Automated Evaluation of Aortic Valve Stenosis from Phase-Contrast Magnetic Resonance Data

Emilie Bollache[1], Carine Defrance[1,2], Ludivine Perdrix[2], Alban Redheuil[1,3], Benoit Diebold[2], Elie Mousseaux[1,3], Nadjia Kachenoura[1]

[1]INSERM U678 / UPMC Univ Paris 6, Paris, France
[2]Echocardiography Department, European Hospital Georges Pompidou, APHP, Paris, France
[3]Cardiovascular Imaging Department, European Hospital Georges Pompidou, APHP, Paris, France

Abstract

Accurate quantification of aortic valve stenosis (AVS) is crucial for relevant patients management. We hypothesized that automated analysis of phase-contrast cardiovascular magnetic resonance (PC-CMR) data might provide accurate AVS evaluation in agreement with the well established transthoracic echocardiography (TTE). We studied 74 subjects (53 AVS patients, 21 controls) who had TTE and CMR on the same day. PC-CMR analysis included dynamic segmentation of left ventricular outflow tract (LVOT) and aortic valve, as well as hemodynamic parameters extraction. We performed 3 estimates of aortic valve area (AVA): AVA_{CMR1} based on Hakki's formula, AVA_{CMR2} based on continuity equation, AVA_{CMR3} simplified continuity equation=LVOT peak flow-rate/aortic peak velocity. Our analysis was reproducible (inter-operator variability<4.56±4.40%). Strong correlations were found for comparisons between CMR and TTE aortic peak velocities and mean gradients (r=0.92, r=0.86 respectively, p<0.0001) and between CMR and TTE AVA (r>0.90, p<0.0001). PC-CMR was able to detect severe AVS (accuracy>92%) as defined by TTE. Our automated AVS evaluation would enhance CMR usefulness for comprehensive evaluation of AVS, while combining this valuable information with myocardial functional and structural findings.

1. Introduction

Aortic valve stenosis (AVS) has become the most frequent cardiac valvular disease [1] and its prevalence is unceasingly increasing with population ageing. Aortic valve area (AVA) is commonly used to evaluate AVS severity [2]. Indeed, a significant reduction in AVA gradually induces hemodynamic changes (in transvalvular aortic velocities and pressure gradients), which have deleterious effects on left ventricular (LV) function and are associated with adverse cardiovascular outcomes [2]. Despite some technical limitations, transthoracic Doppler echocardiography (TTE) is commonly used in clinical routine for the evaluation of AVS. Furthermore, several studies demonstrated the usefulness of cardiovascular magnetic resonance (CMR) in the non-invasive evaluation of AVS by: 1) planimetric analysis of anatomical images [3]. However planimetry is prone to measurement errors, especially in severe AVS, because of voxel size relative to the area, low signal in calcifications as well as within flow turbulences close to the leaflets borders, and irregularity of the stenotic orifice shape. 2) Analysis of velocity-encoded images using continuity equation [4-5] or Hakki's formula [6], derived from Gorlin equation. However, analysis of phase-contrast (PC) CMR data was mostly based on manual delineation, which is subjective and time-consuming. In addition, some studies estimated LV outflow tract (LVOT) area from its diameter [4]. Although this strategy complies with TTE measurements, it does not correspond to the LVOT ellipsoid anatomy and does not take full advantage of PC-CMR data. Indeed, an adequate combination of such data with an accurate segmentation would enable a direct estimation of LVOT area and thus stroke volume.

Accordingly, our objectives were: 1) to design an automated analysis of PC-CMR data, which would enable an accurate and reproducible evaluation of AVA and the underlying transvalvular aortic velocities and gradients, and 2) to test the ability of our method to characterize AVS and its severity in comparison with TTE.

2. Methods

2.1. Study population

We studied a group of 74 subjects, including 53 patients (33 males, age: 75±14years) with AVS and 21 healthy subjects (10 males, age: 50±17years). All subjects had TTE and CMR exams on the same day.

TTE was performed using a GEMS Vivid7 system. Optimal velocity envelope and true maximal transvalvular aortic velocity ($Vmax_{AO}$) were obtained

using continuous Doppler waves from multiple imaging windows. LVOT velocity profile was obtained using apical 5-chamber view by a careful placement of the pulsed wave Doppler sample volume immediately below the aortic valve. LVOT diameter (D) was measured and provided LVOT area, assuming its circular shape: $LVOTarea=\pi \cdot D^2/4$. Systolic velocity time integrals of blood flow were calculated for LVOT (VTI_{LVOT}) and aortic valve (VTI_{AO}). Mean transvalvular aortic pressure gradient was calculated using the modified Bernoulli equation ($\Delta P=4V^2$). Continuity equation was used to assess AVA: $AVA_{TTE}=(LVOTarea \cdot VTI_{LVOT})/VTI_{AO}$. Indexed LV mass (LVMi) and LV ejection fraction (LVEF) were also calculated using TTE.

CMR was performed using a 1.5T GE system with cardiac phased array coil (8 channels). LVOT cine images were acquired, during breath-holding, using steady state free precession (SSFP) sequence in 2 orthogonal planes, and enabled visualization of the systolic jet originating from the aortic valve. These datasets helped positioning velocity-encoded acquisitions that were performed with retrospective gating during breath-holding on cross sectional planes perpendicular to the jet, at the level of LVOT just below the aortic annulus, and 5 mm above the level of tips of the opened aortic leaflets. Averaged scan parameters for velocity-encoded acquisitions were: repetition time=4.3ms, echo time=2.1ms, flip angle=20°, number of excitation=1, slice thickness=8mm, pixel spacing=1.9mm, acquisition matrix=256x128, views per segment=2, effective temporal resolution=17ms. Encoding velocity was Venc=2m/s for LVOT acquisition and for aortic valve acquisitions of healthy subjects, and 5m/s for aortic acquisitions when AVS was suspected.

2.2. PC-CMR image analysis

CMR data analysis was performed by an operator blinded to TTE findings, using a custom software, which included an automated segmentation of PC velocity images based on pixels connectivity in terms of velocity sign. This velocity sign was defined by the local direction of the through-plane blood flow. After rough manual delineation of the structure of interest on a single phase, the segmentation was applied throughout the cardiac cycle to automatically detect blood flow patterns in both LVOT and aortic valve (Figure 1A,C). This segmentation was specified to take into account the presence of several orifices that can be observed in case of severe AVS.

Segmentation enabled the estimation of mean and maximal velocity and flow-rate curves throughout the cardiac cycle. To reduce the effect of noise, maximal velocities were calculated for each phase as the average of velocities greater than 95% of the maximal velocity within the segmented region of interest while excluding boundary pixels. Aortic maximal ($Vmax_{AO}$) and mean velocity peaks and LVOT flow-rate peak ($Qmax_{LVOT}$) as well as the end of systolic phase were estimated using automated peak detection and slope interpolation. Aortic velocity time integral (VTI_{AO}) and LVOT stroke volume (SV_{LVOT}) were automatically calculated by integrating during systole aortic maximal velocity and LVOT flow-rate curves, respectively. Cardiac output (CO) was estimated by combining SV_{LVOT} and cardiac cycle duration. Finally, systolic transvalvular mean ($\Delta Pmean_{AO}$) and maximal ($\Delta Pmax_{AO}$) pressure gradients were calculated using the simplified Bernoulli equation.

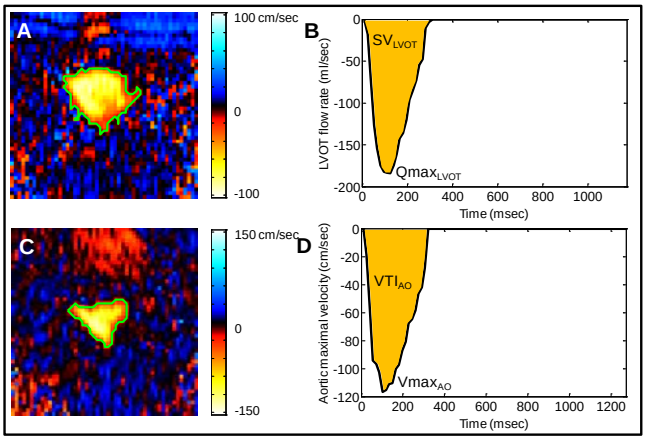

Figure 1. Examples of segmentation of PC-CMR images for LVOT (A) and aortic flow (C) on a single phase, as well as the derived LVOT flow-rate (B) and aortic maximal velocity (D) curves throughout the cardiac cycle.

After estimation of these LVOT and aortic parameters (Figure1B,D), AVA was calculated using 3 methods: 1) using Hakki's formula $AVA_{CMR1}=CO/\sqrt{\Delta Pmax_{AO}}$, 2) using continuity equation $AVA_{CMR2}=SV_{LVOT}/VTI_{AO}$, 3) using simplified continuity equation based on velocity and flow-rate peaks rather than their time integrals: $AVA_{CMR3}=Qmax_{LVOT}/Vmax_{AO}$. This method is commonly used in clinical routine with TTE. Our hypothesis was that using a single phase would introduce less measurement errors than using time integrals, since velocity to noise ratio of the PC-CMR velocity image at peak velocity is higher than during early systole and because accuracy in estimating velocities close from Venc is higher than velocity estimates close to zero.

2.3. Variability measurements

Data of 16 patients and 5 controls were analyzed by 2 independent operators to assess inter-operator variability, in terms of hemodynamic parameters and AVA estimates.

2.4. Statistical analysis

Values are reported as mean±standard deviation. For comparison between controls and AVS patients TTE and PC-CMR measurements, a non-parametric Mann-

Whitney test was used and a p value<0.05 was considered as significant. Correlations between CMR and TTE measurements and their significance were assessed using Pearson's correlation test. Degree of agreement between methods was assessed by Bland-Altman analysis. Sensitivity, specificity and accuracy of CMR detection of severe stenosis, as defined using TTE measurements (AVA_{TTE}<1cm² or TTE $\Delta Pmean_{AO}$>40mmHg) were calculated using receiver operating characteristic (ROC) analysis. Areas under curves (AUC) and abnormality thresholds were provided. Inter-operator variability was calculated for each subject as the absolute difference of repeated measurements in percentage of their mean.

3. Results

Patients and controls characteristics and LV functional parameters as well as TTE and CMR hemodynamic parameters are summarized in Table 1. TTE indicated that 81% of the AVS patients had a severe stenosis.

Table 1. Subjects characteristics, TTE and CMR indices.

	53 AVS	21 Controls	p value
LVEF (%)	59±14	66±5.8	0.07
LVMi (g/m²)	112±33	79±23	<0.0001
TTE parameters			
$Vmax_{AO}$ (m/s)	4.21±1.05	1.30±0.31	<0.0001
$\Delta Pmean_{AO}$ (mmHg)	45±20	3.6±1.7	<0.0001
VTI_{LVOT} (cm)	22±5.9	21±4.6	0.62
VTI_{AO} (cm)	97±31	26±6.5	<0.0001
AVA_{TTE} (cm²)	0.87±0.44	2.96±0.59	<0.0001
CMR parameters			
$Vmax_{AO}$ (m/s)	3.82±1.24	1.24±0.27	<0.0001
$\Delta Pmean_{AO}$ (mmHg)	27±15	2.9±1.3	<0.0001
SV_{LVOT} (ml)	62±20	66±23	0.7
VTI_{AO} (cm)	67±24	23±6.5	<0.0001
AVA_{CMR1} (cm²)	0.64±0.30	2.03±0.52	<0.0001
AVA_{CMR2} (cm²)	0.96±0.45	2.85±0.75	<0.0001
AVA_{CMR3} (cm²)	0.93±0.46	3.13±0.58	<0.0001

All developments were integrated in a custom interface developed on Matlab (Mathworks, Natick, MA, USA), which was used to analyze PC data. For each subject, processing time of valvular and LVOT levels was less than 3 minutes on a personal computer (CPU 2.67GHz, 3Gb RAM). This processing time is equivalent to those of direct planimetry on a single selected SSFP image, but much lower than the 20 minutes needed for manual delineation of flow patterns on the whole cardiac cycle.

Variability measurements of CMR 3 AVA and LVOT and aortic hemodynamic parameters resulted in high reproducibility (inter-operator variability<4.56±4.40%).

Table 2 summarizes results of the comparison between CMR and TTE parameters. Although CMR underestimated hemodynamic indices when compared to TTE values, high correlations were found between the two measurements. Moreover, a strong correlation was obtained for the comparison of AVA_{CMR1}against AVA_{TTE}, despite the significant differences that were increased for higher values of AVA. Finally, AVA_{CMR2} and AVA_{CMR3} provided higher correlation coefficients and very low mean biases when compared to AVA_{TTE}. These low differences were also reflected by the slopes close to 1 obtained from linear regressions of comparisons between AVA_{CMR2} (0.90), AVA_{CMR3} (1.01) and AVA_{TTE}.

Table 2. Comparisons between CMR and TTE indices.

	r	p value	Bland-Altman bias
$Vmax_{AO}$	0.92	<0.0001	-0.29±0.62m/s
$\Delta Pmean_{AO}$	0.86	<0.0001	-12±15mmHg
AVA_{CMR1}	0.90	<0.0001	-0.45±0.52cm²
AVA_{CMR2}	0.94	<0.0001	0.01±0.38cm²
AVA_{CMR3}	0.97	<0.0001	0.09±0.28cm²

Table 3 indicates the ability of AVA values assessed from PC-CMR data to detect severe AVS, as defined by TTE, with high sensitivity, specificity and accuracy.

Table 3. Ability of CMR AVAs to detect AVS severity.

	Sens. (%)	Spec. (%)	Accuracy (%)	AUC	Threshold (cm²)
AVA_{CMR1}	98	84	92	0.97	0.95
AVA_{CMR2}	95	94	94	0.99	1.13
AVA_{CMR3}	98	90	95	0.98	1.21

4. Discussion

Accurate evaluation of stenosis severity is crucial for clinical decision making in patients with AVS. Several indices such as AVA and transvalvular peak velocities and mean pressure gradients have been proposed to assess AVS severity [2]. In our study, an automated segmentation of LVOT and aortic flow patterns from PC-CMR data was designed and combined with an automated analysis of velocity and flow-rate curves. The whole process was tested on controls and patients with AVS, providing reproducible indices that were highly correlated with those provided by TTE and able to detect severe AVS as defined by TTE.

An original feature of our method relies on the segmentation process and its ability to segment various flow patterns regardless of their size, shape and temporal variation in geometry during the cardiac cycle. Indeed, thanks to the local connectivity of pixels in terms of velocity sign property, our segmentation was successfully used in our study to detect LVOT and aortic flow. Of note, for aortic flows, our segmentation algorithm was designed to take into account multiple orifices. This situation occurred in our cohort because of the high prevalence of patients with severe AVS. Moreover, reproducibility analysis of our method, in terms of parameters evaluation, resulted in low inter-operator variability. Finally, the automated segmentation of LVOT enabled a direct estimation of its stroke volume

conversely to most of PC-CMR studies, which estimated LVOT area from its diameter [4] while assuming a circular shape that was found to be erroneous [5].

Our process for PC-CMR aortic valve and LVOT data analysis enabled the estimation of transvalvular aortic peak velocities and mean gradients as well as AVA. For velocity and gradient measurements, high correlations were obtained for comparisons between PC-CMR and TTE. For AVA measurements, the 3 CMR methods resulted in high correlations when compared against TTE, with a slight superiority for methods based on the continuity equation. This superiority was expected since: 1) as for TTE, AVA_{CMR2} and AVA_{CMR3} were also calculated using the continuity equation, and 2) Hakki's formula includes simplifications inducing an underestimation of AVA_{CMR1}, which was previously described in another CMR study [6]. Hypothesis underlying this underestimation is that AVA calculated by Hakki's formula is conversely proportional to maximal transvalvular gradient, which is commonly estimated using the simplified Bernoulli equation while neglecting sub-valvular maximal velocity that was assumed to be well under valvular velocity. Thus, Hakki's formula reliability is jeopardized for subjects with nearly normal AVA in which the assumption of widely unbalanced sub-valvular and valvular velocities becomes erroneous.

Estimation of AVA using continuity equation has been reported in few previous PC-CMR studies [4-5]. These studies proposed various formulations of continuity equation, which can be mainly distinguished by the methodology used to calculate LVOT stroke volume. The best results were obtained when this volume was calculated from PC-CMR data [5]. Although a direct comparison is not possible because of differences in databases, comparison of our AVA findings to those of Garcia et al. [5] indicated a slight superiority of our results. Indeed, they reported a correlation coefficient $r=0.92$ and bias=$0.06\pm0.29 cm^2$ for AVA estimations in a group of 31 patients with AVS and 7 healthy subjects. Moreover, coefficients of variability obtained for our three AVA evaluation techniques were lower than those of 7±5% reported by Garcia et al. Of note, the larger proportion of patients with severe AVS, and thus with a complex aortic valve morphology, that were included in our study, confirmed the robustness of our method.

Another continuity equation based on a single systolic phase was tested in our study, resulting in the highest correlations and also in low bias for AVA comparison against TTE. This PC-CMR approach has never been compared against TTE. The slight superiority of this latter technique might be due to the fact that differences between PC-CMR and TTE in velocity and flow-rate estimations were less significant in a single phase at peak velocity than when calculating time integrals. Indeed, time integrals result in accumulated errors especially when velocities are far from encoding velocity.

ROC analysis used for the evaluation of the ability of CMR techniques to detect severe AVS as defined by TTE resulted in the highest sensitivity, specificity and accuracy values when considering continuity equation-based PC-CMR AVA measurements.

Our study lacks a reliable gold standard, however there is no such method for in vivo evaluation of AVA. The invasive evaluation of AVA by applying the Gorlin formula to catheterization data could be used as an alternative to TTE in our study. However, these data were not available for our patients since such invasive exam was not approved by the local institutional review board because of the associated increased risk for patients especially for those with heavily calcified valves. Moreover, such invasive measurements might be prone to pressure recovery effects within the aortic valve.

Our automated method was fast, reproducible and successfully used on PC-CMR data of 74 subjects, including a large proportion of patients with severe AVS. Aortic valve peak velocities, mean transvalvular pressure gradients and AVA estimated in our study were highly correlated with TTE measurements. In addition, PC-CMR AVA estimations based on the continuity equation presented a slight superiority in terms of correlation with TTE as well as ability to accurately detect AVS severity. The addition of PC-CMR evaluation of aortic valve hemodynamic and AVA to the well established CMR evaluation of LV hypertrophy, concentric remodeling, and myocardial fibrosis might be clinically useful.

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Address for correspondence. Emilie Bollache - Inserm U678, 91 Bd de l'Hôpital, Paris, France, emilie.bollache@imed.jussieu.fr