Right ventricular systolic function in hypoplastic left heart syndrome: A comparison of manual and automated software to measure fractional area change

Hanna K. Ruotsalainen MD1,2 | Hannah R. Bellsham-Revell MBBS MD(res) MRCPCH3 | Aaron J. Bell MBChB MRCPCH3 | Jaana I. Pihkala MD PhD1 | Tiina H. Ojala MD PhD1,2 | John M. Simpson MD FRCP FESC3

1Department of Pediatric Cardiology, Children’s Hospital, University Hospital of Helsinki and University of Helsinki, Helsinki, Finland
2Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland
3Department of Congenital Heart Disease, Evelina London Children’s Hospital, London, United Kingdom

Correspondence
Tiina H. Ojala, Department of Paediatric Cardiology, Children’s Hospital, University Hospital of Helsinki and University of Helsinki, Helsinki, Finland.
Email: tiina.h.ojala@hus.fi

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Background: Quantitative echocardiographic assessment of right ventricular function is important in children with hypoplastic left heart syndrome (HLHS). The aim of this study was to examine the repeatability of different echocardiographic techniques, both manual and automated, to measure fractional area change (FAC) in patients with HLHS and to correlate these measurements with magnetic resonance imaging (MRI)-derived ejection fraction (EF).

Methods: Fifty-one children with HLHS underwent transthoracic echocardiography and cardiac MRI under the same general anesthetic as part of routine inter-stage assessment. FAC was measured from the apical four-chamber view using three different techniques: velocity vector imaging (VVI) (Syngo USWP 3.0; Siemens Healthineers), QLAB (Q-lab R 10.0; Philips Healthcare), and manual endocardial contour tracing (Xcelera, Philips Healthcare). Intra- and inter-observer variability was calculated using intra-class correlation coefficient (ICC). FAC was correlated with MRI EF calculated using a single standard method.

Results: Fractional area change had a good correlation with MRI-derived EF with an R value for VVI, QLAB, and manual methods of .7, .6, and .4, respectively. Intra- and inter-observer variability for FAC was good for automated echocardiographic methods (ICC>.85) but worse for manual method particularly inter-observer variability of FAC and end-systolic area. Both automated techniques tended to produce higher FAC values compared with manual measurements (P<.001).

Conclusion: Automation improves the repeatability of FAC in HLHS. There are some differences between automated software in terms of correlation with MRI-derived EF. Measurement bias and wide limits of agreement mean that the same echocardiographic technique should be used during the follow-up of individual patients.

Keywords
automation, fractional area change, hypoplastic left heart syndrome, myocardial function, velocity vector imaging
1 | INTRODUCTION

Hypoplastic left heart syndrome (HLHS) is the most common congenital heart defect resulting in a functionally single ventricle circulation. Current surgical management consists of staged palliation culminating in a total cavopulmonary connection. Right ventricular (RV) myocardial systolic dysfunction is a known risk factor for morbidity and mortality in children with HLHS throughout staged palliation emphasizing the importance of accurate and reproducible assessment of the function of the systemic RV.\(^1\)\(^-\)\(^4\)

Assessment of ventricular function in the functionally single ventricle circulation is a complex interaction of both diastolic function and systolic function. Quantification of RV function is more complicated than that of the left ventricle (LV) because of its complex anatomy. In patients with HLHS, there are significant variations in the size and morphology of the hypoplastic LV, and this can affect the ventricular-ventricular interaction. Because of these difficulties, measuring echocardiographic RV function in patients with HLHS has largely been based on subjective observation.\(^5\) However, repeatability and reliability of these subjective evaluations have been shown to be poor,\(^6\)\(^,\)\(^7\) and therefore, quantitative methods are needed. Magnetic resonance imaging (MRI), particularly ejection fraction (EF), is currently considered the noninvasive “gold standard” for the evaluation of RV systolic function in patients with HLHS.\(^8\) MRI is less widely available than echocardiography and often requires general anesthesia in small children, which limits its use in serial assessment and clinical follow-up. Therefore, accurate and reliable echocardiography-based methods are needed for clinical and study purposes.

Fractional area change (FAC) is well suited for the objective assessment of global RV function by echocardiography.\(^9\) We have previously shown that, comparing velocity vector imaging (VVI)-derived FAC, strain, and strain rate, FAC had the best correlation with EF measured by MRI.\(^10\) In recent years, several echocardiographic automated software programs have been developed for automatic assessment of FAC based on speckle tracking.

The first aim of our study was to examine the correlation of two automated methods and one manual method of measurement of right ventricular FAC with MRI-derived EF in HLHS. The second aim was to compare the intra- and inter-observer error of the automated vs the manual approaches, and whether different methods can be used interchangeably.

2 | METHODS

2.1 | Patients

Patients with classical HLHS at different stages of palliation (between Norwood and hemi-Fontan, between hemi-Fontan and Fontan, and after Fontan completion) undergoing routine cardiac MRI with echocardiography under the same general anesthetic at Evelina London Children’s Hospital, London, United Kingdom, were included. HLHS was defined as any combination of mitral stenosis or atresia with aortic stenosis or atresia (with atrioventricular and ventriculoarterial concordance) with no ventricular septal defects necessitating Norwood palliation.\(^11\) Patients were excluded if there was cardiovascular instability during the MRI scan precluding additional time for echocardiography or if the quality of apical four-chamber view was insufficient for manual FAC analysis. As the effect on the RV was more likely to be due to the residual morphology of the LV than the presence/absence of forward flow, LV morphology was described as follows: no LV visible or slit-like LV; globular LV; or borderline LV. Borderline LV was defined as a more mildly hypoplastic LV that could be considered potentially able to support the systemic circulation. In general, the no visible LV or slit-like LV corresponded to the mitral atresia and aortic atresia subgroup, the globular LV to the mitral stenosis and aortic atresia subgroup, and the borderline LV to the mitral stenosis and aortic stenosis subgroup.\(^11\) Ethical and institutional approval was granted for this prospective study, and informed consent was obtained from parents or legal guardians before examination.

2.2 | Magnetic resonance imaging

Magnetic resonance imaging scans were performed on a Philips 1.5-T Achieva scanner (Philips Healthcare, Best, The Netherlands) and were re-evaluated using ViewForum EWS version 2.0 (Philips Healthcare). MRI-derived EF was calculated as we have described previously with excellent inter- and intra-observer reproducibility.\(^11\) Two-dimensional steady-state free precession cine imaging oriented to the short axis of the right ventricle was used to calculate ventricular volumes using the disk summation method. End-diastolic and end-systolic contours were manually traced (excluding major trabeculations from the volume) to determine end-diastolic volume, end-systolic volume, and EF.

2.3 | Echocardiography

Echocardiography was performed on a Philips iE33 ultrasound system (Philips Healthcare, Einthoven, The Netherlands) using S8-3 or S5-1 probes as appropriate for patient size with frame rates of 80-120 Hz. An apical four-chamber view was used for analysis and the sector width adjusted to include the full endocardial border. For functional analysis, cardiac ultrasound data was transferred in a standard Digital Imaging and Communication in Medicine (DICOM) format to the functional analysis programs. VVI program used DICOM frame rate of 30 Hz for analysis and QLAB program (Philips Healthcare) used native frame rates.

All cardiac functional analyses were performed by one of the authors (HR), blinded to the clinical status and MRI results of the patients. FAC was analyzed using manual technique and two automated techniques: the VVI technique (Syngo USWP 3.0; Siemens Healthineers, Erlangen, Germany) and 2D automated technique (Q-lab R 10.0; Philips Healthcare). The same apical four-chamber view was utilized for all echocardiographic images analyzed.

Manual measurement of FAC was taken using a single analysis package (Xcelera; Philips Healthcare). RV areas were measured by
manual planimetry of the endocardial border at end-diastole marked by the onset of the QRS complex and then in end-systole when the RV area was the smallest (Figure 1). Tracing began from lateral side of the tricuspid valve annulus and ended at the medial side of tricuspid valve annulus. Papillary muscles and trabeculations were left inside the tracing. FAC was calculated from the difference of these areas divided by the area in diastole and expressed as a percentage.

In the VVI program (Syngo USWP 3.0; Siemens Healthineers), manual tracing of the RV subendocardial surface was performed in a single still frame in mid-systole. Tracing began at the edge of the tricuspid valve annulus on the free wall, extended to the apex of the ventricle, and returned basally to the tricuspid valve annulus on the septal side. Velocity vectors were then automatically calculated for each frame of the cardiac cycle by the VVI algorithm and displayed for the complete loop (Figure 1). Tracings were accepted only if the sub-endocardial border was correctly followed throughout the whole cardiac cycle. If necessary, individual regions of the border were adjusted until the border was correctly tracked for each frame. FAC was automatically calculated by VVI algorithm from largest area in diastole and smallest area in systole.

In the QLAB analysis program (Q-lab R 10.0; Philips Healthcare), points were placed at the tricuspid annulus at the right ventricular free wall, ventricular septum, and apex at end-diastole (frame 1). The rest of the tracing was then automatically carried out by the program. Points were adjusted until the myocardium was correctly followed throughout the whole cardiac cycle. FAC was calculated by QLAB program algorithm from largest area in diastole to the smallest area in systole.

All measurements were repeated twice and the mean value was used in the analyses, which reflected our normal practice. For intra- and inter-observer reproducibility, 10 randomly selected studies were analyzed twice by the same investigator (HR) and the second analysis was performed 2 weeks after the initial analysis, and once by another investigator (HB-R). Time for analysis was measured for all measurements. Time started when echocardiography loop was ready for analysis at analyzing program and ended when measurements were accepted and ready for data saving.

2.4 | Statistics

Intra- and inter-observer agreement was assessed for 10 randomly selected patients for all methods. Reproducibility was assessed from the corresponding repeated measures using intra-class correlation coefficients with 95% confidence intervals. The relationship between echocardiography measurements and MRI-derived EF was assessed using Pearson’s correlation coefficient for normally distributed data. Data are expressed as mean±standard deviation (SD) or median (range). The impact of stage of palliation or HLH morphology to reliability different FAC techniques to reflect RV systolic function was estimated by testing statistical significance of the difference between correlation coefficients at different stages of palliation or different HLHS morphology group. Bland-Altman analysis was used to compare FAC measurements by different techniques. Kolmogorov-Smirnov test with Lilliefors significance correction was used to test normality of parameters. A P-value of <.05 was used to define significance. SPSS for Windows version 22 (SPSS Inc/IBM Corporation, Somers, NY, USA) was used to perform statistical analysis.

3 | RESULTS

Fifty-one patients had both MRI and echocardiographic studies available for analysis. Clinical data of patients are presented in Table 1. Manual FAC was measured for all 51 patients; VVI analysis was possible for 49 patients and QLAB analysis for 44 patients. QLAB analysis was not possible in seven cases because the tracking was not deemed adequate through the cardiac cycle. Four of these cases had a globular LV and three had either a slit-like or no discernable LV. The duration of FAC analysis, including manual corrections, for manual technique
was 1 minute 39 seconds (55 seconds–2 minutes 20 seconds), for VVI 4 minutes 5 seconds (3 minutes 9 seconds–5 minutes 30 seconds), and for QLAB 2 minutes 58 seconds (1 minutes 40 seconds–2 minutes 44 seconds; \( P < .002 \)). Intra- and inter-observer variability was good for all echocardiographic methods except manually derived FAC where it was poor, particularly with regard to the end-systolic area (Figure 2, Table 2).

All FAC measurements correlated significantly with MRI-derived EF \((R>.4, \text{Figure 3})\). Higher correlation was found using automated software (VVI FAC \(R=.7\) and QLAB FAC \(R=.6\)) than the manual method \((R=.4)\). The correlation coefficients between VVI and manual technique were statistically different \((P=.03)\), but there was no difference between two automated techniques \((P=.5)\) or between QLAB and manual technique \((P=.2)\).

The correlations did not differ either between the operative stages for any technique (manual \(P>.7\), VVI \(P>.6\), QLAB \(P>.3\)) or between different morphology groups for manual and VVI technique (manual \(P>.4\), VVI \(P>.2\)). QLAB FAC correlation with MRI EF was lower for slit/none LV morphology group \((R=.2)\) than globular morphology group \((R=.8, P=.02)\).

Bland-Altman assessment of the agreement between the different techniques is shown in Figure 4. Both automated techniques tended to produce lower FAC values compared with manual measurements (VVI FAC –7.2%, \(P<.0001\) and QLAB FAC –9.8%, \(P<.001\)). Also VVI technique produced 2.4% units higher values than QLAB technique \((P<.0001)\). Limits of agreement were wide between manual and automated techniques but narrower between two automated techniques (Figure 4).

### DISCUSSION

Our study shows that automation improves repeatability and reliability of echocardiographic FAC measurements of RV in HLHS children. Both automated FAC measurement programs (VVI, Siemens Syngo USWP 3.0; Siemens Healthineers and QLAB, Q-lab R 10.0; Philips Healthcare) correlated better with MRI measurements \((R=.7, R=.6, \text{respectively})\) than the manual tracing technique \((R=.4)\). Our data suggest that automated speckle tracking techniques are a valid and practical alternative to MRI to assess systolic ventricular function in a patient group in whom systolic function is known to impact prognosis.\(^{1-4}\)

Previously, manual FAC has been measured in 12 HLHS children before stage 2 operation with good correlation \((R=.8, P=.001)\) to EF measured by MRI.\(^{13}\) However, there are no previous echocardiographic studies comparing automated and manual tracing measurements of FAC for RV function in patients with HLHS. In those HLHS studies, were FAC has been measured manually or automatically by VVI, intra- and inter-observer repeatabilities have not been reported.\(^{4,13-19}\)

Intra-observer repeatability was better than inter-observer repeatability especially for manual technique. This reflects the fact that

#### TABLE 1 Demographics of 51 HLHS children

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>2.0 (0.1-13.7)</td>
</tr>
<tr>
<td>Male/female, n (%)</td>
<td>36 (71%)/15 (29%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>9.7 (3.0-45.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>78.0 (49.0-160.0)</td>
</tr>
<tr>
<td>Morphology group A/B/C, n (%)</td>
<td>18 (35%)/10 (20%)/23 (45%)</td>
</tr>
<tr>
<td>Stage 1/2/3, n (%)</td>
<td>23 (45%)/22 (43%)/6 (12%)</td>
</tr>
<tr>
<td>MRI EF (%)</td>
<td>58.9±9.2</td>
</tr>
</tbody>
</table>

A, slit/none LV; B, borderline LV; C, globular LV. Stage 1, before hemi-Fontan; Stage 2, before TCPC; Stage 3, after Fontan completion.

HLHS=hypoplastic left heart syndrome; MRI=magnetic resonance imaging; EF=ejection fraction; LV=left ventricle.

#### TABLE 2 Inter- and intra-observer correlations and MRI EF comparison for echocardiographic FAC measured by manual tracing or by two automated techniques VVI (Siemens Syngo USWP 3.0; Siemens Healthineers) and QLAB (Philips Q-lab R 10.0; Philips Healthcare)

<table>
<thead>
<tr>
<th>Echocardiographic technique</th>
<th>ICC</th>
<th>( R ) MRI EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVI FAC</td>
<td>.997 (989 to .999)/.976 (902 to .994)</td>
<td>.7 ((P&lt;.0001))</td>
</tr>
<tr>
<td>QLAB FAC</td>
<td>.976 (.903 to .994)/.891 (.561 to .973)</td>
<td>.6 ((P&lt;.0001))</td>
</tr>
<tr>
<td>Manual technique FAC</td>
<td></td>
<td>.774 (.427 to .922)/-.205 (-.498 to .269)</td>
</tr>
<tr>
<td>End-diastolic area</td>
<td>.95 (.845 to .984)/.837 (.492 to .948)</td>
<td></td>
</tr>
<tr>
<td>End-systolic area</td>
<td>.942 (.818 to .981)/-.395 (-.806 to .188)</td>
<td></td>
</tr>
</tbody>
</table>

ICC=intra-class correlation coefficient; \( R \)=correlation coefficient; MRI=magnetic resonance imaging; EF=ejection fraction; VVI=velocity vector imaging; FAC=fractional area change.
standardizing a manual tracing technique is more difficult between different investigators. In HLHS children, the shape of systemic RV is usually quite complex and trabeculated. Therefore, it may be difficult to find the exact endocardial border exactly and it is especially challenging in systole when trabeculations are coarsest. In our study, the inter-observer manual tracing repeatability was poor especially in systole. In diastole, the ECG makes the frame selection easier. In automated programs, it is relatively easy to notice if the myocardium is not tracked throughout the whole cardiac cycle, and corrections can be carried out. In our study, there was no difference on intra- or inter-observer repeatability between two automated techniques. Both automated techniques produced lower FAC values than the manual technique. Further VVI produced values of FAC a mean of 2.4% higher than QLAB. Thus, the same echocardiographic technique should be used during the follow-up of individual patients, especially so in HLHS children with no normal reference values for RV FAC. Limits of agreement were wide between manual and automated techniques, reflecting poor repeatability of the manual technique.

**FIGURE 3** Correlations between magnetic resonance imaging (MRI)-derived ejection fraction (EF) and fractional area change by different echocardiography-based techniques (FAC). A. Velocity vector imaging, B. QLAB, and C. manual

**FIGURE 4** Bland-Altman analysis of different techniques to measure fractional area change (FAC). Comparison of (A) velocity vector imaging and manual, (B) QLAB and manual, (C) velocity vector imaging and QLAB
However, limits of agreement were narrower between two different automated techniques.

There are some limitations in the use of the automated softwares. Some of them (e.g., QLAB; Philips Healthcare) are limited to specific echo machines, and for other software, the data need to be transferred to a different program (VVI). Thus, the total time taken will vary according to the degree of integration of the analysis software into the imaging archive. Once imported into the software package, the time required for actual analysis is short, supporting the use of the technique as practical in terms of patient workflow. Further, obtaining an apical four-chamber view is usually rapid and a view which is routinely obtained in clinical practice.

4.1 Study limitations

The vast majority of patients had EF in the normal range and we had limited number of patients with diminished myocardial function. This represents a degree of selection bias, as those with very poor function are at higher risk for hemodynamic instability during anesthetic and for mortality. All echocardiography examinations were performed under general anesthetic. Without anesthesia, the quality of echocardiography for VVI analysis might be lower which could affect reliability. However, it is important to perform both MRI and echocardiography in the same clinical condition, that is, in this study, during anesthesia.

5 CONCLUSIONS

Automation improves repeatability in echocardiographic measurement of systolic function by FAC in patients with HLHS. There are some differences between automated programs in terms of correlation with MRI-derived EF. Limits of agreement between these methods remained wide, however, suggesting that the same echocardiographic technique should be used during follow-up in the clinical practice.

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