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Quantification of mitral and aortic regurgitation using high pulse repetition frequency three-dimensional color Doppler

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Norsk Sammendrag

Det er utviklet og patentert en tredimensjonal ultralyd Doppler metode (multibeam high pulse repetition frequency color Doppler eller MULDO) for kvantitering av klaffelekkasjer. Ved hjelp av Doppler kan blodstrøms hastigheter måles. Ved en klaffelekkasje vil den smaleste delen av blodstrømmen gjennom en defekt kalles vena contracta der alt blodet har samme fart (laminær blodstrøm). Maksimale blodhastigheter i vena contracta er typisk mellom 4 og 6 m/s, som er høyere enn det pulset Doppler kan måle. Vi benytter HPRF (high pulse repetition frequency) for å kunne måle Doppler-signalet fra vena contracta. Styrken i Dopplersignalet (Doppler power) er proporsjonalt med størrelsen på lekkasjedefekten (vena contracta areal) og måles ved hjelp av mange ultralydbølger (multibeam) og kalibreres ved hjelp av en referansebølge med gitte egenskaper. I studie 1 ble metoden testet i simuleringsforsøk og i laboratorium samtidig som vi gjorde kliniske pilotforsøk for å se om metoden kunne brukes på pasienter. I studiene 2 og 3 ble metoden testet hos pasienter med hhv. mitral- og aortaklaff lekkasje. For å beregne lekkasjevolum brukte vi produktet av vena contracta arealet ved MULDO og hastighet-tidsintegralet av lekkasjejeten ved kontinuerlig Doppler. Det var rimelig bra samsvar med referansemetoder som todimensjonal Doppler ultralyd og magnetisk resonans imaging (MRI) hos pasienter med moderat og stor lekkasje, men metoden overestimerte små lekkasjer. Dette var i samsvar med simulering-og laboratorieresultater fra studie 1 som skyldes begrensninger i romlig oppløsning av metoden.

Konklusjon: MULDO kan brukes som supplement til andre Doppler parametre for kvantifisering av moderat til alvorlig mitral- og aortaklaff lekkasje. Vi tror kombinasjoner med nyere teknikker med parallell stråleforming kan forbedre 3D kvantifisering av klaffelekkasjer.

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My former chiefs Eiliv Brenna and Siegfried Gutschmidt at the Department of Medicine, St Olav`s University Hospital in Orkdal, Norway, made it possible to start a 50% research career combined with clinical work, and my current chief Rune Wiseth, head of the Department of Cardiology, St Olav`s University Hospital, Trondheim, has similarly made this combination of clinical work and research possible, which I greatly appreciate. I am also thankful for working with my colleague Tore Salvesen in Orkdal. Knut Bjørnstad was the former head of the Department of Cardiology, St Olav`s University Hospital in Trondheim, as well as former chief of the Department of Medicine, St Olav`s University Hospital in Orkdal. He helped me to get in touch with Bjørn Olav at the beginning of the research period. Nowadays, I very much enjoy working with Knut and learn from his experience. I appreciate all of my colleagues at the Department of Cardiology, St Olav`s University Hospital in Trondheim, and am grateful for the chance to do this "50/50" work.

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List of papers

Paper 1: Hergum T, Skaug TR, Matre K, Torp H. Quantification of valvular regurgitation area and geometry using HPRF 3-D Doppler. IEEE Transactions, Ferroelectrics, and Frequency Control, Vol. 56, No. 5, May 2009, s 975 – 982.

Paper 2: Skaug TR, Hergum T, Amundsen BH, Skjærpe T, Torp H, Haugen BO. Quantification of mitral regurgitation using high pulse repetition frequency three-dimensional color Doppler. Journal of the American Society of Echocardiography 2010 Jan; 23(1):1 – 8. Epub 2009 Nov 13.

Paper 3: Skaug TR, Amundsen BH, Urheim S, Torp H, Haugen BO. Quantification of aortic regurgitation using high pulse repetition frequency three-dimensional colour Doppler. European Heart Journal Cardiovascular Imaging 2014 Jun; 15(6): 615 – 22. Epub 2013 Dec 15.

Abbreviation list

AR = aortic regurgitation

CW = continuous wave

EF = ejection fraction

ERO area = effective regurgitant orifice area

Eq. = Equation

HPRF = high pulse repetition frequency

LVEDd = left ventricular end-diastolic dimension

LVESd = left ventricular end-systolic dimension

M-mode = motion mode

MRI = magnetic resonance imaging

MR = mitral regurgitation

MULDO = multibeam high pulse repetition frequency color Doppler

PISA = proximal isovelocity surface area

PRF = pulse repetition frequency

PW = pulsed wave

Reg. vol. = regurgitant volume

ROI = region of interest

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

VCA = vena contracta area

VCW = vena contracta width

VTI = velocity time integral

2D = two-dimensional

3D = three-dimensional

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1 Introduction

1.1 Echocardiography

1.1.1 Selected history

For a wide range of cardiac diseases there is a need for non-invasive tools to assess and quantify disease processes. The development of cardiac ultrasound started in Sweden with the first description of an ultrasonic reflectoscope by Edler and Hertz in the early 1950s to obtain echoes from cardiac structures,[1] and later two-dimensional echograms of the heart by Hertz and Åsberg.[2, 3] In the 1960s Feigenbaum used ultrasound to visualize the left ventricle and measure wall thickness.[4] In 1976 Holen and Åslid investigated the pressure gradients in mitral stenosis by Doppler.[5] Omoto et al. demonstrated color Doppler in valvular regurgitation.[6]

The ultrasound research group in Trondheim pioneered by Bjørn Angelsen and Liv Hatle made important contributions in establishing Doppler methods. In 1976, Bjørn Angelsen and colleagues developed PEDOF (Pulsed and continuous wave Doppler) which was validated by Liv Hatle et al. in mitral valve diseases,[7, 8] aortic stenosis,[9] and for systolic pulmonary artery pressure.[10] Vingmed included Doppler into a two-dimensional echo scanner in 1982 and color Doppler in 1986. In 1984, Ihlen et al. from the research group in Oslo demonstrated that cardiac output could be calculated by Doppler.[11] There were further studies by Hegrenæs and Skjærpe in Trondheim in 1985 and 1986, validating Doppler in aortic stenosis for the assessment of severity,[12, 13] and for the estimation of systolic pressure in the right ventricle in patients with tricuspid regurgitation.[14] In 1993, Rossvoll and Hatle validated pulmonary venous flow velocities for estimation of left ventricular end-diastolic pressure.[15] Strain rate imaging by Doppler was developed and validated by Heimdal and Støylen.[16, 17]

1.1.2 Principles of ultrasound

Ultrasound is sound waves with a frequency higher than the range of human hearing, and can be characterized by its frequency (f), wavelength (λ) and amplitude (intensity). Medical ultrasound transducers typically use frequencies between 1 and 20 MHz. The propagation velocity (c) of sound in the heart is about 1540 m/s. The relation between the wavelength (λ), frequency (f) and propagation velocity (c) of the ultrasound wave in the heart; given by Eq. 1:

$$Eq.\,1)\; \lambda \cdot f = c$$

Sound waves move along a straight beam that can be focused. When sound waves reach a medium with different acoustic properties, they will be reflected at the boundaries. However, small structures (< 1 wavelength) such as blood cells result in scattering of the ultrasound signal in all directions. The amplitude of the sound wave is in decibels, and the amplitude of the received ultrasound signal is dependent on the transmitted amplitude, acoustic impedance of the tissues, the depth (R) and the transmitting frequency. Ultrasound is generated by piezoelectric crystals in the transducer, which induce expansion and compression from electric signals, and the reflected or backscattered echoes are converted to electric signals. The time (t) between the transmission and return of echoes determines the depth (R) of the reflecting object, Eq. 2:[18]

$$Eq.\,2)\; 2 \cdot R = c \cdot t$$

1.1.3 Spatial resolution

The radial resolution is dependent on the length of the transmitted ultrasound pulse, with a higher transducer frequency allowing a shorter pulse and improved resolution. The lateral resolution is dependent on the width of the ultrasound beam which is proportional to the wavelength and the focal depth and is inversely proportional to the transducer diameter.[18, 19]

1.1.4 Basic principles of Doppler

Doppler echocardiography is based on detection of the Doppler shift from moving structures such as red blood cells or myocardium. If the ultrasound is backscattered from moving structures, there will be a change in frequency, and the difference in frequency between the backscattered (f) and transmitted (f_0) signals is the Doppler shift. When the structure is moving toward the transducer, the backscattered frequency is higher than the transmitted frequency, and the Doppler shift is positive. When the structure is moving away from the transducer, the backscattered frequency is lower and the Doppler shift is negative. The relation between the Doppler shift (f_d) and blood flow velocity (v) is given by Eq. 3:

$$Eq. 3)\ f_d = f - f_0 = 2 \cdot f_0 \cdot \frac{v \cos \theta}{c}$$

This is the Doppler equation, and θ is the angle between the ultrasound beam and the direction of the blood flow. The radial velocities are calculated, and the ultrasound beam should be aligned as parallel with the direction of the blood flow as possible so that θ is close to 0° and cos θ can be assumed to be 1. Alignment is important as a θ of 20°, 40° and 60° will cause an underestimation of the flow velocity of 6%, 23% and 50%, respectively.

1.1.5 Grey scale imaging

In grey-scale imaging the amplitude is displayed as brightness of the scatterers versus depth. By repeating pulse transmission and receiving cycles along one scan line and recording time along the horizontal axis, there is a motion (M-) mode (see the left part of Figure 1). In two-dimensional (2D) imaging, a pulse is transmitted along a scan line, waiting for echoes to return, and then the next pulse is rotated in a step-wise manner to make up another scan line by a phased array probe (see the right part of Figure 1). Frame rate is determined by the scan depth (R) and number of scan lines.[18, 19] A reduction of the number of scan lines will increase the frame rate at the cost of poorer lateral resolution.
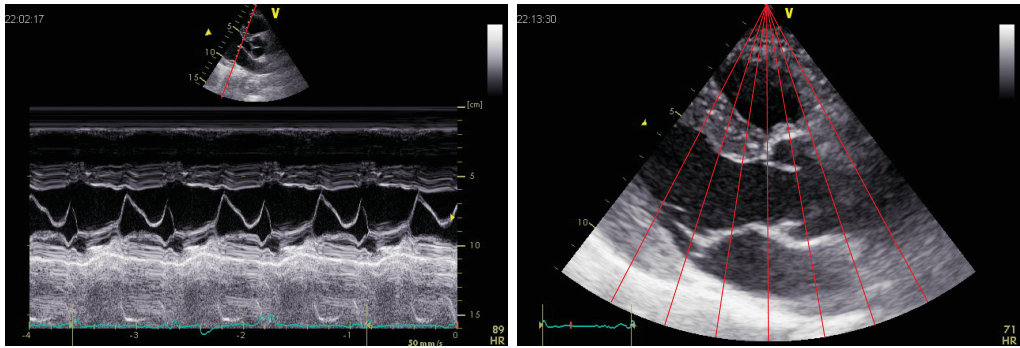
Figure 1: Left: M-mode imaging along one beam (red line) through the mitral valve vs. time. Right: One frame of 2D imaging of the heart made up of several scan lines (red lines).

1.1.6 Pulsed wave and continuous wave Doppler

In pulsed wave (PW) Doppler the blood flow velocities from a specific depth are sampled; this is called the sample volume. An ultrasound pulse of short duration is transmitted and, after an interval determined by the depth of interest, the backscattered signal is sampled or received at the transducer. The length of the sample volume is determined by the duration of the pulse, and the width of the beam corresponds to the width of the sample volume. Another pulse of ultrasound can be beam transmitted when the first one is received at the transducer, and the interval of time (t) between the pulses is dependent on the depth to the sample volume (R), as demonstrated in Eq. 2. The frequency of pulses is called the pulse repetition frequency (PRF). For PW Doppler, there is a maximum limit to velocity that can be measured unambiguously, called the Nyquist limit. The maximum detectable Doppler shift (f_d) is equal to half of the PRF. The Nyquist limit (V_{Ny}) is given by Eq. 4:

$$\text{Eq. 4)} \; V_{Ny} = \frac{c^2}{8 \cdot f_0 \cdot R \cdot \cos \theta}$$

If the velocity of interest exceeds the Nyquist limit, there is signal aliasing, giving incorrect information of the direction and velocity. As the PRF is successively increased, using high pulse repetition frequency (HPRF), the Nyquist limit is increased, but there will be

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more sample volumes and range ambiguity. By transmitting and sampling continuously, continuous wave (CW) Doppler high velocities can be measured without aliasing. Velocities are measured from any depth, and there is no range resolution.

The frequency content of the Doppler signals is displayed as spectral analysis, with time versus velocities, as shown in Figure 2. Blood flow direction towards and away from the probe is displayed as positive and negative velocities. The intensity of the velocity spectrum indicates the amplitude of the Doppler signals and the amount of moving blood cells.[18-20]
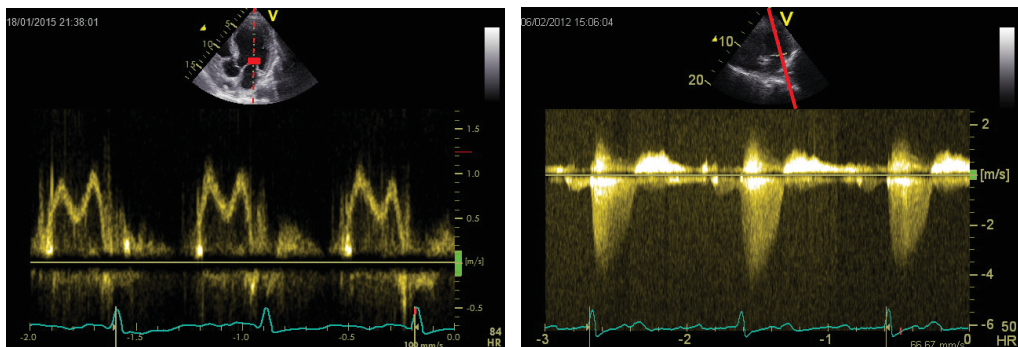
Figure 2: Left: PW Doppler of the laminar flow of the mitral inflow measured at the tip of the mitral leaflets, one sample volume (red box), displays a narrow spectral signal (narrow bandwidth). Right: CW Doppler of severe mitral regurgitation measuring velocities from any depth along the beam (red line), up to 4 m/s in this case, including turbulent flow.

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1.1.7 Color Doppler imaging

In Color Doppler, there are multiple sample volumes along each scan line. An ultrasound pulse is transmitted, and the Doppler signals from each sample volume are received. Several pulses (3 – 15) along each scan line are used, and the estimation of flow velocities is made from the Doppler signals

The Doppler signal amplitude has high values inside blood flow and low values outside flow. In laminar flow with narrow bandwidth, the mean frequency gives information of the velocity. The radial velocity data at each depth are encoded in color showing flow

towards the transducer as red and away from the transducer as blue. If the Nyquist limit is exceeded, the color shifts from red to blue or vice versa. Turbulent flow with high velocities causes multiple aliasing and uncertainty in determining the velocity. Turbulent flow is displayed by including green/yellow with red/blue to the color-coding. Color Doppler imaging is shown in Figure 3.
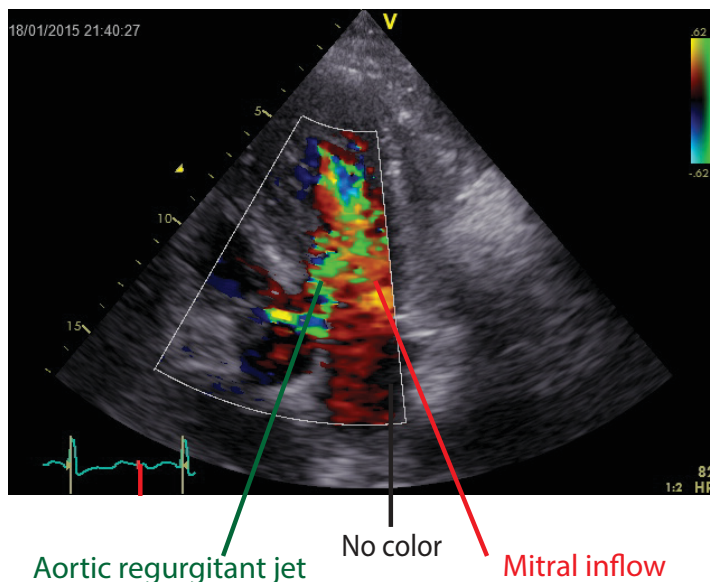
Figure 3: Color Doppler imaging, adapted from Hans Torp.

The Nyquist limit is determined by the scan depth (R). The frame rate is determined by the scan depth, the number of scan lines and the number of ultrasound pulses along each scan line. The sensitivity to detect blood flow is dependent on the number of scan lines.[18-20]

1.1.8 Power Doppler

In power Doppler, there are multiple sample volumes along each scan line, similar to color Doppler, but the signal processing differs. The power of the Doppler signal is proportional to the amount of moving red blood cells, independent of flow direction and velocity.[18, 20]

1.1.9 Three dimensional imaging

The ultrasound beam is transmitted in a similar way as a 2D scan and then repeated successively in a fan-like manner in the elevation plane to make a pyramid-shaped 3D volume, as demonstrated in Figure 4, using matrix array probe technology.
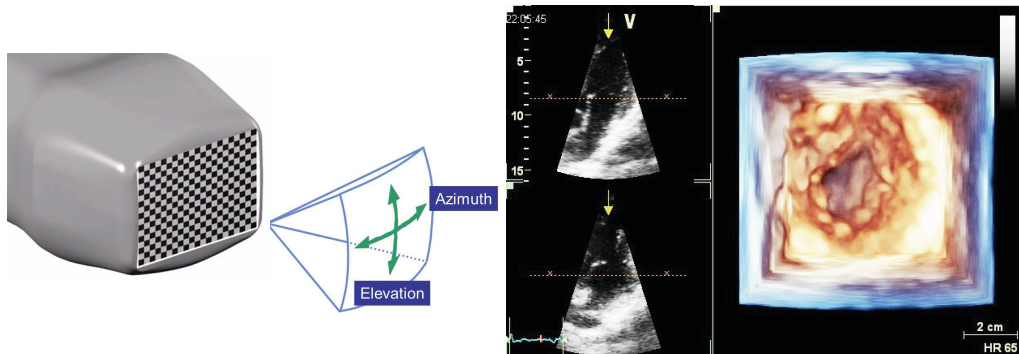
Figure 4: Left: Matrix array probe adapted from Hans Torp, typically with about 2400 elements for beam forming, steering and focusing in the azimuthal and elevation plane. Right: Pyramidal-shaped 3D volume visualizing the mitral valve in one diastolic volume.

For 3D imaging, the volume rate can be improved by limiting the number of scan lines at the cost of poorer spatial resolution. These limitations can be addressed by acquiring subvolumes for each R-R interval and then stitching these subvolumes (typically 4 - 7) to produce a full volume dataset. One major limitation is stitching artefacts. Color Doppler is implemented in 3D imaging, and the limitations are those inherent for both techniques.[21]

1.2 Mitral regurgitation

1.2.1 Background

The prevalence of moderate to severe valvular heart disease in the USA has been reported to be as high as 2.5%, with mitral regurgitation (MR) being the most common (1.7%) lesion.[22] In

Europe, MR has been reported to be the second most common form of valvular heart disease needing surgery.[23]

The anatomy of the mitral valve is shown in Figure 5, and dysfunction of any of these structures can cause abnormal leaflet coaptation and MR of varying degree.[24]
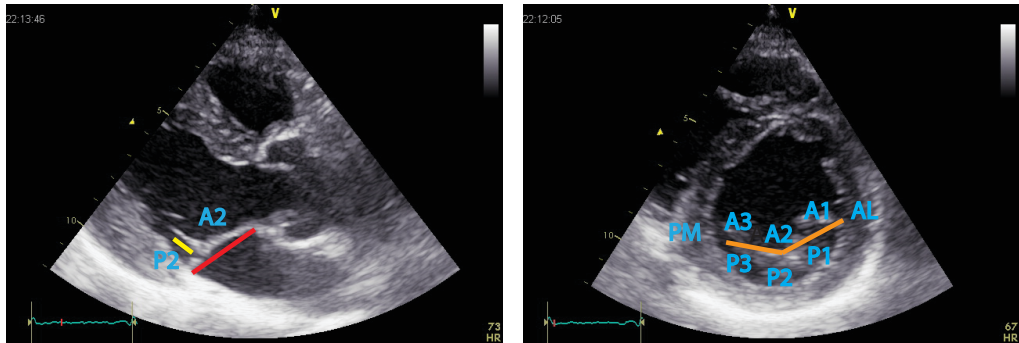
Figure 5: Parasternal long axis and short axis views of the mitral valve The posterior mitral leaflet is divided into three scallops: anterolateral (P1), middle (P2) and the posteromedial scallop (P3). The opposing segments of the anterior leaflet are defined as A1, A2 and A3. The base of the leaflets is attached to the annulus (mitral annular plane is marked in red) and the areas where the two leaflets come together at their insertion are the posteromedial and anterolateral commissures (PM and AL). When the mitral valve is closed the line of contact between the leaflets is called the coaptation line (marked in orange), and the leaflets overlap by several millimeters (coaptation length is marked in yellow) to ensure valve competency. The chorda tendinea originate from the papillary muscles and insert into the leaflets to prevent prolapse.

Carpentier introduced a functional classification of MR based on leaflet movement:[24, 25]

Type 1: Normal valve movement: annular dilatation or leaflet perforation.

Type 2: Excessive movement: billowing, mitral valve prolapse or flail.

Type 3a: Systolic and diastolic restriction.

Type 3b: Systolic restriction.

In primary (organic) MR, there is a primary valve lesion. In western countries, the most common etiology of primary MR is degenerative mitral valve disease (myxomatous degeneration and fibroelastic deficiency), resulting in billowing (see the left part of Figure 6) or a mitral valve prolapse. If there are rupture of chords, a portion of the mitral valve becomes

flail, which results in incomplete coaptation and leaflet diastasis.[26] These lesions represent a type 2 dysfunction. Rheumatic disease and endocarditis are less common. There is typically a type 3a dysfunction in rheumatic disease and type 1 or 2 dysfunction in endocarditis.

In secondary (functional) MR, there is primary myocardial disease. The most common etiology of secondary MR is ischemic heart disease.[27, 28] In left ventricular global remodeling, there is apical and inferior displacement of the papillary muscles together with non-extensible chorda resulting in symmetrically tethered and apically displaced leaflets as well as flattening and dilatation of the mitral annulus. As demonstrated in the right part of Figure 6, the deformation of the mitral valve can be quantified by the degree of tenting of the leaflets.[29, 30] Localized left ventricular remodeling, such as in basal inferoposterior infarctions, can result in asymmetric leaflet tethering.[31] These changes cause a type 3b dysfunction.
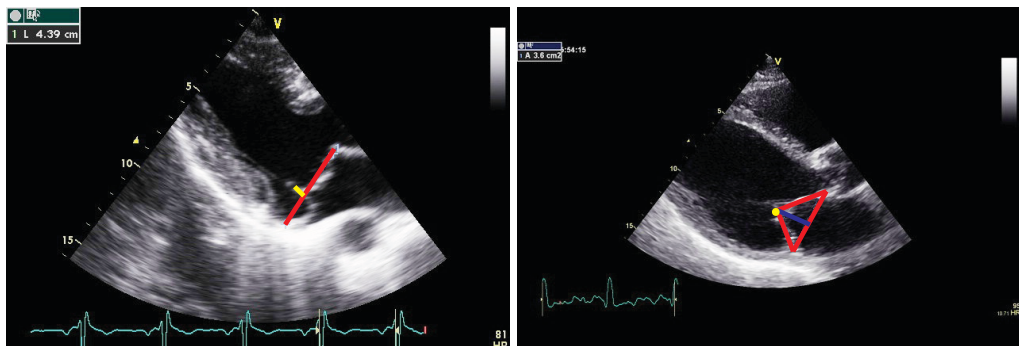
Figure 6: Left: Billowing of the mitral valve in Barlow's disease. Both leaflets protrude below the annular plane (red); however, the coaptation (yellow) is preserved above the annular plane. In mitral valve prolapse, the coaptation is below the annular plane.

Right: Symmetrical tethering resulting in tenting of the mitral leaflets in dilated cardiomyopathy. The distance between the annular plane and the point of coaptation (yellow) is the coaptation distance (blue). The systolic tenting area is the area between the coaptation point, the leaflets and the annular plane (red triangle). The coaptation length is reduced.

1.2.2 Hemodynamic consequences and outcome of mitral regurgitation

In acute disease, the regurgitant volume ejected into a normal-sized left atrium results in markedly increased left atrial and pulmonary pressures together with reduced stroke volume

by a normal-sized left ventricle.[32] In chronic compensated primary disease, there is a gradual eccentric remodeling of the left ventricle and atrium in response to volume overload. Severe, long-standing MR can result in an increase in left atrial and pulmonary pressures and irreversible myocardial damage. In patients with MR due to flail leaflet treated medically, there was an annual incidence of heart failure of 6.3% and a 10 year-incidence of 63%.[33] In secondary MR, the pathophysiology and outcome is different since this is a myocardial disease.[34]

1.2.3 Assessment of severity of mitral regurgitation by 2D Doppler

The echocardiographic assessment of the severity of MR is performed by TTE as an integrated approach. Color Doppler is sensitive for diagnosing MR, but the jet area is not recommended to quantify the severity of MR. Semi-quantitative approaches by PW Doppler such as the dimensionless ratio of mitral inflow to left ventricular outflow VTI in primary MR and the pulmonary venous flow patterns are additional parameters to assess severity; however, these are influenced by the left atrial filling pressure or atrial fibrillation. Quantitative approaches provide the regurgitant volume and the effective regurgitant orifice area (ERO area).[35-39]

Quantitative Doppler is time-consuming, requiring several steps of calculation, and is not recommended as a first line method. The PISA method is recommended for quantification, and its principle is based on the continuity principle.[39] As blood approaches a circular orifice, its velocity increases, forming concentric and hemispheric shells of increasing velocity and decreasing surface area, visualized as proximal flow convergence zones. The flow in each of these hemispheres equals the flow through the orifice. Color Doppler offers the ability to visualize one of these hemispheres corresponding to the Nyquist limit by adjusting the baseline shift to optimize visualization. Color flow M-mode imaging of a proximal flow convergence zone is shown in Figure 7.
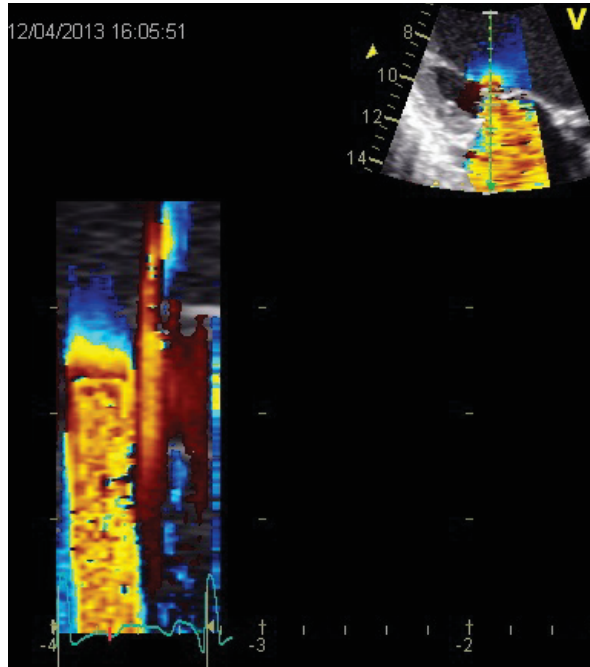
Figure 7: Dynamic changes of flow rate (early systolic peak and gradual decrease) during systole using color M-mode of the proximal flow convergence in functional MR.

The PISA is measured at mid-systole corresponding to maximal velocity (V_{max}) of the regurgitant jet by CW Doppler. The calculations are shown: Eq. 5, 6, 7, 8 and Figure 8.[39, 40]

$$Eq.5)\ PISA = 2 \cdot \pi \cdot R^2$$

$$Eq.6)\ Flow\ rate = PISA \cdot Aliasing\ velocity$$

$$Eq.7)\ ERO_{area} = \frac{Flow\ rate}{V_{max}}$$

$$Eq.8)\ Regurgitant\ volume = ERO_{area} \cdot VTI$$
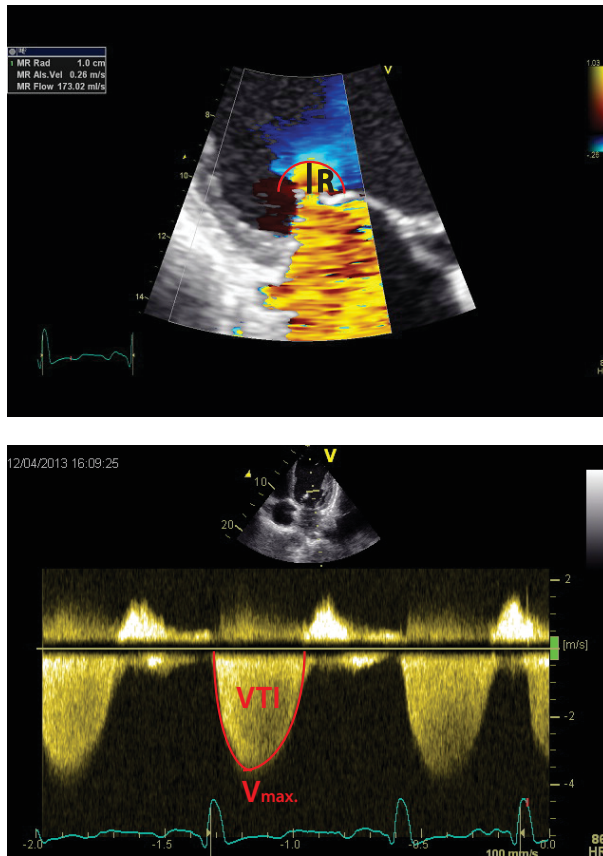
Figure 8: Upper: A proximal flow convergence zone is visualized by color Doppler imaging at the transition from blue to red/yellow corresponding to blood flow velocity of 26 cm/s, called the aliasing velocity. The proximal isovelocity surface area (PISA) is calculated as the surface area of a hemisphere, marked as a red hemisphere with a radius (R) marked in black. Flow rate is found by multiplying the PISA with the aliasing velocity. Lower: CW Doppler of the mitral regurgitant flow to find the VTI, marked by a red envelope, and Vmax and to calculate both the ERO area and regurgitant volume.

Quantitative parameters have demonstrated prognostic value in primary MR with worse outcome in those with an ERO area $\geq$ 40 mm^2 and regurgitant volume $\geq$ 60 mL.[41] In secondary MR an ERO area $\geq$ 20 mm^2 and regurgitant volume $\geq$ 30 mL are associated with worse outcome.[42-44]

It is recommended to get the best possible alignment between flow and the ultrasound beams, usually from the apical view. In eccentric jets, there will also be misalignment of flow and Doppler signals causing errors and limiting the use of the PISA-method.[39, 40] There is

dynamic variation of the mitral regurgitant flow rate and the ERO area during systole, which is demonstrated in Figure 7. In secondary MR, there is typically an early and late systolic peak and mid-systolic decrease or an early peak followed by a gradual decrease in flow rate, in rheumatic disease the flow is relatively constant until a decrease in end-systolic and in mitral valve prolapse there is a late-systolic increase of the flow rate.[45, 46] Time integral PISA methods have been introduced; however, these are cumbersome.[47]

Another approach to quantify MR is the vena contracta. As a regurgitant jet passes through an anatomic orifice, the jet continues to constrict for a certain distance before it expands radially into the receiving chamber. The vena contracta is the narrowest portion of the regurgitant jet downstream to the anatomic orifice and corresponds to the physiologic orifice or effective regurgitant orifice (ERO), which is slightly smaller than the anatomic orifice.[48] Both the shape of the proximal flow convergence and the vena contracta are defined by the geometry of the anatomic orifice, and the vena contracta area (VCA) is equivalent to the physiologic orifice area or ERO area. Making assumptions that the geometry of the anatomic orifice is perfectly circular, the flow convergence zone will form a 3-dimensional hemispheric shape on which the PISA formula is based, and the vena contracta will be circular.[49]

The vena contracta is typically viewed and measured perpendicular to the mitral commissural line, such as in the parasternal long axis or apical 4-chamber to measure the vena contracta width (VCW), as demonstrated in Figure 9. A Nyquist limit of 50 – 70 cm/s is recommended. The color sector should be as narrow as possible to maximize lateral and temporal resolution. As there is dynamic variation of the ERO area and thus the vena contracta, depending on the etiology, each systolic frame should be examined to identify the frame with the largest diameter of the vena contracta.[39, 40, 50]
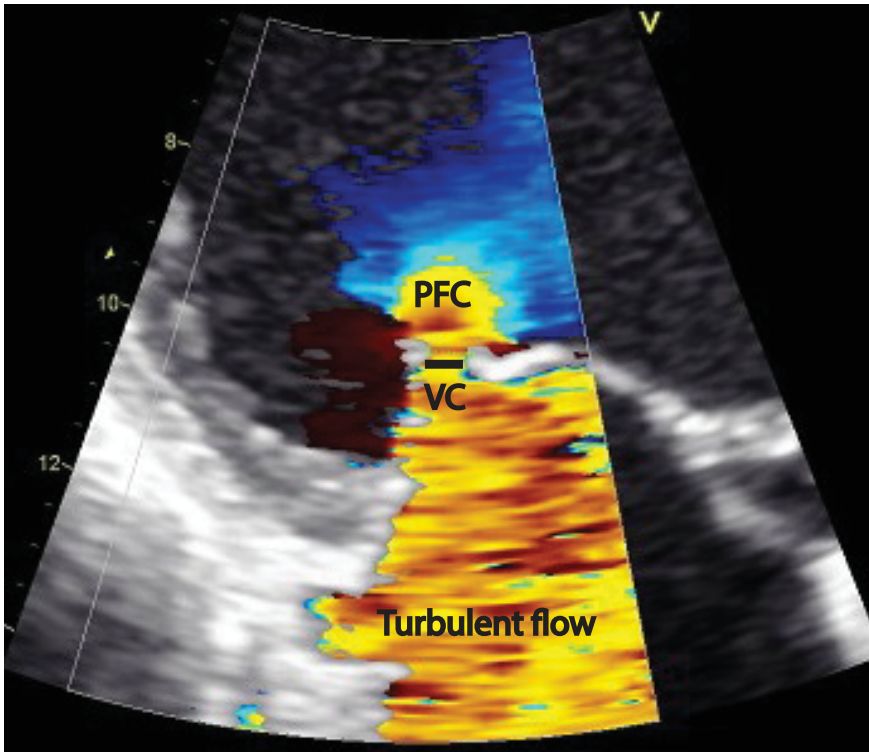
Figure 9: The proximal flow convergence (PFC), vena contracta (VC) and turbulent jet of a regurgitant jet are visualized.

Assuming that the vena contracta is circular, an estimate of ERO area would be, Eq. 9:

$$Eq. 9)\ ERO\ area \approx \pi \cdot \left(\frac{VCW}{2}\right) \cdot \left(\frac{VCW}{2}\right)$$

In noncircular jets the 2-chamber view of the vena contracta will overestimate the MR severity (see Figure 10). According to guidelines, a vena contracta width (VCW) ≥ 7 mm along the long-axis plane or a mean VCW (4-chamber and 2-chamber) > 8mm is regarded as a specific sign of severe MR.[51, 52]
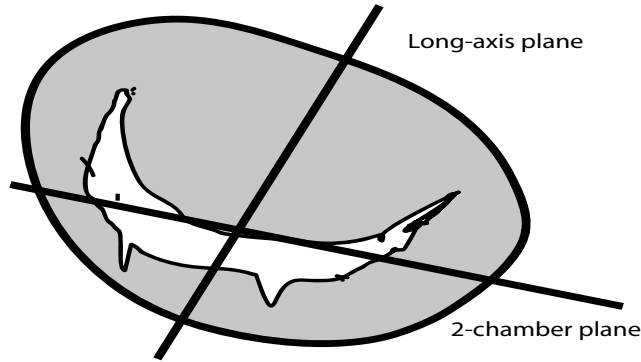
Figure 10: A short axis view of the mitral valve leaflets and the corresponding long-axis plane, while the two-chamber plane is parallel to the commissural line. The vena contracta width (VCW) will appear different in the long-axis and 2-chamber views in asymmetric jets.

1.2.4 Assessment of severity of mitral regurgitation by 3D Doppler

Real-time 3D Doppler echocardiography has demonstrated that the PISA is hemielliptic rather than hemispheric in secondary MR, resulting in underestimation of the ERO area by the hemispheric approach. PISA can be calculated from a hemielliptic surface area formula using the 3D dataset to measure the PISA radius, width and length.[53-55] The regurgitant flow rate is calculated from the hemielliptic (HE) PISA and the aliasing velocity, Eq. 10. The ERO area and regurgitant volume is calculated from flow rate, the peak velocity and VTI of the regurgitant jet by CW Doppler, similar to Eq. 7 and 8:

$$Eq.\,10) \; Flow\;rate = HE\;PISA\;formula\;(radius, width, length) \cdot Aliasing\;velocity$$

Direct and automated measurement of 3D PISA is feasible making no geometric assumptions.[56] A time-integrated automated PISA method, Eq. 11, in patients with secondary MR, was more accurate than using only one frame (volume) to calculate the regurgitant volume; N= number of systolic color Doppler volumes.[57]

$$Eq.\,11) \; Regurgitant\;volume = \sum_{1}^{n} \frac{automated\;3D\;PISA_n \cdot Aliasing\;velocity}{color\;Doppler\;volume\;rate}$$

A 3D color Doppler method to calculate mitral inflow and aortic stroke volume has been validated,[58] and the mitral regurgitant volume can be calculated as the difference.[59]

By 3D color Doppler, it was first demonstrated that the direct measurement of VCA was feasible and showed better correlation with angiographic grading than the VCW.[60] Later studies validated VCA against different 2D Doppler methods to calculate the ERO area (PISA, quantitative Doppler, VCW),[55, 61-63] and regurgitant volume by MRI.[64, 65] Either the apical or parasternal windows were used for pyramidal full-volume acquisitions made from 7 – 14 subvolumes.[55, 61-63, 65] The 3D dataset was manually cropped by an image plane perpendicular to the jet direction and moved along the jet until the vena contracta was identified, as demonstrated in Figure 11. The volume with the largest vena contracta,[61-63] the most relevant lesion size,[64, 65] and the mid-systolic frame in secondary MR and late-systolic frame in mitral valve prolapse, where the ERO area is usually the largest, were used.[55] VCA was measured by direct planimetry, as a measure of ERO area, Eq. 12.

$$Eq.\,12)\ ERO\ area = VCA$$
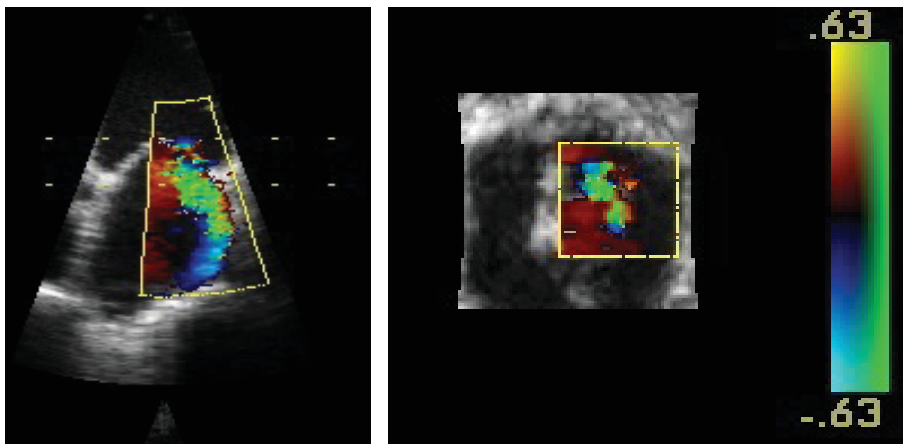
Figure 11: 3D color Doppler acquisition of a mitral regurgitant jet; in 4-chamber view (left) and a cross-sectional view through the vena contracta demonstrating an asymmetric physiologic orifice or effective regurgitant orifice. Measurement of the VCA is performed by planimetry.

Little et al. demonstrated that the VCA correlated well with the shape and area of the orifice in vitro, while VCA was asymmetric in 89% of the cases *in vivo*.[61] Kahlert et al. demonstrated that the shape of the VCA was noncircular and elongated along the commissural line in secondary MR due to leaflet tethering and incomplete mitral valve closure. In mitral valve prolapse, there was moderate asymmetry of the VCA, and in other degenerative diseases, the VCA was closer to a circular defect caused by a fixed lesion resulting from leaflet stiffening and thickening.[55] Zeng et al. also demonstrated that the VCA was asymmetric in the majority of patients, regardless of etiology, but more elliptical and elongated in secondary MR than in primary MR.[63] The ERO area by 2D PISA significantly underestimated the VCA in all patients, and to a greater degree in secondary MR.[55, 63] VCA was feasible in both eccentric and central jets.[62] In a recent study in patients with secondary MR and more than one MR jet, it was demonstrated that the vena contracta areas could simply be added together to approximate the total ERO area.[66]

By multiplying the VCA by the VTI by CW Doppler, the regurgitant volume can be calculated, Eq. 13.[64, 65]

$$Eq.\,13)\; Regurgitant\; volume = VCA \cdot VTI$$

1.2.5 Guidelines

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are the key examinations for evaluation of mechanism, etiology and feasibility of valve repair. Quantification of MR is based on 2D Doppler methods. Different 3D methods are evolving because of the limitations of 2D methods, but need further validation.

In acute severe disease, surgery is indicated. In severe chronic primary MR, valve repair or replacement is indicated if there are symptoms, left ventricular dysfunction, pulmonary hypertension or atrial fibrillation, as they are predictors of events.[33, 51, 52, 67-71] In asymptomatic severe chronic primary MR with preserved LV-function there is a 2a indication

for valve repair if there is a high probability of successful repair and low expected mortality.[52] In severe secondary MR, there is indication for mitral valve surgery when there is concomitant CABG.[51, 52]

1.3 Aortic regurgitation

1.3.1 Background

In the Euro heart Survey on valvular disease, aortic regurgitation (AR) represented 13.3% of patients with single native left-sided disease.[23]

The anatomy of the aortic valve is demonstrated in Figure 12, and dysfunction of any component of the aortic valve complex can cause incomplete coaptation and AR.
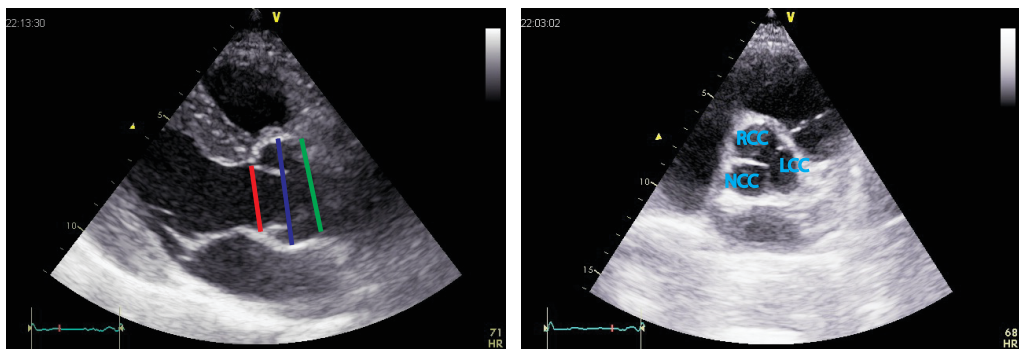
Figure 12: Left: Parasternal long axis view of the aortic root; diameter at the annulus (red), Sinus Valsalva (blue) and sino-tubular junction (green). Right: Short axis of the aortic valve: right coronary cusp (RCC), non-coronary cusp (NCC) and left coronary cusp (LCC).

In western countries, AR is most frequently caused by leaflet abnormalities such as a bicuspid valve or a degenerative, calcific valve disease. Other causes are aortic root dilatation secondary to hypertension or connective tissue diseases. In developing countries, rheumatic disease is the most prevalent cause of leaflet abnormalities and severe AR. Acute aortic regurgitation is caused by endocarditis and aortic dissection.

1.3.2 Hemodynamic consequences and outcome of aortic regurgitation

In acute disease, there is an acute volume overload leading to reduced forward stroke volume and increased end-diastolic pressure. In chronic compensated disease, there is chronic volume overload and increased forward volume ejected into the aorta leading to a combination of eccentric and concentric hypertrophy and dilatation. Long-standing severe AR can cause irreversible myocardial damage. Measures of LV function are prognostic markers for outcome.[51, 52, 72-74]

1.3.3 Assessment of severity of aortic regurgitation by 2D Doppler

The severity of AR is evaluated by TTE and requires an integrated approach of 2D Doppler parameters.[40, 75] Color Doppler imaging is sensitive to detect AR, but the jet area and length are not recommended for quantification due to weak correlation to severity of AR. The pressure half time (PHT) of the regurgitant jet by CW Doppler reflects the pressure difference between the aorta and the left ventricle. A PHT < 200 ms is consistent with severe AR, but the PHT is influenced by both aortic and chamber compliance as well as chamber pressures.[76] Holo-diastolic flow reversal of the upper descending aorta by PW Doppler and end-diastolic velocity of > 18 cm/s is a sensitive sign of severe AR.[77] However, reduced aortic compliance results in increased duration and velocity of the flow reversal. Both PHT of the regurgitant jet and diastolic flow reversal of the descending aorta are semi-quantitative parameters that are critically dependent on alignment of the Doppler beam and flow measurements.[75]

Quantification is recommended, but the assessment of PISA is less extensively performed in AR compared with MR; however, when feasible, PISA is recommended to quantify the severity of AR.[40, 75, 78] In addition to the assumption of hemispheric geometry, there are some additional limitations for aortic regurgitation such as interposition of valve tissue and difficulty in identifying PISA. There might also be obtuse flow convergence angles such as those with dilatation of the ascending aorta, perforation of a cusp or commissural

regurgitation. Quantitative Doppler is an alternative approach to quantifying AR, requiring several steps of calculations of stroke volumes, each having the potential for errors. An ERO area of 30 mm^2 or a regurgitant volume > 60 mL indicate severe AR.[40, 51, 52, 75]

The vena contracta is a direct measure of the ERO, and VCW correlates to the severity of AR.[79, 80] It is recommended to measure the VCW in parasternal long axis and use the frame with the largest and most clearly defined vena contracta, as demonstrated in Figure 13 a. According to Guidelines, a VCW ≥ 6 mm is regarded as severe AR.[40, 51, 52, 75]

1.3.4 Assessment of severity of aortic regurgitation by 3D Doppler

VCW measurements might under- or overestimate AR severity because the vena contracta shape is not always circular. From 3D color Doppler imaging, we can measure the VCA without making geometric assumptions, and VCA has proven to be better than VCW measurements. This was first demonstrated by Fang et al.[81] A cut-off value of VCA for severe AR, assessed by quantitative Doppler and aortography as a reference, was proposed at 50 mm^2.[82] In a few studies VCA, was validated against MRI aortic phase contrast imaging.[83, 84] Either a parasternal or apical window were used for a full-volume acquisition of the aortic regurgitation made from 4 to 7 subvolumes. The dataset was cropped just downstream of the aortic valve in a plane perpendicular to the direction of the aortic regurgitant jet to identify the vena contracta as the narrowest part of the jet. The frame (volume) with the largest VCA,[81] a mid-diastolic frame (volume),[83] or the frame (volume) with the most relevant lesion size,[84] or an unspecified frame(volume) were used.[82] VCA was measured by direct planimetry in all studies, as a measure of ERO area, Eq. 12.

To calculate regurgitant volume, VCA was multiplied by VTI of the mitral regurgitant jet by CW Doppler (MR VTI), Eq. 13.[84] In Figure 13 b and c, measurements of the VTI by CW Doppler and direct measurement of the VCA by 3D color Doppler are demonstrated.
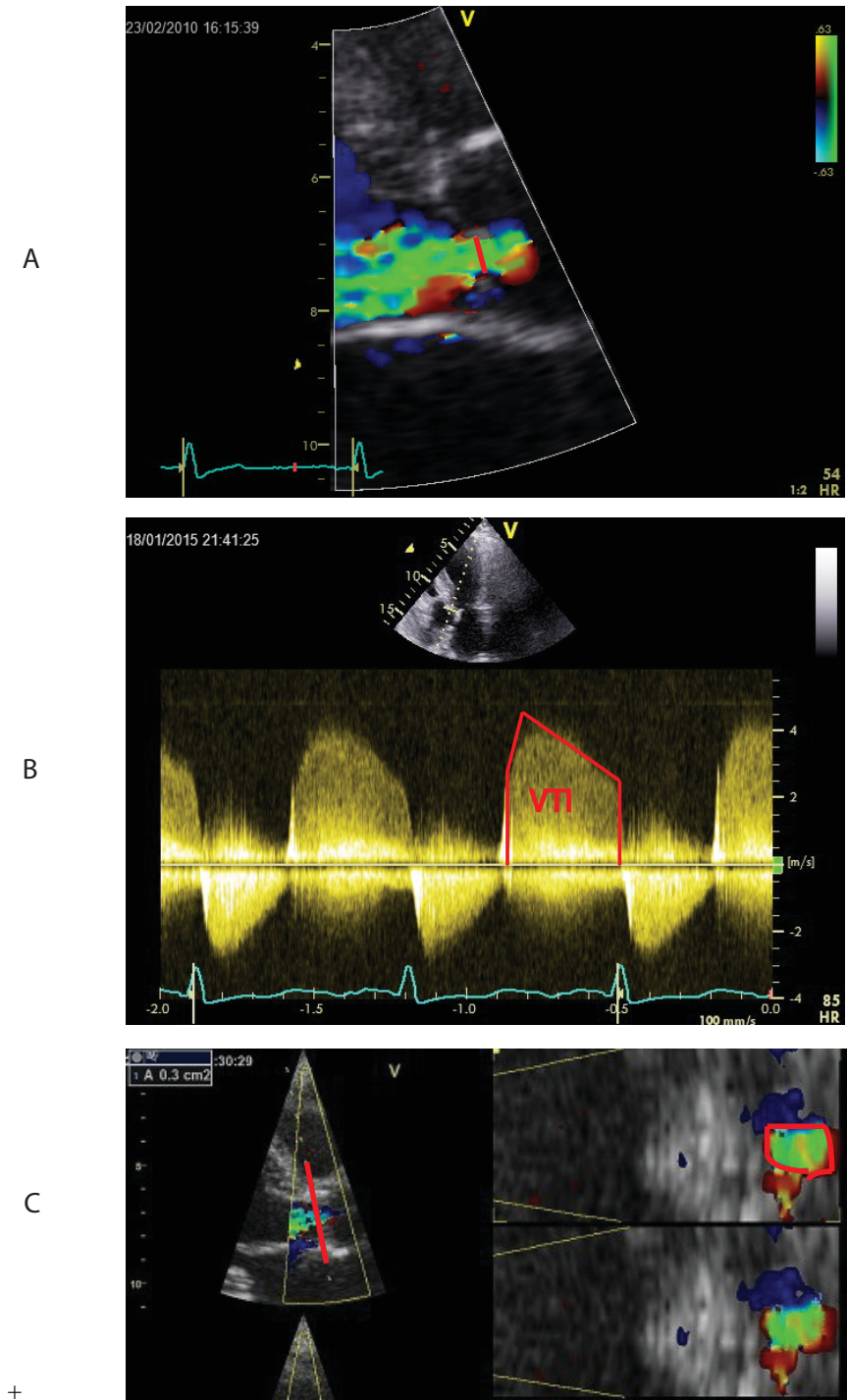
Figure 13: 2D and 3D echocardiographic acquisition and analyses: a) The vena contracta width (red line) measured from the parasternal long axis, b) The velocity time integral (VTI) measured from the apical window in central jets, c) 3D color Doppler of the vena contracta and direct planimetry.

1.3.5 Guidelines

TTE and TEE are key examinations for evaluation of the mechanism, etiology and feasibility of valve repair. In the current guidelines, quantification of AR is recommended, based on 2D Doppler methods. With 3D color Doppler, a VCA of 50 – 60 mm^2 has been proposed to define severe AR, but this needs further validation.

In acute severe AR, urgent surgical intervention is indicated. In chronic severe AR, valve replacement or repair is indicated in patients with either symptoms or LV-dysfunction or in patients undergoing CABG or surgery of the ascending aorta.[51, 52]

1.4 MRI

MRI is an accurate and reproducible technique for assessing both the left and right ventricular volumes.[85-87] Left ventricular stroke volume is calculated as the difference between the end-diastolic and systolic volume from short-axis ventricular image slices, as demonstrated in Figure 14. The accuracy of the left ventricular volumes is dependent on correct placement of the basal ventricular image slice, with correct differentiation of the atrium and ventricle, as well as correct endocardial contour placement during post processing.
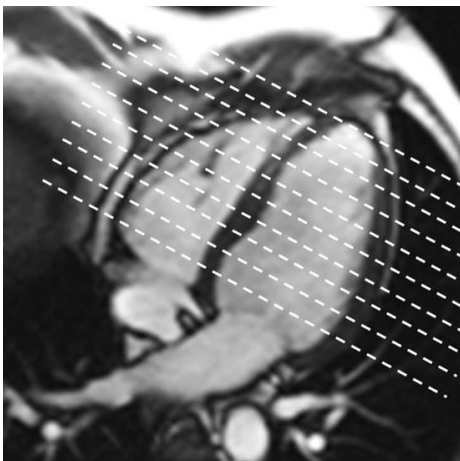
Figure 14: MRI for assessing the left ventricular volumes. Image Courtesy of Brage H. Amundsen.

By using phase-contrast imaging, flow can be directly quantified. This technique is based on the property of protons moving in a magnetic field causing phase shift, and the magnitude of this phase shift is proportional to their velocity. Velocity can be measured and is displayed in grey-scale images, as demonstrated in the left part of Figure 15. Flow is derived from through-plane velocity maps by integrating the velocity of each pixel and its area over time, as demonstrated in the right part of Figure 15. There is good accuracy of flow measurements in *in vivo* studies.[88-90] However, *in vivo* validation studies are limited by the lack of a true gold standard for comparison. Further, flow measurements are dependent on a homogenous magnetic field. The frame rate of about 25 – 30 Hz can be a limitation for the measurement of fast-changing velocities.
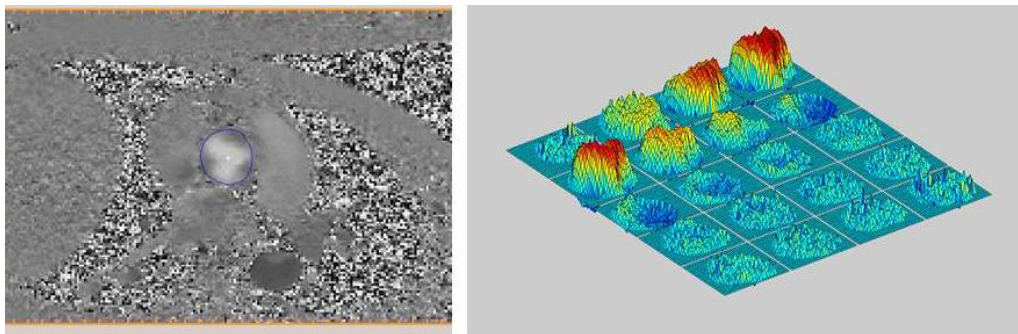
Figure 15: Left: Through-plane phase-contrast velocity mapping from one systolic frame from the ascending aorta. Right: Aortic flow patterns from several systolic (red/yellow) and diastolic frames (blue/green). Image courtesy of Brage H. Amundsen.

In most cases, Doppler echocardiography provides the data needed for evaluation of valvular disease. MRI is indicated in patients with chronic primary MR or chronic AR to assess ventricular volumes, EF or severity of the regurgitation when these issues are not adequately addressed by TTE or TEE. Outcome data using MRI volumes is, however, lacking.[51, 52] MRI is not as widely available as Doppler echocardiography, as MRI is more time-consuming, expensive and, most importantly, there are some contraindications.

1.4.1 MRI in mitral regurgitation

Mitral regurgitant volume can be obtained by various methods, and is usually performed indirectly. The mitral regurgitant volume can be calculated as the difference between the left ventricular stroke volume from short-axis image slices of the left ventricle and the aortic stroke volume by phase-contrast measurement in the ascending aorta, Eq. 14.[91] This relies on a combination of two different MRI techniques and increases the measurement errors. Alternatively, the difference between the left and right ventricular stroke volume can also calculate the mitral regurgitant volume, Eq. 15.[92] This assumes the absence of an intra-cardiac shunt or another valvular regurgitation to be valid as well as accurate contour placement for volumetric assessment. Alternatively, using the difference between phase-contrast measurements from the mitral inflow and ascending aorta, the mitral regurgitant volume can be calculated, Eq. 16.[93] By using phase-contrast measurements at the level of the mitral valve, the mitral regurgitant volume can be measured directly from the retrograde flow.[94] Phase-contrast measurements at the mitral annulus are difficult due to the highly mobile mitral valve.

$$Eq. 14)\ Mitral\ reg.\ volume\ =\ LV\ volumetry\ SV\ -\ PC\ of\ aortic\ SV$$

$$Eq. 15)\ Mitral\ reg.\ volume\ =\ LV\ volumetric\ SV\ -\ RV\ volumetric\ SV$$

$$Eq. 16)\ Mitral\ reg.\ volume\ =\ PC\ of\ mitral\ inflow\ volume\ -\ PC\ of\ aortic\ SV$$

1.4.2 MRI in aortic regurgitation

MRI has been validated in several studies in AR.[88, 95-101] It is most common to assess AR by using aortic phase-contrast, measuring forward and regurgitant flow in the ascending aorta by

placing the imaging slice just above the aortic valve, and thus directly quantitating regurgitant volume from the regurgitant flow during one cardiac cycle and regurgitant fraction from the ratio between regurgitant and forward (systolic) volume, Eq. 17.[88, 98, 100, 101]

$$Eq.\,17)\;Aortic\;regurgitant\;fraction = \frac{Regurgitant\;volume}{Aortic\;forward\;volume}$$

1.5 Multibeam HPRF color Doppler (MULDO)

In laminar flow such as in the vena contracta, the backscattered Doppler power is proportional to the volume of blood in a sample volume of an ultrasound beam.[102] The attenuation compensated volume flowmeter to measure volume flow in arteries was introduced by Hottinger and Meindl.[103] Buck et al. hypothesized that this principle could be applied at the vena contracta, and that the total backscattered Doppler power (power integral) was proportional to the cross-sectional area of the vena contracta. They calculated volume flow through the vena contracta from the power-velocity integral and the regurgitant volume from the power-velocity-time integral and finally calculated mean VCA, by means of a single wide measurement beam and a narrow beam for calibration; Broad-beam spectral Doppler.[104, 105]

We have extended this principle to using multiple narrow ultrasound beams covering the vena contracta region as well as using HPRF to be able to isolate the high-velocity Doppler signals in the vena contracta. HPRF is demonstrated in the left part of Figure 16 and multiple beams in Figure 17. With HPRF, several pulses are fired before the deep echoes from the first pulses have returned to the probe, such that exact range information is lost in exchange for increased velocity span. We used a 3D color Doppler mode, with PRF typically being about 20 kHz and a transmitted frequency of 2.1 MHz, resulting in a Nyquist limit of about 3 m/s; a 3D HPRF color Doppler flow of the vena contracta is demonstrated in the right part of Figure 16. We used a clutter-filter with a cut-off frequency corresponding to 1.5 m/s to

remove the signals from the "spurious" sample volumes outside the jet. This acquisition uses a packet-size of 8 in each direction, and thus enables a reasonable volume rate of about 7 Hz.
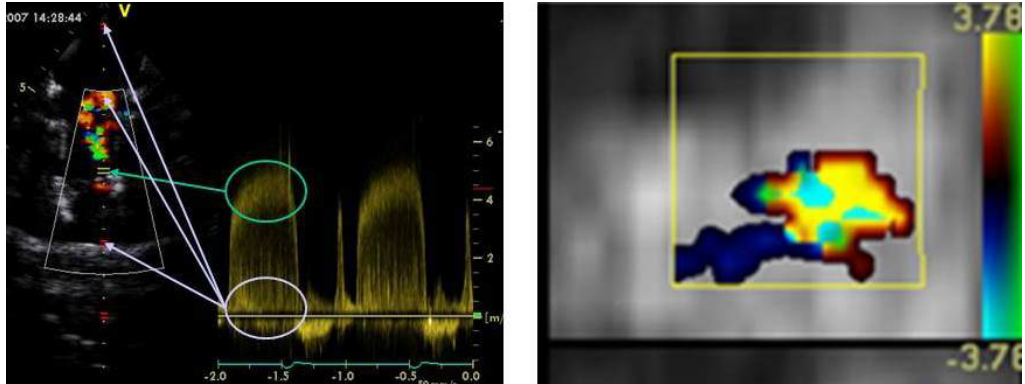
Figure 16: This picture is from an in-vitro model of a regurgitant jet as demonstrated by a 2D triplex-scan (left). HPRF increased the Nyquist limit and was implemented for 3D color Doppler (right) to isolate the vena contracta. Image Courtesy of Torbjørn Hergum.

There were several narrow ultrasound beams (black), as shown in figure 17 a, covering the vena contracta region, and a composite measurement beam (blue) was made by summing the contribution from all beams. The region of interest (ROI) must be short radially (elevation) to enable HPRF. A wide single measurement beam (green), as used by Buck et al., is included for comparison. Our approach, multibeam HPRF color Doppler (MULDO), will ensure a more homogenous sensitivity of the measurement beam and higher signal-to-noise ratio compared with a single wide measurement beam (Figure 17 b).
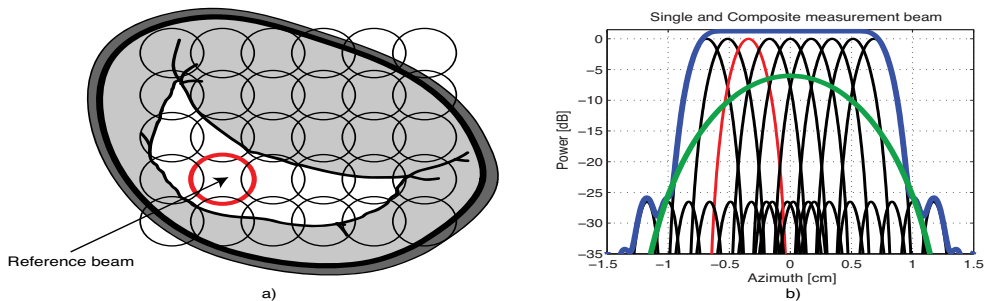
Figure 17: a) Cross-sectional view through the vena contracta region. The reference beam (red), the beam with most Doppler power, is selected automatically as this beam is most likely to be within the jet of the vena contracta. A composite measurement beam (blue) is made by adding multiple narrow beams (black) together. b) In this sketch, nine narrow beams have been added to make a wide flat beam or a composite measurement beam (blue). The green line shows the beam profile of a single wide measurement beam from a smaller transducer. The peak sensitivity of this beam is about 8 dB lower than for the composite measurement beam (blue), and the sensitivity varies significantly. Picture from JASE, 2010; 23(1):1 – 8, reprinted with permission.

As the flow through the vena contracta is laminar, the Doppler power of the composite measurement beam is proportional to the blood volume within the sample volume, and for a thin disk-like sample volume the Doppler power (P_{meas}) will be proportional to the cross-sectional area of the vena contracta. To get a calibrated Doppler power measurement, a reference beam (red) was chosen as the beam with the greatest Doppler power (P_{ref}) because this beam was most likely within the regurgitant jet. A computer model provides the cross-sectional area (A_{ref}) of the reference beam and the constant, k. The VCA was proportional to the calibrated Doppler power, and therefore independent of attenuation or display parameters such as gain or tissue priority, and found by solving Eq. 18:

$$Eq.\,18)\ \frac{P_{meas}}{VCA} = k \cdot \frac{P_{ref}}{A_{ref}}$$

2 Aims

2.1 General aims

The main objective was to determine the accuracy of a new Doppler method, MULDO, for the quantification of valvular regurgitation. The evaluation was focused on to what extent this new method could produce more accurate information than current Doppler methods.

2.2 Specific aims

1) To study and validate MULDO in an *in vitro* model.

2) To study and validate MULDO in patients with mitral regurgitation, and compare it with conventional Doppler methods, echo grading based on an integrated approach and MRI.

3) To study and validate MULDO in patients with aortic regurgitation, and compare it with conventional Doppler methods, echo grading based on an integrated approach, 3D color Doppler of the vena contracta and MRI.

3 Materials

Study 1: This was a simulation study as well as an *in vitro* study using a pulsatile flow phantom and 6 prosthetic porcine valves with precisely cut circular holes varying from less than 10 to 40 mm^2 to provide varying degrees of regurgitation performed at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, and at the Institute of Medicine, University of Bergen, Bergen, Norway. A few patients (N = 8) with moderate to severe MR at the Department of Cardiology, St Olav`s University Hospital in Trondheim, Norway, from October 2007 until February 2008 were studied in order to identify technical adjustments necessary prior to a larger *in vivo* testing of the method. This was a simplified protocol (without MRI) of the one approved by the Regional Committee for Medical and Health Research Ethics (REK, Midt-Norge) for study 2.

Study 2: This study was performed at the Department of Cardiology, St. Olav`s University Hospital in Trondheim, the Department of Medicine, St Olav`s University Hospital in Orkdal, Norway, and at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, from March 2008 until March 2009. The inclusion criteria were adult patients, who were followed on a regular outpatient basis, with mild to severe chronic MR of any etiology in sinus rhythm. Exclusion criteria were AR, cardiac arrhythmias and contraindications to MRI. We sought participants from the outpatient registry from the previous year`s consultations with MR as the main diagnosis and selected those without exclusion criteria for invitation to participate. The patient information and letter of invitation is in the Appendix; we sent requests to 71 patients. Thirty-five patients with mild to severe MR consented to participate. Three participants were excluded because of poor MULDO acquisition and quality due to

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misalignment of the Doppler beam and jet direction, difficulty in in identifying the vena contracta and incorrect positioning of the region of interest (ROI). In cases of exclusion due to poor MULDO quality, there were no jet signals above the noise level in the systolic frames during acquisitions over several heart beats, resulting in inability to measure the VCA. Four participants were excluded because of poor MRI quality caused by arrhythmias, and 1 participant was excluded because of the requirement of hemodialysis between the investigations. There were 27 participants included in the analysis of the study. There were 11 women and 16 men with a median age of 51 (range 28 – 81) years. In 11 participants, there was secondary (functional) MR, while the remaining participants had primary (organic) MR. Eccentric jets were present in 10 participants with primary MR and in 4 participants with secondary MR. The median EF was 50 (range 23 – 65)%.

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK, Midt-Norge) and the Norwegian Social Science Data Service.

Study 3: This study was performed at the Department of Cardiology, St Olav`s University Hospital in Trondheim, the Department of Medicine, St Olav`s University Hospital in Orkdal, Norway, and at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, from December 2009 until February 2012. The inclusion criteria were adult patients, followed on a regular outpatient basis, with mild to severe chronic AR of any etiology in sinus rhythm. Exclusion criteria were cardiac arrhythmias, concomitant aortic stenosis or any contraindication to MRI. We sought participants from the outpatient registry at St Olav`s University Hospital in Trondheim and Orkdal from the previous year`s consultations with AR as the main diagnosis and selected those without exclusion criteria for invitation to participate. The patient information and letter of invitation is shown in the Appendix; we sent

requests to 60 patients. Twenty-nine of these patients consented to participate. Another 7 patients with AR at the Department of Cardiology, Oslo University Hospital, Rikshospitalet, Norway, participating in another study fulfilling our inclusion criteria consented to participate in the MULDO study; being performed at Rikshospitalet from April 2011 until September 2011. Finally, there were 36 patients participating. Due to poor MULDO acquisition and quality because of misalignment of the Doppler beam and jet direction, difficulty in identifying the vena contracta and incorrect positioning of the region of interest (ROI), we were not able to measure the VCA in 7 participants. In these cases, there were no jet signals above the noise level in the diastolic frames during acquisitions over several heart beats, and they were excluded from the analyses. There were 29 participants included in the analyses. There were 7 women and 22 men with a median age of 58 (range 18 – 83) years. The etiology was degenerative valve disease in 9, bicuspid aortic valve in 7, cusp prolapses in 3, aortic root disease in 6 and unknown in 4 participants. In 16 participants, there were eccentric jets and central jets in 13. The median EF was 60 (range 30 – 71)%. The median LVEDd was 61 (range 45 – 72) mm, and the median LVESd was 39 (range 25 – 52) mm. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK, Midt-Norge).

4 Methods

4.1 Study design

Study 1: MULDO was tested in a simulation model and an *in vitro* model with a pulsatile flow phantom and porcine valves with orifices of known sizes (circular defects from less than 10 to 40 mm^2). The flow phantom was filled with blood-mimicking fluid, and the porcine valves were inserted into the flow phantom to provide various regurgitation severities. Several MULDO recordings were performed for each orifice size, both with stationary and pulsatile flow, performed and analyzed by Torbjørn Hergum.

To obtain HPRF, the ROI had to be small in the radial direction; at the same time, there were clinical pilot trials in patients with MR performed by Thomas R. Skaug and Torbjørn Hergum to define the needs for this this method to work in a clinical setting. The azimuthal and elevation dimensions of the ROI should be large enough to measure any mitral regurgitation. At an early phase we used a ROI with a small radial depth of a 2 mm, as demonstrated in the left part of Figure18. The ROI had to be small in the radial direction to obtain HPRF. This was, however, difficult to use in patients, and we did not manage to obtain representative Doppler data until the ROI was subsequently increased in the radial direction up to 8 mm without significant loss of velocity resolution, as demonstrated in the right part of Figure 18.
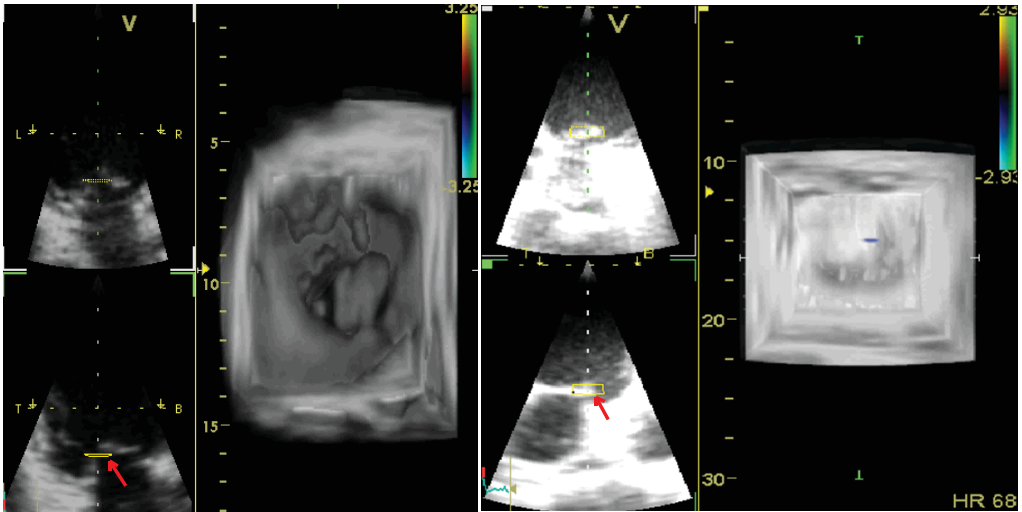
Figure 18: MULDO acquisition from patients from some early clinical pilot trials in patients with mitral regurgitation. The left part of the picture shows ROI (red arrow points at the ROI)) with a radial depth of a few millimeters, which was difficult to use in patients. The right part of the picture after some modification of the method shows ROI depth of 8 mm (red arrow points at the ROI).

Study 2: A clinical feasibility and validation study in patients with MR. We performed MULDO and 2D TTE exams (Thomas R. Skaug) before an MRI exam (Brage H. Amundsen and Thomas R. Skaug). All analyses were performed off-line to assess severity of MR by 2D Doppler and PISA measurements, regurgitant volume by MRI and MULDO analyses. There were different observers for the different analyses (MRI by Brage H. Amundsen, 2D Doppler and PISA by Terje Skjærpe and MULDO analyses by Thomas R. Skaug). MULDO was analyzed semi-automatically, and we assessed inter-observer variability of the same sets of recordings by the two investigators (Thomas R. Skaug and Torbjørn Hergum). MULDO was compared with different reference methods (2D Doppler parameters and MRI) to assess correlation and agreement.

Study 3: A clinical feasibility and validation study in patients with AR. MULDO, 2D and 3D TTE exams were performed (N = 25 by Thomas R. Skaug, N = 4 by Stig Urheim) before an MRI exam (N = 25 by Brage H. Amundsen and Thomas R. Skaug, N = 4 performed at Oslo

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University Hospital, Rikshospitalet) on the same day. All analyses were performed off-line to assess the severity of AR by 2D Doppler by an integrated approach, measuring VCW and VTI by CW Doppler, manual planimetry of VCA by 3D color Doppler and regurgitant volume and fraction by MRI and MULDO analyses. There were different observers for the different analyses (MRI by Brage H. Amundsen, 2D Doppler by Bjørn Olav Haugen (N = 25) or by Stig Urheim (N = 4) and 3D color Doppler analyses by Thomas R. Skaug). The MULDO recordings were validated by Torbjørn Hergum and/or Thomas R. Skaug before fully-automatic MULDO analyses. MULDO was compared with different reference methods (2D Doppler, 3D color Doppler, MRI) to assess correlation and agreement.

The MULDO recordings were analyzed semi-automatically in the first 20 participants by Thomas R. Skaug and Torbjørn Hergum to assess agreement between the semi-automatic and fully automatic measurements.

4.2 *Echocardiography acquisition and analyses*

In studies 1 and 2, all the participants were examined with a Vivid 7 scanner (GE Vingmed, Horten, Norway) with a phased-array (M3S) probe for the 2D recordings. In study 3, 25 participants were examined with a Vivid 7 scanner with a M3S probe for the 2D recordings and a matrix array (3V) transducer for the 3D recordings, while in 4 participants an E9 scanner was used with a phased array (M4S) and a 3V probe, respectively.

Study 2: A standard 2D TTE examination was performed to assess the left ventricular function and evaluate the valvular lesions. We used PW-Doppler to measure the mitral and pulmonary flow as well as the flow in LVOT. A color Doppler acquisition was used to visualize the PISA, the vena contracta and the regurgitant jet from the parasternal long axis view as well as from apical 4 chamber, 2 chamber and long axis views. The Nyquist limit was

lowered, such that a flow convergence as close as possible to a hemisphere was shown in an apical view. The VTI and the peak regurgitant jet velocity were measured using CW Doppler. The mitral regurgitant flow rate by PISA was measured at the time of the peak regurgitant jet velocity and the PISA ERO area and regurgitant volume was calculated by a hemispheric approach, as demonstrated in Figure 8 and Eq. 5 - 8. We performed an integrated MR grading as follows: 1 = mild; 2 = mild to moderate; 3 = moderate to severe; and 4 = severe, according to recommendations.[40]

Study 3: A standard 2D TTE examination was performed to evaluate the left ventricular function and evaluate the valvular lesions. We used CW Doppler from the parasternal long axis in eccentric jets and also from the apical five-chamber view in central jets to get the best possible alignment of the ultrasound beam and the regurgitant jet to measure the VTI and pressure half-time of the regurgitant aortic jet. Assessment of diastolic flow reversal in the descending aorta by PW Doppler was performed. A color Doppler acquisition was performed from both the parasternal long axis view and apical five-chamber view to visualize the vena contracta using a Nyquist limit of about 60 cm/s. The frame with the largest diameter of the vena contracta was selected to measure the VCW. Based on an integrated approach, AR severity was graded as: 1 = mild; 2 = moderate; and 3 = severe, according to recent recommendations.[75] A 3D color Doppler examination was performed from the parasternal long-axis view. Full-volume of the flow data was acquired from six consecutive cardiac cycles, and the volume rate was about 15 volumes per second. The Nyquist limit was about 60 cm/s, and we used a default clutter filter with a cut-off frequency corresponding to 20 cm/s. The dataset was cropped just downstream from the aortic valve in a plane perpendicular to the aortic regurgitant jet to find the vena contracta. The volume (frame) with the largest area of the vena contracta was chosen and measured by planimetry. Regurgitant volume was

calculated as: VCA • VTI measured separately by CW Doppler. 2D and 3D acquisitions and analysis are demonstrated in Figure 13.

4.3 MRI acquisition and analyses

In study 2 and 3, all patients were examined during supine rest using a Siemens Avanto 1.5-T system with a body matrix coil (Siemens, Erlangen, Germany). True fast imaging with steady-state precession cine images were acquired during end-expiratory breath holds in 4-chamber, 2-chamber and short axis from the base to the apex of the left ventricle. Steady-state free precession phase-contrast sequences were acquired during breath hold for flow quantification in the ascending aorta at the level of the right pulmonary artery. The encoding velocity was adjusted to just above maximal systolic velocity. The images were aligned perpendicular to the vessel wall. All images were analyzed using Segment.[106] The MRI settings for acquisition of left ventricular volumes and aortic flow are shown in Table 1.

Settings	LV-acquisition	Aortic Flow acquisition
Retrospective ECG gating	Yes	Yes
Typical in plane resolution	0.9 x 0.9 mm	1.3 x 1.3 mm
Typical echo time	1.12 ms	3.09 ms
Typical repetition time	58 ms	61.05 ms
Slice thickness	6 mm	6 mm
Slice gap	4 mm	
Frame rate	25 – 30 Hz	25 – 30 Hz

Table 1.

Study 2: The left ventricular stroke volume was calculated semi-automatically drawing endocardial contours in short-axis images in end-diastole and end-systole (aortic valve closure). Systolic long-axis excursion was quantified by measuring the descent of the septal, lateral, inferior and anterior points of the mitral annulus in the 4- and 2-chamber views. The average value was incorporated into the stroke volume estimate in the software. Systolic flow in the ascending aorta was quantified from the phase-contrast images by drawing a ROI in the ascending aorta. The mitral regurgitant volume was quantified as the difference between the left ventricular stroke volume and the aortic stroke volume, Eq. 14.[91]

The accuracy of this method was tested in an *in vivo* validation study in which the same measurements as those described above were taken in 9 subjects (4 healthy and 5 with recent myocardial infarction) in whom the absence of MR was confirmed by echocardiography. The estimated error was 3 ± 5 mL/stroke.

Study 3: Systolic and diastolic flow in the ascending aorta was quantified from the phase-contrast images by drawing an ROI in the reconstructed magnitude images. The aortic regurgitant volume was calculated from the diastolic retrograde flow, and the regurgitant fraction was calculated by dividing the regurgitant volume with the forward volume during systole, Eq. 17. This approach will slightly overestimate the regurgitant volume, as coronary flow during diastole will be included. We sought to reduce phase-offset errors in the velocity measurements by positioning the phase-contrast image in the isocenter, and using as low encoding velocity as possible.[107]

4.4 MULDO acquisition and analyses

We used a Vivid 7 scanner (GE Vingmed, Horten, Norway) with a matrix array (3V) transducer in studies 1, 2 and 3 except for 4 participants in study 3, who were examined by an E9 scanner and a 3V transducer.

Study 1: There were Doppler simulations to investigate the reference beam and the estimated VCA. In the *in vitro* study, the data acquisition was performed in two steps to ensure that the vena contracta was within the sample volume. First, the vena contracta was found by using a triplex scan (B-mode, HPRF PW Doppler and color Doppler) searching for the region with a high velocity, low spectral bandwidth and high power, as demonstrated in the left part of Figure 14, and subsequently switched to a 3D HPRF Doppler mode. The transmit frequency and the PRF were chosen with a reasonable tradeoff. A high PRF and low transmit frequency were required to obtain a high Nyquist limit. On the other hand, a high transmit frequency was desirable to increase the spatial resolution. The ultrasound settings are shown in Table 2. The 3D data were clutter filtered and analyzed off-line with Math lab (The Math Works, Natick, MA) to find the VCA from the calibrated Doppler power (Eq. 18). In the clinical pilot testing, MULDO recordings were acquired from the apical view in two steps and analyzed in a similar way as described for the *in vitro* study.

Ultrasound parameter	Value
Center frequency	2.1 MHz
Pulse length	5.5 periods
PRF	21 KHz
ROI (azimuth x elevation x radial)	19.2 x 18.0 x 8 mm
Volume rate	7 Hz
Focal depth	8.9 cm
Packet size	8

Table 2

Study 2: The MULDO recordings were acquired from the apical view in two steps, similar to the *in vitro* study. With the scanner in a triplex mode, the vena contracta was located by moving the pulsed-wave sample volume into the jet flow shown by color Doppler imaging and adjusted to include the highest velocities with a low/narrow spectral bandwidth. The scanner was then switched to multibeam HPRF color Doppler mode, with the position of the 3D ROI centered on the pulsed-wave sample volume, as demonstrated in Figure 19.

The depth of the ROI was about 9 – 10 cm, and the ultrasound parameters are demonstrated in Table 2. We obtained a Nyquist limit of about 3 m/s, so that a jet flow of about 6 m/s could be resolved. Each recording consisted of about 10 – 15 heart cycles of real-time 3D data with a volume rate of about 7 – 10 Hz.
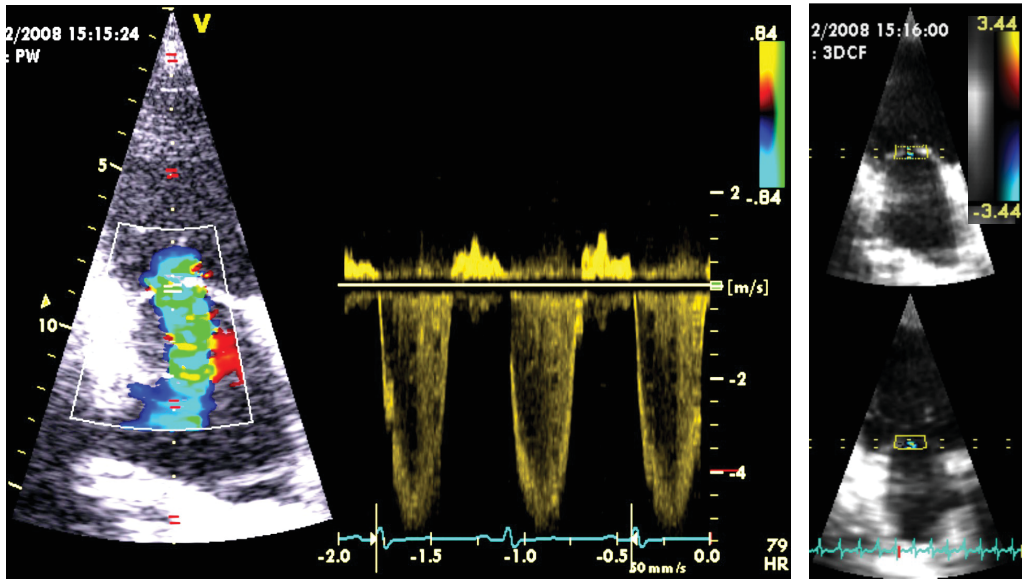
Figure 19: Two-step acquisition using a triplex-scan (left part of the figure) to localize the vena contracta before switching to multibeam HPRF color Doppler mode (right part of the figure). Picture is modified from JASE 2010, reprinted with permission.

Cross-sectional images of multibeam HPRF color Doppler flow of the vena contracta could be visualized, as demonstrated in Figure 20.
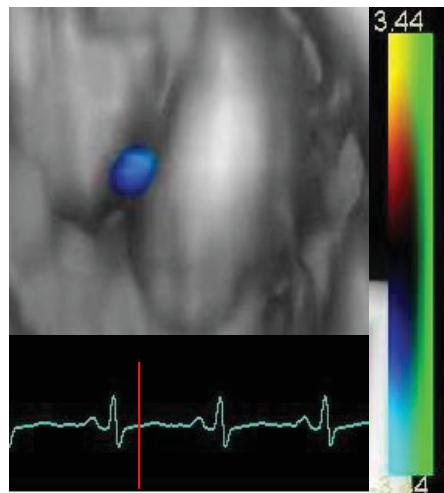
Figure 20: Cross-sectional image of multibeam HPRF color Doppler flow of the vena contracta from one systolic frame.

The raw 3D Doppler data were analyzed semi-automatically to find the VCA using custom software (GC mat). Frames corresponding to systole were selected manually by the observer, and some frames were excluded by the observer according to the following criteria:

- There was no visible jet above the noise level

- The ROI did not cover the jet area

- The vena contracta was not within the ROI.

The output was cross-sectional Doppler power images of the vena contracta, as demonstrated in two of the frames in Figure 21, and calibrated Doppler power measurements and estimates of the VCA from all of the selected systolic frames, Eq. 18. We chose the median value of the measurements as an estimate of the VCA.

To assess inter-observer variability of the MULDO analyses, another blinded observer randomly analyzed 18 of the subjects. The regurgitant volume was calculated as the product of VCA and the VTI of the regurgitant jet, measured separately by CW Doppler.
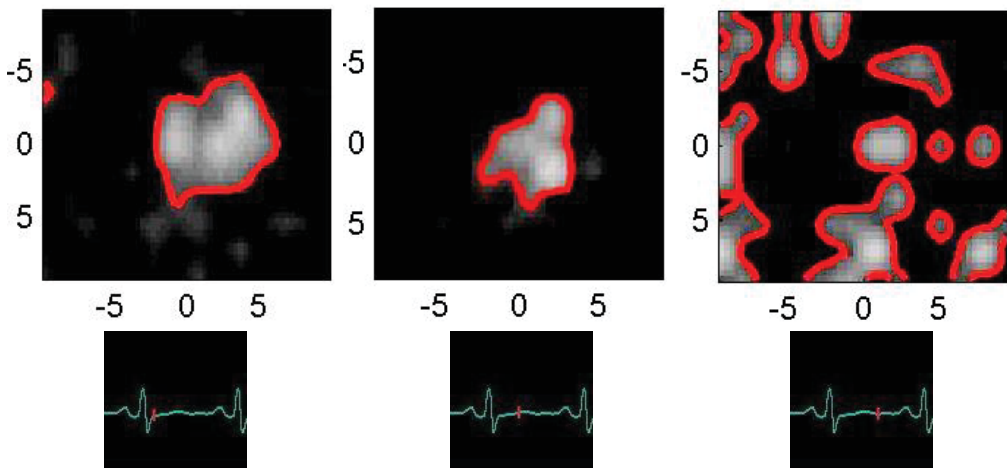
Figure 21: Cross-sectional Doppler power images of the vena contracta from two systolic frames in mitral regurgitation. Note that there is a visible jet and that the vena contracta was within the ROI. The third frame was excluded as there was no jet signal above the background noise level.

Study 3: MULDO recordings were acquired from the apical 5-chamber view for central jets and from the parasternal long axis or eccentric jets to get the best possible alignment of the ultrasound beam and the aortic regurgitant jet. The vena contracta was found by using a triplex mode and then switched to the multibeam HPRF color Doppler mode in a similar way as described under study 2. Acquisitions from the parasternal long axis and from the apical 5-chamber views are shown in Figure 22.
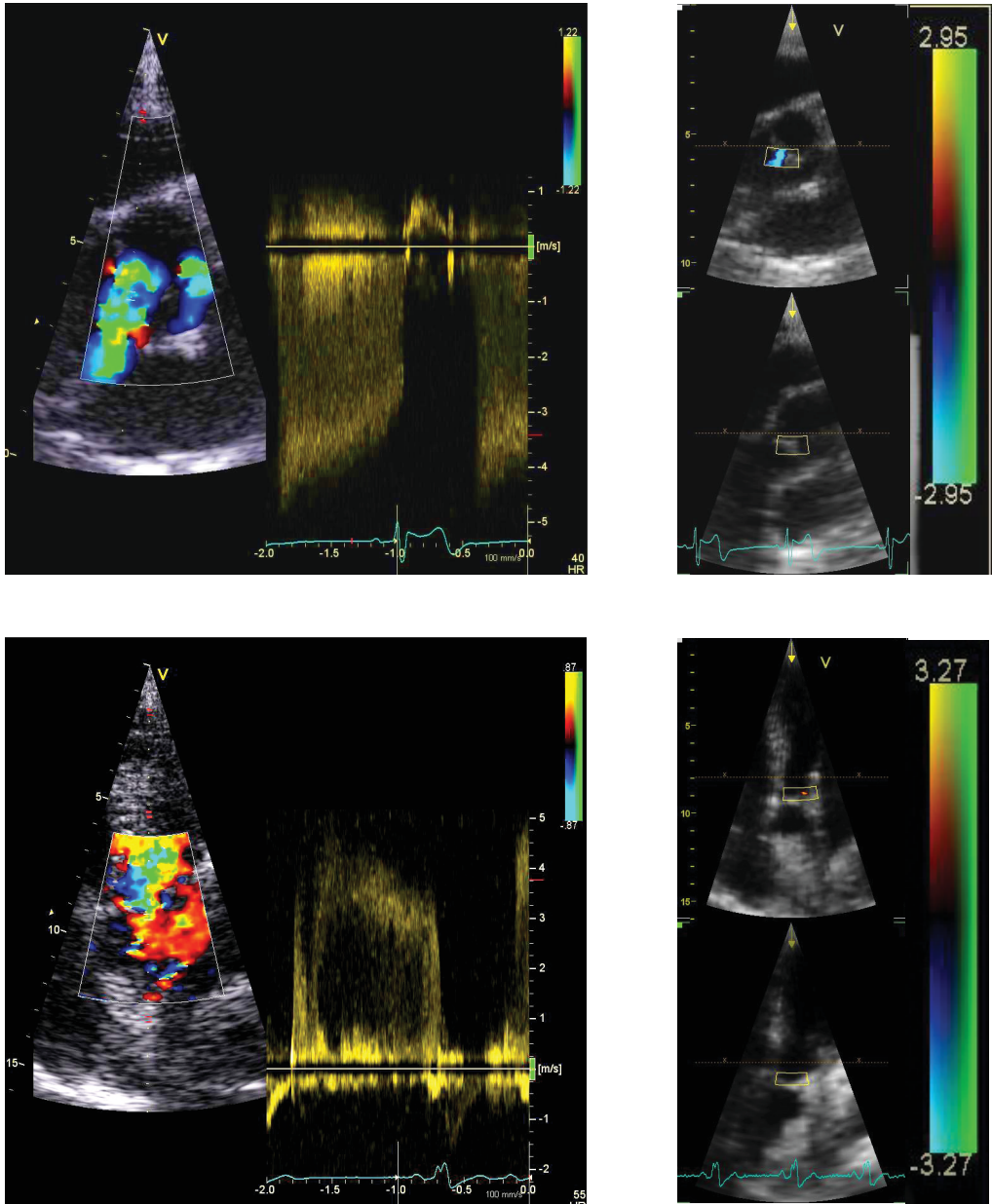
Figure 22: Two step acquisition (left: triplex mode and right: multibeam HPRF color Doppler acquisition) from the parasternal long-axis view (upper) in an eccentric aortic regurgitation with jet direction towards the anterior mitral leaflet and from the apical 5-chamber view (lower) in a central aortic regurgitation. Picture is modified from EHJ-CI 2014 and reprinted with permission.

The ROI was typically at a depth of 5 – 12 cm, depending on the apical or parasternal window. The ultrasound parameters were not different from those described in study 1 and 2. The Nyquist limit was about 3 m/s. A recording consisted of 10 – 15 heartbeats of real-time 3D data with a volume rate of about 7 – 10 Hz. Cross-sectional images of multibeam HPRF color Doppler flow of the vena contracta could be visualized, as demonstrated in Figure 23.
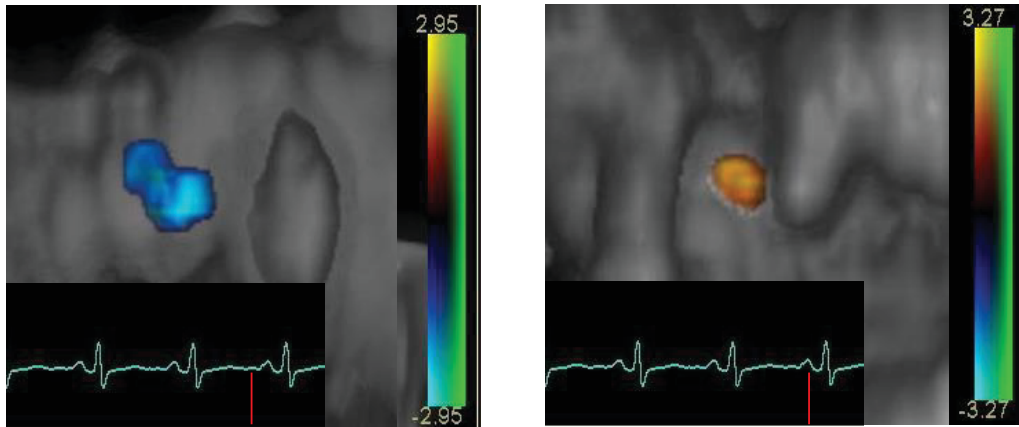
Figure 23: In the left part of the figure cross-sectional images of multibeam HPRF color Doppler flow of the vena contracta acquired from the parasternal long axis, and in the right part of the figure are those acquired from the apical 5-chamber view, in two subjects with aortic regurgitation.

The raw 3D Doppler data were analyzed fully automatically using Math lab (The Math Works, Natick, MA). All of the diastolic frames during a recording were automatically found by the software. The output was cross-sectional Doppler power images of the vena contracta, as demonstrated in Figure 24, and the calibrated Doppler power measurements and estimate of the VCA from all diastolic frames. The median value of all measurements was chosen as an estimate of the VCA.
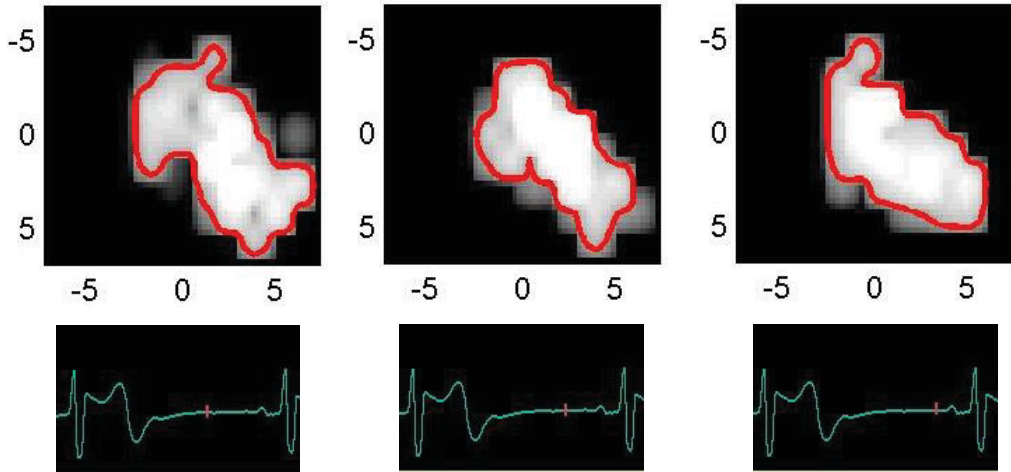
Figure 24: Cross-sectional Doppler power images of the vena contracta from three diastolic frames in aortic regurgitation.

All recordings in 29 patients were validated by an observer to assure that the cross-sectional Doppler power images displayed a jet above the noise level and that the vena contracta was within ROI, as demonstrated in Figure 24; however, there was no need for manual interactions to calculate the VCA. To assess repeatability, a separate and repeated recording from the same subject was similarly analyzed. The regurgitant volume was calculated as the product of VCA and VTI of the regurgitant jet, measured separately by CW Doppler.

Fully automatic vs semi-automatic analysis of MULDO (not published data): In the first 20 patients with AR in study 3, the same MULDO data was assessed by two observers to estimate VCA semi-automatically, as described in study 2, in addition to fully automatically, as described in study 3, to assess agreement between the fully automatic and semiautomatic measurements.

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4.5 Statistics

For both study 2 and 3 descriptive values were reported as median and range, and Spearman`s rank correlation was used because the continuous variables were not normally distributed. Because the differences were normally distributed, we used paired sample t test to compare the regurgitant volume and VCA by different methods, being reported as mean (95% confidence interval). The agreement between the continuous variables was assessed by calculating the 95% limits of agreement (mean difference ± 2 SD). To assess agreement between different or categorical variables, we used κ (kappa) statistics. Inter-observer variability and repeatability were assessed as the coefficient of repeatability, defined as 2 SD of the differences. The statistical analyses were performed using SPSS (SPSS, Inc., Chicago, IL, USA).

5 Summary of results

Study 1: Simulation results demonstrated that the Doppler power estimate of the reference beam was increasingly overestimated with an increasing number of beams within the orifice and thus the orifice size. With less than 10 beams within an orifice, the reference beam will be overestimated by up to 20%, resulting in underestimation of the vena contracta area. *In vitro,* the estimated vena contracta area and true areas of several orifices were investigated using both stationary and pulsatile flow in the flow phantom, and the results followed the same trend as the simulated results. There was a slight overestimation of the small areas and underestimation of the larger areas. These simulation and *in vitro* results are shown in Figure 8 of this paper. The results from the pilot clinical testing of 5 patients with MR were presented at Euro Echo 2008 with PISA for comparison (see Appendix).[108]

Study 2: In 3 of the 35 participants, MULDO was not feasible and another 5 participants were excluded for other reasons described in the Materials section. This study showed that this method was feasible in MR. The 95% limits of agreement between MRI and MULDO regurgitant volume (N = 27) were -3.0 ± 26.2 mL. We were not able to measure PISA in 5 of the 27 participants. Omitting the 5 participants in whom we were not able to measure PISA, the 95% limits of agreement between MRI and PISA regurgitant volume (N = 22) were 4.7 ± 30.6 mL. The agreement between echocardiographic MR grade and regurgitant volume measured by MRI and MULDO is demonstrated in Figure 25. Inter-observer analysis of MULDO VCA in 18 participants demonstrated a coefficient of repeatability of 8.7 mm^2 and a corresponding coefficient of repeatability for MULDO regurgitant volume of 9.8 mL.
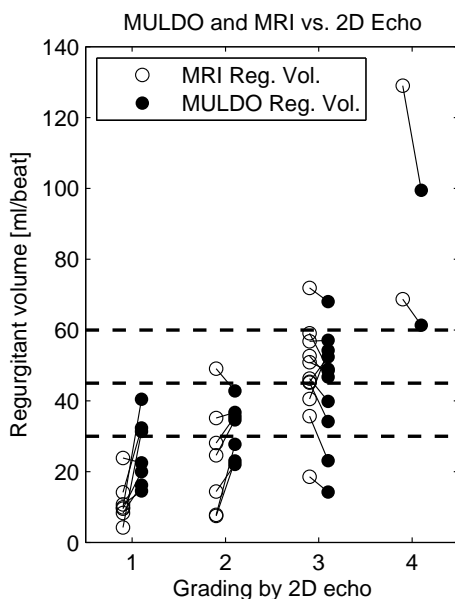
Figure 25: Kappa agreement between echocardiographic MR grade and MULDO regurgitant volume and between echocardiographic MR grade and MRI regurgitant volume were 0.44 and 0.48, respectively. There were four echocardiographic MR grades based on severity (1=mild, 2=mild to moderate, 3=moderate to severe, 4=severe) and four categories of regurgitant volume (<30 mL, 30 to 44 mL, 45 to 59 mL and ≥ 60 mL) used to assess agreement. Figure from JASE 2010; reprinted with permission.

Study 3: In 7 of the 36 participants, MULDO data were not representative. In the remaining 29 participants, MULDO was feasible. The 95% limits of agreement between regurgitant volume by MRI and MULDO and between MRI and 3D color Doppler were -14.4 ± 29.1 mL and -47.8 ± 60.9 mL, respectively. The agreement between echocardiographic AR grade and VCA by MULDO and 3D color Doppler, respectively, is demonstrated in Figure 26. The analysis of MULDO VCA was made fully automatically; consequently, there was no inter- or intra-observer variability. In a separate recording from the same participant, the coefficient of repeatability for MULDO VCA estimates was 9.4 mm^2.
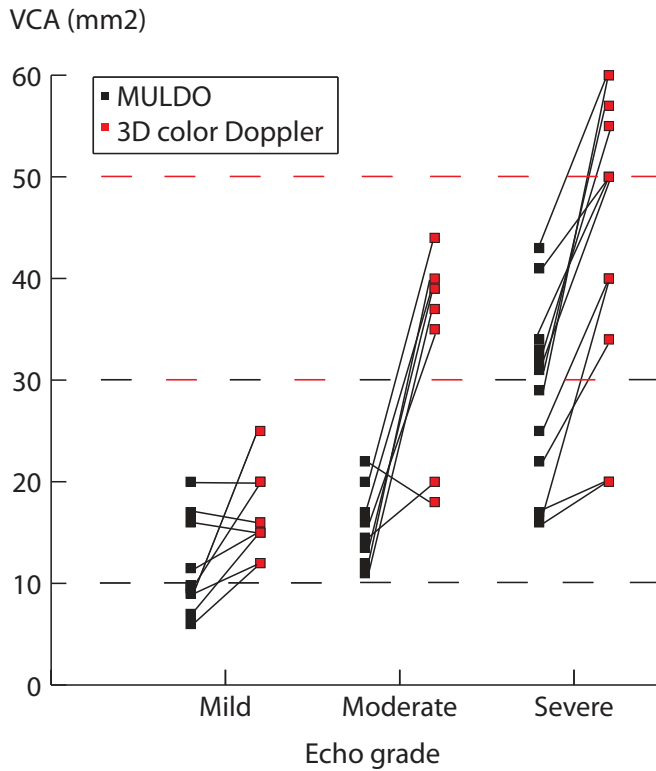
Figure 26: Kappa agreement between echocardiographic AR grade and MULDO VCA and between AR grade and 3D CFI VCA was 0.50 and 0.64, respectively. Figure from EHJ-CI 2014; reprinted with permission.

Fully automatic vs. semiautomatic analyses (Unpublished data): The 95% limits of agreement between fully automatic VCA vs. semi-automatic VCA by observer 1 and observer 2, respectively, in 20 participants with AR were 0.6 ± 3.0 mm^2 and 0.5 ± 4.2 mm^2, respectively (Figure 27 a and b). The 95% limits of agreement between semi-automatic VCA by observer 2 and observer 1 in 20 participants with AR were -0.1 ± 3.4 mm^2 (Figure 27 c).
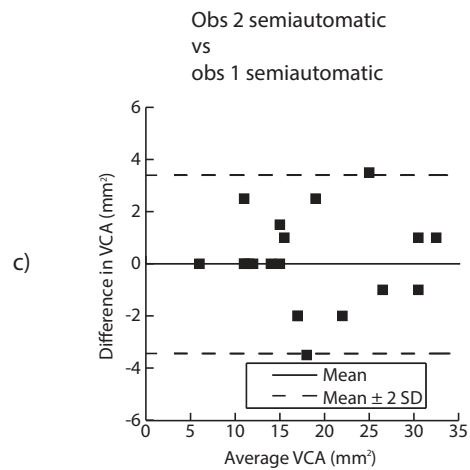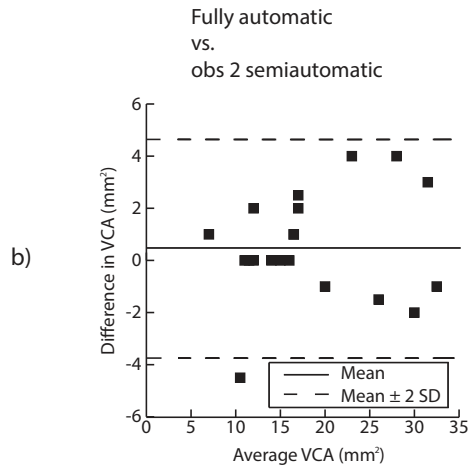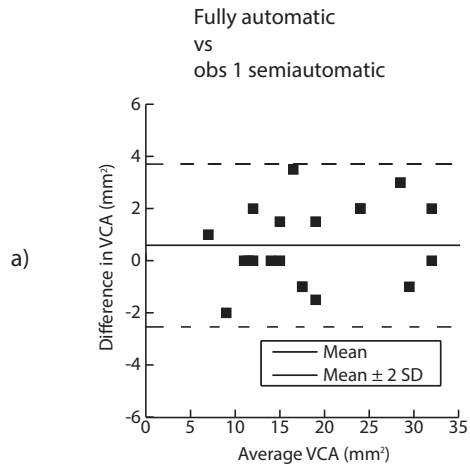
Figure 27: a) and b) 95% limits of agreement between fully automatic and semiautomatic VCA estimate between two observers, c) and 95% limits of agreement between semiautomatic VCA between two observers. Unpublished data.

6 Discussion

6.1 Main findings/feasibility

A 3D echo Doppler method, multibeam HPRF color Doppler (MULDO), was developed for the quantification of valvular regurgitation, and was validated *in vitro* and *in vivo*. In study 1, simulation and *in vitro* results were presented, and it was demonstrated that the vena contracta area (VCA) could be quantified for various orifice sizes from less than 10 to 40 mm^2 corresponding to mild to severe regurgitation. In simulation and *in vitro* the VCA was overestimated when the orifices were small and the reference beam was not entirely within the orifice. For larger orifices with several potential reference beams within the orifice the power of the reference beam was overestimated due to stochastic variation of the Doppler signals in simulation, and thus the estimate of the VCA was to some degree underestimated. However, the in vitro results were closer to the true values for larger orifices than the simulation results. In study 2, it was demonstrated that MULDO was feasible in both primary and secondary MR as well as in central and eccentric jets, except in 3 out of 35 participants. The severity of MR could be quantified using this method, and there was good agreement between MRI and multibeam HPRF color Doppler in moderate and severe MR, which was lower in mild MR. In study 3, it was demonstrated that MULDO was feasible in both central and eccentric AR jets regardless of etiology, except in 7 out of 36 participants. The severity of AR could be quantified by this method, and there was good agreement between MRI and multibeam HPRF color Doppler in moderate and severe AR, but relatively poor agreement in mild AR. VCA by MULDO was found semi-automatically in studies 1 and 2 and fully automatically in study 3, and VTI was found separately by CW Doppler.

6.2 Choice of reference methods

In study 1, MULDO was validated against the true size of the orifices of porcine valves in a pulsatile flow phantom. In a clinical setting in studies 2 and 3, there was no similar gold standard to assess valvular regurgitation. In most cases Doppler echocardiography provides the data needed for clinical decision-making in valvular regurgitation based on the mechanism of regurgitation, an integrated echo grading of severity and evaluation of its hemodynamic consequences and ventricular function together with a clinical evaluation of symptoms. However, it may sometimes be difficult to assess the severity of a valvular regurgitation with a need for supplemental investigation by TEE or MRI.

By MRI phase contrast imaging, the regurgitant jet can be visualized and measured using long-axis and short axis cines. Theoretically, the vena contracta could be measured, which would be an ideal comparison for MULDO. However, this method is not widely used and is subject to significant variability depending on acquisition parameters such as image slice thickness and frame rate, post-processing and experience of the user. It is therefore not recommended to measure the vena contracta by MRI.[109, 110] On the other hand, flow measurements have been validated *in vitro* and *in vivo* using invasive measurements and Doppler measurements as a reference.[89, 90] Left ventricular volumes can be calculated accurately using steady-state free precession sequences, but the accuracy of the left ventricular volumes is dependent on correct planimetry of short-axis ventricular image slices in both end-diastole and end-systole during post-processing to measure the left ventricular stroke volume.[85-87]

There are different MRI techniques for MR quantification which have been validated in clinical trials by comparison with echocardiography and angiography, showing good correlation; however, a true gold standard is lacking.[91-93, 97] In study 2, we used MRI to quantify mitral regurgitant volume, while MULDO estimated the VCA. By multiplying the

VCA with the VTI measured separately by CW Doppler, the regurgitant volume was calculated, making it comparable to MRI. Quantification of the mitral regurgitant volume by MRI is commonly performed indirectly by subtracting aortic systolic flow measured by phase contrast from the left ventricular stroke volume by volumetry.[91] We tested the accuracy of this method (the difference between the left ventricular stroke volume and aortic systolic flow) in an *in vivo* validation in 9 subjects without valvular regurgitation, and the estimated error was 3 ± 5 mL/stroke. Patients with concomitant AR have to be excluded to make this method valid for the quantification of mitral regurgitant volume. Alternatively, the mitral regurgitant volume could be calculated indirectly by comparing the difference in ventricular stroke volumes assuming the absence of intra-cardiac shunts and another valvular regurgitation. It also assumes correct planimetry for both ventricles in systole and diastole, which can be particularly difficult for the right ventricle.

Further, we used 2D TTE to quantify regurgitant volume from PISA, and MR echo grading was divided into mild, moderate, moderate to severe and severe MR, corresponding to grades 1, 2, 3 and 4, according to the recommendations of an integrated approach.[40] Some of the limitations of PISA were discussed in the section 1.2.3; this made the assumption that the geometry of the regurgitant orifice area was circular, but this method has demonstrated prognostic value in both primary and secondary MR.[41, 42] The severity of valvular regurgitation is based on echo grading. PISA is not always feasible or valid for quantification, or the calculations may be erroneous, while echo grading is based on an integrated approach of quantitative, semi-quantitative and qualitative parameters, each of which has its strengths and limitations.[39]

By using aortic phase-contrast imaging both the aortic regurgitant volume and fraction can be measured directly, and it has been validated in both *in vitro* and clinical studies. There is no true gold standard for the comparison of accuracy of aortic phase-contrast measurements

in vivo. However, the aortic regurgitant quantification using aortic phase-contrast imaging correlates well with angiographic grading and Doppler echocardiography, and has demonstrated excellent repeatability of measurements.[88, 100, 101, 111] In study 3, MRI aortic phase contrast was used as a reference method to measure regurgitant volume.

3D color Doppler has been validated in previous studies,[81-84] and we measured the VCA by direct planimetry and compared it to VCA by MULDO in study 3. By multiplying VTI measured separately from CW Doppler and VCA measured by either MULDO or 3D color Doppler, we calculated the regurgitant volume by both methods to make it comparable to MRI regurgitant volume. We similarly used 2D TTE as another reference method, but PISA is less well validated and technically more difficult for AR than for MR. We measured the VCW from 2D Doppler, and AR echo grading was divided into mild, moderate and severe AR according to the latest recommendations.[75] As there are no established cut-off values for MULDO, we used recommended ERO areas by 2D quantitative methods as cut off values to establish agreement between AR grade and MULDO. To assess agreement between AR echo grade and 3D color Doppler VCA, we used cut-off values of 30 and 50 mm^2 for mild and severe AR, respectively, as proposed by Chin et al.[82]

Further, agreement between MRI regurgitant fraction and MULDO could be of interest, but there are no consensus cut-off values of regurgitant fraction to define AR severity categories such as mild, moderate and severe. In a recent study, qualitative and semi-quantitative echo Doppler parameters were used as a reference method to establish MRI cut-off values with which to assess AR severity. The aortic phase-contrast regurgitant fraction cut-off value that best defined severe AR was ≥ 30 % at the Sino-tubular junction or mid-ascending aorta, which should be noted as being different from the Doppler-based regurgitant fraction range criteria. They demonstrated that the positioning of the image slice of phase contrast flow measurements influences the measurements of regurgitant volume and fraction,

and that the regurgitant volume and fraction were significantly higher when measured at the Sino-tubular junction than at the distal ascending aorta.[98] In another recent study, qualitative and semi-quantitative echo grading was as well used as a reference method to establish aortic phase-contrast cut-off values measured at the level of the pulmonary artery bifurcation, and a regurgitant fraction > 46% best defined severe AR. There are several possible explanations for these differences.[97] About 40% of the patients in the study by Gabriel et al. had a congenitally deformed valve, which was associated with eccentric and turbulent flow through the ascending aorta, and may be one possible explanation for the differences in studies, since phase-contrast measurements rely on laminar flow. There is also a lack of data evaluating the accuracy of flow measurements in large aortic diameters.

Outcome studies are sparse, except for a prospective study by Myerson et al. of 113 asymptomatic patients which demonstrated that a regurgitant fraction > 33% was the optimal threshold for identifying patients with the development of symptoms and the need for valve replacement within a few years (sensitivity of 85% and specificity of 92%).[112] Due to differences in various studies and no consensus, we did not categorize AR severity as mild, moderate and severe according to aortic phase-contrast regurgitant fraction values to establish agreement with MULDO or 3D color Doppler, even though the study by Myerson was interesting and defined a cut-off value with outcome data.

6.3 Agreement

6.3.1 Agreement between MRI and MULDO compared with other 2D and 3D Doppler methods

In study 2, there was good correlation between MRI and MULDO. There was a significant difference between these methods in those with mild MR, defined as MRI regurgitant volume

< 30 mL, but no significant difference in those with moderate to severe MR, defined as MRI regurgitant volume ≥ 30 mL. The 95% limits of agreement between these methods were quite wide (−3.0 ± 26.2 mL), which can be explained by the overestimation of mild MR by MULDO. Buck et al. demonstrated excellent agreement between the Broad-beam spectral Doppler method and MRI in patients with MR, reporting a mean difference of 0.4 mL and 1 SD of 3.2 mL corresponding to 95% limits of agreement of 0.4 ± 6.4 mL.[105] There are some differences to note. Our population was characterized by a wider range of regurgitant volume measured by MRI (4 – 129 mL) than in the population investigated by Buck et al. (6 – 46 mL). We measured VCA from 12.0 to 59 mm^2, regurgitant volume from 14.2 to 99.0 mL by MULDO. Buck et al. reported mean VCA from 11 to 61 mm^2 and regurgitant volume from 11.5 to 36.9 mL by the Broad-beam spectral Doppler method. Interestingly, the results from the individual participants are listed in Table 1 in the paper by Buck et al., which give some idea of the relationship between the mean VCA and the regurgitant volume by their method. In one of the participants with degenerative MR, the mean VCA and regurgitant volume was 0.61 cm^2 and 35.8 mL and in another participant 0.40 cm^2 and 27.6 mL, respectively. In one of the participants with ischemic cardiomyopathy, the mean VCA and regurgitant volume was 0.11 cm^2 and 15.7 mL and in another they were 0.39 cm^2 and 18.8 mL, respectively. It is worth noticing lower regurgitant volumes relative to VCA in the study by Buck et al. The regurgitant volume and the mean VCA were calculated directly from the same acquisition. We measured VCA by MULDO and VTI separately by CW Doppler, from 74 to 213 cm, to calculate the regurgitant volume. The VTI is dependent on the pressure difference between the left ventricle and left atrium, as well the duration of the regurgitant flow, which can explain discrepancies in VCA and regurgitant volume. Further, there can be dynamic variation of flow and ERO area. In the study by Buck et al., 63% of the participants had secondary MR, while 41% of the participants in our study had secondary MR; the remaining

37% and 59%, respectively, had primary MR. The calculation of MRI regurgitant volume was somewhat different, as we measured the left ventricular stroke volume by volumetric measurements of the left ventricle, while Buck et al. used phase-contrast measurements of the mitral inflow. We both used phase contrast to measure aortic stroke volume. The regurgitant volume was calculated as the difference between either the mitral inflow or left ventricular stroke volume and the aortic stroke volume.

Marsan et al. used 3D color Doppler to measure the VCA and CW Doppler to measure the VTI to calculate the regurgitant volume in secondary (functional) MR, with MRI as a reference method. The 95% limits of agreement between 3D color Doppler and MRI were -0.08 ± 7.6 mL.[65] They used the systolic frame with the most relevant lesion size to measure the VCA, and the phase-contrast measurement at the level of the mitral valve to calculate regurgitant volume directly. This was in contrast to our study using the indirect method (see Eq. 14), using volumetry of the left ventricle and aortic phase contrast. It is difficult to assess in what way these different MRI methods affect the agreement between the various methods, as the different MRI methods have their strengths and limitations. Mitral phase-contrast imaging can, however, be difficult in cases of excessive mitral annular movements which is not uncommon in primary MR in contradiction to secondary MR.

More recently, Shanks et al. used 3D TEE color Doppler to measure the VCA and CW Doppler to measure the VTI to calculate regurgitant volume in patients with secondary (53.3%) and primary (46.7%) MR, with MRI as a reference method. The 95% limits of agreement between 3D TEE color Doppler and MRI were -2.3 ± 16.3 mL.[64] They used the systolic frame with the most relevant lesion size to measure the VCA, and used the difference between volumetric measurements of the left ventricular stroke volume and aortic stroke volume by phase contrast to the measure regurgitant volume, similar to the method we used. One advantage of TEE is a shorter scan depth with higher volume rate, as well as better

visualization of the valve and improved resolution, which should improve the accuracy of measurements. In our study, PISA was feasible in 22 out of 27 participants, and we demonstrated wider 95% limits of agreement between MRI and PISA (4.7 ± 30.6 mL) than between MRI and MULDO (−5.1 ± 23.9 mL). We used PISA by 2D Doppler using the frame corresponding to the peak regurgitant jet velocity and a hemispheric approach. Shanks et al similarly demonstrated that 95% limits of agreement between PISA by 2D TEE and MRI was −12.4 ± 33.2 mL.[64] The limits of agreement between MRI and PISA in the study by Shanks et al. and the current one were similarly wide, with both studies making an assumption of the PISA geometry by 2D color Doppler.

In study 3, there was moderately good correlation between MRI and MULDO, but the regurgitant volume calculated from MULDO and CW Doppler overestimated the severity of AR compared with MRI; however, agreement was better for those with MRI regurgitant volume ≥ 30 mL compared with those with MRI regurgitant volume < 30 mL. The 95% limits of agreement between these methods were quite wide (−14.4 ± 29.1 mL). The regurgitant volume calculated from 3D color Doppler and CW Doppler significantly overestimated the severity compared with MRI, and the 95% limits of agreement between MRI and 3D color Doppler were wider (−47.8 ± 60.9 mL). In a recent study by Ewe et al., there was excellent agreement between MRI and 3D color Doppler.[84] They similarly used aortic phase-contrast imaging as a reference method. There are some differences to note. We measured VTI from the apical window in central jets and from the parasternal window in eccentric jets, while Ewe et al. measured VTI from the apical window in both central and eccentric jets. If we were to measure VTI from the apical window in eccentric jets, we would underestimate the VTI compared with measurements from the parasternal window. This would result in a lower regurgitant volume by both MULDO and 3D color Doppler and less overestimation by these methods compared with MRI, and probably better agreement. We performed 3D color

Doppler acquisition from the parasternal window, while Ewe et al. used both the apical and parasternal window. With 3D color Doppler, we used the frame with the largest VCA, while Ewe et al. used the frame with "the most relevant lesion size". If we used "a more relevant lesion size", VCA by 3D color Doppler could possibly be lower than using the largest VCA, and the regurgitant volume would be lower with less overestimation compared with MRI. Finally, there were different scanners and probes, and there might be some differences regarding the spatial and temporal resolution.

6.3.2 Agreement between 2D/3D Doppler echocardiography and MULDO

In study 2, we demonstrated that PISA by the hemispheric approach was significantly lower than MULDO, both ERO area and regurgitant volume. The 95% limits of agreement were -0.08 ± 0.28 cm^2 and -9.8 ± 37.0 mL. In 3D studies, it has been demonstrated that the PISA is hemielliptic rather than hemispheric because of asymmetric geometry of the regurgitant orifice area, especially in secondary MR. This results in significant underestimation of ERO area by a hemispheric PISA approach as compared with either a hemiellliptic PISA approach,[53, 54] or VCA by 3D color Doppler.[55, 63, 113] Kahlert et al. demonstrated that the 95% limits of agreement between ERO area measured by a hemispheric and hemielliptic approach were -0.2 ± 0.4 cm^2, and the 95% limits of agreement between a hemispheric PISA approach and VCA was -0.09 ± 0.28 cm^2. Comparing all methods, they used the mid-systolic frame in secondary and some of the primary MR, while they used the late-systolic frame in mitral valve prolapse where the ERO area is usually the largest.[55]

There was moderately good agreement between echo MR grade and regurgitant volume assessed by MULDO ($\kappa = 0.44$). As MULDO overestimates mild regurgitation (MRI regurgitant volume < 30 mL), this can contribute to some of the overlap, especially between MR grade 1 and 2, as illustrated in Figure 25. Agreement was better for primary than

secondary MR between the various methods. This probably stems from the same source as the overestimation of mild MR. The regurgitant orifice is often asymmetric and noncircular in secondary MR, meaning that the cross-sectional area may be large, but still not able to encompass the full reference beam. Besides, those with primary MR were part of a higher regurgitant volume population than those with secondary MR.

In study 3, we demonstrated reasonably good correlation between VCA measured by 3D color Doppler and MULDO, but 3D color Doppler measurements were significantly higher than MULDO, which explains the difference in regurgitant volume by the two 3D methods in our study. There are several differences between these methods, which are further discussed under "Methodological differences".

We did not calculate the ERO area from 2D Doppler methods in study 3. In a recent study by Sato et al., they demonstrated good correlation and agreement between 2D VCA and 3D VCA (r = 0.97 and 95% limits of agreement -0.36 ± 8.1 mm^2). There was also good correlation and agreement between 2D VCA and ERO area by PISA (r = 0.89 and 95% limits of agreement 4 ± 14.2 mm^2).[114] PISA is challenging in AR, and it also makes assumptions of the geometry of the ERO area. We did not measure the VCA from 2D parasternal short axis views, as it is difficult to assure that the imaging plane is through the vena contracta and that the imaging plane is perpendicularly aligned to the jet direction, especially in eccentric jets, both of which result in overestimation of the VCA.

Correlation and agreement between AR grade and VCA by MULDO were moderately good ($r_s = 0.76$ and $\kappa = 0.50$). Chin et al. demonstrated good correlation between 3D color Doppler VCA and AR severity assessed by Doppler methods,[82] and we similarly demonstrated moderately good correlation and agreement between AR grade and VCA by 3D color Doppler ($r_s = 0.76$ and $\kappa = 0.64$).

6.4 Methodological differences

In both studies 2 and 3, MRI was a reference method calculating the regurgitant volume. In study 2, the mitral regurgitant volume was calculated as the difference between LV volumetric stroke volume and aortic phase contrast stroke volume. In study 3, the aortic regurgitant volume was calculated directly from the aortic phase contrast retrograde flow, and thus somewhat different from the mitral regurgitant volume in study 2.

The VCA by MULDO was found semi-automatically in study 2 and fully automatically in study 3 from the calibrated Doppler power of the vena contracta, requiring no manual calculations, and we used the median value of VCA from frames/volumes over several heart beats. The VCA is a measure of the ERO area, and calculation of regurgitant volume requires the VTI measured separately by CW Doppler.

In study 2, we used PISA, based on 2D color Doppler, making assumptions of a hemispheric geometry of the PISA and a circular regurgitant orifice, to calculate flow rate. We measured the flow rate by PISA at the time of maximal regurgitant jet velocity. An additional step was required to calculate the ERO area from this method, dividing PISA flow rate by the maximal velocity of the regurgitant jet by CW Doppler. Regurgitant volume was similarly calculated from the ERO area and VTI by CW Doppler. As discussed in section 6.3.2, calculations of ERO area and regurgitant volume by the hemispheric PISA approach was significantly lower than VCA and regurgitant volume by MULDO.

In study 3, we used VCA measured by 3D color Doppler as a reference method, and it was significantly higher than VCA by MULDO, which explains the differences in regurgitant volume, calculated as the product of VCA by both methods and VTI measured separately by CW Doppler.

3D color Doppler and MULDO differ in several ways. Most importantly, the HPRF and clutter filter in the proposed method enabled the isolation of the high-velocity core of the vena

contracta, in contrast to regular color Doppler, which also measured low-velocity entrained blood. The clutter filter cut-off frequency corresponded to 1.5 m/s for multibeam HPRF color Doppler and 0.2 m/s for 3D color Doppler.

Secondly, in 3D color Doppler, it was common to reduce the lateral resolution somewhat to gain some extra frame rate. The MULDO algorithm automatically compensated for the overestimation due to limited lateral resolution as long as the reference beam was within the vena contracta jet.

Thirdly, altering the display parameters such as gain and tissue priority during acquisition did not affect the MULDO data. On the other hand, the 3D color Doppler was gain-dependent, and the width and area of a regurgitant orifice could be overestimated with approximately one beam width in each direction (azimuth and elevation).

Furthermore, each recording of MULDO consisted of 10 to 15 heartbeats of real-time full-volume datasets, while 3D color Doppler datasets were reconstructed from several heartbeats of subvolumes to make a full volume, which can predispose to stitching artefacts and overestimation of the VCA.

The measurements of the Doppler power in all the diastolic frames in a MULDO recording were fully automatic, and the median value of these measurements was chosen as the VCA. The 3D color Doppler dataset post-processing on the other hand consisted of sequential cropping of the regurgitant jet, manual tracing, and the volume (frame) with the largest area of the vena contracta was chosen, similarly to VCW.[75]

Dynamic variation of the regurgitant orifice area could be another contributing factor for the differences in VCA measurements. Using the volume (frame) with the largest VCA in 3D color Doppler, with a volume (frame) rate of ~ 15 volumes per second, and the median VCA of several measurements in MULDO, with a volume rate of 7 – 10 volumes per second, could enhance this confounding effect.

6.5 Semi- and fully automatic analysis and repeatability

In both studies 1 and 2, the MULDO datasets were analyzed semi-automatically, and the observer had to investigate all of the frames from a recording and identify which frames to be measured. Inter-observer analysis in study 2, investigating the same recordings in 18 participants, demonstrated a coefficient of repeatability of 8.7 mm^2 for the semiautomatic analysis, corresponding to 9.8 mL. The criteria for inclusion and exclusion were well defined, but there were still some frames of uncertain nature, which explained the inter-observer variability. The measurement of the Doppler power and thus calculation of VCA was, however, performed automatically. In study 3, software identified all of the diastolic frames (volumes) during a recording of aortic regurgitation, making no manual interaction necessary, and thus making this a fully automatic method. We validated this fully automatic method in the first twenty participants in this study, and there was good agreement between semi-automatic and fully automatic measurements of VCA by two independent observers. Additionally, in all patients, the recordings were validated by an observer to ensure that the Doppler power images displayed a jet above the noise level and that the vena contracta was within ROI, but no manual interaction or selection of frames were necessary. All data in study 3 were based on fully automatic measurements of the VCA. In a separate and repeated recording from the same subject, we demonstrated a coefficient of repeatability for VCA of 9.4 mm^2. This is in agreement with the findings in study 1, in which the standard deviation of the *in vitro* VCA estimates was quite large. This can partly be explained by stochastic variations of the Doppler signal, which is demonstrated in paper 1.

7 Limitations

The Nyquist limit of about 3 m/s for MULDO is usually lower than the maximum mitral and aortic regurgitant jet velocities. However, as long as the maximal velocity is less than two times the Nyquist velocity and the direction of the jet is known, the velocity of the jet can be determined unambiguously. To achieve HPRF, the ROI must be small in the radial direction. An ROI of 2 mm was challenging to apply in patients with mitral regurgitation. The size of ROI in the radial direction was extended as much as possible and up to 8 mm without any significant loss of velocity resolution. It can still be challenging to position the ROI correctly *in vivo*, especially with large displacements of the valve in hyperdynamic ventricles. As demonstrated in the simulation and to some degree *in vitro* in study 1, MULDO will overestimate the regurgitant orifice area in mild disease when the orifice is narrow relative to the size of the reference beam. This also corresponds with *in vivo* results. This limitation is inherent to similar techniques requiring reference measurements.[104] For larger orifices, MULDO can underestimate the orifice size due to stochastic variations of the Doppler signals. Typically, the reference beam can be overestimated by up to 20% when up to 10 beams are candidates as the reference beam with most power. The *in vitro* results were however closer to the true values for larger orifices than the simulation predicted. The variability of repeated measurements is demonstrated in studies 1 and 3, and can partly be explained by stochastic variations of the Doppler signals.

MULDO was validated for circular defects *in vitro*, but *in vitro* studies of non-circular defect are lacking. In study 2, we investigated both primary and secondary MR. Previous studies have demonstrated that the regurgitant orifices *in vivo* are frequently asymmetric and non-circular in the majority of patients with MR, but especially in secondary MR with a greater degree of asymmetry.[55, 61, 63] We demonstrated better agreement between MULDO and MRI for primary (organic) than for secondary (functional) MR. This probably stems from the

same source as the overestimation of small orifices and thus mild MR. In addition, the regurgitant orifice may be large, but still not able to encompass the full reference beam due to asymmetry.

The area estimation by MULDO is angle-dependent, and misalignment will lead to overestimation of the VCA. This overestimation of the VCA may be cancelled out by underestimation of the VTI by CW Doppler. The regurgitant volume relies on both correct measurement of the VCA and VTI. Consequently, different acquisitions by different probes raise the possibility of differences in beam alignment and thus errors in calculating the regurgitant volume.

The vena contracta and ERO area can vary during systole,[40, 45-47] and the current volume rate of 7 – 10 Hz is probably too low for short-duration regurgitation and dynamic variations. However, by MULDO, we used the median VCA from multiple frames, but this choice was somewhat arbitrary. If we had used the volume (frame) with the largest VCA, the comparison with 3D color Doppler in study 3 would have been more relevant. On the other hand, as the ERO area is dynamic and displays variability, we assumed that the median value of VCA would be an appropriate measure to report. In both the semi-automatic and fully automatic analyses, the median VCA were reported. In a similar way as in a number of the 3D color Doppler studies, we could have chosen "the most relevant lesion sizes". As previously discussed, there is typically an early and late systolic peak and mid-systolic decrease or an early peak followed by a gradual decrease in flow rate in secondary (functional) MR, while in rheumatic disease, flow is relatively constant until a decrease in end-systolic and in mitral valve prolapse, there is a late-systolic increase in the flow.[45, 46] We could have chosen these frames for MULDO in a semiautomatic approach, but not in a fully automatic approach as chosen in study 3.

In 3 out of 35 participants in study 2 and 7 out of 36 in study 3, we were not able to acquire representative Doppler data, because of a difficulty in identifying the vena contracta, or misalignment or incorrect positioning of the small ROI outside the vena contracta. Other clinical limitations may include an inability to hold the breath for 10 to 15 s, causing respiratory movements, and displacement of the ROI during acquisition. Poor acoustic windows or heavy valvular calcification can cause attenuation of the Doppler signals. Tachyarrhythmia can also be a limitation due to current volume (frame) rate.

8 Further perspectives

Future generation of 3D probes are expected to have improved resolution, which will make it possible to obtain better estimates for the calibration beam and will enable MULDO to measure smaller orifices with less bias. By using a broad unfocused beam on transmit (plane wave transmission) and parallel receive beam forming, it is possible to increase the frame rate compared with conventional focused beam on transmit and receive, but with some reduction in spatial resolution. With an increased volume (frame) rate, regurgitant volume could be derived directly from the MULDO dataset. A PW Doppler technique measures radial velocities from a fixed spatial position and is susceptible to spectral broadening and aliasing. Similar to other Doppler techniques, MULDO is dependent on alignment of the direction of a regurgitant flow and the ultrasound beams, measuring radial velocities. 2D tracking Doppler is a new technique using plane wave transmissions and parallel receive beamforming, which can overcome some of the limitations of PW-Doppler. The blood scatterers can be followed along the direction of flow in the axial and lateral directions, giving less spectral broadening and higher spectral velocity resolution than PW-Doppler. This has been demonstrated *in vitro* and in carotid artery stenosis.[115, 116]

There are, however, some challenges using tracking Doppler in a cardiac application compared to velocity estimation in the carotid artery using a linear probe. In cardiac applications, a phased-array probe is used with smaller aperture, and the region of interest is deeper. This leads to decreased spatial resolution. Further, the smaller width of plane waves transmitted from a phased array probe potentially limits the size of the tracking region for high velocities. In a recent study, tracking Doppler was investigated using a cardiac application in simulation and *in vitro,* and we performed an *in vivo* testing in a volunteer with mild to moderate AR (See Thesis of Jørgen Avdal at NTNU, 2015). Implementation for this technique on a 3D probe is a possible future improvement.

9 Conclusion

In the present work with MULDO, we have demonstrated that:

- *In vitro*: The cross sectional area of the vena contracta or vena contracta area (VCA) can be measured when the reference beam is entirely inside the regurgitant orifice. For small orifices, the estimate of the VCA can be overestimated.

- In mitral regurgitation: The regurgitant volume, calculated from the VCA by MULDO and VTI by CW Doppler, significantly overestimated mild regurgitation, while there was no significant bias for moderate and severe MR when compared with regurgitant volume by MRI.

- In aortic regurgitation: In this study, VCA by MULDO was calculated fully automatically, while VCA was calculated semi-automatically in the two previous studies. There was good agreement between regurgitant volume measured by MRI and regurgitant volume calculated from VCA by MULDO and VTI by CW Doppler in moderate and severe AR, while agreement for those with mild AR was modest with significant overestimation by MULDO. VCA measured by 3D color Doppler was significantly higher than VCA by MULDO. Agreement between VCA and AR grade by 2D echo was moderately good.

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Study 1 was published in IEEE Trans Ultrason Ferroelect Freq Control 2009; 56 (5): 975-82.

It is available online at: http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=4976282.

"In reference to IEEE copyrighted material which is used with permission in this thesis, the IEEE does not endorse any of NTNU's products or services. Internal or personal use of this material is permitted." Study 2 was published in the Journal of the American Society of Echocardiography in 2010; 23(1):1-8. It is available online at: http://www.sciencedirect.com/science/article/pii/S0894731709009109. There is a license agreement between the author and Elsevier provided by Copyright Clearance Center (CCC) which allows reuse of the full article in a thesis/dissertation (license number: 3561561141018). Study 3 was published in European heart Journal Cardiovascular Imaging 2014; 15 (6): 615-622. "This is a pre-copy-editing, author-produced PDF of an article accepted for publication in EHJ -CI following peer review. The definitive publisher-authenticated version is available online at: http://dx.doi.org/10.1093/ehjci/jet255. "As part of the copyright agreement with Oxford University Press the author has retained the right, after publication, to include the article in full or in part in a thesis or dissertation.

11 Appendix

Forespørsel om deltagelse i en vitenskapelig undersøkelse:
"Kvantitering av mitralinsuffisiens med en ny tredimensjonal (3D) hjerteultralyd sammenliknet med MR-undersøkelse av hjertet.
"

Ultralydundersøkelser for å kartlegge hjertets pumpeevne og eventuelle sykelige forandringer er i daglig bruk på sykehus verden over.

Undersøkelsesmetoden er blitt svært populær fordi den er :
1. Ufarlig
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3. Gir verdifull informasjon om hjertets pumpeevne.

Vi er stadig på jakt etter ny informasjon og viten for å forbedre metoden og tolke måleresultatene riktig.
Beregning av størrelsen på lekkasjer gjennom hjerteklaffen mellom venstre forkammer og hovedkammer er vanskelig. Dagens metoder basert på todimensjonal ultralyd og hjertekateterisering har klare begrensninger.
Det aktuelle forskningsprosjektet går ut på å bruke en ny metode for å kvantitere lekkasjen. Metoden er basert på tredimensjonal ultralyd og vil bli sammenlignet med etablerte metoder som er i daglig bruk ved Klinikk for Hjertemedisin ved St. Olavs Hospital.
Rent praktisk vil undersøkelsen utføres med forsøkspersonen liggende på en benk i venstre sideleie og tar maksimalt en time. Undersøkelsen utføres ved Klinikk for Hjertemedisin.

MR-undersøkelse av hjertet ved MR-senteret er en del av studien. Dette planlegges utført samme dag som ultralydundersøkelsen. Dette regnes også som en trygg undersøkelse og gir et mål på hvor stor lekkasjen er. Du må kunne ligge stille i en trommel i ca 30 min. mens undersøkelsen pågår. Det er ingen smerte forbundet med undersøkelsen. Du kan ikke delta dersom du har operert inn pacemaker, metallklips, metallproteser osv. Dersom du er plaget med klaustrofobi, kan det også være vanskelig å få gjennomført undersøkelsen. Her gjelder vanlige retningslinjer for å gjennomføre MR-undersøkelse.

De nevnte undersøkelser i forbindelse med forskningsprosjektet kommer i tillegg til en ordinær ultralydundersøkelse utført ved Klinikk for Hjertemedisin. Det er frivillig å delta, og du kan når som helst trekke deg fra videre deltagelse uten at dette går ut over ordinær utredning eller behandling.

Ved deltagelse i prosjektet vil det bli innhentet nødvendige opplysninger vedr. din hjertesykdom fra sykehusets pasientjournal. Deltagelse vil ikke anføres i din pasientjournal, og det vil ikke bli lagret opplysninger der.

Prosjektmedarbeiderne har taushetsplikt i henhold til Forvaltningslovens § 13 og Helsepersonellovens § 21. Undersøkelsene utføres av leger og samarbeidspartnere i prosjektet. All informasjon og databehandling behandles konfidensielt og lagres etter vanlige retningslinjer. Prosjektet planlegges avsluttet ila mars 2009, og alle lagrede data vil da bli anonymisert.

NTNU / Institutt for Sirkulasjon og Bildediagnostikk er ansvarlig for prosjektet. Prosjektet er tilrådd av personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS og av Regional komité for medisinsk og helsefaglig forskningsetikk (REK i Midt-Norge).

Ordningen for pasientskadeerstatning omfatter også forsøkspersoner som deltar i medisinsk forskning.

Ved spørsmål kan du ta kontakt med prosjektmedarbeider / lege Thomas R. Skaug, som organiserer den praktiske gjennomføringen (tlf 72470000- medisinsk avd., St. Olavs Hospital, avd. Orkdal eller 40607557) eller evt med prosjektleder (tlf 73868000- Klinikk for hjertemedisin, St. Olavs Hospital og 73598888-NTNU, ISB) for mer informasjon.

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Det medisinske fakultet, NTNU
Medisinsk teknisk forskningssenter
7489 Trondheim

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Trondheim   /   2008.

Forespørsel om deltagelse i en vitenskapelig undersøkelse:
"Kvantitering av aortainsuffisiens med en ny tredimensjonal (3D) hjerteultralyd sammenliknet med MR-undersøkelse av hjertet. "

Ultralydundersøkelser for å kartlegge hjertets pumpeevne og eventuelle sykelige forandringer er i daglig bruk på sykehus verden over.

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Dagens metoder basert på todimensjonal ultralyd og hjertekateterisering har klare begrensninger.
Det aktuelle forskningsprosjektet går ut på å bruke en ny metode for å kvantitere lekkasjen. Metoden er basert på tredimensjonal ultralyd og vil bli sammenlignet med etablerte metoder som er i daglig bruk ved Klinikk for Hjertemedisin v St. Olavs Hospital.
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MR-undersøkelse av hjertet ved St. Olavs Hospital er en del av studien. Dette planlegges utført samme dag som ultralydundersøkelsen. Dette regnes også som en trygg undersøkelse og gir et mål på hvor stor lekkasjen er. Du må kunn ligge stille i en tromme i ca 30-45 min. mens undersøkelsen pågår. Det er ingen smerte forbundet med undersøkelsen. Du kan ikke delta dersom du har operert inn pacemaker, metallklips, metallproteser osv. eller dersom du har hjerteflimmer. Dersom du er plaget med klaustrofobi, kan det også være vanskelig å få gjennomført undersøkelsen. H gjelder vanlige retningslinjer for å gjennomføre MR-undersøkelse.

De nevnte undersøkelser i forbindelse med forskningsprosjektet kommer i tillegg til en ordinær ultralydundersøkelse utfør ved Klinikk for Hjertemedisin. Det er frivillig å delta, og du kan når som helst trekke deg fra videre deltagelse uten at dette går ut over ordinær utredning eller behandling.

Ved deltagelse i prosjektet vil det bli innhentet nødvendige opplysninger vedr. din hjertesykdom fra sykehusets pasientjournal. Deltagelse vil ikke anføres i din pasientjournal, og det vil ikke bli lagret opplysninger der.

Prosjektmedarbeiderne har taushetsplikt i henhold til Forvaltningslovens § 13 og Helsepersonellovens § 21. Undersøkelsene utføres av leger og samarbeidspartnere i prosjektet. All informasjon og databehandling behandles konfidensielt og lagres etter vanlige retningslinjer. Prosjektet planlegges avsluttet innen 5.oktober 2011. Av kontrollhensy blir grunnlagsdata oppbevart forsvarlig nedlåst fram til 5.oktober 2016. Deretter vil data bli slettet. Det er lege Thomas R. Skaug som er ansvarlig for datamaterialet i denne perioden. Instanser som kan tenkes å kontrollere grunnlagsmaterialet f. eks. forskningsansvarlige, Uredelighetsutvalget for forskning og Helsetilsynet.

NTNU / Institutt for Sirkulasjon og Bildediagnostikk er ansvarlig for prosjektet. Prosjektet er tilrådd Regional komité for medisinsk og helsefaglig forskningsetikk
(REK i Midt-Norge).

Ordningen for pasientskadeerstatning omfatter også forsøkspersoner som deltar i medisinsk forskning.

Ved spørsmål kan du ta kontakt med overlege /stipendiat Thomas R. Skaug, som organiserer den praktiske gjennomføringen (tlf 72 47 00 00- medisinsk avd., St. Olavs Hospital, avd. Orkdal eller tlf 406 07 557).

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Medisinsk teknisk forskningssenter
7489 Trondheim

Samtykkeskjema for deltagelse i klaffelekkasje-studien som er beskrevet over

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Trondheim   /   2009/10/11.

Abstract Information

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Abstract Content   **90%**

Purpose: A new three-dimensional (3D) high pulse repetition frequency (hprf) Doppler method called MULDO (MULtibeam hprf Doppler) has been developed to calculate the cross sectional area of the vena contracta (VCA) and quantify the severity of mitral regurgitation (MR).

Methods: The power of the received Doppler signal is proportional to the amount of blood flowing through the sample volume. We have isolated the Doppler signal from mitral jet flow by using MULDO. It uses a very high pulse repetition frequency, giving a Nyquist limit near the peak velocity of the jet. The VCA is found by summing the power of the Doppler signal from multiple beams distributed over the laminar vena contracta region and compensating for the attenuation and beam geometry by using a reference beam within the jet.

Materials: In a preliminary study five patients with moderate to moderate-severe MR (grade 2 and 3) were investigated by two-dimensional (2D) echocardiography and MULDO.

Results: The results are presented in the table.

Conclusion: As expected there are some discrepancy between the various methods to determine the severity of MR.The MULDO method does not make assumptions about the geometry and is not gain dependent. We believe that it will become a valuable tool in quantification of MR but warrants further investigations.

Table

Case	2D grade(a)	2D grade(b)	PISA-EROA	MULDO-VCA	PISA-RV	MULDO-RV
1	2	3	0,60	0,68	53	61
2	2	2-3	0,44	0,24	44	24
3	2-3	3	0,39	0,26	76	51
4	3	3	0,36	0,33	34	31
5	2-3	2-3	0,36	0,40	51	57

2D echocardiographic qualitative grading (grade 1-4; mild-moderate-moderate severe-severe) by two investigators (a and b), effective regurgitant orifice area (EROA=cm2) and regurgitant volume (RV=ml/beat) calculated by the 2D PISA method, VCA (cm2) by MULDO and MULDO-RV (ml/beat) calculated as the product of MULDO-VCA and 2D CW Doppler Velocity Time Integral of the regurgitant jet.

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Paper 1

Is not included due to copyright

Paper 2

CLINICAL INVESTIGATIONS
VALVULAR HEART DISEASE

Quantification of Mitral Regurgitation Using High Pulse Repetition Frequency Three-Dimensional Color Doppler

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Background: The aim of this study was to validate a novel method of determining vena contracta area (VCA) and quantifying mitral regurgitation using multibeam high–pulse repetition frequency (HPRF) color Doppler.

Methods: The Doppler signal was isolated from the regurgitant jet, and VCA was found by summing the Doppler power from multiple beams within the vena contracta region, where calibration was done with a reference beam. In 27 patients, regurgitant volume was calculated as the product of VCA and the velocity-time integral of the regurgitant jet, measured by continuous-wave Doppler, and compared with regurgitant volume measured by magnetic resonance imaging (MRI).

Results: Spearman's rank correlation and the 95% limits of agreement between regurgitant volume measured by MRI and by multibeam HPRF color Doppler were r_s = 0.82 and −3.0 ± 26.2 mL, respectively.

Conclusion: For moderate to severe mitral regurgitation, there was good agreement between MRI and multibeam HPRF color Doppler. Agreement was lower in mild regurgitation. (J Am Soc Echocardiogr 2010; 23:1-8.)

Keywords: Mitral regurgitation, Multibeam HPRF color Doppler, PISA, Vena contracta area, Regurgitant volume

The echocardiographic assessment of the severity of mitral regurgitation (MR) is challenging, because it requires the integration of different 2-dimensional (2D) Doppler parameters with inherent strengths and weaknesses.[1] The proximal isovelocity surface area (PISA) method provides measures of mitral regurgitant flow rate, effective regurgitant orifice area (EROA) and regurgitant volume.[2-4] However, the PISA method has limitations because the regurgitation is dynamic throughout systole and because it assumes a hemispheric flow

convergence and a circular regurgitant orifice.[5-8] A different approach to quantify MR is to look at the vena contracta, which is slightly smaller than the anatomic orifice and thus a measure of EROA.[1] According to guidelines, a vena contracta width ≥ 7 mm and an EROA and regurgitant volume as measured by PISA ≥ 0.4 cm^2 and ≥ 60 mL, respectively, are regarded as specific signs of severe MR.[1,9] Three-dimensional (3D) color flow imaging (CFI) can be used to quantify the vena contracta area (VCA)[10-12] and PISA.[13,14] Measuring the VCA by planimetry of 3D CFI has shown better correlation with angiographic grading than measuring the vena contracta width by 2D CFI.[10] The shape of the VCA was investigated using 3D CFI and demonstrated to be noncircular in functional MR, resulting in poor estimation of EROA by measuring the vena contracta width.[12]

In laminar blood flow such as in the vena contracta, the backscattered Doppler power is proportional to the volume of blood in the sample volume of an ultrasound beam.[15] This can be calibrated to give an absolute measurement of volume flow, as was shown for measurements in arteries by Hottinger and Meindl[16] in 1979. This principle can be used in the quantification of MR, as shown by Buck et al,[17] who estimated volume flow through the vena contracta from the power-velocity integral by means of a single wide measurement beam and a narrow beam for calibration.

We have recently extended this principle[17] to using multiple beams covering the vena contracta. Summing these beams provides a more homogeneous measurement compared with using a single beam. The proposed method has recently been validated in vitro as well as in computer simulations.[18] In this study, the proposed method was

1

used in vivo to quantify VCA semiautomatically, which was multiplied by the velocity-time integral (VTI), found independently using continuous-wave (CW) Doppler, to obtain the regurgitant volume. We used magnetic resonance imaging (MRI) as one of the reference methods for flow quantification of MR, which has previously been validated for this purpose.[19,20]

METHODS

Multibeam High–Pulse Repetition Frequency (HPRF) Color Doppler

The maximum velocity (the Nyquist limit) that can be resolved with CFI is typically 1 m/s for cardiac applications, which is much lower than the typical velocity of 4 to 6 m/s in a MR jet. We increased the Nyquist limit using a custom 3D HPRF color Doppler mode. With HPRF, several pulses are fired before the deep echoes from the first pulse have returned to the probe, such that exact range information is lost in exchange for an increased velocity span. However, this is not a problem, because the spurious sample volumes are outside the jet, and these signals are removed by a high-pass filter. Several ultrasound beams are spread out across the valve, as shown in the left part of Figure 1, and 3D Doppler data are recorded from a wide but short region of interest (ROI) covering the vena contracta. (The ROI must be short radially to enable HPRF.) A composite measurement beam is made by summing the contribution from all the beams. The right part of Figure 1 shows these individual beams (black) to scale, together with the composite measurement beam (blue). A wide single measurement beam (green), as used by Buck et al,[17] is included for comparison. The composite beam has a more homogeneous sensitivity and a higher signal-to-noise ratio than the single wide beam. Additional beams can be included to make the composite beam arbitrarily large without decreases in signal-to-noise ratio.

Blood flow through the vena contracta is known to be laminar, and for laminar blood flow, the power of the Doppler signal, P_{meas}, is proportional to the blood volume within the sample volume. The factor of proportionality, the ratio of the Doppler power P_{ref} to the beam area A_{ref}, is determined from the beam with the most Doppler power, because this beam is most likely to be within the regurgitant jet or orifice, as demonstrated in the left part of Figure 1. A computer model provides the cross-sectional area, A_{ref}, as well as a constant, k, relating the power of the composite beam to the reference beam. Because the power-to-area ratio is constant, the VCA is found by solving

$$\frac{P_{meas}}{VCA} = k \times \frac{P_{ref}}{A_{ref}}.$$

Being a numerical method, it is independent of display parameters such as gain and tissue priority. The reason "color" is included in "3D HPRF color Doppler" is because the acquisition uses just a few beams in each direction, just like CFI, compared with pulsed wave Doppler, which typically uses 50 to 100 pulses to make one spectrum. A few samples are sufficient to separate the Doppler power from the high-velocity jet from the surroundings, enabling a reasonable frame rate. However, it is dependent on the transmit frequency and transducer size for lateral resolution, which ultimately limits minimum beam width and thus valid calibration measurements. Additionally, the grid of beams makes it possible to obtain cross-sectional images of the vena contracta, but this was not investigated in this study. Further details can be found in Hergum et al.[18]

Data Acquisition and Processing

Equipment. A Vivid 7 Dimension (GE Vingmed Ultrasound AS, Horten, Norway) with a 3V matrix-array probe and an M4S 2D cardiac probe was used to acquire HPRF 3D color Doppler and standard 2D images. Custom software was used for postprocessing of the raw 3D Doppler data to calculate VCA. EchoPAC (GE Vingmed Ultrasound AS) was used to analyze the 2D images.

Subjects. The study was performed at the Department of Cardiology of St Olav's Hospital (Trondheim, Norway). The primary exclusion criteria were aortic regurgitation, cardiac arrhythmias, and contraindications to MRI. Of 35 subjects with mild to severe MR who consented to participate, 3 were excluded because of poor multibeam HPRF color Doppler quality, 4 because of poor MRI quality caused by arrhythmias, and 1 because of a requirement for hemodialysis between investigations. Consequently, the study included 27 subjects, 11 women and 16 men, with a median age of 51 years (range, 28-81 years). Sixteen subjects had organic mitral valve disease or unidentified etiology, and 11 had functional regurgitation. Eccentric jets were present in 10 of 16 patients with organic MR and in 4 of 11 subjects with functional MR. All were in sinus rhythm, and the median ejection fraction measured by echocardiography was 50% (range, 23%-65%). The interval between the examinations was within 1 day in 22 of the subjects and within 1 to 5 days in 5 subjects, and there were no changes in medications. The median heart rate was 63 beats/min (range, 43-104 beats/min) during Doppler echocardiography and 64 beats/min (range, 48-110 beats/min) during MRI. The study was approved by the Regional Committee for Medical and Health Research Ethics, Norwegian Social Science Data Service, and conducted according to the Declaration of Helsinki.

Two-Dimensional Doppler Echocardiography. A standard 2D Doppler echocardiographic examination was performed, including an assessment of jet area by CFI compared with left atrial size and mitral and pulmonary vein flow. We measured the mitral regurgitant flow rate by PISA at the time of peak regurgitant jet velocity. The Nyquist limit was lowered, such that a flow convergence as close as possible to a hemisphere was shown in an apical view. The VTI and peak regurgitant jet velocity were measured using CW Doppler, and the PISA EROA and regurgitant volume were calculated using a hemispheric approach.[1,4] We were unable to assess the PISA flow rate in 5 subjects. A highly qualified echocardiography observer, blinded to the MRI and multibeam HPRF color Doppler results, analyzed PISA and MR grade as follows: 1 = mild, 2 = mild to moderate, 3 = moderate to severe, and 4 = severe.

Multibeam HPRF Color Doppler. Multibeam HPRF color Doppler recordings were made in the apical view in two steps, as illustrated in Figure 2. With the scanner in triplex mode (B mode, CFI, and pulsed-wave Doppler), the vena contracta was located by moving the pulsed-wave sample volume into the jet flow shown by CFI and adjusted to include the highest velocities. The scanner was then switched to the custom multibeam HPRF color Doppler mode, with the position of the 3D ROI centered around the pulsed-wave sample volume. Depending on the depth of the ROI, the transmit frequency and the pulse repetition frequency were set to obtain a Nyquist velocity of about 3 m/s, so that a jet flow of nearly 6 m/s could be resolved. Typically, the transmit frequency was 2.1 MHz and the pulse repetition frequency 20 kHz. In a typical subject, the depth of the ROI was at about 9 - 10 cm. Altering display parameters such as gain and tissue priority during acquisition to visualize the
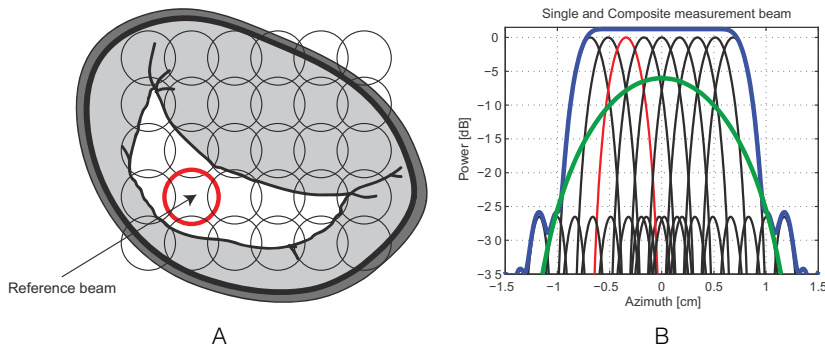
Figure 1 **(A)** Sketch of a leaking valve, with multiple beams shown. The reference beam *(red)*, the beam with the most Doppler power, is selected automatically as the beam that is most likely to be within the orifice. A composite measurement beam is made by adding multiple narrow beams together. **(B)** In this 2D sketch, 9 narrow beams have been added to make a wide, flat beam. The *green line* shows the beam profile of a single wide beam from a smaller transducer. The peak sensitivity of this beam is about 8 dB lower than for the *blue* composite beam, and the sensitivity varies significantly.

regurgitant jet optimally did not affect the raw 3D Doppler data we used for analysis. Each recording consisted of several cycles of real-time data, and the procedure was repeated to make sure that the vena contracta was within the ROI despite patient movement. The size of the ROI was $7 \times 20 \times 21$ mm (radial $\times$ azimuth $\times$ elevation). Currently, the frame rate is limited to about 10 volumes/s because of the large number of transmitted ultrasound beams necessary for each acquired volume. The raw 3D Doppler data were analyzed semiautomatically to find the VCA using custom software. Radial smoothing was applied to reduce the variance of the estimates. Frames corresponding to the systolic jet were selected, and the estimate of the VCA was the median value of these measurements. Some frames were excluded according to the following criteria:

- there was no visible jet above the noise level,
- the ROI did not cover the jet area, or
- the vena contracta was not within the ROI.

Multibeam HPRF color Doppler was analyzed by an observer blinded to the MRI data, MR grade, and the PISA results. To assess interobserver variability, another blinded observer randomly analyzed 18 of the subjects. The multibeam HPRF color Doppler regurgitant volume was calculated as the product of the VCA and the VTI of the regurgitant jet, measured separately by CW Doppler. Because the direction of flow was known, the velocity could also be found from the color flow data by maximum baseline shift. However, we chose to use separate VTI measurement because of the current low temporal resolution of 3D color flow data.

MRI Study. All patients were examined during supine rest using a Siemens Avanto 1.5-T system with a body matrix coil (Siemens Medical Systems, Erlangen, Germany). True fast imaging with steady-state precession cine images were acquired during end-expiratory breath holds in the 4-chamber and 2-chamber views and in the short axis from the base to the apex of the left ventricle with the following settings: retrospective electrocardiographic gating; in-plane resolution, 0.9×0.9 mm; echo time, 1.12 ms; repetition time, 58 ms; flip angle, 80°; slice thickness, 6 mm; slice gap, 4 mm; and 25 to 30 frames/beat. Flow in the ascending aorta was quantified using a steady-state free precession phase-contrast sequence with the following settings: retrospective

electrocardiographic gating; in-plane resolution, 1.3×1.3 mm; minimal repetition time (61.05 ms) and echo time (3.09 ms); slice thickness, 6 mm; encoding velocity adjusted to just above maximal systolic velocities; and 25 to 30 frames/beat. All images were analyzed using Segment[21] by an observer unaware of the echocardiographic results. The left ventricular stroke volume was calculated by semiautomatically drawing endocardial contours in the short-axis images in end-diastole and end-systole (aortic valve closure). Systolic long-axis excursion was quantified by measuring the descent of the septal, lateral, inferior, and anterior points of the mitral annulus in the 4-chamber and 2-chamber views. The average value was incorporated into the stroke volume estimate in the software. Systolic flow in the ascending aorta was quantified from the phase-contrast images by drawing an ROI in the ascending aorta. The MRI regurgitant volume was quantified as the difference between the left ventricular stroke volume and the aortic stroke volume.[19] The accuracy of the method was tested in an in vivo validation study in which the same measurements as described above were done in 9 subjects (4 healthy subjects, 5 with recent myocardial infarctions) in whom the absence of MR was confirmed by echocardiography. The estimated error was 3 $\pm$ 5 mL/stroke.

Statistical Analysis. The null hypothesis corresponded to no difference between the multibeam HPRF color Doppler, MRI, and 2D echocardiography in the quantification of MR. Including 27 patients resulted in power > 90% at the 5% significance level for detecting a difference in regurgitation volume of 5 mL, assuming 1 standard deviation (SD) of 3.2 mL. Spearman's rank correlation (r_s) was used because the continuous variables were not normally distributed. The agreement between the continuous variables (multibeam HPRF color Doppler, MRI, and PISA) was assessed by calculating the 95% limits of agreement (mean difference $\pm$ 2 SDs).[22] Because the differences were normally distributed, we used paired-samples t tests to compare the regurgitant volume measured by the different methods as well as the heart rate. To assess the agreement between MR grade (1-4), MRI regurgitant volume (milliliters per beat), multibeam HPRF color Doppler regurgitant volume (milliliters per beat), and VCA (square millimeters), we used κ statistics. In accordance with current guidelines for EROA, we divided the VCA results into 4 categories:
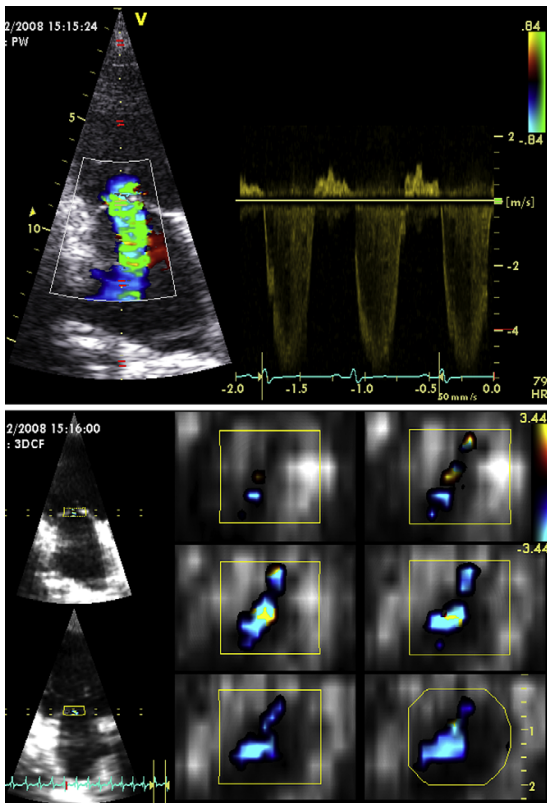
Figure 2 Two-step multibeam HPRF color Doppler data acquisition. *(Top)* Triplex scan. *(Bottom)* Three-dimensional HPRF color flow of the vena contracta. Note the Nyquist limit and the ROI. The VCA was calculated from the Doppler power; not the color flow images.

$1 = 0$ to 19 mm^2, $2 = 20$ to 29 mm^2, $3 = 30$ to 39 mm^2, and $4 = \geq 40$ mm^2. We divided regurgitant volume into 4 categories: $1 = 0$ to 29 mL, $2 = 30$ to 44 mL, $3 = 45$ to 59 mL, and $4 = \geq 60$ mL.[1]

We assessed the interobserver variability of the multibeam HPRF color Doppler VCA and regurgitant volume in 18 subjects as the coefficient of repeatability, defined as 2 SDs of the differences.

Descriptive values are reported as medians and ranges, and 95% limits of agreement are reported as mean ± 2 SDs. Results of paired t tests are reported as mean (95% confidence interval [CI]). The statistical analyses were performed using SPSS (SPSS, Inc, Chicago, IL).

RESULTS

The descriptive results are presented in Table 1. The mean difference in heart rate between MRI and Doppler echocardiography was 2.4 beats/min (95% CI, −1.4 to 6.2 beats/min).

Spearman's rank correlation (n = 27) was better between regurgitant volume measured by MRI and multibeam HPRF color Doppler ($r_s = 0.82$, $P < .001$) than between MRI regurgitant volume and multibeam HPRF color Doppler VCA ($r_s = 0.64$, $P < .001$). Similarly, Spearman's rank correlation was better between MR grade and multibeam HPRF color Doppler regurgitant volume ($r_s = 0.66$, $P < .001$) than between

Table 1 Study results

Variable	Median	Range
MULDO VCA (mm^2) (n = 27)	25.7	12.0-59.0
VTI by CW Doppler (cm) (n = 27)	150	74-213
Peak jet velocity by CW Doppler (m/s) (n = 27)	5.3	4.3-6.3
MULDO regurgitant volume (mL) (n = 27)	35.6	14.2-99.0
In functional MR (n = 11)	32.3	14.5-54.2
In organic MR (n = 16)	39.8	14.2-99.0
In central MR (n = 13)	32.3	14.2-99.0
In eccentric MR (n = 14)	37.7	20.0-61.3
MRI regurgitant volume (mL) (n = 27)	35.1	4.2-129.0
In functional MR (n = 11)	14.3	7.8-46.3
In organic MR (n = 16)	47.1	4.2-129.0
In central MR (n = 13)	23.9	8.3-129.0
In eccentric MR (n = 14)	45.2	4.2-68.7
PISA regurgitant volume (mL) (n = 22)	22.2	2.2-80.0

MULDO, Multibeam HPRF color Doppler.

MR grade and multibeam HPRF color Doppler VCA ($r_s = 0.41$, $P = .036$). The 95% limits of agreement between regurgitant volume measured by MRI and multibeam HPRF color Doppler (n = 27) were −3.0 ± 26.2 mL. Omitting the 5 subjects (n = 22) in whom we were unable to measure PISA, Spearman's rank correlation and the 95% limits of agreement between regurgitant volume measured by MRI and multibeam HPRF color Doppler were $r_s = 0.79$ ($P < .001$) and −5.1 ± 23.9 mL, respectively (Figure 3a). Similarly, Spearman's rank correlation and the 95% limits of agreement between MRI and PISA were $r_s = 0.78$ ($P < .001$) and 4.7 ± 30.6 mL, respectively (Figure 3b), and between PISA and multibeam HPRF color Doppler were $r_s = 0.63$ ($P = .002$) and −9.8 ± 37.0 mL, respectively (Figure 3c). Spearman's rank correlation between PISA EROA and multibeam HPRF color Doppler VCA was $r_s = 0.40$ ($P = .065$), and the 95% limits of agreement were −0.08 ± 0.28 cm^2. There was no significant difference between regurgitant volume measured by MRI and multibeam HPRF color Doppler or between MRI and PISA. Both PISA regurgitant volume and PISA EROA were significantly lower than multibeam HPRF color Doppler regurgitant volume and VCA.

There was a significant difference between regurgitant volume measured by MRI and multibeam HPRF color Doppler in patients with mild MR, defined as MRI regurgitant volume < 30 mL (n = 13), with a mean difference of −11.8 mL (95% CI, −17.9 to −5.6 mL). In patients with moderate and severe MR, defined as MRI regurgitant volume ≥ 30 mL (n = 14), the mean difference between regurgitant volume measured by MRI and multibeam HPRF color Doppler was 5.2 mL (95% CI, −0.6 to 11.0 mL). The mean difference between regurgitant volume measured by MRI and multibeam HPRF color Doppler was 1.1 mL (95% CI, −5.7 to 7.9 mL) in organic MR, while the mean difference was −8.8 mL (95% CI, −16.8 to −0.8 mL) in functional MR. There were no significant differences between regurgitant volume measured by MRI and multibeam HPRF color Doppler in central and eccentric mitral regurgitant jets. The mean differences were −2.0 mL (95% CI, −10.9 to 7.0 mL) and −3.8 mL (95% CI, −10.7 to 3.1 mL), respectively.

The κ agreement between the various methods is presented in Table 2 and Figure 4. Agreement between the methods was better for organic than functional MR, as seen in Table 2.

Interobserver analysis of the multibeam HPRF color Doppler VCA in 18 subjects demonstrated that the coefficient of repeatability was 8.7 mm^2. Because of the interobserver variability with VCA, the coefficient of repeatability for multibeam HPRF color Doppler regurgitant volume was 9.8 mL.
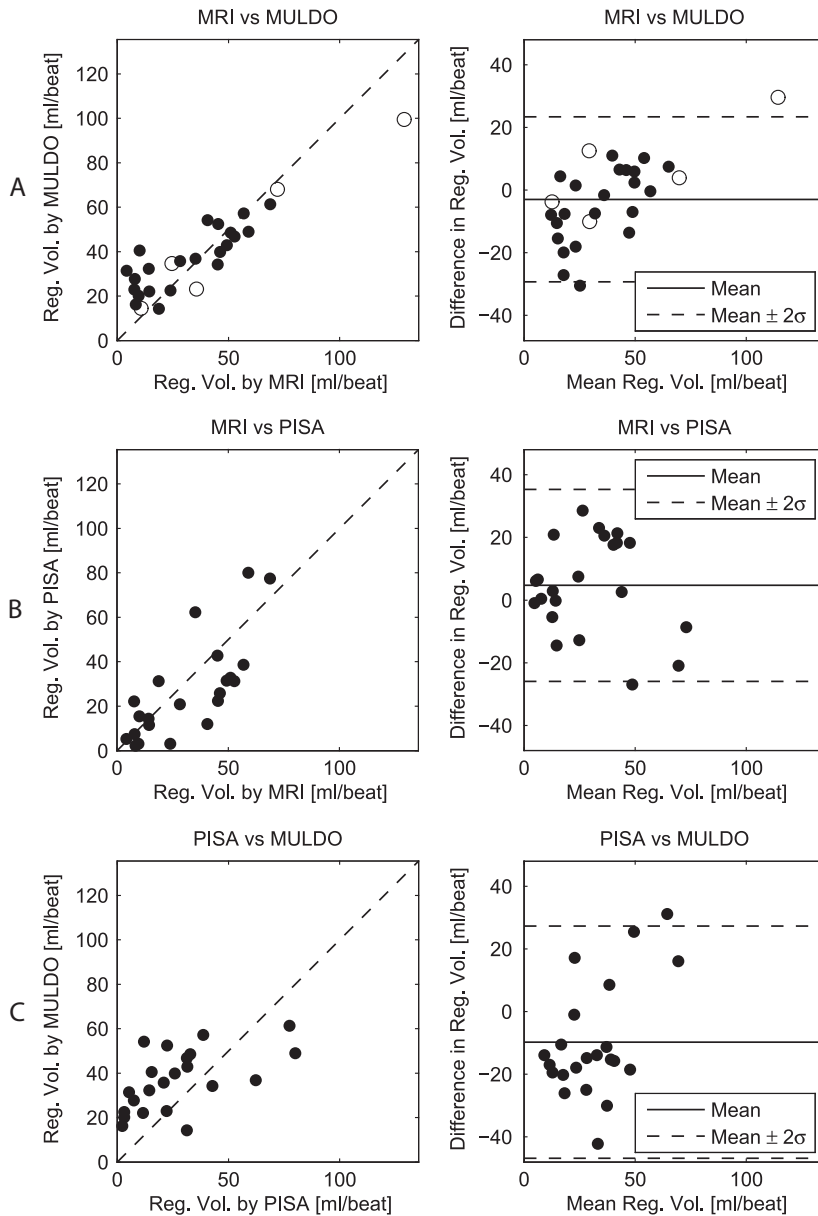
Figure 3 Spearman's rank correlation and 95% limits of agreement between regurgitant volume (Reg. Vol.) (n = 27) measured by **(A)** MRI and multibeam HPRF color Doppler (MULDO) were r_s = 0.82 and -3.0 ± 26.2 mL, respectively. Omitting the 5 subjects *(open dots)* in whom we were unable to measure PISA, Spearman's rank correlation and the 95% limits of agreement between regurgitant volume (n = 22) measured by MRI and multibeam HPRF color Doppler were r_s = 0.79 and -5.1 ± 23.9 mL, respectively. **(B)** Spearman's rank correlation and 95% limits of agreement between MRI and PISA were r_s = 0.78 and 4.7 ± 30.6 mL, respectively. **(C)** Spearman's rank correlation and 95% limits of agreement between PISA and multibeam HPRF color Doppler were r_s = 0.63 and -9.8 ± 37.0 mL, respectively.

DISCUSSION

In patients with more than mild mitral regurgitant jets evaluated by standard 2D Doppler echocardiography, it is necessary to quantify

the regurgitant volume to discriminate between moderate and severe MR.[1] The present study shows that the severity of MR can be quantified with a new 3D echocardiographic method based on multibeam HPRF color Doppler. The method is an extension of a previous

Table 2 Agreement

Agreement	κ	P
MRI regurgitant volume vs MULDO VCA (n = 27)	0.32	.005
MRI vs MULDO regurgitant volume (n = 27)	0.49	< .001
MR grade vs MULDO VCA (n = 27)	0.12	.30
MR grade vs MULDO regurgitant volume (n = 27)	0.44	< .001
MR grade vs MRI regurgitant volume (n = 27)	0.48	< .001
MRI vs MULDO regurgitant volume in functional MR (n = 11)	0.11	.60
MR grade vs MULDO regurgitant volume in functional MR (n = 11)	0.19	.36
MR grade vs MRI regurgitant volume in functional MR (n = 11)	0.30	.12
MRI vs MULDO regurgitant volume in organic MR (n = 16)	0.67	< .001
MR grade vs MULDO regurgitant volume in organic MR (n = 16)	0.58	< .001
MR grade vs MRI regurgitant volume in organic MR (n = 16)	0.57	< .001

MULDO, Multibeam HPRF color Doppler.
Multibeam HPRF color Doppler and MRI regurgitant volume categories:
1 = 0 to 29 mL, 2 = 30 to 44 mL, 3 = 45 to 59 mL, and 4 = ≥60 mL. Multi-
beam HPRF color Doppler VCA categories: 1 = 0 to 19 mm^2, 2 = 20 to 29
mm^2, 3 = 30 to 39 mm^2, 4 = ≥40 mm^2. MR grades assessed by 2D echo:
1 = mild, 2 = mild to moderate, 3 = moderate to severe, 4 = severe.

Figure 4 The κ agreement (n = 27) between MR grade and multi-
beam HPRF color Doppler (MULDO) regurgitant volume (Reg.
Vol.), between MR grade and MRI regurgitant volume, and be-
tween regurgitant volume measured by MRI and multibeam
HPRF color Doppler was 0.44, 0.48, and 0.49, respectively.
MR grades assessed by 2D echo: 1 = mild, 2 = mild to moderate,
3 = moderate to severe, 4 = severe. Multibeam HPRF color
Doppler and MRI regurgitant volume categories: 1 = 0 to 29
mL, 2 = 30 to 44 mL, 3 = 45 to 59 mL, and 4 = ≥60 mL.

method described by Buck et al.[17] VCA was measured from the back-
scattered Doppler power, while the regurgitant volume was calculated
as the product of VCA and the VTI of the regurgitant jet, found sepa-
rately from CW Doppler. The agreement between regurgitant volume
measured by MRI and multibeam HPRF color Doppler and between
MR grade and multibeam HPRF color Doppler regurgitant volume
was moderately good. In organic MR, the agreement between the
methods was even better, and there was no significant difference be-
tween regurgitant volume measured by MRI and multibeam HPRF
color Doppler. The agreement was poor in functional MR, with the
multibeam HPRF color Doppler regurgitant volume being signifi-
cantly higher. Similarly, in patients with MRI regurgitant volumes <
30 mL, there was significant overestimation by multibeam HPRF color
Doppler regurgitant volume, but there was no bias in those with MRI
regurgitant volumes ≥ 30 mL. The 95% limits of agreement between
regurgitant volume measured by MRI and multibeam HPRF color
Doppler were relatively wide, which is explained by the significant
overestimation of mild regurgitation by multibeam HPRF color Dopp-
ler. Unlike direct measurement with planimetry of VCA by 3D CFI,[10]
multibeam HPRF color Doppler estimates VCA on the basis of a
calibrated measurement of the backscattered Doppler power and
requires no manual tracing; the calculations can be done semiauto-
matically, are not affected by display settings such as gain and tissue pri-
ority, and are not limited by a Nyquist limit of <1 m/s. The major
advantage of extending the method from one measurement beam
and one reference beam[17] to multiple beams is more homogeneous
sensitivity of the measurement beam, which ensures that a slight lateral
shift of the ROI will not result in a different measurement. The signal-
to-noise ratio is also improved. Because the reference beam is
automatically selected within a grid of beams, it is easier for the sonog-
rapher to obtain a valid reference measurement, compared with the
use of only a single beam.

In the present study, we found better correlation and agreement
between regurgitant volume measured by MRI and multibeam
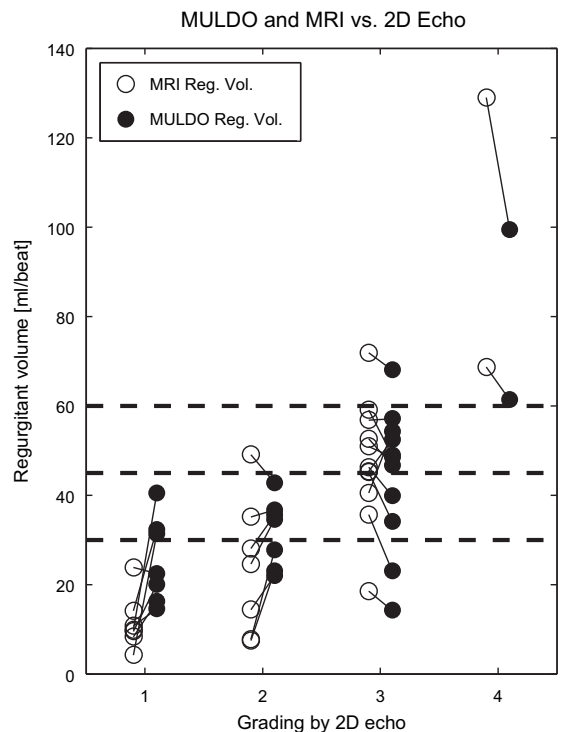HPRF color Doppler than between MRI regurgitant volume and mul-

tibeam HPRF color Doppler VCA. This is not surprising, because the
regurgitant volume is given not only by the EROA but also by the du-
ration of regurgitation and the pressure gradient across the mitral
valve, expressed as the VTI. As demonstrated in Figure 3a, the 95%
limits of agreement between regurgitant volume measured by MRI
and multibeam HPRF color Doppler were wide in our study, whereas
Buck et al[23] demonstrated excellent agreement. They reported
a mean difference of 0.4 mL and 1 standard deviation of 3.2 mL, cor-
responding to 95% limits of agreement of 0.4 ± 6.4 mL, between
broad-beam spectral Doppler and MRI measurements in MR. There
are some differences to note. Our population was characterized by
a wider range of regurgitant volume measured by MRI (4-129 mL)
than in the population investigated by Buck et al[23] (6-46 mL). Sec-
ond, we measured VCA by multibeam HPRF color Doppler, but
the VTI of the regurgitant jet was measured separately by CW Dopp-
ler. In the power-velocity integral method used by Buck et al,[23] both
the area and the velocity integral across the flow cross-sectional area
were measured. Further, the calculation of MRI regurgitant volume
was somewhat different, as we calculated the left ventricular stroke
volume by volumetric measurements in short-axis and long-axis im-
ages, whereas Buck et al[23] measured mitral inflow using phase con-
trast imaging. Another recently described 3D CFI method based on

dealiasing of mitral vena contracta flow to calculate mitral regurgitant volume was validated by Plicht et al,[24] and the 95% limits of agreement between this 3D CFI method and MRI in vivo were -1.8 ± 14.2 mL. In our study, in vivo validation results showed that the MRI measurements contributed only to a modest part of the total difference between the methods, and the error was in the same range as previously reported for the approach used by Buck et al and Plicht et al.[20,23,24] We demonstrated significant overestimation by multibeam HPRF color Doppler regurgitant volume for mild regurgitation, defined as MRI regurgitant volume < 30 mL, but no significant bias for MRI regurgitant volume $\geq$ 30 mL. Similarly, in vitro, there was an overestimation of the VCA in the small valvular defects.[18]

We found a significant correlation ($r_s = 0.66$) and moderately good agreement ($\kappa = 0.44$) between MR grade and multibeam HPRF color Doppler regurgitant volume. The fact that multibeam HPRF color Doppler overestimates mild regurgitation (regurgitant volume < 30 mL) is clearly illustrated in Figure 4. This contributes to some overlap between MR grades 1 and 2. Agreement was better for organic than for functional MR between the various methods, as demonstrated in Table 2. This probably stems from the same source as the overestimation of mild regurgitation: the reference beams are too large for some orifices. The regurgitant orifice is usually asymmetric and noncircular in functional as opposed to organic MR,[12,13] meaning that the cross-sectional area may be large but still not able to encompass the full reference beam. Additionally, those with an organic etiology in our study were part of a higher regurgitant volume population than those with a functional etiology.

In our study, a standard hemispheric PISA was feasible in 22 out of 27 patients. The 95% limits of agreement between regurgitant volume measured by MRI and PISA were wider than between MRI and multibeam HPRF color Doppler (Figure 3). One of the limitations of this PISA method is the dynamic variation of the mitral regurgitant flow rate and the EROA during systole.[6,7] This was demonstrated in a validation study using 4 different hemispheric PISA methods. There was significant underestimation of mitral regurgitant volume by two single-point PISA methods, measuring instantaneous flow rate, compared with MRI (95% limits of agreement, -13.3 ± 20.4 and -13.5 ± 20.6 mL) and to a lesser degree by two time-integral PISA methods compared with MRI (95% limits of agreement, -8.0 ± 12.8 and -8.7 ± 14.8 mL).[8] In 3D CFI studies, it has been demonstrated that the proximal flow convergence area is hemielliptic rather than hemispheric, especially in functional MR, because of the asymmetric geometry of the regurgitant orifice area. This results in significant underestimation of PISA EROA measured by a hemispheric approach by 2D CFI.[13,14] Similarly, VCA measured by 3D CFI has been demonstrated to be significantly larger than PISA EROA measured by a hemispheric approach, especially in patients with elliptical orifice shapes.[12,25] Kahlert et al[12] demonstrated that the 95% limits of agreement between PISA EROA measured by a hemispheric and a hemielliptic approach, respectively, and VCA measured by 3D CFI were -0.2 ± 0.4 and -0.09 ± 0.28 cm^2, respectively. We demonstrated that the 95% limits of agreement between regurgitant volume measured by a hemispheric approach to PISA and multibeam HPRF color Doppler were wide (Figure 3c). Multibeam HPRF color Doppler regurgitant volume was significantly larger than PISA regurgitant volume, and multibeam HPRF color Doppler VCA was significantly larger than PISA EROA.

Limitations

The Nyquist limit should ideally be equal to the mitral regurgitant jet velocity. However, the velocity of the mitral regurgitant jet can be determined unambiguously as long as the direction of the jet is known and the peak velocity is <2 times the Nyquist limit of about 3 m/s. To achieve such an HPRF, and thus a high Nyquist limit, the ROI must be small in the radial direction. It can be challenging to position the ROI correctly, especially with large displacements of the mitral valve in hyperdynamic ventricles. As shown in the experimental study, multibeam HPRF color Doppler VCA will overestimate the regurgitant orifice area in mild disease when the orifice is narrow relative to the size of the reference beam.[18] This limitation is inherent to all similar techniques requiring reference measurements.[17] Accordingly, agreement was better for the moderate and severe regurgitations in the present study. The regurgitant volume relies on measuring both the multibeam HPRF color Doppler VCA and VTI of the regurgitant jet by CW Doppler accurately. Area estimation by multibeam HPRF color Doppler is angle dependent, like other Doppler methods, and misalignment will overestimate VCA. The regurgitant volume will not be angle dependent, because the overestimation of VCA will be canceled out by the underestimation of the VTI from CW Doppler. The vena contracta and the EROA can vary during systole,[1,6-8,26] and the current frame rate of 10 volumes/s is probably too low for short-duration regurgitation or dynamic variations during systole. However, multibeam HPRF color Doppler acquires real-time data over several cardiac cycles to make sure that the vena contracta is within the 3D ROI. The criteria for the inclusion and exclusion of frames were well defined, but there were still some frames that were of uncertain nature, which explains the interobserver variability of the VCA.

Further Perspectives

We expect the next generation of 3D probes to increase the aperture size to match the currently available 2D probes. This will enable narrower reference beams, enabling multibeam HPRF color Doppler to measure smaller orifices and narrower and asymmetric functional MR with less bias. The current low frame rate of about 10 volumes/s is also expected to increase significantly with the use of parallel received beams.

CONCLUSION

For the quantification of MR, calculation of VCA by multibeam HPRF color Doppler overcomes several of the limitations of CFI, as well as the assumptions made by PISA that lead to the underestimation of noncircular defects. However, multibeam HPRF color Doppler regurgitant volume significantly overestimated mild regurgitation, but this condition can easily be identified as such by standard 2D Doppler examinations, making further quantitative efforts unnecessary. There was no significant bias for moderate and severe MR when regurgitant volume measured by multibeam HPRF color Doppler was compared with MRI. We believe that multibeam HPRF color Doppler regurgitant volume calculated as the product of VCA and VTI by CW Doppler can supplement 2D Doppler for the quantification of moderate and severe MR.

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Paper 3

Quantification of aortic regurgitation using high-pulse repetition frequency three-dimensional colour Doppler

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Aims	The aim of this study was to validate and assess the feasibility of a previously described method using multibeam high-pulse repetition frequency (HPRF) colour Doppler to quantify the vena contracta area (VCA) in aortic regurgitation (AR).
Methods	Twenty-nine patients with mild to severe AR were studied. Regurgitant volume and fraction measured by magnetic resonance imaging (MRI) were used as the standard of reference. The VCA was measured automatically by combining the Doppler power from multiple beams with a priori knowledge of the individual beam profiles, to give an absolute measurement of the VCA. The regurgitant volume was calculated as the product of the VCA and the velocity time integral, measured separately by continuous wave Doppler.
Results	The Spearman's rank correlation between regurgitant volume by MRI and multibeam HPRF colour Doppler was $r_s = 0.73$ ($P < 0.01$), with 95% limits of agreement of -14.4 ± 29.1 mL. The mean difference between the methods in those with MRI regurgitant volume of ≥ 30 mL ($n = 14$) was -7.6 (95% confidence interval -13.9 to -1.2) mL.
Conclusion	There was good agreement between MRI and multibeam HPRF colour Doppler in patients with moderate to severe AR, while agreement for those with mild AR was modest.
Keywords	Aortic regurgitation • Multibeam HPRF colour Doppler • 3D colour Doppler • Vena contracta area • Regurgitant volume

Introduction

The evaluation of aortic regurgitation (AR) with echocardiography requires an integrated approach of semi-quantitative and quantitative two-dimensional (2D) Doppler parameters.[1,2] Quantitative parameters such as the proximal isovelocity surface area to calculate the effective regurgitant orifice area (ERO area) and regurgitant volume are recommended when feasible.[1–3] One of the limitations is the hemispheric assumption of the flow convergence. The vena contracta is a direct measure of the ERO and correlates to the severity of AR.[4,5] From 3D colour Doppler imaging, we can measure the vena contracta area (VCA) making no assumptions of the geometry,[6–8] but these measurements are gain-dependent.

The attenuation compensated volume flowmeter to measure volume flow in arteries was introduced by Hottinger and Meindl.[9] In laminar flow, the backscattered Doppler power is proportional to the volume of blood in the sample volume of an ultrasound beam.[10] This principle has been used in the quantification of mitral regurgitation using one measurement beam and one reference beam.[11] We have extended this principle by using multiple narrow beams (multibeam) to provide a homogenous measurement and additionally by high-pulse repetition frequency (HPRF) to increase the Nyquist limit. This method, multibeam HPRF colour Doppler, has been described and validated *in vitro*,[12] and in patients with mitral regurgitation to quantify the VCA semi-automatically.[13] In the present study, we have extended the method to perform a fully

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automatic quantification of the VCA, and applied this in patients with AR. To obtain the regurgitant volume, the VCA was multiplied with the velocity time integral (VTI), found separately using continuous wave (CW) Doppler. Our primary aim was to assess agreement between multibeam HPRF colour Doppler and phase-contrast magnetic resonance imaging (MRI).[14–17] Our secondary aim was to compare the new method with 3D colour Doppler,[1,6] and AR echo grade by 2D Doppler echocardiography.[1]

Methods

Equipment

A Vivid 7 Dimension or E9 (GE Vingmed Ultrasound, Horten, Norway) was used with an M4S or M5S cardiac probe to acquire 2D Doppler echocardiography images, and we used a 3 V matrix array probe to acquire multibeam HPRF colour Doppler and 3D colour Doppler images. EchoPac BT 11 (GE Vingmed Ultrasound) was used to analyse 2D and 3D colour Doppler images. The custom software was used for post-processing of the raw multibeam HPRF colour Doppler data to calculate the VCA (MATLAB 7.8.0, Math Works).

Subjects

This study was performed at the Department of Cardiology, St. Olav's Hospital, Trondheim University Hospital, Norway, and the Department of Cardiology, Oslo University Hospital, Rikshospitalet, Norway. The inclusion criteria were adult patients with mild to severe chronic AR in sinus rhythm. The exclusion criteria were cardiac arrhythmias or any contraindication for MRI. Thirty-six subjects with mild to severe chronic AR consented to participate and successfully underwent the echo and MRI exams. Due to difficulty in identifying the vena contracta, misalignment of the Doppler beam and jet direction or incorrect positioning of the region of interest (ROI) in four subjects with eccentric jets and three subjects with central jets we were not able to measure the VCA by multibeam HPRF colour Doppler in 7 of 36 subjects, and these subjects were excluded from the analyses. There were 7 women and 22 men with a median age of 58 (range 18–83) years. The aetiology of the AR were degenerative disease in nine, bicuspid aortic valve in seven, cusp prolapse in three, aortic root disease in six, and other uncertain mechanisms in four subjects. In 16 subjects, there were eccentric jets, and in the remaining 13, there were central jets. The median ejection fraction measured by 2D echocardiography was 60 (range 30–71)%. The median left ventricular end-diastolic and end-systolic dimensions were 61 (range 45–72) mm and 39 (range 25–52) mm, respectively. All echocardiographic recordings were performed immediately before the MRI study. Median heart rate during Doppler echocardiography was 60 (range 40–92) bpm and that during MRI was 65 (range 43–96) bpm. The study was approved by the Regional Committee for Medical and Health Research Ethics and conducted according to the Helsinki Declaration.

Multibeam HPRF colour Doppler

We used HPRF and a clutter filter to be able to separate the Doppler signals in the vena contracta from the entrained blood with lower velocities surrounding the jet. In this study, the Nyquist limit was about 3 m/s, and we used a clutter filter with a cut-off frequency corresponding to 1.5 m/s. There were several narrow ultrasound beams (multibeam) spread across the vena contracta region to measure the power of the vena contracta Doppler signal (P_{meas}). To get a calibrated Doppler power measurement, a reference beam was chosen as the beam with the most Doppler power (P_{ref}) because this beam was most likely

within the regurgitant jet. A computer model provided the cross-sectional area (A_{ref}) of the reference beam and a constant (k). The VCA was proportional to the calibrated Doppler power, and therefore independent of attenuation, gain or tissue priority, and found by solving:

$$\frac{P_{meas}}{VCA} = k\frac{P_{ref}}{A_{ref}}$$

Multibeam HPRF colour Doppler acquisition and processing

Multibeam HPRF colour Doppler recordings were made from the apical five-chamber view for the central jets (*Figure 1*) and from the parasternal long-axis view for the eccentric jets (*Figure 2*) to get the best possible alignment of the ultrasound beams and the regurgitant jet. The vena contracta was located using a triplex-mode, in which the pulsed-wave (PW) sample volume was moved into the regurgitant jet shown by colour Doppler imaging, and we used approximately a few minutes to locate the vena contracta. The scanner was then switched to the multibeam HPRF colour Doppler mode, with the position of the 3D ROI centred on the PW sample volume. The transmit frequency was 2.1 MHz. The ROI was typically at a depth of 5–12 cm during acquisition, and the size of the ROI was 7 mm × 20 mm × 21 mm. The frame rate was ∼7–10 HPRF colour volumes per second. A recording consisted of 10–15 heartbeats of real-time 3D data acquired in less than half a minute. More details can be found in previous publications.[12,13]

The multibeam HPRF colour Doppler recordings were analysed using the custom software to measure the VCA. The output was cross-sectional Doppler power images of the vena contracta and estimates of the VCA for each frame. In *Figure 3*, six diastolic frames of multibeam HPRF colour Doppler data during a single heartbeat are demonstrated. The Doppler measurements from all the diastolic frames during a recording of 10–15 heartbeats were calculated fully automatically, and we used the median value as the estimate of the VCA. The recordings were validated by a blinded observer to assure that they were representative consisting of: (i) a Doppler signal above the noise level and (ii) a Doppler signal within the ROI. However, there were no manual interactions in order to calculate the VCA. To assess repeatability, a separate recording from the same subject was similarly analysed. Regurgitant volume was calculated as: VCA × VTI measured separately by CW Doppler.

3D colour Doppler

A 3D colour Doppler examination was performed from the parasternal long-axis view. The Nyquist limit was ∼60 cm/s. Full-volume of the flow data was acquired from six consecutive cardiac cycles, and the frame rate was ∼15 volumes per second. We used a default clutter filter with a cut-off frequency corresponding to 20 cm/s. The dataset was cropped just downstream from the aortic valve in a plane perpendicular to the aortic regurgitant jet to find the VCA. The frame with the largest area of the vena contracta was chosen and measured by planimetry. Regurgitant volume was calculated as: VCA × VTI measured separately by CW Doppler.

2D colour Doppler

We measured the VTI and pressure half time of the regurgitant aortic jet with CW Doppler from the parasternal long-axis view in eccentric jets and also from the apical five-chamber view in central jets to get the best possible alignment of the ultrasound beam and the regurgitant jet. The colour Doppler sector size was optimized, and the frame with the largest diameter of the vena contracta was selected to measure the vena contracta width (VCW). The Nyquist limit was ∼60 cm/s.
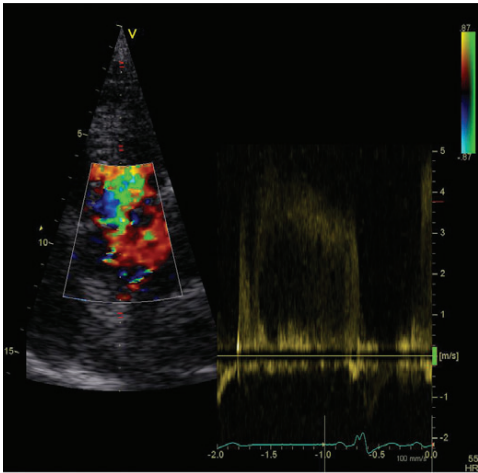
Figure 1: Two-step multibeam HPRF colour Doppler data acquisition with triplex scan (upper panel) and multibeam HPRF colour flow of the vena contracta (lower panel) from the apical five-chamber view in central AR.
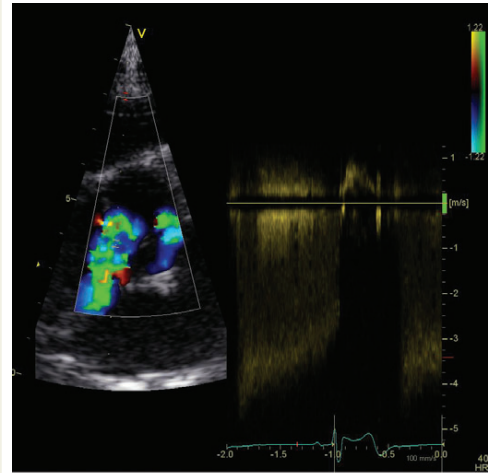

Figure 2: Two-step multibeam HPRF colour Doppler data acquisition with triplex scan (upper panel) and multibeam HPRF colour flow of the vena contracta (lower panel) from the parasternal long-axis view in eccentric AR.

Assessment of diastolic flow reversal in the descending aorta by PW Doppler was performed. Further, assessment of the left ventricular function and dimensions were performed. A cardiologist blinded for the MRI, multibeam HPRF, and 3D colour Doppler results analysed these data. Based on qualitative and semi-quantitative parameters, AR severity was graded as: 1 = mild, 2 = moderate, and 3 = severe.[1]

MRI study

All patients were examined during supine rest using a Siemens Avanto 1.5-T system with a body matrix coil (Siemens, Erlangen, Germany). Balanced steady-state free precession cine images were acquired during end-expiratory breath holds in the long- and short-axis views of the left ventricle. Flow in the ascending aorta, at the level of the right pulmonary artery,[15] was quantified using a steady-state free precession phase-contrast sequence. The image was aligned perpendicular to the vessel walls guided by two previously acquired perpendicular cine images positioned along the centre of the ascending aorta. The following settings were used: end-expiratory breath hold, retrospective ECG-gating, in-plane resolution 1.3×1.3 mm, minimal TR (61.05 ms) and TE (3.09 ms), slice thickness 6 mm, V_{enc} adjusted to just above maximal systolic velocities, and 30 frames/beat. All images were analysed in Segment[18] by one observer unaware of the echocardiographic results. Systolic and diastolic flow in the ascending aorta was quantified from the phase-contrast images by drawing an ROI in the reconstructed magnitude images. The aortic regurgitant volume during diastole was quantified, and the regurgitant fraction was calculated by dividing the regurgitant
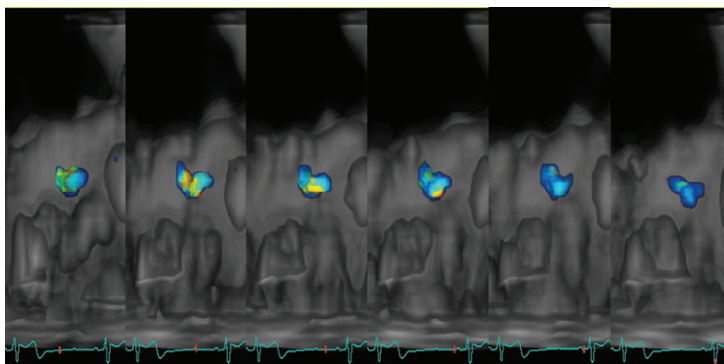
Figure 3: Multibeam HPRF colour Doppler flow from the vena contracta during one heartbeat, and six diastolic frames are depicted. This recording was obtained from the parasternal long-axis, as shown in *Figure 2*.

volume with the forward volume during systole. This approach will overestimate the regurgitant volume slightly as coronary flow during diastole will be included. We sought to reduce phase-offset errors in the velocity measurements by positioning the phase-contrast image in isocentre, and using as low V_{enc} as possible.[19]

Statistics

Descriptive values are reported as median and range, and Spearman's rank correlation (r_s) was used because the continuous variables were not normally distributed.

Because the differences were normally distributed, we used paired sample *t*-test to compare the VCA and regurgitant volume, respectively, by the different methods. The level of significance was chosen at $P < 0.05$. The agreement between the continuous variables was assessed by calculating the 95% limits of agreement (mean difference $\pm$ 2 SD). The mean difference between two methods was reported as 95% confidence interval (CI).

To assess the agreement between AR echo grade and VCA, we used kappa statistics. According to current recommendations for the ERO area by 2D echo Doppler, we divided multibeam HPRF colour Doppler VCA into: $1 = <10$ mm^2, $2 = 10-29$ mm^2, and $3 = \geq 30$ mm^2.[1] In accordance with proposed cut-offs by Chin *et al.*,[7] we divided 3D colour Doppler VCA into: $1 = <30$ mm, $2 = 30-49$ mm^2, and $3 = \geq 50$ mm^2.

Repeatability of the multibeam HPRF colour Doppler VCA in separate recordings was assessed as the coefficient of repeatability, defined as 2 SD of the differences.

The statistical analyses were performed using SPSS Statistics 19 (SPSS, Inc., Chicago, IL, USA).

Results

The descriptive results are presented in *Table 1*, and the Spearman's rank correlation between the different methods is presented in *Table 2*. The mean difference between the heart rate during the MRI and Doppler echocardiography was 3.6 (95% CI 1.0−6.1) bpm.

There was a better correlation between VCA measured by multibeam HPRF colour Doppler or 3D colour Doppler and MRI regurgitant fraction than between VCW and MRI regurgitant fraction (*Table 2* and *Figure 4*). The Spearman's rank correlation and the 95% limits of agreement between MRI regurgitant volume and multibeam HPRF colour Doppler VCA × VTI were $r_s = 0.73$ ($P < 0.01$) and $−14.4 \pm 29.1$ mL, respectively (*Figure 5A*). The mean differences between the methods in groups based on direction of the jet and AR severity are presented in *Table 3*. The Spearman's rank correlation and the 95% limits of agreement between MRI regurgitant volume and 3D colour Doppler VCA × VTI were $r_s = 0.75$ ($P < 0.01$) and $−47.8 \pm 60.9$ mL, respectively (*Figure 5B*), while between 3D colour Doppler and multibeam HPRF colour Doppler VCA there were $r_s = 0.74$ and 13.3 ± 20.3 mm^2 (*Figure 5C*).

Based on AR echo grading, there was mild AR in 9, moderate AR in 8, and severe AR in 12 subjects. There was a good correlation between AR echo grade and VCA by both multibeam HPRF colour Doppler and 3D colour Doppler, and agreement was $K = 0.50$ ($P < 0.01$) and $K = 0.64$ ($P < 0.01$), respectively (*Figure 6*).

The analysis of the VCA estimate was made fully automatically, and consequently, there was no inter- or intraobserver variability. In a separate recording from the same subject, the coefficient of repeatability for multibeam HPRF colour Doppler VCA estimates was 9.4 mm^2.

Discussion

The present study showed that fully automatic calculation of the VCA in AR was feasible using multibeam HPRF colour Doppler, and that the correlation with MRI regurgitant volume and fraction was good. Similar to other echocardiographic methods, the major clinical advantages of multibeam HPRF colour Doppler vs. MRI are availability and no contraindications. According to the ESC guidelines, in patients with inadequate echocardiographic quality or discrepant results, MRI should be used to assess the severity of valvular lesions, particularly regurgitant lesion.[2] Interestingly, both 3D methods, multibeam HPRF colour Doppler and 3D colour Doppler VCA, were more closely correlated to MRI regurgitant volume and fraction than VCW, measured in 2D. This is in line with

Table 1 Descriptive results

Parameter	Median	Range
MULDO VCA (mm^2) ($N = 29$)	17.0	6.0–43.0
In central AR ($n = 13$)	16.0	9.0–32.0
In eccentric AR ($n = 16$)	19.5	6.0–43.0
3D colour Doppler VCA (mm^2) ($N = 29$)	35	12–60
In central AR ($n = 13$)	20	12–50
In eccentric AR ($n = 16$)	40	12–60
VCW (mm) ($N = 29$)	5	2–12
In central AR ($n = 13$)	4	3–7
In eccentric AR ($n = 16$)	6	2–12
VTI (cm) ($N = 29$)	250	109–430
In central AR ($n = 13$)	250	135–430
In eccentric AR ($n = 16$)	248	109–387
MULDO VCA × VTI (mL) ($N = 29$)	41.7	12.0–83.7
In central AR ($n = 13$)	39.8	17.8–75.6
In eccentric AR ($n = 16$)	45.1	12.0–83.7
3D colour Doppler VCA × VTI (mL) ($N = 29$)	65.0	23.8–168.0
In central AR ($n = 13$)	52.8	23.8–150.5
In eccentric AR ($n = 16$)	97.8	24.0–168.0
MRI regurgitant volume (mL) ($N = 29$)	25.0	2.3–87.8
In central AR ($n = 13$)	19.0	2.3–58.1
In eccentric AR ($n = 16$)	38.0	3.0–87.8
MRI regurgitant fraction (%) ($N = 29$)	23.1	4.4–77.0
In central AR ($n = 13$)	19.1	4.4–77.0
In eccentric AR ($n = 16$)	33.9	4.4–50.2

MULDO VCA × VTI calculates regurgitant volume.
3D colour Doppler VCA × VTI calculates regurgitant volume.
MULDO, multibeam HPRF colour Doppler; VCA, vena contracta area; AR, aortic regurgitation; VCW, vena contracta width by 2D colour Doppler; VTI, velocity time integral of the aortic regurgitant jet by CW Doppler.

Table 2 Correlation

Spearman's rank correlation	r_s	P-value
MULDO VCA (mm^2)		
vs. MRI regurgitant fraction (%)	0.77	<0.01
vs. MRI regurgitant volume (mL)	0.81	<0.01
vs. 3D colour Doppler VCA (mm^2)	0.74	<0.01
vs. echo grade (mild, moderate, and severe)	0.76	<0.01
MULDO VCA × VTI (mL)		
vs. MRI regurgitant fraction (%)	0.67	<0.01
vs. MRI regurgitant volume (mL)	0.73	<0.01
vs. echo grade (mild, moderate, and severe)	0.67	<0.01
3D colour Doppler VCA (mm^2)		
vs. MRI regurgitant fraction (%)	0.83	<0.01
vs. MRI regurgitant volume (mL)	0.87	<0.01
vs. echo grade (mild, moderate, and severe)	0.76	<0.01
Echo grade (mild, moderate, and severe)		
vs. MRI regurgitant fraction (%)	0.71	<0.01
vs. MRI regurgitant volume (mL)	0.78	<0.01
VCW (mm)		
vs. MRI regurgitant fraction (%)	0.68	<0.01
vs. MRI regurgitant volume (mL)	0.75	<0.01

MULDO VCA × VTI calculates regurgitant volume.
Echo grade, severity of aortic regurgitation by 2D Doppler parameters.
MULDO, multibeam HPRF colour Doppler; VCA, vena contracta area; VCW, vena contracta width by 2D colour Doppler; VTI, velocity time integral of the aortic regurgitant jet by CW Doppler.
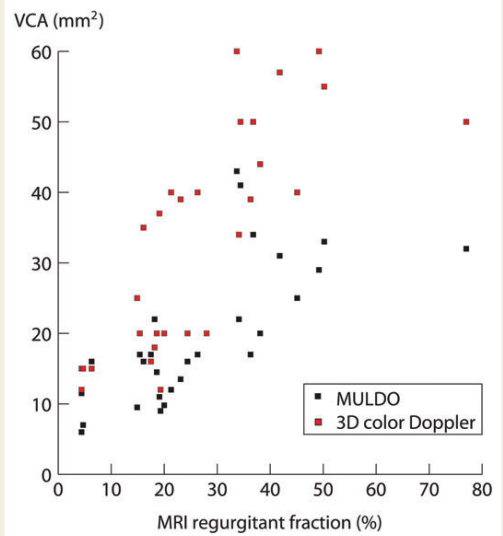
Perez de Isla et al.[8] who demonstrated better accuracy with 3D colour Doppler VCA than 2D Doppler to assess AR severity, defined by MRI parameters. The regurgitant volume calculated from multibeam HPRF colour Doppler and CW Doppler overestimated the severity of AR compared with MRI, but the agreement between the methods was better for those with MRI regurgitant volume of ≥30 mL compared with those with MRI regurgitant volume of <30 mL. The regurgitant volume calculated from 3D colour Doppler and CW Doppler significantly overestimated the severity compared with MRI, and the limits of agreement between MRI and 3D colour Doppler was wider than between MRI and multibeam HPRF colour Doppler. In a recent study, Ewe et al.[20] found excellent agreement between 3D colour Doppler and MRI. These results differed from ours, for both 3D methods. There may be several reasons for this. In our study, the heart rate during MRI was slightly higher than during Doppler, which could contribute to some overestimation by both 3D methods. We measured VTI by CW Doppler from the apical view in central AR and the parasternal view in eccentric AR, as recommended.[1] Ewe et al. measured VTI from the apical view in eccentric and central AR. Ultrasound beam

Figure 4: Comparison of the VCA by multibeam HPRF colour Doppler (MULDO) and 3D colour Doppler vs. MRI regurgitant fraction. The Spearman's rank correlation was $r_s = 0.77$ and 0.83, respectively.
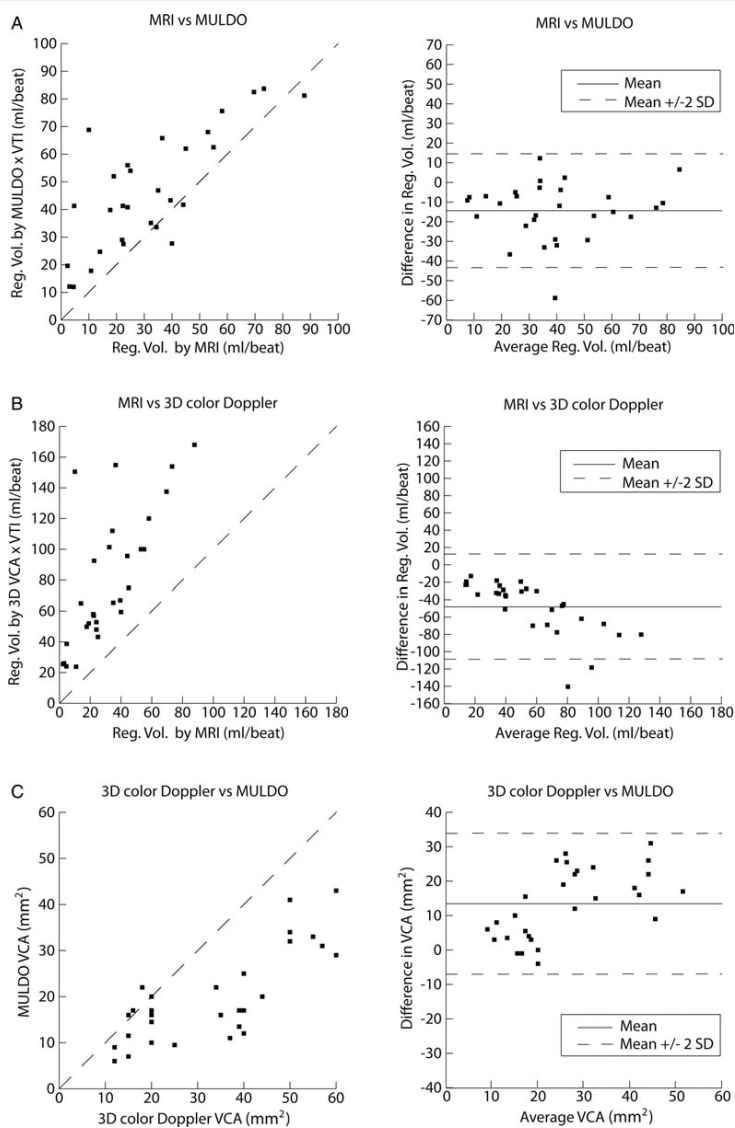
Figure 5: The correlation and Bland−Altman plots of (*A*) the regurgitant volume (Reg.Vol.) measured by MRI and multibeam HPRF colour Doppler (MULDO) VCA × VTI, (*B*) the regurgitant volume (Reg.Vol.) measured by MRI and 3D colour Doppler VCA × VTI, and (*C*) VCA by 3D colour Doppler and multibeam HPRF colour Doppler.

misalignment can underestimate the VTI and the regurgitant volume. We performed the 3D colour Doppler acquisition from the parasternal view, and Ewe *et al.* used both the apical and parasternal views. We used the frame with the largest VCA, while Ewe *et al.* used the frame 'with the most relevant lesion size'. Furthermore, scanners and probes were different.

The VCA measured by 3D colour Doppler was significantly higher than by multibeam HPRF colour Doppler, and this explains the

differences in regurgitant volume by the two 3D methods in our study. There were several differences between these methods. Most importantly, the HPRF and clutter filter in the proposed method enabled the isolation of the high-velocity core of the vena contracta, in contrast to regular low-PRF colour Doppler, which also measured low-velocity entrained blood. The clutter filter cut-off frequency corresponded to 1.5 m/s for multibeam HPRF colour Doppler and 0.2 m/s for 3D colour Doppler. Secondly, in

Table 3 The mean differences between regurgitant volume by MRI and multibeam HPRF colour Doppler (MULDO) in subgroups

MRI vs. MULDO Reg.Vol. (mL)	Mean difference	95% CI
In central jets ($n = 13$)	−20.3	−31.2 to −9.4
In eccentric jets ($n = 16$)	−9.6	−14.4 to −4.7
In those with MRI Reg.Vol. of <30 mL ($n = 15$)	−20.7	−29.0 to −12.5
In those with MRI Reg.Vol. of ≥30 mL ($n = 14$)	−7.6	−13.9 to −1.2
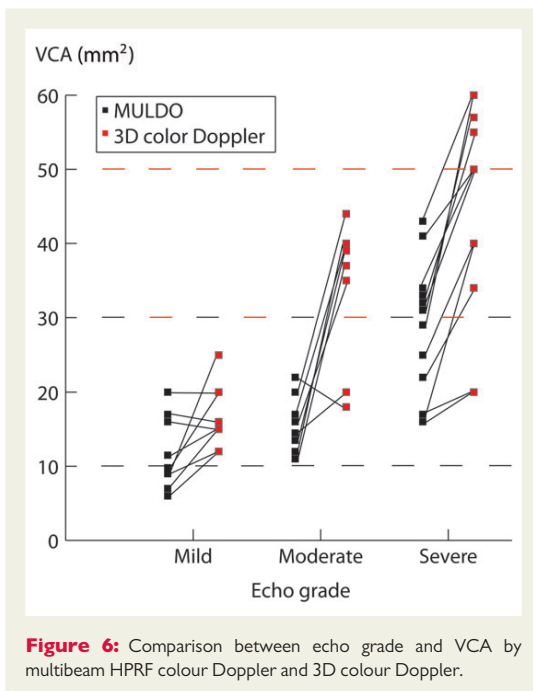
Figure 6: Comparison between echo grade and VCA by multibeam HPRF colour Doppler and 3D colour Doppler.

3D colour Doppler, it was common to reduce the lateral resolution somewhat to gain some extra frame rate. The multibeam HPRF colour Doppler algorithm automatically compensated for the overestimation due to limited lateral resolution as long as the reference beam was within the vena contracta jet. Altering the display parameters such as gain and tissue priority during acquisition did not affect the multibeam HPRF colour Doppler data. The 3D colour Doppler was gain-dependent, and the width and area of a regurgitant orifice could be overestimated with approximately one beam width in each direction (azimuth and elevation). Furthermore, each recording of multibeam HPRF colour Doppler consisted of 10−15 heartbeats of real-time full-volume datasets, while the 3D colour Doppler dataset was reconstructed from several heartbeats of subvolumes to make a full volume, which can predispose to stitching

artefacts and overestimation of the VCA. The measurements of the Doppler power in all the diastolic frames in a multibeam HPRF colour Doppler recording were fully automatic, and the median value of these measurements was chosen as the VCA. The 3D colour Doppler dataset post-processing on the other hand consisted of sequential cropping of the regurgitant jet, manual tracing, and the frame with the largest area of the vena contracta was chosen, similarly to VCW.[1] Dynamic variations of the regurgitant orifice area could be another contributing factor for the differences in the VCA measurements. Using the frame with the largest VCA in 3D colour Doppler, with a frame rate of ∼15 volumes per second, and the median VCA of several measurements in multibeam HPRF colour Doppler, with a frame rate of ∼7−10 volumes per second, could enhance this confounding effect.

Semi-quantitative echo Doppler methods are part of an integrated approach to grade AR.[1] Chin et al.[7] demonstrated good correlation between 3D colour Doppler VCA and AR severity assessed by Doppler methods. They proposed cut-off values for 3D colour Doppler VCA of 30 and 50 mm^2 for mild and severe AR, respectively, and we used these cut-offs to assess agreement between AR echo grade and 3D colour Doppler VCA. To assess agreement between multibeam HPRF colour Doppler VCA and AR echo grade, we chose the reference values for the ERO area by quantitative Doppler. Agreement between AR echo grade and VCA by both 3D colour Doppler and multibeam HPRF colour Doppler, however, based on different reference values, was moderately good.

Limitations

From MRI aortic phase contrast, we calculated regurgitant volume and fraction, but there are different reference values for regurgitant fraction to assess severity.[14,15] The Nyquist limit of ∼3 m/s for multibeam HPRF colour Doppler is usually lower than the maximum aortic regurgitant jet velocity. However, as long as the peak velocity is less than two times the Nyquist velocity and the direction of the jet is known, the velocity of the regurgitant jet can be determined unambiguously. The size of the ROI is small to achieve this Nyquist limit. Unlike 3D colour Doppler with a large colour Doppler sector where you can do the analysis and cropping of the vena contracta online, correct positioning of the small ROI of multibeam HPRF colour Doppler in the vena contracta region is essential during acquisition. In 7 of the 36 subjects in this study, we were not able to acquire representative Doppler data, because of difficulty in identifying the vena contracta, misalignment or incorrect positioning of the small ROI outside the vena contracta, or possibly if the valve was at a depth which made one of the transmitted HPRF pulses too close (in time) to the receiver, such that it was saturated. Other clinical limitations are inability to hold the breath for ∼10−15 s causing respiratory movements and displacement of the ROI during acquisition, poor acoustic windows, or heavy valvular calcification causing attenuation of the Doppler signals. Owing to the current frame rate, tachyarrhythmia can as well be a limitation.

Previous studies have demonstrated that multibeam HPRF colour Doppler using the semi-automatic approach overestimates mild regurgitation.[12,13] This is also in correspondence with current findings in AR for this fully automatic approach. Acquisition parameters such as transmit frequency and pulse repetition frequency will affect the lateral resolution and the Nyquist limit. Multibeam HPRF colour

Doppler will overestimate the VCA when the regurgitant orifice is small relative to the reference beam and when the reference beam is not entirely within the regurgitant orifice.

The frame rate of ∼7–10 volumes per second is too low to acquire accurate VTI from the multibeam HPRF colour Doppler data. To quantify aortic regurgitant volume, we measured VTI separately by CW Doppler and VCA by multibeam HPRF colour Doppler. Using different probes and separate acquisitions raise the possibility for differences in beam alignment and thus error in calculating the regurgitant volume. However, we used the parasternal window in eccentric jets and the apical window in central jets, respectively, for both acquisitions to try to minimize such errors.

Further perspectives

Future generations of 3D probes are expected to have improved resolution, which will make it possible to obtain better estimates for the calibration beam necessary for multibeam HPRF colour Doppler. The trend of plane wave imaging promises 'ultrafast' frame rates, but with some reduction in spatial resolution. With an increased frame rate, regurgitant volume could be derived directly from the multibeam HPRF colour Doppler dataset. Large transducers with numerous parallel beam formers will probably lead the way to creative combinations of the raw HPRF Doppler data that might solve some of the current limitations. With 3D TEE probes, there will be in closer approximation to the valvular defect, thus increased resolution, less reverberation, and better estimate of the VCA. Studies are needed to assess clinical outcome.

Conclusion

Quantification of AR with multibeam HPRF colour Doppler was feasible. Multibeam HPRF colour Doppler with automatic calculation of the VCA overcomes many of the limitations of 3D colour Doppler. There was good agreement between regurgitant volume measured by MRI and multibeam HPRF colour Doppler in patients with moderate to severe AR, while agreement for those with mild AR was modest. Agreement between VCA and AR echo grade was moderately good.

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