

# Left Ventricular Outflow Tract Planimetry by Cardiovascular Magnetic Resonance Differentiates Obstructive from Non-Obstructive Hypertrophic Cardiomyopathy

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## ABSTRACT

The relation to the pressure gradient as assessed by echocardiography and the CMR-derived planimetry of the LVOT is not known, no values for the differentiation of obstruction exist. We studied 37 patients with hypertrophic cardiomyopathy and 14 healthy controls using standard sequences with 3D coverage of the left ventricular outflow tract. A cutoff value of 2.7 cm<sup>2</sup> identified obstruction as defined by echocardiography with 100% accuracy. CMR planimetry at rest is a promising tool to evaluate patients with hypertrophic cardiomyopathy.

## INTRODUCTION

A crucial step in the diagnostic work-up of patients with hypertrophic cardiomyopathy (HCM) is to differentiate between obstructive and non-obstructive forms of the disease. In patients with obstruction of the left ventricular outflow tract (LVOT), the Doppler echocardiography-derived pressure gradient (PG) is currently the accepted approach (1, 2); however, it is limited by the variability of the measurements (3) and the need to apply stress to detect the 'latent' obstruction (4). Furthermore,

PG measurements vary significantly in relation to hemodynamic conditions (5, 6). More than 20 years ago, Spirito et al. (7) introduced the planimetry of LVOT-area by transthoracic echocardiography. The method however was not applicable in clinical routine due to technical limitations of available ultrasound technique. Recently, 3D echocardiography partly overcame this limitation (8), yet complex image processing is needed (9), and a significant fraction of patients may not be evaluated due to poor image quality (8). Transesophageal 3D-echocardiography was also used to measure the LVOT in HCM patients before and after myectomy (10). However, the technique is relatively invasive, frequently requires sedation and is not very well tolerated by many patients. Finally, in all echocardiographic approaches, the actual position of the obtained views cannot be easily controlled for accuracy.

A unique feature of CMR is the ability to provide non-invasive, reproducible and direct planimetric quantification of complex-shaped structures such as stenotic valves (11–13). We have shown the feasibility and relevance of LVOT planimetry using CMR (14). The results correlate well with the clinical severity of the disease both before and after septal artery embolization.

Yet, there are no reports using CMR or 3D echocardiography that attempted to assess the LVOT area in the full scale of HCM, i.e., obstructive, latent obstructive and non obstructive HCM. Furthermore, there are neither CMR-LVOT area

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measurements from healthy subjects available nor a validation against the well-established PG measurements in HCM patients. CMR assessment of the LVOT area would allow for relating obstruction to tissue changes such as edema or focal fibrosis.

This study was designed to measure LVOT area by CMR in different forms of HCM and healthy subjects in comparison to pressure gradient measurements as the standard technique.

## METHODS

### *Patients*

Thirty-seven HCM patients were consecutively enrolled. HCM was defined based on the echocardiographic demonstration of a hypertrophied (wall thickness of 15 mm or more), non-dilated left ventricle in the absence of another related cardiac or systemic disorder. The clinical status of the patients was classified depending on the degree of dyspnea following the classification of the New York Heart Association (NYHA). Exclusion criteria were atrial fibrillation with large RR-interval-variations, contraindications to CMR and poor ultrasound imaging conditions.

### *Control group*

Fourteen healthy subjects (10 males,  $28 \pm 10$  years) with no current or previous cardiovascular disorders and with normal ECG served as our control group. Those subjects underwent only CMR but not Doppler echocardiography.

### *Echocardiography*

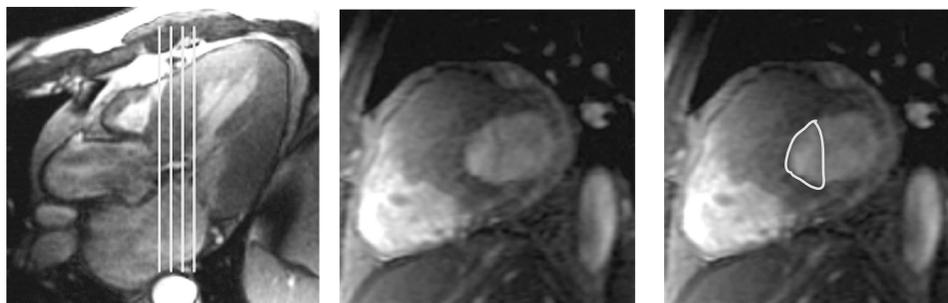
Echocardiographic examinations were performed on a commercially available instrument (Acuson Sequoia C256, Siemens Medical Solutions, Erlangen, Germany) with a 3.2 MHz transducer. Left-ventricular dimensions, ejection fraction and wall thickness of the anteroseptal and posterior wall were measured in the parasternal long axis according to the guidelines of the

American Society of Echocardiography. Maximum thickness of the septal wall was measured in the apical four-chamber view using 2D-echocardiography. The maximum velocity within the LVOT was measured at rest and after Valsalva maneuver in the five-chamber view, applying multiple PW- and CW-Doppler-measurements. We cautiously tried to avoid contamination of the Doppler-signal by flow from mitral regurgitation or flow through the aortic valve. The maximum PG was calculated from velocity measurements.

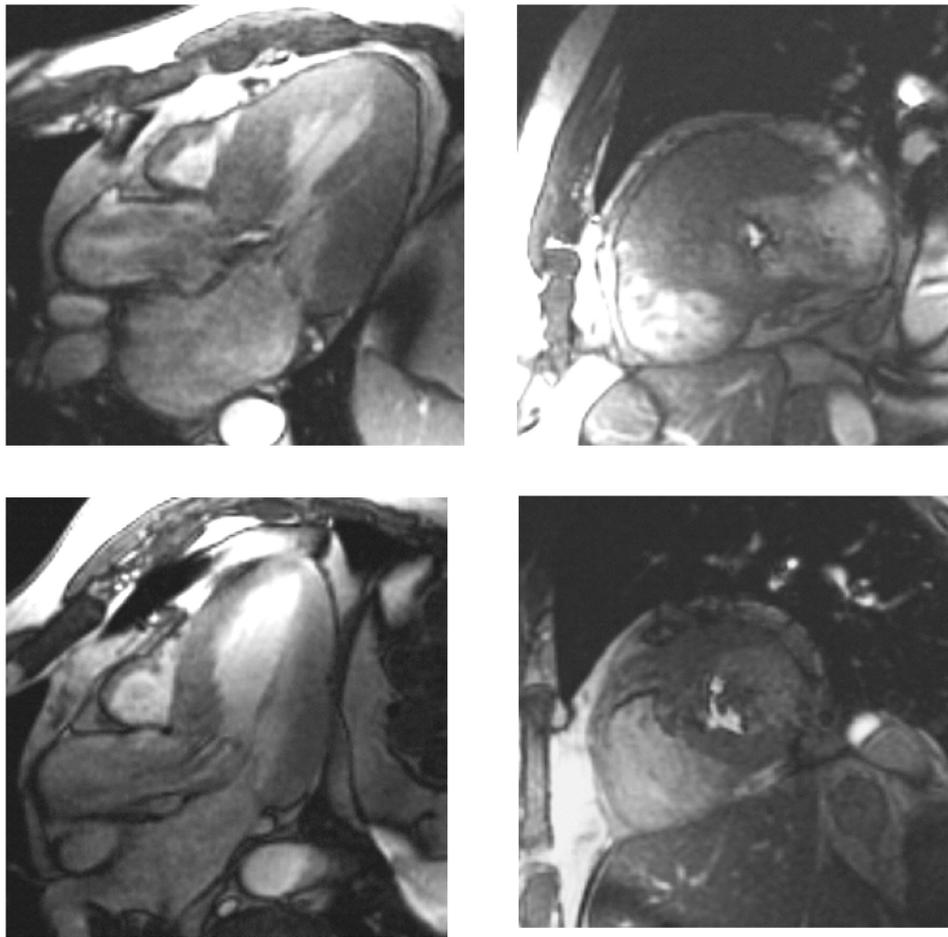
Patients were divided into 3 groups based on their PG: a) non-obstructive HCM (HNCM) (PG < 30 at rest and after provocation, n = 12); b) latent obstructive HCM (LHOCM) (PG < 30 at rest and >30 after provocation, n = 8) and c) obstructive HCM (HOCM) (PG > 30 at rest, n = 17).

### *CMR*

CMR studies were performed in a 1.5 Tesla system (Signa CV/i, GE medical systems, Milwaukee, WI, USA) using a four-element phased array coil with the patient in the supine position. Breath-hold, real-time scout images and a subsequent series of breath-hold gradient-echo images (SSFP/steady-state free precession, TR 4.5 ms, TE 1.8 ms, matrix:  $256 \times 192$ , FOV:  $32 \times 32$ – $38 \times 38$  cm, number of phases: 20–30) were used for localization of the LVOT (Fig. 1). Based on long-axis views of the LVOT, a stack of cross-sectional views was obtained to cover the whole LVOT (cine mode, 6–8 slices, slice thickness 5 mm, no gap). The LVOT in HCM was defined as the whole region bounded by the anterior mitral valve leaflet and the septal wall. The smallest LVOT area obtained in these slices was measured during systole, including the effect of the systolic movement of the anterior mitral valve leaflet. The smallest area during systole was accepted as hemodynamic relevant and was documented. A reader blinded to other subject-related data manually traced the LVOT area using the anterior mitral valve leaflet and the septum as anatomical borders. Figure 2 shows the LVOT in different forms of disease.



**Figure 1.** Localization and planimetry of the left ventricular outflow tract - Stepwise localization of LVOT: Left: LVOT defined by the interventricular septal wall and the anterior leaflet of the mitral valve with lines visualizing the slices for coverage of the LVOT. It is demonstrated in a patient with HNCM; Middle: short axis through the LVOT; Right: short axis through the LVOT with region of interest giving the quantified area of the LVOT.



**Figure 2.** Alteration in size of the LVOT area in patients with obstructive forms of hypertrophic cardiomyopathy: Top: HOCM signal void to obstruction in the whole LVOT (area = 1.0 cm<sup>2</sup>); Bottom: LHOCM signal void is also assessable (area = 1.9 cm<sup>2</sup>); In both: left: long axis view of the LVOT; right: short axis view of the LVOT.

### Statistics

All statistical tests were performed using a commercially available statistical program (SPSS 11 for Macintosh, Cupertino, CA, USA). Data are presented as mean  $\pm$  one standard deviation. Continuous variables were compared using ANOVA. Correlations between continuous variables were tested using linear regression and the Pearson correlation coefficient. A p-value of less than 0.05 was considered significant. Non-parametric data were compared by Mann Whitney U-test, Receiver operated curves were used to define the cutoff values of LVOT area to differentiate patients from controls as well as obstructive from non-obstructive HCM. As the gradient measure showed a non-linear relation to area, we applied a cubic root transformation prior to correlation analysis.

### RESULTS

Table 1 summarizes the patients' characteristics. The mean duration between echocardiography and CMR was  $5 \pm 6$  days.

Forty-three percent of the patients however underwent both examinations on the same day. LVOT was evaluable in all but one patient. CMR assessment of myocardial mass and volume could not be performed in 4 patients, due to incomplete coverage of the left ventricle.

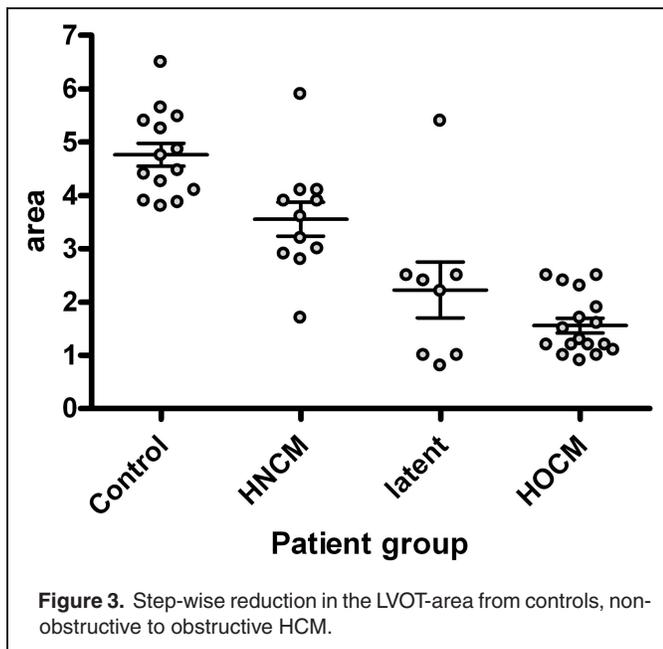
**Table 1.** Characteristics of the study's patient population

	Non-obstructive	Latent obstructive	Obstructive
Number of subjects	12	8	17
EF	71 $\pm$ 9%	76 $\pm$ 10%	79 $\pm$ 10%*
LVM	197 $\pm$ 51 g	207 $\pm$ 25 g	249 $\pm$ 78 g
LVM/height	1.2 $\pm$ 0.3 g/cm	1.2 $\pm$ 0.2 g/cm	1.5 $\pm$ 0.7 g/cm
Age	48 $\pm$ 15	57 $\pm$ 14	61 $\pm$ 12*
Male gender	67%	50%	53%

\*p < 0.05.

EF = ejection fraction.

LVM = left ventricular mass.

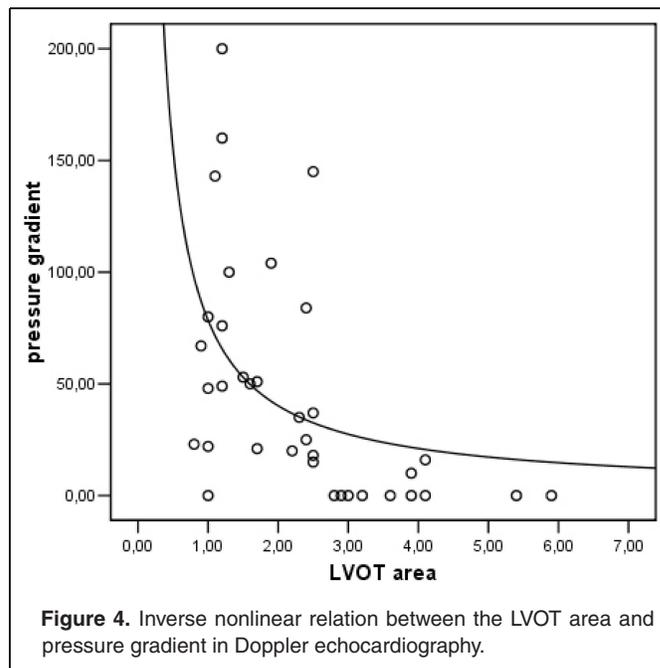


### LVOT area by CMR

Figure 3 shows the relation of the size of the LVOT area to the presence or absence of the pressure-gradient-defined obstruction. Compared to volunteers with a mean LVOT area of  $4.8 \pm 0.8 \text{ cm}^2$ , the area was significantly smaller in patients with HNCM ( $3.6 \pm 1.1 \text{ cm}^2$ ,  $p < 0.004$ ), LHOCM ( $2.2 \pm 1.5 \text{ cm}^2$ ,  $p < 0.002$ ) and HOCM ( $1.6 \pm 0.6 \text{ cm}^2$ ,  $p < 0.0001$ ), respectively. Patients with HNCM had significantly larger LVOT than latent ( $p = 0.013$ ) or HOCM ( $p < 0.0001$ ), respectively. When the latent obstructive and obstructive forms were considered together as obstructive HCM, significant differences in LVOT still existed between the obstructive and non-obstructive ( $1.8 \text{ cm}^2 \pm 1.0$  vs.  $3.6 \pm 1.1 \text{ cm}^2$ ,  $p < 0.0001$ ) forms of the disease. No significant difference was found between the LVOT in LHOCM and HOCM ( $p = 0.478$ ) (Fig. 3). The comparison of the mean values (Bland-Altman plots) in a representative sample showed an excellent agreement between readers (correlation = 0.97). Based on ROC analysis, a cutoff value of  $3.7 \text{ cm}^2$  could be shown to differentiate patients from controls (sensitivity 83%, specificity 100%, positive and negative predictive values 100% and 70%, respectively). On the other hand, a cutoff value of  $2.7 \text{ cm}^2$  was able to differentiate HOCM from HNCM with a sensitivity and specificity of 100%.

### Correlation between PG and LVOT

There was no significant relation of area or gradient with height and weight. Age showed a significant inverse correlation to area ( $r = -0.68$ ), even after restricting the analysis to patients only ( $r = -0.50$ ). There was no significant correlation between age and gradient ( $r = 0.22$ ). The correlation between area and gradient was  $-0.67$  and remained significant after correction for age (partial correlation  $r = -0.68$ ) (Fig. 4).



## DISCUSSION

This is the first report describing CMR planimetry of the LVOT in different forms of HCM compared to healthy subjects. We could verify the step-wise reduction of the LVOT area from HNCM, LHOCM to HOCM, as expected by the disease definition. These findings can be explained by the inverse relation between flow velocity and the size of the anatomic structure, mainly described by the smallest systolic LVOT area. Based on this theory, however, one would expect a linear correlation between LVOT area and PG, which was not the case neither in ours nor in previous reports using 3D echocardiography (8, 10). This is likely related to two factors: first, the susceptibility of PG measurements to minor changes in loading conditions (6) and/or the variability of PG measurement from day to day (3). This is especially true for LVOT areas with borderline hemodynamic relevance at rest. Second, based on simple considerations on flow dynamics in obstructed vessels, the linearity between flow velocity and a narrowed LVOT is expected to get lost once a 'critical' LVOT area range is reached. In such a case (likely to be accompanied by symptoms in HCM patients), small changes as induced by preload variations may lead to a significant increase of resistance and thus of measured pressure gradients.

The finding that the LVOT area was significantly reduced at rest in apparently non-obstructive forms of HCM (LHOCM and HNCM) deserves special attention. Panza et al. (15) found that a reduction of the LVOT diameter in children with HNCM was predictive of the future development of SAM and significant obstruction. Although extrapolation of these results to adult patients should be taken with care, it seems conceivable that a mild obstruction although not yet hemodynamically overt will have a relevant predictive value.

A LVOT cutoff value of  $3.7 \text{ cm}^2$  appears to offer a promising screening tool to rule out the disease whereas a LVOT value

of 2.7 cm<sup>2</sup> has an accuracy of 100% to differentiate obstructive from non-obstructive HCM. This value is larger than the 2.0 cm<sup>2</sup> identified by Qin et al. (8) using 3D echocardiography. The reason of this difference is most likely related to the PG cut-off value to define obstructive HCM. Whereas we used a value of 30 mmHg (1), Qin et al. defined obstruction as values above 50 mmHg.

### *Clinical implications*

An emerging role of CMR to evaluate HCM is being shaped with unique features to assess tissue structure and ventricular function (16–20). Planimetry of the LVOT area provides relevant additional information and may have an important role within a comprehensive CMR exam of HCM patients.

### *Limitations and technical considerations*

The major limitation of this study is the limited number of patients in the subgroups. The aim however was to validate the concept that LVOT is related to the degree of obstruction. Future studies in larger patient cohorts are definitely warranted. Due to the known day-to-day variation in PG measurements it would have been ideal to perform both Doppler and CMR on the same day. For logistical reasons, this demand was fulfilled in only 43% of our patients. Yet, the correlation between PG and LVOT area measurement remained significant even after correcting for the inter-study duration.

## CONCLUSION

CMR planimetry of the LVOT accurately differentiates obstructive from non-obstructive HCM without the need for hemodynamic provocation .

## ABBREVIATIONS

CMR = cardiovascular magnetic resonance  
HCM = hypertrophic cardiomyopathy  
HOCM = hypertrophic obstructive cardiomyopathy  
HNCM = hypertrophic non-obstructive cardiomyopathy  
LHOCM = latent hypertrophic obstructive cardiomyopathy  
LVOT = left ventricular outflow tract  
PG = pressure gradient  
Echo = echocardiography

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