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Cardiac Ultrasound

Flow-Dependent Changes in Doppler-Derived Aortic Valve Effective Orifice Area Are Real and Not Due to Artifact

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OBJECTIVES We sought to determine whether the flow-dependent changes in Doppler-derived valve effective orifice area (EOA) are real or due to artifact.

BACKGROUND It has frequently been reported that the EOA may vary with transvalvular flow in patients with aortic stenosis. However, the explanation of the flow dependence of EOA remains controversial and some studies have suggested that the EOA estimated by Doppler-echocardiography (EOA_{Dop}) may underestimate the actual EOA at low flow rates.

METHODS One bioprosthetic valve and three rigid orifices were tested in a mock flow circulation model over a wide range of flow rates. The EOA_{Dop} was compared with reference values obtained using particle image velocimetry (EOA_{PIV}).

RESULTS There was excellent agreement between EOA_{Dop} and EOA_{PIV} ($r^2 = 0.94$). For rigid orifices of 0.5 and 1.0 cm^2, no significant change in the EOA was observed with increasing flow rate. However, substantial increases of both EOA_{Dop} and EOA_{PIV} were observed when stroke volume increased from 20 to 70 ml both in the 1.5 cm^2 rigid orifice (+52% for EOA_{Dop} and +54% for EOA_{PIV}) and the bioprosthetic valve (+62% for EOA_{Dop} and +63% for EOA_{PIV}); such changes are explained either by the presence of unsteady effects at low flow rates and/or by an increase in valve leaflet opening.

CONCLUSIONS The flow-dependent changes in EOA_{Dop} are not artifacts but represent real changes in EOA attributable either to unsteady effects at low flow rates and/or to changes in valve leaflet opening. Such changes in EOA_{Dop} can be relied on for clinical judgment making. (J Am Coll Cardiol 2006;47:131–7) © 2006 by the American College of Cardiology Foundation

Although patients with severe aortic stenosis (AS) and severely reduced left ventricular (LV) ejection fraction represent approximately 5% of AS patients, they also represent the most challenging subset. In the setting of a low ejection fraction, the force applied against the valve leaflets

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may indeed not be high enough to completely open the aortic valve, and the valve effective orifice area (EOA) measured by Doppler-echocardiography or cardiac catheterization may therefore overestimate the AS severity. It is thus difficult to separate patients with true anatomically severe AS and concomitant LV systolic dysfunction from those with pseudo-severe AS, i.e., reduced valve opening caused by poor LV function in the setting of incidental mild to moderate valve obstruction (1,2).

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The evaluation of the changes in valve EOA during a gradual infusion of a low dose of dobutamine may be helpful in differentiating truly severe from pseudo-severe AS (1,3–5). However, previous studies have suggested that the EOA estimated by Doppler echocardiography with the use of the continuity equation may underestimate the actual EOA at low flow rates and that a change in the velocity profile within the vena contracta may be the cause for this underestimation (6–8). It is therefore uncertain whether the flow dependence of the Doppler-derived EOA that is often reported in patients with AS undergoing dobutamine stress echocardiography is attributable to an actual change in the anatomic orifice area and/or to artifacts related to limitations inherent to the continuity equation in the context of low flow rates.

The objectives of this study were thus to determine whether Doppler-derived EOAs are accurate estimates of the actual EOA as well as to examine the conditions by which flow-dependent changes in EOA may actually occur.

METHODS

Experimental model. One bioprosthetic valve and three rigid stenotic orifices were tested in a mock flow circulation model under a wide spectrum of flow rates ranging from the very low output state as observed in patients with severe LV

Abbreviations and Acronyms

AS	= aortic stenosis
EOA	= effective orifice area
EOA_{Dop}	= EOA estimated by Doppler-echocardiography
EOA_{PIV}	= EOA estimated by particle image velocimetry
GOA	= geometrical orifice area
LV	= left ventricular
Q_{mean}	= mean flow rate during the systolic phase
Q_{max}	= peak flow rate during the systolic phase
St	= Strouhal number
SV	= stroke volume
T	= left ventricular ejection time
V	= velocity vector

dysfunction to normal resting outputs. The model used for this study has been described in detail in our previous publications (9,10). Briefly, it is an anatomically shaped silicone-made model of the left heart cavities and aorta. The ventricle is activated by a pump driven by a computer. The circulatory fluid is a mixture of water (60%) and glycerol (40%) (viscosity, 4 centipoise).

Doppler echocardiographic measurements. Doppler echocardiographic measurements were performed using an ATL Ultramark 9 with a probe of 2.25 MHz. The probe was applied at the surface of the aorta and oriented to obtain optimal alignment of Doppler beam and flow across the stenosis. The transvalvular flow velocity was measured by continuous-wave Doppler. The measurement of transvalvular Doppler velocity was performed over five to seven cycles and averaged. Transvalvular flow rate was measured with an ultrasonic flowmeter (Transonic probe 28A31; accuracy 1%) at the level of the ascending aorta. Valve EOA was determined by the standard continuity equation using the stroke volume measured by ultrasound flowmeter and the velocity-time integral by Doppler. The mock flow model does not allow measurement of pre-valvular velocities by pulsed-wave Doppler. The reproducibility of the Doppler measurement of EOA in this in vitro setting is excellent (mean difference between two consecutive measurements, ±3%).

Particle image velocimetry measurements. Particle image velocimetry is an optical method of measuring the flow velocity field within a region of interest. A double-pulsed mini–yttrium-aluminum-garnet laser (120 mJ, 15 Hz) (TSI Inc., Shoreview, Minnesota) was used to illuminate longitudinal cross sections of the jet distal to the valve. The circulatory fluid was seeded with Amberlite particles. A 30-Hz coupled charge device camera (PIVCAM30, TSI Inc.) was used to capture two consecutive images of the flow. The images were subdivided into small regions of interrogation. A cross correlation between these two consecutive laser images was performed, and the average displacement of the particles within each region of interrogation was measured. Knowing the time between the two images, the velocity field was then computed (11,12) (Fig. 1).

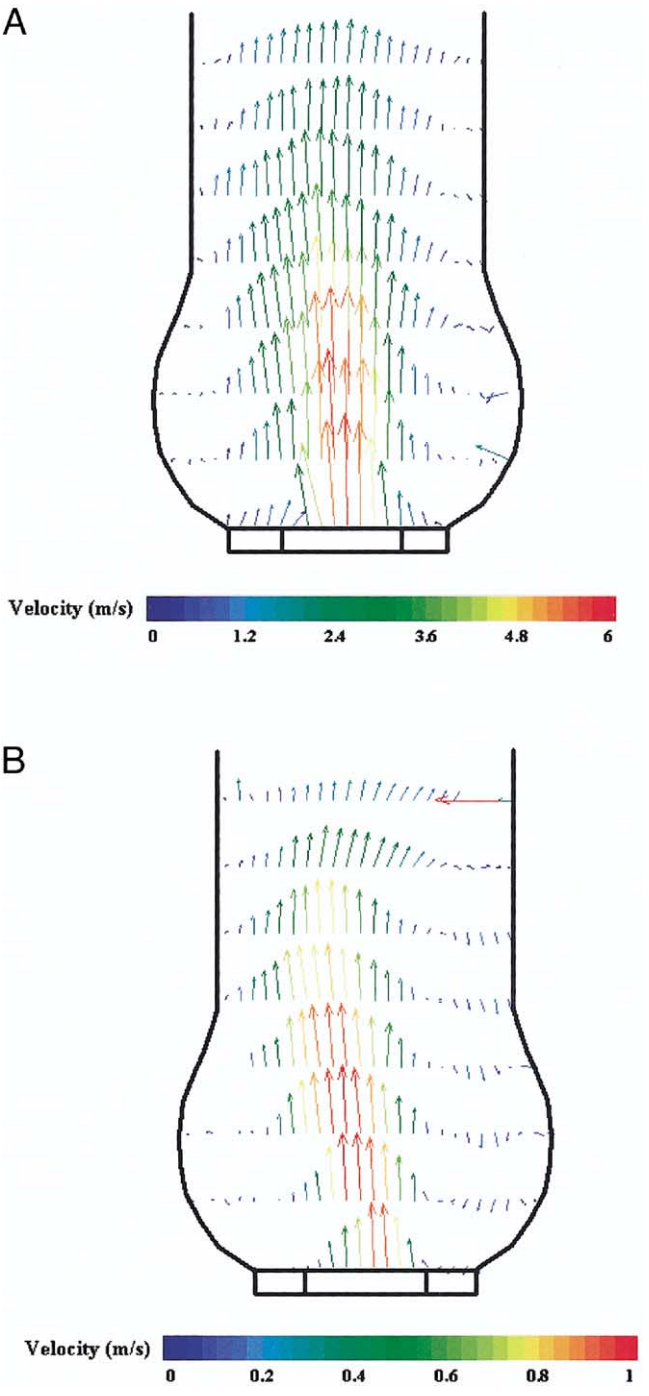

Figure 1. Velocity field contours measured by particle image velocimetry downstream from the 1.5-cm^2 rigid circular orifice at peak systole for a stroke volume of 20 ml **(A)** and 70 ml **(B)**.

The PIV measurements were performed at 13 time points during systole to allow for measurement of mean EOA. The time between two successive time points was 25 ms. As the nature of flow was highly pulsatile during systole, important temporal velocity gradients may exist. Hence, to obtain high-quality velocity profiles at the level of the vena contracta, it was necessary to adjust the time shift (Δt) between the two laser pulses depending on the temporal position of the PIV measurement in the systolic phase. For this

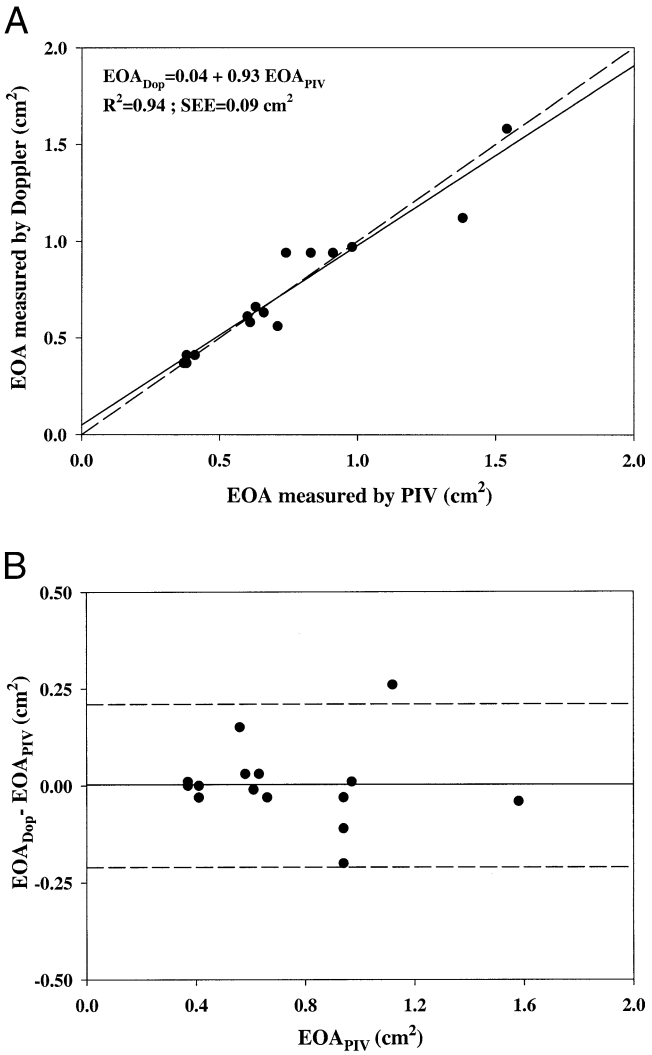

Figure 2. Comparison between the effective orifice area (EOA) measured by Doppler (EOA_{Dop}) and the EOA measured by particle image velocimetry (EOA_{PIV}). **(A)** Correlation between EOA_{Dop} and EOA_{PIV}. The **solid line** is the regression line, and the **dashed line** is the identity line. **(B)** Bland-Altman plots of the difference between EOA_{Dop} and EOA_{PIV} as a function of EOA_{PIV}. SEE = standard error of estimate.

purpose, the continuous-wave Doppler signal was analyzed first to determine the instantaneous velocity at each of the 13 PIV measurement times during systole (Fig. 2). The (Δt) was then estimated with respect to the one-quarter rule (11,13) and applied to the PIV system.

Determination of the effective orifice area using the acoustical source term. In a recent article (14), we proposed an original and accurate technique for determining the EOA from PIV measurements. This technique was based on the acoustical source term computed from the velocity field and was found to be superior to other conventional methods for the determination of the diameter of vena contracta and thus of the EOA.

Briefly, the flow disturbance and separation downstream from an aortic stenosis produce vortices within the flow, and in turn, these vortices generate a sound that is caused by the flow vorticity (15). This concept of sound generated by flow (i.e., hydro-acoustics) is mainly based on the vortex sound theory developed first by Lighthill (1952) (16) and then by Powell (1963) (17) and Howe (2002) (18). In this theory (Appendix) (19), the term $(\nabla \cdot \vec{\omega} \wedge \vec{V})$, where ∇ is the nabla operator, ω is the vorticity field, and V is the velocity field, is called the acoustical source term and is responsible of the sound generated by unsteady fluid motion. This method provides an accurate and simple way of separating the jet-like zone from the recirculation zone at the level of the vena contracta (14).

From the PIV measurements of the velocity field obtained in the ascending aorta, the acoustical source term field was computed and plotted at the level of the vena contracta. The position of the vena contracta was defined as the section where the velocity was maximal within the velocity field. Finally, the vena contracta diameter was measured, at each time point, as the distance between the two negative peaks of the acoustical term source, and the EOA was calculated assuming that the vena contracta has a circular shape. The mean EOA was calculated by averaging the instantaneous EOAs measured at each of the 13 time points during the systole, and it was then compared with the EOA estimated by Doppler. The inter-experiment variability of the EOA measurement by PIV is ±4% in this in vitro experimental setting.

Experimental conditions. Three rigid sharp-edged circular orifices with geometric orifice areas (GOAs) of 0.5, 1.0, and 1.5 cm^2 (thickness: 5 mm) and one Medtronic Mosaic bioprosthesis (size 25 mm) were tested under four stroke volumes (20, 30, 50, and 70 ml), with heart rate (70 beats/min) and left ventricular ejection time (300 ms) held constant. This corresponded to an increase in mean transvalvular flow rate (stroke volume/ejection time) from 67 ml/s up to 233 ml/s.

Statistical analysis. The agreement between the EOA measured by Doppler (EOA_{Dop}) and that measured by PIV (EOA_{PIV}) was assessed by the Pearson correlation coefficient and the Bland-Altman method.

RESULTS

Overall, there was excellent correlation (r^2 = 0.94) and agreement between EOA_{Dop} and EOA_{PIV} (Fig. 2). The mean absolute and relative differences between the two methods were 0.003 ± 0.103 cm^2 and 7.6 ± 8.5%, respectively.

Figure 3 shows the effect of changes in stroke volume on EOA_{Dop} and EOA_{PIV} for the different orifices and valve tested in this study. In the case of the bioprosthetic valve (Fig. 3A), both EOA_{Dop} and EOA_{PIV} increased significantly (EOA_{Dop}, +0.59 cm^2 [+62%]; EOA_{PIV}, +0.61 cm^2 [+63%]) when stroke volume was increased from 20 to 70 ml. For this valve, it was impossible to measure the EOA_{PIV} at a stroke volume of 20 ml because of the sedimentation of many Amberlite particles in the circulatory model. This phenomenon was attributable to the low flow conditions and resulted in a weak signal-to-noise ratio on PIV images.

In rigid orifices with a GOA of 0.5 cm^2 and 1.0 cm^2, there was no significant change in EOA_{Dop} (0.5 cm^2, −0.04

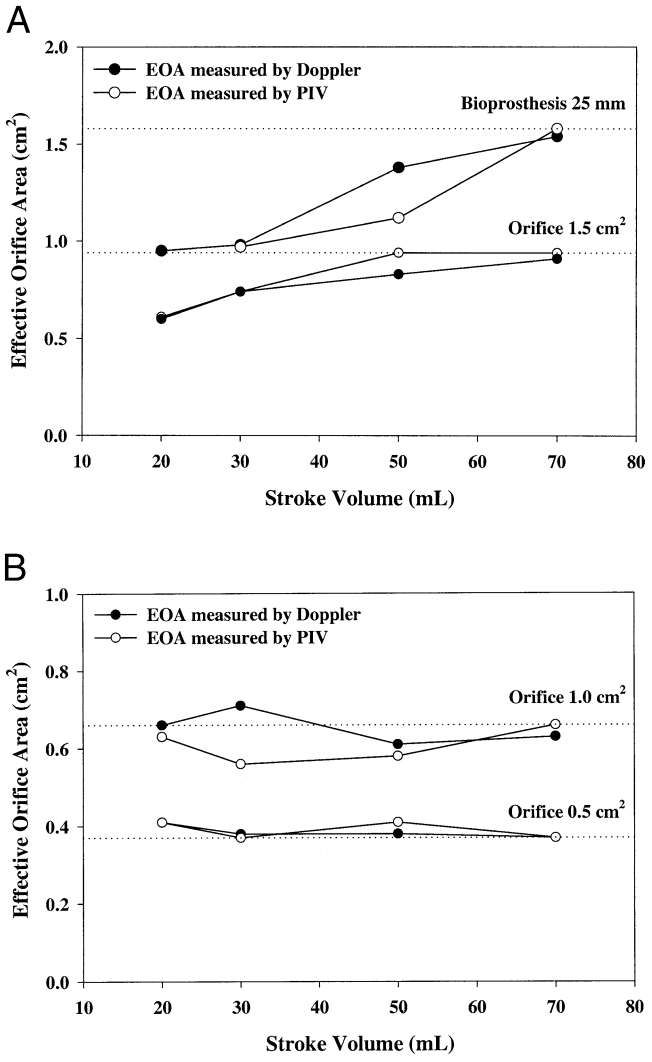

Figure 3. Effect of the variation in stroke volume on the effective orifice area (EOA) measured by Doppler and the EOA measured by particle image velocimetry (PIV) for the bioprosthetic valve **(A)** and the 1.5-cm^2 **(A)**, 1.0-cm^2 **(B)**, and 0.5-cm^2 **(B)** rigid circular orifices.

cm^2 [−10%]; 1.0 cm^2, −0.03 cm^2 [−5%]) and EOA_{PIV} (0.5 cm^2, −0.04 cm^2 [−10%]; 1.0 cm^2, +0.03 cm^2 [+5%]), when stroke volume was increased from 20 to 70 ml (Fig. 3B). In contrast, the EOA measured by both methods increased significantly with flow in the rigid orifice with a geometric area of 1.5 cm^2 (EOA_{Dop}, +0.31 cm^2 [+52%]; EOA_{PIV}, +0.33 cm^2 [+54%]) (Fig. 3A).

We hypothesized that the flow-related changes in EOA, when they occur, might be attributable at least in part to the predominance of unsteady effects at low flow rates. The Strouhal number (St) reflects the ratio of unsteady effects to inertial effects and can be computed as proposed by Clark et al. (20):

$$St = 2.87 \frac{Q_{max}}{Q_{mean}} \frac{GOA^{3/2}}{SV} \quad [1]$$

where Q_{max}, Q_{mean}, GOA, and SV are the peak flow during the systolic phase, the mean flow rate during the systolic phase, the geometric area of the orifice, and the stroke volume, respectively. It can be seen that the Strouhal number increases significantly from 0.13 (SV = 70 ml; Q_{mean} = 233 ml/s) to 0.54 (SV = 20 ml; Q_{mean} = 67 ml/s). Hence, at normal flow states (SV = 70 ml), the flow can be considered as quasi-steady because the Strouhal number is small, and at such a level of Strouhal number the unsteady effects are negligible (19). However, at low flow rates, the unsteady effects become more preponderant. As illustrated in equation 2, it is possible to predict the contribution of the unsteady effects to the variation in EOA with flow rate:

$$\frac{EOA_N}{EOA_L} = \left(\frac{St_L}{St_N}\right)^n \quad [2]$$

where N and L refer to normal and low flow rates, respectively.

When LV ejection time is constant, which is the case in the present study, this equation can be simplified (Appendix) under the form:

$$\frac{EOA_N}{EOA_L} = \left(\frac{SV_N}{SV_L}\right)^n \quad [3]$$

Hence, knowing the EOA at normal flow, it is possible to predict the EOA at low flow using this equation:

$$EOA_L = EOA_N\left(\frac{SV_L}{SV_N}\right)^n \quad [4]$$

When using a coefficient of n = 1/3.5, it was possible to accurately predict the actual changes in EOA that we observed in our 1.5-cm^2 rigid circular orifice (Fig. 4A).

To further and independently validate this semi-empirical formula, we used the in vitro data obtained by Voelker et al. (21). In this study, the investigators examined the effects of a change in transvalvular flow rate on EOA measured by catheterization in rigid circular orifices of different sizes. The results showed that the flow-dependent change in EOA increases with GOA: +6%, +13%, +20%, and +24% for 0.5-, 1.0-, 1.5-, and 2.0-cm^2 orifices, respectively. Interestingly, these flow-related changes in EOA can be predicted using equation 4 with the same coefficient n = 1/3.5 as used in the present study (Fig. 4B).

However, when equation 4 is applied to the data obtained with the bioprosthetic valve (Fig. 4A), the predicted EOA at low flow substantially overestimates the measured EOA (particularly for stroke volumes of 20 ml and 30 ml). This finding suggests that in flexible orifices, only a part of the flow dependence of EOA may be explained by the unsteady effects, and the remaining part is likely attributable to an increase in valve leaflet opening occurring with increasing flow rate.

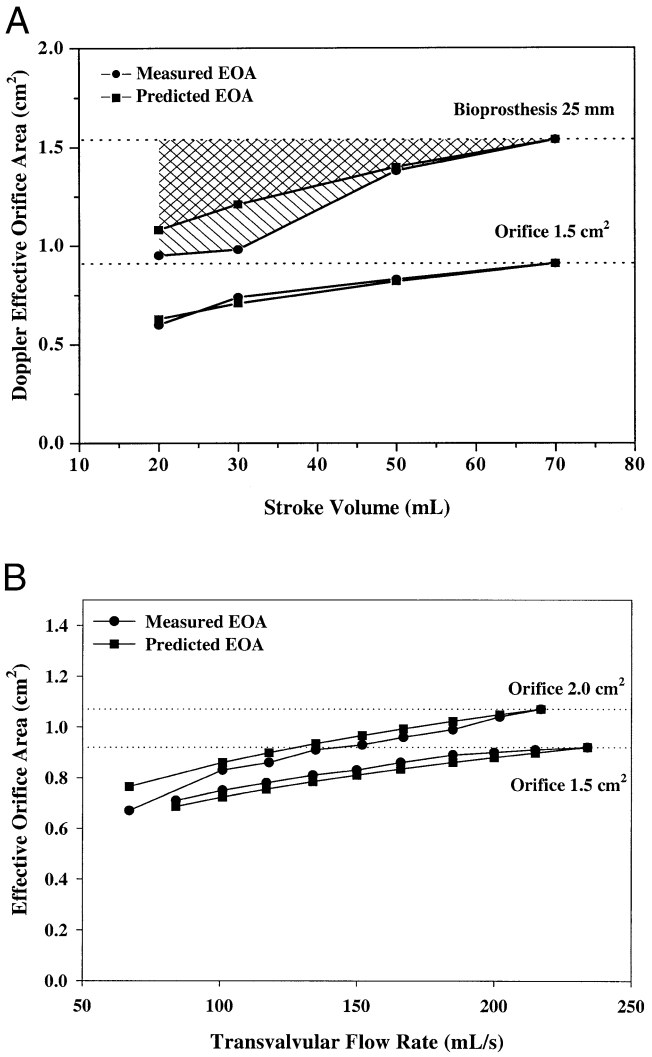

Figure 4. Comparison of the effective orifice area (EOA) measured by Doppler (or by catheter for the data of Voelker et al. [21]) **(circles)** and the EOA predicted from equation 4 **(squares)** for the 1.5-cm^2 rigid circular orifice and the bioprosthetic valve tested in the present study **(A)**, and for rigid circular orifices of 1.5 cm^2 and 2.0 cm^2 tested in vitro by Voelker et al. (21) (only transvalvular flow rate was provided in their study) **(B)**. The **horizontal doted line** indicates the value of the EOA at the normal flow rate. The area in **sparse hatchings** represents the part of the change in EOA that is likely attributable to the unsteady effects, and the area in **right hatchings** likely represents the part that is attributable to the change in the geometric orifice area.

DISCUSSION

The EOA is the minimal cross-sectional area of the transvalvular flow jet (i.e., the cross-sectional area of the vena contracta) downstream of a native or prosthetic valve. The EOA is the standard parameter for the assessment of the severity of aortic valve stenosis, and it was initially believed to be a flow-independent parameter. However, many studies have subsequently reported that EOA determined by Doppler or by catheterization may vary with increasing flow rate in patients with aortic stenosis (22–35). Several in vitro studies have also reported that EOA may increase with flow rate in both rigid and flexible (i.e., bioprosthetic valves) orifices (7,21,29,36,37). In native or bioprosthetic valves, the flow dependence of EOA may be explained by the incomplete opening of the valve leaflets at low flow rates. However, this phenomenon cannot occur in rigid orifices, and the mechanism responsible for the flow-dependence of EOA in such situations thus remains unknown.

Some investigators (6,7) have suggested that the flow dependence of EOA in the case of the rigid orifices might possibly be caused by viscous effects causing lower velocities near the edges of the vena contracta at low flow rates, resulting in a more parabolic or semi-parabolic flow profile. However, these studies were performed under steady flow conditions and non-physiological geometries. Moreover, the peak Reynolds number, which reflects the ratio of inertial to viscous forces, remains relatively high even at low flow states. For example, in the 1.5-cm^2 orifice tested in the present study, the peak Reynolds number was 1,832 at the minimal stroke volume of 20 ml (mean flow rate, 67 ml/s), and in the clinical situation it is extremely rare to see patients with a flow rate lower than 60 to 70 ml/s. At such a Reynolds number, the viscous forces are small compared with the inertial forces, and they can thus hardly explain the magnitude of the variation of EOA observed in this study as well as in previous studies (7,21) in the rigid orifices.

Our hypothesis in this study was that the flow-related changes in EOA observed in rigid orifices are likely attributable to the predominance of unsteady effects at low flow rates, and it is corroborated by our results as well as those previously published by Voelker et al. (21) (Fig. 4). Indeed, the correlation between the EOAs predicted by equation 4 and the measured EOAs in the rigid orifices is $EOA_{Predicted} = 0.01 + 0.99 \times EOA_{Measured}$; $r^2 = 0.91$; standard error of estimate (SEE) = 0.04 cm^2. The concept inherent to these results is best illustrated in Figure 1, whereby at normal flow (Fig. 1A), the kinetic energy (proportional to the velocity squared) of the fluid crossing the orifice is sufficient to break down the vortex structures that are generated downstream from the stenosis and thus enable the formation of a large and well-established flow jet, whereas at low flow rates (Fig. 1B), the reduction in kinetic energy predisposes to the formation of vortices, which tend to squeeze the flow jet and thus the vena contracta, resulting in a smaller EOA. It should be emphasized that this phenomenon is much less pronounced in orifices of smaller size, likely because in these conditions the kinetic energy is still high enough to break down the vortex structures and thus to maintain a relatively constant jet size.

One of the main limitations of previous studies that examined the hemodynamic performance of prosthetic valves or simulated native aortic valves is that the PIV measurements of EOAs were performed either under steady flow conditions or at only one time point during the ejection (generally at peak ejection) when pulsatile flow conditions were used (6,7,38,39). To this effect, it has been well demonstrated that the EOA may vary significantly with

flow rate during ventricular ejection in patients with aortic stenosis (40–42). Therefore, the EOA obtained at peak systole is not necessarily equal to the mean EOA, and the comparison of EOA_{Dop} (mean EOA) with EOA_{PIV} (instantaneous EOA at peak systole) is not necessarily relevant. One of the major strengths of this study was that the experiments were performed in pulsatile flow conditions. Moreover, the EOA was measured at several time points during systole using PIV, which is considered the gold standard method for measuring the velocity field in experimental fluid mechanics (11,39,43,44) and the ideal reference method for in vitro measurement of valve EOA (7,38,39). Therefore, we were able to "compare apples with apples," i.e., the mean EOA by PIV during pulsatile flow conditions with the mean EOA by Doppler during the same pulsatile flow conditions.

Clinical implications. The major implication of this study is that changes in valve area calculated with the Doppler continuity equation are not artifacts but represent real changes in EOA. Given the results in the rigid orifices, the results also confirm that for a given GOA, the EOA may vary considerably (more than 50%) with flow, and that the GOA measured by transthoracic or transesophageal echocardiography therefore has limited value to predict the hemodynamic burden caused by a stenotic valve orifice. Moreover, GOA measurements are usually performed at peak systole, whereas it is well known that both GOA and EOA may vary quite considerably during the cardiac cycle (40,42). For these reasons, the average EOA by Doppler would definitely seem to be preferable to the instantaneous GOA for characterizing the hemodynamic burden imposed by stenosis on the ventricle.

As outlined, our results also suggest that there are two main mechanisms responsible for the EOA increase observed during dobutamine infusion: 1) an increase in leaflet opening and thus in GOA with increasing flow rate, and 2) the predominance of unsteady effects at low flow rates. Therefore, it becomes evident that the observation of an EOA augmentation during dobutamine perfusion should not necessarily be equated with a flexible valve, because it could also be caused by a change in the ratio between the unsteady effects and the inertial forces such as might occur at low flow states. This observation may explain some of the discrepancies reported in previous studies (45,46) in which the EOA measured by Doppler or catheterization was found to increase during dobutamine stimulation, whereas the GOA measured by transesophageal echocardiography remained unchanged. Hence, a rigid valve might nonetheless show an increase in EOA during dobutamine and be mistakenly interpreted as being a flexible valve.

Also noteworthy is the fact that for the 1.5- and 2.0-cm^2 (GOA) orifices tested in this study or in the study of Voelker al. (21), the EOAs were <1.0 cm^2 at low flow rates and would have thus been considered an indicator of severe stenosis on the basis of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, whereas at normal flow rates, the EOAs were close to 1.0 cm^2 or higher and would have then been classified as moderate AS.

Further studies will evidently be necessary to resolve many of these issues, but they can at least be undertaken with the knowledge that the Doppler EOA is a valid hemodynamic measurement, whereas the GOA has many inherent limitations, particularly during low flow states. In this context, it would also seem appropriate to attempt to normalize cardiac output with dobutamine before interpreting results for EOA. Indeed, the ACC/AHA guidelines were established based on observations in patients with normal flow rates, and given the present results, EOA values obtained in the context of a low cardiac output should undoubtedly be interpreted with caution.

Study limitations. The GOA could not be measured in the case of the bioprosthetic valve. Therefore, it was not possible to confirm the exact proportion of the flow-induced augmentation of EOA that was actually related to an increase in valve leaflet opening.

To calculate the EOA by PIV, we assumed that the cross section of the vena contracta had a circular shape. This assumption is valid for circular orifices as well as bioprosthetic valves (47), but may not be applied in rigid orifices with a more complex shape. Additional studies will therefore be necessary to examine the behavior of EOA in such orifices and in particular to determine whether equation 4 and the value of the coefficient n included in this equation can be generalized to other types and sizes of valvular orifices. The measurement of EOA in such circumstances would require the use of a tri-dimensional PIV system.

CONCLUSIONS

Using the PIV method as a reference, the present study shows that Doppler-derived EOAs provide accurate estimates of actual EOAs over a wide range of valve size, function, and flow rates. In particular, the changes in EOA observed with increasing flow during dobutamine perfusion seem to be real and not caused by artifact, and can thus be relied on for making clinical judgments.

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APPENDIX

For the introduction to vortex sound theory and a general theoretical form for the equation of prediction of the EOA at low flow, please see the online version of this article.