Determinants of regurgitant volume in mitral regurgitation: contrasting effect of similar effective regurgitant orifice area in functional and organic mitral regurgitation

Andrea Chiampan[1], Julien Nahum[1], Mohamed Leye[1], Johanna Oziel[1], Caroline Cueff[1], Eric Brochet[1], Bernard Iung[1], Andrea Rossi[2], Alec Vahanian[1], and David Messika-Zeitoun[3]*

[1]Cardiovascular Division, Cardiology Department, AP-HP, Bichat Hospital, 46 rue Henri Huchard, Paris 75018, France; [2]Division of Cardiology, University of Verona, Verona, Italy; and [3]INSERM, U698, University Paris 7, Paris, France

Background	Quantitative assessment of the severity of mitral regurgitation (MR) is based on the calculation of the effective regurgitant orifice (ERO), a measure of lesion severity, and of the regurgitant volume (RVol), a measure of left ventricular volume overload. We aimed at evaluating the determinants of RVol in both organic (OMR) and functional mitral regurgitation (FMR).
Methods and results	MR severity was quantitatively assessed using the proximal isovelocity surface area (PISA) method in 240 patients, 142 with OMR and 98 patients with FMR. By definition, ERO and RVol were strongly correlated both in patients with OMR and FMR (both $R = 0.90$, $P < 0.0001$) but the slopes of the regression lines were significantly different ($P < 0.0001$). This difference remained significant in patients with elevated systolic pulmonary artery pressure (SPAP > 40 mmHg, $P < 0.0001$) but not in patients with normal SPAP ($\leq$40 mmHg, $P = 0.09$). In multivariate analysis, independent determinants of RVol were ERO ($P < 0.0001$), MR mechanism (FMR/OMR) ($P = 0.0003$) and SPAP ($P = 0.03$). In patients with elevated SPAP, ERO ($P < 0.0001$), left ventricular ejection fraction (LVEF) ($P = 0.03$), and MR mechanism ($P = 0.03$) were independently associated with RVol, whereas in patients with normal SPAP, ERO ($P < 0.0001$) was the only independent determinant of RVol.
Conclusion	In the present study, we evaluated the contrasting effect of similar lesion severity in OMR and FMR and showed that similar ERO were associated with lower RVol in FMR compared with OMR. The regurgitant volume is the result of complex interactions of anatomic lesions, LVEF, and SPAP and our results highlight the importance of taking into account these parameters when interpreting RVol values in clinical practice, especially in FMR.
Keywords	Mitral regurgitation • Echocardiography • Quantification • PISA

Introduction

Mitral regurgitation (MR) is a pathological condition defined as systolic retrograde flow from the left ventricle (LV) into the left atrium secondary to the loss of normal coaptation between anterior and posterior mitral leaflets. It is the most frequent valve disease in the USA and the second most common form of valvular heart disease needing surgery in Europe.[1,2] Based on the underlying mechanism, MR is classified as functional mitral regurgitation (FMR), when the valve is structurally normal and the regurgitation is due to ventricular remodelling or organic (OMR), when the mitral valve apparatus itself is primarily damaged.

Echocardiography is the reference method allowing an evaluation of anatomic lesions, MR mechanisms and of the severity of

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the regurgitation.[3] MR degree can be quantitatively assessed by the effective regurgitant orifice (ERO), a measure of lesion severity, and the regurgitant volume (RVol), a measure of left ventricular volume overload. MR degree is determined by the importance of anatomic damages but also by different forces acting on mitral leaflets including tethering forces generated by papillary muscle displacement, annular forces, left ventricular generated closing forces (left ventricular ejection fraction, LVEF), left atrial (LA) pressure and the resultant pressure gradient between the LV and the left atrium. However, the respective influence of anatomic vs. haemodynamic forces as well as the influence of MR mechanism—functional vs. organic—has not been clearly evaluated. As previously shown in mitral and tricuspid regurgitation,[4] we hypothesized that differences in haemodynamic forces in OMR and FMR may result in a different relationship between ERO and RVol. Thus, in a large cohort of patients with both organic and FMR with a wide range of MR severity, we aimed at comparing the relationship between ERO and RVOL in OMR and FMR and at evaluating the determinants of the RVol and more specifically the influence of haemodynamic forces namely the LVEF and the systolic pulmonary artery pressure (SPAP) as a surrogate for LA pressure.

Methods

Population

We retrospectively enrolled all patients with an at least mild mitral regurgitation based on colour Doppler either in sinus rhythm or in atrial fibrillation (AF) who underwent a transthoracic echocardiography (TTE) with a quantitative assessment of the degree of regurgitation using the Proximal isovelocity surface area (PISA) method. Patients with multiple MR jets or with more than moderate-associated valvular heart disease (except for tricuspid regurgitation) were excluded.

Echocardiographic evaluation

The echocardiographic examination was performed by experienced operators using high-quality imaging system (Vivid 7, GE Healthcare, Waukesha, WI, USA or iE 33, Philips Medical Systems, Andover, MA, USA).

Mitral regurgitation mechanism
The mitral valve apparatus (annulus, leaflets, chordae, papillary muscles, and underlying LV myocardium) was carefully analysed and mechanism of the regurgitation classified as functional or organic. OMR was defined as MR due to anatomic alteration of the valvular or sub-valvular mitral apparatus, whereas FMR was defined as MR occurring with structurally normal valves as a consequence of left ventricular remodelling.

Mitral regurgitation severity
The severity of the regurgitation was quantitatively assessed using the PISA method. The PISA method is based on the principle of conservation of mass and is presented elsewhere.[5] Three to five measurements were performed and averaged according to patient rhythm. Severe MR was defined by an ERO ≥ 0.40 cm^2 or a RVol ≥ 60 mL for OMR and 0.20 cm^2 and 30 mL, respectively, for FMR.[3,6−8]

Global echocardiographic assessment
LV and LA dimensions were obtained by M-mode echocardiography. The EF was calculated by the biplane Simpson's method or visually estimated. LV stroke volume was calculated as the product of the left ventricle outflow tract (LVOT) area and left ventricle outflow tract time-velocity integral (LVOT TVI). SPAP was calculated using continuous wave and the tricuspid pressure gradient and the right atrial pressure estimated based on inferior vena cava size and changes during inspiration. A SPAP ≤ 40 mmHg was considered normal.

Statistical analysis

Data are presented as mean $\pm$ SD or number of patients (per cent). OMR and FMR groups were compared with the use of Student's t-test or χ^2 as appropriate. The associations between ERO area and RVol were analysed using linear regression separately in patients with OMR and in those with FMR overall and according to SPAP subgroups. Comparison of the slopes and intercepts of the two regressions was performed by the analysis of covariance. A stepwise multiple linear regression analysis was used to identify determinants of the RVol. A $P < 0.05$ was considered statistically significant.

Results

Population characteristics

Overall
Two hundred and forty patients were enrolled in the present study. Baseline characteristics of the population are summarized in the *Table 1*. Briefly, mean age was 63 ± 16 years, 61% were male, 21% were in AF, and 43% were severely symptomatic (NYHA class III or IV). MR mechanism was organic in 142 patients and functional in 98.

Organic mitral regurgitation
Among the 142 patients with OMR, degenerative and rheumatic were the two most common aetiologies. Mean LVEF was $63 \pm 10\%$ [median 60%, (25−90)]. Mean SPAP, measured in 126 patients, was 41 ± 12 mmHg [median 40 mmHg (25−105)]. Overall, 15 patients (11%) had a reduced LVEF ($\leq 50\%$) and 51 patients (40%) presented with elevated SPAP (>40 mmHg). Mean ERO was 0.42 ± 0.21 cm^2 [median 0.40 cm^2 (0.07−1.60)] and mean RVol 72 ± 32 mL/beat [median 73 mL/beat (13−170)]. A severe OMR (ERO ≥ 0.40 cm^2 or RVol ≥ 60 mL) was observed in 94 patients (66%).

Functional mitral regurgitation
FMR was due to ischaemic disease in 55 patients and dilated cardiomyopathy in 42 patients. Mean LVEF was $34 \pm 11\%$ [median 30% (15−60)] and mean SPAP, measured in 90 patients, 50 ± 14 mmHg [median 50 mmHg (24−90)]. Overall, 91 patients (93%) had a LVEF $\leq 50\%$ and 63 patients (70%) a SPAP > 40 mmHg. Mean ERO was 0.32 ± 0.21 cm^2 [median 0.27 cm^2 (0.03−1.10)] and mean RVol 44 ± 23 mL/beat [median 43 mL/beat (4−115)]. A severe FMR (ERO ≥ 0.20 cm^2 or RVol ≥ 30 mL) was observed in 77 patients (79%).

Table 1 Clinical and echocardiographic characteristics of patients overall and according to the mechanism of the regurgitation (functional or organic)

	Overall (n = 240)	Organic MR (n = 142)	Functional MR (n = 98)	P-value
Age, years	62 ± 16	61 ± 16	63 ± 14	0.31
Male sex, %	147 (61%)	73 (51%)	74 (76%)	0.0002
Body surface area, m^2	1.79 ± 0.20	1.78 ± 0.20	1.80 ± 0.2	0.33
Atrial fibrillation, %	48 (20%)	22 (20%)	26 (33%)	0.03
NYHA class III or IV	77 (43%)	35 (34%)	42 (56%)	0.03
Left ventricular end-diastolic diameter, mm	60 ± 9	57 ± 7	65 ± 10	<0.0001
Left ventricular end-systolic diameter, mm	41 ± 12	35 ± 6	52 ± 11	<0.0001
Ejection fraction, %	51 ± 17	63 ± 10	34 ± 11	<0.0001
Left atrial diameter, mm	48 ± 10	45 ± 8	53 ± 12	<0.0001
Systolic pulmonary artery pressure, mmHg	45 ± 14	41 ± 12	50 ± 14	<0.0001
Heart rate, bpm	73 ± 15	71 ± 13	75 ± 16	0.08
Cardiac output, L/min	4.5 ± 1.5	5.3 ± 1.6	3.8 ± 1.6	<0.0001
Cardiac index, L/min/m^2	2.6 ± 0.9	3.0 ± 0.9	2.0 ± 0.5	<0.0001
Effective regurgitant orifice, cm^2	0.38 ± 0.22	0.42 ± 0.21	0.32 ± 0.21	0.0002
Regurgitant volume, mL/beat	61 ± 32	72 ± 32	44 ± 23	<0.0001
Severe mitral regurgitation	171 (72%)	94 (66%)	77 (79%)	0.02

Data presented are number of patients (per cent) or mean ± SD.

Comparison between organic mitral regurgitation and functional mitral regurgitation

As expected, patients with FMR were more frequently severely symptomatic (*P* = 0.03), in AF (*P* = 0.03), had larger LV dimension, lower LVEF, and higher SPAP (all <0.0001, *Table 1*). Of note the heart rate was not significantly different between groups. Overall, patients with OMR had larger ERO and RVol (*P* < 0.0002 and *P* < 0.0001, respectively) but patients with FMR were more frequently categorized with severe MR (79 vs. 66%, *P* = 0.02).

Relationship between the effective regurgitant orifice and the regurgitant volume

By definition, a strong and linear correlation between ERO and RVol was observed overall (*R* = 0.88, *P* < 0.0001) and in the subgroups of OMR and FMR (*R* = 0.90, *P* < 0.0001 and *R* = 0.90, *P* < 0.0001, respectively). However, as illustrated in *Figure 1*, the slopes of the regression lines for OMR and FMR were significantly different (RVol = 14 + 136 × ERO and RVol = 12 + 98 × ERO, respectively). The covariance analysis of the regression between ERO and RVol showed no difference in the intercept but a flatter slope in FMR than in OMR (*P* < 0.0001).

This difference remained significant in the subgroups of patients with elevated SPAP but not in the subgroup of patients with normal SPAP (≤40 mmHg) (*P* < 0.0001 and *P* = 0.09, respectively, for the covariance analysis of the regression between ERO and RVol) (*Figure 2*).
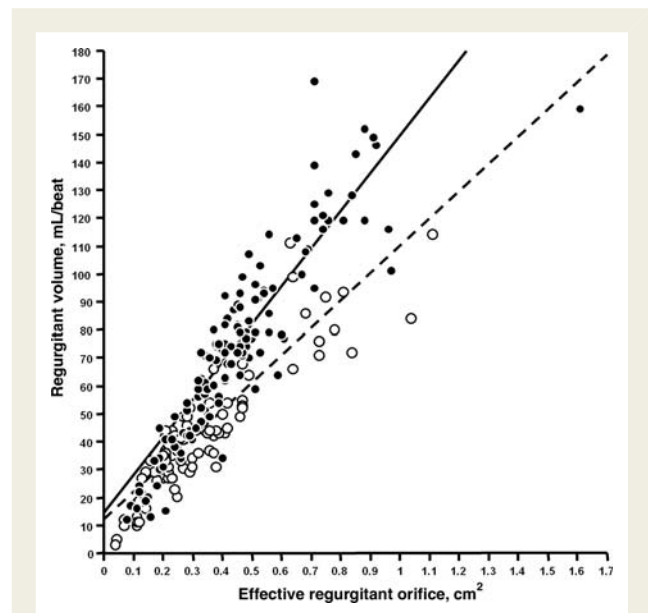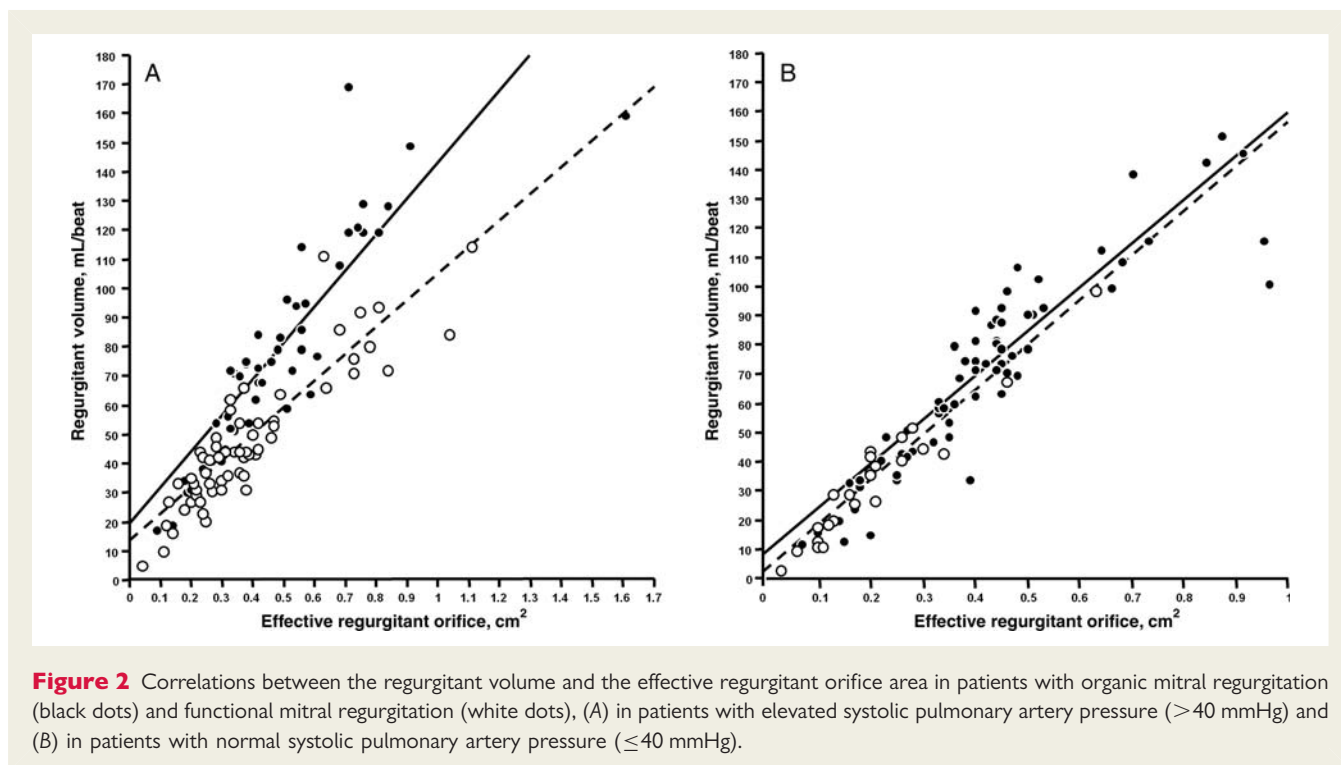

Figure 1 Correlations between the regurgitant volume and the effective regurgitant orifice area in patients with organic mitral regurgitation (black dots) and functional mitral regurgitation (white dots).

Determinants of the regurgitant volume

In multivariate analysis, after adjustment for age and gender, independent determinants of RVol were ERO (*P* < 0.0001), MR mechanism (FMR or OMR) (*P* = 0.0003), and SPAP (*P* = 0.03). After

Figure 2 Correlations between the regurgitant volume and the effective regurgitant orifice area in patients with organic mitral regurgitation (black dots) and functional mitral regurgitation (white dots), (A) in patients with elevated systolic pulmonary artery pressure (>40 mmHg) and (B) in patients with normal systolic pulmonary artery pressure (≤40 mmHg).

exclusion of MR mechanism from the model, the LVEF became highly significant ($P < 0.0001$) while ERO and SPAP remained significantly associated with RVOL. In the subgroup of patients with elevated SPAP, ERO ($P < 0.0001$), LVEF ($P = 0.03$), and MR mechanism ($P = 0.03$) were independently associated with RVol but SPAP was not anymore significant. In patients with normal SPAP, ERO ($P < 0.0001$) was the only independent determinant of RVol. Adding the heart rate into the model only slightly changes our results and ERO remained the only independent determinant of RVol in patients with normal SPAP.

Discussion

In the present study, in a large series of patients with a wide range of MR severity quantitatively assessed, we evaluated the contrasting effect of similar lesion severity in OMR and FMR and showed that the relationship between RVol and ERO was significantly different between OMR and FMR. Similar ERO were associated with lower RVol in FMR compared with OMR. In multivariate analysis, ERO, MR mechanism, and SPAP were independent determinants of RVol. However, in patients with normal SPAP, ERO was the only determinant of RVol, whereas in patients with elevated SPAP, ERO, LVEF, and MR mechanism were independently associated with RVol.

Recent recommendations from the European Association of Echocardiography and the American Society of Echocardiography emphasize the importance of a quantitative assessment of MR severity based on ERO and RVol in the evaluation and management of patients with both organic and FMR.[3,9,10] Multiple studies have demonstrated that ERO and more significantly RVol are dynamic and subject to important changes according to loading conditions.[11] Volume overload is function of anatomic lesions but also of interaction of opposing tethering and closing forces at the two sides of the mitral valve, of LA pressure and of the pressure gradient between the LV and the LA in systole. However, the respective impact of these different forces and their interaction with MR mechanism had never been evaluated.

OMR is due to primary mitral valve lesions, whereas cardiac chambers are usually normal at the initial phase of the disease. LV usually well compensates the volume overload so that LV dysfunction occur most often only at advanced stages. The left atrium has a lower ability to compensate a constant volume overload, resulting in a progressive dilation and in a transmission of the load to the upstream structures, namely the pulmonary vessels and the right heart. In FMR, the mitral valve is structurally normal but functionally abnormal due to complex alterations of segmental and global LV remodelling. A prominent role in determining FMR is attributed to the posterior and apical displacement of papillary muscle leading to the mitral valve tenting. Alteration of annular geometry and loss of annular contraction are also important determinant of FMR.[12,13] In FMR, LV is often hypokinetic with alterations of the equilibrium between the closing forces that are reduced as a consequence of the decreased LVEF and tethering forces that acts on mitral chordae and leaflets preventing its closure.

As expected, the LVEF was on average significantly lower and SPAP significantly higher in FMR as compared with the OMR group. This means that the driving forces pushing backward the blood flow through the incontinent valve, largely determined by the balance between the LVEF and LA pressures (as reflected by SPAP), where consistently lower in patients with FMR than in patients with OMR. In the present study, we show that these

strong differences in haemodynamic forces translate into differences in the relationship between ERO and RVol in OMR and FMR. Thus, after matching patients for ERO, RVol was significantly lower in patients with FMR than in patients with OMR. Since the relationship between ERO and RVol was different in patients with OMR and FMR, we evaluated the determinants of RVOL and the role of these haemodynamic forces (SPAP as a surrogate for LA pressure and LVEF for closing forces). In multivariate analysis, independent determinants of RVol were ERO but also MR mechanism and SPAP. The EF was not independently associated with RVol but its predictive value is probably encompassed by the one of MR mechanism. Indeed, most patients with FMR exhibited reduced EF, whereas EF was normal in most patients with OMR. In addition, an association between EF and SPAP is also expected. SPAP was the second important determinant of RVol. Elevated SPAP is a marker of high LA pressure[14] and patients with elevated SPAP presented with lower RVol for the same ERO. In contrast, in patients with normal SPAP and thus less difference in term of haemodynamic forces between OMR and FMR, the relationship between ERO and RVol were super imposable. Ours results are fully in agreement with previous study showing that for similar MR severity, patients with increased LA pressure exhibit smaller colour jet area than patients with normal LA pressure.[15] It is worth noting that since ERO is a major determinant of the RVol but also of SPAP, on the other side SPAP may in turn affect RVol and RVol may paradoxically decrease when the SPAP increases. This may explain the weaker relationship between RVol and SPAP than between ERO and SPAP.[16] Of note, the heart rate and thus duration of the systole were not different between patients with OMR and FMR and did not affect our conclusions.

The main finding of the present study showing that RVol is the resultant of complex interactions of ERO, SPAP, and LVEF may have important clinical implications. RVol is an instant photography of volume overload and ERO and RVol should not be considered as fully interchangeable. RVol, more than ERO is highly dependent of filling pressures and may significantly diminish after fluid depletion and preload diminution. In addition, especially in patients with depressed EF and elevated SPAP, clinical management, and surgical decision may be falsely oriented by only considering the RVol. Thus, a RVol of 20 mL may be associated with an ERO of 0.25 cm^2 in case of low EF and elevated SPAP in FMR. These findings may also explain the better prognostic value of ERO compared with RVol, both in OMR and FMR.[6,7]

The present study deserves several comments. First, the PISA method has limitations and assumes a hemispheric shape of the flow convergence. However, even if this assumption may prove not to be valid in all patients, the consideration of an hemi-elliptic shape[17–19] would not have affected the relationship between ERO and RVol. Other methods such as quantitative Doppler would have been desirable to confirm our findings but were not performed. Second, MR mechanism was considered as an independent variable despite it is likely that it encompasses at least partially both the ejection fraction and SPAP. This may explain why the EF was only statistically associated to RVol after removal of MR mechanism from the model. Third, other factors such as regurgitant orifice shape, jet duration, or LV dissynchrony may also influence

the RVol but could not be tested in the present study. Finally, this is a retrospective study and we could not exclude bias. However, MR quantification was prospectively performed without any specific hypothesis.

Conclusion

In the present study, in a large series of patients with both functional and organic mitral regurgitation, we showed that the RVol is the result of complex interactions of anatomic lesions, ejection fraction, and SPAP. Our results emphasize the importance of MR quantification and highlight the importance of taking into account these parameters when interpreting RVol values in clinical practice, especially in patients with FMR.

Conflict of interest: none declared.

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IMAGE FOCUS

Carcinoid tricuspid valve disease: incremental value of three-dimensional echocardiography

Denisa Muraru[1]*, Maria Francesca Tuveri[2], Martina Perazzolo Marra[1], Luigi Paolo Badano[1], and Sabino Iliceto[1]

[1]Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Via Giustiniani 2, 35128 Padua, Italy; and [2]Cardiology Department, University of Cagliari, Cagliari, Italy

* Corresponding author. Tel: +39 049 8211332; fax: +39 049 8761764, Email: denisa.muraru@gmail.com

A 51-year-old man previously diagnosed with metastatic carcinoid disease was admitted for shortness of breath and peripheral oedema. Physical examination demonstrated a holosystolic murmur over the left lower sternal border and an enlarged and pulsatile liver, with clear lungs. Echocardiographic study was indicated to rule out right heart valvular disease. Two-dimensional echocardiography showed thickened tricuspid leaflets fixed in a semi-open position (*Panel A*, arrows) with severe, free-flowing regurgitation (*Panel B*). At three-dimensional echocardiography (3DE), the rigid and retracted leaflets displayed a 'board-like' motion (*Panel C*; see Supplementary data online, *Videos S1* and *S2*), delimiting a large, fixed regurgitation orifice with some degree of stenosis. *En face* visualization of all three leaflets simultaneously enabled the identification of individual leaflet involvement and the measurement of tricuspid valve opening orifice by planimetry. Chordae tendineae were thickened and fused, and extensive plaques deposits in the right ventricular cavity were identified (*Panel D*; see Supplementary data online, *Video S3*).

Transthoracic 3DE represents a unique imaging technique for a detailed qualitative and quantitative assessment of the right heart involvement (tricuspid orifice planimetry, right ventricular morphology, volume and ejection fraction; see Supplementary data online, *Video S4*), which is the main predictor of mortality in carcinoid disease. Three-dimensional echocardiography is particularly helpful in the setting of combined valvular lesions, when the presence of a severe regurgitation adversely affects the accuracy of Doppler indices for tricuspid stenosis quantification and conventional parameters of right ventricular function (e.g. TAPSE, Tei index, tissue Doppler velocities). Therefore, 3DE facilitates the timely identification of patients who would benefit from valve replacement surgery, before right ventricular failure ensues.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.