Three-Dimensional Echocardiography-Derived Vena Contracta Area at Rest and Its Increase During Exercise Predicts Clinical Outcome in Mild-Moderate Functional Mitral Regurgitation

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**Background:** This study assessed the independent significance of color Doppler 3-D vena contracta area (VCA) at rest and during exercise as a predictor of clinical outcome in mild-moderate functional mitral regurgitation (FMR).

**Methods and Results:** The subjects consisted of 62 patients (age, 68±11 years; 76% male) with chronic systolic heart failure and mild-moderate FMR (<2+/4) at rest. All patients underwent VCA assessment at rest and during semi-supine bicycle exercise. During median follow-up of 17 months (IQR, 13–20 months), 15 patients (24%) had composite endpoint of all-cause death (n=3), heart failure admission (n=11), and heart transplantation (n=1). At baseline, patients with vs. without endpoint had significantly larger VCA at rest (17±6 mm² vs. 13±7 mm², P=0.002) and at peak exercise (35±16 mm² vs. 21±12 mm², P<0.001). On Cox regression analysis, large (≥15-mm²) resting VCA (HR, 7.6; 95% CI: 1.93–13.02; P=0.004) and large (≥20-mm²) exercise-induced increase of VCA (HR, 5.1; 95% CI: 1.39–15.21; P=0.014) were independently associated with composite endpoint. Concomitant presence of large VCA at rest and its large increase during exercise occurred in 53% of patients with, vs. in only 8% without, endpoint (negative predictive value, 86%).

**Conclusions:** The presence of relatively large VCA at rest and its significant increase during exercise is independently associated with adverse clinical outcome in patients with mild-moderate FMR at rest. (Circ J 2014; 78: 2741–2749)

**Key Words:** Echocardiography; Exercise; Heart failure; Mitral regurgitation; Prognosis

Severe functional mitral regurgitation (FMR) at rest and/or its significant increase during exercise have been shown to be associated with reduced functional capacity and impaired prognosis. In these studies, FMR has been assessed using 2-dimensional (D) quantitative techniques: proximal isovelocity surface (PISA) and pulsed Doppler volumetry. These methods, however, have several known limitations such as geometric assumptions of a hemispherical regular effective regurgitant orifice (ERO), underestimation of ERO in FMR, low reproducibility and indirect measurement of ERO. Recently, color Doppler 3-D echocardiography-derived vena contracta area (VCA) at rest and during exercise have been shown to have higher correlation with the 2-D integrative method or magnetic resonance-derived regurgitant volume than any single 2-D method. The prognostic significance of VCA at rest and its increase during exercise, however, has not been investigated. Therefore, the goal of the present study was threefold: first, to evaluate the feasibility of VCA to quantify FMR during bicycle exercise; second, to assess the independent significance of VCA at rest and its increase during exercise to predict clinical outcome; and, third, to compare the 2-D and 3-D methods for assessing FMR at rest and during exercise.

**Methods**

**Patients**

The subject group consisted of 78 consecutive patients (age, 67±12 years; 78% male) with chronic systolic heart failure who were admitted for acute worsening if they fulfilled the following criteria: (1) left ventricular (LV) systolic dysfunction (LV
All echocardiography was done using a commercially available system (Vivid E9; GE Medical Systems, Horten, Norway) equipped with speckle tracking and 3-D color Doppler imaging. All images were stored in digital format for offline analysis. The mean from at least 3 consecutive beats (5 in atrial fibrillation) was taken for each measurement both at rest and during exercise. Standard assessment of LV dimensions, LV volumes and ejection fraction (bi-apical Simpson method), sphericity index, left atrial volume (bi-apical area-length method) was performed according to the current recommendations.

Mitral Valve Deformation

This was assessed in the apical 4-chamber view. The mitral valve tenting area, coaptation height, anterior and posterior mitral leaflet angle were assessed at mid-systole. Mitral annulus diameter was measured in end-diastole.

Quantification of FMR

In the apical 4-chamber view, full-volume, color Doppler 3-D loops were recorded during respiration using the 3-V active matrix 4-D volume phased array probe using real-time, single-beat acquisition. The narrowest sector possible was used to maximize the frame rate.

Average frame rate for the 3-D color Doppler dataset acquisition was 15±1.8 frames/s. This frame rate provides 7–8 frames per systole at a heart rate of 60 beats/min and 6–7 frames per systole at a heart rate of 100 beats/min. The typical color code bar setting for the assessment of VCA is similar to the setting used for the PISA method, with baseline shift downward to the negative aliasing velocity between 20 and 40 cm/s. The 3-D color Doppler datasets were analyzed using dedicated software (EchoPac for PC, GE) as follows: 3-D color Doppler signals were optimized to distinguish the vena contracta from the proximal flow convergence and a rapidly expanding jet in 2 simultaneous 2D-derived perpendicular planes to ensure the best reproducibility. To identify VCA, the 3-D dataset was rotated to bisect the regurgitant color jet at the level of leaflet coaptation zone perpendicularly to its long axis in 2 orthogonal planes. The image was cropped along the jet direction to visualize the cross-sectional area at the level of vena contracta. The VCA was defined as the high-velocity core of the color spectrum and to avoid the “color bleeding”, that is, the low-velocity flow signal in the periphery of the color spectrum. To facilitate delineation of the VCA, the color gain was lowered. In contrast to low-velocity peripheral flows, the vena contracta flow is less affected by the color gain adjustments. When reducing gain, the high intense core of the high-velocity vena contracta flow is the last to remain. Figure 1 shows examples of the vena contracta flow and low-velocity peripheral flows with the color code bar setting. The VCA at the closest frame preceding mid-systole was magnified and traced manually. Usually, this was the third or fourth systolic frame at rest and the third systolic frame during peak exercise. Furthermore, 3-D color Doppler echocardiography-derived vena contracta cross-section length (VCL) was assessed as the largest diameter of VCA. In the case of multiple jets, VCA and VCL were calculated as the sum of the individual VCA and VCL. Figure 2 shows a representative VCA tracing in 2 patients with mild-moderate FMR at rest, 1 with a significant exercise-induced increase of VCA (Figures 2A,B) and 1 with a stable small VCA during exercise (Figures 2C,D). The 2D-derived assessments of FMR included the PISA method-derived ERO and vena contracta width.

Statistical Analysis

Data are presented as mean±SD for continuous variables and as percentage for categorical variables. The unpaired or paired
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3.8±2.0 min. An additional 9 patients underwent implantation of biventricular pacemaker during the index hospitalization and were excluded. The remaining 62 patients (age, 68±11 years; 76% male) were included in the clinical outcome analysis. During a median follow-up of 17 months (IQR, 13–20 months), 15 patients (24%) reached the composite endpoint (death, n=3; admission for worsening heart failure, n=11; heart transplantation, n=1). Follow-up was obtained in all patients.

Baseline and Exercise Characteristics
At baseline, patients with endpoint compared to patients without endpoint had more advanced heart failure as evidenced by significantly higher NT-proBNP, wider QRS complex and reduced tricuspid annular plane systolic excursion (all \( P<0.05 \); Table 1). Moreover, in the 2 years preceding the study inclusion, patients with endpoint were more likely to be admitted repeatedly for worsening heart failure \( (P<0.001) \) than individuals without endpoint. Prevalence of cardiac resynchronization therapy, ischemic cardiomyopathy or atrial fibrillation was similar in both groups. E/e', degree of global LV remodeling and ejection fraction, and the indices of mitral valve deformation did not differ between groups (Table 1). Furthermore, the

Results
Seven patients (9%) had poor echocardiography image quality at rest and were excluded prior to exercise. In all of the remaining 71 patients (age, 67±12 years; 79% male) the assessment of VCA was feasible both at rest and during exercise (feasibility, 91%). The image post-processing time to obtain VCA was

Figure 2. Individual examples of significant exercise-induced increase of vena contracta cross-sectional area (VCA) (A, B) vs. a stable small VCA (C, D). VCA (white ellipse) was assessed using manual planimetry at the closest frame preceding mid-systole. Care was taken to circle the central area of the high-velocity flow while avoiding the low-velocity color flow signals at the periphery. The first image from the left shows raw color spectrum without delineating line to illustrate this technique. Vena contracta cross-section length (VCL) was measured as the maximum VCA diameter. In the first patient (A, B), a relatively large ellipsoid VCA was observed at rest (A) despite the small color-coded regurgitant jet area and "mild" appearance of functional mitral regurgitation (FMR). Figure 2B shows significant increase in VCA corresponding to significant FMR during low-load exercise (50W). It is noteworthy that proximal isovelocity surface (PISA)-derived effective regurgitant orifice (ERO; B, green circle) showed smaller increase, suggesting underestimation of ERO by the PISA method. Figures 2C, D shows an example of a patient with the small circular VCA both at rest and during exercise, respectively, reflecting stable mild-moderate FMR.
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patients with endpoint but in only 8% of patients without endpoint (negative predictive value, 86%). VCL at rest (area under the curve [AUC]=0.68), VCL at peak exercise (AUC=0.73) and exercise-induced increase in PISA-derived ERO (AUC=0.60) had lower accuracy. On Cox regression analysis, resting VCA ≥15 mm², its ≥20-mm² exercise-induced increase, and VCL ≥13 mm at peak exercise were identified as the only independent predictors of composite endpoint (Table 2). The patients with VCA ≥15 mm² or VCL increase ≥20 mm² had worse prognosis on Kaplan-Meier analysis (Figure 4).

**Predictors of Composite Endpoint**

Resting VCA and its increase were better predictors for the composite endpoint than PISA ERO increase (Figure 3). Resting VCA with a cut-off ≥15 mm² and its increase (cut-off ≥20 mm²) at peak exercise had the highest accuracy for predicting the composite endpoint. Concomitant presence of large VCA at rest and its significant increase during exercise occurred in 53% of patients with endpoint but in only 8% of patients without endpoint (negative predictive value, 86%). VCL at rest (area under the curve [AUC]=0.68), VCL at peak exercise (AUC=0.73) and exercise-induced increase in PISA-derived ERO (AUC=0.60) had lower accuracy. On Cox regression analysis, resting VCA ≥15 mm², its ≥20-mm² exercise-induced increase, and VCL ≥13 mm at peak exercise were identified as the only independent predictors of composite endpoint (Table 2). The patients with VCA ≥15 mm² or VCL increase ≥20 mm² had worse prognosis on Kaplan-Meier analysis (Figure 4).

**2-D vs. 3-D Indices for Assessment of FMR**

At rest, a prognostic ERO (≥20 mm²) was observed in 18 patients (29%) using the 3-D VCA method but in no patients using the 2-D PISA method (Table 1). A total of 26 patients (42%) had large 3-D VCL (≥7 mm) suggesting significant FMR at rest, while no patients had wide 2-D vena contracta. Patients with VCA ≥20 mm² or VCL ≥7 mm had higher occurrence of composite endpoint (8/15 vs. 10/47, P=0.02 for VCA, or 10/15 vs. 16/47, P=0.04 for VCL). At peak exercise, a total of 18 patients (29%) had large (≥20-mm²) exercise-induced increase in VCA, and a total of 15 (24%) had large (≥13-mm²) exercise-induced increase in PISA-derived ERO. Figure 5 shows VCA and PISA-derived ERO at rest and during peak exercise in patients with endpoint. Both VCA and PISA-derived ERO increased

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**Table 1. Clinical and Echocardiography Characteristics**

|                  | Endpoint (+) (n=15) | Endpoint (-) (n=47) | P-value |
|------------------|---------------------|---------------------|---------|
| **Age (years)**  | 65±16               | 68±9                | 0.36    |
| **Sex (% female)** | 20                  | 17                  | 1.0     |
| Diabetes mellitus | 4 (27)              | 11 (23)             | 1.0     |
| Coronary artery disease | 9 (60)           | 25 (53)             | 0.77    |
| ACE/ATII inhibitors | 14 (93)              | 44 (94)             | 1.0     |
| β-blockers       | 12 (80)             | 33 (72)             | 0.74    |
| Spironolactone   | 12 (80)             | 30 (64)             | 0.35    |
| Loop diuretics   | 14 (97)             | 36 (76)             | 0.26    |
| NYHA class       | 2.5±0.5             | 2.0±0.6             | 0.09    |
| NT-proBNP (pg/ml)| 2,180 (1,548–7,100) | 1,400 (546–2,856)   | 0.02    |
| Hospitalization for worsening HF in preceding 2 years | 12 (80) | 20 (43) | 0.017 |
| ≥2 hospitalizations for worsening HF in preceding 2 years | 8 (53) | 2 (4) | <0.0001 |
| Glomerular filtration rate (ml/min) | 61±19 | 60±14 | 0.95 |
| Atrial fibrillation | 7 (47)            | 16 (34)             | 0.54    |
| QRS width (ms)   | 143±33              | 123±33              | 0.031   |
| CRT              | 4 (27)              | 5 (11)              | 0.2     |
| E/e'             | 16.3±6.4            | 13.0±7.5            | 0.14    |
| Mitral valve tenting area (cm²) | 1.9±1.0         | 1.6±0.7             | 0.22    |
| Mitral valve coaptation height (mm) | 8±4     | 7±3     | 0.12    |
| TAPSE (mm)       | 15.5±3.1            | 17.8±4.0            | 0.047   |
| Exercise tolerance (W) | 52±20           | 81±38               | 0.007   |
| Heart rate (beats/min) |               |                     |         |
| Rest             | 69±16               | 72±15               | 0.55    |
| Exercise         | 96±27               | 103±23              | 0.38    |
| Systolic blood pressure (mmHg) |               |                     |         |
| Rest             | 105±17              | 118±19              | 0.021   |
| Exercise         | 126±20              | 146±23              | 0.004   |
| LV EDVI (ml/m²)  |                     |                     |         |
| Rest             | 102±54              | 90±24               | 0.25    |
| Exercise         | 109±18              | 90±26               | 0.06    |

(Table 1 continued the next page.)
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| Endpoint (+) (n=15) | Endpoint (-) (n=47) | P-value |
|---------------------|---------------------|---------|
| LV ESVI (ml/m²)     |                     |         |
| Rest                | 75±47               | 64±19   | 0.62   |
| Exercise            | 78±22               | 60±27†  | 0.08   |
| LV EF (%)           |                     |         |
| Rest                | 29±8                | 29±8    | 0.46   |
| Exercise            | 30±8                | 33±10†  | 0.12   |
| LV sphericity index |                     |         |
| Rest                | 1.52±0.17           | 1.52±0.16| 0.32   |
| Exercise            | 1.58±0.20           | 1.56±0.21| 0.54   |
| Peak TR gradient (mmHg) |             |         |
| Rest                | 21±7                | 23±6    | 0.42   |
| Exercise            | 50±8†               | 45±9†   | 0.056  |
| VCA (3-D) (mm²)     |                     |         |
| Rest                | 17±6                | 13±7    | 0.002  |
| Exercise            | 35±16†              | 21±12†  | <0.001 |
| Rest VCA ≥20 mm²    | 8 (53)              | 10 (21) | 0.02   |
| Exercise-induced VCA increase ≥20 mm² | 9 (60)   | 9 (19)  | 0.007  |
| Exercise-induced VCA increase (mm²) | 17±13   | 8±10    | 0.009  |
| VCL (3-D) (mm)      |                     |         |
| Rest                | 7.0±2.9             | 5.1±2.5 | 0.017  |
| Exercise            | 12.9±6.7†           | 8.1±4.6†| 0.002  |
| ERO (2-D PISA) (mm²) |                     |         |
| Rest                | 11±5                | 8±5     | 0.058  |
| Exercise            | 20±9†               | 14±10†  | 0.07   |
| Rest ERO ≥20 mm²    | 0                   | 0       | NA     |
| Exercise-induced ERO increase ≥13 mm² | 6 (40)   | 9 (19)  | 0.16   |
| Vena contracta width (2-D) (mm) |       |         |
| Rest                | 3.3±0.7             | 2.9±1.3 | 0.2    |
| Exercise            | 5.3±2.3†            | 3.9±1.6†| 0.008  |

Data given as mean ± SD, n (%) or median (IQR). *P<0.05, †P<0.01, ‡P<0.001 rest vs. exercise. ACE/ATII, angiotensin-converting enzyme/angiotensin II; CRT, cardiac resynchronization therapy; D, dimensional; EF, ejection fraction; EDVI, end-diastolic volume index; ERO, effective regurgitant orifice; ESVI, end-systolic volume index; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal of the prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PISA, proximal isovelocity surface; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VCA, vena contracta cross-sectional area; VCL, vena contracta length.

Figure 3. Accuracy of vena contracta cross-sectional area (VCA) at rest, exercise-induced increase in VCA and in proximal isovelocity surface (PISA)-derived effective regurgitant orifice (ERO) to predict the composite endpoint. AUC, area under the curve; Sp, specificity; Ss, sensitivity.

significantly (both P<0.01), but the rest-to-peak exercise difference in VCA was significantly larger than the difference in PISA-derived ERO (18±10 mm² vs. 9±7 mm², P<0.001; Figure 5). A significantly higher proportion of patients with endpoint had ≥20-mm² increase in VCA compared to patients without endpoint (9/15 vs. 9/47, P=0.007). In contrast, the percentage of patients with ≥13-mm² increase in PISA-derived ERO was similar between the groups (6/15 vs. 9/47, P=0.16; Table 1).
In patients with sinus rhythm, the intraobserver and interobserver variability was 7% and 9% at rest, and 8% and 10% during exercise, respectively. In patients with atrial fibrillation, the intraobserver and interobserver variability was 10% and 14% at rest, and 12% and 15% during exercise, respectively.

**Discussion**

The present findings can be summarized as follows. First, the assessment of VCA during bicycle exercise is highly feasible and reproducible. Second, both VCA at rest and its increase during exercise are independent predictors of clinical outcome. VCA at rest has high sensitivity, while its exercise-induced increase has high specificity for identifying patients with adverse clinical outcome. Third, the assessment of VCA seems to be highly sensitive to track exercise-induced changes in FMR, while the PISA method underestimated ERO both at rest and during exercise.

**Table 2. Independent Predictors of Composite Endpoint**

|                        | Univariate     | Multivariate  |
|------------------------|----------------|--------------|
|                        | HR (95% CI)    | P-value      | HR (95% CI)    | P-value      |
| Age                    | 0.99 (0.95–1.03) | 0.69         | 1.00 (0.95–1.06) | 0.33         |
| NYHA class             | 3.1 (1.14–8.33) | 0.024        | 5.02 (1.66–15.03) | 0.005        |
| NT-proBNP              | 1.0 (1.00–1.03) | 0.07         | 1.0 (0.99–1.03) | 0.09         |
| QRS duration           | 1.0 (0.99–1.03) | 0.09         | 1.0 (0.99–1.03) | 0.09         |
| LV EF                  | 0.97 (0.92–1.05) | 0.45         | 1.0 (0.97–1.03) | 0.35         |
| TAPSE                  | 0.86 (0.73–1.00) | 0.054        | 1.0 (0.76–1.35) | 0.83         |
| Exercise-induced PISA-derived ERO increase ≥13mm² | 1.13 (0.10–1.26) | 0.064        | 1.0 (0.86–1.19) | 0.83         |
| VCL at rest ≥7 mm      | 1.32           | 0.024        | 1.32           | 0.024        |
| VCL at peak exercise ≥13 mm | 7.40         | 0.002        | 5.85 (1.67–14.09) | 0.009        |
| Resting VCA ≥15 mm²    | 8.11           | <0.001       | 6.33           | 0.004        |
| Exercise-induced VCA increase ≥20 mm² | 6.33           | <0.001       | 6.33           | <0.001       |

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

**Figure 4.** Kaplan-Meier estimates of the time to death resulting from any cause, admissions for worsening heart failure or heart transplantation. Patients were divided into 2 groups according to (A) presence or absence of vena contracta cross-sectional area (VCA) ≥15 mm² at rest, or (B) presence or absence of exercise-induced increase of VCA ≥20 mm² at peak exercise.

**Large VCA and Small PISA-Derived ERO During Peak Exercise**

This analysis included all 71 patients (age, 67±12 years; 79% male) with good image quality both at rest and during exercise. Of the 24 patients with significant (≥20-mm²) increase in VCA only 14 (58%) had significant (≥13-mm²) increase of PISA-derived ERO. A subgroup of patients, in whom the PISA method failed to identify exercise-induced significant FMR, had significantly higher coaptation height and posterior leaflet angle at rest and during exercise than patients in whom PISA correctly identified exercise-induced FMR (Table 3). In contrast, both subgroups had similar global echocardiography characteristics and VCA at peak exercise. Of note, the exercise capacity was similar in both PISA subgroups, but was significantly lower in patients without exercise-induced increase in VCA.

**Reproducibility**

Reproducibility for VCA both at rest and during exercise was assessed in 20 randomly selected patients in sinus rhythm (n=10) and in atrial fibrillation (n=10) from recorded images. In patients with sinus rhythm, the intraobserver and interobserver variability was 7% and 9% at rest, and 8% and 10% during exercise, respectively. In patients with atrial fibrillation, the intraobserver and interobserver variability was 10% and 14% at rest, and 12% and 15% during exercise, respectively.
Feasibility and Reproducibility

Several studies have demonstrated high feasibility and reproducibility for VCA assessment at rest.\textsuperscript{6,8–13} The current study extends these findings by showing high feasibility (91%) and reproducibility of the VCA measurement also during low-grade exercise, with a short image post-processing time <5 min. The feasibility of color Doppler 3-D echocardiography-derived VCA assessment has been related to the 2-D echocardiography image quality at rest. In all the patients with acceptable 2-D image quality at rest, the assessment of VCA was feasible both at rest and during exercise. Similarly, the intra- and interobserver variability of the VCA assessment was low (<10%) and not significantly affected by bicycle exercise.

VCA at Rest and Clinical Outcome

Previous studies have demonstrated that presence of resting FMR in patients after myocardial infarction or with ischemic LV dysfunction is associated with increased mortality, increased admission rate for worsening heart failure and reduced functional capacity.\textsuperscript{14–16} In those studies, the cut-off for ERO ≥20 mm², assessed using 2-D PISA or pulsed Doppler volumetric method, identified individuals with the worst prognosis. The present study included patients with mild-moderate FMR at rest assessed using the 2-D integrative approach.\textsuperscript{6,17} In line with the inclusion criteria, in the current study, all patients had PISA-derived ERO <20 mm² at rest, and PISA-derived ERO did not predict outcome. In contrast, prognostic VCA ≥20 mm² at rest was observed in 29% of the present subjects, and its presence was associated with significantly higher occurrence of composite endpoint. Moreover, VCA ≥15 mm² emerged as an independent predictor of outcome. Finally, a total of 26 patients (42%) had large 3-D VCL (≥7 mm) suggesting significant FMR at rest, while no patients had wide 2-D vena contracta. This suggests that the presence of relatively large ellipsoid VCA may be a marker of significant FMR with adverse outcome, despite grading of FMR as “mild-moderate” using 2-D PISA or vena contracta width. This also suggests that the 2-D-derived approach may underestimate severity of FMR in some patients. Currently, the 2-D integrative method is the recommended approach to assess severity of FMR.\textsuperscript{6,7} This method integrates several 2D-based indices to circumvent the limitations of each of these techniques. Recent studies have investigated the color Doppler 3-D echocardiography approach for FMR quantification by direct measurement of ERO using VCA\textsuperscript{8–13} VCA at rest has been shown to have a higher correlation with the 2-D integrative method or magnetic resonance-derived regurgitant volume than any single 2-D method.\textsuperscript{8,9} In contrast, in patients with FMR, the PISA method significantly underestimated ERO by 27% due to the geometric and flow assumptions. The irregular hemi-elliptical shape of ERO is relatively common in FMR.\textsuperscript{16} Asymmetric ERO leads to underestimation of FMR severity by commonly used 2-D methods, such as PISA or vena contracta width.\textsuperscript{8–12,16,17} In contrast, the 3-D technique used in the current study allows direct visualization of ERO with precise assessment of its area and longest diameter and gives better results as reflected by AUC for VCA, ERO (PISA) and VCA increase during exercise (Figure 3).

VCA During Exercise and Clinical Outcome

Distinction of dynamic severe from stable mild FMR in patients with systolic LV dysfunction and mild-moderate FMR at rest is critical, because the former are associated with reduced survival.\textsuperscript{3,4,18} The landmark studies of Lancellotti et al showed the wide range of exercise-induced changes in the PISA method- or pulsed Doppler volumetric method-derived ERO in patients with ischemic LV dysfunction.\textsuperscript{19} The exercise-induced increase in PISA-derived ERO ≥13 mm² has been associated with adverse outcome.\textsuperscript{3,4} Corroborating this finding, in the present study, patients with endpoint had significantly larger VCA during exercise than patients without endpoint. Moreover, the exercise-induced increase in VCA ≥20 mm² has been identified as an independent predictor of composite endpoint. In contrast to the previous studies, exercise-induced increase in PISA ERO did not predict outcome in the present study. The reasons may be several. In the present study, only patients with mild-moderate FMR at rest were included. In contrast, the Lancellotti et al studies enrolled patients with higher degrees of FMR at rest.\textsuperscript{3,4} In the present study, both VCA and the PISA-derived ERO increased significantly, but the rest-to-peak exercise difference in VCA was significantly larger than the difference in PISA-derived ERO. Furthermore, the exercise-induced significant increase of PISA-derived ERO (>13 mm²) identified only 10 out of 24 patients (58%) with significant increase in VCA (≥20 mm²). The underestimation of ERO by the PISA method was observed predominantly in patients with severe distortion of the mitral valve geometry, implying highly irregular ERO shape. Finally, direct comparison of VCA and PISA-derived ERO was not possible, because VCA reflects the anatomical surface of the regurgitant orifice, while PISA-derived ERO represents the physiological parameter based on hydrodynamic theory of flow converging towards a restricted orifice. The limitation of a single 2-D measurement in the setting of non-circular ERO may partly be compensated for by using multiple 2-D measurements in different echocardiography planes. This approach, however, may substantially increase the data acquisition time, which may be of particular importance during exercise, when the time window to obtain images is limited. In contrast, a single recording in 1 echocardiography view is needed to acquire color Doppler 3-D dataset for the VCA assessment.

Study Limitations

In the current study, a single-beat (live) 3-D color Doppler ac-
A single-beat recording has relatively lower temporal resolution than the multiple-beat acquisition. In this study, the average number of frames per systole was between 6 and 8. Supine bicycle exercise is associated with shortening of diastole and only minor changes in the duration of systole, therefore the heart rate achieved at peak exercise (average 100 beats/min) was not associated with the significant decrease in number of frames per systole. Single-beat compared to multiple-beat acquisition has several distinct advantages in patients with heart failure undergoing exercise. These severely ill patients often have irregular heart rate due to atrial fibrillation, or frequent premature beats. These individuals are not able to hold their breath during exercise. Irregular heart rate and absence of apnea lead to stitching and respiratory artifacts that hamper the accuracy of multiple-beat-derived VCA during exercise. Therefore, in the present study, single-beat data acquisition was used for a patient serving as his own control between rest and exercise. From the clinical point of view, it is currently unknown whether correction of FMR with significant increase during exercise may change the prognosis, especially in such high-risk patients, but emerging new techniques such as Mitraclip might be of use in these cases.

Conclusions

The present study extends findings of the previous studies by showing that VCA at rest and its increase during exercise are independent predictors of clinical outcome. In patients with mild-moderate FMR at rest, VCA enabled identification of individuals with adverse clinical outcome, who would have been missed using the 2-D-derived indices. The assessment of VCA...
during exercise is feasible, reproducible and reliable for tracking the exercise-induced changes in ERO. VCA assessment is based on a single measurement of directly visualized ERO, thus avoiding geometric and flow assumptions. This may be of value during exercise because the 2-D indices are all indirect, underestimate ERO in FMR and require multiple sampling in different imaging planes. Furthermore, identification of resting predictors of adverse outcome in patients with mild-moderate FMR at rest may be of potential importance, because the expertise and tilted bicycle table used for exercise echocardiography are not widely available. These findings advocate integration of the VCA method into the current approaches for assessing FMR.

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None.

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