Detection of Left Ventricular Asynchrony in Patients With Right Bundle Branch Block After Repair of Tetralogy of Fallot Using Tissue-Doppler Imaging-Derived Strain

Mohamed Y. Abd El Rahman, MD,* Wei Hui, MD,* Moustafa Yigitbasi, MD,* Fatima Dsebissowa, MD,* Stephan Schubert, MD,* Roland Hetzer, MD, P HD,† Peter E. Lange, MD, P HD,* Hashim Abdul-Khaliq, MD, P HD*

Berlin, Germany

OBJECTIVES We aimed to investigate whether patients after tetralogy of Fallot (TOF) repair with right bundle branch block have left ventricular (LV) asynchrony and to assess the influence of ventricular asynchrony on regional and global LV function.

BACKGROUND Patients after TOF repair usually have right bundle branch block. However, no data regarding LV asynchrony in this group are available.

METHODS Twenty-five patients after TOF repair and 25 age-matched healthy control subjects were studied. The regional myocardial deformation of the interventricular septum (IVS) and the LV lateral wall were examined using tissue-Doppler–derived strain. The time interval between the onset of QRS complex and the peak strain was measured for each wall. According to the difference between LV and septum time intervals among the normal subjects, a normal range (mean ± 2 SD) was plotted, and TOF patients in whom the difference was beyond the normal range were considered to have LV asynchrony. The Tei index was used to assess global LV function.

RESULTS Thirteen (52%) of the examined patients after TOF repair had LV asynchrony. Patients after TOF repair with LV asynchrony had a significantly reduced regional septal systolic strain (p < 0.001) and significantly elevated Tei index (p < 0.001) compared with those without.

CONCLUSIONS Left ventricular asynchrony may exist in patients after TOF repair with right bundle branch block. This LV asynchrony is associated with a reduction of both regional and global LV function. (J Am Coll Cardiol 2005;45:915–21) © 2005 by the American College of Cardiology Foundation

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease beyond infancy with a prevalence of 0.26 to 0.8 per 1,000 live births (1). “Corrective” intracardiac repair has been performed for over four decades with good results (2). Nevertheless, long-term follow-up studies have reported reduced right (RV) and left ventricular (LV) function (3,4).

Recent reports have noted that patients with LV dysfunction accompanied by left bundle branch block suffer from LV asynchrony (5). Using current surgical techniques, right bundle branch block after TOF repair is common (6). However, so far no data regarding LV asynchrony in this group of patients are available.

Quantitative assessment of ventricular asynchrony in clinical settings is challenging. Recently, tissue-Doppler imaging (TDI) has emerged as a technique that allows assessment of ventricular asynchrony using data obtained from myocardial motion (7,8). In contrast with myocardial wall motion, tissue-Doppler–derived strain is expected to better reflect regional myocardial function because it is less affected by overall cardiac motion (9,10).

The aim of this study was first to investigate the presence of LV asynchrony among patients after TOF repair using the novel tissue-Doppler–derived strain, and secondly to assess the influence of LV asynchrony on regional and global LV function.

METHODS Subject population. Twenty-five consecutive patients after corrective surgery of TOF were included in this study. None of the examined patients received a pacemaker. Exclusion criteria were arrhythmia and an inadequate transthoracic window for echocardiographic examination. The median age of the patients was 19 years (range 3 to 35 years). Their median age at TOF repair was 2 years (range 12 months to 17 years). The median follow-up period was 10 years (range 12 months to 27 years). During surgical repair the RV outflow tract was reconstructed using a valved homograft in 17 patients (68%) and an RV outflow patch in 8 patients (32%). Fifteen patients (60%) were in New York Heart...
Abbreviations and Acronyms
CDMI = color Doppler myocardial imaging
LV = left ventricle/ventricular
NYHA = New York Heart Association
ROC = receiver-operating characteristic
RV = right ventricle/ventricular
TDI = tissue-Doppler imaging
TOF = tetralogy of Fallot

Association (NYHA) functional class I, while 10 patients (40%) were in class II. Ultrasound data from the patient group were compared with those from 25 age-matched healthy controls, who were examined for an innocent murmur. Their median age was 22 years (range 4 to 39 years). The study protocol was approved by the local ethics committee, and informed written consent was obtained from the patients or their parents.

Electrocardiogram (ECG). All patients had a 12-lead surface resting ECG performed with a Siemens recorder (Siemens, Erlangen, Germany) at a speed of 50 mm/s and 1 mV/cm standardization. Maximal QRS width in any lead was measured from the first to the last sharp vector crossing the isoelectric line.

Standard echocardiography examination and determination of pulsed Doppler-derived Tei index. All patients were examined by echocardiography using a 2.5 to 3.5 MHz transducer interfaced with a Vingmed system V ultrasound system (Vingmed System V Ultrasound, Scannerorten, Norway). Transthoracic imaging was performed in left lateral position. Initially, routine diagnostic imaging was performed, including color flow mapping and continuous-wave Doppler.

The severity of pulmonary regurgitation was assessed by two experienced pediatric cardiologists. Severe pulmonary regurgitation was recognized by the presence of wide color Doppler regurgitation jet at the level of the pulmonary artery with a reverse flow extending up to the pulmonary bifurcation and/or pulsed Doppler pulmonary regurgitation jet lasting less than two-thirds of the diastolic duration (11,12).

Pulsed Doppler flow across the mitral and the aortic valve was assessed with simultaneous ECG recordings in each patient. The usual size of the pulsed Doppler gate was 1.5 mm, and the filter was adjusted to 100 Hz. For optimal acquisition, care was taken to direct the transducer beam as close as possible to the Doppler beam, at <20° in selected planes. No angle correction was made. All parameters were measured on-line. In an apical four-chamber view, the mitral valve inflow velocity profiles were recorded with the Doppler sample placed at the tip of the mitral valve. The “a-value,” the time from closure to opening of the mitral valve, was measured. In an apical five-chamber view, flow velocity was recorded in the LV outflow tract with the sample volume placed just below the aortic valve. The “b-value,” the entire time interval of the aortic valve systolic flow signal, was measured. The Tei index was calculated according to the equation Tei index = (“a-value” − “b-value”)/“b-value” (13).

Determination of regional myocardial function and ventricular asynchrony by tissue-Doppler-derived strain. All subjects included in the study underwent a color Doppler myocardial imaging (CDMI) study during which the regional myocardial deformation was assessed by tissue-Doppler-derived strain. The LV lateral wall and interventricular septum were examined at basal, middle, and apical segments in a standard apical four-chamber view. Two-dimensional and color sector size and depth were chosen to achieve the highest frame rate (150 to 190 frames/s). Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation. The angle between myocardial motion and the ultrasound beam was kept at <30°. Three consecutive cardiac cycles were recorded during normal quiet respiration; CDMI data were stored in digital format and transferred to a computer workstation for off-line analysis with a dedicated software (TVI, GE Vingmed, Echopac, GE Vingmed, Horten, Norway). Regional myocardial strain was estimated by measuring the spatial velocity gradient over a computation distance of 9.7 mm in longitudinal direction (10).

From each myocardial segment, the time interval between the onset of the QRS complex and the peak of regional myocardial strain was assessed. The mean time interval of each wall was then calculated from its respective three segments. The LV delay was quantified by measuring the time difference from the mean time interval of the LV free wall to that of the septal wall. The recordings of 10 patients and 10 normal subjects were randomly selected and analyzed by two independent examiners to assess the interobserver variability of the TDI parameters related to ventricular delay.

Statistical analysis. The statistical software was SPSS 10.0 (SPSS Inc., Chicago, Illinois). Data were expressed as median (range). The nonparametric Mann-Whitney test was used to assess the difference between two unpaired groups. For analysis of correlations, the nonparametric Spearman rank correlation was performed. Interobserver variability was calculated according to the formula:

\[
\frac{|\text{observer 1} - \text{observer 2}|}{(\text{observer 1} + \text{observer 2})/2} \times 100\%
\]

The interobserver variability for the mean LV delay was 5%.

Receiver-operating characteristic (ROC) curves were constructed for the QRS duration for the prediction of LV asynchrony, defined as an LV delay of more than the normal range (mean + 2 SD) calculated from the normal subjects.

RESULTS

Conventional ECG and echocardiographic examination. All examined patients after TOF repair had a right bundle
branch block morphology. The mean ± SD of the QRS duration among them was 145 ± 23 ms (range 100 to 180 ms). Twenty-three TOF patients (92%) had a QRS duration of >110 ms, while in two patients the duration was <110 ms.

Five patients (20%) had severe pulmonary insufficiency, and 20 (80%) had mild-to-moderate pulmonary regurgitation. Of the patients with severe pulmonary regurgitation, three were in NYHA functional class II and the remaining two in class I. Patients with severe pulmonary regurgitation had significantly prolonged QRS duration compared with patients with mild-to-moderate pulmonary regurgitation (p = 0.013). The mean (± SD) gradient across the RV outflow tract was 27.44 (± 19.21) mm Hg. The mean (± SD) LV Tei index in the control group was 0.33 (± 0.035) and in the patient group 0.43 (± 0.092). Compared with the control group, patients after TOF repair had significantly elevated Tei index (p = 0.023). Patients with severe pulmonary regurgitation had significantly elevated Tei index compared with patients with mild-to-moderate pulmonary regurgitation (p = 0.045).

Regional myocardial deformation and time intervals in patients after TOF repair compared with normal subjects. The regional myocardial strain in all examined segments was significantly reduced in patients after TOF repair compared with the normal control group (Table 1).

Among the normal subjects, the mean (± SD) time interval for septal and LV deformation was 362 (± 38) ms and 370 (± 46) ms, respectively. The mean (± SD) LV delay in the control group was −8 (± 16) ms.

Patients after TOF repair had a significantly delayed deformation of the interventricular septum relative to that of the LV when compared with the control group (Fig. 1). The deformation of the interventricular septum was significantly more delayed in TOF patients in NYHA functional class II than in patients in class I (Fig. 2). This delayed deformation of the interventricular septum correlated neither with age at operation nor with the duration of follow-up.

Comparison between patients after TOF repair with and without LV asynchrony. According to the mean LV delay among the normal subjects, a normal range (mean ± 2 SD) was plotted (Fig. 3). Using this normal range, TOF patients

---

**Table 1.** Regional Myocardial Deformation and Time Intervals: Comparison Between Healthy Control Subjects and Patients After Tetralogy of Fallot Repair

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects (n = 25)</th>
<th>Tetralogy of Fallot (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain (%)</td>
<td>Time Interval (ms)</td>
<td>Strain (%)</td>
</tr>
<tr>
<td>LV basal</td>
<td>24 ± 7.7</td>
<td>394 ± 102</td>
</tr>
<tr>
<td>LV middle</td>
<td>23.7 ± 7</td>
<td>362 ± 47</td>
</tr>
<tr>
<td>LV apex</td>
<td>21.3 ± 12</td>
<td>371 ± 56</td>
</tr>
<tr>
<td>LV (mean)</td>
<td>23 ± 6.7</td>
<td>376 ± 46</td>
</tr>
<tr>
<td>Septum basal</td>
<td>23.7 ± 5.3</td>
<td>369 ± 42</td>
</tr>
<tr>
<td>Septum middle</td>
<td>22.8 ± 5.8</td>
<td>344 ± 40</td>
</tr>
<tr>
<td>Septum apex</td>
<td>21.7 ± 7</td>
<td>375 ± 53</td>
</tr>
<tr>
<td>Septum (mean)</td>
<td>22.7 ± 3.4</td>
<td>363 ± 38</td>
</tr>
<tr>
<td>Left intraventricular delay</td>
<td>−8 ± 16</td>
<td></td>
</tr>
</tbody>
</table>

* Tetralogy of Fallot versus normal healthy subjects, p < 0.05.  
LV = left ventricular.

---

**Figure 1.** Comparison of the left ventricular delay between patients after tetralogy of Fallot (TOF) repair and healthy control subjects. Compared with control subjects, patients after TOF repair have significant left ventricular delay. *TOF versus normal healthy subjects, p < 0.05.

**Figure 2.** Comparison of the left ventricular delay between patients after tetralogy of Fallot (TOF) repair in New York Heart Association (NYHA) functional class I and those in class II. Patients in NYHA functional class II have significantly more left ventricular delay when compared with patients in class I. *TOF versus normal healthy subjects, p < 0.05.
were further divided into two groups (Fig. 3). The first group (group 1, TOF patients without LV asynchrony, n = 12, 48%) comprised the patients who had an LV delay within the normal range. The second group (group 2, TOF patients with LV asynchrony, n = 13, 52%) consisted of patients in whom the LV delay was longer than the normal range (i.e., 25.8 ms). The general characteristics, ECG, and echocardiographic findings of these patients are shown in Table 2.

Nine (69%) of 13 patients who had LV asynchrony had a follow-up period of more than 10 years. Compared with those in group 1, patients in group 2 had significantly reduced regional strain in the middle (p = 0.004) and apical segments (p = 0.004) of the interventricular septum (Table 2). The Tei index in group 2 was significantly higher (p = 0.004) and apical 2 SD) was plotted. Using this normal range, TOF patients were further divided into two groups: group 1, TOF patients without left ventricular asynchrony (n = 12, 48%) and group 2, TOF patients with left ventricular asynchrony (n = 13, 52%). Solid circles = patients after TOF repair; open triangles = healthy control subjects.

The QRS duration in group 2 was significantly prolonged (p = 0.004) compared with that in group 1 (Table 3). For prediction of LV asynchrony (defined as LV delay above the normal range, mean ± 2 SD, obtained from the control group), the area (95% confidence ranges) under the ROC curve of QRS duration was 0.77 (0.58 to 0.95) (Fig. 5). A QRS duration of more than 142 ms had 75% sensitivity and 73% specificity in identifying LV asynchrony. Because for a good prediction it is generally accepted that the area under the ROC curve should be more than 0.9, we consider the predictive value of the QRS duration for LV asynchrony to be rather weak.

**DISCUSSION**

**Ventricular asynchrony in patients after TOF repair.** To our knowledge this is the first tissue Doppler imaging study demonstrating that patients after TOF repair with right bundle branch block may have LV asynchrony. Previous studies have demonstrated that adult patients with left bundle branch block have LV asynchrony (8,14–16). Cardiac resynchronization therapy in these patients has consistently demonstrated significant improvements in quality of life, functional state, and exercise capacity (8,17). The data regarding right bundle branch block and LV asynchrony in the literature are sparse. Garrigue et al. (15) reported that patients with ischemic heart disease and dilated cardiomyopathy accompanied by right bundle branch block may have concomitant left-sided intraventricular asynchrony, which is invisible on the surface ECG. In the present study, we found that 52% of the patients examined after TOF repair with right bundle branch block had LV asynchrony, which was mainly due to the significant delay of deformation in the septum rather than in the LV lateral wall (Table 3). This pattern of asynchrony differs from that seen in patients with idiopathic dilated cardiomyopathy in whom the LV asynchrony is due to significant delay of the LV lateral wall (18).

The mechanism of this detected LV asynchrony in patients after TOF repair is most probably multifactorial. The cross-sectional and nonlongitudinal design of the present study cannot provide information on the onset of LV asynchrony in relation to the time of surgery. The

| Table 2. Comparison of the General Characteristics, Electrocardiogram, and Echocardiographic Findings Between Patients After TOF Repair Without LV Asynchrony and Those With LV Asynchrony |
|---------------------------------|---------------------|---------------------|
| **No LV Asynchrony**           | **LV Asynchrony**   |
| TOF Group 1 (n = 12)            | TOF Group 2 (n = 13) |
| Median age in yrs (range)       | 17 (3–35)           | 19 (9–32)           |
| Median age at operation in yrs (range) | 1 (1–12)          | 2 (1–17)            |
| Median follow-up period in yrs (range) | 10 (1–27)         | 13 (2–21)           |
| Number of patients receiving more than one operation | 6                  | 7                    |
| Mean QRS duration in ms (±SD)   | 136 (±22.57)        | 155 (±19.12)*       |
| Mean gradient across the RV outflow tract in mm Hg (SD) | 32 (±21.95)       | 22 (13.98)           |
| Number of patients with severe pulmonary regurgitation | 2                  | 3                    |
| Mean LV Tei index               | 0.38 (±0.06)        | 0.5 (±0.08)*        |

*Patients after TOF repair with LV asynchrony versus patients after TOF repair without left intraventricular asynchrony, p < 0.05.

LV = left ventricular; RV = right ventricular; TOF = tetralogy of fallot.
Does QRS prolongation secondary to right bundle branch block reflect LV asynchrony? Data regarding the value of QRS duration in prediction of LV ventricular asynchrony vary considerably in the literature. Earlier studies showed that patients with left bundle branch block and QRS duration of more than 120 ms are the best responders for cardiac resynchronization therapy (17). More recent studies have reported that cardiac resynchronization therapy can also be effective in patients with narrow QRS duration (22). Therefore, new markers of asynchrony, other than the ECG, which are more directly related to cardiac mechanical function, are desirable.

Tissue-Doppler–derived velocity has been used in recent studies to quantify ventricular asynchrony. In the present study, we used tissue-Doppler–derived strain to identify ventricular asynchrony. Compared with tissue-Doppler–derived velocity, strain is more reliable in reflecting regional myocardial function because it is less affected by the global heart motion (23,24). In our study we found that the predictive value of QRS duration for detection of LV asynchrony was rather weak. Accordingly, we conclude that QRS prolongation associated with right bundle branch morphology is not sensitive for the detection of LV asynchrony in patients after TOF repair. Similar findings were also reported by Garrigue et al. (15) in ischemic adult patients.

Effect of LV asynchrony on regional and global LV function after TOF repair. Impaired systolic LV function after surgical correction of TOF has been previously reported (4,11). However, the influence of ventricular asynchrony on the regional and global ventricular function has not been previously studied in this group of patients. We found that, in patients after TOF repair with LV asynchrony, septal systolic deformation was significantly reduced and delayed compared with those without LV asynchrony. The delayed segments in a ventricle with asynchrony contract under more stress and, thus, will undergo hypertrophy and eventually will have reduced function (25).

Table 3. Regional Myocardial Deformation and Time Intervals: Comparison Between Patients After TOF Repair Without and Those With LV Asynchrony

<table>
<thead>
<tr>
<th></th>
<th>No LV Asynchrony</th>
<th>LV Asynchrony</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOF Group 1 (n = 12)</td>
<td>TOF Group 2 (n = 13)</td>
</tr>
<tr>
<td>Strain (%)</td>
<td>Time Interval (ms)</td>
<td>Strain (%)</td>
</tr>
<tr>
<td>LV basal</td>
<td>21 ± 5.7</td>
<td>372 ± 50</td>
</tr>
<tr>
<td>LV middle</td>
<td>22.4 ± 7.7</td>
<td>369 ± 44</td>
</tr>
<tr>
<td>LV apex</td>
<td>14.5 ± 8.6</td>
<td>356 ± 49</td>
</tr>
<tr>
<td>LV (mean)</td>
<td>19.1 ± 3.6</td>
<td>366 ± 44</td>
</tr>
<tr>
<td>Septum basal</td>
<td>20.6 ± 7.5</td>
<td>348 ± 52</td>
</tr>
<tr>
<td>Septum middle</td>
<td>19. ± 5.1</td>
<td>351 ± 43</td>
</tr>
<tr>
<td>Septum apex</td>
<td>19.8 ± 6.8</td>
<td>351 ± 33</td>
</tr>
<tr>
<td>Septum (mean)</td>
<td>19.8 ± 4.2</td>
<td>350 ± 44</td>
</tr>
<tr>
<td>LV delay</td>
<td>−12 ± 19</td>
<td></td>
</tr>
</tbody>
</table>

*Patients after TOF repair with LV asynchrony versus patients after TOF repair without left intraventricular asynchrony, p < 0.05.
LV = left ventricular; TOF = tetralogy of Fallot.
Using the ordinary M-mode derived fractional shortening to estimate the LV systolic function in patients after corrective surgery of TOF is not adequate because the geometry of the LV is altered secondary to the paradoxical septal motion. In contrast, the Tei index can reflect the global LV function independently of geometrical assumptions (26). We found that the Tei index in the TOF patients was significantly higher than in control subjects, thus reflecting altered global function (Table 1). Furthermore, we found that, in patients with LV asynchrony, the Tei index was significantly higher than in patients without LV asynchrony (Table 3, Fig. 4). This suggests that LV asynchrony in this setting is associated with LV dysfunction.

Prolongation of the QRS duration in patients after TOF repair increases the risk for ventricular arrhythmia and sudden cardiac death (27). Recently, Ghai et al. (28) have demonstrated that LV dysfunction is an additional risk factor for sudden cardiac death when associated with QRS prolongation. However, the underlying pathogenesis for this association was not clarified in their work. The LV asynchrony observed in our study could partially explain it, because we found a close association between QRS prolongation and LV dysfunction as well as LV asynchrony. Therefore, cardiac resynchronization therapy should be considered for TOF patients with LV intraventricular asynchrony.

Study limitations. Ideally, for determination of ventricular asynchrony, both ventricular walls of interest should be visualized simultaneously using a wider sector and examined in the same cardiac cycle. However, this will carry two disadvantages for tissue-Doppler imaging. First, it will reduce the frame rate of the obtained loop, which is unacceptable to measure short existing cardiac events. Second, strain measurements are angle-dependent, possibly more so than other Doppler modalities. If the regional myocardial strain of the interventricular septum and the ventricular lateral wall is simultaneously determined, the angle between the beam and the walls of interest could be more than 30°. This will make the interpretation of the strain curve inaccurate. Therefore, in the current study, each ventricular wall was visualized within the narrowest possible sector and assessed separately. To minimize the effect of heart rate variability on the parameters measured, three consecutive heart cycles were analyzed, and a mean from each parameter was calculated.

Conclusions. Left ventricular asynchrony may exist in patients after TOF repair with right bundle branch block. This LV asynchrony is associated with a reduction of both regional and global LV function.

Acknowledgment

We are grateful to Anne M. Gale, ELS, of the Deutsches Herzzentrum Berlin, for editorial assistance.

Reprint requests and correspondence: Dr. H. Abdul-Khaliq, Klinik für angeborene Herzfehler/Kinderkardiologie, Deutsches Herzzentrum Berlin, D-13353 Berlin, Germany. E-mail: abdul-khaliq@dhzb.de.

REFERENCES