JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 14, 2021

NEW RESEARCH PAPERS

STRUCTURAL

Validation of Prosthetic Mitral Regurgitation Quantification Using Novel Angiographic Platform by Mock Circulation

Hideyuki Kawashima, MD,[a,b,*] Patrick W. Serruys, MD, PhD,[a,c,*] Rodrigo Modolo, MD, PhD,[b,d] Michele Pighi, MD,[e] Rutao Wang, MD,[a,f] Masafumi Ono, MD,[a,b] Jean-Paul Aben, MSc,[g] Chun Chin Chang, MD,[h] Hadewych Van Hauwermeiren, DVM, MLAS,[i] Bill Brunnett, BsME,[j] Martijn Cox, PhD,[j] Liesbeth Rosseel, MD,[a] Darren Mylotte, MD, PhD,[a] Philippe Pibarot, DVM, PhD,[k] Willem J. Flameng, MD, PhD,[l] Yoshinobu Onuma, MD, PhD,[a] Osama Soliman, MD, PhD[a]

ABSTRACT

OBJECTIVES This study aimed to validate a dedicated software for quantitative videodensitometric angiographic assessment of mitral regurgitation (QMR).

BACKGROUND Quantitative videodensitometric aortography of aortic regurgitation using the time-density principle is a well-documented technique, but the angiographic assessment of mitral regurgitation (MR) remains at best semi-quantitative and operator dependent.

METHODS Fourteen sheep underwent surgical mitral valve replacement using 2 different prostheses. Pre-sacrifice left ventriculograms were used to assess MR fraction (MRF) using QMR and MR volume (MRV). In an independent core lab, the CAAS QMR 0.1 was used for QMR analysis. In vitro MRF and MRV were assessed in a mock circulation at a comparable cardiac output to the in vivo one by thermodilution. The correlations and agreements of in vitro and in vivo MRF, MRV, and interobserver reproducibility for QMR analysis were assessed using the averaged cardiac cycles (CCs).

RESULTS In vivo derived MRF by QMR strongly correlated with in vitro derived MRF, regardless of the number of the CCs analyzed (best correlation: 3 CCs $y = 0.446 + 0.994x$; $R = 0.784$; $p = 0.002$). The mean absolute difference between in vitro derived MRF and in vivo derived MRF from 3 CCs was $0.01 \pm 4.2\%$ on Bland-Altman analysis. In vitro MRV and in vivo MRV from 3 CCs were very strongly correlated ($y = 0.196 + 1.255x$; $R = 0.839$; $p < 0.001$). The mean absolute difference between in vitro MRV and in vivo MRV from 3 CCs was -1.4 ± 1.9 ml. There were very strong correlations of in vivo MRF between 2 independent analysts, regardless of the number of the CCs.

CONCLUSIONS In vivo MRF using the novel software is feasible, accurate, and highly reproducible. These promising results have led us to initiate the first human feasibility study comprising patients undergoing percutaneous mitral valve edge-to-edge repair. (J Am Coll Cardiol Intv 2021;14:1523–34) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, National University of Ireland, Galway (NUIG) and CORRIB Corelab and Center for Research and Imaging, Galway, Ireland; [b]Department of Cardiology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; [c]Department of Cardiology, Imperial College of London, London, United Kingdom; [d]Cardiology Division, Department of Internal Medicine, University of Campinas, Campinas, Brazil; [e]Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy; [f]Department of Cardiology, Radboud University Medical Center, Nijmegen, Netherlands; [g]Pie Medical Imaging, Maastricht, the Netherlands; [h]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [i]Medanex Clinic B.V., Preclinical CRO, Diest, Belgium; [j]Xeltis B.V., Eindhoven, the Netherlands; [k]Institut Universitaire de

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2021.04.046

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AUC = area under the curve

CI = confidence interval

EDV = end-diastolic volume

ESV = end-systolic volume

ICC = intraclass correlation coefficient

IQR = interquartile range

LA = left atrium/atrial

LV = left ventricle/ventricular

LVOT = left ventricular outflow tract

MFFV = mitral forward flow volume

MR = mitral regurgitation

MRF = mitral regurgitation fraction

MRV = mitral regurgitation volume

QAR = quantitative videodensitometric angiographic assessment of aortic regurgitation

QMR = quantitative videodensitometric angiographic assessment of mitral regurgitation

RA = reference area

ROI = region of interest

SV = stroke volume

Quantitative videodensitometric angiographic assessment of aortic regurgitation (QAR) severity is based on the concept of comparing opacification of the left ventricular outflow tract (LVOT) to that of the aortic root after aortography (1,2). This QAR method relies on the time-density changes in the LVOT after angiographic contrast medium injection in the aorta and its regurgitation (and subsequently density increase) in the LVOT. The ratio between the areas under the 2 time-density curves of these regions is the aortic regurgitation (AR) expressed as a percentage (3,4).

SEE PAGE 1535

In contrast, angiographic assessment of mitral regurgitation (MR) remains at best semi-quantitative (Sellers classification) (5) and operator dependent. Therefore, there is a need for objective quantitation of MR, particularly in the presence of multiple regurgitation jets, as seen even after mitral valve edge-to-edge repair. Theoretically, by applying the same concept of the QAR to the mitral valve (quantitative videodensitometric angiographic assessment of MR [QMR]) using the CAAS QMR 0.1 (Pie Medical, Maastricht, the Netherlands), it could be possible to translate the method of measurement used for AR to the MR. Traditionally, novel algorithms of measurement have to be validated in vitro and in vivo to establish the accuracy and precision of a novel method of assessment.

The aims of the present study are to develop and validate a QMR platform based on the novel software and validate the MR quantification method in vivo in an ovine model, through a postmortem in vitro assessment using a well-calibrated and controlled mock circulation.

METHODS

PHANTOM VALIDATION OF THE CONCEPT OF VIDEODENSITOMETRY. The most common objection raised by the clinicians with regard to QAR methodology is the potential error in the measurement due to the parallax effect. The videodensitometric approach aims precisely to circumvent that issue; the videodensitometric measurement is the constant product of the area, in which the radiopaque contrast is detected, times the density (hemodilution) of the radiopaque contrast in that area/volume. The detailed methodology of the phantom validation is described in the extended Methods section of the Supplemental Appendix and in Supplemental Figure 1.

IN VIVO TESTING USING A PRECLINICAL OVINE MODEL. A total of 14 sheep underwent surgical mitral valve replacement under general anesthesia (**Central Illustration**). A prototype prosthetic valve with endogenous tissue restoration technology described in the Supplemental Appendix: the Xeltis biorestorative prosthetic surgical aortic heart valve 25 mm (Xeltis BV, Eindhoven, the Netherlands) was implanted reversed in mitral position in 9 animals and compared with a commercially available bioprosthetic (pericardial) aortic valve of 25 mm, which was implanted in mitral position in 5 animals. In the present study, the Xeltis surgical aortic valve was implanted reversed in a mitral position of an ovine model. At predetermined time point, the animals underwent cardiac catheterization and then were euthanatized. The detailed methodology of cardiac catheterization, euthanasia, and explantation are described in the Supplemental Appendix.

The study protocol adhered to the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes and the Guide for the Care and Use of Laboratory Animals and was reviewed and approved by the Test Facility's Ethical Committee for compliance with regulations prior to study initiation.

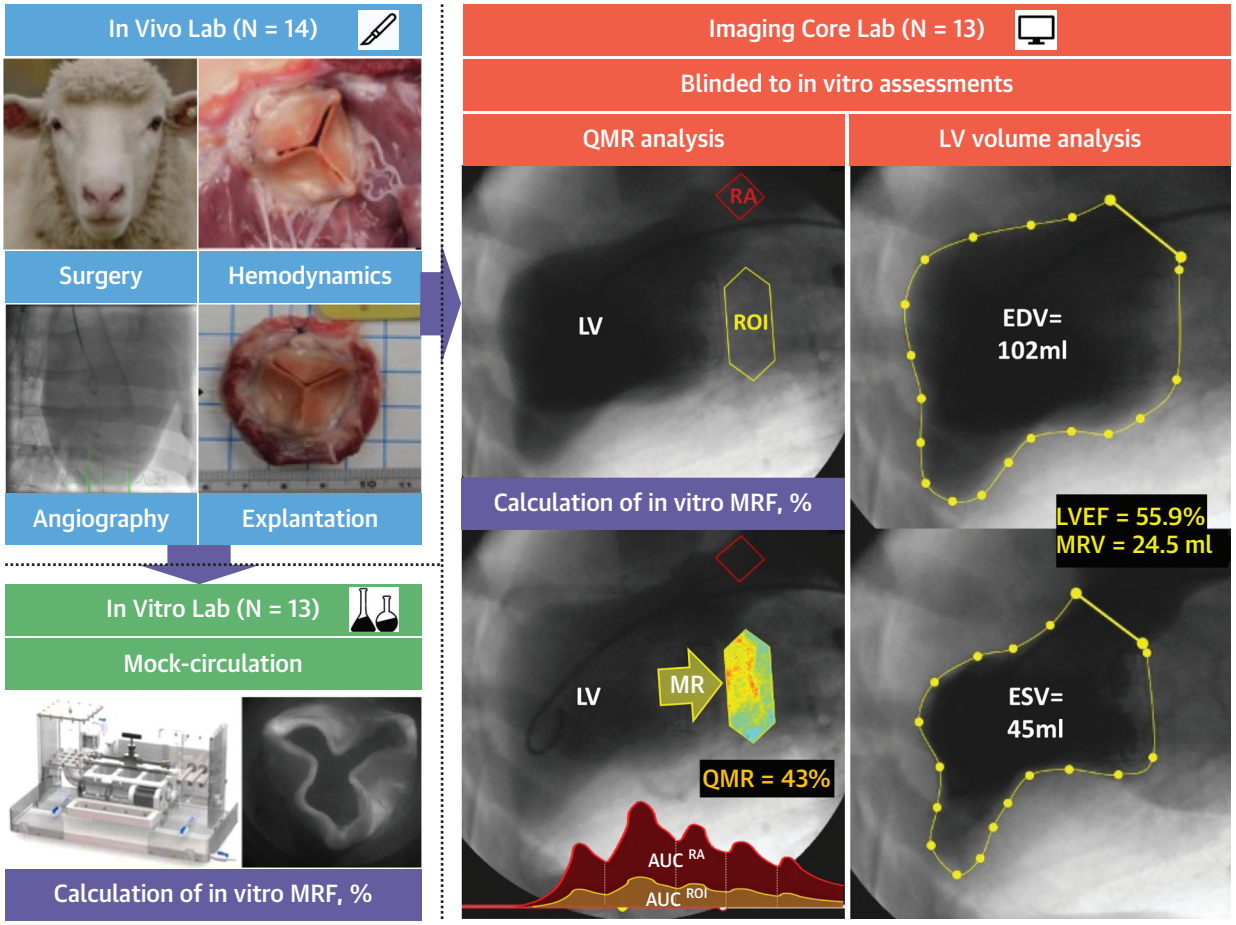
IN VITRO TESTING OF MR. All valves were tested within 48 h of explantation and stored under refrigeration prior to testing. Excessive tissue was removed from the valve to allow the sewing ring to be mounted to the valve holder. Valve performances were tested under normotensive mitral conditions in accordance with the ISO 5840-1: 2015. A mock circulation (HDT-500 Hydrodynamic Test System; BDC Laboratory, Wheat Ridge, Colorado)

Cardiologie et de Pneumologie de Québec/Québec Heart and Lung Institute, Université Laval, Québec City, Québec, Canada; and the [1]Department of Cardiac Surgery, Katholieke Universiteit Leuven, Leuven, Belgium. * Drs. Kawashima and Serruys contributed equally to this work.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 12, 2021; revised manuscript received April 22, 2021, accepted April 27, 2021.

CENTRAL ILLUSTRATION **Flowchart Displaying Analysis Steps of the In Vivo, In Vitro, and the Imaging Core Lab**



Kawashima, H. et al. J Am Coll Cardiol Intv. 2021;14(14):1523-34.

The experiment was conducted at the in vivo and in vitro labs and at the imaging core lab. Mitral regurgitation (MR) parameters were compared between the in vivo and in vitro findings. Please consult the main text for more details. EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MRF = mitral regurgitation fraction; MRV = mitral regurgitation volume; QMR = quantitative videodensitometric angiographic assessment of mitral regurgitation; RA = reference area; ROI = region of interest.

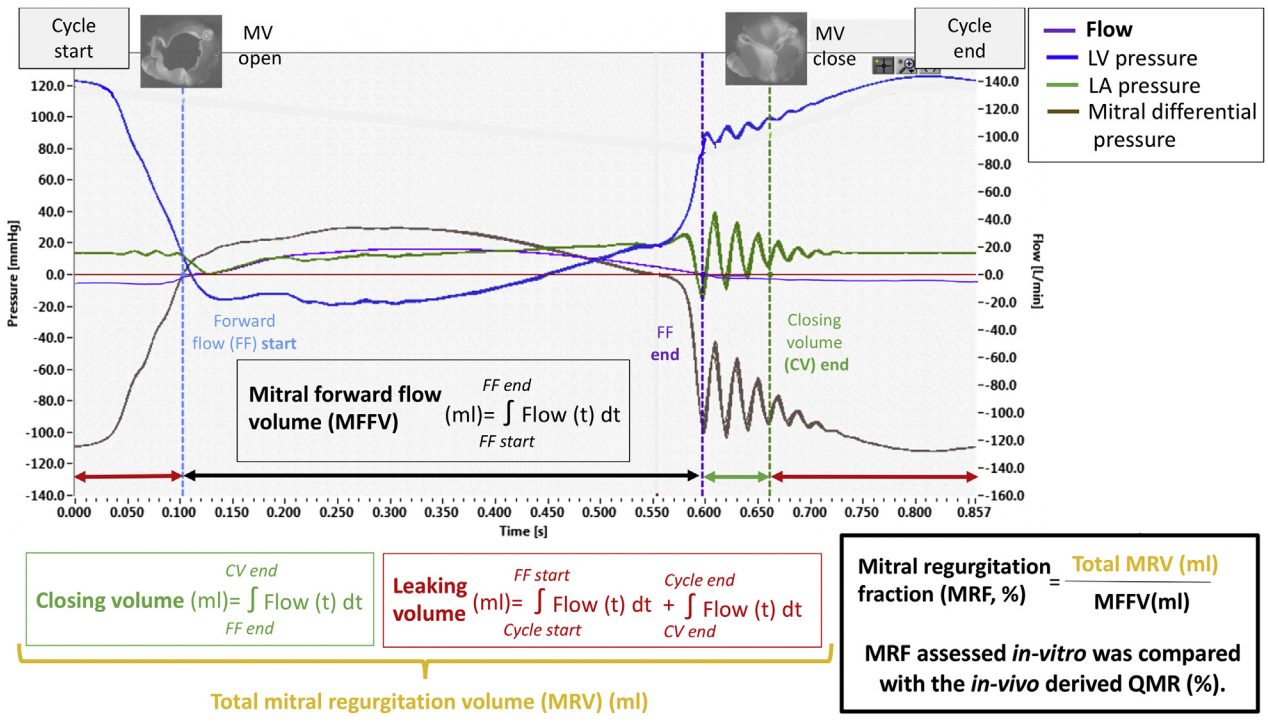
was used to test the impact of different flow conditions (**Central Illustration**). The in vitro parameters were measured at a cardiac output comparable with the measurement obtained by the thermodilution (Supplemental Table 1).

The calculations of the in vitro parameters are shown in **Figure 1**. The in vitro regurgitation output (total MR volume [MRV]) consists of the leaking volume and the closing volume. The mitral forward flow volume (MFFV) is the forward flow through the mitral valve, defined as the volume between the start of forward flow and the end of forward flow. MR fraction (MRF) is calculated using the following formula: MRF (%) = total MRV (ml)/MFFV (ml) × 100.

IMAGING CORE LAB ASSESSMENT OF IN VIVO MR AND LV FUNCTION. An independent imaging core lab (CORRIB Core Lab, Galway, Ireland) received all post-procedural LV angiographies (**Central Illustration**). Core lab analysts were blinded to all other findings of the in vitro lab. In the imaging core lab, the following analyses were preformed: 1) QMR analysis using the QMR software; and 2) global LV function analysis using the CAAS LVA 8.2 (Pie Medical).

QMR ANALYSIS. The principle of the QMR software is to use a left ventriculogram to quantify the time-density area under the curves (AUCs) from the left atrial (LA) (region of interest [ROI], representative of

FIGURE 1 Mock Circulation Hemodynamic and Volumetric Measurements and Calculations of Quantitative Parameters of Mitral Regurgitation



The purple line indicates flow (l/min), the **blue line** indicates left ventricular (LV) pressure, the **green line** indicates left atrial (LA) pressure, and the **brown line** indicates mitral differential pressure. Total mitral regurgitation volume (MRV) (ml) = Closing volume (ml) + Leaking volume (ml). Mitral regurgitation fraction (MRF) (%) = total MRV (ml) / mitral forward flow volume (MFFV) (ml) × 100. MRF assessed in vitro was compared with the in vivo derived MRF obtained by quantitative videodensitometric angiographic assessment of mitral regurgitation (QMR). MV = mitral valve.

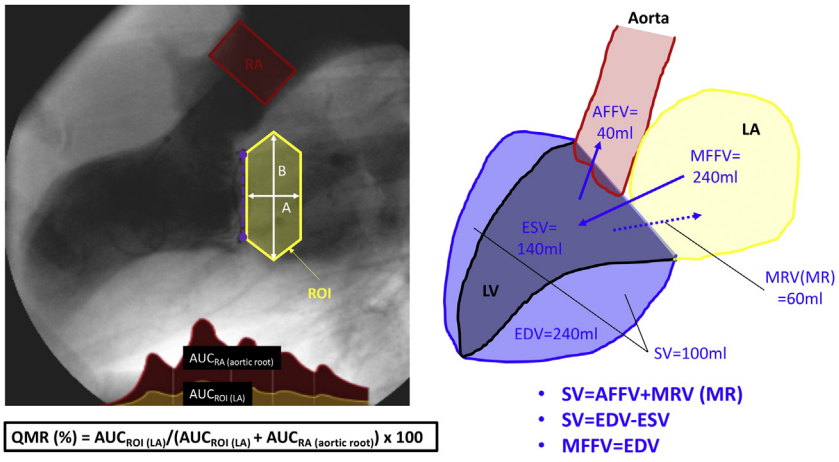
MR) and a reference area at the aortic root (reference area [RA], representative of aortic forward flow) (Figure 2, Video 1). The ROI in the LA is a transit zone of regurgitation with a hexagonal shape to cover eccentric jets. This area is appended to the mitral annulus (purple dotted line in Figure 2). The size and shape of the hexagon is then automatically determined by its short axis and long axis A and B, which are by default related to the length of the purple dotted line: A (mm) = 0.6 · length of purple dotted line (mm) and B (mm) = 1.5 · length of purple dotted line (mm). These multiplying factors (0.6 and 1.5) have been empirically determined from numerous observations of MR in human cases (Figure 2). The in vivo derived MRF by QMR can be calculated from the following formula:

$$\textit{In vivo derived MRF}\left(\%\right) = \left(\frac{AUC_{ROI\ (LA)}}{AUC_{ROI\ (LA)} + AUC_{RA\ (aortic\ root)}}\right) \cdot 100$$

In this formula, the time-density AUC in the aortic root is a surrogate of the aortic forward flow volume (AFFV) and the time-density AUC in the LA is surrogate of MR (MRV) and the sum of both is a surrogate of the stroke volume (SV) (Figure 2). To simplify, if a patient has an end-diastolic volume (EDV) of 240 ml and an end-systolic volume (ESV) of 140 ml, his SV amounts to 100 ml. If 40 ml flow toward the aorta (AFFV) and 60 ml flow backward into the LA (MRV, that is MR), MRF amounts to 60% (60 min/100 ml) (Figure 2). The in vivo derived MRF by QMR was computed using 1 and an average of 2, 3, and 4 cardiac cycles and compared with the in vitro derived MRF. Furthermore, the interobserver reproducibility analysis of the in vivo derived MRF by QMR assessed by 2 independent core lab analysts was performed.

LV FUNCTION ANALYSIS. A complete cardiac cycle was analyzed frame by frame from each post-procedural left ventriculogram. LV contours were manually drawn in each frame using metallic catheter markers (10 mm apart) or a 5-F pigtail catheter as scaling device. Instantaneous volume change was calculated according to Simpson's rule (6). EDV and

FIGURE 2 **Diagram Displaying Basic In Vivo Angiographic Contours and Calculations of MR Using the Novel QMR Platform**



(Left) The principle of the QMR software is to use a left ventriculogram to quantify the time-density area under the curves (AUCs) from the LA (region of interest [ROI], representative of mitral regurgitation [MR]) and the aortic root (reference area [RA], representative of aortic forward flow). The ROI in the LA is a transit zone of regurgitation of hexagonal shape appended to the mitral annulus **(purple dotted line)**. The size and shape of the hexagon is then automatically determined by its short axis and long axis **A and B**, which are by default related to the **length of the purple dotted line**: A (mm) = 0.6 · length of purple dotted line (mm); B (mm) = 1.5 · length of purple dotted line (mm). **(Right)** In presence of MR, the flow from the LV (stroke volume [SV], ml) is divided into LV to aorta (aorta forward flow volume [AFFV], ml) and LV to LA (MRV, ml). The ratio of MR (%) = MRV (ml)/SV (ml). SV (ml) = end-diastolic volume (EDV) (ml) − end-systolic volume (ESV) (ml). MFFV (ml) is the forward flow through the mitral valve, which is equal to EDV. To simplify, if a patient has an EDV of 240 ml and an ESV of 140 ml, their SV amounts to 100 ml. If 40 ml flow toward the aorta (AFFV) and 60 ml flow backward into the LA (MRV, that is MR), MRF amounts to 60% (60 min/100 ml). Abbreviations as in Figure 1.

ESV were measured, and SV, cardiac output, and LV ejection fraction (LVEF) were calculated. The in vivo MRV was calculated by the following formula based on the angiographic QMR analysis:

$$\textit{In vivo}\ \text{MRV}\ (\text{ml}) = \text{SV}\ (\text{ml}) \cdot \textit{In vivo derived MRF}(\%)$$

The calculation of the in vivo MRV was obtained from the in vivo derived MRF averaged from 3 cardiac cycles. The in vivo MRV was compared with the in vitro total MRV. Furthermore, the intraobserver reproducibility analysis of the LVEF measurements was performed in all cases.

STATISTICAL ANALYSIS. Quantitative variables are reported as mean ± SD and median and interquartile range (interquartile range [IQR]). Categorical variables are expressed as numeric values and percentages. The correlation and agreement on the in vitro derived MRF and the in vivo derived MRF by QMR and the in vitro total MRV and the in vivo MRV were analyzed using the Passing-Bablok regression, Spearman's rank correlation, and Bland-Altman method. Similarly, the interobserver reproducibility evaluation of the in vivo derived MRF by QMR assessed by the independent 2 core lab analysts and the intraobserver reproducibility evaluation of LVEF measurements were investigated using the same methods. Furthermore, because those data were continuous, intraclass correlation coefficients (ICCs) were calculated. A 2-sided p value < 0.05 was considered to be statistically significant. All data were processed using SPSS version 26.0 (IBM, Armonk, New York).

RESULTS

VIDEODENSITOMETRIC ASSESSMENT OF RADIOPAQUE VOLUME IN EGG-SHAPED AND SPHERE PHANTOMS DURING ROTATION. The scatterplots in Supplemental Figure 2 show the results of videodensitometric quantification from cine-angiographic recording of an egg-shaped phantom in various projections (top panel). The measurement was robust during the rotation with a maximum error of <2.5%. When the same analysis was performed using a sphere phantom with a high radiopacity, the maximum error was <2.0% (bottom panel).

IN VIVO AND IN VITRO EXPERIMENTS. Thirteen female sheep of a crossbred between Swifter breed and Texel breed (age: mean 14.6 ± 1.6 months, median 15.0 months [IQR: 12.8 to 15.9 months]; weight: 51.3 ± 6.7 and 55.4 kg [IQR: 44.6 to 56.6 kg]) had

TABLE 1 Baseline Characteristics, In Vitro Hemodynamic Parameters of a Mock Circulation, and In Vivo Left Ventriculogram Analysis by an Independent Core Lab in an Ovine Model

	Mean ± SD	Median (IQR)
Baseline characteristics		
Age, months	14.6 ± 1.6	15.0 (12.8–15.9)
Weight, kg	51.3 ± 6.7	55.4 (44.6–56.6)
Mock circulation		
CO-M, l/min	3.1 ± 0.3	3.0 (3.0–3.4)
CO-T, l/min (only for comparison)	3.1 ± 0.5	3.3 (2.8–3.4)
AFFV, ml	39.7 ± 4.5	39.1 (37.2–41.0)
MFFV, ml	44.7 ± 3.6	42.9 (42.9–48.6)
Closing volume, ml	2.1 ± 1.2	1.9 (1.6–2.9)
Leaking volume, ml	2.9 ± 4.1	1.0 (0.6–3.9)
Total MRV, ml	5.0 ± 4.9	3.8 (2.2–6.0)
In vitro derived MRF, %	10.9 ± 9.8	8.9 (5.1–13.3)
Left ventriculogram		
EDV, ml	90.6 ± 15.5	91.3 (80.7–97.8)
ESV, ml	33.6 ± 9.2	34.1 (26.7–36.6)
SV (MFFV), ml	57.0 ± 11.5	57.0 (45.8–67.2)
LVEF, %*	63.0 ± 7.2	63.2 (60.7–66.4)
$AUC_{ROI\ (LA)}$	663.3 ± 930.2	384.4 (219.7–705.1)
$AUC_{RA\ (aortic\ root)}$	4,223.5 ± 1,945.2	3,309.0 (2,643.5–5,265.9)
In vivo derived MRF by QMR, %	10.9 ± 8.7	9.8 (4.2–12.5)
MRV, ml	6.4 ± 6.2	5.6 (2.5–7.5)
AFFV, ml	50.6 ± 10.4	50.4 (41.1–59.7)

Using a preclinical ovine model, the in vitro derived MRF was assessed in a mock circulation at the cardiac output (CO-M) comparable to the one recorded in vivo by thermodilution (CO-T). Total MRV (ml) = Closing volume + Leaking volume. In vitro derived MRF (%) = Total MRV (ml) / MFFV (ml) × 100. SV (ml) = EDV (ml) − ESV (ml). MRV (ml) = SV (ml) · In vivo derived MRF by QMR (%). AFFV (ml) = SV (ml) − MRV (ml). *In vivo derived MRF* $\left((\%) = \left(\frac{AUC_{ROI\ (LA)}}{AUC_{ROI\ (LA)} + AUC_{RA\ (aortic\ root)}}\right) \cdot 100\right)$. *The second LVEF measurements by the independent core lab analyst are described in the table.

AFFV = aortic forward flow volume; AUC = area under the curve; CO-M = cardiac output applied to the mock circulation; CO-T = cardiac output derived from thermodilution; EDV; end-diastolic volume; ESV = end-systolic volume; IQR = interquartile range; MFFV = mitral forward flow volume; MRF = mitral regurgitation fraction; MRV = mitral regurgitation volume; LA = left atrium; LVEF = left ventricular ejection fraction; QMR = quantitative videodensitometric angiographic assessment of mitral regurgitation; RA = reference area; ROI = region of interest; SV = stroke volume.

available data for analysis (**Table 1,** Supplemental Table 1). One animal died before performing left ventriculograms due to a severe impairment of the LV systolic function on echocardiography and acute hemodynamic deterioration following anesthesia. The complete analyses were feasible in all 13 animals. The baseline characteristics of 13 animals are presented in Supplemental Table 1. The mock circulation results are shown in Supplemental Table 2. The results of the core lab analyses of 13 animals according to the left ventriculograms are presented in Supplemental Table 3. The mean ± SD of baseline characteristics, in vitro hemodynamic parameters in a mock circulation, and in vivo left ventriculogram analysis of 13 animals in an independent core lab are summarized in **Table 1**.

IN VITRO VERSUS IN VIVO MR FRACTION. The correlations and agreements between the in vitro derived MRF and the in vivo derived MRF by QMR using 1 and an average of, 2, 3, and 4 cardiac cycles are shown in **Figure 3**. The in vivo derived MRF obtained by QMR strongly correlated with the in vitro derived MRF, regardless of the number of the cardiac cycles analyzed. However, the best correlation was achieved using 3 cardiac cycles ($y = 0.446 + 0.994x$; $R = 0.784$; $p = 0.002$). The Bland-Altman analysis demonstrated a mean absolute difference of 0.01% and SD of ±4.2% between the in vitro derived MRF and the in vivo derived MRF averaged from 3 cardiac cycles. The ICC between the in vitro derived MRF and the in vivo derived MRF averaged from 3 cardiac cycles were excellent (ICC = 0.946; 95% confidence interval [CI]: 0.822 to 0.983).

IN VITRO VERSUS IN VIVO MR VOLUME. The correlation and agreement of the in vitro total MRV (closing volume + leaking volume) and in vivo MRV are shown in **Figure 4**. The in vitro total MRV and in vivo MRV averaged from 3 cardiac cycles were very strongly correlated ($y = 0.196 + 1.255x$; $R = 0.839$; $p < 0.001$). The Bland-Altman analysis demonstrated a mean absolute difference of -1.4 ml and SD of ±1.9 ml between the in vitro total MRV and in vivo MRV averaged from 3 cardiac cycles. The ICC between the in vitro total MRV and in vivo MRV derived from 3 cardiac cycles was excellent (ICC = 0.971; 95% CI: 0.904 to 0.991).

ANGIOGRAPHIC ASSESSMENT OF LV FUNCTION. The results are described in the extended Results section of the Supplemental Appendix and Supplemental Figures 3 and 4.

INTEROBSERVER REPRODUCIBILITY OF THE IN VIVO MR FRACTION BY QMR ANALYSIS. The interobserver reproducibility analysis of the in vivo MRF by QMR using 1, 2, 3, and 4 cardiac cycles is shown in **Figure 5**. The correlations between the 2 independent core lab analysts on the in vivo MRF using 1, 2, 3, and 4 cardiac cycles was very strong, regardless of the number of the cardiac cycles. However, the best correlation was achieved using 4 cardiac cycles ($y = -1.008 + 1.130x$; $R = 0.907$; $p < 0.001$). The Bland-Altman analysis demonstrated a mean absolute difference of 0.2% and SD of ±2.3% between the in vivo MRF averaged from 4 cardiac cycles by the 2 independent core lab analysts. The ICC between the 2 observers regarding the in vivo MRF averaged from 4 cardiac cycles was excellent (ICC = 0.984; 95% CI: 0.948 to 0.995).

DISCUSSION

To the best of our knowledge, this is the first study to investigate QMR, a novel platform for the assessment

of post-interventional MR based on objective and quantitative angiographic method using the relative time-density AUCs. Our study has several important findings: first, angiographic quantification of MR using QMR produces an accurate surrogate value for MRF; this analytical approach was feasible in the in vivo model in all animals treated with surgical mitral valve replacement. Second, the in vivo derived MRF obtained by QMR strongly correlated with the in vitro mock circulation derived MRF. In addition, the in vivo MRV very strongly correlated with the in vitro total MRV. Finally, the interobserver reproducibility of MR values using the QMR platform was excellent.

First of all, the result of the phantom experiment illustrated that the videodensitometry of an elliptical object is highly independent of the angulation of an x-ray system, suggesting that videodensitometry accurately measures the volume of radiopaque material (e.g., contrast media) irrespective of angiographic projections. The fluoroscopic cinefilming, under various x-ray angulations, of an elliptical shape such as an egg-shaped phantom filled with a homogeneous solution of angiographic contrast medium allows us to demonstrate in vitro the constant product (area times density), which is the scientific foundation for the time-density measurement in videodensitometry (7). These in vitro experiments support that, when the time-dependent videodensitometric assessment is applied to the aortic root and LA area, the fraction of contrast volume flowing into the aorta and regurgitating into the LA is assessed accurately and precisely with a minimum variation irrespective of angiographic projections as long as there is no overlap between the aorta, LA, and LV.

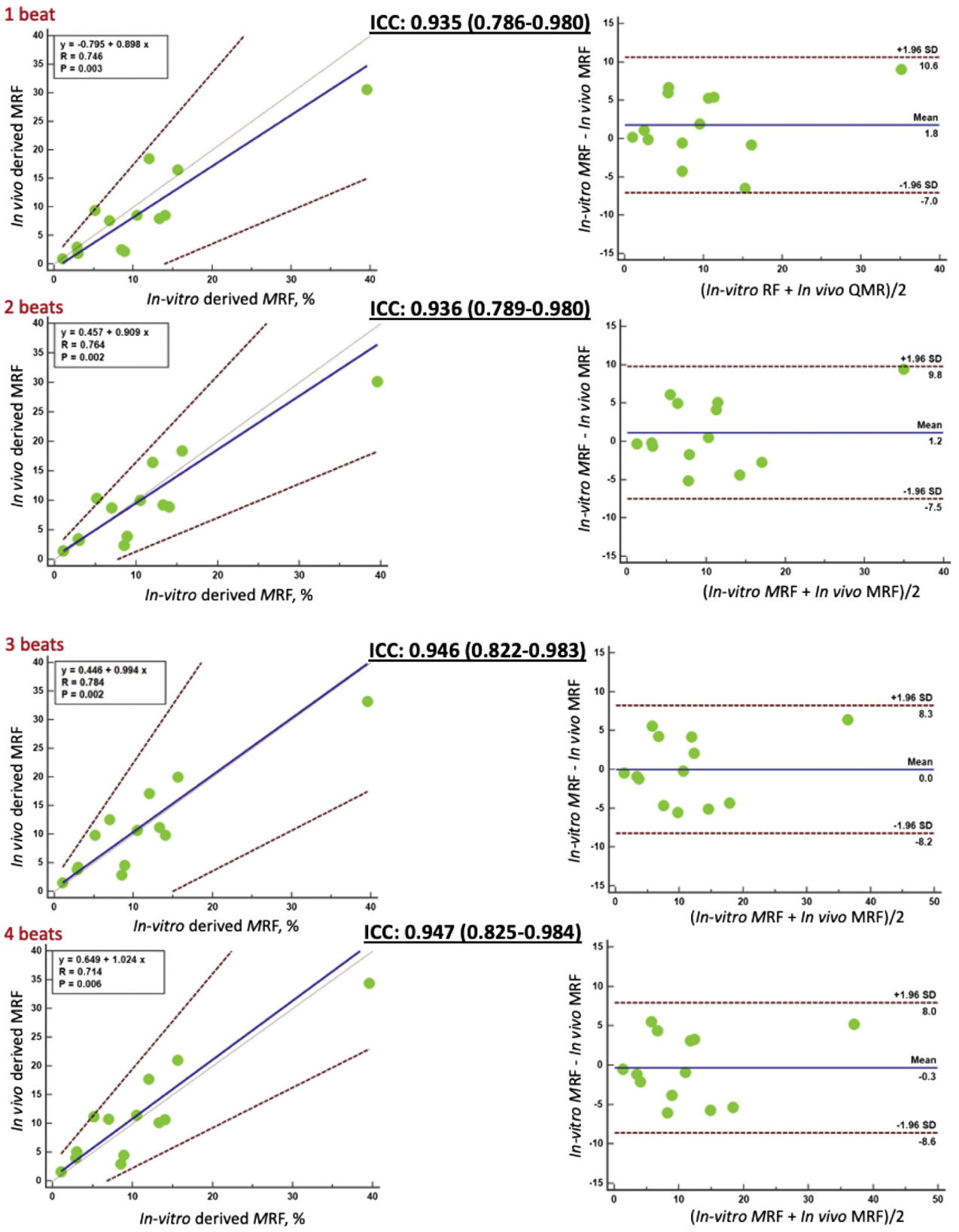
The real-time assessment of post-interventional MR remains a challenge due to the lack of an objective and quantitative method (8,9). Currently, transcatheter mitral valve edge-to-edge repair, using the MitraClip (Abbott Vascular, Santa Clara, California) and the PASCAL system (Edwards Lifesciences, Irvine, California), is increasingly utilized for selective patients with MR (10,11). These procedures are typically guided by real-time 3-dimensional echocardiography. However, periprocedural echocardiographic MR assessment can be challenging due to the presence of multiple regurgitation jets and orifices and due to the inherent technical limitations of some of echocardiographic parameters, such as the proximal isovelocity surface area method (12,13). Likewise, current angiographic assessment of post-procedural MR using the classification of Sellers et al. (5) is subjective and is affected by a poor intra observer and interobserver reproducibility (14). Therefore, there is a need for a more objective tool for MR quantification that is readily available in the cath lab and able to overcome some of the limitations of current modalities.

Quantification of AR from post-transcatheter aortic valve replacement angiography using the CAAS A-Valve (Pie Medical) has proven to be an accurate, reproducible, and objective method to assess transcatheter aortic valve replacement success, particularly in a head-to-head device comparison (3). In the present study, our group developed a platform based on the QMR software to quantify MR using a post-procedural left ventriculogram. This method is based on calculating the time-density AUC from the LA, which is an accurate surrogate of MR.

In fact, there are 2 possible reference regions to assess the degree of regurgitation into the LA, either the LV or the aortic root. However, the dilution of the contrast medium, in the absence of appropriate mixing in the LV, might be heterogeneous following the contrast injection in the LV; hence, the LV may be inappropriate as a reference region. Therefore, in the present study, we used the aortic root as the reference region. In routine clinical practice, a left ventriculogram requires a large amount of contrast (30 to 40 ml/injection) injected over 1 to 3 s (corresponding to a few cardiac cycles) (15). However, a large volume of contrast medium could be detrimental and should be avoided in patients at high risk of contrast complications, such as those patients with heart failure and chronic kidney disease, which is commonly seen in patients with MR undergoing edge-to-edge mitral repair. This particular issue could impact the utility of this method in a significant proportion of patients with MR. However, the choice of the aortic root as the reference region could help to avoid the need for large contrast volume.

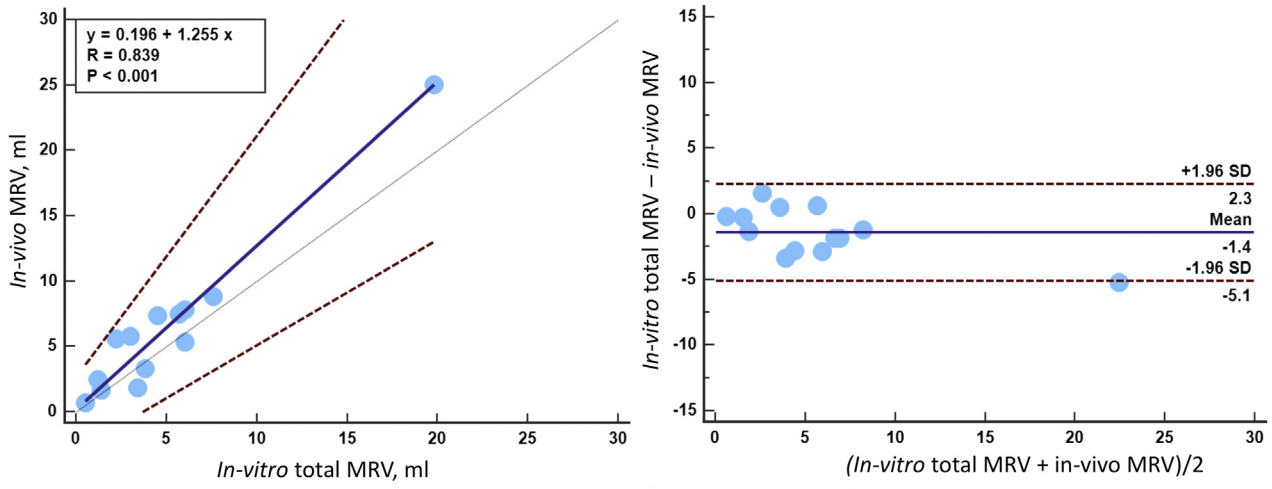
Previously, we tested the accuracy of the QAR using a small contrast volume. In the in vitro mock circulation system, we have validated the accuracy of a single diastolic injection triggered by electrocardiogram with low contrast volume (16). In a preclinical porcine model, electrocardiogram synchronized injection of angiographic contrast medium during aortography has been investigated by our group in different settings (17) and was applied in the present experiment. We found that a synchronized injection in the diastolic phase using electrocardiogram triggered pump ACIST (ACIST Medical Systems, Eden Prairie, Minnesota) can be achieved using contrast volume as small as 12 to 20 ml, without impacting the

FIGURE 3 **In Vitro Derived MRF Versus In Vivo Derived MRF by Angiographic QMR**



Continued on the next page

FIGURE 4 In Vitro Total MRV Versus In Vivo MRV



(Left) Scatterplot showing the correlation of the in vitro total MRV and the in vivo MRV. The **blue line** shows the regression line and the **red dotted lines** show the 95% CI. **(Right)** Bland-Altman plot of the in vitro total MRV and the in vivo MRV. The **blue line** shows the regression line and the **red dotted lines** show the 95% CI. The ICCs (95% CI) were also calculated. Abbreviations as in Figures 1 and 3.

accuracy of MR. Applying this approach in MR angiographic quantification is quite helpful in patients with borderline renal function at risk of contrast nephropathy. Furthermore, limiting LV contrast injection to the diastolic phase minimizes the risk of arrhythmias.

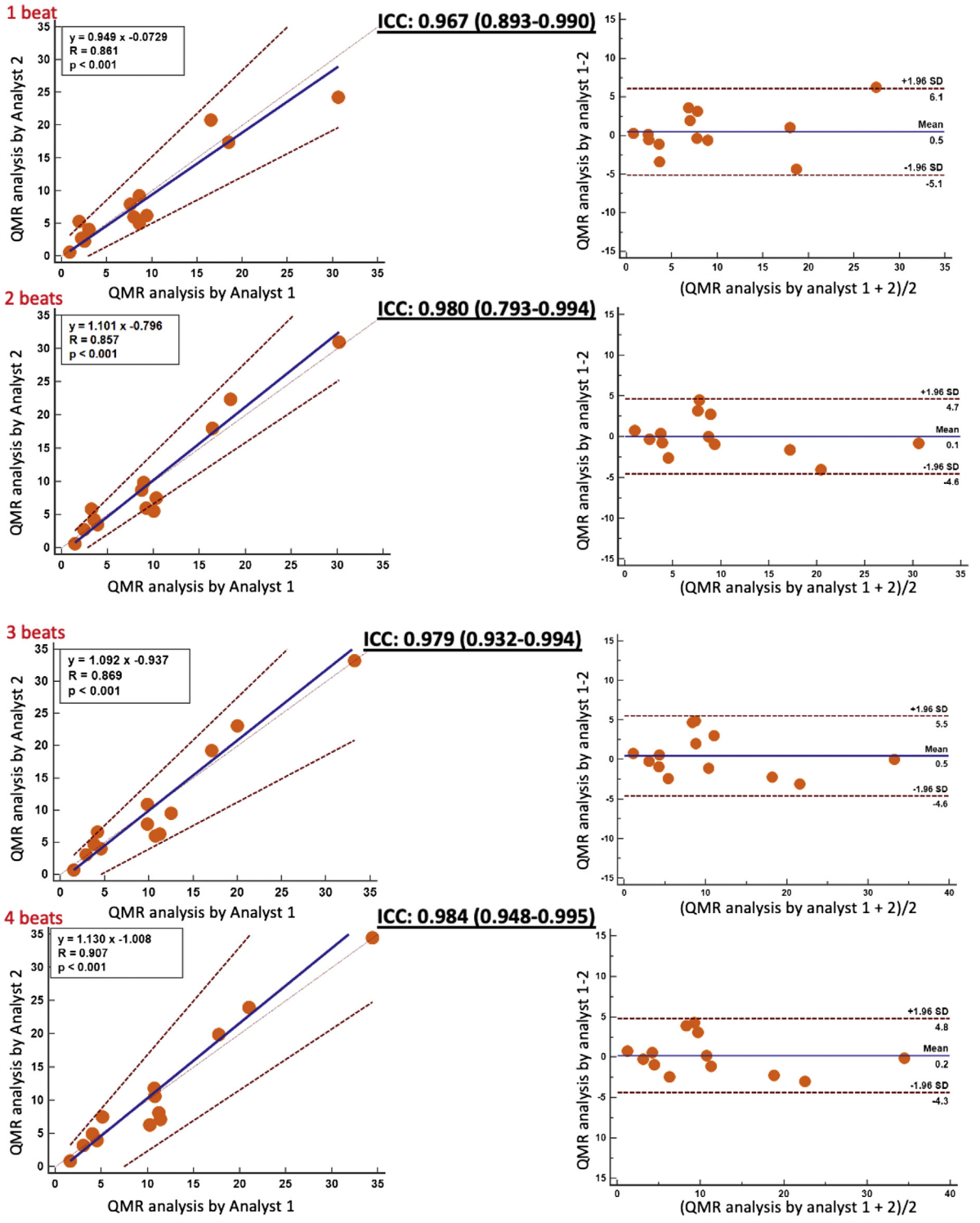
In this study, the in vivo derived MRF by QMR according to a left ventriculogram is an accurate and reproducible method that might be used to assess the post-procedural MR following mitral valve interventions. It has to be emphasized that the videodensitometric method cannot differentiate closing volume from leaking volume, whereas these 2 volumes can be reliably recorded and differentiated with ultrasonic transducers, sensitive to intracavitary directional flow, that are incorporated in the mock circulation. Therefore, the in vivo MRV calculated by the SV and in vivo derived MRF by QMR averaged from 3 cardiac cycles very strongly correlated with the in vitro total MRV (closing volume + leaking volume) (Figure 5). In contrast, the correlation between the in vivo MRV and the leaking volume was somewhat weaker ($R = 0.702$; $p = 0.008$). The videodensitometric parameters of MR severity (in vivo) and MRF (in vitro) were strongly correlated, irrespective of the number of the analyzed cardiac cycles. However, the best results are seen using 3 or 4 cardiac cycles, a strategy we therefore recommend in future studies. Moreover, to calculate the volumetric MR, we combined the data from the CAAS QMR and the CAAS LVA, and subsequently, the volumetric in vivo MR derived from these 2 software platforms very strongly correlated with the in vitro total volumetric MR (Figure 6). Therefore, the next iteration of the QMR software will integrate LV volumetric analysis. A large prospective study in patients undergoing percutaneous mitral valve edge-to-edge repair is currently underway.

STUDY LIMITATIONS. First, the small sample size associated with a certain degree of data clustering may result in biased interpretation of the results, although the Bland-Altman plots are reassuring. Second, it should be acknowledged that the degree of

FIGURE 3 Continued

(Left) Scatterplots showing the correlation of the in vitro (mock circulation) derived MRF and the in vivo derived MRF by QMR. The **blue line** shows the regression line and the **red dotted lines** show the 95% confidence interval (CI). **(Right)** Bland-Altman plots of the in vitro (mock circulation) derived MRF and the in vivo derived MRF by QMR. The **blue line** shows the regression line and the **red dotted lines** show the 95% CI. The intraclass correlation coefficients (ICCs) (95% CI) were also calculated using 1, 2, 3, and 4 cardiac cycles. Abbreviations as in Figure 1.

FIGURE 5 Interobserver Agreements of In Vivo Derived MRF by QMR in a Core Lab Setting



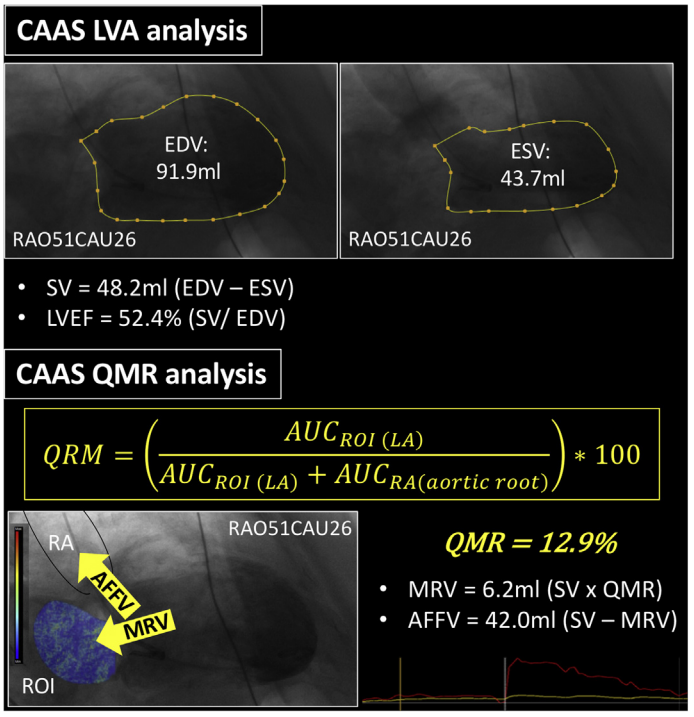
(Left) Scatterplots showing the correlation of the in vivo QMR analysis between the 2 independent core lab analysts. The **blue line** shows the regression line and the **dotted red lines** show the 95% CI. **(Right)** Bland-Altman plots of the in vivo QMR analysis assessed by the 2 independent core lab analysts. The **blue line** shows the regression line and the **dotted red lines** show the 95% CI. The ICCs (95% CI) were also calculated using 1, 2, 3, and 4 cardiac cycles. Abbreviations as in Figures 1, 2, and 3.

MR might differ between the in vivo and in vitro analyses due to different conditions stemming from the environment of the valve, such as valve alignment, intracavitary pressures, sutures, and hemodynamic forces. Third, the inability to differentiate paravalvular from transvalvular regurgitation could be a limitation of this videodensitometric assessment of MR. The strongest value of the QMR at the moment is that it provides a quantitative (regurgitation fraction in relative percentage and in absolute volumetric value), objective, accurate, and reproducible method to quantify MR. Furthermore, the initial release of the software provides a relative localization of the MR jet on a 2-dimensional color-coded parametric image. In essence, the 2-dimensional color-coded parametric map of QMR provides a visual localization of MR jets, while the QMR quantifies and integrates by videodensitometry all the MR jets within the LA. The QMR with its global quantitative assessment that provides an accurate estimation of MRF may be a valuable adjunct to the qualitative and multidirectional assessment of regurgitation jets documented by echocardiography. Furthermore, biplane cine fluoroscopy and 3-dimensional spatial reconstruction of the videodensitometric profiles may be the theoretical solution to this problem (18). Fourth, the existence or suspicion of AR may invalidate this MR quantification method and will mandate the separate assessment of the AR. Further studies are necessary to establish the clinical utility of using the software for quantitative MR assessment. Finally, the feasibility of QMR in clinical practice might differ from the findings of this study. However, the human feasibility study is ongoing (**Figure 6,** Video 2).

CONCLUSIONS

In vivo derived MRF using the novel QMR software is feasible, accurate, and highly reproducible. These promising results have led us to initiate the first human feasibility study comprising patients undergoing percutaneous mitral valve edge-to-edge repair.

FIGURE 6 Combination of CAAS LVA and CAAS QMR for the Volumetric Assessment of MR in a Human Case



A 79-year-old woman underwent a left ventriculogram (RAO51CAU26) following percutaneous mitral valve edge-to-edge repair. **(Top)** CAAS LVA analysis. From the post-procedural left ventriculogram, LV contours at end-systole and at end-diastole were drawn, and by using metallic catheter markers (10 mm apart) as scaling devices, volumes were calculated according to Simpson's rule (6). EDV = 91.9 ml, ESV = 43.7 ml, SV = 48.2 ml, and LVEF = 52.4%. **(Bottom)** CAAS QMR analysis. In the post-procedural left ventriculogram, MR is color-coded according to the time-density change in the LA. The in vivo derived MRF by QMR is calculated from the time density of the AUC in the LA (ROI) and related to the sum of the time density AUC in the LA (ROI) and the time density AUC in the aortic root (RA). The in vivo derived MRF by QMR can be calculated from the following formula (the actual value was 12.9%): *In vivo derived MRF* (%) = $\left(\frac{AUC_{ROI\ (LA)}}{AUC_{ROI\ (LA)}+AUC_{RA\ (aortic\ root)}}\right) \cdot 100$. The in vivo MRV was calculated by the following formulas based on the angiographic QMR analysis: *In vivo* MRV (ml) = SV (ml) · *In vivo derived MRF* (%). The calculation of the in vivo MRV was obtained from the in vivo MRF averaged from 3 cardiac cycles. MRV = 6.2 ml and AFFV = 42.0 ml (SV - MRV). LVEF = left ventricular ejection fraction; other abbreviations as in **Figures 1 and 2**.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Serruys has received personal fees from Biosensors, Medtronic, Micel Technologies, Sinomedical Sciences Technology, St. Jude Medical, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work. Mr. Aben is an employee of Pie Medical Imaging. Dr. Mylotte has served as a consultant for Medtronic, Boston Scientific, and Microport. Dr. Cox and W. Brunnett are employees of Xeltis. Dr. Pibarot has received grants from Cardiac Phoenix, from Edwards Lifesciences, outside the submitted work. Dr. Soliman has received several institutional research grants outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Patrick W. Serruys, National University of Ireland, Galway (NUIG), University Road, Galway H91 TK33, Ireland. E-mail: patrick.w.j.c.serruys@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? This QAR has been extensively vetted and validated in vitro, in vivo, and in the clinical setting, such as after transcatheter aortic valve replacement, and is progressively adopted in transcatheter aortic valve replacement with the advent of a supplemental software.

WHAT IS NEW? By applying the same concept of the QAR to the mitral valve, it could be possible to translate the method of measurement used for AR to the MR. Subsequently, this method was feasible, accurate, and highly reproducible.

WHAT IS NEXT? These promising results have led us to initiate the first human feasibility study comprising patients undergoing percutaneous mitral valve edge-to-edge repair.

REFERENCES

1. Klein LW, Agarwal JB, Stets G, Rubinstein RI, Weintraub WS, Helfant RH. Videodensitometric quantitation of aortic regurgitation by digital subtraction aortography using a computer-based method analyzing time-density curves. *Am J Cardiol* 1986;58:753–6.

2. Grayburn PA, Nissen SE, Elion JL, Evans J, DeMaria AN. Quantitation of aortic regurgitation by computer analysis of digital subtraction angiography. *J Am Coll Cardiol* 1987;10:1122–7.

3. Modolo R, Chang CC, Abdelghani M, et al. Quantitative assessment of acute regurgitation following TAVR: a multicenter pooled analysis of 2, 258 valves. *J Am Coll Cardiol Intv* 2020;13:1303–11.

4. Modolo R, Chang CC, Onuma Y, et al. Quantitative aortography assessment of aortic regurgitation. *EuroIntervention* 2020;16:e738–56.

5. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. *Am J Cardiol* 1964;14:437–47.

6. Piscione F, Hugenholtz PG, Serruys PW. Impaired left ventricular filling dynamics during percutaneous transluminal angioplasty for coronary artery disease. *Am J Cardiol* 1987;59:29–37.

7. Haase J, Slager CJ, Keane D, et al. Quantification of intracoronary volume by videodensitometry: validation study using fluid filling of human coronary casts. *Cathet Cardiovasc Diagn* 1994;33:89–94; discussion 95.

8. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379:2307–18.

9. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;379:2297–306.

10. Chakravarty T, Makar M, Patel D, et al. Transcatheter edge-to-edge mitral valve repair with the MitraClip G4 system. *J Am Coll Cardiol Intv* 2020;13:2402–14.

11. Praz F, Windecker S, Kapadia S. PASCAL: a new addition to the armamentarium of transcatheter repair systems for mitral leaflet approximation. *J Am Coll Cardiol Intv* 2019;12:1379–81.

12. Tabata N, Weber M, Sugiura A, et al. Impact of the leaflet-to-annulus index on residual mitral regurgitation in patients undergoing edge-to-edge mitral repair. *J Am Coll Cardiol Intv* 2019;12:2462–72.

13. Avenatti E, Mackensen GB, El-Tallawi KC, et al. Diagnostic value of 3-dimensional vena contracta area for the quantification of residual mitral regurgitation after MitraClip procedure. *J Am Coll Cardiol Intv* 2019;12:582–91.

14. Schultz CJ, Slots TL, Yong G, et al. An objective and reproducible method for quantification of aortic regurgitation after TAVR. *EuroIntervention* 2014;10:355–63.

15. Tobis J, Nacioglu O, Johnston WD, et al. Left ventricular imaging with digital subtraction angiography using intravenous contrast injection and fluoroscopic exposure levels. *Am Heart J* 1982;104:20–7.

16. Miyazaki Y, Abdelghani M, de Boer ES, et al. A novel synchronised diastolic injection method to reduce contrast volume during aortography for aortic regurgitation assessment: in vitro experiment of a transcatheter heart valve model. *EuroIntervention* 2017;13:1288–95.

17. Modolo R, Miyazaki Y, Chang CC, et al. Feasibility study of a synchronized diastolic injection with low contrast volume for proper quantitative assessment of aortic regurgitation in porcine models. *Catheter Cardiovasc Interv* 2019;93:963–70.

18. Slager CJ, Reiber JH, Schuurbiers JC, Meester GT. Contouromat-a hard-wired left ventricular angio processing system. I. Design and application. *Comput Biomed Res* 1978;11:491–502.

KEY WORDS angiography, in vitro, in vivo, mitral regurgitation, videodensitometry

APPENDIX For an expanded Methods and Results sections as well as supplemental figures, tables, and videos, please see the online version of this paper.