Two-Dimensional Global Longitudinal Strain Rate Is a Preload Independent Index of Systemic Right Ventricular Contractility in Hypoplastic Left Heart Syndrome Patients After Fontan Operation

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Background—Assessment of systemic right ventricular (RV) function in patients with hypoplastic left heart syndrome is important during long-term follow-up after Fontan repair. Traditional echocardiographic parameters to evaluate systolic ventricular function are affected by loading conditions. The only generally accepted load-independent parameter of systolic function, end systolic elastance ($E_{es}$), requires invasive catheterization. Therefore, we sought to determine if parameters obtained by 2-dimensional speckle tracking (2DST) were affected by acute changes in preload and correlated with catheterization-derived indices of RV contractility in hypoplastic left heart syndrome patients after Fontan palliation.

Methods and Results—Fifty-two patients with hypoplastic left heart syndrome (median age, 6.6; range 2.9–22.2 years) were prospectively enrolled to have echocardiography and conductance catheter studies performed simultaneously. We compared traditional echo, 2-dimensional speckle tracking and catheterization-derived parameters during different states of preload at baseline and during dobutamine infusion. Global longitudinal strain (S) showed a tendency to decrease with preload reduction, whereas global longitudinal strain rate (SR) did not change ($S: −17.7±3.4\%$ versus $−16.9±3.8\%$, $P=0.08$; $SR: −1.30±0.29$ versus $−1.34±0.34\ s^{-1}$, $P=0.3$). $S$ did not change with dobutamine infusion ($−17.7±3.4\%$ versus $−18.4±3.9\%$, $P=0.24$), whereas SR increased significantly ($−1.30±0.29$ versus $−2.26±0.49\ s^{-1}$, $P<0.001$). RV $E_{es}$ correlated with SR ($r=−0.47, P<0.001$), but not with $S$ ($r=0.07, P=0.5$) or other echocardiographic parameters.

Conclusions—In contrast to $S$, SR was not affected by preload and correlated with $E_{es}$ of the systemic RV. SR may be a useful noninvasive surrogate of RV contractility and suitable for follow-up of patients with hypoplastic left heart syndrome after Fontan palliation. (Circ Cardiovasc Imaging, 2014;7:880-886.)

Key Words: hypoplastic left heart syndrome  ■  ventricular function

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n patients with hypoplastic left heart syndrome (HLHS), systemic right ventricular (RV) function influences morbidity and mortality after the Fontan operation.1,2 Examination of RV function is an important component during follow up of these patients. However, echocardiographic evaluation of RV function has not been standardized. In daily practice, RV function is widely still estimated by subjective eyeballing owing to geometry and angle of insonation dependence of traditional echocardiographic methods. In recent years, 2-dimensional speckle tracking (2DST) has been increasingly used for measuring global and regional myocardial deformation. This method has potential advantages because it is not subject to limitations posed by the geometry of the ventricle or the angle of insonation. Thus, 2DST seems especially suited for evaluating the more complex geometry of the RV and the single ventricle in congenital heart disease.4

Clinical Perspective on p 886

Multiple studies have shown the feasibility and accuracy of 2DST for the subpulmonary and systemic RV in adult and pediatric patients.5,7 In HLHS, 2DST has been used to compare different anatomic subtypes and surgical techniques and to measure changes in RV function with the consecutive surgical procedures.10-12

By analyzing strain and strain rate (SR), myocardial function can quantitatively be assessed in a noninvasive manner. Yet a relationship between these parameters and intrinsic myocardial function has only been proven for the systemic
left ventricle. Furthermore, there are limited data on the effect of loading conditions on 2D strain and SR. To date, the only accepted method able to generate load-independent parameters of ventricular function is the conductance catheter method. There have been conflicting results regarding the load sensitivity of the strain and SR of the RV when measured by Doppler and speckle tracking studies.

The objectives of this study were to assess the effect of acute preload reduction and increased inotropy on 2D longitudinal strain and SR in patients with HLHS and relate these parameters to simultaneously derived load-independent measures of ventricular function measured by conductance catheter technique.

Methods

Patients

Between February 2010 and April 2013, 56 patients with HLHS and 3 patients with a double outlet right ventricle and left ventricular (LV) hypoplasia after the Fontan procedure were prospectively recruited to be studied simultaneously with echocardiography and the pressure–volume conductance system.

In all patients, a modified Norwood operation with modified Blalock–Taussig shunt was performed as stage one, followed by a superior cavo-atrio-pulmonary anastomosis (Hemi Fontan) as stage two, and a fenestrated intra-atrial lateral tunnel modification of the Fontan operation as stage three.

Conductance data were obtained as part of routine cardiac catheterization. Parents or legal guardians were precisely informed and consented about the clinical indication for the catheter study and the research purposes of the conductance study with administration of dobutamine. The local research ethics committee had approved the study protocol before starting patient recruitment.

Demographic Data

Pertinent patient data were collected and included age, sex, follow-up time since Fontan completion, New York Heart Association functional class, medication, existence of tricuspid and neoaortic valve regurgitation, and oxygen saturation.

Echocardiography

All echocardiographic recordings were obtained using a GE Vivid 7 scanner (GE Healthcare, Wauwatosa, WI) and stored digitally for offline analysis. RV fractional area change (RV FAC) was calculated as end-diastolic area – end-systolic area/end-diastolic area. Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode of the RV free wall at the level of the lateral tricuspid leaflet insertion. Gray scale images optimized for speckle tracking echo analysis were acquired from the apical 4-chamber view. Images were obtained at frame rates between 49 and 102 frames/s. One experienced echocardiographer (I.S.) analyzed the data offline using dedicated software (EchoPac, GE Healthcare). After manual tracing of the endocardial border, the software divided the RV automatically into 6 segments. Segments were excluded if the myocardium was not visualized well enough to allow speckle tracking. Neoaortic valve closure and opening was determined from neoaortic outflow pulsing Doppler tracings. Peak systolic longitudinal strain (S, percent change in segment length from end diastole) and peak systolic longitudinal SR (representing the rate of deformation) were recorded for each segment. From the regional segmental data, global longitudinal S and SR were calculated as mean of all available segments. In 7 patients, acoustic windows were not appropriate for 2D speckle tracking echocardiography because patients could not be optimally positioned during catheterization.

Cardiac Catheterization and Conductance Study

Cardiac catheterization was performed under general anesthesia and included full hemodynamic assessment. To acquire RV pressure–volume (PV) loops, a 4F combined pressure–conductance catheter with 12 electrodes (CD Leycom, Zoetermeer, The Netherlands) was placed in the RV via the aorta. Pressure–volume signals were displayed online and digitized at a sample rate of 250 Hz (CFL 512, CD Leycom, The Netherlands) using a value of blood resistivity determined before data acquisition. The pressure signal was calibrated with a standard calibration pulse from the amplifier (Sentron, Roden, The Netherlands). Conductance-derived RV volume was calibrated for parallel conductance and gain factor Ϝ using the end diastolic and end systolic volume obtained from biplane angiocardiography as previously described. Finally, a 25-mm Latex balloon catheter (Numed, Hopkinton, NY) was placed in the intra-atrial lateral tunnel and prepared to modify preload (Figure 1). Measurements of pressure and volume relationships were repeated after infusion of 10 µg/kg/min of dobutamine for 10 minutes. All data acquisition runs were repeated in triplicate.

Analysis of PV loops was performed with custom made software (Circlab 2011, LUMC, Leiden, the Netherlands). RV pressure and volume data and derived indices, such as cardiac index and ejection fraction (EF), were assessed. Stroke work (SW) was calculated as the area enclosed by the PV loop. Indices of systolic ventricular function were derived from PV loops recorded during the preload reduction maneuver. We determined end systolic elastance (Ees) as the slope of the end systolic PV relationship (Ees; ESP versus end systolic volume) and the slope of the preload recruitable SW relation (M′; SW versus end diastolic volume). In 2 patients, conductance data could not be analyzed because of poor signal quality.

Study Protocol

Figure 2 details the sequence of echocardiographic recordings during the catheterization. Data were acquired at baseline during steady state (echo 1) and then at maximum balloon inflation (echo 2). Measurements were repeated during dobutamine infusion steady state (echo 3) and at maximum balloon inflation (echo 4). All data acquisition runs were repeated in triplicate.

Statistical Analysis

Data are expressed as mean±SD or median (minimum and maximum) as appropriate. Results for each variable were tested for normality using the Kolmogorov–Smirnov method. Comparisons between steady state and preload reduction and baseline and dobutamine data were
made with paired t-tests. Correlation of parameters was assessed using Spearman’s rank correlation coefficient.

Measurement variability of the 2DST parameters global strain and SR was assessed in 20 randomly selected patients by calculation of intraclass correlation coefficients.

For all analyses, a P<0.05 was considered statistically significant. Statistical analysis was performed with MedCalc, version 11.2. (MedCalc Software, Mariakerke, Belgium).

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. Patients were studied at a median of 2.7 years after Fontan completion. Results of traditional echocardiographic parameters to assess RV function are also given in Table 1.

2D Speckle Tracking

Results of the global and regional S and SR at baseline and during dobutamine infusion are given in Table 2. During baseline conditions, S showed a tendency to decrease during preload reduction, a finding that reached significance during dobutamine infusion. SR did not change during preload reduction. SR increased significantly with dobutamine infusion, whereas S remained the same.

Regional 2DST analysis revealed that peak longitudinal S decreased with preload reduction only in the lateral segments. In these segments, there was a significant increase of regional S with dobutamine infusion. Regional SR did not change with preload alteration, but increased in all 6 segments with dobutamine infusion.

Conductance-Derived Data on Systolic Function

Data of hemodynamic parameters and intrinsic RV function at baseline and during dobutamine infusion are given in Table 3. Heart rate, blood pressure, cardiac index, and SW increased during dobutamine infusion, whereas EF remained unchanged. Both $E_s$ and $M_w$ increased with dobutamine infusion.

Correlation Between Conductance and Echocardiography

As shown in Table 4 and Figure 3, there was a good correlation of $E_s$ and $M_w$ with SR. Neither S nor the traditional echocardiographic parameters of RV function, TAPSE and FAC, correlated with $E_s$ and $M_w$.

Intra- and Interobserver Variability of 2D Speckle Tracking Data

Twenty randomly selected patients were reanalyzed by the same observer (J.S.) and by an independent blinded observer (C.P.). Overall, there was acceptable to good intraobserver variability with a coefficient of variation of 0.81 (95% confidence interval [CI], 0.58–0.92) for S and 0.81 (95% CI, 0.52–0.92) for SR. Interobserver variability was also good (S, 0.83 [95% CI, 0.58–0.93]; SR, 0.93 [95% CI, 0.84–0.97]).

Discussion

To our knowledge, this is the first study to simultaneously assess 2DST and invasive PV loops in the single RV of HLHS patients. The main finding of our study was that 2DST-derived global systolic longitudinal SR correlated with end systolic elastance and thus reflected changes in intrinsic myocardial systolic function in this patient population. Furthermore, global SR was not affected by acute changes in preload within the tested range, whereas global strain seemed to be more sensitive to preload reduction, particularly during inotropic stimulation.

Effect of Preload Changes on Strain and SR

In recent years, 2DST parameters have been increasingly used for evaluating RV function. Yet few studies have focused on the effect of changes in loading conditions on these parameters, but this is particularly interesting in congenital heart disease where the RV is often subject to volume or pressure overload. In ASD patients, tissue Doppler-derived myocardial velocities proved to be preload-dependent. Jategaonkar et al showed that RV volume overload was associated with increased S values, which returned to normal after abolishment of the volume overload, whereas SR was found to be less preload-dependent. Their findings represent chronic preload changes in the RV as patients were examined before and 3 months after ASD closure. To our knowledge, ours is the first human study
to examine the effect of acute preload reduction on 2DST parameters of the systemic RV. Our results indicate that SR is not affected by acute preload changes within the range of conditions tested, whereas S seems more susceptible to preload changes. These results are similar to the findings shown for these 2 parameters in the setting of chronic changes in preload.

Because S is a measure of myocardial lengthening and shortening and preload describes the load on the myocardial fibers just before contraction, the preload-dependency of S can be explained by the Frank–Starling mechanism, which enables the heart to respond to elevated preload via enhanced shortening of the myocardium. Decreased S with acute preload reduction has previously been described for the systemic RV. Our results indicate that SR is not affected by acute preload changes within the range of conditions tested, whereas S seems more susceptible to preload changes. These results are similar to the findings shown for these 2 parameters in the setting of chronic changes in preload.

Data are expressed as mean±SD. BP dia indicates diastolic blood pressure; BP sys, systolic blood pressure; CI, cardiac index; Ees, end systolic elastance; EF, ejection fraction; HR, heart rate; Mw, preload recruitable stroke work; and SW, stroke work.

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Looking at the 6 segments of the RV, the decrease of regional S with preload reduction was only significant in the lateral segments. The lateral segments represent the free wall of the RV, whereas the septal segments are adjacent to the remnant of the LV in HLHS. An explanation for this repeatedly published pattern of deformation of the RV in HLHS may be impairment of septal deformation by the adjacent and sometimes fibrotic LV remnant.22,23 The LV remnant does not seem to influence global RV deformation, at least during short and medium term follow-up.23,24

In this study, only the effects of preload changes were examined. In HLHS, the single RV is chronically subjected to high afterload because it has to support the systemic circulation. Thus, the effect of afterload changes on deformation parameters are of high interest. Using sonomicrometry, a decrease of RV SR after acute increase of afterload by pulmonary artery banding was shown in lambs.25 Ferferieva et al showed in a mouse model that in the LV, tissue-Doppler–derived radial and circumferential S was afterload dependent, whereas SR was more sensitive to changes in contractility.14 In a recent study, we were able to show that increased afterload in HLHS patients did not affect RV end systolic elastance.26 To date, the effects of acute and chronic changes in afterload on 2DST-derived S and SR in the systemic RV are unknown and warrant further study.

**Correlation of Strain and SR with Contractility**

For the LV, Greenberg et al found a strong correlation between tissue Doppler–derived SR with ventricular elastance in a canine model.15 Later this relationship was confirmed in a mouse model by good correlation of circumferential SR with preload recruitable SW.16 Yotti et al examined noninvasive indices of global systolic function with simultaneous Doppler echocardiography and PV catheterization in the LV of adults.

Schlangen et al  Strain Rate Is an Index of RV Function in HLHS 883
They found good correlation between ventricular elastance and circumferential S and SR but not with longitudinal parameters. This contrasts our findings at first glance where longitudinal SR correlated with ventricular elastance. However, in humans, correlations between elastance and S or SR seem to depend on fiber orientation and ventricular morphology. In contrast to the mostly circumferential muscle fiber orientation in the LV, in the RV it is predominantly longitudinal, which could explain our findings.

Although the correlation between SR and $E_{cs}$ was only modest (-0.47 (95% CI 0.27–0.63)), we would consider it valuable bearing in mind that functional data from 2 different modalities (2DST and conductance catheter) are related. The study of Yotti et al found correlation factors of these parameters in the same range as ours.

In the present study, we were only able to examine longitudinal deformation from the apical four-chamber view. Timing of the study protocol did not permit changes of the transducer position. We deliberately chose longitudinal deformation because it has been shown to have better reproducibility than circumferential and radial strain. In our experience in patients with HLHS, the parasternal short axis views of the anterior and often enlarged RV often fail to capture the entire cross section of the myocardium, which can lead to incomplete data.

The fact that global SR increased in parallel to elastance during dobutamine infusion may suggest that it can be considered as a noninvasive index of intrinsic RV contractility in these patients. Global S in contrast did not change with dobutamine infusion. This finding is in agreement with the observation that the EF also did not change under dobutamine infusion. It seems that dobutamine mainly affects the velocity of fiber shortening but does not lead to increased fiber shortening in this setting. Thus, the increase in cardiac output in these patients after Fontan palliation is mainly achieved by the increase in heart rate rather than stroke volume, an observation that has been described before.

RV FAC has been described as a quantitative surrogate for the EF assessing global systolic RV function. It has been shown to correlate well with CMR-derived EF, but it underlies the same limitations as the EF. In our cohort, RV FAC did not correlate with intrinsic myocardial function. In our opinion, RV FAC can be a useful parameter of RV global function during longitudinal follow-up of HLHS patients, but limitations regarding load dependence and the complex geometry of the RV should be kept in mind.

Similarly, TAPSE did not correlate with global intrinsic RV function in our study. This is not surprising, however, because TAPSE is considered a regional function parameter that should only be used to measure the longitudinal function of the base of the heart surrounding the tricuspid valve annulus. Avitabile et al recently showed that in HLHS, TAPSE does not correlate with CMR-derived EF. Comparing our results with normal values of the subpulmonary RV, TAPSE values of the systemic RV indexed to body surface area were lower, a finding that has been consistently shown previously by our group.

Because only a limited amount of conductance studies have been performed on single ventricle patients, the predictive value of measuring contractility is to date unclear. Even for a widely studied group of patients, namely adult patients with pulmonary hypertension, where the RV is also subjected to high afterload and multiple studies have shown the predictive value of different parameters of ventricular function (CMR and echo), unfortunately no studies exist that load-independent contractility is
predictive of clinical outcome.\textsuperscript{33} In patients with severe heart failure, the increase of RV elastance with dobutamine infusion was associated with favorable short term outcome.\textsuperscript{44} As shown in Table 3, overall the contractile reserve of our patient cohort was good with a >100\% increase of $E_{\infty}$ and $M_{\infty}$ with dobutamine. In our opinion, identifying patients with reduced contractile reserve should have implications on long term outcome. Further studies evaluating the predictive value of load-independent indices and contractile reserve seem highly warranted.

In our study, 2DST-derived global longitudinal SR emerges as parameter that seems to lend itself as a preload-independent index of RV contractility in patients with HLHS after Fontan palliation. It can be easily measured offline on gray-scale images retrospectively. In addition, it is not dependent on the angle of insonation or the geometry of the ventricle. We therefore suggest adding SR as a useful noninvasive parameter for routine longitudinal monitoring of RV systolic function in this particular patient cohort.

Whether these results can be generalized to include the sub-pulmonary RV in biventricular hearts (eg, the chronically volume loaded RV in tetralogy of Fallot) or the pressure-loaded RV in pulmonary hypertension or after the atrial switch operation in transposition of the great arteries requires further study.

Limitations
The 2DST software was designed for the LV of normal hearts. Therefore, allocation and terminology of the 6 segments does not always correlate with the anatomy of hypoplastic left heart, especially if a left ventricle is almost absent.

The conductance method was developed to obtain PV loops in the more elliptically shaped LV and may be less accurate in the RV. However, several studies have shown that it can be applied accurately in the RV.\textsuperscript{35,36}

Angiographic volumes were calculated using cardiac phase and projection-specific correction factors obtained from cast studies of subpulmonary right ventricles.\textsuperscript{37} Whether these correction factors are appropriate for the variably abnormally shaped ventricles of operated HLHS patients in this study is questionable. However, we have previously reported a good correlation between RV volumes measured by angiocardiography and cardiac MRI in this patient population and therefore believe that angiographic volumetry is sufficiently accurate for this patient population.\textsuperscript{24}

Measurement variability of 2DST parameters in our study was in a similar range as found by other investigators examining the single RV with the same technology,\textsuperscript{10} yet we feel it was not low enough to be disregarded when interpreting results. A specific fact, which may have contributed to variability in our study, was that patients could not be positioned ideally during the catheter study and echocardiographic image quality was not optimal in all cases. For this reason, not all segments of the RV could be analyzed in some patients. All data acquisition runs were repeated in triplicate to improve accuracy. Assessment of interstudy reproducibility would have been valuable additional information, but because a second invasive catheterization would have been necessary, ethical concerns prohibited the data. Data on vendor-specific variance of speckle tracking parameters in children have been published and the authors advise to scan patients consistently on the same machine using the same software to analyze the images.\textsuperscript{38} These limitations are particularly important when using 2DST parameters for routine clinical follow up.

Conclusions
In the systemic RV of patients with HLHS after Fontan operation, 2DST-derived global longitudinal SR was insensitive to acute preload changes and correlated with indices of myocardial contractility in our study. We would like to recommend its use for routine assessment of echocardiographic systolic function in patients with HLHS after Fontan palliation.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Long-term outcome of patients with hypoplastic left heart syndrome is closely related to ventricular performance of the single systemic right ventricle. Therefore, assessment of ventricular performance during routine follow-up of these patients assumes a central role. Unfortunately, echocardiographic evaluation of ventricular function has been particularly challenging in the single right ventricle. The conductance catheter is currently the only method to deliver load-independent data on intrinsic myocardial contractility but because of the invasive nature is not feasible for routine assessment of ventricular performance. In our study, we combined the techniques of conductance catheter with 2D speckle tracking echocardiography. The latter method can be applied independent of ventricular geometry andISON angles. Global longitudinal strain rate emerged in our study as a parameter that can be easily generated with good reproducibility. In addition, it was independent of acute changes in preload and correlated well with conductance catheter–derived end systolic elastance and thus reflected changes in ventricular contractility. We think that our results will stimulate further study to see whether the findings here can be reproduced and also applied to patients with different ventricular morphologies and biventricular circulations as well.
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