The Anatomic Correlate of Ventricular Dysfunction in Tetralogy of Fallot

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SUMMARY

Using a quantitative microscopic technique, we quantitated right and left ventricular interstitial tissue space vs. myocardial fiber space in 4 groups of autopsied hearts: 1) 5 normal hearts; 2) 5 hearts from infants ≤2 years old with tetralogy of Fallot; 3) 10 hearts from children 2½–13 years old with tetralogy of Fallot, and 4) 5 hearts from adult patients ≤20 years old with tetralogy of Fallot. The proportions of interstitial tissue and myocardial fiber were quantitated using planimetry of the projected photomicrographs.

The proportion of interstitial tissue in Group II was similar to that in Group I, except for a mild increase of interstitial tissue in left ventricular apex of Group II. The proportion of interstitial tissue was significantly increased in Groups III and IV when compared with normal controls (p<0.001). When Groups II and III were compared, a significant increase of interstitial tissue in right ventricle (p<0.05) and left ventricular body (p<0.01) was noted in the latter group. And finally a comparison of Groups III and IV showed that although there was no difference between their right ventricles, and left ventricular apices, however the left ventricular body of Group III contained significantly more interstitial tissue and less myocardial fiber (p<0.001). It is thus demonstrated that up to 2 years of age both right and left ventricles of patients with tetralogy of Fallot were comparable to normals as far the proportion of myocardial fiber and interstitial tissue space were concerned.

After this age the proportion of interstitial tissue increases dramatically up to 13 years of age. In patients older than 13 years, the left ventricular myocardial fiber is further reduced with increasing interstitial tissue. Thus the anatomic correlate of myocardial dysfunction documented in older subjects with tetralogy of Fallot before and following total correction, consists of ever increasing interstitial tissue and loss of myocardial fiber, most probably due to persistent and chronic hypoxia. Total correction of tetralogy of Fallot prior to the age of 2, may prevent or halt the progression of such irreversible myocardial damage.

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CONSIDERABLE interest has been generated concerning "myocardial factor" in patients with surgically correctable heart disease.\textsuperscript{1)-4) Quite frequently patients undergo successful operative correction of their anatomic lesions but fail to obtain functionally satisfactory results because of poor myocardial function, rhythm disturbances or sudden death. Although this problem has been mainly recognized in patients with valvular heart disease,\textsuperscript{5)-8) it also occurs in patients with congenital cardiac anomalies.\textsuperscript{2)-4,9)-14) Higgins and Mulder found congestive heart failure (CHF) in more than one third of cyanotic and acyanotic patients with tetralogy of Fallot (TF) who had survived to the third decade of life without operation.\textsuperscript{15) Epstein et al found decreased cardiac output at rest as well as abnormal hemodynamic responses to exercise in 10 patients who were asymptomatic after total correction.\textsuperscript{3) Although successful total correction of TF can be performed in patients over the age of 30, the perioperative and late mortality rates of such patients are high and in the range of 10–20\%.\textsuperscript{16)-21) The importance of the problem of myocardial dysfunction in CHD, especially TF led us to undertake a quantitative microscopic study of the ventricular myocardium in 3 groups of patients with TF and a control group of normal heart. This report is concerned with the results of this quantitative comparative microscopic study.

\textbf{Materials and Methods}

Retrospective quantitation of the right and left ventricular myocardial fiber and interstitial tissue space was done in 4 groups of autopsied hearts uniformly preserved with 10\% formalin.

Group I consisted of 5 grossly normal hearts from children who died of a non-cardiac cause (Table I). Group II consisted of 5 hearts from patients less than 2 years of age with TF who died without operative intervention (Table I). Group III comprised 10 hearts from patients with TF between 2\(\frac{1}{2}\)–13 years of age. Group IV consisted of 5 hearts from adults with TF who were older than 20 years. The cause of death of the patients in Groups III and IV is given in Table I. All hearts were grossly examined, with particular attention to the coronary arteries which were normal in all cases.

In each heart, quantitative analysis of the right and left ventricular interstitial tissue vs. myocardial fiber space was performed from 3 myocardial specimens, 1 of which was taken from the lateral aspect of the right ventricular wall just below the level of the tricuspid valve and the 2 others from the left ventricle, 1 from the anterolateral wall just below the level of the mitral valve attachment and the other from the apex. Six histologic preparations (2 from each site) were made and
Table I. Data Concerning the Autopsied Hearts

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hearts</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Age (range)</td>
<td>1.5–11 yrs</td>
<td>1–24 mos</td>
<td>2.5–13 yrs</td>
<td>20–30 yrs</td>
</tr>
<tr>
<td>mean</td>
<td>6.1 yrs</td>
<td>12 mos</td>
<td>6.25 yrs</td>
<td>25 yrs</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Normal</td>
<td>TF</td>
<td>TF</td>
<td>TF</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Noncardiac</td>
<td>Nonsurgical</td>
<td>Nonsurgical</td>
<td>Nonsurgical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1Following or during shunt procedure: 2Following or during total correction: 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3Following or during total correction: 2</td>
<td></td>
</tr>
</tbody>
</table>

TF = Tetralogy of Fallot

Fig. 1. Photomicrograph of a stained cross-sectional histologic preparation. The amount of interstitial tissue space present within each photomicrograph was measured by planimetry and subsequently expressed as percent of total area.

stained with hematoxylin and eosin. Photographs of the histologic preparations at a magnification of 1000 were taken from the cross-sectional areas of 3 sample sites of each heart. Analysis of the photomicrographs was performed in a blind manner without knowledge of the origin of the histologic preparations and the grouping of the specimens. The photomicrographs were projected in a light projector and the contours of the myocardial fibers were drawn on a plain sheet of paper (Fig. 1). Subsequently the relative areas of myocardial fiber and interstitial tissue space were measured using hand-operated planimeter. The results were calculated as percent proportion of interstitial space vs. myocardial fiber. Mean variations among histologic preparations from the same cardiac region was 4.25%.
RESULTS

The proportion of interstitial tissue to myocardial fiber space in normal control hearts (Group I) was $17.582 \pm 4.024\%$ in the right ventricle, $17.804 \pm 3.236\%$ in the left ventricular wall, and $19.365 \pm 4.767\%$ in the left ventricular apex (Table II). Hearts from infants aged <2 years with TF (Group II) showed the following proportions of interstitial tissue space: right ventricle $19.429 \pm 4.380\%$, left ventricular wall $20.572 \pm 3.930\%$, and left ventricular apex $25.140 \pm 6.580\%$ (Table II). Statistically these values are not significantly different from corresponding values of normal control hearts except for left ventricular apex which showed a $p$ value of less than 0.05 (Fig. 2).

The proportions of interstitial tissue space in the right ventricle, left ventricular wall, and apex in Group III, i.e. older children with TF were

<table>
<thead>
<tr>
<th>Group</th>
<th>Right Ventricle</th>
<th>Left Ventricle (Wall)</th>
<th>Left Ventricle (Apex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>$17.582 \pm 4.024$</td>
<td>$17.804 \pm 3.236$</td>
<td>$19.365 \pm 4.767$</td>
</tr>
<tr>
<td>Group II</td>
<td>$19.429 \pm 4.380$</td>
<td>$20.572 \pm 3.930$</td>
<td>$25.140 \pm 6.580$</td>
</tr>
<tr>
<td>Group III</td>
<td>$32.121 \pm 12.300$</td>
<td>$28.438 \pm 10.980$</td>
<td>$31.350 \pm 12.150$</td>
</tr>
<tr>
<td>Group IV</td>
<td>$36.198 \pm 5.220$</td>
<td>$43.161 \pm 5.220$</td>
<td>$38.204 \pm 6.870$</td>
</tr>
</tbody>
</table>

Fig. 2. Comparison of the proportion of interstitial tissue space between Group I (normal children) and Group II (infants with tetralogy of Fallot <2 years old). RV=Right ventricle, LV=Left ventricle. Bars represent means.
Fig. 3. Comparison of the proportion of interstitial tissue space, between Group I (normal children), Group III (children with tetralogy of Fallot 2½-13 years old), and Group IV (adults with tetralogy of Fallot). RV=Right ventricle, LV=left ventricle. Bars represent means.

Fig. 4. Comparison of the proportion of interstitial tissue space between Groups II (infants with tetralogy of Fallot ≤2 years old) and Group III (children with tetralogy of Fallot 2½-13 years old). RV=Right ventricle, LV=Left ventricle. Bars represent means.
32.121±12.300%, 28.458±10.980%, and 31.350±12.150% respectively (Table II). These values are significantly different from normal controls (p<0.001) for all 3 sample sites (Fig. 3). A comparison of these values with Group II showed a significantly higher proportion of the interstitial tissue space in the right ventricle, and left ventricular wall in Group III (p<0.05 for right ventricle and p<0.01 for left ventricular wall) (Fig. 4).

Group IV hearts showed the following proportions of interstitial tissue space: right ventricle, 36.198±7.880%, left ventricular wall 43.161±5.220%, left ventricular apex 38.204±6.870% (Table II). A comparison of these values with the corresponding normal values showed a significant difference (p<0.001) for all 3 locations (Fig. 3). When proportions of the interstitial tissue spaces for the 3 sites of Groups III and IV were compared it was noted that these proportions were not different for the right ventricle and left ventricular apex, however the left ventricular wall of Group IV contained more interstitial tissue space compared with Group III (p<0.001) (Fig. 3).

**DISCUSSION**

It is well established that total correction of TF in patients older than 30 years carries a high mortality rate of 10–20%.\(^{16)}-^{21)} It is recently stressed that the frequency of CHF after repair of TF increases with age and this has been attributed to adverse effects from prior palliative procedures such as pulmonary vascular obstructive disease or left ventricular dysfunction.\(^{22)}-^{24)} It is well known that older tetralogy patients frequently require cardiac glycosides, salt restriction and diuretics for varying periods of time following successful repair of the lesion, even in the absence of other causes of CHF such as residual ventricular septal defect. Jones and Ferrans compared electron microscopic findings of operatively resected crista supraventricularis muscle from 11 patients aged 1–5 years with 8 patients aged 30–53 years. All patients had CHD associated with muscular right ventricular outflow tract obstruction. Their study showed ultrastructural changes of severe degeneration in the patients over 30 years of age. They interpreted these to reflect the stresses of prolonged right ventricular hypertrophy and hypoxia.\(^{26)} In a group of 58 patients with TF Jarmakani et al found that ejection fraction was significantly reduced in all, and averaged 0.50 following complete correction. The decreased right and left ventricular ejection fractions were attributed to impaired ventricular function despite clinical improvement after a shunt procedure or complete surgical correction.\(^{12)},^{16)} Epstein et al have shown an abnormally low cardiac index response to intense upright exercise in 9 out of 10 postoperative patients with TF aged 12–30 years who were
studied from 6 months to 4 years following surgery. James et al performed a comparative study of the exercise response in 43 asymptomatic patients, aged 7 to 41 years, 1 to 14 years after total surgical correction of TF. They found an inverse relationship between exercise capacity and age at operation irrespective of sex and the presence or absence of a previous aortopulmonary shunt procedure.

In the postoperative patients with body surface area less than 1.2 M² who had corrective surgical procedures at a relatively early age, there was no significant difference in maximal heart rate or physical working capacity in comparison with the corresponding controls. In contrast, in patients with body surface area of 1.2 M² or more, there were significant differences in maximal heart rate and physical working capacity as compared with the corresponding controls. Sunderland et al on the other hand showed normal values of left ventricular ejection fraction in 17 infants with TF who had corrective surgery performed before 24 months of age and were studied at least 12 months following correction. On the basis of their data they concluded that early correction might halt, reverse or eliminate the abnormalities of left ventricular function which continued to be present in the older child following total correction.

It is thus apparent that in patients with TF increasing age augments the risks of surgery and adversely affects the outcome and the postoperative functional ability. It has been shown that the ratio of interstitial tissue to myocardial fiber space does have a significant bearing on the development of CHF and low cardiac output syndrome in adult patients with acquired mitral regurgitation. Although Jones and Ferrans showed remarkable degenerative changes in the hearts of older patients with right ventricular outflow tract obstruction, their findings were qualitative and was concerned with only 2 age groups. Our quantitative study comparing 4 groups of hearts showed that percent of interstitial tissue space vs myocardial fiber in normal control hearts was similar to controls reported by Fuster et al. Thus in normal individuals, the proportion of interstitial tissue space does not seem to increase with age.

Our study is the first quantitative microscopic evaluation, showing remarkable anatomic changes in the ventricular myocardium in tetralogy patients. Thus the anatomical correlate of the abnormalities of the myocardial function in tetralogy patients corrected late in childhood as well as the reason for high operative mortality and morbidity in the older patients with TF become evident. These abnormalities are not due to cardiopulmonary bypass, nor surgery because we have specimens of all categories.

In conclusion our study has shown that:
1. In normal hearts the percent of interstitial tissue is less than 20%.

2. In infants with TF aged less than 24 months, the proportion of interstitial tissue space is similar to normals, except in the left ventricular apical region. The reason for this preferential location of initial abnormality is not clear to us.

3. In older children with TF (Group III) both right and left ventricular myocardium contained increased interstitial tissue compared with normals.

4. A comparison of adult tetralogy patients (older than 20 years) with normals again confirmed severe myocardial fiber loss and increase in the proportion of the interstitial tissue space.

5. Comparison of the infants with TF (Group II) with older children (Group III) showed loss of myocardial fibers and increased proportion of the interstitial tissue space in the right and left ventricular wall of the latter group.

6. Comparison of children with TF (Group III) and adults showed further loss of myocardial fibers and increase in the proportion of interstitial tissue space in the left ventricle of the adult tetralogy patients.

In the 4 groups of hearts, the amount and proportion of interstitial tissue was uniform in each heart, except for the apical region of the left ventricle in Group II and body of the left ventricle in Group IV (Table I). Therefore it seems most likely that the factor causing increased interstitial tissue space is a generalized one, and does not represent a focal process of myocardial fibrosis such as those produced by coronary artery disease, which was excluded in our specimens. We are not able to identify with certainty the material present in the interstitial space of the heart obtained from older patients with TF. Whatever it is, it is not unreasonable to think that such a pronounced increase in the noncontractile element may play a role in the development of myocardial dysfunction in the older operated and nonoperated patients with TF. Based on these findings we now can present an anatomic correlate of the hemodynamic abnormalities found in the postoperative patients reported by Epstein, James, and Jarmakani, and also explain the normal results reported by James and Sunderland in children who were totally corrected before 2 years of age.

We can also offer an explanation for the higher frequency of CHF, the need for digitalis and diuretics in older tetralogy patients and the higher risks of total correction in this category. Based on these results and in concurrence with other workers we recommend early total correction of TF i.e. before 2 years of age, when the myocardial damage is still negligible and when irreversible changes have not yet set in.
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