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Novel 3-dimensional echocardiographic quantification of mitral regurgitant volume

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STUDY TITLE	Novel 3-dimensional echocardiographic quantification of mitral regurgitant volume
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SPONSOR	Hospital University Germans Trias i Pujol

1. SUMMARY

Study title	Novel 3-dimensional echocardiographic quantification of mitral regurgitant volume
Background	Quantification of mitral regurgitation remains challenging and yet is the main reason to perform or not a surgical or transcatheter intervention. Current methodology relies mainly on 2-dimensional echocardiography, which is not ideal as it has many limitations: it assumes that the regurgitant orifice is circular, does not take into consideration the loading conditions or the flow status of the patient, and takes into consideration the maximum radius of the convergence zone at one single frame neglecting how that convergence zone changes along the cardiac systole. Accordingly, the current methodology leads frequently to underestimated effective regurgitant orifice area and regurgitant volume, has poor reproducibility and needs additional data to define the true grade of mitral regurgitation. Current technical developments have allowed the 3-dimensional reconstruction of the convergence zone of the mitral regurgitant jet along the entire systole. This methodology is semiautomated, limiting the manipulation of the observer at minimum and therefore improving reproducibility of the measurement of regurgitant volume. The 3D-CFQ software (proprietary of Philips Ultrasound) has been used in limited cohort of patients and the comparison with 3-dimensional vena contracta area of the regurgitant jet as well as with cardiac magnetic

	resonance-derived regurgitant volume has not been extensively evaluated.
Hypothesis	1.-The 3D-CFQ software provides better agreement with cardiac magnetic resonance to quantify mitral regurgitant volume from 3-dimensional transesophageal echocardiography as compared to 2-dimensional echocardiographic quantification of mitral regurgitant volume. 2.-In addition, the correlation between 3-dimensional vena contracta area measured on 3-dimensional echocardiographic data of the regurgitant jet and the regurgitant volume quantified with the novel 3D-CFQ software is better than the correlation with 2-dimensional effective regurgitant orifice area quantified with the proximal isovelocity surface area method.
Endpoints	1.-To demonstrate that 3D-CFQ software for the quantification of the mitral regurgitation is more reproducible and accurate than the conventional assessment of mitral regurgitation performed with 2-dimensional echocardiography. 2.-To demonstrate the agreement between 3D-CFQ measurement of the mitral regurgitant volume and the cardiac magnetic resonance measurement of the regurgitant volume is better than the agreement between 2-dimensional echocardiography and cardiac magnetic resonance.
Design	Prospective acquisition of clinically acquired transesophageal echocardiographic and cardiac magnetic resonance data of the mitral regurgitation and retrospective analysis of the data.
Study population	Patients with at least moderate mitral regurgitation of any etiology who are referred for transesophageal echocardiographic evaluation.
Number of patients	At least 150 individuals will be included.
Variables	Demographic data include sex and age, and clinical data included cardiovascular risk factors, clinical symptoms and signs, laboratory data. Echocardiographic data (transthoracic and transoesophageal) and cardiac magnetic resonance data will be analysed using standard of care software and novel 3D-CFQ software.
Data source	Demographic and clinical data will be obtained retrospectively from electronic medical records.

	Echocardiographic and cardiac magnetic resonance data will be acquired and stored in PACS.
Medicinal product or medical device subject to evaluation (where applicable)	3D-CFQ software
Statistical analysis	Categorical variables are presented as frequencies and percentages, and continuous variables are reported as mean ± standard deviation or median with interquartile range (IQR) according to the distribution of the variable. The Student T-test was used for comparison of continuous variables, and the Chi-square test was used to compared categorical variables. Correlations will be assessed with the Pearson test. Reproducibility data will be assessed with the intraclass correlation coefficients and the Bland-Altman plots. A p-value of <0.05 was considered statistically significant for all analyses. All statistical tests were two-sided.
Milestones	- **12 months for data Collection:** Retrospective review of electronic medical records - **4 Weeks for data Analysis:** Statistical processing and evaluation - **2 months for manuscript Preparation and Submission:** Final study report preparation for publication in peer-reviewed medical journals

1. BACKGROUND

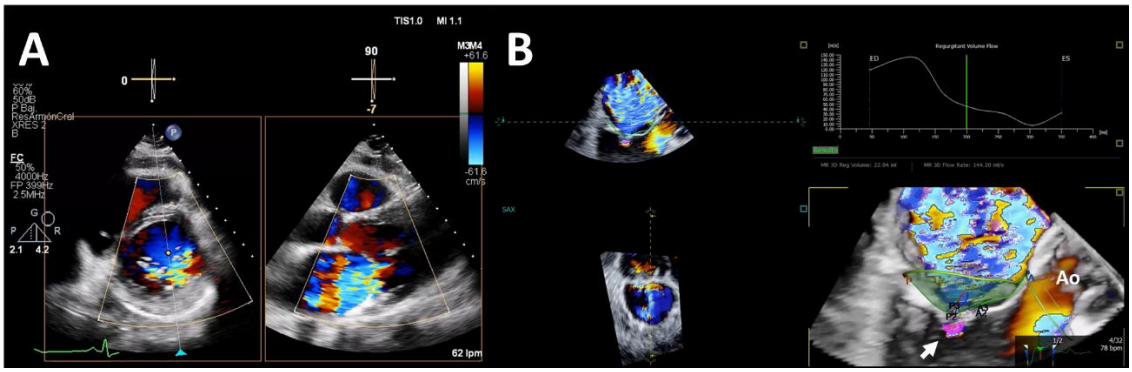
A complete understanding of the etiology of mitral regurgitation (MR) is crucial for a correct diagnosis of valvular dysfunction, and consequently to define and plan the most appropriate therapeutic approach, either surgical or percutaneous. Two main mechanisms have been identified underlying MR (1): Primary or organic MR due to intrinsic involvement of mitral valve (MV) leaflets and chordae tendinae and secondary or functional MR caused by LV pathology. Another classification of mitral valve dysfunction based on leaflet motion was proposed by Carpentier et al in 1983 which is still widely used (2). According to this classification, type I MR is defined as normal leaflet motion, with annular dilatation (by LV or LA dilatation) or leaflet perforation (by endocarditis). Type II MR is characterized by excessive leaflet motion due to degenerative MV disease with chordal elongation or rupture and redundant leaflets, or to papillary muscle rupture (mainly ischemic origin). Finally, type III MR can be distinguished in 2 subtypes: type IIIa, with restricted leaflet motion both in systole and diastole related to leaflet and chordal thickening and retraction secondary to rheumatic valve disease and type IIIb, with restricted leaflet motion only in systole due to LV remodeling (either global or localized) with papillary muscles displacement and chordal tethering. This functional classification can be further refined by segmental MV analysis, including scallops and commissures assessment which permits precise localization of valve dysfunction. Particularly among the degenerative MV diseases (type II MR), this analysis allows the distinction between the 2 most common forms: 1. Barlow disease, where the MV shows multi-segment redundancy, billowing and thickened tissue, and 2. fibroelastic deficiency, where the typical lesion is a chordal rupture with involvement of one single scallop (3). Characterization of MR etiology and MV dysfunction is performed mainly by echocardiography and is crucial to guide surgery or transcatheter intervention. Standard 2-dimensional (2D) transthoracic and transesophageal echocardiography both permit good morphological analysis of MV and subvalvular apparatus with >85% accuracy as compared to surgical inspection (4). However, 2D echocardiography showed suboptimal accuracy in the case of complex mitral lesions, such as commissural prolapse, bileaflet prolapse or cleft. Furthermore, 2D echocardiography is dependent on operator experience and uses geometric assumptions when providing quantitative measures for MR severity (vena contracta width and PISA) or mitral valve dimensions (annular diameters, leaflet height, etc). The introduction of real-time 3D (transesophageal) echocardiography, has significantly improved the diagnostic accuracy, showing a >95% agreement with surgical findings and providing detailed description of MV dysfunction even in complex lesions, allowing a better communication with the surgeon or interventionist (4). Furthermore, when using 3D echocardiography, acquisition and interpretation of the images are faster and less operator-dependent. Finally, 3D echocardiography enables unlimited image plane orientation for better understanding of the complex geometry and spatial relationship between cardiac structures and an optimal alignment for geometric assumption-free measurements.

Transthoracic echocardiography is recommended as the first-line imaging modality for MR assessment and provides useful information including valve anatomy, valve hemodynamics

and hemodynamic consequences. When transthoracic echocardiography is of non-diagnostic value or when further diagnostic refinement is required, transesophageal echocardiography is advocated. Additionally, recent studies have shown the additional value of magnetic resonance imaging (MRI) in assessing the MR severity.
Qualitatively, colour flow imaging is mostly used to assess MR severity. With increasing MR, the size and extent of the regurgitant jet into the LA increases. The presence of a large eccentric jet adhering, swirling and reaching the posterior LA wall supports significant MR. The jet density of the continuous wave (CW) Doppler envelope of the MR jet can be a guide to MR severity. A dense MR signal with a full envelope indicates more severe MR than a faint signal. In severe MR, the CW envelope may be truncated with a triangular contour and an early peak velocity. The presence of flow convergence at a Nyquist limit of 50–60 cm/s should alert to the presence of significant MR. A vena contracta width <3 mm indicates mild MR, whereas a width ≥7 mm defines severe MR. Intermediate values are not accurate for distinguishing moderate from mild or severe MR and require the use of another method for verification. Pulsed wave Doppler evaluation of the pulmonary venous flow pattern helps grading MR severity. A peak E wave velocity >1.5 m/s suggests severe MR in the absence of mitral stenosis. Conversely, a dominant A wave virtually excludes severe MR. The pulsed wave Doppler mitral to aortic time velocity integral (TVI) ratio is also used as an easily measured index in organic MR. A TVI ratio >1.4 strongly suggests severe MR whereas a TVI ratio <1 favours mild MR.
Quantitatively, the flow convergence method is the most recommended quantitative approach. The radius of the proximal isovelocity surface area (PISA) is measured at mid-systole using the first aliasing velocity. Regurgitant volume and effective regurgitant orifice area (EROA) are obtained using the standard formula. The PISA method is based on the assumption of hemispheric symmetry of the velocity distribution proximal to the regurgitant lesion, which may not hold for eccentric jets, multiple jets, or complex or elliptical regurgitant orifices. In the EACVI recommendations (5), primary MR is considered severe if EROA is ≥40 mm^2 and regurgitant volume ≥60 mL. In secondary MR, the thresholds of severity, which are of prognostic value, are 20 mm^2 and 30 mL, respectively. In the 2017, the American Society of Echocardiography focused update on the assessment of MR (6), both primary and secondary MR are considered severe if EROA is ≥40 mm^2, regurgitant volume ≥60 mL and regurgitant fraction ≥50%. Assessment of MR using MRI is reasonable to provide additional information on aetiology and severity, especially for measurements of regurgitant volume and fraction (7,8), whereas the feasibility of MRI for assessing the mechanism of MR and valve repairability are not defined yet. Of note, although MRI is more reproducible, each modality has its potential errors and limitations and is technically demanding. Finally, the presence of severe MR has significant hemodynamic effects, primarily on the LV and LA. When MR is more than mild, it is mandatory to provide the LV diameters, volumes and ejection fraction as well as the LA volume and the pulmonary arterial systolic pressure in the final echocardiographic report.
These highlight the unmet clinical need that we still face in clinical practice: low agreement across methodologies and observers to grade MR, reliance on 2D echocardiographic data with numerous limitations, evaluation of a single frame to extrapolate the quantification of regurgitant volume and limited data to compare 3D imaging techniques (echocardiography and MRI) to establish the true gold standard for the measurement of the regurgitant volume.

Current technical developments have allowed the 3D reconstruction of the convergence zone of the mitral regurgitant jet along the entire systole. This methodology is semiautomated, limiting the manipulation of the observer at minimum and therefore improving reproducibility of the measurement of regurgitant volume. The 3D-CFQ software (proprietary of Philips Ultrasound; see as supplemental material the published white paper and the CE and FDA mark approval) has been used in limited cohort of patients and the comparison with 3-dimensional vena contracta area of the regurgitant jet as well as with cardiac magnetic resonance-derived regurgitant volume has not been extensively evaluated (Figure).

Figure: Assessment of mitral regurgitation using echocardiography. Panel A sows the parasternal biplane views of the mitral regurgitation. Panel B shows the quantification of the regurgitant volume using the novel 3D-CFQ software. The arrow points out the 3D reconstructed convergence zone.



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3. HYPOTHESIS

The present study has two hypotheses:
1.-The 3D-CFQ software provides better agreement with cardiac magnetic resonance to quantify mitral regurgitant volume from 3-dimensional transesophageal echocardiography as compared to 2-dimensional echocardiographic quantification of mitral regurgitant volume.
2.-In addition, the correlation between 3-dimensional vena contracta area measured on 3-dimensional echocardiographic data of the regurgitant jet and the regurgitant volume quantified with the novel 3D-CFQ software is better than the correlation with 2-dimensional effective regurgitant orifice area quantified with the proximal isovelocity surface area method.

4. ENDPOINTS

4.1. Primary and secondary endpoints

The primary objective is to demonstrate that 3D-CFQ software for the quantification of the mitral regurgitation is more reproducible and accurate than the conventional assessment of mitral regurgitation performed with 2-dimensional echocardiography.
The secondary objective is to demonstrate the agreement between 3D-CFQ measurement of the mitral regurgitant volume and the cardiac magnetic resonance measurement of the regurgitant volume is better than the agreement between 2-dimensional echocardiography and cardiac magnetic resonance.

5. METHODS

5.1 Type of study

This is a prospective, multicenter observational study.

5.2 Design

This is a prospective, multicenter observational study. Patients with at least moderate mitral regurgitation of any etiology who are referred for transesophageal echocardiographic evaluation will be included. Patients without contraindications for

cardiac magnetic resonance will undergo this exam to compare the echocardiographic data with the cardiac magnetic resonance data as indicated in the study.

5.3 Study population

Inclusion criteria: Patients 18 year-old or older with at least moderate mitral regurgitation of any etiology who are referred for transesophageal echocardiographic evaluation and provide signed informed consent will be included. Patients without contraindications for cardiac magnetic resonance will undergo this exam to compare the echocardiographic data with the cardiac magnetic resonance data as indicated in the study.
Exclusion criteria: Patients with contraindications for transesophageal echocardiography or cardiac magnetic resonance, patients with mitral valve prosthesis, and patients who do not provide informed consent to participate in the study.

5.4 Variables

5.4.1 Outcome, exposure or effect variables

The study will analyse multiple variables, including demographic characteristics such as age and sex. Clinical parameters will encompass cardiovascular risk factors, presenting symptoms, and relevant laboratory data.
Echocardiographic data: conventional data to define etiology of the mitral regurgitation and grade of mitral regurgitation. Quantitative data of mitral regurgitation including: vena contracta area, effective regurgitant orifice, regurgitant volume.
Cardiac magnetic resonance: conventional data of cardiac chamber dimensions, mitral regurgitant volume with phase contrast sequences.

5.5 Study evaluations:

Transthoracic and transesophageal echocardiography and cardiac magnetic resonance, all clinically indicated for the management of the patients. Patients will not be exposed to additional examinations that are not clinically indicated.

5.6 Sample size

The ideal number of patients for an international, multicenter study comparing three-dimensional transesophageal echocardiography and cardiac magnetic resonance imaging for quantifying mitral regurgitation should be at least 150 patients. This sample size is justified by the need to ensure adequate statistical power for subgroup analyses (e.g., primary vs. secondary mitral regurgitation, varying degrees of severity, and jet morphology), to account for inter-center variability, and to provide robust estimates of agreement and diagnostic accuracy.

Previous multicenter studies comparing echocardiography and CMR for mitral regurgitation have included 103 patients, while meta-analyses have aggregated data from over 1,000 patients across multiple studies, but these have not focused exclusively on head-to-head three-dimensional transesophageal echocardiography vs cardiac magnetic resonance comparisons. Single-center studies with direct 3D TEE-CMR comparison have been limited to 30 patients. Given the heterogeneity of mitral regurgitation and the need for generalizability across diverse populations and imaging platforms, a sample size in the 150-200 range is consistent with contemporary multicenter imaging studies and would allow for meaningful statistical analysis and external validity. This approach aligns with the consensus in the imaging literature that larger, multicenter studies are needed to validate and refine quantitative imaging techniques for mitral regurgitation.

5.7 Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are reported as mean ± standard deviation or median with interquartile range (IQR) according to the distribution of the variable. The Student T-test was used for comparison of continuous variables, and the Chi-square test was used to compared categorical variables. Correlations will be assessed with the Pearson test. Reproducibility data will be assessed with the intraclass correlation coefficients and the Bland-Altman plots. A p-value of <0.05 was considered statistically significant for all analyses. All statistical tests were two-sided.

5.8 Study limitations

The limitations of the study include the possibility of selection bias (only patients with at least moderate mitral regurgitation) and the change in loading conditions between the transesophageal echocardiography and the cardiac magnetic resonance.

6. SOURCES FOR OBTAINING AND MANAGING DATA

6.1 Source of data

The data will be collected from medical records and PACs.

6.2 Data management and quality control

Data will be systematically recorded and stored pseudoanonymised in a secured database. Procedures will be implemented to identify and address missing or erroneous data, including cross-checking and validation against source records.
Imaging (echocardiographic and cardiac magnetic resonance) data will be uploaded to a research platform on the IGTP campus, called ARIADNA (Archive of Imaging Data for the

Development of New Applications). This IT infrastructure allows you to manage and share medical images securely with the project researchers, without violating the confidentiality of the data. The procedure, before transferring the images to the platform, includes a pseudo-anonymization process, this allows the images uploaded to the platform to not contain any personal data, but the process of eliminating the name and data is reversible if necessary, for clinical or research reasons. This is possible because the decoding is recorded on an internal HGTP computer, protected by a password. The pseudonymization of the collected data in the database is performed by a third person with technical and functional independence from the research team and access to SAP. Once the images are pseudo-anonymized and available in ARIADNA, a comparative analysis of the images will be carried out, which must guarantee the coherence of the information obtained from both acquisition techniques.

7. ETHICAL AND LEGAL ASPECTS

Commitment to submitting the study for evaluation by an accredited Research Ethics Committee (CEIm).

Commitment to complying with the fundamental ethical principles outlined in the Declaration of Helsinki (Helsinki, October 2024) and with the specific regulations applicable to the type of study:

- *Research involving the analysis and storage of biological material: Law 14/2007 on Biomedical Research and Royal Decree 1716/2011 on the regulation of Biobanks.*
- *Observational studies with medicinal products: Royal Decree 957/2020, of November 3, regulating observational studies with medicinal products for human use.*

7.1 Benefit-risk assessment for research subjects

If the study demonstrates the hypotheses, the benefit for the patients is obvious since we will be validating a novel method that is more accurate and reproducible to quantify mitral regurgitation, improving the decision making of the patients.

7.2 Information to subjects and informed consent

Patients will be informed about the clinically indicated examinations and the postprocessing of the data for research purposes, without impacting on the decision making of the patients. Patients will be asked to sign the informed consent for the use of the acquired data for research purposes.

7.3 Confidentiality and data protection

All patient data will be pseudoanonymised and handled in compliance with national and EU data protection laws, including the General Data Protection Regulation (GDPR) and Spanish Organic Law 3/2018. Data will be securely stored, with access restricted to authorized researchers only.

7.4 Interference with prescribing and dispensing habits

This is a prospective observational study and the results will not impact on the clinical management of the patients.

7. MANAGEMENT AND COMMUNICATION OF ADVERSE REACTIONS

The examinations that will be performed are clinically indicated and the risk of complications is minimal. However, any significant findings regarding patient safety or potential complications identified in the data analysis will be communicated to the relevant clinical authorities.

8. OBTAINING AND MANAGING BIOLOGICAL SAMPLES

If imaging data is considered a biological sample, the data will be stored in PACS and additionally for the multicenter design of the study, only the echocardiographic and cardiac magnetic resonance data will be uploaded to a research platform on the IGTP campus, called ARIADNA (Archive of Imaging Data for the Development of New Applications). This IT infrastructure allows you to manage and share medical images securely with the project researchers, without violating the confidentiality of the data. The procedure, before transferring the images to the platform, includes a pseudo-anonymization process, this allows the images uploaded to the platform to not contain any personal data, but the process of eliminating the name and data is reversible if necessary, for clinical or research reasons. This is possible because the decoding is recorded on an internal HGTP computer, protected by a password. This process will be done internally at the HGTP. Once the images are pseudo-anonymized and available in ARIADNA, a comparative analysis of the images will be carried out, which must guarantee the coherence of the information obtained from both acquisition techniques.

9. PLANS FOR DISSEMINATION AND COMMUNICATION OF RESULTS

The study findings will be presented at scientific conferences and submitted for publication in peer-reviewed medical journals.

10. SOURCE OF FUNDING

Philips will support providing the ultrasound system equipped with the software and the offline software for analysis of the data.

11. WORK PLAN FOR CARRYING OUT THE STUDY

1 **Data Collection:** Prospective acquisition of echocardiographic and cardiac magnetic resonance data
2 **Data Analysis:** Statistical processing and evaluation
3 **Manuscript Preparation and Submission:** Final study report preparation for publication in peer-reviewed medical journals