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Prosthesis size and prosthesis-patient size are unrelated to prosthesis-patient mismatch

To the Editor:

We read with interest the report of Blackstone and colleagues¹ published in the September 2003 issue of the Journal, as well as the editorial of Gillinov and coworkers² in the August 2003 issue. The implicit conclusion of these two articles was that prosthesis-patient mismatch (PPM) is a rare occurrence after aortic valve replacement and that it has a negligible impact with regard to postoperative outcomes. To define PPM and analyze its consequences, both sets of authors chose, however, to use an indexed area based on the internal geometric dimension of the prosthesis divided by the patient's body surface area, rather than the indexed effective orifice area, which is the physiologic parameter most often used to define PPM. They justified their choice of parameter on the basis that geometric measures "are determined before implantation, have much less variability, and are independent of hemodynamic state."¹

The physiologic and clinical relevance of the indexed internal geometric area as used by these authors must, however, be challenged. Indeed, it has never been shown that this parameter can be related, in any significant manner, to transvalvular pressure gradients; in particular, it has been demonstrated that the indexed internal geometric orifice area cannot be used to predict which patients will have high postoperative gradients.³ Inherent to the pathophysiology

of valve PPM is the concept that too small a prosthesis in too large a patient will produce abnormally high gradients and thus have potentially detrimental consequences such as might occur with a native aortic stenosis. Thus if the indexed internal geometric area cannot be related to postoperative gradients, we do not see how it can logically be used to identify PPM or to characterize its severity.

In contrast, and despite its inherent limitations, the indexed effective orifice area is the only parameter that has consistently been shown to correlate with postoperative gradients, as well as being highly predictive of adverse outcomes.³⁻⁵ Indeed, when the definition of PPM is based on this parameter, the phenomenon has been shown to be highly prevalent (19%-70%, depending on series^{4,5}) and to be associated with less symptomatic improvement, worse hemodynamics at rest and during exercise, less regression of left ventricular hypertrophy, and more cardiac events after operation.^{4,5} A recent report from our own laboratory has clearly shown that PPM has a major impact on early mortality, particularly in patients with poor left ventricular function and that, in contrast to other risk factors, it can easily be prevented by use of a simple strategy at the time of operation.⁵ Such a strategy was recently used by Castro and associates⁶; as a result, the incidence of moderate-severe PPM in their population was only 2.5%, instead of the 17% that would have occurred had this prospective strategy not been used, whereas operative mortality remained low (1%). Extrapolating these findings to the total number of aortic valve replacements being performed each year in North America, it is estimated that approximately 1000 operative deaths could potentially be avoided through use of such a strategy.

In this context, the conclusion of these two articles with regard to the prevalence of PPM and its consequences cannot be accepted at face value, because the parameter used to define PPM is not valid to characterize postoperative hemodynamics.³ To the contrary, we still believe in the "value of concentrating on better hemodynamic performance"¹ and that research aimed at properly identifying PPM, as well as preventing it, can significantly contribute to improved outcomes after aortic valve surgery.

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Reply to the Editor:

We have long respected the excellent and prolific work of Dumesnil and Pibarot, so it is not surprising that we referred to their publications in our articles. However, they are unhappy in part with the way we have interpreted (or misinterpreted) their work,^{1,2} and in part with the surgical recommendations we based on survival data from our multicenter meta-analysis,¹ which differ from their own, which were based largely on functional prosthesis performance data.

What We Studied Survival

We studied the relation of geometric prosthesis size to time-related survival with nine sources of data and nearly 70,000 patient-years of follow-up among 13,258 patients who underwent aortic valve replacement with mechanical prostheses, stent-

mounted bioprostheses, and allografts at multiple institutions on two continents.¹

Long-term survival is a relevant and important goal of aortic valve replacement,³ although how it is associated with efficiency of prosthetic devices remains controversial. Use of small label-size prostheses has been presumed by many surgeons to reduce survival after valve replacement. When patients were stratified by label size in our large study, however, prosthesis size was found to have little impact on survival (in contrast to substantial impact of patient factors, such as age). Unlike all previous studies, ours had the statistical power to detect even small differences in survival, with 1109 prostheses of label size 19 mm or smaller and 2984 of label size 21 mm.

To increase sensitivity, we focused our survival analysis on the geometric dimension of the internal orifice of the prosthesis normalized to patient size (prosthesis-patient size), a concept familiar in congenital heart disease but less so in adult heart disease.⁴ Stratifying patients by prosthesis-patient size revealed no impact on long-term or intermediate survival. However, in risk-adjusted and balancing score-adjusted analyses, when geometric orifice size was less than about the lower 95% confidence limit for normal human aortic valve size, which is uncommon in prudent aortic valve replacement (only 85 patients had prosthesis-patient size smaller than 0.85 cm²/m²), early survival was affected to a small extent (1% to 2%).

Adjusting Prosthesis-Patient Size for Prosthesis Model

Physics of blood flow dictates that as prosthesis geometric orifice size decreases, energy loss at a given flow rate increases. However, inertia, turbulence, other disturbances of blood flow velocity profile, and many other factors also affect energy loss. Therefore, as described in the multi-institutional article,¹ we searched for a relation of prosthesis-patient size to survival that was specific for each model of prosthesis by means of interaction terms. We found none of these to be statistically significant, indicating similarity of the relationship of geometric prosthesis-patient size to survival.

Surgical Inferences

Surgical inferences drawn concerning prosthesis size selection were based on survival data within the context of prudent valve replacement in these numerous representative institutions. We had no functional prosthesis performance data after operation for these patients, which might have further increased sensitivity of the survival analysis, thereby further refining prognosis and possibly surgical recommendations.

What We Did Not Study

Contrary to the letter, we did not study “postoperative outcomes” in general. We focused on one end point only: time-related mortality from any cause after aortic valve replacement. It is possible that either geometric or functional prosthesis-patient size might be more strongly related to other end points—such as sudden death, death in heart failure, or various measures of quality of life—that do not translate into a detectable survival difference.

We also studiously avoided the term *prosthesis-patient mismatch*. No doubt a clinical syndrome of prosthesis-patient mismatch occurs, as described by Rahimtoola⁵ and Rahimtoola and Murphy.⁶ However, through the years its definition has ceased being a clinical diagnosis and has become arbitrarily inferred from postoperative echocardiographic velocity measurements. We had no postoperative echocardiographic data in the assembled databases to address this issue, so we cannot discuss it further.

Alternative Proposal Functional Projected Orifice Size

More interesting is the alternative proposed by Dumesnil and Pibarot: that rather than geometric orifice size, we should use functional projected orifice size.⁷ They claim that projected size is more highly correlated with pressure gradient across a prosthesis than is geometric size.⁸ Thus, logically, it should be more sensitive to differences in time-related survival. This might be the case.

Prerequisites

Before accepting this alternative, several things need to be in place and clarified. Just as we had available an equation relating patient size to normal aortic valve size derived from 6801 measurements,⁹ so we need an equation relating patient size to

functional prosthesis size that is based on a substantial number of measurements. For this, high-quality individual patient postoperative Doppler velocity data for each label size of current aortic valve prostheses would need to be assembled, along with height and weight, and an appropriate analysis would need to be performed to obtain the equation. However, accurate (unbiased), precise (reproducible), and extensive (power) functional estimates of prosthesis size are elusive. They are related to many patient characteristics, left ventricular out-flow complex factors, time, measurement variability, interobserver variability, method of computation, and myriad other factors. It is sobering that even in vitro laboratory estimates of hemodynamic properties of prostheses are fraught with important institutional variation (as much as 200% to 400%)!¹⁰ Thus, it is likely that the in vivo relation will have substantial scatter. Then an association should be sought between survival and functional prosthesis-patient size, with reference to the normalizations suggested in the articles.^{1,2}

Two Notes of Caution

Correlation Between Variables Derived From the Same Data

One premise of the letter is that transprosthesis pressure gradients are more closely correlated with functional prosthesis size than with geometric prosthesis size (and implicitly that pressure gradient is related to survival).⁸ It is not appreciated in such comparisons that the same Doppler velocities are used to compute both pressure gradient and functional prosthesis size. This guarantees a close correlation between the two; they are not independent measurements! This obligatory correlation leads Dumesnil and Pibarot to state that “indexed internal geometric orifice area cannot be used to predict which patients will have high postoperative gradients.” This is, in our opinion, stretching the statistics.

Avoiding 1000 Deaths per Year

The second note of caution is the notion that if a policy of liberal aortic root enlargement accompanying aortic valve replacement were adopted, then “each year in North America...approximately 1000 operative deaths could potentially be avoided.” This too is a stretch of statistics.

The extrapolation is based on Castro and colleagues' observation¹¹ of a single death among 114 patients (70% confidence limits 0.1%-3.0% mortality) in the concurrent setting of 543 patients deemed not in need of aortic root enlargement; the latter sustained a mortality of 4.1% with 70% confidence limits of 3.2% to 5.1%.¹¹ These confidence limits and the context caution against concluding that widespread application of the proposed algorithm is likely to lower operative mortality.

Small sets of data pose two dangers, identifying spurious relations in small subgroups and failing to identify relations because of lack of statistical power. These concerns motivated collaborators in the multi-institutional study to contribute more than 13,000 patients with 70,000 patient years of follow-up.

Disclaimer

In responding to this letter, we must acknowledge that we reside within the institution with the highest volume of heart valve operations on the North American continent. The practice at The Cleveland Clinic Foundation has not been to avoid using small-sized prostheses in small aortic roots. Yet hospital mortality for 881 primary isolated aortic valve replacements in the last 5 years was 1.2%, and for 996 primary combined aortic valve replacements with coronary artery bypass grafting it was 2.0%. In some instances, left ventricular outflow tract myectomy is performed for obstruction at that level, but rarely is aortic root enlargement performed.

We remain interested in performance of prostheses, but we believe that available evidence suggests that other factors have more impact on long-term all-cause mortality than does prosthesis-patient size, however expressed.

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Epidemiologic contrast of predictors' trends for outcomes of coronary artery bypass grafting: Heart failure versus ventricular function versus left main disease

To the Editor:

I read with interest the article by Davierwala and colleagues¹ in the November 2003 issue of the *Journal*. The work analyzed differential change in predictors of in hospital mortality after coronary artery bypass grafting. The study elegantly demonstrated the diminishing statistical significance for left ventricular function greater than 20% as a predictor for mortality during a 12-year period. Several explanations are provided related to patient comorbidity, interventional cardiology, surgeon experience, and intensive patient care. It is well

established that one of the major determinants of morbidity during and after coronary artery bypass grafting is low left ventricular ejection fraction.² The results of numerous coronary artery bypass grafting trials performed in the 1970s and 1980s show that despite this increased morbidity, the benefits of this procedure for patients with multivessel coronary artery disease and low left ventricular systolic function in many cases outweigh the risks.³ The article does not contain data for the actual causes of death in this large group of patients, which would be epidemiologically relevant. Given the data provided, however, it is difficult to observe a contrast in the trends between congestive heart failure (CHF) and left ventricular function as predictor variables. Davierwala and colleagues¹ also stated in their discussion that from studying the data again in Table 1 it is clear to the reader that CHF held an increasing proportion as morbidity in the patient cohort (7.8% vs 9.4% vs 9.4%) during the interval (1990-1993 vs 1994-1997 vs 1998-2001). Moreover, according to the original article's Table 3, after a multivariate analysis CHF showed an increasing trend for odds ratio by year group (1.9 vs 3.6).¹ Given this contrast of predictor outcome trends, the authors should have included other explanations. In simple terms, the CHF increasing trend could reflect an increase in diastolic heart failure, assuming that the proportions of new patients in each time interval were significant. In other words, the decline of the predictor value in left ventricular dysfunction was not related to interyear group patient death. The authors stated that left main disease in a "somewhat counterintuitive finding" was "unmasked" in the last time cohort, with an odds ratio of 1.7 in Table 3 of the original article.¹ From their data, both CHF and left main disease increased in prevalence, yet worsening ventricular dysfunction declined. This constellation may reflect a change in the ventricular dysfunction function from systolic to diastolic biometrically.

Furthermore, the typical risk factors and comorbidities of female gender, diabetes, and hypertension together increased significantly during the entire period of their study. This association has now been found to be the same with diastolic dysfunction.⁴ As we know now, there is growing appreciation of diastolic heart failure as a distinct