JACC: CARDIOVASCULAR IMAGING
VOL. 6, NO. 2, 2013

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2012.09.011

ORIGINAL RESEARCH

Dysfunction of Bileaflet Aortic Prosthesis

Accuracy of Echocardiography Versus Fluoroscopy

Manuela Muratori, MD,* Piero Montorsi, MD,*† Francesco Maffessanti, PhD,*
Giovanni Teruzzi, MD,* William A. Zoghbi, MD,‡ Paola Gripari, MD,*
Gloria Tamborini, MD,* Sarah Ghulam Ali, MD,* Laura Fusini, MS,*
Cesare Fiorentini, MD,*† Mauro Pepi, MD*

Milan, Italy; and Houston, Texas

OBJECTIVES The authors sought to investigate the accuracy of transthoracic echocardiography (TTE)-derived parameters in the identification of bileaflet aortic prosthesis dysfunction, compared with fluoroscopy (FL).

BACKGROUND Identification of bileaflet aortic prosthesis dysfunction is challenging, because high mean pressure gradient (MPG >20 mm Hg) is not proof of prosthetic obstruction (AVPO), and may be due to prosthesis–patient mismatch (PPM). Conversely, high gradients may not be manifest in AVPO and low cardiac output.

METHODS TTE and FL were prospectively performed in 100 nonconsecutive patients with bileaflet aortic prosthesis. TTE included the estimation of MPG, indexed effective orifice area (EOAi), Doppler velocity index (DVI), intraprosthetic regurgitation, acceleration time (AT), ejection time (ET), AT/ET, and the difference (dA) between the expected prosthetic orifice area and EOA. FL allowed the calculation of opening and closing angles, and the discrimination of AVPO from normal (NL) and PPM.

RESULTS On the basis of FL examination and MPG and EOAi at TTE, patients were classified as NL (42%), PPM (32%), and AVPO (26%). High MPG (>20 mm Hg) was present in 65% of the patients, with higher values in PPM (36 ± 8 mm Hg) and AVPO (43 ± 16 mm Hg) than in NL (16 ± 6 mm Hg). DVI was reduced in PPM (0.30 ± 0.05) and AVPO (0.25 ± 0.04) compared with NL (0.42 ± 0.09). In AVPO, dA (0.59 ± 0.32 cm^2), AT (108 ± 20 ms), and AT/ET (0.35 ± 0.05) significantly differed from NL (dA = −0.12 ± 0.43 cm^2, AT = 74 ± 15 ms, AT/ET = 0.25 ± 0.05) and PPM (dA = 0.15 ± 0.24 cm^2, AT = 78 ± 13 ms, AT/ET = 0.26 ± 0.04). Moderate or severe intraprosthetic regurgitation was observed only in AVPO. All considered TTE-derived parameters were found related to obstruction, and dA (accuracy = 87%), AT (94%), and AT/ET (89%) showed the highest accuracy in discriminating normofunctioning prostheses from AVPO.

CONCLUSIONS In the presence of high MPG, TTE parameters play a key role in aortic prosthesis examination. Especially time indices and dA add to the functional assessment of prosthetic aortic valves. However, the TTE discrimination between AVPO and PPM may be suboptimal, and fluoroscopy is a complementary and essential diagnostic step. (J Am Coll Cardiol Img 2013;6:196–205) © 2013 by the American College of Cardiology Foundation

From the *Centro Cardiologico Monzino, IRCCS, Milan, Italy; †Clinical Sciences and Community Health Department, University of Milan, Milan, Italy; and the ‡Methodist DeBakey Heart and Vascular Center, Houston, Texas. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Farooq A. Chaudhry, MD, served as Guest Editor of this paper.

Manuscript received March 21, 2012; revised manuscript received September 7, 2012, accepted September 19, 2012.

Bileaflet prosthetic valves (PV) are the most frequently implanted mechanical valves, but the assessment of their function in aortic position remains a challenge. Doppler transthoracic echocardiography (TTE) is the most widely used tool to assess PV function (1). Nevertheless, the identification of prosthetic leaflet motion by means of 2-dimensional echocardiography has been shown to be poorly feasible (2,3). Moreover, the sole use of gradients in the assessment of prosthetic function is limited, because gradients depend, not only on flow magnitude, but also on valve type and size (4,5). In fact, high transprosthetic velocity alone is not proof of intrinsic aortic valve prosthesis obstruction (AVPO), but rather may be secondary to high flow, to prosthesis–patient mismatch (PPM), or to pressure recovery at the smaller central valvular orifice (6–8). Conversely, high transprosthetic gradients may not be evident in the case of low cardiac output, even in the presence of obstruction (9). Prosthetic effective orifice area (EOA) provides a parameter that is less dependent on flow, but still relies on a priori knowledge of valve size (10). New parameters of AVPO have been recently proposed, in particular delayed peak systolic velocity (1,11), leading to longer acceleration times (AT) and higher acceleration to ejection time (ET) ratios (AT/ET).

The aim of this study was to investigate the accuracy of multiple TTE-derived parameters in the identification of bileaflet AVPO versus normal (NL) prosthesis and PPM, compared with cinefluoroscopy (FL), considered as the gold standard.

METHODS

One hundred patients (age 64 ± 10 years, 41 men) with bileaflet PV admitted to Centro Cardiologico Monzino were prospectively enrolled in the study between 2001 and 2010. Patients were selected among those hospitalized; 49% of the patients were hospitalized because of suspected AVPO on the basis of high gradients, 27% for heart failure, and the remaining for other cardiovascular reasons (cardioversion of atrial fibrillation, coronary artery disease).

The local ethical committee approved the study protocol, and written informed consent was obtained from each patient.

Transthoracic Doppler echocardiography. Two-dimensional and Doppler TTE were performed using a Sonos 7500 or iE33 ultrasound equipped with a S3 sector array probe (Philips Medical Systems, Andover, Massachusetts).

A complete 2-dimensional TTE evaluation was performed in multiple cross-sectional and off-axis views. Color Doppler was used for screening and evaluating the degree of intra- and/or paraprosthetic regurgitation.

Doppler-derived parameters of PV function included peak velocity, mean pressure gradient (MPG), and velocity-time integral of the jet by continuous-wave Doppler performed from apical, right parasternal, right supraclavicular, and suprasternal positions. Prosthetic EOA was derived from the continuity equation and calculated as the product of the cross-sectional area of the left ventricular outflow tract (LVOT), measured during the same TTE examination, and the LVOT velocity-time integral, divided by the velocity-time integral through the aortic prosthesis itself, using continuous-wave Doppler (10,11). The LVOT was measured below the insertion of the PV, as the distance between the junction of the sewing ring and the ventricular septum, and the junction of the sewing ring and the base of anterior mitral leaflet (1). The LVOT velocity-time integral was obtained using pulsed-wave Doppler and positioning the sample volume 5 mm below the aortic prosthesis.

An indexed EOA (EOAi) was defined as the ratio between EOA and the body surface area. Moreover, the difference between expected prosthetic orifice area, as reported in the literature (5), and TTE-derived EOA (dA) was considered. A Doppler velocity index (DVI) was also calculated as the ratio between the proximal velocity-time integral in the LVOT and the velocity-time integral through the valve (1).

The systolic time intervals of flow through the PV were measured using the velocity curve from continuous wave Doppler recording (Fig. 1): ET was measured as the interval from the onset to the end of systolic flow across the PV; AT was defined as the time elapsed from the beginning of systolic flow to its peak velocity. Finally, the AT/ET ratio was calculated. Systolic time intervals were routinely collected only starting from 2009, following the publication of the relevant recommendations (1). Therefore, for those patients enrolled before 2009, the same parameters were retrospectively calculated based on the images digitally stored on the picture archiving and communication system of our institution.

ABBREVIATIONS AND ACRONYMS

AT = acceleration time
AVPO = aortic valve prosthesis obstruction
CA = closing angle
dA = difference between expected prosthetic orifice area and transthoracic echocardiography–derived area
DVI = Doppler velocity index
EOA = effective orifice area
EOAi = indexed effective orifice area
ET = ejection time
FL = fluoroscopy
LVOT = left ventricular outflow tract
MPG = mean pressure gradient
NL = normal
NYHA = New York Heart Association
OA = opening angle
PPM = prosthesis–patient mismatch
PV = prosthetic valve
ROC = receiver-operating characteristic
TTE = transthoracic echocardiography

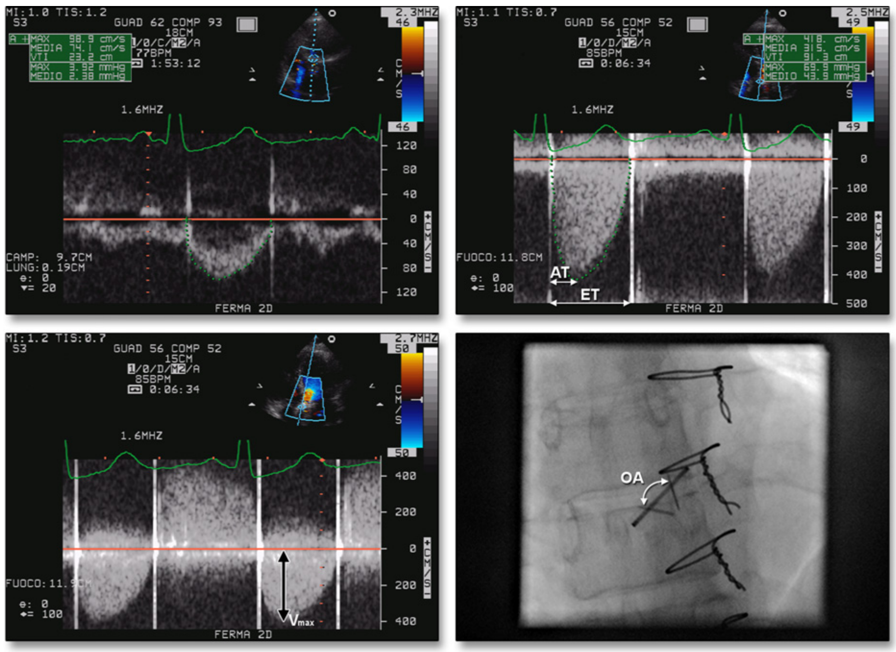

Figure 1. Echocardiographic and Cinefluoroscopic Findings in Prosthetic Obstruction

Example of a patient with obstruction of a St. Jude prosthetic aortic valve (size 19): Main findings: Doppler velocity index 0.25; acceleration time (AT): 100 ms; AT/ejection time (ET) ratio: 0.34; ET: 281 ms **(top right)**; peak and mean pressure gradients **(top left)**; continuous wave Doppler shows aortic prosthetic regurgitation >2+ **(bottom left)**; at fluoroscopy **(bottom right)**, end-systolic opening angle (OA) reached 70°, indicative of severely hypomobile leaflets. Vmax = peak systolic velocity.

All reported measurements were obtained by averaging the values collected over 3 consecutive cardiac cycles for patients in sinus rhythm, and over 5 cardiac cycles for those in atrial fibrillation. In the presence of atrial fibrillation, care was taken to obtain measurements during physiological heart rate conditions, trying to match temporally similar beats and thus preventing unrepresentative results.

Fluoroscopy. Fluoroscopy was performed using Toshiba Infinix CAS 830 equipment with C-arm (Toshiba Medical System Corp, Tustin, California). Evaluation was considered appropriate when the prosthesis tilting disk optimal projection was obtained. This view allows proper visualization of prosthetic leaflet motion so that both opening angle (OA) and closing angle (CA) can accurately be calculated. OA and CA were defined as the angle between discs in the fully open and closed positions, respectively. Reported values of OA and CA were obtained by averaging the values over 3 or 5 consecutive cardiac cycles, in the presence of sinus rhythm or atrial fibrillation, respectively. Normal reference values for OA and CA were obtained from the manufacturer and used to evaluate leaflet motion, specifically for each prosthesis size and type, and are listed in Table 1 together with the expected effective orifice area (5).

Echocardiographic and fluoroscopic examinations were performed and measurements obtained by different cardiologists blinded to each other's results.

PV function. A diagnosis of AVPO was drawn in the presence of the persistent or intermittent alteration of leaflet motion in OA and/or CA at FL examination, with values falling outside the 95% confidence interval obtained in a reference group of patients with a normally functioning valve of the same type and size (12,13).

Diagnosis of PPM was accomplished in the presence of high MPG (≥20 mm Hg), reduced EOAi (≤0.85 cm^2/m^2), and normal leaflet motion at FL examination.

Prostheses were classified as NL in absence of leaflet motion alterations at FL, and lack of simultaneous high MPG (>20 mm Hg) and EOAi ≤0.85 cm^2/m^2.

When feasible, diagnosis of AVPO was confirmed directly, by surgical inspection, or indirectly, by the positive effect of thrombolytic therapy.

Statistical analysis. Continuous data are summarized as mean ± SD or with median and quartiles, when

Table 1. Predicted Value of EOA

Valve	Size (mm)	Patients (n)	Area (cm^2)	Angles (OA, CA)
Carbomedics	19	10	1.0 ± 0.3	<24, >130
	21	19	1.5 ± 0.3	
	23	12	1.6 ± 0.3	
	25	3	2.0 ± 0.4	
	27	5	2.4 ± 0.4	
Edwards Duromedics	21	3	1.3 ± 0.2	<29, 148*
	23	2	1.6 ± 0.3	
Sorin Bicarbon	19	4	1.0 ± 0.3	<24, >135
	21	6	1.6 ± 0.3	
	23	4	1.9 ± 0.4	
St. Jude Medical Standard	19	12	1.0 ± 0.2	<13, >120
	21	11	1.3 ± 0.2	
	23	6	1.5 ± 0.3	
	25	2	1.8 ± 0.4	
	27	1	2.4 ± 0.6	

The predicted values of the effective orifice area (EOA) (± SD) are as reported by Rosenhek et al. (5), and the normal intervals for opening and closing angles assessed using cinefluoroscopy as reported by Montorsi et al. (12,13) for the different model and size of prosthetic valves used. *Value calculated from manufacturer's drawings.
CA = closing angle; OA = opening angle.

not normally distributed, whereas categorical variables are presented as absolute numbers or percentages. Analysis of variance for independent measurements or Kruskal-Wallis test were used to assess differences between the study subgroups for normally or not normally distributed variables, respectively. The association between categorical variables was examined using Fisher exact test.

Significant determinants of AVPO were evaluated by examining their associations with TTE-derived variables by univariate analysis. Receiver-operating characteristic (ROC) curve analysis was performed to assess the accuracy of the TTE-derived parameters in discriminating between normal and obstructed prostheses. Cutoff values maximizing the accuracy of the test were considered as optimal. For all tests, $p < 0.05$ was considered significant.

RESULTS

All patients underwent the complete study protocol. LVOT or prosthetic diameter estimation was inadequate in 17% of the cases, limiting the feasibility of EOAi and dA to 83%. Examinations performed before 2006 (31 cases) were not digitally stored, and therefore, AT and AT/ET parameters are missing in these patients.

As shown in Table 2, FL examination showed abnormal leaflet motion associated with AVPO in 26% of patients. On the basis of MPG and EOAi, patients with normal leaflet motion were classified as PPM (32%) or NL (42%). Of note, 3 AVPO patients had normal MPG in the presence of abnormally high prosthetic OA, compared with the reference value relevant to that particular prosthesis type and size.

The presence of thrombus or pannus was confirmed in 18 of 26 patients (69%), by surgical inspection or by effective thrombolysis. In detail, 10 patients (38%) were immediately referred to surgery, 8 (31%) underwent thrombolysis (in 2, thrombolysis was fully effective, whereas the other 6 were afterwards referred to surgery). In the remaining 8 patients (31%), a wait-and-see approach was adopted.

Clinical parameters. The main clinical characteristics of the study groups are listed in Table 3. Clinical parameters were not different between the groups, except that small prostheses (19 to 21 mm) were more frequent in PPM, New York Heart Association (NYHA) functional class >II was observed only in AVPO, and AVPO had a longer time from PV implantation.

Approximately one-third of the patients (28 patients) were in atrial fibrillation. In these patients, the basal heart rate at echocardiographic assessment was 72 ± 8 beats/min, not significantly ($p = 0.25$) different compared with the heart rate measured in patients in sinus rhythm (68 ± 12 beats/min).

Echocardiographic parameters. Compared with NL, PPM and AVPO showed higher MPG and reduced values for EOA, EOAi, and DVI (Table 4). Moreover, AVPO showed higher MPG and reduced DVI compared with PPM. Left ventricular ejection fraction was similar among the study groups. Moderate or severe intraprosthetic regurgitation was observed only in AVPO, whereas the frequency of paraprosthetic regurgitation was not different between subgroups.

AVPO exhibited AT and AT/ET values significantly higher than in NL and PPM. Of interest, AT and AT/ET were comparable between NL and PPM.

Table 2. Fluoroscopic Parameters for Each of the Study Subgroups

	NL (n = 42)	PPM (n = 32)	AVPO (n = 26)
Opening angle, °	17 ± 5	19 ± 5	54 ± 18*†
Closing angle, °	129 ± 9	131 ± 7	124 ± 13

Values are mean ± SD. *$p < 0.05$ versus NL, and †$p < 0.05$ versus PPM by analysis of variance for independent samples with post hoc comparison (Dunnett's T3 method).
AVPO = aortic valve prosthesis obstruction; NL = normal aortic prosthesis; PPM = prosthesis-patient mismatch.

JACC: CARDIOVASCULAR IMAGING, VOL. 6, NO. 2, 2013
FEBRUARY 2013:196–205

Table 3. **Clinical Characteristics of the Study Population**

	NL (n = 42)	PPM (n = 32)	AVPO (n = 26)	p Value*
Age, yrs	63 ± 11	65 ± 0	64 ± 9	0.693
Men	21 (50)	8 (25)	10 (38)	0.255
NYHA functional class				0.001
I	35 (83)	27 (84)	11 (42)	
II	7 (17)	5 (16)	11 (42)	
III	—	—	3 (12)	
IV	—	—	1 (4)	
Body surface area, m^2	1.77 ± 0.21	1.73 ± 0.16	1.71 ± 0.16	0.414
Rhythm				0.562
Sinus rhythm	32 (77)	22 (69)	16 (63)	
Atrial fibrillation	9 (20)	10 (31)	9 (33)	
Pacemaker	1 (3)	0 (0)	1 (4)	
Mitral prosthesis	15 (36)	12 (38)	11 (42)	0.891
Coronary artery disease	7 (17)	2 (6)	2 (8)	0.326
Prosthetic valve size, mm				<0.001
19–21	17 (40)	31 (97)	14 (54)	
23–27	25 (60)	1 (3)	12 (46)	
Time from implantation, months	72 (36–150)	66 (24–108)	138 (49–192)	0.041

Values are mean ± SD, n (%), or median (interquartile range). *p Values are by analysis of variance for independent samples, and Kruskal-Wallis test or Fisher Exact test when appropriate.
NYHA = New York Heart Association; other abbreviations as in Table 2.

The parameter dA was significantly higher in AVPO than in NL and PPM, as a consequence of obstruction, and slightly increased in PPM compared with NL, likely because of higher flow and velocity in PPM, exaggerating the pressure recovery phenomenon.

Parameters of prosthetic obstruction. Univariate analysis, comparing AVPO to normal functioning prostheses, including both NL and PPM, indicated that all the echocardiographic parameters listed in Table 4 were significantly related to prosthetic obstruction, except left ventricular ejection fraction ($p = 0.50$) and paraprosthetic regurgitation ($p = 0.57$).

ROC curve analysis and classification tree. ROC curve analysis revealed good-to-excellent area under the curve values for all the considered parameters in discriminating between AVPO and not-obstructed prostheses (Table 5). However, MPG, DVI, and EOAi showed only acceptable values of accuracy (≤75%). Conversely, dA and ejection parameters

Table 4. **Echocardiographic Parameters for Each of the Subgroups**

	NL (n = 42)	PPM (n = 32)	AVPO (n = 26)
Mean gradient, mm Hg	16 ± 6	36 ± 8*	43 ± 16*†
DVI	0.42 ± 0.09	0.30 ± 0.05*	0.25 ± 0.04*†
EOA, cm^2	1.79 ± 0.56	1.07 ± 0.14*	0.92 ± 0.26*
EOAi, cm^2/m^2	1.00 ± 0.19	0.62 ± 0.08*	0.55 ± 0.16*
dA, cm^2	−0.12 ± 0.43	0.15 ± 0.24*	0.59 ± 0.32*†
Ejection fraction, %	58 ± 11	64 ± 6	58 ± 13
AT, ms‡	74 ± 15	78 ± 13	108 ± 20*†
AT/ET‡	0.25 ± 0.05	0.26 ± 0.04	0.35 ± 0.05*†
Regurgitation			
Intraprosthetic, >1+	1 (2)	0 (0)	17 (65)
Paraprosthetic, >2+	3 (6)	1 (4)	0 (0)

Values are mean ± SD or n (%). *$p < 0.05$ versus NL, and †$p < 0.05$ versus PPM by analysis of variance for independent samples, and Kruskal-Wallis test or Fisher exact test when appropriate, with post hoc comparison (Tukey HSD or Dunnett's T3 methods). ‡For patients enrolled before 2006, AT and ET could not be calculated retrospectively for 8 of 42 NL patients, 11 of 32 PPM patients, and 12 of 26 AVPO patients.
AT = acceleration time; dA = difference between expected prosthetic orifice area, as reported by the manufacturer, and echocardiography-derived orifice area; DVI = Doppler velocity index; EOAi = effective orifice area normalized for body surface area; ET = ejection time; other abbreviations as in Tables 1 and 2.

Table 5. Results of the ROC Curve Analysis

	AUC	Optimal Cutoff	Accuracy (%)	Sensitivity (%)	Specificity (%)
MPG, mm Hg	0.849	28.0	75	83	74
DVI	0.916	0.29	75	92	84
EOAi, cm^2/m^2	0.876	0.65	67	83	66
dA, cm^2	0.925	0.37	87	92	86
AT, ms	0.936	94.5	94	92	94
AT/ET	0.933	0.31	89	83	90

Receiver-operating characteristic (ROC) curve analysis was performed to assess the accuracy of echocardiography-derived parameters in discriminating between normal and abnormal aortic prosthesis function.
AUC = area under the curve; MPG = mean transprosthetic pressure gradient; other abbreviations as in Tables 2 and 4.

showed area under the curve values >0.9, and were associated with good accuracy in recognizing prosthetic obstruction. In particular, AT was the best parameter, reaching an accuracy of 94% with an optimal cutoff value of 94.5 ms.

Figure 2 depicts the values of several echocardiographic parameters on an individual basis, using FL-derived OA as a reference for comparison (shaded area). The 3 AVPO patients falling in the shaded area have St. Jude Medical valves with a reference OA of 13° (Table 1), and therefore, the FL-derived OA is abnormal. This figure clearly shows a similar distribution of MPG, DVI, and EOAi in PPM and AVPO, with a substantial

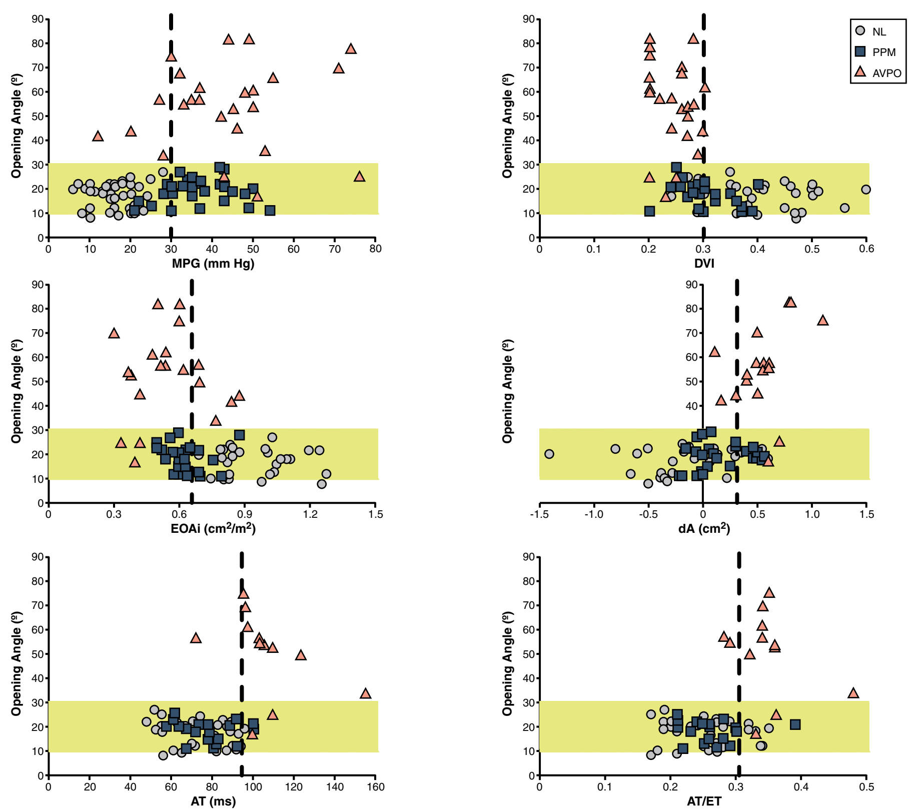

Figure 2. Echocardiographic Parameters Versus Prosthetic OA

Comparison between echocardiographic parameters and OA obtained via fluoroscopy. From **top to bottom, left to right**: transprosthetic mean pressure gradient (MPG), Doppler velocity index (DVI), effective orifice area indexed for body surface area (EOAi), difference between expected and echocardiography-derived orifice area (dA), AT, and AT/ET. Patients are subdivided into 3 groups: normal (NL), **circles;** prosthesis–patient mismatch (PPM), **squares;** prosthetic obstruction (AVPO), **triangles**. Shaded areas show the range of normal function for prosthetic OA. **Dotted lines** represent the cutoff value obtained for each parameter by receiver-operating characteristics analysis (Table 5). Abbreviations as in Figure 1.

overlapping of the TTE-derived measurement, hampering the capability of discriminating AVPO on the basis of these parameters. Conversely, dA and ejection parameters showed a different distribution when comparing AVPO to NL and PPM, which by contrast, were similar.

Classification tree is depicted in Figure 3, together with the optimal threshold values for MPG, AT, and AT/ET to obtain the best overall accuracy. This resulted in an algorithm for differential diagnosis of prosthetic obstruction with a percentage of correct classification of 86%. The percent of correct classification for NL (91%) and AVPO (93%) was optimal, and higher than for PPM (81%). In detail, NL subjects were misclassified as PPM (9%) in presence of MPG ≥24 mm Hg and AT <95 ms; PPM were erroneously classified as AVPO (10%) when high MPG was found in conjunction with AT longer than 95 ms. Interestingly, AVPO misclassification (7%) as PPM was found in the presence of high MPG associated with AT <95 ms and AT/ET <0.32. Of note, 1 of the AVPO patients with low MPG was in low-flow state (left ventricular ejection fraction equal to 22%).

DISCUSSION

The goal of this study was the exploration of the additional role of several TTE-derived parameters to discriminate between bileaflet aortic prostheses with normal function, PPM, and AVPO. Our findings corroborate and extend the findings of Ben Zekry et al. (14) to a population with less severe obstruction, underlining the importance of flow interval parameters, but also demonstrating the importance of fluoroscopy in suspected AVPO, providing further evidence for the recent guidelines (1).

Aortic valve prosthetic obstruction. CLINICAL PARAMETERS. Aortic prosthetic obstruction due to chronic pannus or thrombosis is not common, but potentially is one of the most serious complications of mechanical valve replacement (15,16). Aortic prosthetic obstruction is prevalently due to pannus, localized in proximity to the suture site (17,18). Pannus is known as a slow phenomenon, and its clinical significance can occur many years, or even decades, after aortic valve replacement. Hence, in our population, the AVPO group presented at a later date from implantation compared with the NL or PPM group. The prevalence of AVPO in our patients is higher

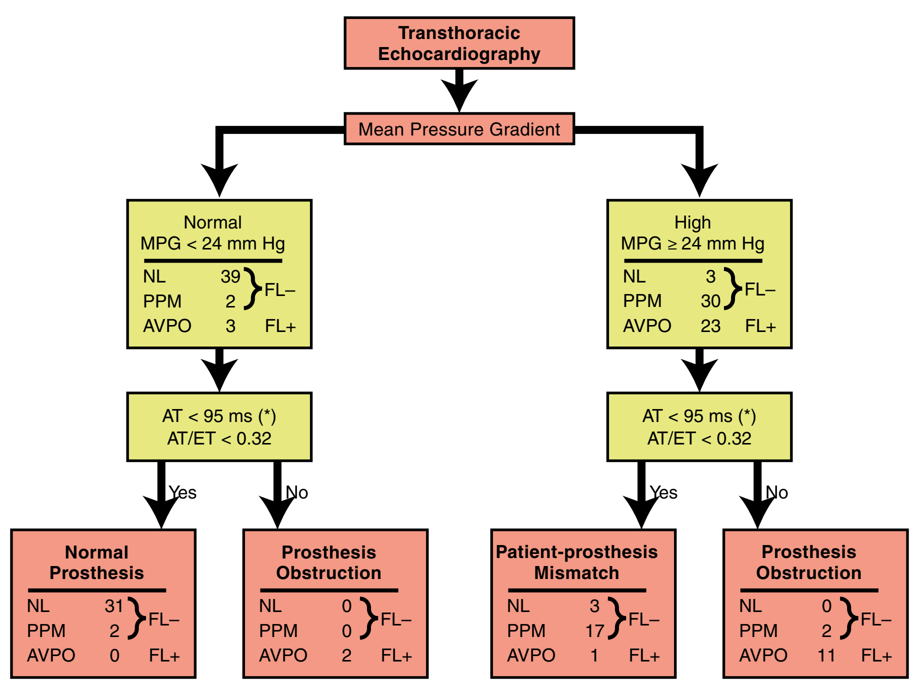

Figure 3. Echocardiographic Classification Tree

Classification tree based on echocardiography-derived mean transprosthetic pressure gradient (MPG), AT, and AT/ET. For each study subgroups, NL, PPM, and, the number of subjects (%) is listed for each branch and leaf. *For patients enrolled before 2006, AT and ET could not be calculated retrospectively for 9 of 44 and 22 of 56 patients on the left branch (normal MPG) and right branch (high MPG) , respectively. Abbreviations as in Figures 1 and 2.

than that observed in an unselected and consecutive population, because enrollment was on the basis of clinical suspicion of AVPO, or among those hospitalized with symptoms. Pannus is associated with variable degrees of obstruction, and patients may present only with mild symptoms for a long period, before a severe symptomatic condition becomes evident. It is worth noting that pannus and thrombus may coexist, and that pannus can lead to prosthetic thrombosis. In this case, prosthesis dysfunction can occur abruptly, severely altering the hemodynamic conditions. In fact, we observed a NYHA functional class >II in a minority of cases (15%) and only in the AVPO group.

ECHOCARDIOGRAPHIC PARAMETERS. Although MPG was a good predictor of prosthetic stenosis in this study, this parameter will tend to be insensitive in patients with depressed cardiac output, as clearly shown in Figure 2 (top left panel) and Figure 3, where patients having MPG <20 mm Hg had prosthetic obstruction. Moreover, the EOA estimated by the continuity equation, EOAi, and DVI are parameters relatively independent of flow, but they presented similar values in the AVPO and PPM groups, showing only acceptable accuracy at ROC curve analysis ≤75% (Table 5). This is because in the current study, the degree of PV dysfunction was not severe, leading to similar valve areas between the PPM and AVPO groups, despite different valve sizes.

In the assessment of abnormally high gradients, several algorithms have been previously proposed (1,19–21), mainly based on the comparison of EOA measured by Doppler TTE with the normal reference value of EOA for the type and size of the implanted PV. Our study confirms, using OA measured at FL as the reference for comparison, a correct distribution of AVPO using dA. On the other hand, dA is problematic when PV size and type are not known in the clinical setting, which is not an infrequent situation.

Rothbart et al. (11) proposed ET parameters, in particular AT, in evaluation of aortic bioprosthetic valve stenosis. More recently, Ben Zekry et al. (14), proposed the study of ejection dynamics, not only in aortic bioprostheses, but also for aortic mechanical prostheses. The present findings corroborate these changes in the time-velocity contour, delay in reaching the maximal velocity across the valve (prolonged AT), and increase of AT/ET in the AVPO group, with a behavior similar to aortic native stenosis (22). In particular, AT was the best parameter to distinguish AVPO from PPM, reaching an accuracy of 94%. Lastly, we found intraprosthetic regurgitation >1+ to be a predictor of AVPO. In particular, in 2 patients, intraprosthetic regurgitation was intermittently severe, and FL evaluation showed an intermittent pathological closing angle due to subvalvular pannus, as confirmed at surgical inspection (23).

The accuracy obtained by the simple classification tree, in which PPM patients were considered as a separate group, was significantly reduced to 80%. The results of the classification tree (Fig. 3) based on echocardiographic parameters clearly demonstrate the accuracy of echocardiographic parameters in the majority of cases, but also a remaining clinical challenge of evaluating prosthetic valve function; therefore, TTE evaluation should systematically include FL evaluation when valvular obstruction is in question and TTE results are equivocal. This is confirmed by the excellent agreement of FL-based diagnosis with surgical findings in the subset of 18 AVPO patients who underwent a redo operation or effective thrombolysis.

Prosthesis–patient mismatch. PPM occurs when the EOA of the implanted PV is too small in relation to the patient's body size, resulting in an abnormally high transprosthetic MPG, despite normal prosthesis function (6).

CLINICAL PARAMETERS. After mechanical implantation the incidence of mismatch may reach 60% (24). In our population, 32 of 58 patients (55%) with high transprosthetic gradients had EOAi ≤ 0.85 cm^2/m^2 (0.61 ± 0.07 cm^2/m^2), with no evidence of intermittent or persistent alteration in leaflet motion at FL, and therefore were classified as moderate-to-severe PPM.

The clinical impact of the PPM phenomenon after aortic valve replacement is still controversial. Several studies reported that severe PPM is associated with more cardiac events and lower survival (25,26). Recent studies reported a negative impact of PPM on long-term outcome in a subgroup of patients with impaired left ventricular function undergoing aortic valve replacement (27,28). In our study, none of the PPM patients belonged to NYHA functional class >II, and none presented with left ventricular dysfunction.

ECHOCARDIOGRAPHIC PARAMETERS. Doppler parameters such as MPG, EOA, and EOAi were not capable of discriminating between PPM and AVPO. Also, DVI showed values similar between PPM and AVPO, and different from those obtained in normally functioning prostheses. Only dA, when prosthetic model and size are known, and systolic time interval parameters, AT and AT/ET, were able to identify normal prosthesis function in

PPM patients, discriminating them from AVPO. This emphasizes the need to know the valve type and size when using parameters such as gradients and effective orifice areas.

ROC curve analysis results (Table 5) clearly show that AT, AT/ET, and dA have the best accuracy (range 87% to 94%) in identifying AVPO, being able to classify PPM as true negative, instead of false positive as occurs based on Doppler parameters. These 3 parameters should be considered and used in the routine assessment of prosthetic valves to allow a comprehensive evaluation of prosthetic function.

A potential explanation for the discriminating capability of the systolic time interval parameters is that in PPM, the prosthetic valve is normally functioning, and the disc opening is driven by transprosthetic pressure gradient only, leading to a Doppler envelope comparable in terms of shape to those obtainable in NL, with similar acceleration and ejection intervals, despite increased peak values. Conversely, AVPO is associated with the presence of pannus or thrombus that interferes with the normal discs opening, increasing their resistance and resulting in a more rounded, less triangular, and with a smoother slope Doppler envelope, characterized by a delayed peak velocity.

Due to the particular design of bileaflet mechanical valves, localized high velocities may occur within the central orifice of the valve. This phenomenon may yield to an overestimation of gradient, an underestimation of EOA, and therefore, to a wrong diagnosis of PPM in some patients. This artifactual PPM, related to central localized high gradient, does not cause any hemodynamic burden on the left ventricle, whereas true PPM is known to have a negative impact on symptomatic status and outcomes. Both true and artifactual PPM are characterized by negative FL, MPG $\geq$20 mm Hg and EOAi $\leq$0.85 cm^2/m^2, and systolic flow parameters similar to those obtained in NL. However, in the case of artifactual PPM associated with localized high gradient, the estimated EOA will significantly differ from the expected EOA, and thus the dA would be substantially larger than zero. By applying such criteria, 8 of 30 of the PPM patients in our study group would be considered as having artifactual PPM. These hypotheses are, however, purely speculative and cannot be proven by our findings.

Another potential misclassification could arise between NL and PPM in the presence of low output. Indeed, in this condition, it is very unlikely for high transprosthetic gradients to develop and therefore PPM diagnosis could only be drawn based on EOAi. Conversely, low EOAi in the absence of increased MPG may be artifactual in NL patients when the LVOT area estimate is suboptimal, hampering the reliability of the EOA obtained using the continuity equation. Therefore, care should be taken when analyzing each parameter as a part of a complex hemodynamic scenario.

Study limitations. This study, compared with others, evaluated detection of milder degrees of dysfunction. The Doppler parameters, therefore, may be a little different than previously reported for more severe obstruction. Due to the limited size of our study population, cutoff values were obtained and tested on the same population. Therefore, the accuracy of values reported may be overestimated. Furthermore, some missing data for AT and ET did not allow the investigation of the determinants of AVPO via multivariate analysis. Further studies with a larger number of subjects are needed to validate and confirm the obtained results, to refine the cutoff values obtained, and to make a more statistically sound classification tree. However, it is worth noting the similarity between the optimal threshold values obtained in our population for MPG (28 mm Hg) and AT (94.5 ms), and those generally accepted, 30 mm Hg and 100 ms, respectively (1).

Lastly, because a majority of the patients were referred to our institution with suspected AVPO on the basis of high MPG, our population is not representative of the universe of patients, and thus the incidence of PPM and AVPO is overestimated.

CONCLUSIONS

In the presence of elevated transprosthetic pressure gradient, TTE parameters play a key role in the evaluation of aortic prosthetic function. The use of traditional Doppler parameters allows good discrimination of NL, PPM, and AVPO, provided that valve size and type are known, otherwise the discrimination is suboptimal. Ejection time indices and dA add to the functional assessment of PV. Fluoroscopy is a rapid, inexpensive, and accurate technique to assess bileaflet prostheses function and should systematically be performed in suspected and equivocal prosthetic obstruction, playing a complementary and fundamental role in differentiating functional from pathological high gradient.

Reprint requests and correspondence: Dr. Manuela Muratori, Centro Cardiologico Monzino, IRCCS, Via Parea, 4, 20138 Milan, Italy. *E-mail: manuela.muratori@ccfm.it*.

REFERENCES

1. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J Am Soc Echocardiogr 2009;22:975–1014.
2. Mohr-Kahaly S, Kupferwasser I, Erbel R, et al. Value and limitations of transesophageal echocardiography in the evaluation of aortic prostheses. J Am Soc Echocardiogr 1993;6:12–20.
3. Muratori M, Montorsi P, Teruzzi G, et al. Feasibility and diagnostic accuracy of quantitative assessment of mechanical prostheses leaflet motion by transthoracic and transesophageal echocardiography in suspected prosthetic valve dysfunction. Am J Cardiol 2006;97:94–100.
4. Baumgartner H, Khan S, DeRobertis M, Czer L, Maurer G. Effect of prosthetic aortic valve design on the Doppler-catheter gradient correlation: an in vitro study of normal St. Jude, Medtronic-Hall, Starr-Edwards and Hancock valves. J Am Coll Cardiol 1992;19:324–32.
5. Rosenhek R, Binder T, Maurer G, Baumgartner H. Normal values for Doppler echocardiographic assessment of heart valve prostheses. J Am Soc Echocardiogr 2003;16:1116–27.
6. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. Circulation 1978;58:20–4.
7. Dumesnil JG, Yoganathan AP. Valve prosthesis hemodynamics and the problem of high transprosthetic pressure gradients. Eur J Cardiothorac Surg 1992;6:S34–8.
8. Baumgartner H, Schima H, Tulzer G, Kuhn P. Effect of stenosis geometry on the Doppler-catheter gradient relation in vitro: a manifestation of pressure recovery. J Am Coll Cardiol 1993;21:1018–25.
9. Ren JF, Chandrasckaran K, Mintz GS, Ross J, Pennock RS, Frankl WS. Effect of depressed left ventricular function on hemodynamics of normal St Jude medical prosthesis in the aortic valve position. Am J Cardiol 1990;65:1004–9.
10. Chafizadeh ER, Zoghbi WA. Doppler echocardiography assessment of the St Jude medical prosthetic valve in the aortic position using the continuity equation. Circulation 1991;83:213–23.
11. Rothbart RM, Castriz JL, Harding LV, Russo CD, Teague SM. 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.
12. Montorsi P, De Bernardi F, Muratori M, Cavoretto D, Pepi M. Role of cine-fluoroscopy, trans-thoracic and trans-esophageal echocardiography in patients with suspected prosthetic heart valve thrombosis. Am J Cardiol 2000;85:58–64.
13. Montorsi P, Cavoretto D, Repossini A, Bartorelli AL, Guazzi MD. Valve design characteristics and cinefluoroscopic appearance of five currently available bileaflet prosthetic heart valves. Am J Card Imag 1996;19:29–41.
14. Ben Zekry S, Saad RM, Özkan M, et al. Flow acceleration time and ratio of acceleration time to ejection time: novel diagnostic parameters for prosthetic aortic valve function. J Am Coll Cardiol Img 2011;4:1161–70.
15. Horstkotte D, Burckhardt D. Prosthetic valve thrombosis. J Heart Val Dis 1995;4:141–53.
16. Deviri E, Sareli P, Wisenbaugh T. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. J Am Coll Cardiol 1991;17:646–50.
17. Rizzoli G, Guglielmi C, Toscano G, et al. Reoperations for acute prosthetic thrombosis and pannus: an assessment of rates, relationship and risk. Eur J Cardiothorac Surg 1999;16:74–80.
18. Barbetseas J, Nagueh SF, Pitsavos C, Toutouzas PK, Quinones MA, Zoghbi WA. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and trans-esophageal echocardiographic parameters. J Am Coll Cardiol 1998;32:1410–7.
19. Bach D. Echo-Doppler evaluation of hemodynamics after aortic valve replacement. Principles of interrogation and evaluation of high gradients. J Am Coll Cardiol Img 2010;3:296–304.
20. Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact and prevention. Heart 2006;92:1022–9.
21. Dumesnil JG, Pibarot P. Prosthesis-patient mismatch: an update. Curr Cardiol Rep. 2011;13:250–7.
22. Chambers J. Aortic stenosis. Eur J Echocardiogr 2009;10:i11–9.
23. Galli CA, Muratori M, Montorsi P, Barili F, Polvani G, Pepi M. Cyclic intermittent aortic regurgitation of a mechanical bileaflet aortic valve prosthesis: diagnosis and clinical implications. J Am Soc Echocardiogr 2007;20:1315.e5–8.
24. Kohsaka S, Mohan S, Virani S. Prosthesis-patient mismatch affects long-term survival after mechanical valve replacement. J Thorac Cardiovasc Surg 2008;135:1076–80.
25. Blais C, Dumesnil JG, Baillot R, Simard S, Doyle D, Pibarot P. Impact of valve prosthesis-patient mismatch on short-term mortality after aortic valve replacement. Circulation 2003;108:983–8.
26. Tasca G, Mhagna Z, Perotti S, et al. Impact of prosthesis-patient mismatch on cardiac events and midterm mortality after aortic valve replacement in patients with pure aortic stenosis. Circulation 2006;113:570–6.
27. Mascherbauer J, Rosenhek R, Fuchs C, et al. Moderate patient-prosthesis mismatch after valve replacement for severe aortic stenosis has no impact on short-term and long-term mortality. Heart 2008;94:1639–45.
28. Monin JL, Monchi M, Kirsch ME, et al. Low-gradient aortic stenosis: impact of prosthesis-patient mismatch on survival. Eur Heart J. 2007;28:2620–6.

Key Words: cinefluoroscopy ■ Doppler echocardiography ■ echocardiography ■ high aortic transprosthetic gradient ■ prosthetic valves.