Adrenergic Nervous Activity in Patients After Surgical Correction of Tetralogy of Fallot

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OBJECTIVES

The study was done to define the role of the autonomic nervous system in postoperative tetralogy of Fallot.

BACKGROUND

Subsequent to surgical correction of tetralogy of Fallot, patients are at long-term risk of sudden death owing to ventricular electrical instability. The status of the sympathetic nervous system in these patients, known to play an important role in other patients at risk, remains unknown.

METHODS

We used 123I metaiodobenzylguanidine (MIBG) with tomographic imaging, combined with assessment of heart rate variability (HRV), to evaluate the activity of the sympathetic nervous system. We analyzed 22 patients who had undergone total correction of tetralogy of Fallot: 13 with either no or minor ventricular arrhythmias, and 9 with sustained ventricular tachycardia or ventricular fibrillation.

RESULTS

Analysis of HRV revealed a reduction in vagal control and sympathetic dominance in all patients compared with a healthy control group of 20 subjects. A significant difference was found in the standard deviation of all the adjacent intervals between normal beats (SDNN) in patients with or without severe ventricular arrhythmias. A significant reduction in uptake of 123I MIBG was demonstrated 30 min after IV injection, and a trend toward reduction after 5 h, associated with reduced washout indices. These data reflect a decrease in the number of nerve endings in the right and left ventricular walls, and an inhomogeneous distribution of the adrenergic nervous system. The uptake of MIBG was significantly reduced in the patients at risk of ventricular tachycardia or fibrillation.

CONCLUSIONS

Subsequent to surgical correction of tetralogy of Fallot, the positive correlation between myocardial uptake of MIBG, SDNN and the QRS dispersion confirmed the usefulness of analysis of the adrenergic nervous system to stratify patients at risk of life-threatening arrhythmias. (J Am Coll Cardiol 2001;38:2043–7) © 2001 by the American College of Cardiology

The adrenergic system plays an important role in regulating cardiac function and modulating its arrhythmogenesis. Both qualitative and quantitative abnormalities of sympathetic innervation have been demonstrated in patients with primary (1–3) or ischemic cardiomyopathies (4), or in patients with severe electrical myocardial instability (5,6). In patients who have undergone surgical correction of tetralogy of Fallot, sudden death is known to be a risk in the long term, particularly during effort. In these patients, sudden death has been related to ventricular arrhythmias, particularly ventricular tachycardia or fibrillation (7). Fibro-fatty substitution at the level of the infundibular and intraventricular septal scars and patchy myocardial fibrosis are considered the anatomical substrates of abnormal depolarization and repolarization causing the ventricular arrhythmias (8). In these patients, a large transmural ventriculotomy, combined with chronic pulmonary and/or tricuspid incompetence, produces severe hemodynamic modifications of the ventricular parietal walls, particularly those of the right ventricle, with secondary electrical instability (mechanoelectrical correlation) (9,10). The aim of this study was to determine whether postoperative patients with tetralogy of Fallot, at risk of electrical ventricular instability, also have abnormal sympathetic myocardial activity.

METHODS

This study was performed following permission of the local ethical committee. The patients had a supine, resting 12-lead electrocardiogram (ECG) on the day of tomography. A 24-h Holter monitoring and a cross-sectional color Doppler echocardiogram were performed the day before the scintigraphic assessment. The status of the autonomic nervous system was determined by iodine-123 (123I) metaiodobenzylguanidine scintigraphy (MIBG) and by analysis of heart rate variability (HRV).

The MIBG and SPECT analysis. Imaging techniques included a MIBG study with both planar and single-photon emission computed tomography (SPECT) techniques, with

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The washout index. Brieﬂy, for both acquisition and processing, repeated 5 h after the injection, using the same parameters, attenuation. Both the planar and SPECT studies were long-axis slices were reconstructed using a Butterworth fi lter, increments. The short-axis and vertical and horizontal 45° each segment was scored with a 3-point scale: 0 = normal, 1 = moderate defect (50% to 75%) and 2 = severe defect (<50%). A severity index was calculated for the 5-h studies by adding the single scores obtained for all 16 segments.

myocardial perfusion and metabolism being additionally evaluated using positron emission tomography (PET).

Thirty minutes after an IV injection of 370 MBq of 123I MIBG, a 10-min planar image in left anterior oblique (45°) projection (matrix 128 × 128) was acquired using a single-headed camera with a large field of view. Immediately after acquisition of the tomographic data in a 64 × 64 matrix (pixel dimension 6.4 mm), the camera was moved on a circular orbit of 180°, from a 45° right anterior oblique to a 45° left posterior oblique position, acquiring 45 of imaging in 6° increments. The short-axis and vertical and horizontal long-axis slices were reconstructed using a Butterworth fi lter (cutoff 0.45 Ny, power 10). No correction was applied for attenuation. Both the planar and SPECT studies were repeated 5 h after the injection, using the same parameters for both acquisition and processing.

Analysis of the planar images included the calculation of the washout index. Brieﬂy, four pixels 3 × 3 in size (about 1 × 1 cm) were selected in the anterior, lateral, inferior and septal walls of the left ventricle for both the 30-min and 5-h images. The mean number of counts in these regions of interest was calculated for both images. The index for the left ventricle was deﬁned as the ratio of the mean myocardial count at 30 min and at 5 h. The index for the right ventricle was calculated in the same manner using a single region of interest in the right ventricular wall. The ratio of counts from the relative to those obtained from the mediastinum was also calculated for both the right and left ventricle using the 30-min and 5-h images. With regard to the SPECT images, normalized short-axis slices were analyzed semiquantitatively by the consensus of three skilled observers. The left ventricular wall was divided into 16 segments, and each segment was scored with a 3-point scale: 0 = normal uptake (>75%), 1 = moderate defect (50% to 75%) and 2 = severe defect (<50%). A severity index was calculated for the 5-h studies by adding the single scores obtained for all 16 segments.

The assessment was completed by metabolism and perfusion myocardial analysis. The PET studies were both performed on the day following the MIBG–SPECT analysis, ﬁrst the N13-ammonia study, and 2 h later the F18-fluorodeoxyglucose (FDG) study. We used a PET scanner with a ﬁeld of view of 16.2 cm and a resolution of about 5 mm in the axial direction and 6 mm in the transaxial planes. The tracers were N13-ammonia (NH3-dose 740 MBq) for perfusion, injected in the basal condition, and FDG (FDG-dose 300 MBq) for metabolism, injected 45 min after an oral load of glucose (50 g). The emission scan started 4 min after the injection of ammonia, and after 45 min of fluorodeoxyglucose, and the acquisition lasted 15 min with both tracers. To check the repositioning of the patient in the scanner, a cross-shaped, low-power laser beam and pen-skin markers were applied. Severity indexes were then calculated both for perfusion and metabolism as in the MIBG SPECT study. Five subjects unaffected by cardiac disease (4 men, 1 woman; mean age 38 ± 11 years, range 28 to 58 years) served as a control group.

Heart rate variability. Twenty-four-hour ECGs were recorded on cassette tapes (dual-channel ICR recorder) and analyzed to determine HRV. The Holter recordings were analyzed by a Del Mar Avionics Holter System 563/A analyzer (operator-controlled analysis). The normal and aberrant complexes were discriminated, and all the adjacent intervals between normal beats (NN) were collected over a period of 24 h. All the normal intervals were then analyzed by a time-domain method. The parameters considered were the SDNN, the RMSSD, and the pNN50.

The recordings, collections and elaboration of the results were made according to guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (11). The control group comprised 20 healthy subjects, 8 men and 12 women, with a mean age of 45 ± 20 years.

Patient selection. Twenty-two patients were studied, 10 men and 12 women, with a mean age at operation of 11 ± 10.33 years and a mean follow-up period of 18.33 ± 6.37 years, who had undergone surgical correction of tetralogy of Fallot by means of a right ventriculotomy. All patients had good surgical results in terms of the residual transpulmonary gradient, which was <25 mm Hg, and intracardiac shunt- ing, pulmonary blood flow/systemic blood flow (QP/QS) at <1.3. All patients provided informed consent. None had a history of allergy to iodine, thyroid dysfunction or consumption of a medication known to interfere with uptake of MIBG, such as tricyclic antidepressants or sympathomimetic cold or decongestant preparations. Beta-blockers were interrupted in two patients 60 days before the study, with more frequent outpatient controls to verify the ventricular instability. In 16 cases (10 without ventricular arrhythmias, 6 with ventricular-sustained tachycardia; mean age at operation 11 ± 10.23 years; mean postsurgical follow-up 18 ± 6.93 years), the Holter recordings were suitable for HRV analysis. The other cases were excluded because of atrial
Table 1. SDNN, RMSSD, pNN50, QRS, QRSd, QTd and QTcd: Comparison Between Patients With and Without Arrhythmias

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients With Arrhythmias</th>
<th>Patients Without Arrhythmias</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>152 ± 18</td>
<td>150 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td>54 ± 22</td>
<td>34 ± 19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>QTd (ms)</td>
<td>92 ± 48</td>
<td>110 ± 49</td>
<td>NS</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>98 ± 0.6</td>
<td>130 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>103 ± 34.8</td>
<td>127 ± 25.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>38.8 ± 25.5</td>
<td>35.6 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>13.4 ± 19.6</td>
<td>12.3 ± 9.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant; pNN50 = percentages of adjacent normal beat intervals differing by more than 50 ms over the entire recording; QRS = QRS duration; QRSd = QRS dispersion; QTd = QT dispersion; QTc = QT-corrected dispersion; RMSSD = square root of the mean of the sum of the square differences between adjacent normal beat intervals; SDNN = standard deviation of normal beat intervals.

fibrillation (one patient) or excessive noise on the trace for an extensive period (five patients). The following electrocardiographic and echocardiographic parameters were measured in all patients: QRS duration (ms), QRS dispersion (ms), QT and QTc dispersion (ms), end-diastolic volume (ml/mg) of right and left ventricles and ejection fraction (%) of right and left ventricles. One patient had an implanted cardioverter device because of aborted sudden death. Ventricular fibrillation had been induced at an endocavitary electrophysiologic study in this patient.

Statistical analysis. The data are expressed as mean ± SD. Differences between groups were examined for statistical significance using analysis of variance. The correlations between two parameters were calculated by the linear regression coefficient. A p value < 0.05 was considered significant.

RESULTS

According to the severity of ventricular arrhythmias recorded on routine 24-h Holter monitoring during clinical follow-up, or on the ECG in the emergency room, we identified two groups of patients. No abnormalities or minor ventricular arrhythmias such as monomorphic or polymorphic isolated ventricular beats or sporadic couples were seen in 13 patients; in contrast, the remaining 9 patients had sustained ventricular tachycardia lasting longer than 30 s or requiring termination because of hemodynamic deterioration, or ventricular fibrillation.

The overall study group showed a reduced value of SDNN when compared with the control group (111.9 ± 32 vs. 154.3 ± 25, p < 0.0001), and no significant difference of pNN50 (13 ± 16 vs. 9.2 ± 5, p = NS), RMSSD (37.7 ± 21 vs. 32.7 ± 8, p = NS), and mean NN (868 ± 131 vs. 829 ± 115, p = NS). The mean values of the electrocardiographic parameters and of the HRV indexes in patients with or without arrhythmias are summarized in Table 1. Only QRS dispersion and SDNN evidenced significant differences in the two subgroups of patients.

Data on scintigraphic imaging are summarized in Tables 2 and 3. All patients undergoing surgical correction had a significant reduction of uptake of 123I MIBG in the images of the right and left ventricle obtained after 5 h in comparison with the normal subjects (Table 2). A reduction in the washout from the right and left ventricle was associated with an increased index of severity of uptake of MIBG. In patients at risk of ventricular tachycardia or fibrillation, the index of severity of uptake of MIBG was significantly more altered when compared to the surgically corrected patients without ventricular arrhythmias (Table 3). No differences were found between the groups of patients in terms of myocardial perfusion and metabolism, with all values being in the normal range. Comparisons between scintigraphic and HRV indexes are shown in Table 4.

DISCUSSION

It is well established that patients undergoing surgical correction of tetralogy of Fallot are at risk of sudden death during long-term follow-up. This tragic event seems to be related to ventricular electrical instability, itself probably due to focal fibrosis or fibro-fatty substitution around the ventricular scars and/or to the modifications of the right ventricular cavity due to chronic volume overload. Increased end-diastolic volume of the right ventricle and high values of QT dispersion and QRS duration, both electrocardiographic signs of abnormal repolarization and depolarization of ventricular myocytes, are known to be significant clinical predictive factors for ventricular electrical instability (12).

Autonomic nervous activity and sudden death. MIBG-SPECT ANALYSIS. Sudden death is also known to be induced by effort, as seen in patients with long QT-syndrome, myocardial ischemia and arrhythmogenic right ventricular cardiomyopathy (13), suggesting a potential role for the autonomic nervous system. In these patients, a myocardial adrenergic derangement has been demonstrated by means of 123I metaiodobenzylguanidine scintigraphy (14). Specifically, in our cohort of patients operated on for tetralogy of Fallot, one of them, not included in this series, suddenly died during physical activity at school, and another two patients, included in this study, had ventricular fibrillation.

Table 2. MIBG Scintigraphy Results: Comparison Between Patients Operated On and the Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>RV WI</th>
<th>LV WI</th>
<th>RV HMR</th>
<th>LV HMR</th>
<th>SI MIBG 30 min</th>
<th>SI MIBG 5 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>1.70 ± 0.20</td>
<td>1.63 ± 0.08</td>
<td>1.72 ± 0.15</td>
<td>2.20 ± 0.45</td>
<td>1.25 ± 1.26</td>
<td>2.25 ± 2.22</td>
</tr>
<tr>
<td>Patients operated on</td>
<td>1.55 ± 0.34</td>
<td>1.58 ± 0.33</td>
<td>1.44 ± 0.33</td>
<td>1.63 ± 0.38</td>
<td>5.43 ± 5.01</td>
<td>6.96 ± 5.26</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

HMR = heart-to-mediastinum ratio; LV = left ventricle; NS = not significant; RV = right ventricle; SI MIBG 30 min = severity index MIBG at 30 min; SI MIBG 5 h = severity index 123I metaiodobenzylguanidine (MIBG) at 5 h; WI = washout index.
and were resuscitated, one in a discotheque and the other while playing soccer.

Noradrenaline is the neurotransmitter of the adrenergic system. It is synthesized in enzymatic steps within the adrenergic nerve terminal, stored in the vesicles, and secreted in the synaptic space by exocytosis as a consequence of neuronal activity. Only a small fraction of the noradrenaline reaches the receptors on the myocyte. The majority returns to the neuron through an efficient uptake system. Metaiodobenzylguanidine is an analogue of noradrenaline. When it is injected intravenously it follows the same route of noradrenaline, utilizing by competition the same uptake system. 

123Iodine-labeled MIBG, therefore, can be used as a scintigraphic agent (14) to study both the sympathetic nervous system activation, evaluated by a higher washout or a lowered myocardial-to-mediastinal ratio on delayed images, and the dispersion of regional innervation, examining the inhomogeneity in the MIBG distribution in the myocardial wall (15). Fifteen minutes after an intravenous injection, the plasma level of 123I MIBG is very low. Good images of the distribution of the tracer on the ventricular wall can be subsequently obtained as the concentration in the ventricular cavity is negligible. The myocardial uptake of 123I MIBG serves as an index of myocardial concentration of sympathetic nerve endings and of the functional integrity of adrenergic neurons. The faster the washout, the more active the adrenergic system is. The activity of the autonomic nervous system on the sinus node can also be studied by means of analysis of variability in heart rate using 24-h Holter ECGs (16).

In our study, both these forms of analysis showed significant abnormalities of the adrenergic nervous system in patients who had undergone surgical correction of tetralogy of Fallot, particularly those at risk of sudden death.

HRV ANALYSIS. No significant changes of the parasympathetic indexes (pNN50 and RMSSD), comparing the results of control group and patient group, were demonstrated, revealing that this branch of the autonomic system has a normal activity.

On the contrary, a reduction of SDNN in patients when compared with the control group was evidenced, reflecting a sympathetic dominance in subjects operated on. The significantly reduced value of SDNN in patients with ventricular arrhythmias suggests an influence of the autonomic activity on the electrical instability in these subjects.

In this study we have demonstrated by means of MIBG–SPECT that significant sympathetic dispersion of regional innervation is found in the entire population of patients undergoing surgical correction of tetralogy of Fallot with transmural ventriculotomy, but particularly in the group with an increased risk of sudden death. A significant reduction of MIBG uptake after 15 min of endovenous injection and a trend toward reduction after 5 h, even if associated with a reduced washout, could reflect a decrease in the number of nerve endings on the right and left ventricular walls, but more relevant in our population was the inhomogeneous distribution of the adrenergic nervous system. Myocardial adrenergic derangement was particularly present in patients who had suffered ventricular tachycardia or ventricular fibrillation. This is consistent with the data reported by other investigators in different groups of patients. In particular, regional heterogeneity of MIBG uptake was reported by other investigators in different groups of patients. In particular, regional heterogeneity of MIBG uptake was particularly present in patients who had suffered ventricular tachycardia and a clinically normal heart (6), long QT-syndrome (17) and dilated cardiomyopathy (1).

Inhomogeneity of adrenergic fibers was most evident in those patients with the highest ventricular end-diastolic volumes and the lowest ejection fraction of the right ventricle. None of our patients had pathologic findings in terms of perfusion and metabolism, but this finding does not exclude focal structural alterations of ventricular myocytes nor abnormal substrates of myocardial depolarization and repolarization. The positive correlation between myocardial MIBG uptake and the value of SDNN and QRS dispersion confirms the value of analysis of the adrenergic nervous system so as to stratify the arrhythmic risk. The accuracy of the MIBG–SPECT study was validated by its consonance with results of HRV. Both show a predominance of sympathetic activity, the first reflected by qualitative and quantitative myocardial adrenergic derangement, and the second detected at the level of the sinus node.

Table 3. MIBG Scintigraphy Results: Analysis of the Operated Patients With and Without Arrhythmias

<table>
<thead>
<tr>
<th>Variable</th>
<th>RV WI</th>
<th>LV WI</th>
<th>RV HMR</th>
<th>LV HMR</th>
<th>SI MIBG 30 min</th>
<th>SI MIBG 5 h</th>
<th>SI NH₃</th>
<th>SI FDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No arrhythmias</td>
<td>1.55 ± 0.38</td>
<td>1.56 ± 0.40</td>
<td>1.41 ± 0.41</td>
<td>1.60 ± 0.50</td>
<td>4.71 ± 2.43</td>
<td>6.43 ± 4.50</td>
<td>2.71 ± 3.20</td>
<td>3.43 ± 3.69</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>1.62 ± 0.12</td>
<td>1.67 ± 0.06</td>
<td>1.48 ± 0.28</td>
<td>1.68 ± 0.24</td>
<td>10.50 ± 4.93</td>
<td>10.25 ± 4.50</td>
<td>2.25 ± 3.86</td>
<td>1.2 ± 0.82</td>
</tr>
</tbody>
</table>

p Value
NS
NS
NS
NS
<0.05
NS
NS
NS

SI NH₃ = severity index N13-ammonia; SI FDP = severity index F18-fluorodeoxyglucose; WI = washout index; other abbreviations as in Table 2.

Table 4. Correlations Between Scintigraphic and HRV Data (16 patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>pNN50</th>
<th>SDNN</th>
<th>RMSSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV WI</td>
<td>r = −0.85</td>
<td>r = −0.70</td>
<td>r = 0.76</td>
</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.01</td>
<td>p = 0.006</td>
</tr>
<tr>
<td>LV WI</td>
<td>r = −0.84</td>
<td>r = −0.67</td>
<td>r = −0.74</td>
</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.02</td>
<td>p = 0.008</td>
</tr>
<tr>
<td>RV HMR</td>
<td>r = −0.71</td>
<td>r = −0.43</td>
<td>r = −0.66</td>
</tr>
<tr>
<td></td>
<td>p = 0.01</td>
<td>p = NS</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>LV HMR</td>
<td>r = −0.76</td>
<td>r = −0.48</td>
<td>r = −0.75</td>
</tr>
<tr>
<td></td>
<td>p = 0.006</td>
<td>p = NS</td>
<td>p = 0.007</td>
</tr>
</tbody>
</table>

HMR = heart-to-mediastinum ratio; HRV = heart rate variability; LV = left ventricle; NS = not significant; pNN50 = percentages of adjacent NN intervals differing more than 50 ms in the entire recording; RMSSD = square root of the mean of the sum of the square differences between adjacent NN intervals; RV = right ventricle; SDNN = standard deviation of all NN intervals; WI = washout index.
In patients who had been operated on, heart rate can be lower because of postoperative sinus node dysfunction, as often seen in congenital heart disease patients. Conversely, the enhanced sympathetic activity, independent of the absolute value of the heart rate, induces bounded, low-frequency variations of the intervals between beats, reflected by lower values of SDNN.

**Study limitations.** The number of patients with a useful Holter monitoring for HRV analysis is relatively low as some patients were excluded for technical reasons. Therefore, we could not repeat the examination because in our prospective study we had programmed the Holter recording the day before the scintigraphic examination as no significant modifications of the autonomic system had changed for a long time.

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**REFERENCES**


