SEVERE TETRALOGY OF FALLOT—PATHOLOGICAL ASPECTS AND PROSPECTS OF SURGICAL REPAIR

By Jack L. Titus

INTRODUCTION

From both clinical and anatomic viewpoints, tetralogy of Fallot may be viewed simply as the combination of (1) congenital obstruction to pulmonary blood flow and (2) a large ventricular septal defect (VSD)[1]. Right ventricular hypertrophy and apparent or real dextroposition of the aorta may be considered to be more or less incidental to these primary anomalies.

The major obstruction to pulmonary flow most commonly is due to abnormality of the right ventricular outflow tract, that is infundibular stenosis, or pulmonary valvular stenosis, or both. Other anomalies obstructing pulmonary flow usually are regarded as associated or complicating conditions but are included in this discussion as part of the spectrum of Fallot's tetralogy. Functionally, the degree of pulmonic obstruction leads to normal or reduced pulmonary arterial pressure in the face of a large VSD. In this relatively simple concept of tetralogy of Fallot, complete obstruction to pulmonic flow may be present so that pulmonary atresia with large VSD can be considered as part of the spectrum of the anomaly.

The large ventricular septal defect (VSD) usually has a characteristic location. In the right ventricle it partly involves the region of the membranous septum, while in the left ventricle, it involves the basilar part of the outflow tract and is closely related to the aortic valve. In general, the defect is more superior in the septum than the usual, uncomplicated VSD. Its position is such that there is ready communication from the right ventricle to the aorta. The requirement that the VSD be large has the functional expression of equalization of the pressures between the right and left ventricles; morphologically, its cross-sectional area generally is equal to or greater than that of the aortic valve. From practical clinical and surgical anatomic considerations, any VSD, or combinations of VSD's, that fulfils these functional and size requirements when associated with significant congenital pulmonic obstruction may be considered tetralogy of Fallot.

It is recognized that while this simple concept of tetralogy of Fallot is useful for clinical therapeutic considerations, it is not always suitable for precise embryologic, pathogenetic, or morphologic studies.

Severe forms of tetralogy of Fallot are situations in which the anatomic features are such that either the functional cardiovascular abnormalities are more marked, or surgical correction is more difficult to achieve than in the majority of patients.

PATHOLOGIC ANATOMY

The pathologic anatomy of the severe forms of tetralogy of Fallot may be considered in the general categories of (A) severe obstruction to pulmonary flow, (B) unusual location of size of the ventricular septal defect, (C) the presence of other cardiovascular malformations, and (D) the presence of cardiovascular abnormalities that are secondary to or complications of the anomaly, including changes secondary to palliative therapeutic measures. This grouping of anatomic factors causing severe forms of Fallot's tetralogy is one of convenience for discussion. It is not intended to reflect exclusive categories nor embryogenetic differences.

Department of Pathology and Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minnesota U.S.A.

A. SEVERE OBSTRUCTION TO PULMONARY FLOW

The severity of the obstruction to pulmonary blood flow may be greater in some patients than in others because of changes in the infundibular region, the pulmonic valve, or the pulmonary arteries. In any of these sites the marked obstruction may be entirely congenital in nature or acquired changes may be superimposed on the congenital abnormality.

Infundibular pulmonic stenosis is the most frequent site of major obstruction to pulmonary blood flow in tetralogy of Fallot. Classically, the obstruction is at the "ostium" of the right ventricular infundibulum and results from the abnormal position of the crista supraventricularis, particularly the parietal limb, coupled with muscular hypertrophy. In some patients the degree of abnormality in development and the hypertrophic muscle may completely obstruct the ostium of the infundibulum. In other patients, the entire infundibulum may be diffusely hypoplastic with thick muscle on all sides. Not uncommonly, there is slight to moderate endocardial thickening in the region. The abnormal hemodynamics resulting from the stenosis cause turbulence of blood in the infundibulum, and in time secondary changes occur in the endocardium. These hemodynamic changes, which are similar to jet lesions, result in increase in endocardial thickness with collagen fibres, pseudo-elastic fibres and a few smooth muscle cells. Additionally, the degree of muscular hypertrophy increases as a result of excess work load. Either alone or in combination, the increased muscular hypertrophy and the endocardial thickening lead to more severe infundibular obstruction which may be total.

The pulmonic valve may be normal in size and anatomy in tetralogy of Fallot. In over one-half of patients the pulmonic valve is stenotic or, less commonly, completely atretic. Significant stenosis at only the pulmonic valve, with non-obstructing hypertrophy of the infundibular region, is uncommon but included for this discussion as a variant of tetralogy of Fallot. The morphologic appearance of the abnormal valve varies. Commonly the stenotic valve is a biscuspid, or less often tricuspid, one that has thickened cusps and fused, ill-defined commissures. Less frequently the stenosis is in the form of an unicommissureal valve with a small, central opening. Occasionally, only rudimentary fragments of tissue may be present in the valvular orifice. Atresia results from either lack of an orifice in the malformed valve, or complete failure of any development of valvular tissue between the right ventricular outflow tract and the pulmonary artery.

When the pulmonic valve is severely stenotic, whatever its morphologic appearance, the apparent annulus of the valve almost always is smaller than appropriate for the size of the right ventricle or the pulmonary artery. This apparently obvious statement merits emphasis because surgical treatment only of the valve may fail to relieve adequately the obstruction to pulmonic blood flow when the valvular ring is of small size.

Any form of valvular stenosis may be worsened, even to the point of complete obstruction, by changes occurring after birth. Abnormal hemodynamics and sometimes healed infection cause fibrotic and fibrocalcific changes in the valvular apparatus that may further narrow the orifice as may thrombosis in severely stenotic valves.

In a small number of cases of severe tetralogy of Fallot, the marked pulmonic obstruction may be contributed to by abnormalities of the pulmonary arteries. Marked stenosis or atresia of the main pulmonary trunk,

including so-called pseudo-truncus, without associated severe valvular and infundibular abnormality are uncommon. On clinical and surgical grounds such cases are included herein but it is recognized that anatomically these are not necessarily true tetralogy of Fallot. Thrombosis of the pulmonary arteries secondary to low blood flow may occur but is rare: when obstructing thrombi are found in tetralogy of Fallot, they usually occur in smaller, intraparenchymal branches of the pulmonary arteries. Congenital stenoses of the peripheral pulmonary arteries may be a site of further pulmonic obstruction in small numbers of patients. Unusual clinical and laboratory findings or technical difficulties at operation may be related to agenesis of one of the main pulmonary arteries. In this situation the absent pulmonary artery may have anomalous origin from the ascending aorta or from a patent ductus arteriosus. When a pulmonary artery originates from any vessel other than the main pulmonary trunk, its ostium commonly is stenotic.

B. ATYPICAL VENTRICULAR SEPTAL DEFECTS

In some patients with the tetralogy of Fallot, the condition may be more severe than usual from the standpoint of surgical repair because of the anatomic features of the ventricular septal defect (VSD). In a small number of patients with otherwise typical findings of the condition, the VSD may not be in the typical location, but be situated more anteriorly or extend more anteriorly in the ventricular septum so that it is closely related to the pulmonic valve as well as to the aortic valve. In this instances, the degree of infundibular obstruction may appear to be somewhat less because of the defect in the "floor" of the infundibulum; closure of this defect could increase the severity of obstruction if there were inadequate resection of the adjacent hypertrophic muscle.

Occasionally the VSD is larger in size than usual, extending into the posterior parts of the septum under the septal leaflet of the tricuspid valve. Such large defects have been termed, "ventricular septal defect of the atrioventricular canal type"[2]. The vectorcardiographic finding of a counterclockwise loop in the frontal plane in tetralogy of Fallot often is associated with this type of large VSD.

The VSD may be so large as to suggest a common (single) ventricle in angiocardiograms in patients whose clinical and anatomic findings are otherwise those of tetralogy of Fallot. This situation, while uncommon, merits recognition because it is amenable to surgical repair by current techniques in contrast to most types of true common ventricle.

One or more defects of the muscular septum may be present in addition to the typical VSD of the tetralogy. Failure to recognize and correct these additional defects may be responsible for an unsatisfactory surgical result. A variety of studies have reaffirmed that muscular ventricular septal defects whose diameter is greater than 3 mm. do have functional significance. It is possible that several rather small VSD's, as for example the "Swiss-cheese" septum, could in the aggregate have the same functional consequences as the usual large VSD of tetralogy of Fallot.

C. OTHER CARDIOVASCULAR MALFORMATIONS

A variety of other cardiac anomalies may be associated with tetralogy of Fallot and make the condition more severe in its clinical features or more difficult to correct surgically.

Anatomic variations of the coronary arteries in the tetralogy usually complicate surgical repair rather than causing functional abnormality. A single coronary artery may originate from the aorta and then give rise to the usual right, anterior descending, and left circumflex coronary arteries. With either a single right or a single left coronary artery, the major branch to the opposite ventricle often passes anteriorly across the outflow tract of the right ventricle in a position in which the vessel is vulnerable to damage by surgical procedures. A similar problem occurs when the major anterior descending coronary artery originates from the right coronary and passes anteriorly across the outflow tract of the right ventricle. Sometimes the same difficulty exists because the conal branch of the right coronary artery or a major right ventricular branch of the anterior descending coronary artery are unusually large and epicardial in location in the same region. A rare anomaly that can be treated successfully is a coronary arterial to pulmonary arterial fistula that occurs in association with severe pulmonic stenosis or atresia; some of these are associated with tetralogy of Fallot[3].

In the atrial septum, patency of the foramen ovale is common in tetralogy of Fallot. Usually the valve of the foramen ovale is competent so that when normal relationships between right and left atrial pressures are present, there is no shunting of blood. Atrial septal defects (ASD) of any type are uncommon. When they do occur as a coincidental anomaly they are most often in the fossa ovalis, that is, secundum type ASD's. Repair of these conditions generally is not considered to be a problem.

A variety of anomalies involving the aorta and especially the aortic arch occur in association with tetralogy of Fallot. As is well-known, a right aortic arch is found in approximately one-fourth of cases. Usually the branches are the mirror image of normal, including instances of the left subclavian artery arising as the fourth branch of the arch, and do not create significant clinical problems. Patent ductus arteriosus is uncommon, even though theoretically it seems advantageous for the ductus to remain open in these patients. Aortic rings of clinical significance, and therefore requiring surgical correction, also are relatively uncommon in the tetralogy. One form of aortic ring in tetralogy of Fallot results from the combination of right aortic arch, anomalous left subclavian artery as the fourth branch of the arch, and a left ligamentum arteriosum connecting the anomalous left subclavian and the left pulmonary arteries. While not strictly an anomaly, large collateral vessels, usually prominent bronchial arteries, may have functional significance because of compression of the esophagus or because they cause major technical problem during surgical repair.

Venous anomalies, either of systemic or pulmonic veins, are distinctly uncommonly associated with tetralogy of Fallot. Depending on the anomaly, it may or may not increase the clinical and surgical problems of the tetralogy. Management of a venous anomaly is, in general, a matter to be dealt with coincidentally with treatment of the tetralogy so that while one complicates the other, the association does not increase the severity of tetralogy of Fallot per se. One of the most common systemic venous anomalies is a persistent left superior vena cava which generally has no functional significance. Partial anomalous pulmonary venous connection occasionally occurs with tetralogy of Fallot.

Abnormalities of valves other than the pulmonic valve are unusual in tetralogy of Fallot and do not usually complicate repair of the tetralogy itself. Endomyocardial changes of significance also are uncommon. Secondary changes such as foci of endocardial sclerosis secondary to hemodynamic abnormalities or, rarely, foci of nonspecific interstitial myocardial fibrosis in older patients, generally do not increase the severity of the basic lesions.

The location of the atrioventricular conduction system in tetralogy has been known for many years. In general the major consideration is the fact that the bundle of His is closely related to the posterior-inferior margin of the VSD where there is danger of injury to the bundle during closure of the VSD.

D. SECONDARY CARDIAC ABNORMALITIES

Some cardiac changes may result from the tetralogy of Fallot, or from palliative treatment of it, and increase the severity of the disease. All are decidedly uncommon. Bacterial infection, depending on the location of the lesion, may increase the pulmonic valvular or infundibular abnormalities or add the problems of tricuspid incompetence. Hemodynamic effects as noted previously may increase pulmonic obstruction by virtue of endocardial reaction, or cause myocardial dysfunction because of extreme hypertrophy and attendant myocardial fibrosis. Complications of palliative shunt operation may increase the severity of the condition and even create inoperable situations. These complications include thrombosis of the shunt, pulmonary arterial thrombosis distal to the shunt in the intraparenchymal pulmonary vessels, and development of obstructive pulmonary vascular disease. The latter usually is a complication of longstanding shunts that permitted high pulmonary blood flows at systemic arterial pressures, such as the Pott's anastomosis.

SURGICAL ANATOMIC CONSIDERATIONS

From pathological studies, the most frequent problems associated with surgical repair of the severe forms of tetralogy of Fallot are those related to adequate relief of the obstruction to pulmonic blood flow, whatever the nature of such obstruction. Therefore, the remainder of this discussion will focus on that problem.

The readily apparent solutions to the problems of marked pulmonic obstruction are adequate resection of obstructing tissues and the use of some material to enlarge the right ventricular outflow tract and pulmonary artery. If these procedures do not provide the necessary relief, then consideration must be given to construction of a conduit from the right ventricle to pulmonary arteries that are, or are made to be, of adequate size. A variety of techniques to accomplish these goals have been proposed and utilized with success. The reports of my colleagues, Dr. D. C. McGoon and his co-workers[4,5] clearly define the prob'ems and present satisfactory solutions to most of the situations.

In the surgical treatment of tetralogy of Fallot by Dr. McGoon[4], the hospital mortality for the five year period 1963 through 1967 was 2% (2/121). Both deaths were due to low cardiac output from residual stenosis. About one-third (44 of 121) of the patients had patch-graft reconstruction of the outflow tract of the right ventricle utilizing autogenous pericardium. Usually (73% of cases) the patch graft extended across the valvular ring. Dilatation or aneurysmal bulging of the reconstructed outflow tract developed in only one of these 44 patients; a similar aneurysm occurred in one other patient in this series who did not have a patch graft. Postoperative right ventricular hypertension, defined as a ratio of 0.6 or greater for right ventricular: left ventricular peak systolic pressures, was most frequent in patients with severe, diffuse infundibular stenosis which frequently was associated with a hypoplastic valve ring. Persistently elevated right ventricular pressures occurred in patients that had an outflow patch graft as well as those who did not. Postoperative cardiac catheterization and angiocardiographic studies showed that the most common site of residual obstruction was the pulmonic valve. Although nearly one-third of the patients were demonstrated to have pulmonic valvular insufficiency after operation, no deleterious effects of this state could be identified specifically. In this regard, no differences in long-term surgical results have been observed in our institution in patients who had essentially no pulmonary valvular tissue compared to all other instances of tetralogy of Fallot.

More recently, McGoon and associates[5] restudied by cardiac catheterization 37 patients between one and four years after complete repair of tetralogy of Fallot. In two-thirds of the patients, the ratio of RV/LV systolic pressure had decreased from that recorded at the completion of the repair. This decrease occurred regardless of the use of a patch graft to reconstruct the outflow tract of the right ventricle. The RV/LV pressure ratio increased in 8 patients; this increase was less likely to occur when a patch graft had been used. All patients with a patch graft had moderate or severe pulmonary insufficiency. The most common site of residual pulmonic obstruction was confirmed to be at valvular level.

These and other studies clearly demonstrate the need for complete relief of pulmonary stenosis and the problems of obtaining it in some cases. Principally for this reason, and to a minor degree the possibility that postoperative moderate or severe pulmonic insufficiency might be a problem, use of valve-bearing prostheses[6] and aortic homografts[7] to construct a conduit from the right ventricle to the pulmonary artery in **carefully selected** instances of tetralogy of Fallot merits consideration. In our institution, aortic homografts have been used for this purpose since experimental studies in dogs[8] suggested their appropriateness. The homograft is a single unit that includes the ascending aorta, aortic valve, and the anterior leaflet of the mitral valve that has been preserved by freezing and sterilized by radiation[9].

The results of the use of such homografts in the four and one-half year period, September, 1967 through March, 1972 in 111 operations to establish continuity between the right ventricle and the pulmonary artery have been summarized by McGoon, Wallace and Danielson[10]. Most of the 111 operations were instances of truncus arteriosus or transposition of the great arteries with pulmonic stenosis. In consideration of the overall results of this use of aortic homografts, at this time the following general observations pertain. (1) All such grafts undergo calcification confined to the media of the aorta; to date this calcification has had no known deleterious effect. (2) The major determinants of immediate and relatively long-term results are the nature of the basic anomaly, the age of the patient (best results in the age group 5 to 12 years), and the clinical and hemodynamic status of the patient at the time of operation (best results in instances of relatively high systemic arterial saturations reflecting relatively good pulmonary blood flows). (3) The technical difficulty of the operation and the relatively long periods of extracorporeal circulation do not appear to be major determinants of risk. (4) In spite of careful attempts to prevent stenosis, pressure gradients after repair have been common between the right ventricle and graft (proximal anastomosis) and also between the graft and the pulmonary arteries (distal anastomoses); the ultimate significance of this disquieting finding remains to be determined. (5) Early deaths, that is within 30 days of operation, occurred in 35 cases, late deaths occurred in four and less than satisfactory results in six survivors. Sixty-four surviving patients appear to have a satisfactory result. Thus, the approximate incidence of a satisfactory long-term result, up to four and one-half years, is at best about 60% for this heterogeneous group of cases with the formidable problem of discontinuity between the right ventricle and pulmonary arteries.

The current surgical practice of my colleagues for relief of marked pulmonic obstruction is to consider first resection of muscular tissue and some form of reconstructive procedure such as patch grafts of autogeneous pericardium, when there is an intracardiac atretic or severely stenotic segment which may be infundibular or valvular or both. Use of a conduit, for which an aortic homograft currently is preferred, is restricted to the relatively small group of patients with atresia of the pulmonary artery as one end of the spectrum of tetralogy of Fallot.

SUMMARY

The pathological features that are responsible for the severe forms of tetralogy of Fallot may be divided into four anatomic groups: marked pulmonic obstruct-

ion, atypical ventricular septal defect(s), associated cardiac anomalies, and secondary cardiac abnormalities. Of these, marked obstruction to pulmonary blood flow is the most frequent major problem. The prospects of successful surgical repair are dependent in part on the anatomic findings. In general it appears that most cases can be managed by reconstruction, often requiring a patch graft, of the outflow tract of the right ventricle and the pulmonary artery. A small number of patients need consideration of the use of a conduit, such as an aortic homograft, to establish continuity between the right ventricle and pulmonary artery.

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LONG-TERM RESULTS OF CORRECTIVE SURGERY FOR THE TETRALOGY OF FALLOT

By Ken-ichi Asano

Corrective surgery of the tetralogy has been performed on 150 patients from April, 1965 to April, 1972. Forty-three patients among them had previously undergone the Blalock-Taussig's anastomosis. Obstruction of the right ventricular outflow tract was classified into three major types, that is, the localized infundibular stenosis, the valvuloinfundibular stenosis and the hypoplastic tubular stenosis. Large ventricular septal defects were all closed with a Teflon or Dacron patch. Outflow tract obstruction which could not be relieved by extensive infundibulectomy was reconstructed with a pericardial or Teflon patch or a homo- or heterologous valve-retaining patch.

The hospital mortality was nine per cent. The most common cause of hospital deaths was low output failure, particularly relating to residual obstruction of the outflow tract. There were seven late deaths. All of them demonstrated congestive heart failure due to large residual shunt associated with pulmonary valve insufficiency. Three of them died immediately after reoperation for closure of the residual defect. No persistent A-V block occurred in this series.

Both residual shunt and pulmonary valve insufficiency were important factors affecting the long-term results. Recently the former has not been experienced in patients with any anatomical types, but the occurrence of pulmonary valve insufficiency after surgery was unavoidable in patients with severe obstruction of the right ventricular outflow tract.

Department of Surgery, University of Niigata School of Medicine, Niigata, JAPAN.

Hemodynamics were studied in 37 follow-up patients Marked residual stenosis demonstrating the systolic pressure of the right ventricle more than 70 mm.Hg. was found in two of 16 patients without an outflow patch, in one of 9 patients with a small patch and in three of 12 patients with a large patch including a valve-retaining patch, respectively. Pulmonary valve insufficiency was reviewed in reference to cardiac function by measuring both the cardiac output and the stroke volume before and after administration of isoproterenol. Their increases after injection of isoproterenol were demonstrated more marked in patients with or without a small patch than in patients with a large patch, and circulatory assessment was more favourable in patients with a valve-retaining patch than in patients with a simple large patch.

On the other hand, hemodynamics concerning pulmonary valve insufficiency with or without stenosis were also studied in animals. In dogs with right ventricular—pulmonary artery bypass by a valveless graft, pulmonary regurgitation decreased after constriction of the graft. In the chronic experiments, comparing dogs of pulmonary valvulectomy to dogs of valvulectomy associated with constriction of the pulmonary artery trunk, both hypertrophy and distention of the right ventricular wall were more severe in the former than in the latter.

In conclusion, it appears that from these clinical and laboratory studies, pulmonary valve insufficiency after reconstruction of the right ventricular outflow tract with a small patch will be tolerable but reconstruction should be performed with a valve-retaining patch in patients with severe obstruction of the outflow tract.