

Natural History of Tetralogy of Fallot in Infancy

Clinical Classification and Therapeutic Implications

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SUMMARY

We employ a classification system for tetralogy (TF) that correlates clinical findings with the nature and severity of right ventricular (RV) outflow obstruction. Group 0 infants are acyanotic, Group 1 and 2 infants have intermittent or mild cyanosis with hypoxic spells, Group 3 infants have severe cyanosis without spells, and Group 4 infants have severe cyanosis and pulmonary artery (PA) hypoplasia without spells. Since 1964, 59 infants were identified as having TF, documented by catheterization. Contrary to previous reports, the *majority* (40 of 59) were acyanotic (Group 0) at birth. Cyanosis and hypoxic spells subsequently developed at mean ages of 6.1 and 13.4 mo respectively, due to increasing muscular infundibular hypertrophy, as well as fibrosis and growth failure of the RV outflow tract, due to diminished pulmonary blood flow. At catheterization (mean age 12.7 mo) only two were still in Group 0. An understanding of the progressive nature of TF suggests that infants in groups 1–3 can have total correction before significant undergrowth of the RV outflow tract occurs. Shunts are performed only in Group 4 infants. Twenty-eight infants from ten weeks to two years old had total correction. Five were under six months. There were two operative deaths (7%) and no late deaths. Heart block did not occur. Late hemodynamic studies in 17 patients reveal good relief of RV obstruction (mean RV-PA gradient 19 mm Hg) and no significant shunts. The natural history of TF in infancy can be successfully interrupted in most cases by early correction.

Additional Indexing Words:

Cyanosis Congenital heart disease Right ventricular outflow obstruction Pulmonic stenosis

TETRALOGY OF FALLOT (TF) is a congenital malformation of the heart with a large nonrestrictive ventricular septal defect and right ventricular outflow obstruction. As a result, right ventricular, left ventricular, and aortic pressures in systole are equal, and they exceed pulmonary artery pressure. Cyanosis may be apparent in the perinatal period, or somewhat later in infancy. In previous reports, cyanosis has been noted within the first six months of life in 75 to 90% of infants with TF,¹ and the onset of cyanosis beyond this age has been

infrequent. Experience at the University of Oregon Medical School Hospital indicates that the majority of infants with TF pass through a precyanotic phase of substantial duration, during which a diagnosis of ventricular septal defect alone may be made. Although the early onset of cyanosis is probably due to closure of a patent ductus arteriosus, correction of neonatal anemia, or increasing activity,¹ Gasul and others have shown by serial catheterization studies that the delayed development of cyanosis is often due to progressing right ventricular outflow obstruction.^{2, 3, 4, 5} Our clinical observations and anatomic findings at operation also suggest that the cyanosis and hypoxic spells that develop after the perinatal period are usually associated with progressive muscular infundibular hypertrophy, as well as growth failure of the right ventricular outflow tract due to diminished pulmonary blood flow.

These assertions have important implications in the surgical management of infants with TF, since total correction in infancy can now be safely carried out in most cases before anatomic deterioration occurs.

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Methods

Clinical Material

The first total correction of TF in an infant under two years of age at the University of Oregon Medical School Hospital was performed in 1964. Since then, 59 patients under two years of age have had TF proven by cardiac catheterization and angiography. All patients have been followed periodically at the Medical School after their first visit, and all information used in this report was obtained by direct patient interview. Clinic visits included history and physical examination by a pediatric cardiologist, chest X-ray, electrocardiogram, and hematocrit determination.

Classification

The patients were classified in clinically distinct groups which related closely to the nature and severity of their right ventricular outflow obstruction (table 1). *Group 0* patients were acyanotic at the time of examination with no history of hypoxic spells. Clinically they resembled patients with ventricular septal defects. *Group 1A* patients had mild or intermittent cyanosis at rest. Hypoxic spells had not yet occurred. *Group 1* patients were similar, but typical hypoxic spells had been noted. Patients in *Group 1* or *1A* often had intermittent left to right shunts and normal oxygen saturations at rest. They had harsh systolic murmurs which decreased in intensity during hypoxic episodes. *Group 2A* patients had moderate persistent cyanosis that frequently increased with crying, but they had not yet developed hypoxic spells. *Group 2* patients were similar, but hypoxic spells had been noted. *Group 3* patients had persistent severe cyanosis and did not develop hypoxic spells. *Group 4* patients had persistent profound cyanosis without spells, and severe hypoplasia or atresia of the main pulmonary artery.

Results

Anatomy

Anatomic findings at surgery correlated closely with the clinical classification and with preoperative cineangiography. Right ventricular cineangiograms in *Group 1* or *Group 2* patients with hypoxic spells revealed that during the first systolic contraction after contrast injection the pulmonary artery opacified first. The aorta opacified later in systole as the infundibular obstruction intensified. At the time

of open intracardiac repair, 19 of 23 infants in *Group 1* or *Group 2* with hypoxic spells had muscular infundibular hypertrophy without pulmonary artery or annular hypoplasia. Four of five infants in *Group 3* without hypoxic spells had infundibular obstruction with moderate hypoplasia of the pulmonary annulus and pulmonary artery. The fifth infant had infundibular obstruction only. Infants in *Group 4* had severe hypoplasia or atresia of the pulmonary annulus and pulmonary artery.

A report of the histologic examination of tissue excised from the right ventricular outflow tract was available in 22 patients. Endocardial fibrosis was present in ten (ages 2-1/2 to 23 mo, mean 13 mo). In nine of these ten (as in most of the other patients as well) the clinical classification had progressed between birth and operation. Hypertrophic muscle fibers alone were described in four (ages 7-19 mo, mean 10 mo). The tissue was histologically normal myocardium in eight (ages 14 to 23 mo, mean 18 mo). Fibrosis was found at operation in patients who were in *Groups 1, 2, and 3* with equal frequency.

Natural History

The clinical classification, and by inference, the anatomic deformity became progressively more severe with the passage of time. At birth, 40 patients were in *Group 0*, three were in *Group 1A*, five were in *Group 2A*, one was in *Group 3*, and ten were in *Group 4* (table 2). At the time of their first visit to this medical center, at a mean age of 4.9 mo,

Table 2

Jan. 1964 - Aug. 1972

59 Patients

\bar{X} AGE (MOS)	GROUPS							
	0	1A	I	IIA	II	III	IV	Total
Birth -	40	3	0	5	0	1	10	59
1st Visit (4.9)	21	8	8	4	4	3	11	59
Cath (9.4)	2	7	17	4	9	9	11	59
Op* (14.5)	0	1	14	1	14	9	13	52

*Correction or Shunt

This table displays the clinical progression in all patients in this report. The clinical classification at birth is displayed on the top line, and with increasing age (displayed parenthetically in column 2) the patients progressed to a more advanced clinical classification. Although 52 patients are shown to have had operations, only 44 operations are mentioned in this report (28 corrections and 16 shunts). The number 52 and the mean age accompanying it include operations performed beyond infancy.

Table 1

Classification of Tetralogy of Fallot in Infancy

Group	Hypoxic spells	Cyanosis
0	No	No
1-1A	Yes-No	Intermittent or Mild
2-2A	Yes-No	Persistent, Moderate
3	No	Persistent, Severe
4	No	Persistent, Severe with pulmonary artery hypoplasia or atresia

only 21 patients were still in Group 0. At the time of cardiac catheterization, at a mean age of 9.4 mo, only two patients were in Group 0, and Groups 1, 2, and 3 had each doubled in relative size. At operation, at a mean age of 14.5 mo, all but two patients were in Groups 1, 2, 3, or 4. (One patient was in Group 1A and one was in Group 2A.)

Most striking is the group of 40 patients (67%) who were acyanotic at birth. At the time of their first clinic visit, at a mean age of 5.8 mo, 19 patients had progressed to more severe symptoms, and presumably, a more serious anatomic deformity, and this progression continued to occur (table 3). Cyanosis was first noted in these 40 patients at a mean age of 6.1 mo, with a range of one week to two years. On the average, there was a six-month interval between birth and the mean age at the onset of cyanosis (6.1 mo), approximately six more months until the mean age when catheterization was performed (12.7 mo), and approximately six more months until operation was carried out (17.7 mo). Hypoxic spells were first noted in 26 patients at a mean age of 13.4 mo.

The eight patients in Group 1A or 2A at birth with mild or moderate cyanosis had catheterization at a substantially younger mean age than Group 0 patients (5.8 vs 12.7 mo) because of their cyanosis. They developed "spells" at approximately the same mean age as Group 0 patients, however, (14.7 vs 13.4 mo) and had operations at a similar mean age (16.4 vs 17.7 mo). The ten patients in Group 4 had the most severe cyanosis and the most severe anatomic deformity. They ordinarily had shunt procedures, and these were required early in life (mean age 1.1 mo).

Table 3

Jan. 1964 - Aug. 1972

40 Patients

\bar{X} AGE (MOS)	GROUPS							Total
	0	1A	I	IIA	II	III	IV	
Birth	40	—	—	—	—	—	—	40
1st Visit (5.8)	21	7	8	1	2	1	0	40
Cath (12.7)	2	6	17	2	6	6	1	40
Op (17.7)	0	1	14	1	12	6	1	35

This table displays the clinical progression of only those 40 patients who were in Group 0 (acyanotic) at birth. Mean age is displayed in parentheses in column 2. As can be seen, at each succeeding clinical event fewer patients remain in Group 0, and an increasing number are found in more advanced classifications. At operation (correction or shunt) no patient remained in Group 0.

Surgical Experience

Twenty-eight patients had total correction in infancy with conventional cardiopulmonary bypass and without circulatory arrest.⁶ The mean age was 13 mo, with a range of 10 weeks to two years. Five patients were less than six months old. There were two operative deaths (7%) and no late deaths. Heart block did not occur. All survivors are asymptomatic, take no medications, and have resumed normal growth. Development has been normal or above normal in 17 patients tested thus far with the Stanford-Binet and Vineland tests of intellectual and social maturity. Of the 28 patients who had total correction, only nine required an outflow patch that crossed the pulmonary annulus. (Four of these had hypoxic spells preoperatively, and five did not.) Ten were treated without a patch graft and nine had a small ventricular patch alone, which could not result in pulmonic insufficiency. Late hemodynamic studies reveal satisfactory relief of outflow tract obstruction and are the subject of a separate report.⁷

Sixteen patients had a shunt procedure, of whom 12 were in Group 4. Seven had pulmonary atresia and five had severe pulmonary hypoplasia with a pulmonary artery less than one third the diameter of the aorta. Two patients in Group 1 and two in Group 3 had shunts early in the series. Currently, they would undergo total correction. There were five deaths (31%). Two occurred within 24 hours and three took place one month postoperatively. This mortality reflects the use of shunts only in cases with the most unfavorable anatomy.

Fifteen patients did not have operations within the first two years of life. One patient with favorable anatomy and occasional hypoxic spells (Group 1) is excluded from discussion. Although corrective surgery was indicated, he died following repair of a T - E fistula and closure of a gastrostomy and cervical esophagostomy which prohibited a median sternotomy incision. Of the 14 remaining patients who were doing well (Group 0 and 1A) when first seen, three died before any operation could be carried out. Six required urgent operative intervention, with three operative deaths. Two patients are being followed with persistent cyanosis. Both have pulmonary artery atresia and a large patent ductus. One patient has moved to another state. Only two patients came to elective operation (at three and one half years of age), and they are doing well.

Discussion

The use of a classification system for patients with TF that correlates clinical findings with the nature and severity of the anatomic deformity has provided valuable insight into the natural history of the disease. Although it is commonly recognized that infants with TF may be acyanotic at birth, the fact that this occurs in the *majority* of infants with TF has not been previously noted. This discrepancy may be attributed in part to the complete data available from birth for the infants in this report. This experience was derived from a heterogeneous group of patients from one state who were followed periodically by direct examinations in the same clinic. In this group with documented TF, *two-thirds (40 of 59) were acyanotic at birth*. Nonetheless, 23 of 40 patients (58%) who were acyanotic at birth came to total correction within the first two years of life.

This experience is supported by epidemiologic evidence that the relative incidence of TF compared with that of other congenital cardiac malformations increases with age (table 4).⁸ Of all congenital cardiac malformations, TF varies from 5 to 8% in relative incidence at birth. In older children and adults, the incidence rises to a mean of 14.5%, despite a high mortality in untreated patients. Concurrently, the relative incidence of ventricular septal defect falls from 28% of 17%. Notwithstanding the frequent spontaneous closure of ventricular

septal defects, this change in relative incidence may be due in part to the delayed development of cyanosis in many cases of TF.⁵

The consequences of delaying corrective operation beyond infancy are numerous. The reported mortality rates of elective correction later in childhood¹⁹ cannot accurately reflect the progressive and lethal natural history displayed by the 15 infants described earlier who did not have operations before age two.

Totally corrective operations in infancy can be carried out before fibrosis and undergrowth of the outflow tract become severe. Late postoperative angiography in our patients has demonstrated growth of the pulmonary annulus.⁶ In contrast, shunt procedures cannot improve the anatomic deformity, as flow through the right ventricular outflow tract is not enhanced. Indeed, TF may progress to pulmonary atresia following a shunt.²⁰ In infants, outflow obstruction is primarily muscular and is substantially relieved by infundibular resection alone. Thus, hypoxic spells are considered an indication of favorable anatomy for total correction, rather than an ominous sign.²¹ Only four of 23 patients with hypoxic spells preoperatively who had total correction required a patch across the pulmonary annulus to reconstruct the right ventricular outflow tract. In ten infants with spells extensive infundibular resection was sufficient to relieve the obstruction. Nine infants had infundibular resection plus a small ventricular patch that did not cross the pulmonary annulus. Even large ventricular patches in infants become insignificant in proportion to heart size as the infants grow, in contrast to the fate of patches in older children. Long-term right ventricular performance should be improved by the absence of pulmonary insufficiency or large adynamic segments. Other late complications have also been reported following shunt procedures.^{22, 23}

Early correction can also prevent the development of other anatomic disturbances which can complicate the technique or compromise the result of subsequent corrective surgery. Increased bronchial collateral circulation, pulmonary vascular obstructive disease due to thrombi, and hypoplasia of the pulmonary vascular bed can all contribute to pulmonary hypertension immediately after delayed total correction.^{24, 25} This pulmonary hypertension may subsequently regress, but it places a burden on the right ventricle in the postoperative period despite adequate relief of right ventricular obstruction. Early correction also prevents inadequate

Table 4

Percentage Distribution of Cardiac Malformations in Different Age Groups

	Birth*	Infants and childrens	Children and adult†
VSD	28.3	24	17
PDA	12.5	15	14.5
ASD	9.7	12	17.5
Coarct	8.8	4.5	7
Trans	8	4.5	1.5
TF	7	11	14.5
PS	6	11	13
AS	3.5	6.5	5
Truncus	2.7	0.5	—
Tricuspid atresia	1	1.5	1.5
All others	12.5	9.5	8.5

Abbreviations: VSD = ventricular septal defect; PDA = patent ductus arteriosus; ASD = atrial septal defect; Coarct = coarctation of aorta; Trans = transposition of great arteries; TF = tetralogy of Fallot; PS = pulmonic stenosis; AS = aortic stenosis; Truncus = truncus arteriosus.

*Mean of three series^{9, 10, 11}

†Mean of four series^{1, 12, 13, 14}

‡Mean of four series^{15, 16, 17, 18}

development of the left ventricle due to diminished pulmonary venous return.^{7, 26}

Our current management of infants with TF reflects this understanding of the natural history of the disease. Infants with slight or intermittent cyanosis and systolic murmurs undergo catheterization and angiography promptly, so that total correction may be undertaken without delay when symptoms progress. Indications for surgery are severe cyanosis, hypoxic spells, or severely retarded growth and development. The age and weight of the patient are of minor importance in considering the operative approach. All patients with pulmonary arteries at least one third the size of the aorta (Groups 1, 2 and 3) undergo total correction. Shunt procedures are reserved for patients with marked hypoplasia or atresia of the pulmonary artery (Group 4). Such patients may later require graft reconstruction of the outflow tract.

The early and late results of this approach compare very favorably with the traditional policy of early shunt procedures and delayed corrective operations. They have been reported in detail elsewhere.^{6, 7}

Comment

This approach to TF in infants should not be assessed in terms of survival rate alone. Children awaiting total correction may have serious behavior problems, often as a result of overly solicitous parents who hope to prevent hypoxic spells or episodes of severe cyanosis. Total correction at an early age often produces striking improvements in behavior. The accompanying relief of parental anxiety and concern has beneficial effects on relationships within the entire family. Following early correction, physical growth and development also return to normal rapidly.^{6, 7} When corrective surgery is delayed, on the other hand, the retarded physical growth and social development that often result may never be completely overcome.

References

1. KEITH JD, ROWE RD, VLAD P: Heart Disease in Infancy and Childhood. The Macmillan Co., New York, 1967, p 605
2. GASUL BM: Ventricular Septal Defect: Their Natural Transformation Into Those With Infundibular Stenosis or Into Cyanotic or Noncyanotic Type of Tetralogy of Fallot. *JAMA* 164: 847, 1957
3. GOTSMAN MS: Increasing Obstruction to the Outflow Tract in Fallot's Tetralogy. *Brit Heart J* 28: 615, 1966
4. LENDRUM BL, AGUSTSSON MH, ARCILLA RA, GASUL BM, MERCADO HG: Natural History of Patients with Acyanotic Tetralogy of Fallot. *Circulation* 24: 979, 1961
5. LYNFIELD J, GASUL B, ARCILLA R, LUAN LL: The Natural History of Ventricular Septal Defect in Infancy and Childhood Based on Serial Cardiac Catheterization Studies. *Amer J Med* 30: 357, 1961
6. STARR A, BONCHEK LI, SUNDERLAND CO: Total Correction of Tetralogy of Fallot in Infancy. *J Thorac Cardiovasc Surg* 65: 45, 1973
7. SUNDERLAND CO, ROSENBERG JA, MATARAZZO RG, MENASHE VD, LEES MH, BONCHEK LI, STARR A: Total Correction of Tetralogy of Fallot Under Two Years of Age. Postoperative Hemodynamic Evaluation. (abstr) *Circulation (Suppl II)* 46: II-98, 1972
8. CAMPBELL M: *In Paediatric Cardiology*, edited by WATSON H. St. Louis, C. V. Mosby Co., 1968
9. MACMAHON B, McKEOWN T, RECORD RG: The Incidence and Life Expectation of Children with Congenital Heart Disease. *Brit Heart J* 15: 121, 1953
10. CARLGREN LE: The Incidence of Congenital Heart Disease in Children Born in Gothenberg 1941-50. *Brit Heart J* 21: 40, 1959
11. HAY J, SMITHELLS RW: Personal Communication to H. Watson on Children Born in Liverpool 1960-64
12. NADAS AJ: *Pediatric Cardiology*, ed. 2. Philadelphia, W. B. Saunders Company, 1963
13. STUCKEY D: The Pattern of Congenital Heart Disease in Infancy and Childhood. *Medical Journal of Australia* 2: 433, 1954
14. HAIGE J: City of Liverpool Education Committee's Report on the Work of the School Health Service for 1963
15. CAMPBELL M: Strickland Goodall Memorial Lecture, 1957 (not published)
16. WOOD P: *Diseases of the Heart and Circulation*, ed. 2. London, Eyre and Spottiswoode, 1956
17. SCHRIRE V: Experience with Congenital Heart Disease at Groote Schuur Hospital, Capetown. *South African Medical Journal* 37: 1175, 1963
18. BLUEMENTHAL F: The Incidence of Congenital Cardiac Malformation. *Transactions of American College of Cardiology* 3: 209, 1953
19. PUGA FJ, DUSHANE JW, MCGOON DC: Treatment of Tetralogy of Fallot in Children Less Than Four Years of Age. *J Thorac Cardiovasc Surg* 64: 247, 1972
20. SABISTON DC, CORNELL WP, CRILEY JM, NEILL CA, ROSS RS, BAHNSON HT: The Diagnosis and Surgical Correction of Total Obstruction of the Right Ventricle. *J Thorac Cardiovasc Surg* 48: 577, 1964
21. CUMMING GR, CARR W: Hemodynamic Effects of Propranolol in Patients with Fallot's Tetralogy. *Amer Heart J* 74: 29, 1967
22. ROSS RS: Late Hemodynamic Complications of Anastomotic Surgery for Treatment of Tetralogy of Fallot. *Circulation* 18: 553, 1958

23. MCGAFF CJ: The Development of Elevated Pulmonary Blood Flow From Systemic Pulmonary Anastomosis. *Amer J Med* 33: 201, 1962
24. RICH AR: A Hitherto Unrecognized Tendency to the Development of Widespread Pulmonary Stenosis (Tetralogy of Fallot). *J Hopk Hosp Bull* 82: 389, 1948
25. WINDSOR RVJ: Obstructive Changes in the Pulmonary Arteries of Flalot's Tetralogy. *Ann Rep, Auckland (NZ) Med Res Foundation* 15: 19, 1962-1963
26. GUNTHEROTH WC: *In Heart Disease in Infants, Children, and Adolescents*, edited by Moss AK, ADAMS FH. Baltimore, The Williams and Wilkins Co., 1968, p 440

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