Ejection fraction-velocity ratio for the assessment of aortic bioprosthetic valves in patients with systolic dysfunction

Paolo Cattaneo MD^{1,2}, Paolo Marchetti MD³, Massimo Baravelli MD^{1,2}, Andrea Rossi MD^{1,2},
Giovanni Mariscalco MD³, Sergio Ghiringhelli MD³, Claudio Anzà MD^{1,2}

P Cattaneo, P Marchetti, M Baravelli, et al. Ejection fraction-velocity ratio for the assessment of aortic bioprosthetic valves in patients with systolic dysfunction. *Can J Cardiol* 2009;25(3):e78-e81.

BACKGROUND: The continuity equation (CE) represents the 'gold standard' for the evaluation of aortic valve area in patients with aortic stenosis, but it is time-consuming and subject to error, and can be technically demanding. Recently, a new echocardiographic nonflow corrected index was introduced and demonstrated excellent accuracy in quantifying the effective orifice area (EOA) in native aortic valves and bioprostheses. This new index, the ejection fraction (EF)-velocity ratio (EFVR), is obtained by dividing the percentage left ventricular EF by the maximum aortic gradient.

OBJECTIVE: To assess the usefulness of this echocardiographic index for quantifying the EOA in patients with aortic bioprosthesis and left ventricular dysfunction.

METHODS: A total of 70 patients (25 women and 45 men) with aortic bioprosthesis and left ventricular dysfunction (EF of 49% or less) were studied. The mean ($\pm$ SD) age of the study population was 71.4 ± 9 years. The EOA was evaluated, both by the CE and by the EFVR.

RESULTS: A significant linear correlation between the CE and the EFVR was found ($r=0.80$; $P<0.0001$). The receiver operating characteristic curve analysis showed good agreement between the CE and the EFVR. An EFVR value of 1.15 or less was found to have a good sensitivity (89%) and good specificity (91%) in identifying patients with an EOA of 1.0 cm^2 or smaller, with positive and negative predictive values of 79% and 95%, respectively.

CONCLUSIONS: The EFVR, a simple index that is less time-consuming than the CE, allows the identification of patients with aortic bioprosthesis stenosis with excellent sensitivity and specificity. It may be taken into consideration in clinical practice for the evaluation of patients with aortic bioprosthesis stenosis and left ventricular dysfunction.

Key Words: Aortic stenosis; Bioprosthesis; Echocardiography

Rapport fraction d'éjection:vitesse pour l'évaluation des bioprothèses valvulaires aortiques chez des patients souffrant de dysfonction systolique

HISTORIQUE : L'équation de continuité (ÉC) représente la norme pour l'évaluation de l'aire valvulaire aortique chez les patients souffrant de sténose aortique, mais elle est fastidieuse, sujette à l'erreur et parfois exigeante sur le plan technique. Récemment, un nouvel indice échocardiographique non corrigé en fonction du flux a été introduit et a permis de calculer avec une excellente précision l'aire efficace de l'orifice (AEO) des bioprothèses valvulaires aortiques et des valvules aortiques natives. Ce nouvel indice, le rapport fraction d'éjection (FÉ):vitesse (RFÉV), s'obtient en divisant le pourcentage de la FÉ ventriculaire gauche par le gradient aortique maximum.

OBJECTIF : Évaluer l'utilité de cet indice échocardiographique pour quantifier l'AEO chez les patients porteurs de bioprothèses aortiques et souffrant de dysfonction ventriculaire gauche.

MÉTHODES : En tout, 70 patients (25 femmes et 45 hommes) porteurs d'une bioprothèse aortique et atteints de dysfonction ventriculaire gauche (FÉ $\leq 49\%$) ont été étudiés. L'âge moyen ($\pm$ É.-T.) de la population étudiée était de $71,4 \pm 9$ ans. L'AEO a été évaluée au moyen de l'équation de continuité et du RFÉV.

RÉSULTATS : Une corrélation linéaire significative entre l'ÉC et le RFÉV a été observée ($r = 0,80$, $p < 0,0001$). L'analyse de la courbe ROC a montré une bonne concordance entre l'ÉC et le RFÉV. Une RFÉV de 1,15 ou moins s'est révélée dotée d'une bonne sensibilité (89 %) et d'une bonne spécificité (91 %) pour l'identification des patients dont l'AEO est de $1,0 \text{ cm}^2$ ou moins, avec des valeurs prédictives positives et négatives de 79 % et 95 %, respectivement.

CONCLUSION : Le RFÉV, un indice simple, moins fastidieux que l'ÉC, permet, avec un excellent degré de sensibilité et de spécificité, d'identifier les patients présentant une sténose de leur bioprothèse aortique. On peut en tenir compte dans la pratique clinique pour l'évaluation des patients qui présentent une sténose de leur bioprothèse aortique et une dysfonction ventriculaire gauche.

The continuity equation (CE) method represents the 'gold standard' for the assessment of aortic stenosis severity and can provide an accurate evaluation of effective orifice area (EOA) in aortic prosthetic valves (1,2). Nevertheless, the CE method has significant limitation (2,3) in native and prosthetic valves (eg, distorted anatomy and poor image resolution). In elderly patients with calcified aortic valve stenosis, measurements of the left ventricular (LV) out-flow tract (LVOT) diameter and the time-velocity flow integral are

time-consuming and may be technically difficult to perform. A new echocardiographic 'function-corrected' method for the evaluation of aortic stenosis – the ejection fraction (EF)-velocity ratio (EFVR) – was first described by Antonini-Canterin et al (4,5). This index is the ratio of the percentage LVEF to the maximum aortic gradient. The aim of the present study was to assess the usefulness of this echocardiographic index for measuring EOA in patients with aortic bioprosthetic valves and systolic LV dysfunction.

¹Department of Cardiology and Cardiac Rehabilitation, Clinical Institute Multimedica Holding Santa Maria, Castellanza; ²Department of Cardiology and Cardiac Rehabilitation, Multimedica Sesto San Giovanni, Milano; ³Department of Cardiology and Cardiac Surgery, University of Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Italy

Correspondence: Dr Paolo Cattaneo, Department of Cardiology and Cardiac Rehabilitation, Clinical Institute Multimedica Holding Santa Maria, viale Piemonte 70, 21053, Castellanza, Varese, Italy. Telephone 39-033-139-3111, fax 39-033-139-3111, e-mail p.cattaneo@tin.it

Received for publication March 14, 2007. Accepted May 21, 2007

TABLE 1
Clinical and echocardiographic variables

Patients, n	70
Age, years, mean $\pm$ SD	71.4 $\pm$ 9
Men:women, n	45:25
Prosthetic size, mm, mean $\pm$ SD	22.3 $\pm$ 2.31
Stented valves, n	21
Stentless valves, n	49
LVEF for consistency, %, mean $\pm$ SD	36 $\pm$ 8.6
Mean gradient, mmHg, mean $\pm$ SD	35.23 $\pm$ 23.01
Effective orifice area*, cm ² , mean $\pm$ SD	1.51 $\pm$ 0.62
EFVR, mean $\pm$ SD	1.68 $\pm$ 0.74

*Obtained by the continuity equation. EFVR Ejection fraction-velocity ratio; LVEF Left ventricular ejection fraction

METHODS

Patient population

A series of patients with LV systolic dysfunction (EF of 49% or less) who received a bioprosthesis in the aortic position were studied. Patients with significant aortic and/or mitral regurgitation (grades II to IV), assessed by colour Doppler imaging, were excluded; no patients were excluded for technical reasons. A total of 70 patients (25 women and 45 men) with a mean ($\pm$ SD) age of 71.4 $\pm$ 9 years were enrolled. Transthoracic echocardiography was performed in all patients, and EOA was measured by the CE. All examinations were performed by the same physician (PC). The EFVR was calculated by another investigator (PM) who was unaware of the CE results.

Echocardiography

All examinations were performed using an echocardiographic system equipped with a 2.5 MHz transducer (Sonos 5500; Hewlett-Packard, USA). The diameter of the LVOT was obtained from the parasternal LV long-axis view of a two-dimensional image in early systole. Flow velocity in the LVOT, flow velocity across the bioprosthetic valve and its time integral were measured by Doppler recordings. Pulsed wave Doppler was used to measure mean and maximum systolic blood flow velocities (V_{mean} and V_{max} , respectively) in the LVOT, and continuous wave Doppler was used to measure systolic blood flow velocities through the aortic valve (AV). Peak and mean transvalvular gradients were obtained using the modified Bernoulli equation:

$$\text{Peak gradient (mmHg)} = 4 \times (V_{\text{AVmax}}^2 - V_{\text{LVOTmax}}^2)$$

$$\text{Mean gradient (mmHg)} = 4 \times (V_{\text{AVmean}}^2 - V_{\text{LVOTmean}}^2)$$

The EOA was calculated by the CE:

$$\text{EOA (cm}^2\text{)} = \frac{(\text{CSA}_{\text{LVOT}} \times \text{TVI}_{\text{LVOT}})}{\text{TVI}_{\text{AV}}}$$

CSA_{LVOT} indicates LVOT cross-sectional area ($\pi r^2/4$) in cm², TVI_{LVOT} indicates LVOT time-velocity integral of forward blood flow in cm, and TVI_{AV} indicates transvalvular time-velocity integral of forward blood flow in cm. End-diastolic and end-systolic dimension, wall thickness and LV cavity size were measured from M-mode echocardiograms. The LVEF was determined using the Simpson method. The EFVR was obtained by dividing the percentage LVEF by the maximum aortic gradient:

$$\text{EFVR} = \frac{\text{EF}}{4V^2}$$

In eight patients (11.5%), an echocontrast agent (Levovist; Schering AG, Germany) was intravenously administered to determine LVEF because of poor subendocardial resolution.

Mean values for each measurement were derived from three beats in patients in sinus rhythm and from five beats in patients

Figure 1 Linear regression analysis between Doppler aortic bioprosthetic valve area assessed by the continuity equation and ejection fraction-velocity ratio (EFVR) ($r=0.80$; $P<0.0001$). EOA Effective orifice area

with atrial fibrillation. The severity of mitral and aortic regurgitation was estimated by colour Doppler flow-mapping, as previously described (6,7).

Statistical analysis

The identification of an EOA of 1 cm² or smaller was considered to be clinically significant (8,9). The results are expressed as mean $\pm$ SD. The correlation between EOA and EFVR was assessed using simple linear regression analysis, considering the CE to be the 'gold standard'. Sensitivity (defined as EFVR below a cut-off point in the presence of significant aortic bioprosthetic stenosis), specificity (defined as EFVR above a cut-off point in the absence of significant aortic bioprosthetic stenosis) and predictive value of the different indexes were calculated according to standard methods (10). A receiver operating characteristic (ROC) curve analysis assessed the performance of each index and the reliability of the conventional cut-off values of severity. Statistical analysis was performed using the SPSS 13.0 statistical software package (SPSS Inc, USA).

RESULTS

The clinical characteristics of the patients are listed in Table 1. LVEF was 36 $\pm$ 8.6%. EOA, obtained by the CE, varied between 0.3 cm² and 2.6 cm²; 19 patients (27.1%) had EOA values of 1.0 cm² or smaller. The EFVR varied from 0.55 to 3.2. A good correlation between the EFVR and EOA was observed ($r=0.80$; $P<0.0001$; Figure 1) in the 70 patients studied. The ROC analysis showed a good agreement between CE and EFVR (Figure 2). An EFVR value of 1.15 or less was found to have a good sensitivity (89%) and good specificity (91%) in identifying patients with an EOA of 1.0 cm² or smaller, with positive and negative predictive values of 79% and 95%, respectively.

DISCUSSION

Bioprosthetic valves are preferred in elderly patients because degeneration is extremely rare when these valves are implanted in patients older than 70 years of age and because they do not require long-term anticoagulation treatment, which is often hazardous in this class of patients. Evaluation of bioprosthetic function and EOA measurement

Figure 2 Receiver operating characteristic (ROC) analysis for the diagnosis of severe aortic stenosis defined as an aortic valve area $\leq 1.0 \text{ cm}^2$. The vertical scale represents the true-positive fraction (TPF; sensitivity) and the horizontal scale represents the false-positive fraction (FPF; $1 - \text{specificity}$). The area under the ROC curve is 0.95; the best cut-off point for ejection fraction-velocity ratio (EFVR) to identify continuity equation values of $\leq 1.0 \text{ cm}^2$ is 1.15

is mandatory in patients receiving a biological prosthesis in the aortic position. In the presence of poor LVEF, the evaluation of the severity of aortic stenosis may be problematic; the undemanding calculation of maximum aortic jet velocity is inadequate because reduction in transaortic volume flow rate results in decreased gradients across the valve (11). Oh et al (12) observed that a mean aortic gradient of more than 50 mmHg was highly specific (94%) but poorly sensitive (48%) for identifying patients with severe aortic stenosis. In fact, transprosthetic gradients are particularly sensitive to transprosthetic flow rate and they change significantly with modifications in the hemodynamic state of the patient. The calculation of aortic valve area at cardiac catheterization is an invasive method and may be associated with potential risks for cerebral embolization due to the dislodgement of calcific particles from the native valve or prosthesis. Moreover, a flow-related discrepancy between Gorlin aortic valve area and Doppler aortic valve area occurs in patients with isolated valvular aortic stenosis (13). Echocardiographic Doppler evaluation of aortic stenosis severity, based on the CE, has revolutionized the management of patients with this pathology (1). The CE, however, is potentially time-consuming, and requires an accurate measurement of LVOT diameter and subvalvular blood flow velocity at the same level. In patients with calcific bioprosthetic aortic valve stenosis or poor echocardiographic views, the calculation of LVOT diameter is difficult or almost impossible. Furthermore, measurement of LVOT diameter and Doppler flow velocity, recorded at the same anatomical site, may be problematic because of the axial movement of the aortic annulus during systole and the skew distribution of velocity flow pattern in the LVOT, with the highest velocities along the anterior wall and septum (14). Aortic valve resistance, the simple ratio between mean transvalvular pressure gradient and flow, has been proposed as an alternative index, but this method has the same limitations found for the measurement of LVOT diameter and

subvalvular velocity (15). Moreover, valve resistance is flow-dependent and is not superior to aortic valve area calculations for the assessment of aortic stenosis, especially in low flow-low gradient aortic stenosis (16). In patients with a small aortic valve area but low flow rate, distinguishing between truly severe aortic stenosis and moderate aortic stenosis remains challenging because EOA can be only functionally small. Gradual infusion of a low dose of dobutamine can increase stroke volume and can therefore be useful to identify low gradients across the valve due to real severe lumen reduction rather than a low-output state (pseudosevere aortic stenosis). In fact, in cases of truly severe aortic stenosis, dobutamine infusion increases peak velocity and TVI equally, both at the LVOT and aortic valve level, so that the ratio of TVI_{LVOT} to TVI_{AV} remains unchanged. In cases of pseudo- or functionally severe aortic stenosis, the increase in peak velocity and TVI at the LVOT is larger than at the aortic valve (the valve opens widely); therefore, the ratio of TVI_{LVOT} to TVI_{AV} increases (17).

The 'function-corrected' method (EFVR) overcomes all the limitations of CE (5,18). This method represents a functional correction (by LVEF) of the maximum aortic gradient ($\text{EFVR} = \text{EF}/4V^2$) and seems to be helpful for the evaluation of patients with native aortic stenosis and LV dysfunction (4). By incorporating the EF in the numerator of the formula, the EFVR is able to identify patients with severe aortic stenosis, even if they have low transvalvular gradients. There is another 'function-corrected' index validated for the evaluation of aortic stenosis – the fractional shortening-velocity ratio (FSVR). This index is the ratio of the extent of LV percentage fractional shortening at the mid-ventricular level to $4V^2$, where V is the peak Doppler-derived instantaneous flow velocity across the stenotic aortic valve (19):

$$\text{FSVR} = \frac{\text{FS} (\%) }{4V^2}$$

This method, validated by a linear relationship with the aortic valve area at cardiac catheterization (Gorlin formula), has significant limitations because a 'symmetrical left ventricle' is required. In fact, it is unreliable in patients with regional wall motion abnormalities, conduction defects or pacemakers, which are common conditions in elderly patients with aortic stenosis (20). Recently, Antonini-Canterin et al (21) showed a good correlation between CE and EFVR in 141 consecutive patients with aortic bioprostheses ($r=0.88$; $P<0.0001$). The ROC analysis showed good agreement between CE and EFVR, with an optimal EFVR cut-off value of less than 1.06 for the identification of subjects with an EOA smaller than 1.0 cm^2 . In the present study, we evaluated the usefulness of this simple echocardiographic method for measuring EOA in patients with aortic bioprosthesis and systolic dysfunction (EF of 49% or less). The EFVR showed good correlation with the aortic valve area estimated using the CE ($r=0.80$; $P<0.0001$; Figure 1). Using a ROC analysis, different cut-off values of EFVR were used to identify patients with severe aortic bioprosthetic stenosis (EOA of 1 cm^2 or smaller). An EFVR value of less than 1.15 was found to have the best sensitivity (89%) and specificity (91%), with positive and negative predictive values of 79% and 94%, respectively. The present study confirms the results by Antonini-Canterin et al (21) in patients with bioprosthetic aortic stenosis and poor LVEF. The EFVR, a simple ratio of two parameters routinely calculated in a standard echocardiographic study (EF and maximum aortic gradient), can be easily obtained when measurements for the CE are technically difficult to perform.

CONCLUSION

The severity of aortic stenosis is traditionally assessed using indexes (flow gradients and valve area by the CE) whose cut-off values are well established and defined. Our study validates data expressed by Antonini-Canterin et al, encouraging the routine use of this relatively new and simple index in clinical practice and the development of new studies aimed to further validate the best cut-off values to identify patients with severe aortic stenosis. In the study by

Antonini-Canterin et al, the ROC analysis showed a good agreement between CE and EFVR. The area under the ROC curve was 0.97 (versus 0.95 in our study) and the best EFVR cut-off point for identifying CE values of 1.0 cm² or smaller was 1.06 (versus 1.15 in our study). Moreover, in the subgroup of patients with an EF of 50% or less, EFVR confirmed good sensitivity (79%), specificity (97%), positive predictive value (75%) and negative predictive value (95%), which was consistent with our study. Furthermore, it should be noted that normally functioning prosthetic valves can have high postoperative transvalvular gradients. This is often due to a phenomenon called prosthesis-patient mismatch (22). These transvalvular gradients are determined by the EOA of the valve and transvalvular flow. Blood flow velocities are related to the cardiac

output that, at rest, is dependent on the body surface area. Consequently, indexed EOA is the most accurate parameter for the evaluation for stenosis severity (22). In the present study, EFVR was related to EOA, but not to indexed EOA. It is interesting to point out that, among the six patients who presented with a discrepancy between the EOA and EFVR (ie, EFVR of 1.15 or less and EOA of 1.0 cm² or larger), four (66%) presented with an indexed EOA of 0.85 cm²/m² or smaller (indicating the presence of prosthesis-patient mismatch), correctly detected by values of EFVR of 1.15 or less.

The major limitation of the present study was the exclusion of patients with significant aortic and/or mitral regurgitation (grade II to IV). In this subgroup of patients, the values of EFVR would be high, secondary to the overestimation of EF (falsely negative results).

REFERENCES

1. Otto CM, Pearlman AS, Comess KA, et al. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. *J Am Coll Cardiol* 1986;7:509-17.
2. Skjaerpe T, Hegrenaes L, Hatle L, et al. Non-invasive estimation of valve area in patients with aortic stenosis by Doppler ultrasound and two-dimensional echocardiography. *Circulation* 1985;72:810-8.
3. Come PC, Riley MF, Ferguson JF, et al. Prediction of severity of aortic stenosis: Accuracy of multiple non-invasive parameters. *Am J Med* 1988;85:29-37.
4. Antonini-Canterin F, Pavan D, Burelli C, et al. Validation of the ejection fraction-velocity ratio: A new simplified "function corrected" index for assessing aortic stenosis severity. *Am J Cardiol* 2000;86:427-33.
5. Antonini-Canterin F, Huang G, Cervesato E, et al. Reliability of new and old Doppler echocardiographic indexes of the severity of aortic stenosis in patients with a low cardiac output. *Ital Heart J* 2002;3:248-55.
6. Helmcke F, Nanda NC, Hsiung MC, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation* 1987;75:175-83.
7. Perry JC, Helmcke F, Nanda NC, et al. Evaluation of aortic insufficiency by Doppler color flow mapping. *J Am Coll Cardiol* 1987;9:952-9.
8. Bonow RO, Carabello B, De Leon AC, et al. ACC/AHA guidelines for the management of patients with valvular heart disease. *J Am Coll Cardiol* 1998;32:1486-588.
9. Rothbart MD, Jorge L, Linda V, et al. Determination of aortic valve area by two-dimensional and Doppler echocardiography in patients with normal and stenotic bioprosthetic valves. *J Am Coll Cardiol* 1990;15:817-24.
10. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1994;271:389-91.
11. Burwash IG, Thomas DD, Sadahiro M, et al. Dependence of Gorlin formula and continuity equation valve area on transvalvular volume flow-rate in valvular aortic stenosis. *Circulation* 1994;89:827-35.
12. Oh JK, Taliercio CP, Holmes DR, et al. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: Prospective Doppler-catheterization correlation in 100 patients. *J Am Coll Cardiol* 1988;11:1227-34.
13. Burwash IG, Dickinson A, Teskey RJ, Tam JW, Chan KL. Aortic valve area discrepancy by Gorlin equation and Doppler echocardiography continuity equation: Relationship to flow in patients with valvular aortic stenosis. *Can J Cardiol* 2000;16:985-92.
14. Zhou YQ, Faerstrand S, Matre K, et al. Velocity distribution in the left ventricular outflow tract in patients with valvular aortic stenosis. Effects of the measurement of aortic valve area by using the continuity equation. *Eur Heart J* 1995;16:383-93.
15. Antonini-Canterin F, Faggiano P, Zanuttini D. Is aortic valve resistance more clinically meaningful than valve area in aortic stenosis? *Heart* 1999;82:9-10.
16. Mascherbauer J, Schima H, Rosenhek R, et al. Value and limitations of aortic valve resistance with particular consideration of low flow-low gradient aortic stenosis: An in vitro study. *Eur Heart J* 2004;25:787-93.
17. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from non-severe valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol* 1995;75:191-4.
18. Al-Ghamdi AM, Melendez LJ, Massel D. Ejection fraction velocity ratio as an indicator of aortic stenosis severity. *Echocardiography* 2005;22:195-202.
19. Mann DL, Usher BW, Hammerman S, Bell A, Gillam LD. The fractional shortening-velocity ratio: Validation of a new echocardiographic Doppler method for identifying patients with significant aortic stenosis. *J Am Coll Cardiol* 1990;15:1578-84.
20. Climent VE, Marin F, Valencia J, et al. Fractional shortening-velocity ratio for assessment of aortic stenosis severity in patients with systolic dysfunction. *Int J Cardiol* 2003;92:229-34.
21. Antonini-Canterin F, Allocca G, Rivabem D, et al. Use of the ejection fraction-velocity ratio in the hemodynamic assessment of aortic bioprosthetic valves. *Echocardiography* 2006;23:97-102.
22. Dumesnil JG, Honos GN, Lemieux M, Beauchemin J. Validation and applications of indexed aortic prosthetic valve areas calculated by Doppler echocardiography. *J Am Coll Cardiol* 1990;16:637-43.