Pulmonary Regurgitation Is an Important Determinant of Right Ventricular Contractile Dysfunction in Patients With Surgically Repaired Tetralogy of Fallot

A. Frigiola, MD; A.N. Redington MD, FRCP; S. Cullen, MB, BCh, BAo, FRCPI; M. Vogel, MD, PhD

Background—Evaluation of right ventricular (RV) function in patients with pulmonary regurgitation (PR) after tetralogy repair remains challenging because of abnormal RV loading conditions.

Methods and Results—We examined 124 patients, aged 21±11.4 years, who had tetralogy repair at 3.7±3.5 years. By Doppler echocardiography, 33 patients had mild, 22 moderate, and 69 severe PR; 55 had significant tricuspid regurgitation (TR). Myocardial velocities, myocardial acceleration during isovolumic contraction (IVA), strain, and strain rate were measured at RV and LV base. Tricuspid valve annulus was measured in a 4-chamber view. QRS, QT, and JT intervals and their dispersions were measured from 12-lead electrocardiogram. IVA in the RV was lower in all patients compared with controls (0.8±0.4 versus 1.8±0.5, P<0.0001) and correlated with the severity of PR (r=−0.43, P<0.0001), whereas myocardial velocities, and strain/strain rate did not. LV IVA correlated with PR (r=−0.32, P<0.001) and with RV IVA (r=0.28, P<0.003). Patients with severe PR had a higher incidence of TR (r=0.69, P<0.0001) and lower RV IVA (1.0±0.4 versus 0.6±0.3, P<0.0001), a larger tricuspid valve ring diameter (P<0.0001), and prolonged electrical depolarization (P<0.001). Age at surgery or examination did not correlate with PR and with RV function assessed by IVA. In the RV, IVA correlated inversely with QRS duration (P<0.01).

Conclusions—Although load-dependent myocardial velocities and strain are not influenced by the severity of PR and presence of significant TR, IVA demonstrates reduced contractile function in relation to the degree of PR and may be an early, sensitive index for selecting patients for valve replacement. (Circulation. 2004;110[suppl II]:II-153–II-157.)

Key Words: tetralogy of Fallot • pulmonary regurgitation • tissue Doppler • right ventricular function

The detrimental impact of pulmonary regurgitation (PR) on the long-term well being of patients after repair of tetralogy of Fallot (TOF) is increasingly being recognized.1–3 Many centers advocate pulmonary valve replacement for these patients.4,5 In a recent study, a positive effect of pulmonary valve replacement on right ventricle (RV) contractile function could only be demonstrated in patients with preserved RV function, whereas those with an impaired RV function showed no improvement.5 The conclusion from this study was that pulmonary valve replacement had been performed too late. However, so far, little attempt has been made to assess RV function in relation to the severity of pulmonary regurgitation. Furthermore, previous studies have used ejection-phase indices to determine RV function, which have their limitations in patients with abnormal loading conditions.6,7 We have recently validated isovolumic myocardial acceleration (IVA) in an experimental and a clinical study as a new tissue Doppler based index of systolic RV function.8,9 In addition to being a sensitive index of myocardial function, IVA was found to be less load-dependent than ejection-phase indices. The purpose of this study was to apply IVA in the clinical setting of patients with pulmonary regurgitation after repair of TOF.

Patients
We examined 124 consecutive patients who were seen at the out-patients department of the Great Ormond Street Hospital for Sick Children and the grown-up congenital heart unit at the Heart Hospital, London, between December 1999 and March 2003. The patients were not selected based on any clinical symptoms but rather on the basis that they had undergone an echocardiographic examination using tissue Doppler at the time of a scheduled routine out-patients clinic appointment and were in sinus rhythm at the time of presentation. All case notes were reviewed and clinical data including age, date, and method of surgery obtained. From the standard 12-lead electrocardiogram (ECG), QRS, QT, and JT duration and their dispersion were measured.

Echocardiography
Color-coded myocardial (tissue) Doppler echocardiography was performed with a frame rate between 126 and 211 Hertz using a GE Vingmed System 5 or ViVid 7 ultrasound scanner. The heart was imaged in an apical 4-chamber view. IVA, systolic and diastolic velocities, and strain/strain rate were measured in the myocardium at the base of the RV and LV free wall as previously described.8–11 IVA in patients with tetralogy was compared with IVA in 176 age-matched controls with normal hearts. Strain and strain rate data were compared with published normal values in the literature.12,13

Materials and Methods

From the Grown up Congenital Heart Unit (A.F., S.C.), The Heart Hospital, Westmoreland Street, London, UK; The Hospital for Sick Children (A.N.R.), Toronto, Canada; Kinderherzpraxis (M.V.), München, Germany.
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The diameter of the tricuspid valve ring was measured in diastole from a 4-chamber view. Standard blood pool Doppler interrogation was performed to determine the presence and degree of tricuspid and pulmonary valve regurgitation. Pulmonary regurgitation was classified as mild (no retrograde diastolic flow in pulmonary trunk with detectable regurgitant jet in the RV outflow tract), moderate (retrograde diastolic flow in main pulmonary artery), and severe (additional retrograde diastolic flow in branch pulmonary arteries).14

**ECG Analysis**
A standard 12-lead ECG was performed on the same day of the echocardiographic examination at a paper speed of 25 mm/s. QRS, QT, and JT durations and dispersions were measured manually.13 QRS duration was defined as mean of the QRS length in the 12 leads, from the first inflection to the final sharp vector crossing the baseline. The end of the T wave was taken as its return to baseline. JT interval was calculated by subtracting QRS from QT. QRS/QT/JT dispersions were defined as the difference between the maximum and the minimum QRS/QT/JT intervals in any of the 12 leads.16

**Analysis of Data**
The person (M.V.) who analyzed the echocardiographic studies was blinded to the analysis of the electrocardiograms (A.F.). Statistical analysis was performed using SPSS version 11.0 program. An unpaired Student t test was performed to compare results between patient groups; a 1-way ANOVA test was performed to compare data between different groups of patients with varying degree of pulmonary regurgitation.

P<0.05 was considered to indicate a significant difference between patient groups. Previously, data on intra-observer and inter-observer variability of tissue Doppler echocardiographic measurements8 and measurements of time intervals on the surface ECG had been established.9 To assess the reliability of the Doppler data, a sample of 40 random patients was selected and a second observer (S.C.), who was blind to the results of the first observer (M.V.), analyzed the degree of pulmonary regurgitation. The weighted kappa was 0.61, with a standard error for kw=0 of 0.14 and for kw=0 of 0.13. This indicates a very good agreement. We have chosen the weighted kappa because it is the method of choice for categorical variables.17

**Results**
Patients underwent operation at a mean age of 3.7 (median 2.6, range 0.1 to 18) years, and were examined at a mean age of 21 (median 19.5, range 1.5 to 61) years. The mean interval between surgical intervention and the echocardiographic examination was 17.3 (median 16.5, range 1 to 43) years. Among these 124 patients, 78 had been operated on using a transannular patch, 40 underwent infundibular resection with or without a patch placement, 3 had a patch with a monocusp pulmonary valve implanted, and 3 had no operative notes available (Table 1). We identified 33 patients with mild, 22 with moderate, and 69 with severe pulmonary regurgitation; 55 had significant tricuspid regurgitation (TR). Thirty-three patients had symptoms (Table 2). At time of the echocardiographic examination, those with previously documented atrial flutter/fibrillation were in sinus rhythm. Nine patients in New York Heart Association class II and III with a reduced exercise tolerance underwent pulmonary valve replacement at a mean age of 27.8±8.7 (median 24.9, range 17.9 to 40.8) years. These 9 patients survived the pulmonary valve replacement by a homograft implantation, but the follow-up in most patients is too short (<1 year) to provide meaningful data on the effect of pulmonary valve replacement on RV and LV function.

In all tetralogy patients, systolic function of the RV as evaluated by IVA, s-wave velocity, strain, and strain rate measurements was reduced compared with normal controls (Table 3). Patients with severe pulmonary regurgitation had a significantly lower IVA than those with mild or moderate pulmonary regurgitation, whereas systolic myocardial velocities, strain, and strain rate were not different between groups of varying severity of pulmonary regurgitation. Patients with a transannular patch had a significantly higher degree of PR compared with patients who had a subvalvular resection with or without a RV outflow tract patch (P<0.0001), whereas there was no difference between the last 2 groups.

### Table 1. Age at Surgery, Time of Examination, Electrocardiographic Measurements, and Tricuspid Valve Ring Diameter in 124 Tetralogy of Fallot Patients With Different Severity of Pulmonary Regurgitation

<table>
<thead>
<tr>
<th>Mild PR</th>
<th>Moderate PR</th>
<th>Severe PR</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, y</td>
<td>4±3.3</td>
<td>3.7±3.8</td>
<td>3.6±3.2</td>
</tr>
<tr>
<td>Age at examination, y</td>
<td>23±12</td>
<td>21±11</td>
<td>20±11</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>130±28</td>
<td>124±22</td>
<td>144±25</td>
</tr>
<tr>
<td>QT duration, ms</td>
<td>390±42</td>
<td>383±34</td>
<td>397±47</td>
</tr>
<tr>
<td>JT duration, ms</td>
<td>260±34</td>
<td>257±28</td>
<td>258±33</td>
</tr>
<tr>
<td>QRS dispersion, ms</td>
<td>51±38</td>
<td>41±17</td>
<td>47±27</td>
</tr>
<tr>
<td>QT dispersion, ms</td>
<td>88±59</td>
<td>82±37</td>
<td>100±43</td>
</tr>
<tr>
<td>JT dispersion, ms</td>
<td>114±70</td>
<td>98±56</td>
<td>119±62</td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>866±160</td>
<td>804±124</td>
<td>837±141</td>
</tr>
<tr>
<td>TV ring, cm</td>
<td>2.8±0.7</td>
<td>3.0±0.7</td>
<td>3.3±0.8</td>
</tr>
<tr>
<td>TV ring/BSA, cm²/m²</td>
<td>2.0±0.5</td>
<td>2.0±0.4</td>
<td>2.2±0.6</td>
</tr>
</tbody>
</table>

PR indicates pulmonary regurgitation; TV, tricuspid valve; BSA, body surface area; P, statistical difference of the mean between groups (assessed by 1-way ANOVA test).

### Table 2. Clinical Symptoms and Medications in Patients With Different Severity of Pulmonary Regurgitation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mild PR (n=33)</th>
<th>Moderate PR (n=22)</th>
<th>Severe PR (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>26</td>
<td>19</td>
<td>46</td>
</tr>
<tr>
<td>Chest pains</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Palpitations</td>
<td>8</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>AF/AFF</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>VF</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NYHA I</td>
<td>33</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>NYHA II</td>
<td>—</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>NYHA III</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Propanolol</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Amiodarone &amp; warfarin</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Diuretics</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

n indicates number of patients; AF/AFF, atrial fibrillation/flutter; VF, ventricular fibrillation; NYHA, New York Heart Association class.
Patients with a higher degree of PR had a higher incidence of significant tricuspid regurgitation TR \((r=0.69, P<0.0001)\), a larger tricuspid valve ring diameter corrected for the body surface area \((r=0.34, P<0.0001)\) and a prolonged electrical depolarization (QRS duration) on the surface ECG \((r=0.30, P<0.001)\), both surrogate indexes of RV dimensions. There was no correlation between PR and the other ECG parameters. Age at time of examination or age at time of surgery had no positive correlation with PR and with IVA, strain, or stain rate in the RV or in the LV. There was a negative correlation between tricuspid valve diameter, and QRS duration (surrogates of RV size) and IVA, whereas strain and strain rate did not correlate (Figure 1a and b).

There was a significant correlation between the degree of PR and IVA in the RV \((r=-0.43, P<0.0001)\), whereas RV myocardial systolic velocities, strain, and strain rate did not correlate with PR. LV IVA also correlated with PR \((r=-0.32, P<0.001)\) but LV systolic myocardial velocities, strain, and strain rate did not.

Interestingly, there was a strong correlation between systolic and diastolic myocardial velocities in both ventricles. In the LV, IVA correlated with s-velocities \((P<0.0001)\), whereas in the RV there was no correlation between any tissue Doppler derived indices of systolic function (Table 4). There was a positive correlation between RV and LV IVA \((r=-0.28, P<0.003)\). IVA in the LV was affected by the severity of pulmonary regurgitation in a similar way as IVA in the RV. Whereas IVA in the LV was within normal range in patients with mild and moderate pulmonary regurgitation, it was abnormally low in patients with severe pulmonary regurgitation. Patients with significant TR had a lower IVA in the RV \((0.6\pm 0.04 \text{ vs } 1.0\pm 0.05 \text{ m/s}^2, P<0.0001)\) but systolic velocities \((7.1\pm 1.9 \text{ vs } 7.5\pm 2.1 \text{ cm/s, NS})\), strain \((-29.2\pm 6.6 \text{ vs } -26.8\pm 3.9 \text{ %, NS})\), and strain rate \((-12.8\pm 2.2 \text{ vs } -11.8\pm 1.8 \text{ %/s, NS})\).
versus $-28.1 \pm 6.7\%$), and strain rate ($2.4 \pm 0.7$ versus $2.2 \pm 0.7$ per second) did not differ.

**Discussion**

This study demonstrates that RV and LV systolic function in patients with surgically treated TOF is affected by pulmonary regurgitation. This is independent of age of the patient at the time of surgery or at the time of the clinical examination. Patients, who in addition to PR have developed tricuspid valve regurgitation together with a distended tricuspid valve ring, have markedly reduced RV systolic function.

Previous studies have demonstrated that the presence and degree of pulmonary regurgitation influences exercise tolerance, the incidence of atrial and ventricular arrhythmias, and the risk for sudden unexpected cardiac death.\(^\text{15,16}\) Pulmonary valve replacement has been shown to improve ventricular function, functional class, stabilize QRS duration, and reduce atrial and ventricular arrhythmias.\(^\text{18–20}\)

In this study, we also examined the effect of pulmonary regurgitation on LV function and interestingly demonstrated a negative impact of severe PR on LV systolic function as well. This highlights the importance of right–left heart ventricular interaction in congenital heart disease, which has been previously demonstrated.\(^\text{21}\) In addition, moderate–severe LV dysfunction has been shown to have a predictive value of sudden cardiac death after repair of TOF, especially in combination with QRS duration $>180$ ms.\(^\text{22}\)

A previous study has demonstrated that if RV function is significantly impaired, it is unlikely to recover after pulmonary valve replacement.\(^\text{5}\) This study was a cross-sectional rather than a longitudinal study, which would be required to assess the temporal evolution of ventricular dysfunction in relation to the degree of pulmonary regurgitation. However, to be able to determine the optimal timing of pulmonary valve replacement, we need prospective data on patients with serial examinations of ventricular function at regular intervals.

The optimal timing of pulmonary valve replacement late after repair of TOF is controversial. A robust marker of preclinical RV dysfunction is required to facilitate decision-making, especially with the recent introduction of transcatheter valve implantation.\(^\text{23}\) At present, methods, which are currently available, include angiography, magnetic resonance imaging, and the various echocardiographic techniques.\(^\text{1,6–7,9}\)

Most measurements are performed during the ejection phase and thus are load-dependent, which makes their interpretation difficult. Previous studies failed to demonstrate a direct effect of pulmonary regurgitation on systolic RV function assessed angiographically or through cardiovascular magnetic resonance imaging.\(^\text{1,21}\) This is in agreement with data from our study, which failed to demonstrate any correlation between RV (or LV) systolic velocities and strain/strain rate with the degree of pulmonary regurgitation. This may be because of the load-dependent nature of systolic myocardial velocities, strain, and strain rate, which are all ejection-phase indices.\(^\text{11,13}\) Experimentally, strain rate, like strain, was found to be markedly load-dependent, whereas strain rate was somewhat more robust to changes in loading conditions than strain.\(^\text{24,25}\) IVA, which has the theoretical advantage of being even less affected by altered loading conditions, was significantly related to the degree of pulmonary regurgitation. We recently demonstrated experimentally\(^\text{8}\) and clinically\(^\text{9}\) that IVA provides a noninvasive, reproducible measurement of RV systolic function, which can be rapidly obtained and thus can be used in the long-term monitoring of these patients. Potentially, IVA may be useful in detecting early preclinical ventricular dysfunction, ie, before the onset of symptoms. One may speculate that interventions performed before obvious deterioration of systolic function\(^\text{3}\) may provide a better long-term results regarding preservation of systolic function. The latter may be influenced by the preoperative ventricular function and complicated by the effects of cardiopulmonary bypass during surgical intervention. It is evident that serial examinations before and after any intervention will be necessary to address this issues. We propose that IVA as a noninvasive easily obtained index that is less affected by changes in loading conditions than the conventional ejection-phase indices may be used for this purpose.

### TABLE 4. Correlation Between IVA, Myocardial Velocities, Strain, and Strain Rate

<table>
<thead>
<tr>
<th></th>
<th>RV (m/s²)</th>
<th>LV (m/s²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA (m/s²)</td>
<td>Pearson correlation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Significant (2-tailed)</td>
<td>0.520</td>
</tr>
<tr>
<td>s-Velocities (cm/s)</td>
<td>Pearson correlation</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>Significant (2-tailed)</td>
<td>1</td>
</tr>
</tbody>
</table>

IVA indicates isovolumic acceleration; s-velocities, myocardial systolic velocities; RV, right ventricle; LV, left ventricle.

*Correlation is significant at the 0.05 level (2-tailed).
†Correlation is significant at the 0.01 level (2-tailed).
Limitation of This Study
Although IVA has been evaluated clinically in patients with a systemic RV after Mustard/Senning repair of complete transposition, we have not formally compared it to the invasive gold standard: the analysis of pressure–volume loops by conductance catheterization in patients with repaired tetralogy. However, our recent clinical data suggest that IVA can be used similarly in the RV in a subpulmonary position. Like other previous studies, this study suffers from the lack of long-term longitudinal analysis and correlations with repeated formal exercise testing. To overcome this limitation, we have designed a new prospective study examining patients with TOF at 6-month intervals for a longer follow-up period incorporating exercise tests at regular yearly intervals.

We found a negative correlation between IVA and the duration of the QRS complex. Although the duration of the QRS complex can be considered a surrogate of RV size, it may also result in a prolonged isovolumic time interval and thus negatively influences IVA. Because the number of patients (especially those with complete right bundle branch block) is relatively small for a multivariate analysis, we did not perform such an analysis. We propose that this should be performed in a larger study in the future.

From the data of this study, we conclude that IVA, a tissue Doppler-based index, is well-suited to clinically assess RV function in patients after repair of TOF.

References
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