are their simplicity, but they have severe disadvantages in that conclusions are based on aggregates of all the data available from an individual and the extra value possible from the repeated measures cannot be exploited, nor can any effect over time be adequately investigated. Repeated measures ANOVA is a more complex analysis, but did produce smaller estimates of the parameters and their corresponding standard errors. However, the standard errors depend on a correct specification of the covariance structure in the model, and between- and within- subject variance components are combined. The marginal model produced similar results to the repeated measures ANOVA, but with greater standard errors and hence, lower statistical significance of treatment effects. This method may be particularly susceptible to effects of relatively large amounts of missing data, although all methods assume that data is missing at random. The two-level multilevel model, here, considers the repeated measure as nested within subject, hence directly allows separation of the variance components. The first analysis, with time included as a fixed effect, produced larger parameter estimates and standard errors than other methods except summary statistics. The multilevel model was then extended to include time as a random effect, i.e. varying among individuals. This model produced smaller estimates and errors, similar to the repeated measures ANOVA. The study also looked closely at the variance components of the multilevel model. As would be expected in this type of study, there was a much larger variance between individuals than within individuals, indicating that greater precision of the dataset would be achieved, not by increasing the numbers of repeated measures, but rather by increasing the numbers of individuals assessed. Although the assumption of "missing at random" is probably not tenable for this dataset, comparison of the whole dataset with the results obtained for only those individuals with compete datasets indicated that the missing data did not significantly influence the conclusions drawn.

Bahmaie et al (2000) have assessed the development of foetal lung tissue by volumetric measurement, using 3-dimensional ultrasound, serially throughout gestation, from 18 weeks to 41 weeks. In this case, multilevel modelling was used to account for correlation between multiple sequential observations on single subjects. The paper focuses mainly on the value of the foetal development information rather than the usefulness of the multilevel modelling to the specific problems of the application.

It is apparent from the literature that multilevel modelling is not only appropriate, but also extremely useful in situations where the data structure is hierarchical. The technique has largely been applied to large datasets with complex explanatory variable effects. The present application is much simpler, conceptually, but, nonetheless, does have a hierarchical structure appropriate to multilevel modelling methods. The potential advantage of these methods for the analysis of valve performance is the possibility of directly assessing the variance components at each level of the hierarchy. This would allow the possibility of assessing the variability of the test method, the variability of the valve manufacturing process, as well as the mean differences among valve types. In the future, it should also be possible to investigate covariate influences such as Young's modulus of the material or leaflet thickness effects. In the present study, there were insufficient numbers of different valve types and manufacturing limitations, which prevented consideration of these effects. All these levels of variance are important in terms of the valve assessment process. Quality control limits may be addressed for valve testing and for valve manufacture, allowing precise setting of rejection criteria. The relative performance of a variety of valve designs may also be directly assessed over the whole range of physiological flow rates. The dataset for valves is much smaller than other data types addressed in the literature, but has the advantage of relative simplicity and a lesser degree of individual variation, which will compensate to some degree for the lesser amount of data. It is likely, however, that the small amounts of data will reduce the power of the analysis to detect differences and adversely affect the precision of variance estimates.

5.3 Multilevel regression modelling

The multilevel regression model is also known as the "random coefficient model", the "variance component model" and the "hierarchical linear model". The model assumes a hierarchical structure to the data with a dependent variable measured at the lowest level of the hierarchy, with explanatory variables, as required, defining the various levels of the hierarchy. Published explanations of the model define the terms as used in social sciences. The model will be explained here with reference to the current problem, using one example typical of the current study, although other models will be fitted (see Chapter 6). Theoretical background was obtained from Hox (1995) and Goldstein (1999). Specific descriptions of procedures applicable to MLwiN, the multi-level modelling software available to the project, were obtained from Rasbash et al (2000). The simplest multilevel model contains two levels, with level 1 nested within level 2. In the present study level 1 refers to the test run replicates and level 2 to the individual valves of one particular design. We have an appropriate dependent variable 'Y', e.g. $\log_e$ {mean pressure gradient}, and the "explanatory" variable X, $\log_e$ {RMS flow}. This allows us to describe a regression equation, similar to the simple linear regression situation of Chapter 3:

$$Y_{ij} = \beta_{0j} + \beta_{1j}X_{ij} + \varepsilon_{ij} \qquad \{5.1\}$$

In this case, the subscript, j, applies to the level 2 valves (j = 1….6) and the subscript, i to the level 1 replicates (i = 1….5). β_{0j} is the intercept term, β_{1j} is the gradient of the regression line and ε_{ij} is the residual error term. The additional subscript, j, introduces the assumption that each level 2 valve has a different intercept and slope coefficient. Similarly to the simple regression situation, ε_{ij}, the random error terms, are assumed to $\sim N(0, \sigma_e^2)$.

To formulate a true two-level model from the model described above, the coefficient terms must be transformed into random variables, i.e. the coefficients for the population of all valves of a particular design have a distribution with associated mean and variance. Thus, for the jth valve in the sample,

$$\beta_{0j} = \beta_0 + u_{0j}, \quad \beta_{1j} = \beta_1 + u_{1j}$$

in which u_{0j} and u_{1j} are random variables (residual error terms), with distributions $\sim N(0, \sigma_{u0}^2)$ and $\sim N(0, \sigma_{u1}^2)$, respectively, and covariance, cov $(u_{0j}, u_{1j}) = \sigma_{u01}$. These error terms are assumed to be independent of the errors at level 1, ε_{ij}.

We can rewrite equation {5.1} as

$$Y_{ij} = \beta_0 + \beta_1 X_{ij} + (u_{0j} + u_{1j}X_{ij} + \varepsilon_{ij}), \ \text{var}(\varepsilon_{ij}) = \sigma_e^2 \qquad \{5.2\}$$

Thus we have expressed our response variable as the sum of a set of fixed ($\beta_0 + \beta_1 X_{ij}$), and a set of random ($u_{0j} + u_{1j}X_{ij} + \varepsilon_{ij}$) terms in the equation. In this two-level model, we require to estimate two fixed (β_0, β_1) and four random parameters (σ_{u0}^2, σ_{u1}^2, σ_{u01} and σ_e^2). The equations {5.1} and {5.2} allow for both different intercepts and different slopes at level 2. In the situation where the assumption of equal slopes holds, the slope parameter is common to all valves of this particular design and the equation simplifies to

$$Y_{ij} = \beta_0 + \beta_1 X_{ij} + (u_{0j} + \varepsilon_{ij}), \;\; \text{var}(\varepsilon_{ij}) = \sigma_e^2 \qquad \{5.3\}$$

Here, only two random parameters require estimation, σ_{u0}^2 and σ_e^2, in addition to the fixed parameters.

The set of covariance matrices for all levels of the analysis is defined as $\Omega = \{\Omega_1, \Omega_2, ...\}$. For the example in which both intercepts and slopes are random, and a level 2 unit has two level 1 units, the matrix Ω_2 is the covariance matrix of the random intercept and slope at level 2. The matrix Ω_1 is the covariance matrix for the set of level error terms, which has, here, a single variance term.

The covariance matrix $\begin{pmatrix} A & B \\ B & C \end{pmatrix}$ for the random vector (Y_{1j}, Y_{2j}) is defined,

where

$$A = \left\{\sigma_{u0}^2 + 2\sigma_{u01} x_{1j} + \sigma_{u1}^2 x_{1j}^2 + \sigma_e^2\right\}$$

$$B = \left\{\sigma_{u0}^2 + \sigma_{u01}\left(x_{1j} + x_{2j}\right) + \sigma_{u1}^2 x_{1j} x_{2j}\right\}$$

$$C = \left\{\sigma_{u0}^2 + 2\sigma_{u01} x_{2j} + \sigma_{u1}^2 x_{2j}^2 + \sigma_e^2\right\}$$

giving $\begin{pmatrix} A & B \\ B & C \end{pmatrix} = X_j \Omega_2 X_j^T + \begin{pmatrix} \Omega_1 & \\ & \Omega_1 \end{pmatrix}$, and

$$X_j = \begin{pmatrix} 1 & x_{1j} \\ 1 & x_{2j} \end{pmatrix}, \qquad \Omega_2 = \begin{Bmatrix} \sigma_{u0}^2 & \sigma_{u01} \\ \sigma_{u01} & \sigma_{u1}^2 \end{Bmatrix}, \qquad \Omega_1 = \sigma_e^2 .$$

The multilevel software available for the current study was MLwiN version 1.10, which uses the Iterative Generalized Least Squares (IGLS) method as the default method for analysing data. The mathematical descriptions above, under this methodology, may be generalized as described below.

We begin by considering the model described in equation {5.3} above, the simple two-level, common slopes model. MLwiN attaches an x_0 term to the β_0 intercept parameter in the model, which is defined as a constant vector term (a column of '1's), which, in this software package, explicitly models the intercept. From knowledge of the values of the variances, the variance-covariance matrix at level 2, Ω_2, can be constructed. The normal Generalized Least Squares estimation procedure can then be applied to calculate the fixed coefficient estimator

$$\hat{\beta} = \left(X^T \Omega_2^{-1} X\right)^{-1} X^T \Omega_2^{-1} Y, \qquad \{5.4\}$$

where

$$X = \begin{Bmatrix} 1 & x_{11} \\ 1 & x_{21} \\ \vdots & \vdots \\ \vdots & \vdots \\ 1 & x_{IJ} \end{Bmatrix} \qquad Y = \begin{Bmatrix} y_{11} \\ y_{21} \\ \vdots \\ \vdots \\ y_{IJ} \end{Bmatrix}$$

with J level 2 units and I level 1 units in the j-th level 2 unit. This procedure gives maximum likelihood estimates provided the residuals are Normally distributed. The estimation procedure is an iterative one, beginning from 'reasonable' estimates of the fixed parameters, generated from an ordinary least squares fit to the data (i.e. the fit obtained if the intercepts were common, as well as the slopes), giving the estimator of the fixed coefficient, $\hat{\beta}^{(0)}$. The "raw" residuals are then calculated as

$$\tilde{y}_{ij} = y_{ij} - \hat{\beta}_0^{(0)} - \hat{\beta}_1^{(0)} x_{ij} .$$

Written as vector notation, the vector of raw residuals is: $\tilde{Y} = \left\{ \tilde{y}_{ij} \right\}$. Ω_2 is the expected value of the cross-product matrix, $\tilde{Y}\tilde{Y}^T$ and the relationship between the vector transformations of these matrices may be expressed as a linear model:

$$\begin{Bmatrix} \tilde{y}_{11}^2 \\ \tilde{y}_{21}\tilde{y}_{11} \\ \vdots \\ \vdots \\ \tilde{y}_{22}^2 \end{Bmatrix} = \begin{Bmatrix} \sigma_{u0}^2 + \sigma_e^2 \\ \sigma_{u0}^2 \\ \vdots \\ \vdots \\ \sigma_{u0}^2 + \sigma_e^2 \end{Bmatrix} + R = \sigma_{u0}^2 \begin{Bmatrix} 1 \\ 1 \\ \vdots \\ \vdots \\ 1 \end{Bmatrix} + \sigma_e^2 \begin{Bmatrix} 1 \\ 0 \\ \vdots \\ \vdots \\ 1 \end{Bmatrix} + R , \qquad \{5.5\}$$

where R is a residual vector. The estimation of the coefficients, σ_{uo}^2 and σ_e^2, uses an application of Generalized Least Squares, assuming Normality and using the estimated covariance matrix of the vector $\left(\tilde{Y}\tilde{Y}^T\right)$, i.e. $2\left(\Omega_2^{-1} \otimes \Omega_2^{-1}\right)$, where $\otimes$ is the Kronecker product. Once these estimates are calculated, the estimation oscillates between the fixed parameter estimation of equation {5.4} and the random estimation of equation {5.5} until the iterations converge.

The multilevel model produces several residuals at all the different levels of the model. If y_{ij} is the observed value for the ith valve in the jth design, and $\hat{y}$ is the predicted value from the average regression line, then the raw residual for that individual is $r_{ij} = y_{ij} - \hat{y}_{ij}$. The raw residual for the jth design is the mean of these residuals over all N_j valves in the design group (r_{+j}). The predicted level 2 residual for this design is found by the following equation

$$\hat{u}_{0j} = \left\{\sigma_{u0}^2 / \left(\sigma_{u0}^2 + \sigma_e^2 / N_j\right)\right\} r_{+j}$$

The factor multiplying r_{+j} is always less than or equal to 1, hence the estimated residual is smaller than the raw residual (sometimes termed a "shrunken" residual). The degree of shrinkage will be greater when N_j is small or the larger σ_e^2 is compared with σ_{u0}^2. This situation would hold when we have comparatively little information about the designs, i.e. when the number of valves of each design is small or the valves within each design are very variable. The level 1 residuals may be calculated from the $\hat{u}_{0j}$, by the equation

$$\hat{e}_{ij} = r_{ij} - \hat{u}_{0j}$$

The residual estimates are not unconditionally unbiased, but they are consistent. The level 2 residuals may be interpreted as random variables with a distribution whose parameter values inform us about the variation among level 2 groups. They may also provide efficient estimates for the fixed coefficients, and individual estimates for each level 2 group, assuming they belong to a population and predicting their values. The residuals can also be used to check the model assumptions, specifically the assumptions of Normality and constant variance. Diagnostic residuals are generally standardised by dividing them by the appropriate standard errors, because of the dependence of their values on the values of the fixed coefficients.

5.4 Use of Residuals

Apart from their use in diagnostic procedures, residuals at different levels can be used to plot the differences of each individual from the overall mean. For instance, at level 2 for this project, the valves, the residuals with their 95% confidence limits can be calculated for each of the intercept and slope fixed parameters of the model. These can then be plotted to demonstrate the departure of each valve from the common slope mean or the common intercept mean (zero lines plotted on the appropriate residual plots). The calculated data can also be fitted into an equation specific to each design, giving a mathematical description of the fixed parameters for each design. This process may be repeated for each design group to define the fixed parameter equations for each valve within each design, and, if desired, for each repetition within each valve. The deviation of the residual from the common mean is indicative of the significance of its difference from other group members and from the common mean. If the individual residual with its 95% confidence interval does not overlap the common mean, then that individual has a slope and/or an intercept that is significantly different from the common mean. Similarly, if an individual residual with its 95% confidence interval does not overlap the 95% confidence interval of the slope and/or intercept of another individual, then the two are significantly different from each other. For testing the overlap of any individual with the zero line, the 95% confidence intervals are calculated using the conventional 1.96 standard deviations. For comparisons between pairs of individuals at a specified level (e.g. valve designs at level 3), the 95% confidence intervals are calculated using 1.4 standard deviations (Goldstein & Healy, 1995). This type of analysis is not of particular interest in the present study, where our main interest is the separation of different valve designs.

5.5 Summary

The data to be analysed in the current study are ordered in a hierarchical way. Simple linear regression analysis is insufficient to provide a comprehensive view of the overall performance of valves at different levels of interest. Multi-level modelling offers the possibility of analysing valve performance comparing several fixed design groups, with a structural analysis which can include analysis of the variability associated with individual valves within a design, as well as the variability of the test procedure itself by analysis of the replications of individual valves.

Chapter 6: Multi-level Modelling of Hydrodynamic Function Data

This chapter first examines the multi-level model applied to a single valve design, design LE. In this instance the individual valve is allocated to level 2, with the replications of each valve at level 1. The second stage examines the two designs of chapter 3, design GE and design LE. Finally, the complete set of five valve designs, GE, LE, LL, L4 and L5, is examined. For multiple valve comparisons the "baseline" design (reference category) is taken as design GE, since it is experimentally regarded as the "best" design.

The assessment of the significance of parameters in the model may be made in two ways. Each analysis of a model produces a value for -2(loglikelihood) by an iterative generalised least squares (IGLS) procedure. Provided one model is nested within the other to be compared, then the difference between the two values of -2(loglikelihood), known as the deviance statistic, can be compared to a χ^2 distribution with degrees of freedom determined by the difference between the numbers of parameters in the two models. Fitting greater numbers of parameters to a model decreases the numerical value of -2(loglikelihood). In a few cases, the final selection was among models, which were not nested. In these situations, the final model was selected on the basis of the Akaike Information Criterion, $l + 2p$, where p is the number of parameters in the specified model and l is the -2(loglikelihood), as recommended in the MLwiN software documentation. This index does not depend on the models being nested, one within another. The lowest value is likely to be the "best" model. Significance testing may also be performed using large sample Wald tests: however, as will be discussed further in Chapter 7, these are less reliable in the current context. Essentially, for datasets with small numbers, deviance testing is more reliable for testing the significance of parameters in the model than Wald tests. In the case of mean pressure gradient for which there is some deviation from the assumption of normality, the reliability of the Wald test is likely to be further compromised.

6.1 Valve design LE

This design has leaflets made of the polyurethane material, Estane. Six valves were examined, with five replications of each valve test, giving a total of 150 data points for analysis. The simplest model considered is of the form described in Chapter 5, equation {5.3},

$$Y_{ij} = \beta_{0ij} X_0 + \beta_1 X_{ij}$$

where X_0 is a constant, equal to 1, β_0 (the intercept) is allowed to vary with valve (j) and replicate (i), and β_1 models a common slope throughout. β_{0ij} is divided into fixed and random parts. The fixed term is β_0 and the random parts are $u_{0,valve}$ and $\varepsilon_{0,\, replication,\, valve}$, being the measures of the variability associated with the intercepts of the individual valves at level 2 ($u_{0,j}$) and the replications at level 1 given the individual valve ($\varepsilon_{0\, ij}$), respectively. In this case, $u_{0,\, \text{valve}} \sim N(0, \Omega_u)$: Ω_u being the variance associated with the intercept due to differences among the six valves tested, σ_{u0}^2. Similarly, $\varepsilon_{0,\, replication,\, valve} \sim N(0, \Omega_\varepsilon)$: Ω_ε being the variance associated with the intercept due to differences among the replicates of a given valve, $\sigma_{\varepsilon 0}^2$. This notation is idiosyncratic of the software modelling definitions. The error term associated with random variation of the slope parameter at level 1 is undefined in this analysis and contained within the term, $\sigma_{\varepsilon 0}^2$. The expectation of common slopes among the six valves was confirmed by repeating the analysis with β_{1j} replacing β_1, to allow for random variation in the slope among the six valves. In this case, the variance/covariance matrix associated with the valve variability is designated as

$$\begin{bmatrix} u_{0,valve} \\ u_{1,valve} \end{bmatrix} \sim N(0,\Omega_u) : \Omega_u = \begin{bmatrix} \sigma_{u0}^2 & \\ \sigma_{u01} & \sigma_{u1}^2 \end{bmatrix}$$

In the analysis of two measures, $\log_e$\{mean pressure gradient\} and $\log_e$\{regurgitation\}, the final model did indeed require to allow for different slopes at level 2, valve, in this way. Table 6.1 details the parameter estimates calculated using such a multi-level regression model applied to the single valve design, LE.

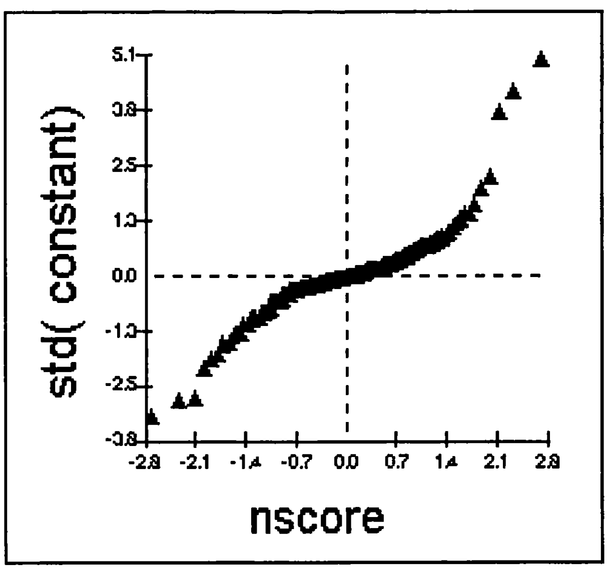
Table 6.1 Valve Design LE, Parameter Estimates (e.s.e.)

Hydrodynamic Function Measure	Fixed parameter estimate (intercept) β_0	Fixed parameter estimate (slope) β_1	Random parameter estimate (valve) σ_{u0}^2	Random parameter estimate (valve) σ_{u1}^2	Random parameter estimate (valve) σ_{u01}	Random parameter estimate (replicate) $\sigma_{\varepsilon 0}^2$
$\log_e$ \{mean pressure gradient\}	-6.218 (0.127)	1.541 (0.018)	0.080 (0.056)	0.001 (0.001)	-0.010 (0.008)	0.003 (0.000)
$\log_e$ \{regurgitation\}	1.185 (0.148)	-0.042 (0.027)	0.093 (0.076)	0.003 (0.002)	-0.016 (0.014)	0.007 (0.001)
leakage	6.886 (0.453)	-0.906 (0.079)	0.167 (0.101)	-	-	0.207 (0.024)
$\log_e$ \{energy loss forward flow\}	-5.033 (0.089)	1.760 (0.014)	0.012 (0.007)	-	-	0.007 (0.001)
energy loss closing	-22.913 (4.806)	9.570 (0.887)	4.300 (3.088)	-	-	26.103 (3.076)
energy loss closed	107.350 (6.500)	-13.194 (1.136)	33.576 (20.373)	-	-	42.755 (5.039)
maximum orifice area	-0.529 (0.056)	0.381 (0.009)	0.005 (0.003)	-	-	0.003 (0.000)

6.1.1 $\log_e$\{mean pressure gradient\}

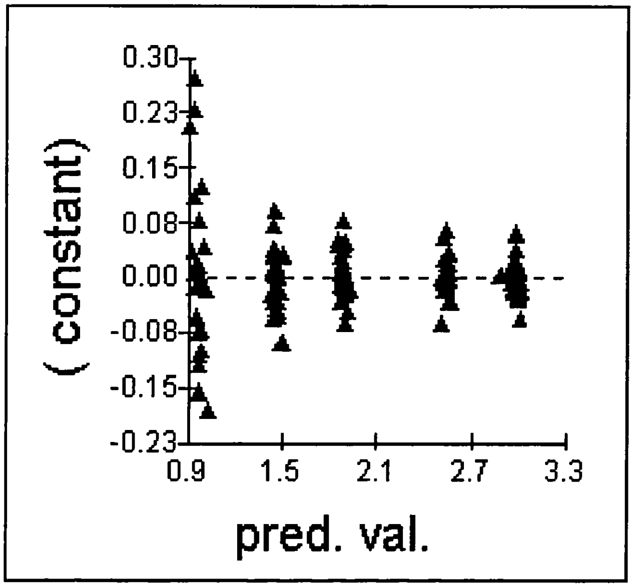
In the case of mean pressure gradient, the common slopes model produces a -2(loglikelihood) of -392.903 and the different slopes model -401.520, a deviance statistic of 8.617 at 2 d.f. This value is significant ($p = 0.013$). Therefore, the final model allows for different slopes among the individual valves. The slope and intercept parameter estimates are similar to those arising from the simple linear regression model (Chapter 3, Table 3.15). The residual plots indicate some deviation from normality, similar to that found in Chapter 3 and suggestive of under-dispersion of the data (figure 6.1, standardised level 1 residuals *vs* normal scores), although, similarly to the findings of Chapter 3, the distribution of residuals is symmetric. The amount of data available at level 2 was insufficient to generate informative residual plots.

Figure 6.1 Normal Probability Plot of standardised level 1 residuals for $\log_e${mean pressure gradient}



As noted for the simple linear regression in Chapter 3, there is a small amount of heteroscedasticity, particularly associated with the lowest flow rate, an applied cardiac output of $3.6 l.min^{-1}$, demonstrated in figure 6.2, below.

Figure 6.2 Plot of Standardised level 1 Residuals vs Predicted Values for $\log_e$\{mean pressure gradient\}



There is a positive association between mean pressure gradient and flow rate through the valve, i.e. as the flow rate increases, the mean pressure gradient across the valve rises. The greatest variance is associated with the intercept parameter estimate at level 2, the valve-to-valve variability. The random error due to replication is very small.

6.1.2 $\log_e$\{regurgitation\}

The slope and intercept parameter estimates are, again, similar to those arising from the simple linear regression model. There is a small negative slope for the relationship between flow rate and regurgitation, i.e. as flow rate increases, there is less regurgitation (reverse flow) through the closing valve. The common slopes model was tested similarly to 6.1.1 above. The deviance statistic for comparison of the two models was 6.144, again at 2 d.f., $p = 0.046$, also significant. Both fixed parameter estimates were significant. Again greater variance was associated with the intercept parameter at level 2 than with the slope parameter or with the random error at level 1, replicate. The data conformed well to normality in this case, and variance was approximately constant.

6.1.3 leakage

The slope and intercept parameter estimates are, again, similar to those arising from the simple linear regression model. The data conform to the assumption of normality and variance was approximately constant. Here, as flow rate increases, leakage through the closed valve decreases, so that the valve closes more effectively at high flow rates than at low flow rates. In clinical terms, this means that there is more efficient pumping of oxygenated blood through the heart to the general circulation with smaller losses arising from reverse flow, due to inefficiency of the valve. The simpler model with common slopes was tested in the way described in 6.1.1 above. The deviance statistic for comparison of the two models was 0.419, again at 2 d.f., not significant. Both fixed parameter estimates were significant. There was greater variance associated with the random error at level 1, replicate than with the level 2 random error (valve). Leakage is particularly affected by variation in leaflet trimming. If one leaflet is cut slightly low, not only can this increase the leakage through a closed valve, but it may also affect repeat testing of the valve as the leakage measurement might be sensitive to orientation in the tester. This may explain some of the relatively high variance associated with the replicate tests compared with the valve-to-valve variability.

6.1.4 $\log_e$ {energy loss in forward flow}

The slope and intercept parameter estimates are, again, similar to those arising from the simple linear regression model. The assumption of normality is valid, but the variance structure is similar to that for mean pressure gradient with slightly higher variance at the lowest flow rate. The energy losses in forward flow parallel the behaviour of the mean pressure gradient: as flow rates increases, the energy losses rise. A lower rate of rise is preferable to a high rate of rise. The model with common slopes was tested as described in 6.1.1 above. The deviance statistic for comparison of the two models was 1.109, at 2 d.f., not significant. Both fixed parameter estimates were significant. Level 2 variance (between valves) is greater than level 1 variance (between replicates), as would be expected.

6.1.5 energy loss closing

The slope and intercept parameter estimates are, again, similar to those arising from the simple linear regression model, although there is a larger difference in the estimate of the intercept here than for other parameters. The assumptions of normality and equal variance appear to be valid. Closing energy losses increase as flow rate increases in contrast to the behaviour of regurgitation. The model of common slopes was tested in the way described in 6.1.1 above. The deviance statistic for comparison of the two models was 1.176, at 2 d.f., not significant. Both fixed parameter estimates were significant. There is a greater variance associated with the replicate (level 1) compared with the valve (level 2). This may result from similar causes to the same observation for leakage, given that energy losses here are a composite measure derived from both pressure and flow measures, and that flow is measured with less precision than pressure.

6.1.6 energy loss closed

The slope and intercept parameter estimates are, again, similar to those arising from the simple linear regression model, though, similarly to the closing energy loss (6.1.5) there is a larger difference in the estimate of the intercept here than for other parameters. The assumptions of normality and equal variance appear to be valid. Closed energy losses parallel the behaviour of leakage flow through the closed valve: energy loss decreases as flow rate increases. The model of common slopes was tested as described in 6.1.1 above. The matrix, Ω_u, resulting from the different slopes model, contained only zero terms. The –2(loglikelihood) value was anomalous, being greater in value than the reduced model it was compared with. This may be an effect of the zero variances apparently associated with the random parameters under investigation and suggests over-parameterisation of the model. The final model was selected on the basis of the Akaike Information Criterion, $l + 2p$, where p is the number of parameters in the specified model and l is the -2(loglikelihood). This index does not depend on the models being nested, one within another. The lowest value is likely to be the "best" model and confirmed the "common slopes" model. Both fixed parameter estimates were significant. Again, replicate level variance was greater than for valve level variance, similar to the situation for leakage.

6.1.7 effective orifice area at maxima

The slope and intercept parameter estimates are, again, similar to those arising from the simple linear regression model. The assumption of equal variances seemed valid. The normal probability curve deviated slightly, similar to, though less than, that for mean pressure gradient. The valve orifice area increases with flow rate, effectively enabling a greater flow volume through the heart as demand for oxygenated blood increases. The model of common slopes was tested as described in 6.1.1 above. The matrix, Ω_u, resulting from the different slopes model, contained only zero terms, with a similar anomaly to that found in analysing the two models for closed energy loss (6.1.6). Again, the Akaike Information Criterion was used to select the final "common slopes" model. Both fixed parameter estimates were significant. In this case, the valve-to-valve variability associated with the intercept parameter was, as expected, greater than the replicate variability.

6.1.8 Summary of multi-level modelling for design LE alone

The multi-level model for this valve design produced results consistent with the random regression model of Chapter 3. There was no significant variation in slope associated with either valve at level 2 or replicate at level 1, except for the slope random variation with valve detected for the measures, mean pressure gradient and regurgitation. In general, there was a small, but significant variation in intercept associated with valve at level 2, greater in magnitude than the variability associated with the replicates at level 1, as would be expected for mean pressure gradient, regurgitation, energy losses during forward flow and maximum orifice area. These include all the more precisely measured terms, based on differential pressure measurement, with the exception of regurgitation. Those measures which have greater variation in the intercept related to replicate variability are, in general, those in which repeat testing may be influenced by the orientation of the valve in the tester, this increasing the range of the measured data. In the cases of mean pressure gradient and regurgitation, the variability associated with the slope at level 2 is lower than that associated with the intercept. The data suggest that the analysis might be improved by the inclusion of a greater number of valves at level 2.

6.2 Multi-level model with two valve designs, LE and GE

The designs to be compared are the same designs (and data) used to apply the random regression model of Chapter 3. Both designs have leaflets made of the polyurethane material, Estane. The engineering designs are similar but there are minor differences in the leaflet geometries and in the resting orientation of the leaflets. The model is similar to that of section 6.1, with valve at level 2 and replicate at level 1. In this case, however, design must be entered into the model. There were six valves representing each design, and 5 replicates of each valve test, providing a total of 300 data points for analysis. There is no inherent variability in design as a variable: it is a fixed factor describing a valve. Therefore design is entered as an additional fixed parameter into the model. In this case, for design 1, $E(Y|x) = \beta_{01} + \beta_{11}x$ and, for design 2, $E(Y|x) = \beta_{02} + \beta_{12}x$, in a random regression model, with slope and intercept parameters in the same notation as described in Chapter 3, the second subscript designating design 1 or 2, as appropriate. Now, we introduce a dummy variable, δ_2, where $\delta_2 = 1$, if design =2 and 0 if design = 1. Combining these, we revise the model to

$$E(Y|x) = \beta_{01} + (\beta_{02} - \beta_{01})\delta_2 + \beta_{11}x + (\beta_{12}-\beta_{11})\delta_2 x \qquad \{6.1\}$$

where the constant (intercept) parameter of design 1 is represented by β_{01}, the slope parameter of design 1 is represented by β_{11}, the difference in intercept between designs 1 and 2 by $(\beta_{02} - \beta_{01})$, and the difference in slope between design 1 and 2 by $(\beta_{12}-\beta_{11})$. The common slopes model is similarly derived as

$$E(Y|x) = \beta_{01} + (\beta_{02} - \beta_{01})\delta_2 + \beta_1 x.$$

This structure is easily set up in MLwiN. The model specifies the same variances for both designs. Valve design GE was designated as design 1, with valve design LE as design 2, referring to the model above. Both random slopes and common slopes models were investigated. Using the deviance statistic to test among models, no slope difference for any hydrodynamic function measure was statistically significant. Therefore, the final model applied was that of same slopes for both designs.

6.2.1 $\log_e$\{mean pressure gradient\}

Table 6.2.1 Parameter estimates for $\log_e$\{mean pressure gradient\}

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	-6.659	0.060
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	0.408	0.063
β_1 common slope	1.547	0.008
σ_{u0}^2 variance of intercept due to valve variability	0.012	0.005
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.004	0.000

The two designs have a common slope parameter estimate that is estimated to lie in the range 1.547 ± 0.015 (95% C.I.). The intercept parameter estimate for design GE is –6.659 ± 0.118 (95% C.I.). Considering the increments associated with design LE, the intercept parameter estimate for design LE is –6.251 ± 0.124 (95% C.I.). The parameter estimates for design LE are in close agreement with those derived from analysis of design LE alone (Table 6.1). The variance parameter estimates associated with the intercepts of different valves and different replicates of a valve are both significant in this analysis, using the Wald test, in contrast to the findings for analysis of the single design, although the absolute values of the estimates obtained from the two models are similar. The estimation of the variances has become more precise, probably due to the larger number of valves available at level 2.

The difference in intercept parameters, together with the common slope, indicates that design GE has a significantly lower mean pressure gradient than design

LE, consistently over all tested cardiac outputs applied (Wald tests of fixed parameter estimates, $\chi^2 = 41.436$, 1d.f.). A 95% C.I. for the mean difference, at any given flow rate, is 0.284 to 0.532. This property of design GE would be regarded as better from the clinical point-of-view, as it is an indicator of easier valve opening.

6.2.2 $\log_e$\{regurgitation\}

Table 6.2.2 Parameter estimates for $\log_e$\{regurgitation\}

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	1.269	0.066
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	-0.069	0.045
β_1 common slope	-0.045	0.011
σ_{u0}^2 variance of intercept due to valve variability	0.006	0.003
σ_{ε}^2 variance of intercept due to replicate variability, given valve	0.008	0.001

The two designs have a common slope parameter, which is estimated to lie in the range –0.045 ± 0.021 (95% C.I.). The intercept parameter estimate for design GE is 1.269 ± 0.130 (95% C.I.). Considering the increments associated with design LE, the intercept parameter estimate for design LE is 1.200 ± 0.089 (95% C.I.). The figures for design LE are in close agreement with the parameter estimates derived from analysis of design LE alone (section 6.1). Although there was no significant improvement in the fit of the model by allowing random variation of the slope parameter at level 2 (common to both designs), the variance estimates seemed more consistent with expectations. In contrast with the reduced model (Table 6.2.2) in which valve-to-valve variation on the intercept parameter estimate is less than the equivalent replicate level variation, the level 2 (valve) variance on the intercept parameter estimate is increased to 0.063 (0.041) similar to that for the single valve analysis of section 6.1. Allowing for different slopes as described may allow an increase in the precision of measurement of the variances and, although the models are not significantly different, might suggest that the preferred model should be that allowing for different slopes among the valves. There is little difference in the fixed parameter estimates between the two models.

Design LE has lower mean regurgitation than design GE, at any given flow rate, although the difference is not significant using the Wald test ($\chi^2 = 2.327$, 1d.f.). As noted before, regurgitation decreases as applied cardiac output, and flow rate, increases. Less regurgitation implies higher efficiency of valve operation, given that a lesser volume of oxygenated blood is lost to the circulation in reverse flow during valve closing. However, ease of valve opening is a higher priority for consideration than regurgitation for clinical purposes.

6.2.3 leakage

Table 6.2.3 Parameter estimates for leakage

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	6.213	0.323
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	0.617	0.207
β_1 common slope	-0.895	0.054
σ_{u0}^2 variance of intercept due to valve variability	0.121	0.052
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.195	0.016

The two designs have a common slope, which is estimated to lie in the range -0.895 ± 0.106 (95% C.I.). The intercept parameter estimate for design GE is 6.213 $\pm$ 0.632 (95% C.I.). Considering the increments associated with design LE, the intercept parameter estimate for design LE is 6.830 $\pm$ 0.406 (95% C.I.). The figures for the intercept parameter estimate of design LE are in close agreement with the estimates derived from the single design multi-level model of section 6.1. The variance parameter estimates associated with the intercepts of different valves and different replicates of a valve are, again, both significant in this analysis, using the Wald test, in contrast to the findings for analysis of the single design. The estimation of the variances seems to have become more precise, probably due to the larger number of valves available at level 2.

The mean leakage in design LE is significantly higher than in design GE, likely to lie in the range 0.211 to 1.023 (95% C.I.), with the difference, again, being maintained across all applied cardiac outputs ($\chi^2 = 8.889$, 1d.f.). Low leakage is an important aim in valve design as this restricts the amount of oxygenated blood lost to the circulation when the valve is closed.

6.2.4 $\log_e${energy loss in forward flow}

Table 6.2.4 Parameter estimates for $\log_e${energy loss in forward flow}

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	-5.424	0.069
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	0.419	0.064
β_1 common slope	1.755	0.010
σ_{u0}^2 variance of intercept due to valve variability	0.012	0.005
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.007	0.001

The two designs have a common slope parameter estimate, which is estimated to lie in the range 1.755 ± 0.019 (95% C.I.). The intercept parameter estimate for design GE is –5.424 ± 0.136 (95% C.I.). Considering the increments associated with design LE, the intercept parameter estimate for design LE is –5.005 ± 0.125 (95% C.I.). The figures for design LE are in close agreement with the parameter estimates derived from analysis of design LE alone (section 6.1). The variance parameter estimates associated with the intercepts of different valves and different replicates of a valve are both significant in this analysis, using the Wald tests, in contrast to the findings for analysis of the single design, although of similar numerical value. The estimation of the variances seems to have become more precise, probably due to the larger number of valves available at level 2.

Design GE has significantly lower mean opening energy losses than design LE, at any given flow rate (χ^2 = 42.940, 1d.f.), which is likely to lie in the range 0.294 to 0.544 (95% C.I.). The opening energy losses increase with applied cardiac output. From a clinical point of view, lower energy losses mean that the heart has less work to do in pumping blood, and the heart is able to work more efficiently. Reference to the χ^2 values suggests a similar sensitivity of mean pressure gradient and opening energy losses in detecting differences between the two designs.

6.2.5 energy loss closing

Table 6.2.5 Parameter estimates for closing energy loss

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	-23.414	3.399
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	-1.525	1.255
β_1 common slope	9.952	0.617
σ_{u0}^2 variance of intercept due to valve variability	3.707	1.930
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	25.415	2.118

The two designs have a common slope parameter, which is estimated to lie in the range 9.952 ± 1.209 (95% C.I.). The intercept parameter estimate for design GE is –23.414 ± 6.661 (95% C.I.). Considering the increments associated with design LE, the intercept parameter estimate for design LE is –24.939 ± 2.459 (95% C.I.). The figures for design LE are in close agreement with the parameter estimates derived from analysis of design LE alone (section 6.1). The variance parameter estimates associated with the intercepts of different valves are not significant, using the Wald test, ($p = 0.055$) in this analysis similarly to the findings for analysis of the single design, although the standard errors associated with the parameter estimates are smaller than for the single design analysis.

The difference in closing energy loss between the two designs is not significant ($\chi^2 = 1.477$, 1d.f). Although the behaviour of this measure of hydrodynamic function tends to parallel regurgitation, it does increase with applied cardiac output unlike regurgitation.

6.2.6 energy loss closed

Table 6.2.6 Parameter estimates for closed energy loss

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	92.592	4.718
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	7.225	2.906
β_1 common slope	-11.776	0.798
σ_{u0}^2 variance of intercept due to valve variability	23.636	10.345
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	42.558	3.547

The two designs have a common slope parameter, which is estimated to lie in the range -11.776 ± 1.564 (95% C.I.). The intercept parameter estimate for design GE is 92.592 ± 9.244 (95% C.I.). Considering the increments associated with design LE, the intercept parameter estimate for design LE is 99.817 ± 5.695 (95% C.I.). The slope parameter estimate for design LE is in closer agreement with the parameter estimates derived from the simple linear regression model of Chapter 3, although the intercept parameter estimate is closer to that of the single design multi-level model of section 6.1, above. The variance parameter estimates associated with the intercepts of different valves and different replicates of a valve are both significant in this analysis, using the Wald tests, in contrast to the findings for analysis of the single design. The estimation of the variances seems to have become more precise, probably due to the larger number of valves available at level 2.

The closed energy losses are significantly higher for design LE than design GE ($\chi^2 = 6.181$, 1d.f.), likely to lie in the range 1.530 to 12.920 (95% C.I.) at any given flow rate, suggesting that design LE valves do not seal as efficiently as design GE valves when closed.

6.2.7 effective orifice area at maxima

Table 6.2.7 Parameter estimates for effective orifice area at maxima

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	-0.315	0.053
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	-0.294	0.048
β_1 common slope	0.396	0.008
σ_{u0}^2 variance of intercept due to valve variability	0.007	0.003
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.004	0.000

The two designs have a common slope parameter, which is estimated to lie in the range 0.396 ± 0.015 (95% C.I.). The intercept parameter estimate for design GE is –0.315 ± 0.105 (95% C.I.). Considering the increments associated with design LE, the intercept parameter estimate for design LE is –0.609 ± 0.095 (95% C.I.). The figures for design LE are in close agreement with the parameter estimates derived from analysis of design LE alone (section 6.1). The variance parameter estimates associated with the intercepts of different valves and different replicates of a valve are both significant in this analysis, using the Wald tests, in contrast to the findings for analysis of the single design, with a small increase in the variance estimate associated with the intercept parameter of different valves. Again, the estimation of the variances seems to have become more precise, probably due to the larger number of valves available at level 2.

Design GE has a significantly greater effective orifice area than design LE ($\chi^2 = 37.044$, 1d.f), which is likely to lie in the range 0.199 to 0.389 (95% C.I.), at any given flow rate. The effective orifice area is a measure that reflects the actual open area available to a valve. A larger orifice will a permit a larger flow volume, hence will be more beneficial in clinical terms by allowing a greater throughput of oxygenated blood. The orifice increases with applied cardiac output over the range examined, i.e. the valve opens wider as the flow rate through it increases.

6.3 Summary of multi-level regression model as a means of comparing two valve designs

The multi-level model has enabled discrimination between designs GE and LE, in valves fabricated from the same material. In fact, a greater number of the hydrodynamic function measures have significant differences between the two designs compared with the random regression approach of Chapter 3. Careful interpretation of the results is required. Using the deviance statistic to determine inclusion or exclusion of parameters from the model suggests that included parameters are significant. However, some of these parameters are not significant when tested by using the Wald tests. The problems of using Wald tests are discussed in more detail in Chapter 7. In the present case, if both the Wald test and the deviance statistic agree, then confidence in the significance of a specified parameter estimate is high. If the two methods of testing significance do not agree, then the deviance statistic is likely to be more reliable, but the outcome should be considered in light of the practical expectations of what may be reliably measured in the experimental tests. In the multi-level model the mean differences in leakage behaviour and effective orifice area are significant, in contrast to these measures by simple linear regression. Only regurgitation and energy loss during valve closing indicate no significant differences on average between the designs, using the Wald tests. The improvement in discrimination achieved by the multi-level modelling approach compared with the random regression approach is most likely due to the explicit use of all 300 data points in the analysis compared with the use of two summary measures from each valve to compare designs as used in the random regression model, which should increase the precision of the estimates.

The application of the model was simple and straightforward, once the data were structured appropriately. The outcome was apparent with a single analysis process, rather than the sequential analytical process required of simple linear regression (Chapter 3), in which an initial analysis of each individual valve had to be performed, followed by calculation of mean parameter estimates which were then entered into another statistical procedure.

One potential advantage of multi-level modelling here was the anticipation of being able to assign quality control limits to valve-to-valve variation and reproducibility of the hydrodynamic test procedure itself. The relevant terms in the model are σ_{u0}^2 and $\sigma_{\varepsilon 0}^2$, respectively. The single valve design analysis of section 6.1 raised some concern that the variance due to valve-to-valve variability was less precisely determined in some cases than the variance due to replicate variability, given valve. The simultaneous analysis of two designs appears to have made the determination of these variances more precise and more consistent with expectations.

Although the absolute values of the parameter estimates are similar, their standard errors are lower in the two-design model, and the intercept parameter estimates for valve-to-valve variance are therefore statistically significant, with the exception of those for regurgitation and energy loss during valve closing. It is likely that the relatively small number of valves available at level 2 for any given design caused this problem, and that the increased numbers available for the two-design analysis have improved the estimation procedure. It must also be remembered that these variances at level 2 are modelled to be constant for all valve designs, so that, if we increase the number of designs to be analysed, then we must continue to assume that the valve-to-valve variability is similar for all designs. If this is not the case, then we will over- or under-estimate the variability due to valve manufacture depending on which design we are interested in. In practice, provided a skilled operator is manufacturing valves, it is likely that the variability among valves is similar regardless of design, provided that a similar leaflet thickness distribution is targeted for any individual design.

6.4 Multi-level model with five valve designs

Ideally, multi-level modelling could be used to compare a selection of valve designs to order them from best to worst, so that a simple assessment could be made quickly as to whether one design was truly better than another. The designs to be compared are those described in Chapter 2, Table 2.1. Both designs examined above are included, with the addition of three further designs, all based on the engineering design L above, but with different leaflet materials, designs LL, L4 and L5.

The model is similar to that of section 6.2, with valve at level 2 and replicate at level 1, with design entered into the model as a fixed factor. There were six valves representing each design, and 5 replicates of each valve test, providing a total of 750 data points to be analysed. In this case, the model must be expanded to include separate dummy variables for all the design contrasts using a similar process to that of section 6.2. In this case, because the new valve leaflet materials have quite different properties from the two designs examined so far, there is a strong likelihood that the slope of the regression model will deviate for one or more designs. Therefore, we must model the regression with different slopes as well as different intercepts. This requires a second variable for each design, with the appropriate dummy variable crossed with the $\log_e$ {RMS flow} variable. One possible parameterisation of the model, adapting equation {6.1}, is

$$E(Y|x) = \beta_{01} + (\beta_{02} - \beta_{01})\delta_2 + (\beta_{03} - \beta_{01})\delta_3 + (\beta_{04} - \beta_{01})\delta_4 + (\beta_{05} - \beta_{01})\delta_5 + \beta_{11}x + (\beta_{12}-\beta_{11})\delta_2 x + (\beta_{13}-\beta_{11})\delta_3 x + (\beta_{14}-\beta_{11})\delta_4 x + (\beta_{15}-\beta_{11})\delta_5 x$$

where β_{01} and β_{11} are the intercept and slope parameters for the "baseline" design, here design 1 (design GE). The $\delta_2 \ldots. \delta_5$ variables are dummy variables representing designs 2 ….5, respectively, coded as a 1 if the specified design is present and 0 else. $(\beta_{02} - \beta_{01})$ represents the increment on the intercept parameter for design 1 that derives from inclusion of design 2 (design LE) in the model; $(\beta_{03} - \beta_{01})$ represents the increment on the intercept parameter for design 1 that derives from inclusion of design 3 (design LL), and so on. $(\beta_{12}-\beta_{11})$ etc. are the increments on the slope parameter for design 1 that derive from inclusion of design 2 etc. in the model.

We have already seen in section 6.2, above, that designs GE and LE can be assumed to have common slopes in the multi-level model, although they appear to have significantly different intercepts for most hydrodynamic function measures examined. Given the differences in materials used for designs LL, L4 and L5, it is unlikely that all these will support a common slopes assumption: it is also possible that some of these designs may have intercepts in common. Therefore, the multi-level analysis procedure began, in every case, with the full model. The model was reduced using the differences in –2(loglikelihood) to assess the significance of the various parameters in the model, as described above. The normal probability plots and standardised residual *vs* fitted value plots were reasonable for all measures with the exception of mean pressure gradient (discussed below).

6.4.1 $\log_e$ {mean pressure gradient}

In this case, all parameter estimates proved significant with the exceptions of the differences in slope parameter associated with designs LE and LL. The reduced model was not a significantly poorer fit than the full model using the deviance statistic ($\chi^2 = 0.060$, 2 d.f). In this case, the normal probability plot indicates some deviation from normality with relatively large tails to the distribution (figure 6.3). The plot of standardised residuals vs fitted values appears to suggest a better fit to the model than for the single design (figure 6.4).

Figure 6.3 Normal Probability Plot of standardised level 1 residuals for $\log_e$ {mean pressure gradient} for five designs, level 1 residuals on intercept parameter

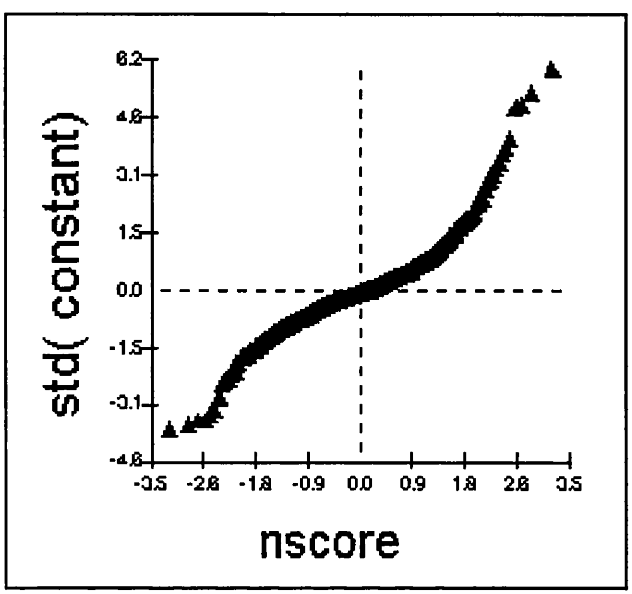
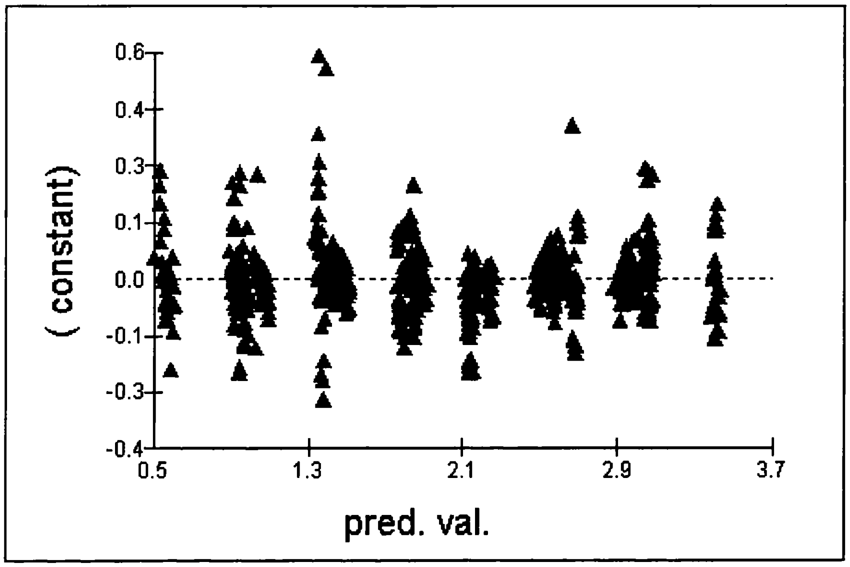


Figure 6.4 Standardised Residuals vs Fitted Values

for $\log_e$\{mean pressure gradient\} for five valve designs



The parameter estimates are tabulated below.

Table 6.4.1.1 Parameter estimates for $\log_e$\{mean pressure gradient\}

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	-6.635	0.161
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	0.401	0.063
$(\beta_{03} - \beta_{01})$ increment on intercept for design LL	0.341	0.063
$(\beta_{04} - \beta_{01})$ increment on intercept for design L4	2.066	0.316
$(\beta_{05} - \beta_{01})$ increment on intercept for design L5	2.964	0.316
β_{11} slope of designs GE, LE & LL	1.544	0.026
$(\beta_{14} - \beta_{11})$ increment on slope for design L4	-0.272	0.053
$(\beta_{15} - \beta_{11})$ increment on slope for design L5	-0.358	0.053
σ_{u0}^2 variance of intercept due to valve variability	0.420	0.114
σ_{u1}^2 variance of slope due to valve variability	0.012	0.003
σ_{u01}^2 covariance of intercept and slope (level 2, valve)	-0.069	0.019
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.005	0.000

According to the Wald tests available with the MLwiN software, 95% confidence intervals for the parameter estimates correspond closely to estimate ± (2 x the standard error of the estimate). Significant differences between parameter estimates were confirmed from these. Designs GE, LE and LL were modelled with common slopes. Design L4 had a significantly lower slope than these. Design L5 had a lower slope than design L4, but the difference was not significant, using the Wald test. The higher slopes for designs GE, LE and LL indicate that the mean pressure gradient increases with flow rate for these designs at a higher degree than for designs L4 and L5, with designs GE, LE and LL having the greatest mean pressure gradients with increasing flow. Thus, as greater work is demanded from the heart, these designs, theoretically, require more effort to operate. The lowest intercept parameter estimate is achieved by design GE. Designs LE and LL are significantly higher but not significantly different from each other. Design L4 has a significantly higher intercept parameter estimate than these three valves, with design L5 being greater still, although the difference between designs L4 and L5 is not significant by the Wald test. The intercept parameter is an indicator of how easily the valve may be opened at low flow rates, when the patient is at rest and relatively little work is demanded of the heart. The difference in significance testing noted between those parameter estimates which are significant in terms of their inclusion in the model using the deviance statistic to test their inclusion and the significance testing resulting from the use of the Wald test will be discussed in detail in Chapter 7. However, limitations on the analysis resulting from the relatively small number of valves available for each design suggest that the deviance statistic is more relevant for interpretation of the data than the Wald test results. The intercepts and slopes for each of the valve designs, calculated from the model parameter estimates are tabulated below. The predicted regression lines for each valve are plotted in Figure 6.5. This figure demonstrates the relative ranking of each valve design. Design GE is demonstrated to be the best valve design at all observed flow rates. There is little difference between designs LE and LL, although design LL is slightly the better of the two. Although design L4 has a higher mean pressure gradient at low flow rates, it can be seen to converge with designs LE and GE at the highest flow rates of interest, and, in fact, seems to be better than either of these designs at the highest flow rate. Design L5 is consistently worse than any other design.

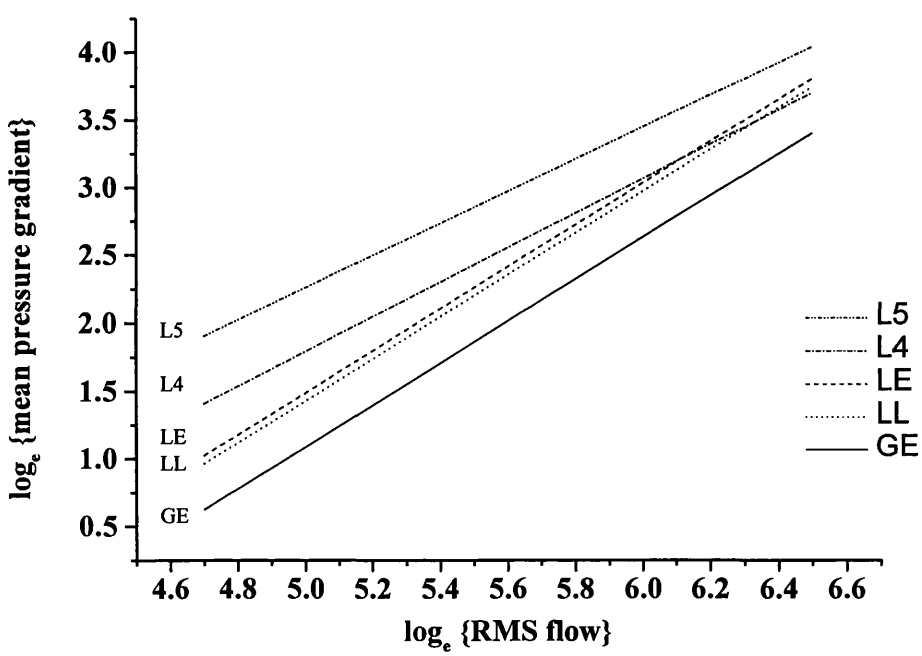
Table 6.4.1.2 Intercept and slope parameter estimates for

$\log_e$ {mean pressure gradient}

Design	Intercept	Slope
GE	-6.635	1.544
LE	-6.234	1.544
LL	-6.294	1.544
L4	-4.569	1.272
L5	-3.671	1.186

Figure 6.5 Predicted regression lines for all valve designs

for $\log_e$ {mean pressure gradient} regressed on $\log_e$ {RMS flow}



The intercept and slope parameter estimates for design LE are very similar to those derived from the model containing the single design, LE, and, for both designs GE and LE, these estimates are close to those derived in the two-design model. The ability of the five-design model to discriminate these two designs is similar to that of the two-design model. The variances of the intercept due to valve variability and replicate variability are increased in this full model compared with the single design and two-design models, but with a further decrease in their standard errors. As expected, valve-to-valve variability is greater than replicate-to-replicate variability. The larger number of cases available for analysis seems to have increased the precision of estimation of the random parameters.

The most important parameter of valve function here is the intercept parameter estimate, because it is most important to be able to open the valve at resting heart rates, otherwise there is a danger of circulatory insufficiency at rest or a risk of longer term problems developing due to poor blood flow dynamics through the valve causing thrombosis or stenosis of the valve. However, if the intercept parameter estimate is tolerable, then, as a secondary consideration, the slope parameter should be lower rather than higher. The risk of high mean pressure gradients includes the possibility of high shear forces acting on the red cells and platelets in blood, causing haemolysis and/or activation of thrombotic cascade reactions as the blood is damaged.

In this case, in terms of mean pressure gradient, design GE performs best, with fairly good performance from designs LE and LL. Designs L4 and L5 are much harder to open and, all else being equal, would be less desirable in terms of their functional performance by this measure. However, design L4 may prove acceptable, if fabricated with leaflets of similar thickness to those of designs GE, LE and LL.

6.4.2 log$_e${regurgitation}

In this case, the intercept parameter estimates showed no significant differences among designs. The slope parameter estimates associated with designs LE and LL were not significant. Omitting these parameters from the model, the reduced model did not fit significantly less well than the full model, as seen from the deviance statistic (χ^2 = 8.635, 6 d.f). The parameter estimates are tabulated below.

Table 6.4.2.1 Parameter estimates for log$_e${regurgitation}

regression parameter	estimate	standard error of estimate
β_{01} intercept of all designs	1.057	0.077
β_{11} slope of designs GE, LE & LL	-0.018	0.013
$(\beta_{14} - \beta_{11})$ increment on slope for design L4	0.082	0.008
$(\beta_{15} - \beta_{11})$ increment on slope for design L5	0.103	0.008
σ_{u0}^2 variance of intercept due to valve variability	0.139	0.046
σ_{u1}^2 variance of slope due to valve variability	0.003	0.001
σ_{u01}^2 covariance of intercept and slope (level 2, valve)	-0.022	0.008
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.212	0.065
$\sigma_{\varepsilon 1}^2$ variance of slope due to replicate variability, given valve	0.007	0.002
$\sigma_{\varepsilon 01}^2$ covariance of intercept and slope (level 1, replicate, given valve)	-0.037	0.012

Designs GE, LE and LL had common slopes, with a negative slope parameter estimate indicating decreasing regurgitation with increasing flow, suggesting that the leaflets may close faster at higher flow rates. Designs L4 and L5 were not significantly different from each other, but both had significantly greater slope estimates than designs GE, LE and LL. Furthermore, for these designs, the slope estimate was positive, indicating increasing regurgitation with increasing flow through the valve. The intercept parameter estimates are not significantly different from each other.

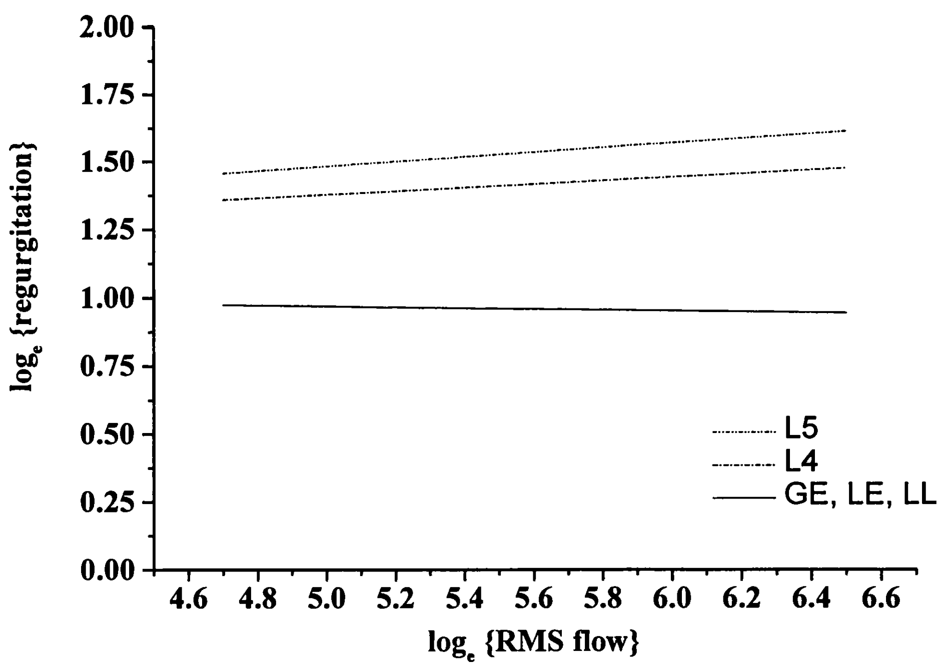
The intercepts and slopes for each of the valve designs, calculated from the model parameter estimates are tabulated below, with the predicted regression lines for each design plotted in figure 6.6.

Table 6.4.2.2 Intercept and slope parameters for $\log_e$\{regurgitation\}

Design	Intercept	Slope
GE	1.057	-0.018
LE	1.057	-0.018
LL	1.057	-0.018
L4	1.057	0.064
L5	1.057	0.085

The intercept and slope parameter estimates for design LE are very similar to those derived from the model containing the single design, LE, and, for both designs GE and LE, these estimates are close to those derived in the two-design model. The variances of the intercept due to valve variability are increased in this full model compared with the single design and two-design models. Valve-to-valve variability is less than replicate-to-replicate variability. It seems that the precision of estimation of valve-to-valve variability has improved greatly going from a single design model to a two-design model and then again, to the full five-design model. The larger number of cases available for analysis is likely to have increased precision of estimation of the random parameters. However, although there are valve-related effects that may cause relatively high variability over replicate tests, the higher variance estimates associated with replicate variation compared with valve-to-valve variability suggest that there is still some imprecision in the estimation of the random parameters.

Figure 6.6 Predicted regression lines for all valve designs for $\log_e$ {regurgitation} regressed on $\log_e$ {RMS flow}



The graph of predicted regression lines demonstrates that there is little difference among the designs GE, LE and LL in terms of regurgitation. In fact the regurgitation is almost constant over the range of flow rates of interest, with a slight decrease as flow rate increases. The higher regurgitation of designs L4 and L5 is clearly demonstrated, as is the trend towards increasing regurgitation with increasing flow rate. Regurgitation indicates the amount of flow volume passing backwards through the valve as it closes. The most likely reason for true differences in regurgitation would be that one design spends less time closing than another design so that the time available for reverse flow is reduced and hence less reverse flow can occur. However, it is also likely that variations in leaflet cutting, which result in varying leaflet length from base to centre free edge, will affect the regurgitation through the closing valve. In this case, there seems to be no significant difference among valves at low flow rates. However, as demand on the heart increases, the more efficiently the valve functions the better blood flow can respond to that demand. If the valve closes more quickly as flow rate rises, then back-flow through the closing valve reduces and blood is more efficiently pumped. Thus, in principle, a negative slope estimate would be preferred. Therefore, designs L4 and L5, with increasing regurgitation as flow rate increases, have less desirable characteristics. In general, regurgitation varies less than mean pressure gradient for most similar valve designs, and would be regarded as a lower priority measure. In the present analysis, there is no separation of designs GE and LE, in contrast to the findings for the two-design model. The slope divergence of designs L4 and L5 compared with the other three designs might indicate sufficient difference in valve behaviour in response to closing forces that, while the model can discriminate among very different designs, it may be less able to discriminate among similar designs.

6.4.3 leakage

A series of models were compared using the Akaike Information Criterion as described above. The final model included one common intercept term for designs

GE and LE, a separate common intercept term for designs LL, L4 and L5, one common slope term for designs GE and LE, a separate common slope term for designs L4 and L5, and a separate slope parameter for design LL. The parameter estimates are tabulated below.

Table 6.4.3.1 Parameter estimates for leakage

regression parameter	estimate	standard error of estimate
β_{01} intercept of designs GE, LE	6.165	0.426
$(\beta_{03} - \beta_{01})$ increment on intercept for design LL, L4 & L5	3.296	0.550
β_{11} slope of designs GE & LE	—0.830	0.071
$(\beta_{13} - \beta_{11})$ increment on slope for design LL	-0.550	0.099
$(\beta_{14} - \beta_{11})$ increment on slopes for designs L4 & L5	-0.846	0.093
σ_{u0}^2 variance of intercept due to valve variability	1.090	0.570
σ_{u1}^2 variance of slope due to valve variability	0.023	0.016
σ_{u01}^2 covariance of intercept and slope (level 2, valve)	—0.119	0.090
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	2.659	1.875
σ_{e1}^2 variance of slope due to replicate variability, given valve	0.071	0.065
σ_{e01}^2 covariance of intercept and slope (level 1, replicate)	-0.422	0.350

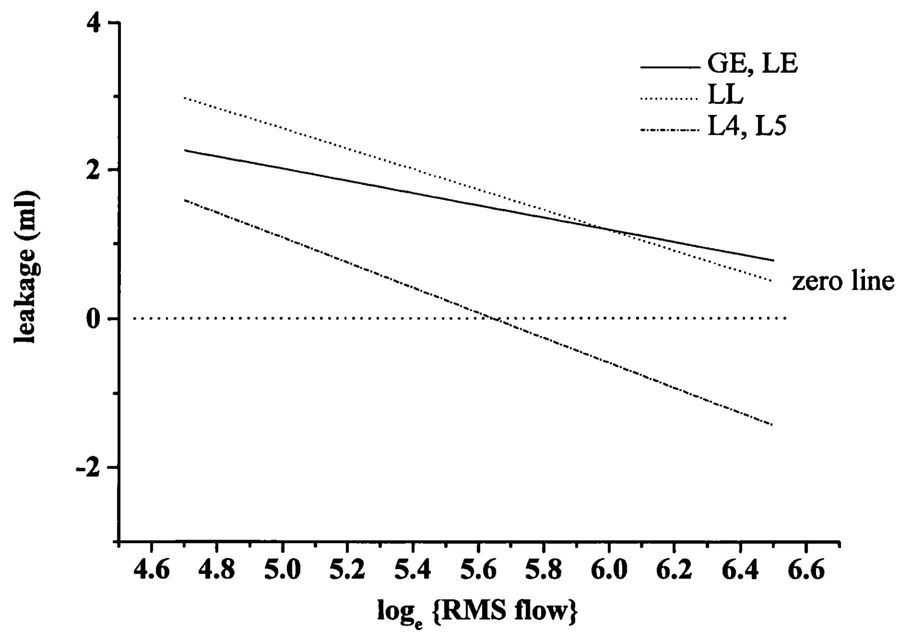
Designs GE and LE, had common slopes, with negative parameter estimates indicating less leakage as flow rate increases. Design LL had a significantly lower slope parameter estimate than designs GE and LE. Designs L4 and L5 had a common slope parameter estimate that was also the lowest slope parameter estimate. The lowest intercept parameter estimate was achieved by designs GE and LE, with no significant difference between them. Designs LL, L4 and L5 had a separate, common intercept parameter estimate that was significantly higher than designs GE and LE. In principle, leakage, being a measure of backwards flow through the closed valve, is an indicator of a "leaky" and inefficient closed valve. The slope parameter, similarly to regurgitation, would, preferably, be close to zero or negative so that the valve seals more effectively as flow rate rises. Leakage is the hydrodynamic function measure that is probably most seriously affected by inaccurate leaflet trimming. If a leaflet is cut slightly low, it will not be able to close symmetrically with its neighbours, allowing a small orifice for reverse flow through the closed valve. If the leaflets are cut very low, it may still open well, but the three leaflets can no longer meet together in the closed position and the valve will leak. As each leaflet is cut individually, there is scope for a wide range in variability in the whole valve as all three leaflets can vary in differing degrees. The intercepts and slopes for each of the valve designs, calculated from the model parameter estimates are tabulated below. The predicted regression lines for each design are plotted in figure 6.7.

Table 6.4.3.2 Intercept and slope parameters for leakage

Design	Intercept	Slope
GE	6.165	-0.830
LE	6.165	-0.830
LL	9.461	-1.380
L4	9.461	-1.676
L5	9.461	-1.676

Figure 6.7 Predicted regression lines for all valve designs

for leakage regressed on $\log_e$ {RMS flow}



The intercept and slope parameter estimates for design LE are similar to those derived from the model containing the single design, LE, and, for both designs GE and LE, in the two-design model. The predicted regression lines for designs GE and LE are superimposed (fig. 6.7) and confirm the decrease in leakage as flow rate increases. The predicted regression line for design LL indicates slightly higher leakage for this design at low flow rates compared with designs GE and LL, but a steeper slope indicates equal or better performance at high flow rates. All these designs have higher leakage than designs L4 and L5 at all flow rates. This is likely to be related to the moulded position of the leaflets. In the designs used for this project, all valves are formed with the leaflets in a partially closed "natural" position. The relative stiffness of the materials used for these two designs would tend to reinforce their tendency to "prefer" the closed position in contrast to the lower modulus materials of designs GE, LE and LL, which allow easier leaflet opening. Lower modulus materials may also allow a degree of leaflet prolapse in the closed position, particularly for valves with unevenly trimmed leaflets. Leakage performance would be a secondary consideration to measures of valve opening in judging overall valve performance. The predicted regression lines for designs L4 and L5 are superimposed and pass through the zero leakage point around the mid-point of the flow range of interest. This may be an artefact of the regression, but the measurement of flow is also less precise than that of pressure and, around the zero position, the error is much higher due to poor signal:noise ratios. It is possible that both these valve designs reach a position in the valve cycle where they are fully closed and do not leak, and, therefore, have somewhat different distributions than designs GE, LE and LL, although substantial deviations from the model assumptions were not apparent from the residual plots. Thus the regression would only be valid to the zero cross-over point and comparison of these designs with the other three designs may be improved with a more complex modelling process accounting for these differences in the data distributions, beyond the scope of this study. This may also account for the loss of discrimination in the five-design model between designs GE and LE, compared with the two-design model. There may be fundamental differences among valve designs related, for example, to ease of leaflet trimming when different modulus materials are used to fabricate the leaflets. It is also more likely that hydrodynamic test data would be influenced by the orientation of a valve with leaflets of varying height in the test rig, and such influences may not be the same for all valve designs. More detailed investigation of the relative performances of designs GE, LE and LL might be better done using a three-design model focussing on these designs alone.

The variances of the intercept due to valve variability and replicate variability are increased in this full model compared with the single design and two-design models, with an increase in their standard errors. The variance of the replicate intercept parameter estimate is also increased compared with that of the valve intercept parameter, suggesting that, not only does valve-to-valve variability have a significant effect, but that influences such as orientation of the valve in the rig on replicate testing may influence the test results. This is probably related to the problems of leaflet trimming discussed above.

6.4.4 $\log_e${energy loss in forward flow}

In this case, all parameter estimates proved significant with the exceptions of the slope parameter estimates associated with designs LE and LL, similar to the case for mean pressure gradient. The reduced model did not fit significantly less well than the full model using the deviance statistic ($\chi^2 = 0.356$, 2 d.f). The parameter estimates are tabulated below.

Table 6.4.4.1 Parameter estimates for $\log_e$\{energy loss in forward flow\}

regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	-5.109	0.148
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	0.417	0.068
$(\beta_{03} - \beta_{01})$ increment on intercept for design LL	0.357	0.068
$(\beta_{04} - \beta_{01})$ increment on intercept for design L4	1.630	0.288
$(\beta_{05} - \beta_{01})$ increment on intercept for design L5	2.675	0.288
β_{11} slope of designs GE, LE & LL	1.697	0.024
$(\beta_{14} - \beta_{11})$ increment on slope for design L4	-0.191	0.048
$(\beta_{15} - \beta_{11})$ increment on slope for design L5	-0.300	0.048
σ_{u0}^2 variance of intercept due to valve variability	0.335	0.094
σ_{u1}^2 variance of slope due to valve variability	0.010	0.003
σ_{u01}^2 covariance of intercept and slope (level 2, valve)	-0.055	0.016
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.106	0.050
$\sigma_{\varepsilon 1}^2$ variance of slope due to replicate variability, given valve	0.002	0.002
$\sigma_{\varepsilon 01}^2$ covariance of intercept and slope (level 1, replicate, given valve)	-0.014	0.009

Designs GE, LE and LL had common slopes. Design L4 had a significantly lower slope than these. Design L5 had a lower slope than design L4, but this difference was not significant. The higher slopes for designs GE, LE and LL indicate that the energy required to open the valve increases with flow rate for these designs at a higher degree than for designs L4 and L5. Thus, as greater work is demanded from the heart, these designs, theoretically, require more effort to operate. The lowest intercept parameter estimate is achieved by design GE. Designs LE and LL are significantly higher but not significantly different from each other. Design L4 has a significantly higher intercept parameter estimate than these three valves, with design L5 having a significantly higher intercept parameter estimate than design L4. The intercept parameter is an indicator of how easily the valve may be opened at low flow rates, when the patient is at rest and relatively little work is demanded of the heart. The measure is related to the mean pressure gradient but is a more comprehensive measure of the work required to open a valve. The intercepts and slopes for each of the valve designs, calculated from the model parameter estimates are tabulated below. The predicted regression lines for each design are plotted in figure 6.8.

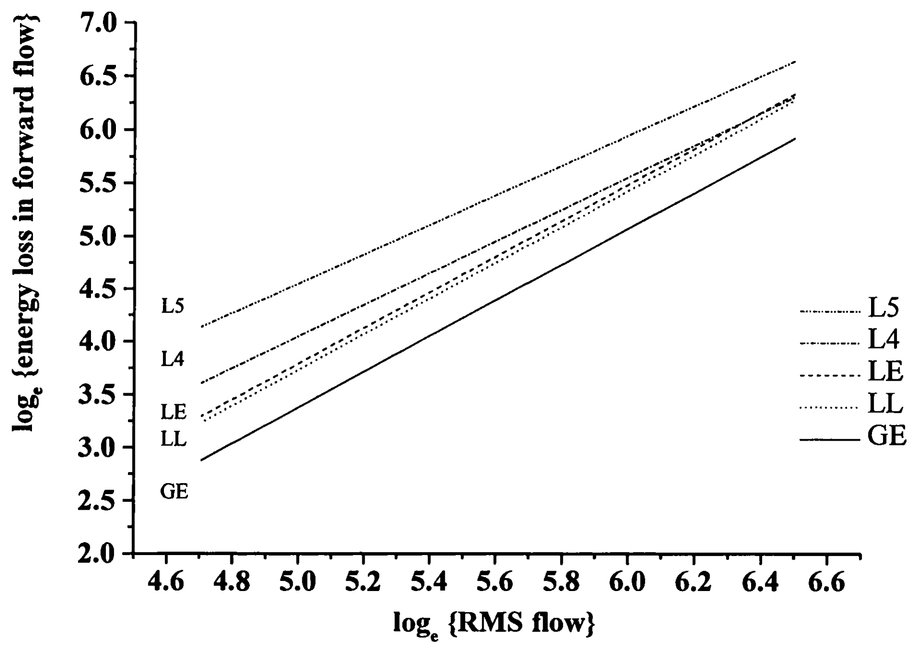
Table 6.4.4.2 Intercept and slope parameters for

$\log_e$\{energy loss in forward flow\}

Design	Intercept	Slope
GE	-5.109	1.697
LE	-4.692	1.697
LL	-4.752	1.697
L4	-3.479	1.506
L5	-2.434	1.397

Figure 6.8 Predicted regression lines for all valve designs

for $\log_e$ {energy loss in forward flow} regressed on $\log_e$ {RMS flow}



The intercept and slope parameter estimates for design LE are very similar to those derived from the model containing the single design, LE, and, for both designs GE and LE, these estimates are close to those derived in the two-design model. The variances of the intercept due to valve variability and replicate variability are increased in this full model compared with the single design and two-design models, with a decrease in their standard errors. As expected, valve-to-valve variability is greater than replicate-to-replicate variability. The larger number of cases available for analysis seems to have increased the precision of estimation of the random parameters.

It is clearly demonstrated in figure 6.8 that design GE has lower energy losses in forward flow at all flow rates of interest. The results are similar to those for mean pressure gradient, with design L5 having the worst performance at all flow rates. Design L4 is worse than designs GE, LE and LL at low flow rates, but converges with designs LE and LL at high flow rates. The most important parameter of valve function here is the intercept parameter estimate, similarly to the mean pressure gradient measure. Similarly, if the intercept parameter estimate is tolerable, then, as a secondary consideration, the slope parameter should be lower rather than higher. In this case, in terms of energy loss in forward flow, design GE has the best performance with designs LE and LL performing fairly well. Designs L4 and L5 are much harder to open, with L5 being worse than L4, and, all else being equal, would be less desirable in terms of their functional performance by this measure. However, as previously stated, design L4 has much thicker leaflets than the other designs and may perform well at lower leaflet thickness values. Further investigation would be required to determine whether the slope of design L4 changes with leaflet thickness as well as the intercept. The discrimination of designs GE and LE is similar to that achieved with the two-design model.

6.4.5 energy loss closing

In this case, only the base intercept and slope parameter estimates of design GE and the intercept parameter estimate associated with design L5 proved significant, testing the parameter estimates using Wald tests. The reduced model, however, was significantly different from the full model using the deviance statistic ($\chi^2 = 28.399$, 7 d.f, $p = 0.0002$). It was not, however, obvious how to redefine the model to include any other parameters, as none was either close to being significant or notably less insignificant than any other. Sequential testing of all the removed parameters was investigated and a final model including a common intercept for designs GE, LE and LL, common slope for all designs and separate intercept parameters for designs L4 and L5 produced a model with all parameter estimates now testing significant using Wald tests and that did not fit significantly less well than the full model using the deviance statistic ($\chi^2 = 1.759$, 6 d.f, $p = 0.940$). The parameter estimates for this model are tabulated below.

Table 6.4.5.1 Parameter estimates for closing energy loss

regression parameter	estimate	standard error of estimate
β_{01} intercept of designs GE, LE & LL	-26.069	7.307
$(\beta_{04} - \beta_{01})$ increment on intercept for design L4	25.568	3.914
$(\beta_{05} - \beta_{01})$ increment on intercept for design L5	33.852	3.914
β_{11} slope of all designs	10.562	1.324
σ_{u0}^2 variance of intercept due to valve variability	57.182	17.812
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	294.062	15.498

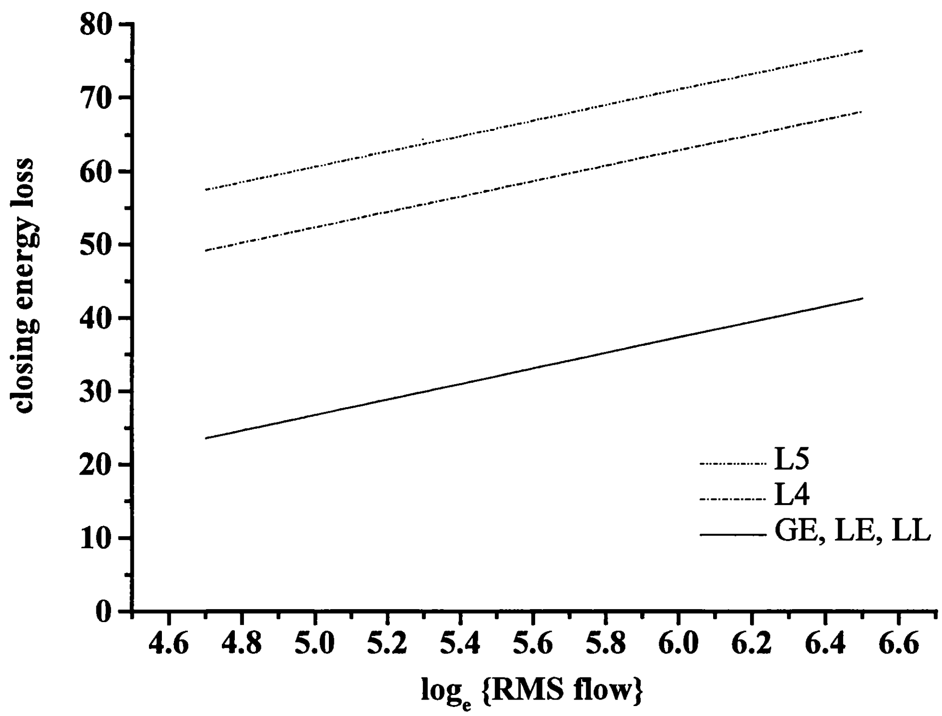
Designs GE, LE and LL have the lowest intercept parameter estimate in common. Design L4 has a significantly higher intercept parameter estimate than these three designs. Design L5 has a significantly higher intercept parameter estimate than design L5. The intercept parameter is an indicator of how easily the valve may be moved into the closed position at low flow rates, when the patient is at rest and relatively little work is demanded of the heart. The intercepts and slopes for each of the valve designs, calculated from the model parameter estimates are tabulated below. The predicted regression lines for each valve design are plotted in figure 6.9.

Table 6.4.5.2 Intercept and slope parameters for closing energy loss

Design	Intercept	Slope
GE	-26.069	10.562
LE	-26.069	10.562
LL	-26.069	10.562
L4	-0.501	10.562
L5	7.783	10.562

Figure 6.9 Predicted regression lines for all valve designs

for closing energy loss regressed on $\log_e$ {RMS flow}



The intercept and slope parameter estimates for design LE are similar to those derived from the model containing the single design, LE, and, for both designs GE and LE, these estimates are close to those derived in the two-design model. The graph indicates that there are no differences among designs GE, LE and LL at all flow rates. These findings are similar to those of the two-design model for designs GE and LE. The closing energy losses for designs L4 and L5 are considerably higher than the other three designs, at all flow rates. The variances of the intercept due to valve variability and replicate variability are considerably increased in this full model compared with the single design and two-design models. Valve-to-valve variability is less than replicate-to-replicate variability.

In general, the less energy required for a task, then the easier or more efficiently that task can be carried out. Hence, to close a fully open valve, it would be preferred that the valve has a low intercept parameter estimate and, if possible, a low slope parameter estimate. In this case, design L5 seems much harder to close than any other design. Design L4 is easier to close than design L5 but is harder to close than designs GE, LE or LL.

6.4.6 energy loss closed

In this case, the model selection faced the same problems as for the analysis of leakage and the model selection process used the Akaike Information Criterion to select the final model. The final model included a common intercept parameter for all designs, a common slope parameter for designs GE, LE and LL ($\beta_{11} = \beta_{12} = \beta_{13}$), with a separate common slope parameter for designs L4 and L5 ($\beta_{14} = \beta_{15}$). The parameter estimates are tabulated below.

Table 6.4.6.1 Parameter estimates for closed energy loss

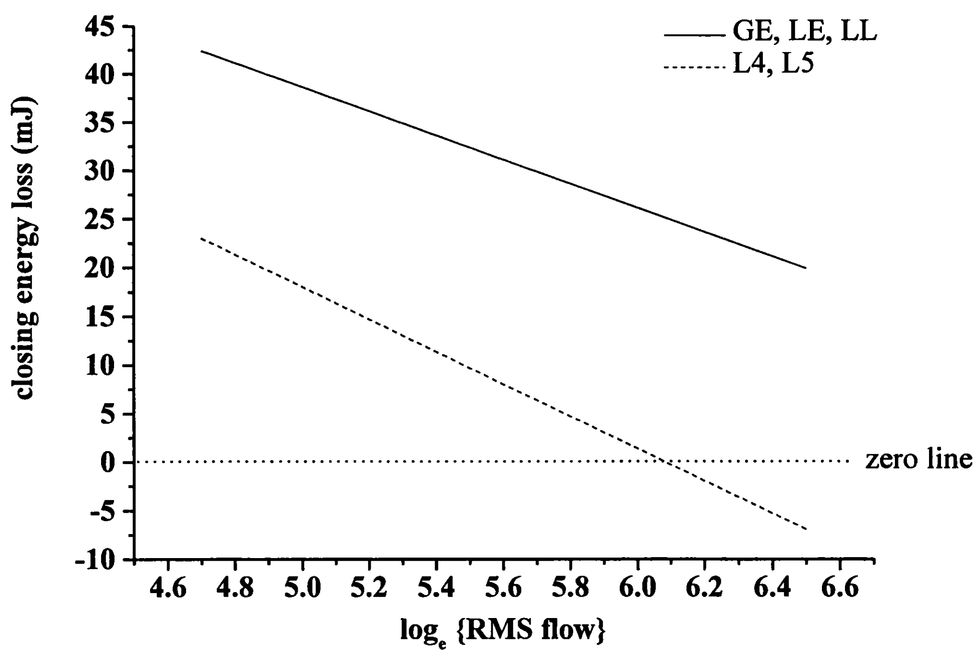
regression parameter	estimate	standard error of estimate
β_{01} intercept of all designs	101.147	7.684
β_{11} slope of designs GE, LE and LL	-12.506	1.260
$(\beta_{14} - \beta_{11})$ increment on slope for designs L4 and L5	-4.121	0.330
σ_{u0}^2 variance of intercept due to valve variability	1454.931	459.767
σ_{u1}^2 variance of slope due to valve variability	36.019	12.239
σ_{u01}^2 covariance of intercept and slope (level 2, valve)	-227.464	74.699
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	62.060	3.341

Designs GE, LE and LL had the highest slope estimate. Designs L4 and L5 had significantly lower slope parameter estimates than these three designs. The intercept parameter estimate is an indicator of the energy required to maintain the closed valve: it will be increased by a "leaky" valve. The slope parameter indicates the change in energy required to keep the valve closed as the flow rate rises. In general, the slope decreases with flow so that the valve is more easily maintained in the closed position at high flow rates. This being the case, a more negative slope parameter estimate would make the valve easier to keep tightly closed. The intercepts and slopes for each of the valve designs, calculated from the model parameter estimates are tabulated below. The predicted regression lines are plotted in figure 6.10.

Table 6.4.6.2 Intercept and slope parameters for closed energy loss

Design	Intercept	Slope
GE	101.147	-12.506
LE	101.147	-12.506
LL	101.147	-12.506
L4	101.147	-16.627
L5	101.147	-16.627

Figure 6.10 Predicted regression lines for all valve designs for energy loss when the valve is closed regressed on $\log_e$ {RMS flow}



The intercept and slope parameter estimates for design LE are very similar to those derived from the model containing the single design, LE, and, for both designs GE and LE, these estimates are close to those derived in the two-design model. The graph demonstrates the superposition of the regression for designs GE, LE and LL. Designs L4 and L5 are also superimposed, but have lower closed energy losses than the other three designs. There is a similar zero cross-over point in the regression as seen in the case of leakage flow. The reasons for this are similar to those discussed previously for the leakage flow and are likely to cause similar difficulties in model selection and design discrimination. The variances of the intercept due to replicate variability and, especially, valve variability are increased in this full model compared with the single design and two-design models. Valve-to-valve variability is greater than replicate-to-replicate variability, but the differences suggest a problem with the estimation, especially in the estimation of level 2 variance of the intercept parameter estimate. The larger number of cases available for analysis seems to have improved estimation of the random parameters associated with level 1 (replicates). However, the problems with model selection may indicate that the final model chosen either is not, in fact, the best model, or that there are fundamental differences related to specific valve designs that affect their influence on the modelling.

The closed energy losses are rather more difficult to interpret than other measures of hydrodynamic function. The valve designs under consideration here are moulded in a nearly closed position. They, therefore, have a "natural" position nearly closed rather than nearly open. Ideally, it should be easy to close the valve, but, if the valve does close easily, and it is moulded in this position, then it may be harder to open than an alternative design either moulded in a partially open position, or with a different material. A stiffer material may have a lesser tendency to collapse back over itself under high loading pressures on the closed valve than a lower modulus material. The closed energy losses are likely to be a relatively low priority consideration for a valve design (within a quite large range) compared with other hydrodynamic function measures. They may also be more useful with a better-controlled valve fabrication method and when examining substantially different designs where the engineering design is altered significantly as well as the leaflet material. On the basis of the intercept here, all designs are functionally similar, with little to choose among them, although the graph demonstrates that the slope differences separate the designs at the lowest flow rate of interest so that designs L4 and L5 seem to perform best by this measure.

6.4.7 effective orifice area at maxima

In this case, the final model included separate intercept parameters for all valve design, a common slope parameter for designs GE, LE, LL and L5, and a separate slope parameter for design L4. The reduced model was not significantly different from the full model using the deviance statistic ($\chi^2 = 2.014$, 3 d.f). The parameter estimates are tabulated below.

Table 6.4.7.1 Parameter estimates for effective orifice area

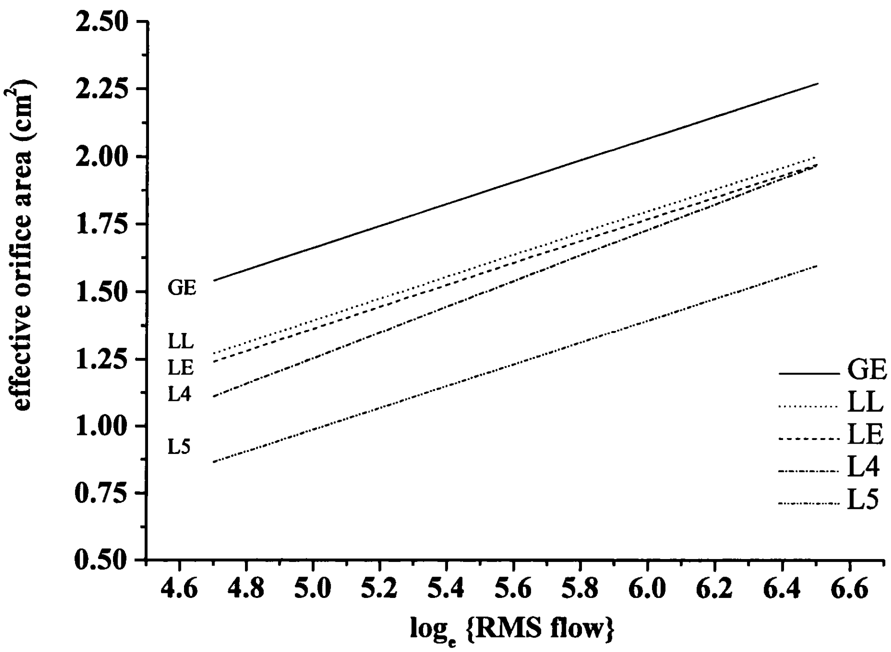
regression parameter	estimate	standard error of estimate
β_{01} intercept of design GE	-0.372	0.078
$(\beta_{02} - \beta_{01})$ increment on intercept for design LE	-0.300	0.045
$(\beta_{03} - \beta_{01})$ increment on intercept for design LL	-0.270	0.045
$(\beta_{04} - \beta_{01})$ increment on intercept for design L4	-0.759	0.167
$(\beta_{05} - \beta_{01})$ increment on intercept for design L5	-0.676	0.045
β_{11} slope of designs GE, LE, LL & L5	0.407	0.013
$(\beta_{14} - \beta_{11})$ increment on slope for design L4	0.070	0.030
σ_{u0}^2 variance of intercept due to valve variability	0.111	0.033
σ_{u1}^2 variance of slope due to valve variability	0.004	0.001
σ_{u01}^2 covariance of intercept and slope (level 2, valve)	-0.020	0.006
$\sigma_{\varepsilon 0}^2$ variance of intercept due to replicate variability, given valve	0.096	0.030
$\sigma_{\varepsilon 1}^2$ variance of slope due to replicate variability, given valve	0.003	0.001
$\sigma_{\varepsilon 01}^2$ covariance of intercept and slope (level 1, replicate, given valve)	-0.017	0.006

Design L4 had a significantly higher slope than all other designs. The lower slopes for designs GE, LE, LL and L5 indicate that these designs have a more slowly increasing orifice with increasing flow rates than does design L4. Design L4 had the lowest intercept parameter estimate. Design L5 was not significantly different from this, using the Wald test. Design GE had the highest intercept parameter estimate and hence was the "best" valve in this respect, although the differences between it and designs LE and LL were not significant, using the Wald tests. Designs L4 and L5 were significantly worse than designs GE, LE and LL. The intercept parameter is an indicator of how wide the valve may be opened at low flow rates, when the patient is at rest and relatively little work is demanded of the heart. The slope parameter indicates how much wider the valve will open as the flow rate rises with demand on the heart. The intercepts and slopes for each of the valve designs, calculated from the model parameter estimates are tabulated below. The predicted regression lines for all valve designs are plotted in figure 6.11.

Table 6.4.7.2 Intercept and slope parameters for effective orifice area

Design	Intercept	Slope
GE	-0.372	0.407
LE	-0.672	0.407
LL	-0.642	0.407
L4	-1.131	0.477
L5	-1.048	0.407

Figure 6.11 Predicted regression lines for all valve designs for effective orifice area regressed on $\log_e$ {RMS flow}



The intercept and slope parameter estimates for design LE are very similar to those derived from the model containing the single design, LE, and, for both designs GE and LE, these estimates are close to those derived in the two-design model. The predicted regression lines plotted in figure 6.11 indicate that design GE has a substantially greater valve orifice than any other design at all flow rates of interest. Design L5 has the smallest orifice at all flow rates. Designs LE and LL have intermediate performance, while design L4 is worse than these at low flow rates but converges at higher flow rates. Again, the relatively poor performance of design L4 is likely to be related to its greater leaflet thickness and this design may perform well at similar leaflet thickness to designs GE, LE and LL. The variances of the intercept due to valve variability and replicate variability are low and similar to the single design and two-design models, with a small decrease in their standard errors. As expected, valve-to-valve variability is greater than replicate-to-replicate variability. The larger number of cases available for analysis seems to have slightly improved estimation of the random parameters.

Both slope and intercept fixed parameters of this model are important. It is important to have a wide valve orifice at low flow rates so that sufficient blood may be pumped through the valve when the patient is at rest. However, it is also important that the valve should be able to respond to an increased demand on the heart and, by opening wider as the flow rate rises, it enables the pumping of a larger volumetric flow rate through the valve. This enables the patient to pursue more energetic activities successfully, without developing shortness of breath.

Chapter 7: Evaluation of the Multi-level Modelling Approach

The application of multi-level modelling to the data under consideration has enabled a relatively complex problem to be analysed in a reasonably straightforward way, using all the data available in the analysis, in contrast to the random regression modelling of Chapter 3. In the sociological problems commonly analysed by this means, a dataset with such small numbers would likely have been uninformative as a result of the low power available from the method to detect important parameters. However, although the estimation of certain parameters may have been affected to some degree, in that random parameters in particular may have been underestimated, the differences between designs that are of practical consequence are, generally, much greater than differences within designs so that parameter estimation was both possible and precise enough to be useful.

In the results presented in Chapter 6, the significance of parameter estimation has been tested using a combination of tests on the deviance statistic and the Wald tests provided by the software. In general, Wald tests should be used with caution for datasets with small numbers, particularly when the assumptions of the model are not strongly adhered to, and the likelihood ratio test using the deviance statistic is regarded as preferable (Goldstein, 1999). In all cases of the full five design analysis, however, when the level 2 variance intercept parameter was tested using the deviance statistic, omission of the parameter resulted in a significantly poorer model, suggesting that this parameter was consistently significant. The significance was generally greater using this test than the Wald test, but the interpretation of the model was unaffected. This observation is particularly relevant in the selection of the final model for closing energy losses, in which Wald tests conflicted with the results of testing the deviance statistic. The final model, therefore, was always selected on the basis of the likelihood ratio tests of the deviance statistic or, in a few cases, the Akaike Information Criterion where models to be compared were not nested, one within the other.

There was a further decision to be made on whether to use separate or joint 95% confidence intervals (Wald tests) to test significance of individual fixed parameters. There is an issue here of multiple testing whereby the ideal choice might be thought to be joint intervals, particularly given the small numbers of valves available for analysis. However, joint 95% confidence intervals are extremely conservative and, in practice, potentially misleading. In the present case, separate 95% confidence intervals were used to test significance of fixed parameters. Although there is a risk of detecting differences where none truly exists, in this particular case, where we are seeking to optimise design and performance, it is better to detect differences than to miss detection and separate 95% confidence intervals were deemed to be preferable.

7.1: The fixed parameter estimates

The single and two-design multi-level models have been discussed in comparison with the simple linear regression model (Chapter 6). As discussed in Chapter 6, for leakage and closed energy losses, for multiple design models where the designs perform substantially differently from each other, there may be a benefit in using the larger model for initial assessment, followed by a model restricted to the "best" group of designs (here designs GE, LE and LL) to improve discrimination among these. The following discussion focuses on the five-design model.

As expected certain hydrodynamic function measures were more able to distinguish design-related differences than others. The worst measures in this respect were regurgitation, leakage, closing and closed energy losses. In the case of $\log_e$ {regurgitation} no design-related differences were apparent from the intercept parameter estimates: all designs had similar regurgitation behaviour at low flow rates. Designs L4 and L5 had increasing regurgitation as flow rate increased, in contrast to the other designs. The materials of designs GE, LE and LL are more flexible than those of designs L4 and L5, i.e. lower modulus materials. In contrast to closing energy losses, which are dependent on both the reverse flow through the closing valve and the pressure gradient measured across the closing valve, regurgitation is simply the volumetric flow measured through the closing valve. Hence, either the lower modulus material valves are closing more quickly or have a smaller orifice for a longer time during closing, when forward flow has ceased. Both of these are possibilities. A more flexible material will respond more easily to an applied force. In the case of leakage, only design L5 was worse than any other with greater leakage as determined by the intercept parameter, although the increase in leakage with flow was less for this design than any other. This material was the stiffest of all the leaflet materials and hence less able to conform to a tightly closed morphology. Thus the increased leakage is not surprising, although there may be some relationship to difficulty in trimming leaflets to a consistent height in the stiffer material. A leaflet that is cut slightly too low will allow greater reverse flow through the closed valve than a higher-cut leaflet. Design L5 also performed worst in terms of closing energy losses, with a higher intercept parameter than any other design. This may also be related to its relatively stiff character, producing a greater inertia of the leaflets as they move towards the closed position and hence slowing down the rate of closure compared with other designs. Further practical experimentation could confirm this by using sequential time-lapse photography of the valve during hydrodynamic testing. This would allow assessment of the actual time taken for the valve to close. This design has a similar slope to the other four designs, suggesting that, at higher flow rates, the valve tends to close faster with the greater forces involved assisting in overcoming the leaflet inertia. Design L4, while it has a better performance in respect of closing energy losses than design L5, has a poorer performance than designs GE, LE and LL at low flow rates. This material has an intermediate modulus. It is significantly stiffer than the materials of designs GE, LE and LL, but less stiff than that of design L5. Again, time-lapse photography of leaflet closure may assist in explaining the findings. The worst discriminant measure was the closed energy loss. In tÅis case, all designs have similar intercept parameters. In terms of the slope parameter, design L4 has the lowest slope, with decreasing energy loss with increasing flow rate. Design L5 also has a relatively low slope. Both these valves have a greater response to the increased forces applied by high flow, and by this measure would seem to perform relatively well compared with designs GE, LE and LL. Design L5 has unexpectedly low energy losses in this case, considering the leakage results. The reasons for this are not obvious. In this case, because the valves cannot close tightly due to the high modulus of the material, a passage is left for a small amount of reverse flow through the valve. It may be the case that the stiffer leaflets are less subject to "flutter" in the flow field so that they are more stable in the closed position, even although they do not close as efficiently as other designs. In the closed position, the leaflet materials of lower modulus may be subject to some collapse of the leaflet free edge due to their high flexibility, increasing the pressure component of the energy loss calculation in this case.

The behaviour of these materials is well-characterised in terms of their simple mechanical properties, but it is uncertain how these properties relate to measures of hydrodynamic function and it is not easy to explai0 all the findings in terms of properties as simple as the material modulus. The valve is a complex three-dimensional device, operating in a flow field of varying complexity that is generally assumed to be streamlined, although there are local regions of flow turbulence and vortex formation in the vicinity of the valve. Differences in material properties that seem to be clearly defined may have unexpected consequences to some measures of hydrodynamic function when the interactions of pressure and flow are considered.

The value of the hydrodynamic function measures discussed above seems to be limited in that they do not differentiate among most designs examined. However, those dPMigns that are distinguished from the rest are worth careful consideration and may lead to improvements in understanding of the relationships between material properties, design and functional behaviour.

The most important measures in assessing valve hydrodynamic function are the mean pressure gradient, the energy losses during forward flow and the maximum orifice area attainable by the valve. These three measures were best able to discriminate among design performance. Maximum orifice area was least effective among these three measures. Given that this measure, too, is a derived value from consideration of both pressure and flow, perhaps this is notPMurprising. Again, this measure suffers from a lower precision of measurement of flow, although, because it uses the maximum flow achieved at any specific applied cardiac output, it is measured more accurately than flow in the regurgitant or leakage phases of valve function. It therefore seems to be a better discriminator than measures related to those phases of the valve operation. The smallest maximum orifice areas (intercept parameter estimates) are associated with designs L4 and L5, which behave in a similar manner. Design LL has a larger orifice, with design LE larger still. Design GE has the largest 07ifice area. The difference between designs GE and LE suggests that design G, a different engineering design than design L made with leaflets of the same material, is the best design in terms of the opening that can be achieved by the valve to allow blood to flow. It might be expected that design LL would have the best performance by this measure as it has leaflets made of the lowest modulus material. Its leaflets, however, are slightly thicker (Table 2.1) than those of design LE, which might explain its slightly worse performance in comparison. It has leaflets of similar thickness to design GE, which again reinforces the finding that design GE indeed has a larger orifice area than the other designs. Designs L4 and L5 have similar orifice areas, notably smaller than other designs. There are two reasons for this. One is that the materials have higher modulus than the other designs, potentially making them harder to open. The other may be related to differences in leaflet thickness. The modulus of design L4 leaflets is approximately half that of design L5 leaflets, so that it would be expected to have a larger orifice area. However, the leaflet thickness for these valves was considerably higher than L5 valves. This large difference in leaflet thickness is sufficient to explain the similar orifice areas of these two designs, in spite of the modulus differences. The leaflet thickness difference is also likely to explain at least part of the difference between design L4 and the wider orifice designs. Design L4 has the steepest slope parameter estimate, suggesting that its orifice area increases more than other designs as flow rate increases. In this case, the effects of leaflet thickness and modulus are more easily overcome in this material than in design L5, which has a lower slope parameter estimate. This seems to suggest that design L4 may perform better at higher flow rates, but this finding must be interpreted in conjunction with the intercept parameter estimates. If a valve perfo¿1Xrms very well, it will open to nearly full orifice at low flow rates, so that the amount by which it can increase its orifice as flow increases is relatively small. A valve that has a small orifice at low flow rates has the potential for much wider opening, but the amount by which the orifice actually increases will then be dependent on other factors such as leaflet thickness and material modulus.

Analyses of mean pressure gradient and energy losses during forward flow have similar ability 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. Design LL was next best, followed by design LE, then design L4 and, worst of all, design L5. Design GE had leaflets made of the same material as design LE, but its leaflets were slightly thicker, suggesting a greater significance might be associated with its 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 (Bernacca et al, 2000; 2001). Thus it is uncertain, in this case, how much of the difference may be attributed to differences in leaflet thickness. Design L4 has lower intercepts 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 modulus lies somewhere between the modulus of material 4 and material 5 (Bernacca et al, 2000; 2001). The slopes of designs GE, LE and LL may be regarded as common. Thus there seems to be little difference in the hydrodynamic function measures of mean pressure gradient and energy loss during forward flow as flow rate increases among these designs. The slope seems to be more influenced by large differences in leaflet thickness or leaflet material modulus. Design L4 has a steeper slope parameter estimate than design L5, however, suggesting that modulus has the greater effect on this parameter.

Overall, design GE has a significantly better hydrodynamic performance than any other design. Designs LE and LL have fairly good performance, but are not as good as design GE. Designs L4 and L5 have the poorest hydrodynamic performances, with design L4 being significantly better than design L5. Design L4 may, in fact, perform rather better than it appears here if the leaflet thicknesses were matched to those of the better designs, as was not possible in this study. Hydrodynamic function is an extremely important feature of valve performance. If the hydrodynamic function is poor, then the valve will not open at low flow rates and this can be critical for a patient with already poor cardiac function. However, it is not the whole story. It is also important that the valve is capable of being able to function for long periods (preferably in excess of twenty years) without failure of the leaflet material, either due to biodegradation of the leaflet material or to fatigue failure mechanisms. In this respect, research suggests that higher modulus materials may provide an advantage in durability terms (O'Connor et el, 2000). 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. The balance between the two factors is critical. In this case, 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.

7.2 The random parameter estimates

The random parameter estimates provide measures of the amount of variance attributable to valve differences at level 2 of the multi-level model and to replicates at level 1 of the model, given valve. The valve-related variance is an indicator of the reproducibility of the valve manufacturing process and the replicate variance is a measure of the reproducibility of the hydrodynamic function testing. These variances are estimates which should yield some indication of quality control limits that can reasonably be set on the performance of individual valves within a group of valves and the amount of variability during hydrodynamic function testing that can reasonably be allowed to be attributed to testing differences rather than valve-related differences. In the present study, only random parameters associated with the intercept parameter were included in the model for all measures: attempts to include random parameters associated with the slope parameter generally were not significant in the model or the model failed due to lack of convergence, particularly for variance associated with replicate testing.

There are some problems with the interpretation of these parameter estimates. The Iterative Generalised Least Squares (IGLS) method is a maximum likelihood method used by MLwiN in a standard analysis and performs well with large numbers of level 2 units in a two-level model. It is known that this method tends to produce biased estimates in small samples, because sampling variation of the parameter estimates is not accounted for in the algorithm. In general, the fixed parameter estimates appear unbiased, but their standard errors may carry relatively large bias and are usually underestimated (Hox, 1998). The MLwiN software offers an alternative analysis, Restricted IGLS (RIGLS), which provides a bias-adjusted parameter estimate, making use of regression coefficient estimates, which carry a degree of uncertainty. In theory this method should lead to better estimates especially for datasets with small numbers (Hox, 1998). The effects of different methods of analysis of a two-level multi-level model have been investigated, comparing IGLS, RIGLS and Bayesian fitting algorithms (Browne & Draper, 2000). These authors investigated the effects of different analytical methods on a series of simulated design configurations, comparing a dataset with a small number of level 2 units (12) with one containing more level 2 units (48). They showed that all methods produced nearly unbiased estimates of β_0, β_1 and σ_e^2, with greater than 90% coverage of 95% confidence intervals for the small dataset. They found that IGLS underestimated the variance of the level 2 units, but that RIGLS methods often corrected this bias to some degree but was still subject to under-coverage of the confidence intervals. Given the complexity of alternative analytical methods and the minor improvements in performance noted, the authors were not able to make any specific recommendation for handling datasets with small numbers of level 2 units. It has further been suggested, using simulation studies, that multi-level modelling parameter estimates remain unbiased when the assumptions of normality and large sample size are not met, but again, their standard errors are underestimated (Hox, 1998). Estimates of the random parameter at the lowest level are usually accurate. Reference to sociological research has suggested that, for accurate estimation of parameters and their standard errors, a sample of at least 30 groups with at least 30 individuals within each group would be preferred, depending on which part of the analysis is of interest (Hox, 1998). These recommendations also include a consideration of the costs incurred in performing the analysis.

The hydrodynamic function data, as discussed throughout Chapter 6, gave rise to some inadequately estimated variances, particularly the level 2 variance of the intercept. This variance seemed to be estimated more efficiently as the numbers of level 2 units increased, as more designs were added to the model. For some measures, where the experimental data was more variable, the random parameter estimates were very dependent on the model selected. This may be related to the differences in the valve designs, in terms both of material modulus and differences among valves both between and within designs in leaflet thickness distributions. There may, as a result, be some complex covariate influences, which, if accounted for, would improve the estimation procedures for these models.

In order to examine the effect of an alternative analysis, the models were reanalysed, using RIGLS as the analytical method and the estimates, σ_{u0}^2, compared with the results from the IGLS method.

Table 7.1 σ_{u0}^2 (s.e.), the level 2 estimate of variance on the intercept parameter of the model: IGLS compared with RIGLS

Hydrodynamic function measure	IGLS	RIGLS
$\log_e${mean pressure gradient}	0.016 (0.004)	0.019 (0.005)
$\log_e${regurgitation}	0.008 (0.002)	0.010 (0.003)
leakage	0.343 (0.522)	0.481 (0.558)
$\log_e${energy loss in forward flow}	0.016 (0.004)	0.019 (0.005)
closing energy loss	57.241 (17.814)	64.748 (19.752)
closed energy loss	44.901 (12.277)	54.043 (14.625)
maximum orifice area	0.006 (0.002)	0.007 (0.002)

Differences in estimates of other parameters and their standard errors between the IGLS and RIGLS methods were trivial or non-existent for all the fixed parameters and for the random parameter, σ_{e0}^2. The IGLS method does appear to underestimate the variance of the level 2 units compared with RIGLS, although the actual differences are quite small. However, in determining quality control limits, we would reject fewer valves if the RIGLS method were used to determine the acceptable variance. The variances associated with leakage, closing and closed energy losses are relatively high. It is likely that improvements in manufacturing methods to reduce the variability in, for example, leaflet trimming would improve these parameter estimates. The current results suggest a need to examine these factors more carefully, although the measurement of flow is likely to be a significant component of the variance associated with these measures.

The best way to improve the random parameter estimates would be to test more valves at level 2. This might be a possibility for analysis of a smaller number of designs, although the testing is quite labour-intensive. However, it is a bigger problem for the study of clinical quality valves where the cost of a single valve is likely to be several thousand pounds sterling and, due to commercial and financial constraints, no laboratory is likely to have large numbers of valves available for such testing. In practice, it is unlikely that more than six valves in any one design or size of valve would be available. The variance remains relatively small, however, for this parameter estimate, at least for the best measures of hydrodynamic function. In this respect, this study has advantages over the sociological analysis commonly using multi-level modelling methods, in that the measurement of hydrodynamic function is inherently more accurate than most sociological measures and is not dependent on measures which are, to some extent, subjective in nature and which are, generally, based on scoring methods rather than an objective, continuous quantitative measurement. There is also less natural variability amongst valves than amongst school pupils (for instance)!

Chapter 8: Conclusions and Future Directions

This study has demonstrated that the techniques of multi-level modelling can be used in a new type of application, the analysis of engineering problems, as well as datasets that are of a sociological or epidemiological nature. The particular problem addressed by this thesis cannot be easily analysed by other statistical methods to provide both parameters that describe individual valve designs in terms of their hydrodynamic function and a differentiation of designs with a statistical significance attached to that differentiation. The analysis could be improved in statistical terms by the availability of larger numbers of valves in each design to be examined. However, even if this is not possible, multi-level modelling is capable of useful discriminatory testing for this application. Previously, descriptions of valve hydrodynamic function properties have been made almost entirely by purely subjective means, using observation of very few valves of a design and plotting the hydrodynamic function curves of interest. This has encouraged selection of the "best" valve curves to demonstrate the desired effect. The availability of multi-level modelling will enable objective assessment of valve hydrodynamic function using reasonably straightforward, readily available statistical software.

The software package, MLwiN, was fairly easy to use, although the user interface is rather different from other software in general use and requires some study to use effectively. The manual is directed towards the analysis of sociological data and the transfer of knowledge to other applications requires some care in fully understanding and developing appropriate models. The software is amenable to handling datasets created in commonly used spreadsheets such as MS Excel, although the spreadsheet cannot be opened directly into MLwiN, but must be copied and pasted. The details of the process are not well explained for the novice and some trial and error was required before this was successful. It is critical to the analysis that the spreadsheet is formulated in a suitable way. The structure of the spreadsheet is easily performed in MS Excel, although it is likely to require some alteration from the way the data has been originally entered. In particular, the MLwiN software spreadsheet only handles numeric data, so that descriptive entries copied into the spreadsheet are lost. Data can be recoded *in situ* as categorical, where appropriate, in which case an alpha-coded name can be replaced into the variable. This entails good record keeping so that different groups are accurately identified throughout. The graphing capability of MLwiN requires some experimentation for the novice to achieve the desired display. The software has been written by statisticians for a specific purpose. It would benefit from an iterative feedback process from a variety of users in different situations. By this process, the help facility and manuals could be extended to improve the explanations of details. Efforts in this direction would encourage wider use of the package and enable the development of its applications in the broader scientific community.

There is ample scope for extending the work begun in this study. In particular for valves fabricated from synthetic elastomers, there are covariate effects that would be of interest to investigate. The most obvious of these are the leaflet material modulus and the leaflet thickness distribution. Measurement of the material modulus is straightforward, but would require a set of valves of similar design and similar leaflet thickness distribution. This is more difficult to achieve under laboratory conditions as leaflet thickness variability is difficult to tightly control and sufficient numbers of valves would be required for precise parameter estimation. The investigation of leaflet thickness effects is likely to be easier to begin with. In this case, it would be best to fix the design and leaflet material and fabricate a set of valves of varying leaflet thickness distribution. Since the leaflet thickness is not uniformly distributed over the leaflet, it would be necessary to investigate a series of covariates to determine the most sensitive measure of thickness influence. These might include mean leaflet thickness, median leaflet thickness, maximum and minimum leaflet thicknesses. This investigation would be particularly useful in determining the optimum leaflet thickness distribution to achieve good valve hydrodynamic function, which is, at present, done largely by a process of trial and error. This would enable a scientific assessment of the best valve design parameters, considering the durability performance of valves in fatigue testing alongside hydrodynamic function performance. These investigations might also enable improved modelling of those hydrodynamic function measures that were less successfully applied here.

In Chapter 6 a number of modelling issues arose which should be investigated further. For example, the use of a weighted model might improve the parameter estimation by dealing with the non-constant variance of some measures. It might also be useful to apply a non-linear model to investigation of some measures, for example closed energy losses.

In conclusion, multi-level modelling has been successfully applied in a novel scientific arena, to an engineering problem. The method has enabled discrimination of different valve designs by any of several hydrodynamic function measures and allowed a statistical assessment of their relative performances.

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Appendix

Table 3.1 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, $\log_e$\{mean pressure gradient\} data (n=10 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	-6.33	1.57	99.3	-6.46	1.60	99.8
GE2	-6.31	1.55	99.5	-6.34	1.55	99.8
GE3	-6.38	1.55	99.5	-6.55	1.59	99.8
GE4	-6.77	1.62	98.9	-6.88	1.64	99.6
GE5	-6.15	1.49	98.8	-6.18	1.50	99.0
GE6	-6.06	1.53	99.8	-6.10	1.54	99.8
LE1	-5.93	1.54	99.2	-6.16	1.58	98.6
LE2	-6.31	1.60	99.8	-6.30	1.60	99.8
LE3	-5.82	1.54	99.6	-5.79	1.54	99.7
LE4	-5.48	1.49	99.6	-5.36	1.47	99.8
LE5	-5.71	1.53	99.8	-5.70	1.53	99.8
LE6	-6.30	1.61	98.7	-6.22	1.59	99.8

Table 3.2 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, $\log_e${regurgitant flow} data (n=10 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	1.01	-0.03	17.9	1.01	-0.03	18.5
GE2	0.93	0.01 NS	-0.3	1.04	-0.01	-1.4
GE3	1.31	-0.04	25.7	1.30	-0.04	20.2
GE4	1.33	-0.04	25.8	1.33	-0.04	26.2
GE5	1.34	-0.03	11.6	1.38	-0.04	15.4
GE6	1.01	0.01 NS	-0.5	1.09	-0.01 NS	-1.3
LE1	1.43	-0.08	42.7	1.54	-0.10	54.5
LE2	1.12	-0.03	8.5	1.16	-0.04	17.2
LE3	1.14	-0.02 NS	4.9	1.15	-0.03	5.9
LE4	0.97	0.00 NS	-2.0	1.01	-0.00 NS	-1.1
LE5	0.84	0.02 NS	3.3	0.80	0.02 NS	5.3
LE6	1.23	-0.04	6.6	0.98	0.00 NS	0.0

Table 3.3 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, leakage flow data (n=10 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	3.33	-0.58	51.9	3.26	-0.57	49.9
quadratic	$18.6932-6.64781x+0.593703x^2$; R^2 (adj) 59.7					
GE2	4.26	-0.73	55.3	3.08	-0.51	35.0
quadratic	$25.523988-9.110785x+0.818736x^2$; R^2 (adj) 64.8					
GE3	5.04	-0.83	65.0	5.30	-0.90	58.8
quadratic	$20.920538-7.106817x+0.614089x^2$; R^2 (adj) 69.4					
GE4	4.31	-0.72	60.1	4.39	-0.73	64.6
quadratic	$23.576969-8.327796x+0.744982x^2$; R^2 (adj) 68.8					
GE5	3.12	-0.56	37.1	2.83	-0.50	39.0
quadratic	$25.500577-9.405997x+0.866256x^2$; R^2 (adj) 48.9					
GE6	4.32	-0.71	61.4	4.26	-0.70	54.7
quadratic	$18.747312-6.410852x+0.559173x^2$; R^2 (adj) 66.2					
LE1	4.49	-0.72	49.1	5.24	-0.87	54.9
quadratic	$28.6751-10.275x+0.936183x^2$; R^2 (adj) 62.0					
LE2	4.76	-0.76	58.2	4.59	-0.77	58.2
quadratic	$28.7351-10.2367x+0.939535x^2$; R^2 (adj) 69.8					
LE3	4.90	-0.75	58.2	4.59	-0.70	49.0
quadratic	$32.031492-11.482345x+1.052624x^2$; R^2 (adj) 74.0					
LE4	4.90	-0.82	69.2	4.52	-0.74	76.1
quadratic	$27.836809-9.91461x+0.893558x^2$; R^2 (adj) 80.2					
LE5	4.73	-0.73	57.4	4.77	-0.74	59.6
quadratic	$29.019863-10.359174x+0.945594x^2$; R^2 (adj) 70.5					
LE6	5.26	-0.72	53.8	5.31	-0.72	61.0
quadratic	$27.4648-9.5048x+0.861115x^2$; R^2 (adj) 64.1					

Table 3.4 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, $\log_e$\{energy losses forward flow\} data (n=10 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	-5.27	1.78	99.1	-4.92	1.71	99.5
GE2	-5.16	1.74	99.1	-4.61	1.63	99.4
GE3	-5.37	1.77	99.3	-4.92	1.69	99.3
GE4	-5.64	1.81	98.9	-5.21	1.73	99.3
GE5	-5.13	1.71	98.8	-4.70	1.63	99.1
GE6	-5.05	1.75	99.4	-4.77	1.70	99.4
LE1	-4.48	1.66	84.5	-4.17	1.62	98.4
LE2	-5.33	1.82	99.3	-5.05	1.77	99.4
LE3	-4.80	1.76	99.1	-4.35	1.68	99.3
LE4	-4.52	1.72	99.1	-4.06	1.64	99.3
LE5	-4.73	1.76	99.4	-4.24	1.67	98.9
LE6	-5.20	1.81	98.5	-4.59	1.69	99.3

Table 3.5 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, energy losses closing data (n=10 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	-2.07 NS	6.33	70.5	11.2	3.87	61.6
quadratic	$-223.904+93.9151x-8.56982x^2$; R^2 (adj) 89.1					
GE2	-11.90	9.64	67.8	-8.62	8.25	79.0
quadratic	$-313.332705+127.853933x-11.608011x^2$; R^2 (adj) 83.9					
GE3	-7.35 NS	8.62	70.8	-13.19	9.60	81.8
quadratic	$-305.824158+126.495818x-11.538386x^2$; R^2 (adj) 89.0					
GE4	-9.40	9.30	68.9	-18.46	10.96	79.7
quadratic	$-365.26305+149.846047x-13.758568x^2$; R^2 (adj) 90.4					
GE5	-14.00	10.37	75.2	-20.32	11.61	79.2
quadratic	$-285.938497+117.842508x-10.526216x^2$; R^2 (adj) 85.8					
GE6	-17.40	9.92	73.0	-21.80	10.74	79.4
quadratic	$-230.894384+94.355538x-8.276157x^2$; R^2 (adj) 79.9					

LE1	-15.8 NS	9.65	4.3 NS	-6.9 NS	7.58	9.7
quadratic	$-345.022+139.768x-12.7458x^2$; R^2 (adj) 7.8, regression NS					
LE2	-7.33 NS	8.02	68.8	-10.71	8.59	76.8
quadratic	$-254.9003931+105.930411x-9.59867x^2$; R^2 (adj) 82.1					
LE3	-11.26	9.24	72.7	-15.39	10.00	78.1
quadratic	$-219.061612+91.491183x-8.070346x^2$; R^2 (adj) 80.3					
LE4	-12.05	9.08	84.3	-14.07	9.41	89.0
quadratic	$-191.071734+80.052831x-6.975368x^2$; R^2 (adj) 91.1					
LE5	-9.01	7.87	62.1	-9.00	7.86	65.8
quadratic	$-184.688978+77.499209x-6.839986x^2$; R^2 (adj) 68.1					
LE6	-4.26 NS	7.30	76.1	-4.73 NS	7.33	82.3
quadratic	$-165.373+71.0241x-6.24757x^2$; R^2 (adj) 83.8					

Table 3.6 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, energy losses closed data (n=10 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	45.9	-7.24	47.7	45.7	-7.23	47.1
quadratic	$267.402-94.6975x+8.5571x^2$; R^2 (adj) 57.2					
GE2	57.91	-9.02	51.1	55.60	-8.53	51.8
quadratic	$335.070211-118.271309x+10.673281x^2$; R^2 (adj) 60.8					
GE3	68.91	-10.53	61.3	71.89	-11.29	54.9
quadratic	$270.585992-90.174386x+7.796065x^2$; R^2 (adj) 65.4					
GE4	57.91	-8.68	60.2	57.24	-8.50	65.2
quadratic	$286.251103-98.864532x+8.828327x^2$; R^2 (adj) 68.6					
GE5	42.76	-6.56	32.7	38.21	-5.61	33.0
quadratic	$342.621961-125.061109x+11.606986x^2$; R^2 (adj) 46.5					
GE6	54.31	-7.89	53.6	55.61	-8.20	51.2
quadratic	$249.133237-84.937883x+7.552427x^2$; R^2 (adj) 59.8					
LE1	59.50	-8.94	29.3	52.20	-7.62	23.1
quadratic	$329.81-115.745x+10.4625x^2$; R^2 (adj) 36.5					
LE2	74.71	-11.45	64.5	72.95	-11.17	61.7
quadratic	$369.4999-128.031066x+11.429529x^2$; R^2 (adj) 72.9					
LE3	76.55	-11.39	65.8	79.39	-12.22	59.0
quadratic	$381.973207-132.288672x+11.86184x^2$; R^2 (adj) 75.5					
LE4	68.19	-10.65	68.4	62.64	-9.37	77.8
quadratic	$373.324707-131.62459x+11.889179x^2$; R^2 (adj) 79.9					
LE5	70.33	-10.43	63.7	71.93	-10.72	66.2
quadratic	$347.06795-120.106047x+10.774503x^2$; R^2 (adj) 72.9					
LE6	86.20	-12.1	67.1	89.10	-12.60	73.3
quadratic	$325.271-106.643x+9.2699x^2$; R^2 (adj) 72.2					

Table 3.7 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, mean effective orifice area data (n=10 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	-0.06 NS	0.28	85.5	-0.07 NS	0.28	84.8
GE2	-0.28	0.34	94.9	-0.24	0.33	94.9
GE3	-0.34	0.36	94.3	-0.22	0.33	94.7
GE4	-0.04 NS	0.30	87.3	0.02 NS	0.292	84.8
GE5	-0.17	0.33	82.2	-0.17	0.33	82.0
GE6	-0.18	0.30	96.8	-0.18	0.30	97.1
LE1	-0.37	0.31	94.2	-0.27	0.29	92.9
LE2	-0.14	0.28	92.2	-0.17	0.29	94.6
LE3	-0.40	0.31	94.8	-0.50	0.33	94.9
LE4	-0.42	0.30	92.4	-0.38	0.29	92.1
LE5	-0.34	0.29	95.5	-0.35	0.29	96.1
LE6	-0.26	0.30	92.9	-0.32	0.31	94.6

Table 3.8 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, $\log_e$\{mean pressure gradient\} data (n=5 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	-6.378	1.584	99.6	-6.503	1.608	99.8
GE2	-6.147	1.516	99.4	-6.344	1.552	99.9
GE3	-6.147	1.516	99.4	-6.344	1.552	99.9
GE4	-6.988	1.657	99.7	-6.950	1.650	99.5
GE5	-6.222	1.506	98.6	-6.482	1.553	99.5
GE6	-6.057	1.532	99.8	-6.108	1.541	99.8
LE1	-5.771	1.511	98.8	-6.107	1.573	97.3
LE2	-6.306	1.599	99.7	-6.24	1.587	99.6
LE3	-5.993	1.575	99.7	-5.891	1.557	99.8
LE4	-5.512	1.499	99.6	-5.369	1.474	99.7
LE5	-5.624	1.517	99.8	-5.660	1.523	99.7
LE6	-5.885	1.528	98.8	-6.144	1.575	99.9

Table 3.9 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, $\log_e$\{regurgitant flow\} data (n=5 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	1.071	-0.044	26.1	1.088	-0.047	27.3
GE2	0.946	0.009 NS	-3.2	1.008	-0.002 NS	-4.3
GE3	1.341	-0.050	39.3	1.334	-0.050	53.2
GE4	1.383	-0.053	33.8	1.370	-0.050	32.2
GE5	1.417	-0.048	24.5	1.357	-0.038	16.3
GE6	0.985	0.014 NS	-2.2	1.080	-0.006 NS	-3.9
LE1	1.440	-0.085	44.6	1.513	-0.099	52.0
LE2	1.189	-0.044	16.6	1.209	-0.049	17.4
LE3	1.132	-0.022 NS	2.2	1.062	-0.009	-3.5
LE4	0.988	-0.002 NS	-4.2	1.080	-0.021	7.1
LE5	0.978	-0.008 NS	-3.2	1.024	-0.090 NS	1.6
LE6	1.250	-0.041 NS	1.9	0.796	0.042	18.9

Table 3.10 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, leakage flow data (n=5 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	3.844	-0.666	54.9	3.793	-0.656	52.8
Quadratic weighted	$17.466-6.045x+0.527x^2$; R^2 (adj) 58.3 $16.9-5.81x+0.503x^2$; R^2 (adj) 55.5					
GE2	4.203	-0.719	48.9	3.811	-0.638	51.8
Quadratic weighted	$25.888-9.266x+0.835x^2$; R^2 (adj) 57.4 $23.3-8.23x+0.732x^2$; R^2 (adj) 57.9					
GE3	5.464	-0.924	69.9	5.297	-0.909	58.3
Quadratic weighted	$17.108-5.519x+0.450x^2$; R^2 (adj) 71.1 $24.9-8.67x+0.764x^2$; R^2 (adj) 66.3					
GE4	4.275	-0.731	61.5	4.089	-0.677	76.0
Quadratic weighted	$26.436-9.474x+0.855x^2$; R^2 (adj) 72.7 $25.2-8.95x+0.803x^2$; R^2 (adj) 83.7					
GE5	2.976	-0.555	32.8	1.383 NS	-0.272 NS	5.9
Quadratic weighted	$36.853-13.924x+1.308x^2$; R^2 (adj) 60.0 $39.7-15.1x+1.43x^2$; R^2 (adj) 56.9					
GE6	4.704	-0.764	58.9	4.713	-0.768	55.2
Quadratic weighted	$23.566-8.226x+0.731x^2$; R^2 (adj) 65.5 $24.5-8.59x+0.767x^2$; R^2 (adj) 62.1					

LE1	4.312	-0.692	39.4	4.158	-0.671	34.0
Quadratic weighted	$27.487-9.852x+0.897x^2$; R^2 (adj) 47.4 $28.3-10.2x+0.926x^2$; R^2 (adj) 43.8, but plots look a bit better					
LE2	4.603	-0.717	45.8	3.709	-0.590	19.7
Quadratic weighted	$32.109-1.592x+1.066x^2$; R^2 (adj) 59.1 $45.6-17.0x+1.60x^2$; R^2 (adj) 59.5					
LE3	4.723	-0.693	57.3	3.564	-0.493	36.7
Quadratic weighted	$33.523-12.093x+1.118x^2$; R^2 (adj) 78.9 $35.9-13.0x+1.21x^2$; R^2 (adj) 73.2					
LE4	5.518	-0.929	79.5	5.316	-0.878	85.5
Quadratic weighted	$27.297-9.570x+0.850x^2$; R^2 (adj) 88.9 $26.9-9.39x+0.831x^2$; R^2 (adj) 92.6					
LE5	5.121	-0.820	59.5	5.127	-0.815	62.5
Quadratic weighted	$30.483-10.880x+0.989x^2$; R^2 (adj) 71.2 $26.7-9.40x+0.847x^2$; R^2 (adj) 70.7					
LE6	4.690	-0.605	45.1	5.056	-0.660	67.3
Quadratic weighted	$28.711-10.123x+0.935x^2$; R^2 (adj) 60.1 $24.5-8.41x+0.760x^2$; R^2 (adj) 74.6					

Table 3.11 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, loge{energy losses forward flow} data (n=5 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	-5.341	1.794	99.3	-4.945	1.723	99.4
weighted	$-12.313+4.548x-0.270x^2$; R^2 (adj) 99.6 $-11.9+4.39x-0.256x^2$; R^2 (adj) 99.6, plots a bit better esp. normal prob.					
GE2	-5.017	1.707	99.3	-4.637	1.635	99.7
weighted	$-11.254+4.136x-0.240x^2$; R^2 (adj) 99.5 $-13.4+4.95x-0.313x^2$; R^2 (adj) 99.9					
GE3	-5.344	1.764	99.2	-5.124	1.724	99.5
weighted	$-10.826+3.928x-0.212x^2$; R^2 (adj) 99.4 $-12.6+4.60x-0.276x^2$; R^2 (adj) 99.6					
GE4	-5.829	1.842	99.0	-5.502	1.781	99.2
weighted	$-14.439+5.239x-0.332x^2$; R^2 (adj) 99.5 $-13.3+4.80x-0.290x^2$; R^2 (adj) 99.5					
GE5	-5.139	1.705	98.7	-4.697	1.623	99.3
weighted	$-12.363+4.556x-0.279x^2$; R^2 (adj) 99.1 $-9.79+3.55x-0.182x^2$; R^2 (adj) 99.5					
GE6	-5.021	1.744	99.4	-4.591	1.663	99.3
weighted	$-13.066+4.925x-0.312x^2$; R^2 (adj) 99.8 $-9.85+3.67x-0.191x^2$; R^2 (adj) 99.6					

LE1	-4.682	1.713	98.9	-5.872	1.961	97.3
weighted	$-10.933+4.183x-0.242x^2$; R^2 (adj) 99.1 $-14.4+5.38x-0.344x^2$; R^2 (adj) 97.8					
LE2	-5.281	1.814	99.2	-5.005	1.761	99.3
weighted	$-13.523+5.073-0.319x^2$; R^2 (adj) 99.6 $-12.2+4.57x-0.271x^2$; R^2 (adj) 99.6					
LE3	-4.938	1.785	99.0	-4.318	1.671	99.1
weighted	$-15.777+6.075x-0.421x^2$; R^2 (adj) 99.8 $-14.1+5.43x-0.360x^2$; R^2 (adj) 99.7					
LE4	-4.560	1.729	99.0	-4.220	1.667	99.2
weighted	$-14.060+5.498x-0.371x^2$; R^2 (adj) 99.6 $-15.0+5.86x-0.407x^2$; R^2 (adj) 99.7					
LE5	-4.664	1.746	99.4	-4.278	1.679	98.9
weighted	$-12.080+4.687x-0.289x^2$; R^2 (adj) 99.8 $-13.9+5.41x-0.359x^2$; R^2 (adj) 99.7					
LE6	-4.879	1.747	98.9	-4.337	1.648	99.3
weighted	$-10.469+3.962x-0.218x^2$; R^2 (adj) 99.1 $-11.9+4.54x-0.276x^2$; R^2 (adj) 99.6					

Table 3.12 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, energy losses closing data (n=5 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	-0.343 NS	6.021	63.6	-4.556 NS	6.849	73.3
Quadratic weighted	$-257.775+107.688x-9.951x^2$; R^2 (adj) 89.4 $-258+108x-10.0x^2$; R^2 (adj) 91.6					
GE2	-12.364	9.137	73.2	-1.959 NS	7.079	75.6
Quadratic weighted	$-280.983+114.897x-10.332x^2$; R^2 (adj) 86.8 $-188+78.8x-6.83x^2$; R^2 (adj) 83.2					
GE3	-5.491 NS	8.245	63.7	-9.707 NS	8.840	78.9
Quadratic weighted	$-336.114+138.767x-12.771x^2$; R^2 (adj) 86.1 $-336+138x-12.7x^2$; R^2 (adj) 93.2					
GE4	-6.583 NS	8.699	66.6	-10.019 NS	9.533	63.1
Quadratic weighted	$-362.601+149.166x-13.737x^2$; R^2 (adj) 90.7 $-399+164x-15.2x^2$; R^2 (adj) 91.0					
GE5	-12.007 NS	10.114	72.4	-9.594 NS	9.573	76.2
Quadratic weighted	$-311.198+128.190x-11.548x^2$; R^2 (adj) 85.9 $-306+126x-11.3x^2$; R^2 (adj) 88.2					
GE6	-19.140	10.468	78.0	-32.928	13.392	86.9
Quadratic weighted	$-208.839+85.507x-7.356x^2$; R^2 (adj) 83.0 $-310+127x-11.6x^2$; R^2 (adj) 95.1					

LE1	1.982	6.330	59.4	-0.663	6.737	78.5
Quadratic	$-219.279+93.785x-8.568x^2$; R^2 (adj) 74.7					
weighted	$-212+90.5x-8.19x^2$; R^2 (adj) 88.4					
LE2	-4.190	7.408	63.6	-5.780	7.653	69.3
Quadratic	$-245.028+102.629x-9.332x^2$; R^2 (adj) 77.2					
weighted	$-246+103x-9.35x^2$; R^2 (adj) 81.3					
LE3	-13.674	9.762	77.3	-16.403	10.298	81.7
Quadratic	$-207.895+86.637x-7.543x^2$; R^2 (adj) 83.4					
weighted	$-238+99.5x-8.90x^2$; R^2 (adj) 87.8					
LE4	-11.757	9.129	83.9	-14.155	9.542	88.3
Quadratic	$-203.528+85.217x-7.483x^2$; R^2 (adj) 91.7					
weighted	$-201+84.2x-7.36x^2$; R^2 (adj) 94.5					
LE5	-7.811	7.923	78.1	-7.396	7.806	82.1
Quadratic	$-150.484+64.510x-5.563x^2$; R^2 (adj) 83.0					
weighted	$-151+64.5x-5.55x^2$; R^2 (adj) 86.8					
LE6	-6.591	7.716	79.0	-4.450	7.318	78.8
Quadratic	$-122.323+53.575x-4.504x^2$; R^2 (adj) 82.2					
weghted	$-135+58.7x-4.99x^2$; R^2 (adj) 83.5					

Table 3.13 Estimates, b_0 and b_1, for valves GE and LE fabricated from Estane, energy losses closed data (n=5 iterations)

	unweighted regression			weighted regression		
valve	b_0	b_1	R^2(adj)	b_0	b_1	R^2(adj)
GE1	52.081	-8.233	51.5	51.531	-8.105	51.2
Quadratic weighted	$256.742-89.059x+7.911x^2$; R^2 (adj) 56.9 $249-85.7x+7.56x^2$; R^2 (adj) 55.8					
GE2	57.228	-8.936	44.1	52.939	-8.009	47.4
Quadratic weighted	$344.238-122.063x+11.051x^2$; R^2 (adj) 52.7 $323-114x+10.2x^2$; R^2 (adj) 54.3					
GE3	74.466	-11.698	67.2	71.351	-11.279	55.7
Quadratic weighted	$215.259-67.279x+5.438x^2$; R^2 (adj) 68.0 $303-102x+8.94x^2$; R^2 (adj) 61.4					
GE4	57.139	-8.747	61.0	56.201	-8.340	77.5
Quadratic weighted	$322.043-113.265x+10.222x^2$; R^2 (adj) 72.1 $317-111x+10.0x^2$; R^2 (adj) 84.9					
GE5	42.721	-6.884	32.8	20.236	-2.934	3.2
Quadratic weighted	$471.576-176.131x+16.553x^2$; R^2 (adj) 61.3 $531-200x+19.0x^2$; R^2 (adj) 63.5					
GE6	56.791	-8.261	46.0	57.377	-8.402	44.0
Quadratic weighted	$323.533-113.777x+10.344x^2$; R^2 (adj) 55.2 $335-119x+10.9x^2$; R^2 (adj) 53.8					

LE1	66.241	-10.116	46.0	65.443	-10.068	40.9
Quadratic weighted	$349.575-122.106+10.972x^2$; R^2 (adj) 52.2 $376-132x+12.0x^2$; R^2 (adj) 49.4					
LE2	74.669	-11.325	54.7	61.039	-9.339	26.5
Quadratic weighted	$411.054-144.323x+13.035x^2$; R^2 (adj) 63.7 $612-225x+20.9x^2$; R^2 (adj) 61.4					
LE3	79.200	-11.693	66.8	87.582	-13.834	59.4
Quadratic weighted	$376.377-129.318x+11.541x^2$; R^2 (adj) 75.4 $557-202x+18.8x^2$; R^2 (adj) 82.0					
LE4	75.189	-11.864	78.9	70.708	-10.851	83.3
Quadratic weighted	$357.692-123.952x+11.023x^2$; R^2 (adj) 88.3 $355-123x+10.9x^2$; R^2 (adj) 91.4					
LE5	73.801	-11.325	67.7	74.453	-11.427	68.5
Quadratic weighted	$357.297-123.766x+11.054x^2$; R^2 (adj) 76.2 $351-122x+10.9x^2$; R^2 (adj) 76.5					
LE6	77.127	-10.187	62.1	82.445	-11.007	81.4
Quadratic weighted	$359.713-122.162x+10.997x^2$; R^2 (adj) 71.8 $297-96.7x+8.44x^2$; R^2 (adj) 84.9					