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Accurate quantitation of regurgitant volume with MRI in patients selected for mitral valve repair☆

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Abstract

Objective: Echocardiography, the currently preferred diagnostic approach for mitral valve regurgitation, cannot accurately quantify the amount of regurgitation. Flow quantification with MRI is possible, but the conventional method (1-directional velocity-encoding) acquires the flow at a fixed location during the cardiac cycle, which is not necessarily the location of the mitral valve during the whole cycle. In this study, the exact flow through the mitral valve was quantified with a 3-directional velocity-encoded MRI approach. **Methods**: Ten patients with severe mitral valve regurgitation (class 3–4+with echocardiography) resulting from systolic restrictive motion of both leaflets (Carpentier IIIb) which were selected for valve repair and 10 healthy volunteers without cardiac valvular disease confirmed with echocardiography were included in this study. The intra-ventricular flow was sampled with a radial stack of six acquisition planes parallel to the long-axis of the left ventricle. Three-directional velocity-encoded MRI was performed resulting in the intra-ventricular flow velocity vector field for 30 phases during the cardiac cycle. The position of the mitral valvular plane in this vector field was indicated manually for each phase. Velocity values perpendicular to this plane determined the flow through the mitral valve. Both the 3-directional encoded mitral valve flow and the 1-directional encoded mitral valve flow were compared with the flow determined with MRI at the ascending aorta. **Results**: One-directional velocity-encoded MRI showed a mean overestimation ($P<0.01$) of 25 ml/cycle compared to the aortic flow. Correlation was very poor ($r_P=0.15$, $P=0.68$). The 3-directional velocity-encoded MRI on the other hand, showed no over/underestimation and a good correlation ($r_P=0.91$, $P<0.01$ for volunteers, $r_P=0.90$, $P<0.01$ for patients). The regurgitant flow fractions were between 3 and 30%. **Conclusion**: With 3-directional velocity-encoded MRI, measurement of the flow through the mitral valve is accurate and reproducible. This is a valuable tool for diagnosing and absolute quantification of regurgitant volume.

Keywords: Magnetic resonance imaging; Mitral valve; Regurgitation; Flow quantification; Image processing

1. Introduction

When diagnosing patients with valvular disease, insight in the function of the valve and the pathology provides invaluable information for planning the strategy and timing of surgery [1–5]. Currently, classification of the severity of mitral valve (MV) regurgitation is based on echocardiography, both two-dimensional trans-thoracic echocardiography (TTE) [3–6] and multi-plane trans-esophageal echocardiography (TEE) with colour Doppler [7–10]. Quantification of the exact trans-valvular flow velocities based on Doppler measurements copes with two sources of error: first, only flow in the same direction aligned with the ultrasound beam can be quantified and second, the sample volume cannot be adapted to the motion of the annulus [11,12]. The direction of the flow may be asymmetric, like in case of a prolapse, particularly of the commissuriae. There are even cases when TEE misses these very asymmetric jets.

Besides measurement restrictions, geometrical models are applied to deduct physiological parameters describing the cardiac condition from the echo Doppler measurements. These geometrical models are not generally applicable to all individual subjects.

Furthermore, imaging the region of interest in TTE can be complicated by the acoustic attenuation from structures inside the thorax (lungs, subcutaneous tissues and ribs) and the heart (prosthetic valve construction materials and calcification). TEE is less limiting, but this technique is semi-invasive and patients often experience this as a discomforting examination.

Magnetic resonance imaging (MRI) is a non-invasive and patient-friendly technique, which is applied for the determination of global and regional left ventricular anatomy and function [13]. As a three-dimensional (3D)

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imaging technique, volumetric measurements are performed directly and do not rely on model assumptions. Velocity-encoded cine MRI provides quantitative information on moving spins and can be applied to determine intra-ventricular blood flow [14,15]. These qualifications make MRI a very suitable modality for quantifying trans-valvular blood flow.

Previous attempts have all encountered the motion of the heart during contraction and relaxation as the main obstacle towards direct acquisition of the trans-valvular flow. The mitral annulus moves 12–16 mm towards the apex during contraction [16]. Kayser et al. showed that correction for this through-plane motion is indispensable [17]. This correction is performed retrospectively. But since, the flow quantification is performed in a single, fixed plane during the complete cardiac cycle, the location of the data acquisition is not identical to the plane of the MV during the whole cardiac cycle. This implies that flow quantification does not represent the true trans-valvular flow.

An acquisition method with a motion-adapted acquisition plane is described by Kozerke et al. [18]. The accurate positioning of the acquisition plane enables measurement of the true valvular flow during the whole cycle. This technique requires dedicated scanning software not widely available on all commercial MR scanners, and the prospective triggering that is necessarily used implies inaccurate flow quantification at a regurgitant mitral valve. With prospective triggering, the final part of the RR-interval is not acquired and therefore, the diastolic flow quantification will not be complete.

In this study, a new acquisition method is introduced using velocity-encoded MRI to obtain the velocity vector field of the intra-ventricular blood flow during the complete cardiac cycle. In this 3D velocity vector field, the MV-plane is indicated retrospectively. The vector components of the flow velocity going through the MV-plane will be reconstructed which results in the trans-valvular flow velocity. Regurgitation will be evident as the flow fraction passing the valve during systole, flowing from the left ventricle into the left atrium. In 10 patients with severe mitral valve regurgitation and selected for mitral valve repair, the MV-flow will be quantified and the regurgitant volume will be determined.

2. Material and methods

2.1. Subjects

Ten patients (eight men, two women; age 35–67 years, mean 53±12 years) with severe left ventricular dysfunction (left ventricular ejection fraction 36±11%, NYHA class 3.3±0.4) and severe pure MV regurgitation (class 3–4) were recruited. The mechanism of the regurgitation was a systolic restrictive motion of both leaflets (Carpentier IIIb) with normal leaflet tissue. These patients were included consecutively and underwent later a stringent restrictive mitral annuloplasty (two sizes under) by means of a complete semi-rigid or pliable ring. Ten volunteers without cardiac valvular disease as confirmed by TTE and TEE (nine men, one woman; age 33–67 years, mean 54±10 years) were recruited for comparison purposes. All patients and volunteers gave informed consent and approval from the Medical Ethical Committee of our hospital was obtained on all examinations.

2.2. MRI acquisition

MRI was performed on a 1.5 T scanner (ACS-NT15 Gyroscan with the Powertrack 6000 gradient system; Philips Medical Systems, Best, The Netherlands). The intra-ventricular blood flow was sampled with a radial stack of six acquisition planes parallel to the long-axis of the left ventricle (Fig. 1). The specific 3-directional velocity-encoded MRI [19] scanning parameters and the image processing methods to obtain the 3D intra-ventricular flow velocity vector field from the MRI data were described previously [20]. In each consecutive imaging plane, velocity values were acquired in three directions, with a maximum velocity sensitivity value of 100 cm/s in each direction. The reconstructed velocity values in three directions represent the velocity vector components. Slice thickness of the imaging planes was 8 mm, Field-of-view=370 mm (60% rectangular), scan matrix=128×102. The flip angle $\alpha=10^{\circ}$, TR/TE=5.8/3.5; two signal averages were used to increase the signal-to-noise ratio. For each subject, the intra-ventricular flow velocity vector field was obtained in 30 phases during the cardiac cycle (obtained with retrospective cardiac synchronisation). The spatial resolution

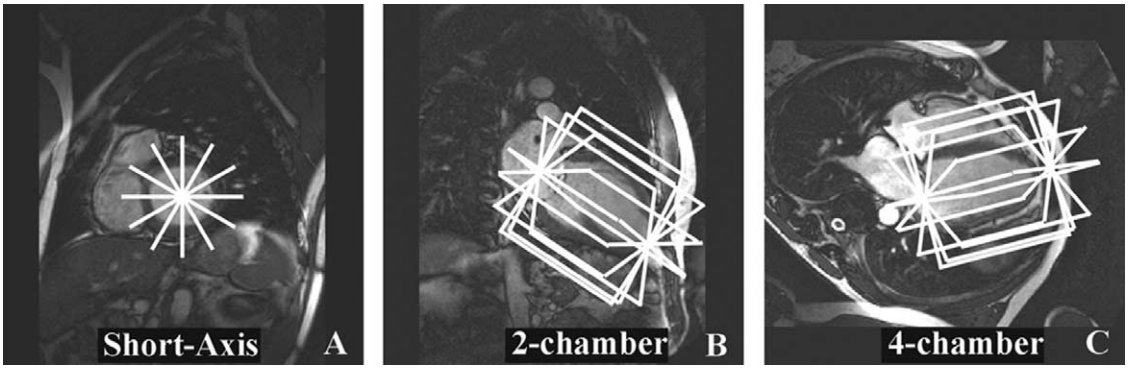

Fig. 1. The radial stack of 6 acquisition planes for intra-ventricular flow MR quantification. Six planes with an inter-slice angulation of 30° are placed on the left ventricle. The long-axis, from MV-annulus to apex, coincides with the radial axis of the stack. On a short-axis view (A), a 2-chamber (B) and a 4-chamber (C) view, the position of the stack is planned as illustrated. From the acquired 3D velocity vector field, the 3-dir MV-flow is determined.

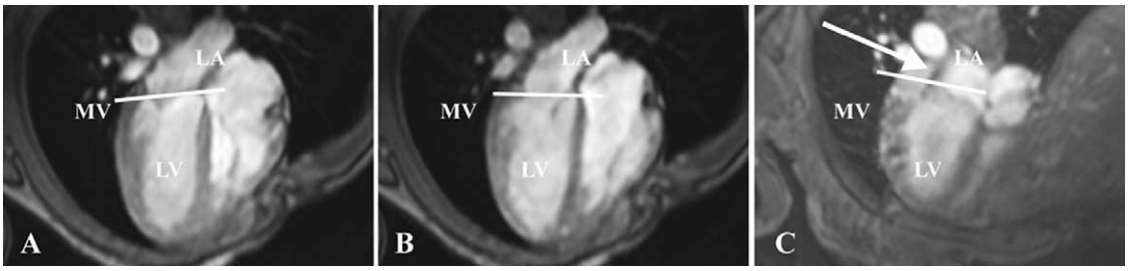

Fig. 2. In each of the six acquisition planes, the annulus of the mitral valve (MV) was manually indicated by placing a straight line on the closed valve leaflets during systole and on the annulus and perpendicular to the left ventricular inflow direction during diastole. In (A), this is illustrated for an acquisition plane in a volunteer during systole (LV, left ventricle; LA, left atrium). In (B), the line is placed on the annulus during diastole. In patients, for phases with regurgitation during systole with the appearance of a regurgitant jet flowing from the ventricle into the atrium (C, arrow), the line was placed perpendicular to this jet.

was $2.89 \times 2.89 \times 8.0\,mm^3$. Typical examination time was 9–12 min, depending on the subject's heart rate.

2.3. MV-flow quantification

From the 3D velocity vector field of the intra-ventricular blood flow, the flow through the MV was reconstructed. To achieve this, the MV plane was determined for each of the cardiac phases in the 3D velocity vector field. In each of the six acquisition planes the mitral valve annulus was manually indicated by a straight line positioned on the closed valve leaflets during systole (Fig. 2A) and on the annulus and perpendicular to the left ventricular inflow direction during diastole (Fig. 2B). For phases with regurgitation during systole, with the appearance of a regurgitant jet flowing from the ventricle into the atrium (Fig. 2C, arrow), the line was placed perpendicular to the jet. This line was positioned in each of the 30 phases and each of the six slices and copied to the velocity-encoded images. The velocity components perpendicular to each of the six MV-lines were projected onto a single two-dimensional (2D) plane, representing the MV-plane. The centre of each of the six lines was positioned in the centre of this MV-plane. Tri-angular interpolation between the sample points on the six lines was used to obtain velocities for the complete 2D MV-plane.

The velocities measured perpendicularly to the reconstructed MV-plane need to be corrected for the motion of the myocardium in basal/apical direction in order to obtain the true trans-valvular velocity of the blood flow [17]. The velocity of the MV annular plane was obtained from the two- and four chamber acquisitions. From the displacement of the MV annulus in these images, the through-plane velocity of the MV was determined. This velocity value was subtracted from the through-plane MV-flow velocities measured at the reconstructed plane, resulting in the corrected velocity values with respect to the MV-annulus. Finally, the trans-valvular volume flow was obtained after manually drawing a contour in the reconstructed velocity image of each phase, containing the trans-valvular velocities and integrating these velocities over the area. The MV-flow volume was obtained by calculating the Riemann sum of the flow graph (i.e. discretized approximation of the area under the flow graph).

2.4. Validation

For each subject, the MV-flow volume determined with the new method described above (from hereon noted as the '3-dir MV-flow') was validated by comparing it with the flow volume measured with MRI at the ascending aorta (described by van der Geest et al. [21]), referred to as the AO-flow volume. The same MRI acquisition protocol was used as for the MV-flow, but now with a single imaging plane positioned perpendicular to the ascending aorta. Only velocity values in through-plane direction, perpendicular to the acquisition plane, were considered. The aortic flow was determined using the FLOW software (Medis, Leiden, The Netherlands) [21].

Furthermore, for each subject, the 3-dir MV-flow volume was compared with the conventional one-directional MV-flow volume measurement with through-plane motion correction [17]. The same imaging protocol was used, with the single imaging plane positioned at the MV during end-systole. Again, only the velocity values in through-plane direction were considered. The through-plane velocity of the myocardium was assessed in a region-of-interest, drawn inside the myocardium for each of the phases, by measuring the mean velocity inside this region-of-interest. This velocity value was subtracted from the velocity measured at the MV annulus. The MV-flow volume measured with this method is referred to as the '1-dir MV-flow volume'.

For ten volunteers and ten patients, the MV-flow volume was determined with the 3-dir MV-flow method, as well as with the 1-dir MV-flow method, and compared with the AO-flow. The regurgitant flow volume in the patients was determined by calculating the flow volume during systole going from the left ventricle into the left atrium. The regurgitant flow fraction, a measure for the severity of regurgitation, was determined by the ratio between the regurgitant flow volume during systole and the inflow volume through the MV during diastole.

2.5. Statistical analysis

Correlations between the AO-flow volume measurement and both the conventional 1-dir MV-flow volume and the new 3-dir MV-flow volume were tested with the Pearson correlation coefficient r_P, under the assumption that the parameters were distributed normally. This assumption was tested with Kolmogorov–Smirnov tests. The approach described by Bland and Altman [22] was followed to study

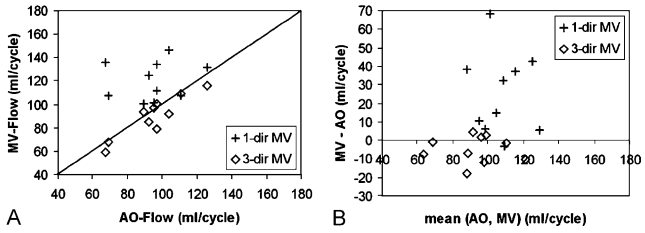

Fig. 3. MV-flow volume measurements in healthy volunteers, determined with the conventional 1-dir MV-flow method and the new 3-dir MV-flow method, respectively. The MV-flow volumes are compared with the flow volume measured at the Aorta (A). In (B), the differences between MV-flow volumes and AO-flow volume are presented and analyzed following the approach by Bland and Altman.

the differences between both MV-flow volume measurements and the AO-flow volume. The mean differences were determined and the statistical significance of these differences was tested by a paired-samples *t*-test.

3. Results

The new 3-dir MV-flow method was first tested on ten healthy volunteers and compared to the conventional 1-dir MV-flow. The effective forward flow volume measured at the MV with either method, was compared to the flow volume measured with 1-directional through-plane velocity-encoded MRI at the Aorta (AO-flow). The results are presented in Fig. 3A. Kolmogorov–Smirnov tests were performed to prove that the data of each of the parameters were distributed normally ($P=0.84$ for 1-dir MV-flow, $P=0.99$ for 3-dir MV-flow, $P=0.89$ for AO-flow). The correlation between the MV-flow volumes acquired with both methods, respectively, and the AO-flow volume was tested with Pearson correlation coefficients. The correlation between the 1-dir MV-flow volume and the AO-flow volume is not statistically significant: ($r_P=0.15$, $P=0.68$), whereas the correlation between the 3-dir MV-flow volume and the AO-flow volume is statistically significant: ($r_P=0.92$, $P<0.01$).

Differences between the MV-flow volume and the AO-flow volume were analysed following the approach described by Bland and Altman [22]. The results are presented in Fig. 3B. The 1-dir MV-flow volume shows an over-estimation compared to the AO-flow volume. The mean difference ± standard deviation = 25 ± 22 ml, and this difference is statistically significant ($P<0.01$). On the other hand, no systematic difference between the 3-dir MV-flow volume and the AO-flow volume is found. The mean difference ± standard deviation = −5 ± 7 ml ($P=0.06$).

Next, the new method for measuring the MV-flow volume was performed on the ten patients selected for mitral valve repair. The regurgitant flow fractions were between 3 and 30% (mean ± standard deviation = 16 ± 8%) in these patients. The results of the MV-flow measurements are presented in Fig. 4A. Again, Kolmogorov–Smirnov tests were performed and prove that the flow values can be considered as distributed normally ($P=0.98$ for 1-dir MV-flow, $P=0.91$ for 3-dir MV-flow, $P=0.68$ for AO-flow). The correlation between the 1-dir MV-flow volume and the AO-flow volume is not statistically significant: ($r_P=0.08$, $P=0.82$), whereas the correlation between the 3-dir MV-flow volume and the AO-flow volume is statistically significant: ($r_P=0.90$, $P<0.01$).

The differences between the MV-flow volume and the AO-flow volume are presented in Fig. 4B. The 3-dir MV-flow volume shows no systematic difference with the AO-flow volume (mean difference ± standard deviation = −4 ± 7 ml ($P=0.15$)). For the 1-dir MV-flow, the mean difference ± standard deviation = 19 ± 28 ml, but this difference is not statistically significant ($P=0.06$) due to the large standard deviation.

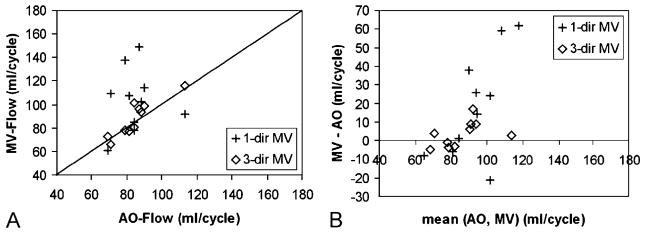

Fig. 4. MV-flow volume measurement in patients selected for mitral valve repair, determined with the conventional 1-dir MV-flow method and the new 3-dir MV-flow method, respectively. The MV-flow volumes are compared with the flow volume measured at the Aorta (A). In (B), the differences between MV-flow volumes and AO-flow volume are presented and analyzed following the approach by Bland and Altman.

4. Discussion

Besides information on the function of the regurgitant valve and the pathology, knowledge of the transvalvular flow and acquisition of the regurgitant flow fraction provide the cardiothoracic surgeon with the essential information necessary for planning strategies. This is particularly valuable in the setting of ischaemic mitral valve regurgitation and/or dilated cardiomyopathy where a regurgitant volume of 30 ml at rest already has an ominous influence on left ventricular function as highlighted by Grigoni et al. [23].

In this study, a new MRI method is used to provide information on the exact regurgitant flow fraction. MRI is a reliable non-invasive imaging modality, readily applied for studying global and regional left ventricular anatomy and function [13]. Velocity-encoded MRI enables intra-ventricular flow quantification. Kayser et al. used single-slice 1-directional velocity-encoded MRI for measuring the flow at heart valves [16]. From their data, through-plane motion correction was proven to be necessary. But this is not the only condition for acquiring accurate transvalvular blood flow. Adaptation of the acquisition plane to the motion of the valve of interest needs to be performed, as is illustrated by the data of our study. In the volunteers, a statistically significant over-estimation of 25 ± 22 ml of the MV-flow volume was found when performing the conventional 1-dir MV-flow method. Furthermore, there was no correlation with the AO-flow volume. Also for the patient data, the same results were found. The difference between 1-dir MV-flow

volume and AO-flow volume (19 ± 28 ml) was not statistically significant ($P=0.06$) due to the large standard deviation. The large spread in data also indicates the inaccuracy and unreliability of this method.

The new 3-dir MV-flow method provides small, non-significant differences compared with the AO-flow volume and good agreement between the flow measured at both locations. In a previous study, this 3-dir MV-flow method was subjected to an intra- and inter-observer variation study [20]. A high reproducibility was found, excellent correlation between repeated analyses and the differences between analyses were very small and not statistically significant.

When measuring the MV-flow volume and using the AO-flow volume as a standard of reference, the flow to the coronaries has to be taken into account. The AO-flow was acquired at a level distal to the branches of the coronaries. This implies that the AO-flow volume measured at this location will be smaller than the MV-flow volume. In our study, this small systematic difference was not detectable. The contribution of the flow to the coronaries, only 0.5% of the cardiac output [24], was too low to be detected by this method.

The new 3-dir MV-flow method enables accurate and reproducible quantification of the true trans-valvular MV-flow in a patient-friendly and easy-to-use manner. The three-dimensional velocity vector field of the intra-ventricular blood flow enables quantification of asymmetric regurgitant flow jets, a limitation of TEE which can miss asymmetric jets due to prolapse of the commissurae.

The new method can be applied on most commercially available MRI scanners. The acquisition of the radial stack of 6 imaging planes takes 9–12 min and depends on the patient's heart rate. Scout images, standard 2- and 4-chamber views and a set of short-axis images are needed to plan the radial stack of slices. This process takes approximately 15–20 min of examination time. The manual post processing is currently very laborious and needs to be automated before this method can be introduced in daily clinical practice. The reconstruction of the velocity vector field and the manual contour drawing, all needed for the flow analysis, can take up to 1 h per patient. Automating the manual processing (i.e. the indication of the mitral valve in the long-axis images as well as the contour drawing in the reconstructed trans-valvular velocity images) will result in a clinically applicable method.

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Appendix A. Conference discussion

Mr D. Wheatley (*Glasgow, UK*): The anatomical demonstration of the heart and the mitral valve with resonance imaging is superb. Do you get the same sort of correlation of the regurgitation to the anatomy as you get on the crude pictures, on the original pictures? In other words, can you use this to guide a surgeon as to which particular area is regurgitant?

Dr Westenberg: Yes, I think that is very much possible. At this point this method is being used for scientific purposes, not clinically generally applied yet, but I think the possibilities are certainly there to do this in a clinical routine.

Dr P. Kolh (*Liege, Belgium*): Have you compared and validated your results with an invasive method such as, for example, the conductance catheter?

The Leiden group, Baan and Steendijk for example, has extensively published on the use of the conductance catheter to generate pressure-volume loops. So I wonder if you have any plan to validate your measurements with this technique?

Dr Westenberg: At this point that is not being done but we are indeed going into that direction by measuring flows with the same technique in the aorta and compare that with intravascular measured flows, that's right.

Dr R. De Simone (*Heidelberg, Germany*): Actually the quantification of mitral regurgitation with MRI is nothing new; there are many groups working on this. I have two questions for you. First, you stated that your measurement, the positioning of the mitral valve, was taken manually. Do you think that you can define manually very well the complex geometry of the mitral orifice? You showed also in your data that the orifice changed during systole. This is the first question.

The second question, you just used six planes, and we saw that the velocities between the planes were interpolated. How accurate are your measurements? You know that in our experience we use 90 slices in order to define the complex geometry of the regurgitant jets and we were able to show the data. And just a comment. By the way, echocardiography is not based on a model assumption. It is based on real measurements

Dr Westenberg: First I want to come back to that last remark. Indeed, echocardiography is a real measurement, too, but to quantify the amount of regurgitation, for instance, there has to be applied, for the PISA method, for instance, some model assumptions.

Now coming back to your questions, indeed, we are manually indicating the mitral valvular plane, but as you can see in the movies that I showed here, it is very evident to find the mitral valvular annulus in these images.

And for your second question, we are using six acquisition planes. That is because there is some time constriction involved. It is indeed true if you use more acquisition planes that you have to do less interpolation. We use triangular interpolation between these six planes and more measurements will be more accurate. But as you can see from the results that I have presented, there are no large statistical over or under estimations when we are doing it this way with six planes.

Dr R. Frater (*Bronxville, New York, USA*): I am sure you recognize that what people are worrying about is whether this isn't truly accurate. It is an extraordinarily beautiful demonstration of how to get the data and so on. I would suggest really strongly you go back to 30, 40 years ago, put a flow probe above the mitral valve, and you can quantify it absolutely precisely and then see if that correlates with these beautiful images and calculations that you have been doing. It is the gold standard, after all, an electromagnetic flow probe over the mitral valve.

Dr Westenberg: Yes, thank you, but we didn't go that invasive with this study.