Jacqueline Bernheim Prize 2021

FONDS POUR LA CHIRURGIE CARDIAQUE asbl – 11 rue Tenbosch – 1000 Bruxelles - 02 644 35 44

Continuous wave Doppler for echocardiographic grading mitral regurgitation: validation of the Average Pixel Intensity method

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Introduction

Mitral regurgitation

Mitral regurgitation (MR), also called mitral insufficiency or mitral incompetence, is defined as an abnormal reversal of blood from the left ventricle (LV) to the left atrium (LA), mostly during systole. MR is one of the most common valve diseases in the Western world.

In **primary MR**, a structural abnormality of one or more components of the mitral valve apparatus leads to MR. In **secondary MR** however, the MR is caused indirectly by LV disease (induced by ischemic or non-ischemic causes), resulting in remodelling of the LV, either global or local. In addition, the reduced LV contractility and LV dyssynchrony impair the MV closing forces.

Grading of MR

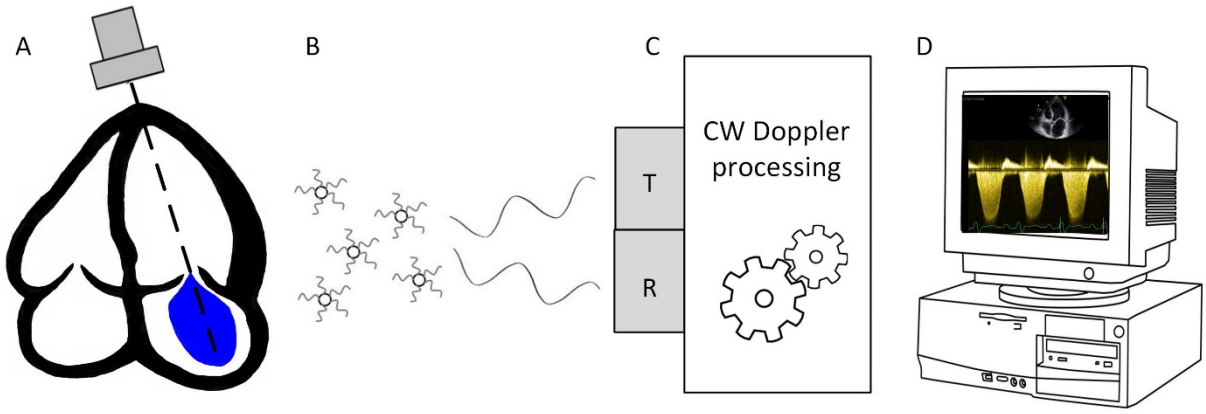
MR severity grading is important for prognostication and decisions regarding timing of surgical or percutaneous intervention. Echocardiography is the cornerstone for diagnosis and grading of MR. Since the introduction of echocardiography, the assessment of MR severity evolved and several qualitative and quantitative methods have been developed to assess the severity of MR. Current international guidelines recommend a multiparametric approach for the assessment of MR. Yet, the echocardiographic grading of MR is challenging and the grading parameters all have several important limitations in terms of real-life accuracy, applicability and sensitivity to machine settings. Moreover, the proposed severity cut-offs vary between European and American guidelines and between MVP-MR and FMR.

We developed and validated a novel echocardiographic parameter to grade MR, the average pixel intensity (API) method, based on pixel intensity analysis of the Continuous Wave Doppler signal. As guidelines mention the supportive role of “eyeballing” the CW intensity, we specifically investigated the feasibility of directly quantifying the CW intensity.

The API method

Concept

MR grading with the API method relies on analysis of the returning and processed backscatter energy. According to the backscatter concept/theory, the API method assumes that the signal intensity of the CW envelope is proportional to the insonated blood flow, hence to the regurgitant blood volume. A CW Doppler ultrasound (US) wave with a given output power and frequency is transmitted by the probe to interrogate the MR jet (panel A in Figure 6). The RBCs in the MR jet act as the major source of scatterers in the CW beam, yielding the final (Doppler shifted) backscatter through constructive and destructive wave interference (B). The frequency and amplitude is extracted from the Doppler shifted signals and processed by the echo machine (C), then displayed as a parabolic envelope with a given velocity profile and pixel intensities (D).



As shown in the figure, the pixel intensity of the CW envelope reflects the severity or amount of MR, and thus allows quantitative grading of MR. This concept may appear simple, however, the theoretical and practical variables governing the CW Doppler intensity of a regurgitant jet are multiple, complex and partially unresolved. Comprehensive theoretical explanation can be found in the PhD thesis.

Validation of the API method

In this research project, we elaborated and validated the API method in a translational fashion from 'bench' to 'bed', using a systematic approach:

- In-vitro validation using a cardiac phantom
- Applicability in different MR aetiologies
- Assessment of reproducibility (inter-/intra-observer agreement)
- Correlations with indirect measures of MR severity such pulmonary pressures and atrial and ventricular dimensions
- Correlations with conventional MR grading methods such as PISA-method, VCW, color Doppler
- Prediction of clinical outcome in different types of MR

1) In-vitro validation

Our group validated the API method in a pulsatile in vitro cardiac phantom with variable EROAs and RVs. The in vitro experiments showed a significant correlation between increasing RVs and API (r=0.81). Similarly, an in vitro increase in the EROA (regardless of stroke volume) from 0.12 to 0.78 cm^2 resulted in a significant increase in API (r=0.88). Furthermore, there was a high inter- and intra-observer agreement for the API method.

2A) Clinical validation in primary MR: prolapse

The API method was feasible in 89 % of all MVP patients (68%, 71% for VCW and PISA method, respectively; $p<0.001$). 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 (such as PISA-EROA, PISA-RV and VCW) and indirect (such as pulmonary pressures and atrial and ventricular dimensions) measures of MR severity.

Based on receiver operating curves (ROC), an API cutoff value of 125 au was suggested to identify severe MR in MVP. Non-holosystolic MR jets (i.e. MR occurs only in the last part of the systolic phase, which is typical in MVP) was mainly associated with non-severe MR (API<125), whereas the majority of holosystolic MVP-MR jets had severe MR (API>125).

Finally, we investigated the medium-term outcome in consecutive MVP patients (n=149). The degree of MR severity by the API method was highly significant for the prediction of events. An API cut-off of 111 au was defined as "severe" MVP-MR with an overall superior sensitivity and specificity compared to cut-offs for established MR grading parameters. In patients who did not have a MACE during the follow-up period (n=92), no significant changes in measures of MR severity were found on follow-up echocardiography.

2B) Clinical validation in primary MR: degenerative non-prolapse MR

In the third study, we describe the echocardiographic characteristics of degenerative non-prolapse mitral regurgitation (DMR) and assess the outcome at medium-term follow-up using the API method. The API grading method had a higher feasibility (94%) compared to proximal isovelocity surface area (PISA) (60%) method and vena contracta width (VCW) (71%) for assessing MR. The API method was predictive for events.

3) Clinical validation in secondary MR in heart failure patients with reduced ejection fraction.

We also investigated the feasibility and added value of the API method more specifically in patients with SMR. Overall, the API method had significant correlations with direct parameters of FMR severity, ejection fraction, atrial and ventricular dimensions, pulmonary pressures and New York Heart Association class.

Similarly to PMR, we performed a medium-to-long term outcome study. During a median follow-up of 24 months, 98 patients (43%) had a major adverse cardiac event (MACE; cardiovascular mortality (n=50, 22%), heart failure hospitalization (n=44, 19%), mitral valve surgery (n=11, 5%), percutaneous mitral intervention (n=12, 5%), heart transplantation (n=5, 2%)). On log-rank test, the API method was highly significant in predicting clinical outcome. On multivariable Cox proportional hazard analysis, SMR grading with the API method was an independent predictor of clinical outcome (along with NYHA class and right ventricular systolic pressure; $p<0.001$), increasing the event risk by 9% per 10 au API rise ($p=0.001$). In the same multivariable analysis, PISA-EROA or PISA-RV were not independent predictors of events ($p=0.18$ and 0.26, respectively).

Importance of the project and future perspectives

In this project, we clinically validated the API method. The project was conceived to improve echocardiographic grading of this common valve problem and as such guide optimal treatment of MR. The concept of API as a processed surrogate for MR flow has the potential to assist in grading MR. First, current guidelines already 'recommend' CW Doppler as a qualitative parameter, with a 'dense MR signal with a full envelope indicating more severe MR than a faint signal'. Second, given the difficulties encountered in grading MR with traditional methods and the increasing complexity on definitions and thresholds for severe MR (AHA/ACC vs. ESC), more feasibility and simplicity in grading MR is desirable to allow broad application. The practical advantages of the API method have been demonstrated at several levels in this project: high inter- and intra-observer agreement, feasibility rates >90% (efficacy versus effectiveness) and a relatively simple and fast application. Third, at the conceptual level, the API method integrates flow dynamics, timing and duration of MR and in contrast to several other echocardiographic methods, it does not rely on (geometric) assumptions, complex and multiple measurements or calculations. This makes the API method suitable for quick assessment and follow-up of MR in the busy clinical practice.

Yet, the translation from this surrogate "flow-measuring" concept into clinical practice remains challenging. Technical issues remain an important limitation. Second, the interest from industry is limited because the focus and future are on 3D automated MR grading (e.g. based on CFD-driven algorithms) and the intensity concept is considered 'old school'. Of note, as it concerns a digital application, the API concept would lend itself easily for the emerging field of artificial intelligence within echocardiography. Third, the current results apply to a strict monocenter experience.

Therefore, further validation of the API method is mandatory to allow the API method to unlock its full potential and make a clinical difference for a significant number of patients. Future research is focusing on improving the conceptual method for grading MR. For instance, we will analyse through in-vitro, in-vivo and in-silico models whether analysis of uncompressed API values (or raw backscatter signals) can improve the concept. Also, a multicenter trial is ongoing and the use of the API method will be tested in stress echocardiography and in tricuspid regurgitation.