

# Effects of Valve Characteristics on the Accuracy of the Bernoulli Equation: A Survey of Data Submitted to the U.S. FDA

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**Background and aim of the study:** In 1988, valve manufacturers petitioned the U. S. Food & Drug Administration (FDA) to replace catheter with Doppler ultrasound measurements of pressure gradient ( $\Delta P$ ) in clinical studies. Manufacturers agreed to submit bench data validating the Bernoulli equation used to calculate  $\Delta P$ :  $\Delta P = K(V_d^2 - V_p^2)$ , where  $K$  = constant,  $V_d$  = distal Doppler velocity, and  $V_p$  = proximal Doppler velocity. Previous studies suggest that  $K$  may vary from the idealized 4.0, which could lead to incorrect valve assessment and clinical errors.

**Methods:** Variation in  $K$ -values in marketing application data submitted to the FDA was assessed. Pulse duplicator data included four bileaflet valves, two stented bioprostheses, and seven stentless bioprostheses, sized from 19 to 33 mm. Effects of valve type, valve size, blood-mimicking fluid used, and distal pressure tap position (DPTP) were evaluated via an analysis of variance.

**Results:**  $K$ -values varied from 2.50 to 7.40 ( $n = 90$ ).  $K$  was found to be dependent on valve type ( $p < 0.0001$ ),

blood-mimicking fluid ( $p < 0.0001$ ) and DPTP ( $p < 0.0001$ ), but not valve size. At DPTP = 30 mm,  $K = 3.43 \pm 0.56$ ,  $5.15 \pm 0.81$ , and  $4.81 \pm 1.02$ , for bileaflet, stented and stentless valves, respectively.  $K$  averaged 10% less using the 100-mm DPTP, due to pressure recovery. Variations due to blood-mimicking fluid were likely related to the fluid density.

**Conclusion:** Variations due to DPTP and fluid used are consistent with physical mechanisms of pressure recovery and fluid density. Results from previous studies have suggested that effects of valve type on  $K$  are also real. The magnitude of these effects appeared to be  $\pm 25\%$ . Extrapolation to patients is difficult, but clinicians should be aware that Doppler measurements may vary by similar amounts. Doppler pressure gradients should be interpreted qualitatively and moderated by other diagnostic measures of valve performance.

The Journal of Heart Valve Disease 2004;13:461-466

Doppler echocardiography has become the primary method for determining the transvalvular pressure gradient ( $\Delta P$ ), an important index of valve performance for both native and prosthetic heart valves. This technique uses the Bernoulli equation for incompressible fluid flow as the basis for calculating  $\Delta P$ . The Bernoulli equation is essentially one of conservation of kinetic and potential energy, and is given for steady or quasi-steady flow by (1,2):

$$P_p + \frac{1}{2} \rho V_p^2 = P_d + \frac{1}{2} \rho V_d^2 + R_{pd}, \quad (1)$$

Presented as poster at the Second Biennial Meeting of the Society for Heart Valve Disease, 28th June-1st July 2003, Palais des Congrès, Paris, France

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where  $P_p$  and  $P_d$  are the upstream (proximal) and downstream (distal) pressures along a streamline, respectively,  $V_p$  and  $V_d$  are the corresponding velocities,  $\rho$  is the fluid density, and  $R_{pd}$  is an energy loss factor between the two measurement locations. Equation (1) neglects acceleration effects, which are assumed to be negligible (1).  $R_{pd}$  can be caused by resistive effects at the interface of the valve or vascular structures, including viscous, turbulence, and flow separation effects. If  $R_{pd}$  is assumed to be negligible, then Eqn. (1) can be (and usually is) rewritten as:

$$P_p - P_d = \Delta P = K(V_d^2 - V_p^2). \quad (2)$$

With the pressure expressed in mmHg, velocity expressed in m/s, and the density of blood assumed to be  $1.06 \text{ g/cm}^3$ , then  $K$  is approximately 4.0. Equation (2) is used to transform Doppler ultrasound-derived velocity data into  $\Delta P$ . In fact, often the proximal veloc-

ity  $V_p$  is itself assumed to be negligible, and the following simplified equation is obtained (1):

$$\Delta P = 4V_d^2 \quad (3)$$

Clinicians typically use the software that comes with commercial diagnostic ultrasound systems to calculate  $\Delta P$ , in which the factor  $K$  is usually fixed equal to 4.0, and cannot be changed.

As part of pre-marketing submissions, the U. S. FDA has long required that prosthetic heart valve manufacturers perform clinical studies, which include the monitoring of post-implantation valve performance. Prior to 1988, only direct, invasive pressure measurements via cardiac catheterization techniques were allowed (3). In 1988, valve manufacturers petitioned the FDA to allow the use of Doppler ultrasound to determine  $\Delta P$  values instead. The claim was made that Doppler ultrasound was accurate and reproducible enough for reasonable valve assessment. A further impetus for allowing the use of ultrasound techniques was that few patients were willing to submit to post-implantation catheterization, thus hampering the gathering of adequate data. Studies have shown that Eqn. (2) can provide a reasonable correlation between Doppler and catheter measurements in a variety of prosthetic valves (4-6) in vivo. The FDA concluded that ultrasound techniques were sufficient to allow the use of non-invasive Doppler ultrasound in the clinic, despite evidence of problems with both the technique and the resulting data.

Two classes of errors in Doppler-catheter correlations have been reported: substantial scatter in the data, and systematic errors which affect the value of  $K$ . Scatter has been found both in vivo (6,7) and in vitro (8,9). For example, in a clinical Doppler-catheter study of prosthetic valves (6), patients with a peak catheter gradient of 22 mmHg had peak Doppler gradients which ranged from 8 to 25 mmHg, while patients with a mean catheter gradient of 13 mmHg had mean Doppler gradients ranging from 4 to 13 mmHg. In an in-vitro study, catheter and Doppler-derived  $\Delta P$  values were shown to differ by as much as 44 mmHg for one bileaflet valve (9). Scatter in the Doppler data may result from experimental error: localized, high-velocity peaks may occasionally be missed by Doppler, or observed at an angle which would tend to reduce the recorded velocity. Differences in patients' anatomy and temporal variations in cardiac output may also contribute to the scatter. A non-negligible  $R_{pd}$ , unaccounted for in Eqn. (2), may also play a role.

More troubling are systematic errors (7-12), which may be present even if the scatter is low. Overestimation of the Doppler-derived  $\Delta P$  is common, with the slope between the catheter and Doppler-derived  $\Delta P$  ranging as high as 1.76 (9), thus giving a  $K$ -value as

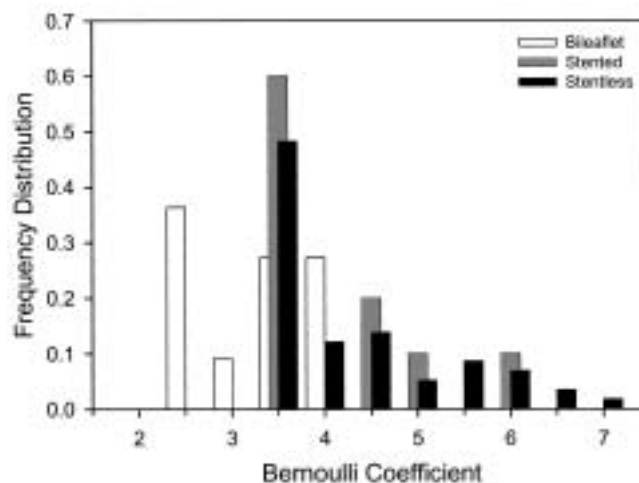


Figure 1: Frequency distribution of Bernoulli constants from data submitted to the U. S. FDA.

low as 2.27. Underestimation by Doppler in vitro has also been reported (13), with  $K$  ranging from 4.5 for a 1 cm-long stenosis to as much as 7 for a 4 cm-long stenosis. Some systematic errors may be caused by localized, high-velocity peaks near the valve, which are easily detected by continuous-wave Doppler but may be missed by the catheter (8,12), especially if care is being taken to avoid touching the leaflets with the catheter tip.

A related mechanism of the discrepancy between the catheter and Doppler  $\Delta P$  is pressure recovery, whereby the blood's kinetic energy is converted back to potential (pressure) energy distal to the valve as the mean velocity decreases (8,11). The overall degree of pressure recovery depends on the loss mechanisms,  $R_{pd}$ , distal to the location of maximum velocity. Pressure recovery has also been shown to be a function of valve type, size, and flow rate (10). For one bileaflet mechanical prosthetic valve, pressure recovery extends only to 2 cm downstream of the valve plane, while for a tilting disc valve it continues to 6 cm downstream (10). Values of  $K$  between 2 and 2.5 for a bileaflet valve, and near 4 for both a ball and cage valve and a tilting disc valve have been reported (9).

A mathematical model of aortic stenosis (14) was used to argue that loss mechanisms (including those proximal to the valve), together with pressure recovery, fortuitously give an effective constant  $K$  close to 4.0 in Eqn. (2) (15). Thus, using  $K = 4.0$  might not be appropriate in all cases, depending on the prosthetic heart valve design and size, the blood flow rate, and other characteristics affecting loss mechanisms and pressure recovery. The scatter and systematic errors observed can be explained by the inability of the Bernoulli equation to adequately characterize complex

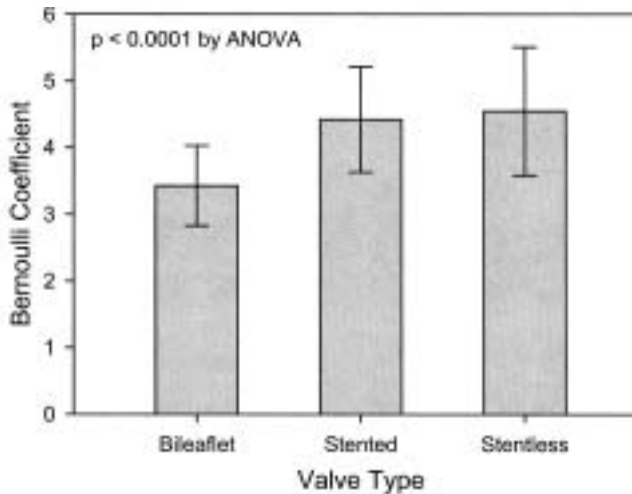


Figure 2: Effect of valve type on the Bernoulli coefficient.

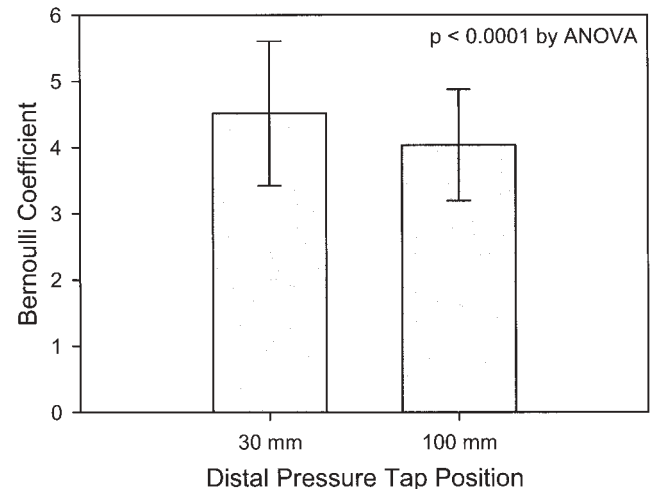


Figure 3: Effect of distal pressure tap position on the Bernoulli coefficient.

flow phenomena in heart valves.

In light of the above, in 1993, the FDA changed its guidance document for heart valve manufacturers (16) to ask that valve manufacturers submit bench data validating the Bernoulli equation prior to valve approval. Valve manufacturers have been reluctant to publish this information, however, possibly because of the perception that deviations in  $K$  from 4.0 means that something is 'wrong' with the valve. This perception is untrue; if anything, it is the underlying theory that may not be adequate in all cases.

The goal of this study was to present this important information, gathered over the past decade, to the heart valve community. Herein, the information is presented in the aggregate using statistical analysis, to remove references to specific manufacturers. The intent is to stimulate discussion of the possibility of errors when using Doppler-derived  $\Delta P$ s. It is hoped that this information will contribute to better assessment of prosthetic heart valve characteristics and improved diagnosis and treatment of heart valve disease.

## Materials and methods

### Manufacturers' tests

The analysis was performed on Bernoulli data submitted to the FDA over the past decade, from 13 different valve pre-marketing applications. The data included four mechanical bileaflet valves, two stented bioprostheses, and seven stentless bioprostheses, covering a range of valve sizes from 19 to 33 mm. Data were generated from in-vitro pulse duplicator tests, with the valves in the aortic position. The mean  $\Delta P$ s across the valves were measured directly by pressure

transducers, fixed approximately 30 mm proximal to the valve (in the mock ventricle), and 30 and 100 mm distal to the valve (in the mock aorta). No catheter 'pullback' was performed, in order to make the tests easier for the manufacturers; however, the 30 and 100 mm distal measurements provided some accommodation for pressure recovery. In the case of the stentless valves, compliant aortas were generally used, while rigid aortas were used in the other two valve types. The blood-mimicking fluid used in the pulse duplicator was either saline or aqueous glycerin solution, but the type of fluid used was not consistently associated with any of the three particular valve types.

Pulsed Doppler ultrasound was used to measure  $V_p$ , and continuous-wave Doppler to measure  $V_d$ . Data were generated at four levels of cardiac output between 2 and 7 l/min. The coefficient  $K$  was then determined by linear regression between  $\Delta P$  measured by transducer and  $(V_d^2 - V_p^2)$ .

### Statistical analysis

Simple statistics and an analysis of variance (ANOVA) using a general linear model were performed in Minitab release 12.22 running on a personal computer.  $K$  was used as the dependent variable. The valve type (bileaflet, stented, stentless), valve size (19, 21, 23, 25, 27, 29, 33 mm), distal pressure tap position (30 or 100 mm), and type of blood-mimicking fluid (saline or aqueous glycerin) were used as independent (fixed) variables. The aortic compliance and mean aortic pressure (in the stentless valves) were ignored in the ANOVA, because they were not relevant for the bileaflet and stented valves. Variations in the design of the pulse duplicator used were also ignored. A total of 90 complete data sets was analyzed.

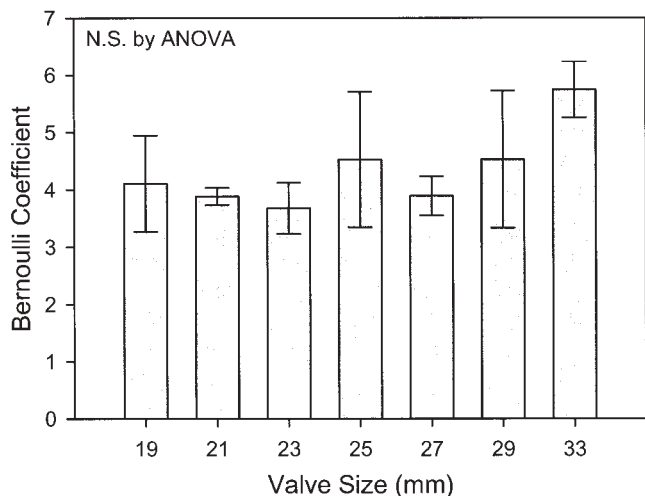


Figure 4: Effect of valve size on the Bernoulli coefficient.

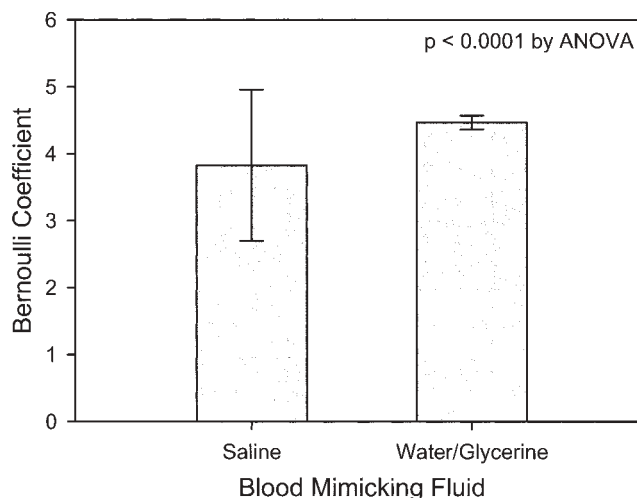


Figure 5: Effect of blood-mimicking fluid on the Bernoulli coefficient.

## Results

### Simple statistics

Values of the Bernoulli constant  $K$  from the surveyed applications covered a wide range, from approximately 2.5 to 7.5 (Fig. 1). The bileaflet valves tended toward the low end of the range, while the stented and stentless valves tended toward the middle to high end. The mean values of  $K$  by valve type (averaged over all valve sizes and fluid used) are shown in Table I. It should be noted that the 95% confidence intervals for  $K$  excluded 4.0 at the 30 mm distal pressure tap position for all the valve types, and excluded 4.0 at the 100 mm distal pressure tap position for the bileaflet valves.

### Analysis of variance

In a preliminary analysis, an ANOVA was performed with only three categories: valve type, valve size, and

distal pressure tap position. In this case, the dependence of  $K$  on all three categories was found to be statistically significant: valve type ( $p < 0.0001$ ), distal pressure tap position ( $p = 0.016$ ), and valve size ( $p = 0.024$ ). The ANOVA was subsequently rerun, with four categories, the three described above plus the blood-mimicking fluid used. In this case, the dependence of  $K$  on three of the four categories was statistically significant by ANOVA: valve type ( $p < 0.0001$ ), distal pressure tap position ( $p < 0.0001$ ), and blood-mimicking fluid used ( $p < 0.0001$ ). However, the effect of valve size on  $K$  was found to be not significant. The effects of valve type and distal pressure tap position on  $K$  are shown in Figures 2 and 3, respectively. The effects of valve size and blood-mimicking fluid used are shown in Figures 4 and 5, respectively.

Table I: Variation in  $K$ -value by valve type.

Valve type	Distal pressure tap position (mm)	K-value <sup>a</sup>	Lower CI	Upper CI
Bileaflet	30	3.43 ± 0.56	3.07	3.80
	100	3.25 ± 0.72	2.78	3.72
Stented	30	5.15 ± 0.81	4.23	6.08
	100	4.41 ± 0.86	3.44	5.38
Stentless	30	4.81 ± 1.02	4.42	5.19
	100	4.29 ± 0.70	4.00	4.57

<sup>a</sup>Values are mean ± SD, averaged over valve size and blood-mimicking fluid used.

CI: Confidence interval.

## Discussion

Variations in the Bernoulli constant among different prosthetic heart valve types have been well documented in the literature. Overestimation of  $\Delta P$  by Doppler in bileaflet valves is thought to be due in many cases to small but high-velocity jets between the leaflets, which leads to K values less than 4.0. The results of the present study were consistent with earlier findings, showing a generally smaller K for bileaflet valves than for stented and stentless valves (9). Therefore, the statistical significance is likely due to a real dependence of K on valve type.

The difference between pressure gradients found at the 30 and 100 mm distal pressure tap positions is probably due to the well-known process of pressure recovery downstream of an orifice (8). Fluid moving through an orifice speeds up, converting pressure (potential) energy to kinetic energy. Then, downstream of the orifice, the fluid slows down and some of the kinetic energy is converted back to pressure energy. The measured pressure gradient is therefore higher at the high-velocity jet than it is downstream. Because continuous-wave Doppler automatically detects the highest velocity jet, the ratio of the Doppler to catheter pressure gradients is expected to be greater there than it is downstream. Thus, as expected, K at the 30-mm distal pressure tap position was found to be generally greater than at the 100-mm position.

The dependence of K on the blood-mimicking fluid used can be explained by the higher density of aqueous glycerin solution, which appears as  $\rho$  in Eqn. (1). Aqueous glycerin solutions generally contain about 40% glycerin; hence, as pure glycerin has a density of 1.26, a 40% aqueous glycerin solution would be expected to have a density of approximately 1.12. Thus, K in 40% aqueous glycerin solutions would be expected to be about 12% higher than that in saline solution alone. In the present study, K was seen to be about 17% higher for the aqueous glycerin solution than for the saline, which was consistent with theory. Aqueous glycerin also has about three times the viscosity of saline, which may also affect  $R_{pd}$  in Eqn. (1); however, it is unclear whether  $R_{pd}$  would increase or decrease with the addition of glycerin because competing mechanisms exist. As the viscosity increases, the laminar  $R_{pd}$  increases, but the intensity of turbulence also decreases with viscosity so that  $R_{pd}$  associated with turbulence decreases.

Despite earlier studies suggesting that K is dependent on valve size (10,11), the effects of valve size in the present study were significant ( $p = 0.024$ ) only when blood-mimicking fluid was not included, and to a smaller degree than type ( $p < 0.0001$ ) or distal pressure tap position ( $p = 0.016$ ). When blood-mimicking fluid

was included, valve size became non-significant, and the p-values for the other three categories all became  $< 0.0001$ . Thus, it is concluded that K was much less dependent on valve size than on the other three variables in this data set. The data by valve size show considerable scatter (Fig. 4), which may be due to the fact that the valve sizes actually tested were not consistent across the data set.

The possibility of errors in these measurements cannot be discounted. It is conceivable that some or most of the wide range in measured K-values was simply due to measurement errors. Thus, the wide range reported may actually represent less of a problem than it appears. For example, these data suggest that one can be 95% confident that K for bileaflet valves ranges from 3.07 to 3.80 at the 3.0-mm distal pressure tap position (Table I). This is in line with what is known about small jets issuing from the central opening of bileaflet valves. On the other hand, for stentless valves, these data suggest that one can be 95% confident that K is between 4.42 and 5.19. Thus, for all the valves the range of K is most likely not as broad as the raw data might suggest. Values of K between 3.0 and 5.0 suggests pressure gradients that are off by about  $\pm 25\%$ . Of course, larger variations may occur with a low probability, for a specific valve and clinical situation. Given the other sources of errors in echocardiographic measurements, perhaps this is not unduly worrisome.

One of the inherent problems in using K values specific to the valve type in this way is the unknown differences between in-vitro and in-vivo testing. These K values were measured in pulse duplicators, and many of the differences in characteristics between this in-vitro system and the clinical situation are unknown. Thus, using a value of K derived from a pulse duplicator in a patient should be done with caution, unless there has been adequate clinical validation. Conceivably, if the clinical trial were to include multiple simultaneous catheter-Doppler studies, and a K-value different from 4.0 were found, then it might be best to use that valve-specific K. However, it is unlikely that such a prospective study would be undertaken, given the known morbidity of catheter studies that have motivated the use of Doppler in the first place. One approach is an interlaboratory comparison of in-vitro measurements, which may help further our understanding of how and why K varies from 4.0. Such an interlaboratory comparison is currently under way.

One suggestion is that, instead of providing a valve-specific K-value from in-vitro tests, manufacturers should provide information on the qualitative characteristics of echocardiographic examinations learned from the clinical trial (Dr. John Chambers, personal communication). For example, manufacturers of

bileaflet valves may want to include pictures and explanations of the small, high-velocity forward flow jets between the leaflets, and the deliberate hinge-washing regurgitant jets, to help those echocardiographers who are unfamiliar with these features. This type of qualitative information could be readily derived from clinical trials, once the sponsors have become familiar with the specific features of the valve under study. Although this might be a valuable useful addition, it is not a substitution for in-vitro data. In-vitro studies could still be helpful, by providing advance guidance in what to look out for - for example, the high-velocity jets seen in some bileaflet valves - in these same clinical trials.

*It is concluded* from this analysis of data submitted by manufacturers that errors on the order of 25% may be inherent in the  $K = 4.0$  commonly used in Doppler measurements of pressure gradient. Previous experimental and theoretical studies lend support to the conclusion that the observed effects of valve type on the constant  $K$  are real. Although some progress has been made on understanding the effects of pressure recovery and localized jets, further in-vitro studies are needed to understand more fully the effects of valve type on  $K$ , especially in stented and stentless valves. Some questions that remain to be addressed include how much  $K$  actually varies clinically, and what the reoperation/explant rate actually is as a result of inaccurate Doppler data. The message to clinicians is to be aware of the possibility of errors, to treat the numbers as a trend or indicator rather than as an exact measurement (such as temperature), and to use additional data in their clinical decision making.

#### Acknowledgements

Any reference to commercial products, their source, or their use in connection with material reported herein, is not to be construed as either an actual or implied endorsement of such products by the U.S. Department of Health and Human Services.

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