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Grading of mitral regurgitation in mitral valve prolapse using the average pixel intensity method☆

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ABSTRACT

Aims: We recently reported the feasibility of the average pixel intensity (API) method for grading mitral regurgitation (MR) in a heterogeneous MR population. Since mitral valve prolapse (MVP) is an important cause of primary MR, we more specifically investigated the feasibility of the API method and the MR flow dynamics in patients with MVP.

Methods: Transthoracic echocardiography was performed by a single operator in consecutive MVP patients ($n = 112$). MR was assessed using the API method, color Doppler, vena contracta width (VCW), effective regurgitant orifice area (PISA-EROA) and regurgitant volume (PISA-RV).

Results: The API method was feasible in 89% of all MVP patients (68%, 71% for VCW and PISA method, respectively ;$p < .001$). Inter- and intra-observer correlations for API in MVP with non-holosystolic MR were 0.989 and 0.995. For the overall MVP-MR population, API had significant correlations with direct and indirect measures of MR severity. Based on ROC curves, an API cutoff value of 125 au was suggested to identify severe MR in MVP and a MR duration/systolic time ratio < 100% (i.e. non-holosystolic MVP-MR) identifies patients with non-severe MR (API < 125), whereas the majority of holosystolic MVP had severe MR (API > 125). Finally, API analysis of the proto-, mid- and telesystolic phases of MR in MVP showed different kinetics in non-holosystolic compared to holosystolic MVP.

Conclusions: The API method is a feasible and reproducible method for grading MVP-MR. As the API method takes into account the temporal MR flow changes during the entire systolic cycle, it may be of added value in clinical practice.

1. Introduction

Mitral valve prolapse (MVP) is an important cause of primary, organic mitral regurgitation (MR) and a significant part of these patients will progress to severe MR that heralds important morbidity and mortality [1–3]. Timing of surgery in asymptomatic severe organic MR remains controversial [4,5] and guidelines have defined thresholds for surgical interventions based on symptoms, direct and indirect echocardiographic measures of MR severity [6–8]. Direct echocardiographic measures of MR severity have been categorized as qualitative (e.g. color Doppler area), semi-quantitative (vena contracta width (VCW)) and quantitative (e.g. proximal isovelocity surface area (PISA) method), the latter to estimate the effective regurgitant orifice area (PISA-EROA) and the regurgitant volume (PISA-RV) [6,7]. Given the strengths and weaknesses of each method [9–11], an integrative multi-parametric approach to grade MR severity and guide surgical decisions has been recommended by guidelines [6–8].

Recently, we introduced a novel approach for grading MR severity, based on the average pixel intensity (API) of the continuous wave (CW) Doppler of the MR flow in a heterogeneous population of MR with few MVP patients [12]. As guidelines mention the supportive role of "eyeballing" the CW intensity [6,11], we specifically investigate the feasibility and value of directly quantifying the CW intensity for grading MVP-MR severity. Since the API method avoids geometric assumptions and takes into account the entire systolic cycle and timing/duration of MR, the API approach may have some advantages over current qualitative and quantitative measures of MR severity in MVP [12,13]. For instance, the PISA method, VCW and the color Doppler jet area in MVP may

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misclassify MR severity when timing/duration of the MR flow is not considered, which is an important issue in MVP [10,14–18]. Although guidelines recognize this important limitation, no agreed-on method for adjusting the temporal variability of MR flow has been proposed when using color Doppler, PISA or VCW grading methods.

Finally, as the API method captures the time-varying pixel intensity of the MR jet, we also investigated the API kinetics from the proto- to mid- and telesystolic phases of MR to identify specific patterns in patients with various degrees of holosystolic and non-holosystolic MR. Although unique flow patterns have been described using the PISA method in non-holosystolic MVP-MR [15,17], the API method may provide further insights into the kinetics of MR in MVP.

2. Material and methods

2.1. Patient selection and transthoracic echocardiography

Consecutive MVP-MR patients (>18 years, $n = 112$), referred for transthoracic echocardiographic examination (all performed on VIVID E9 XDclear echo machine, General Electric, Horten, Norway; M5Sc-D probe) at Gent University Hospital were prospectively included between 2015 and 2017. MVP was defined as an abnormal systolic bulging of one or both mitral leaflets into the left atrium (displacement >2 mm above the annular plane in parasternal long axis (PLAX) view) [11,19]. MVP-MR patients were excluded from the analysis in case of suboptimal imaging quality, the presence of ≥2 large MR jets, failure to capture or align the CW beam with the MR jet which can occur in nearly horizontal jets, malcapture of the VCW with the CW-cursor, or in case of variable jet orientation during systole. Patients with a clearly distorted/constrained flow convergence zone (FCZ) and suboptimal vena contracta (VC) area were also excluded from analysis. The study was approved by the local Ethical Committee.

2.2. Echocardiographic assessment of MR with the API method

The API method was applied as previously reported [12]. In brief, CW envelopes of MVP-MR were manually traced in all holosystolic and non-holosystolic patients starting from the mitral closure signal to the end of the CW envelope, also referred to as 'API' or specifically 'API full-trace' (see Figs. 1 and 2). In case of non-holosystolic MR, the MR jet starts later than mitral closure. In addition to the 'API full trace' value, we also determined the API of only the CW envelope independent from mitral valve closure, referred to as 'API jet-only' (see Fig. 2). All echocardiographic acquisitions were performed by a single operator (FT). API analyses were performed using custom-made generic software by the same operator (VK), blinded to the clinical and echocardiographic characteristics of the patients. For the inter- and intra-observer testing, 20 non-holosystolic MVP-MR patients were randomly selected and API tracings were performed by three blinded investigators with different levels of experience. To study API dynamics during MR, the systolic cycle was automatically divided into three phases with equal duration: a proto- (T1), mid- (T2) and telesystolic (T3) phase and the API values were calculated for each phase. The ratio MR duration/systolic time was also calculated, being <100% in non-holosystolic and 100% in holosystolic MR-MVP (Fig. 1, middle and lower panels). An arbitrary MR duration/systolic time cutoff was set at 50% to define MR jets with relative short duration (<50%) and MR jets with relative longer duration (>50%).

2.3. PISA-based methods, VCW and color Doppler grading

The VCW, PISA-EROA and PISA-RV were assessed as previously reported and according to consensus recommendations [11,12]. To determine the PISA-RV, PISA-EROA is multiplied with the time velocity integral (TVI) [11], which was assessed in the 'conventional way', following the contours of the CW envelope. Color Doppler grading of the MR jet was performed by using PLAX, AP2CH, AP4CH and AP5CH chamber views, as described previously [12] and in the supplemental method.

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD (or median with IQR for non-normal distributions) and dichotomous variables as percentage. Normality of data distribution was tested with Shapiro-Wilk test. Analysis of variance (ANOVA) test or Kruskal-Wallis test (for continuous variables) and $\chi 2$ test (for dichotomous variables) were used to evaluate significant group differences. Linear trend among quartiles was evaluated with Jonckheere-Terpstra test or Mantel linear-by-linear test. Correlations were calculated using Pearson's coefficient and Spearman's rank order coefficient. Receiver operator characteristics (ROC) curves were plotted and analyzed in SigmaPlot (Systat, San Jose, USA). All other statistical analyses were performed in SPSS Statistics V.24 (IBM, Armonk, New York, USA). P values < .05 were considered statistically significant.

3. Results

3.1. Feasibility of the API method in MVP-MR

The API method was applicable in 100 out of 112 (89%) MVP patients (non-holosystolic, $n = 47$; holosystolic, $n = 53$). The applicability of VCW and PISA-based methods was lower than the API method (76/112 (68%) and 80/112 (71%), respectively; $p \le .001$).

In Fig. 1, a representative API measurement is shown in a non-holosystolic and holosystolic CW MR envelope (upper and middle panels). In the lower panels, the dynamics of the API is illustrated during the systolic cycle. In non-holosystolic MVP-MR, the pixel intensity increases/appears abruptly at the end of the systole, whereas in the holosystolic example, a more stable pixel intensity during the cardiac cycle is observed.

3.2. Intra- and inter-observer variability of the API method in MVP-MR

As the contours of the CW envelope in non-holosystolic MVP-MR can sometimes be ambiguous, in Fig. 2 (panel A and B), we illustrate how different TVI tracings may impact PISA-based calculation of the RV in a single patient. In our non-holosystolic cohort, 12 patients (26%) had unclear CW envelope borders. A blinded echocardiographer was asked to trace two TVI in the selected patients: a stringent and less stringent TVI tracing. The different tracings resulted in significantly different TVI values (average 158 cm vs 111 cm; $p \le .001$) and significantly different RVs (average 32 ml vs 23 ml; $p < .001$). To assess the reproducibility of the API method in non-holosystolic MVP-MR, we analyzed the intra- and inter-observer variability of the API in this specific cohort because the "imaginary" tracing of the protosystolic phase could possibly introduce significant API measurement error. However, the inter-observer variability between 3 echocardiographers in 20 random patients showed excellent agreement between the different measurements (intra-class correlation (ICC) 0.989, $p < .001$). Intra-observer variability ($n = 20$) had similar results (ICC 0.995, $p < .001$). This illustrates that API tracing of a non-holosystolic CW envelope is a simple and reproducible application.

3.3. Clinical and echocardiographic characteristics

Table 1 shows the clinical and echocardiographic characteristics of non-holosystolic and holosystolic MVP-MR. Holosystolic MVP-MR was significantly more severe than non-holosystolic MVP-MR, which was consistent among all MR grading methods and indirect measures of MR severity such as left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrium (LA) volume or right ventricular systolic pressure (RVSP). Ejection fraction (EF) was not different between both groups (58% vs. 59%, $p = .92$). 55% of patients had Barlow mitral valve disease and 72% of eccentric jets are within the more severe holosystolic cohort, suggesting that eccentric jets have more extensive degeneration of the prolapsing leaflet(s). Finally, the average RV/EROA ratio was 10.3 ml/0.1 cm^2 in the non-holosystolic group versus 18 ml/0.1 cm^2 in the holosystolic group, reflecting the obvious differences in MR duration and thus TVI values between non-holosystolic and holosystolic MVP-MR. Of interest, these values are similar to the values of Topilsky et al. [14]