Systemic Hypertension and Polycythemia in Tetralogy of Fallot

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SUMMARY

In our series of 111 cases of tetralogy of Fallot, the result revealed that cases with high Hb-content was accompanied more frequently by hypertension. However, their causes and effect relationship could not be clarified and more complicated mechanism was imagined to be acting.

From this series, these conditions of high Hb-content, hypertension and positive urinary protein will be estimated to occur in a patient at about the age of 10 years with tetralogy of Fallot, but for surgical point of view, such conditions do not contraindicate primary corrective surgery for the disease. Palliative operations are also found to be preferable to improve these conditions. In patients of an advanced age with hypertension, careful examinations including renal biopsy will be helpful to make the final decision for surgery.

Additional Indexing Words:

Polycythemia Hypertension Blalock operation Corrective surgery Renal biopsy

WITH an increase in numbers of corrective surgery for tetralogy of Fallot, some difficulties on operative indication and technique have been occasionally experienced because of accompaniment of other cardiovascular abnormalities or pathologic conditions to the original disease. One of these indicates tetralogy of Fallot with systemic hypertension and clinical follow-up on this condition has rarely been performed. In this report, we present 4 patients with systemic hypertension who revealed interesting pre- and postoperative course following Blalock operation and/or corrective surgery.

MATERIALS

In our Department, corrective surgery for tetralogy of Fallot has been done in 129 cases since 1965. Operative mortality was noted in 11 cases, indicating

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Table I

Group 1	Corrective surgery alone and post Blalock operation with unavailable previous records	85 cases
Group 2	Blalock operation followed by corrective surgery	26 cases

8.5% of its rate. Late death was found in 7 cases. In this report, 111 cases, consisting of 85 cases with respective unavailable records following the previous Blalock operation and corrective surgery alone, and 26 cases which Blalock operation was followed by corrective surgery, were investigated (Table I).

As standard values for Hb-content, blood pressure and the presence of urinary protein, respective 18 Gm/100 ml, 140 mmHg (systolic) and/or 90 mmHg (diastolic), and reactions of Albustix were used.

RESULTS

In group 1 of 85 cases, 30 cases revealed the value more than 18 Gm/100 ml of Hb-content and in these, 8 cases (25%) had systemic hypertension. Two cases with hypertension showed the presence of urinary protein. On the other hand, out of the remaining 55 cases with Hb-content less than 18 Gm/100 ml, 4 cases (7%) exhibited hypertension, however, no case of positive urinary protein was detected (Table II).

In group 2, before Blalock operation, 16 of 26 cases (62%) showed Hb-content of more than 18 Gm/100 ml. Five patients with high Hb-content revealed hypertension and of which, 2 cases were also positive in urinary protein (Table III). Following Blalock operation, 10 out of 16 cases with high Hb-content improved below a standard value. Five patients accompanied by hypertension were also ameliorated. However, positive urinary protein in 2 cases continued thereafter. Hb-content in all cases decreased below 18 Gm/100 ml after corrective surgery, but urinary protein in only 1 case remained unchanged (Table IV). The distribution of the age of patients with high

Table II. Group 1

1. Hb 18 Gm/100 ml	over 30/85 (38%) Below 55/85 (62%)
2. Blood pressure >140 mmHg (syst.) and/or >90 mmHg (diast.)	8/30 (27%) 4/55 (7.3%)
3. Positive urinary protein	2/8 0/4

Hb-content, hypertension and positive urinary protein in the group 1 and 2 ranged from 13 to 30 years. Operative death was noted in 4 of 8 cases with high Hb-content and hypertension in group 1, but no death in group 2 (Tables V and VI).

Table III. Group 2 (Before Blalock operation)

1. Hb 18 Gm/100 ml	over 16/26 (62%) below 10/26 (38%)
2. Blood pressure >140 mmHg (syst.) and/or >90 mmHg (diast.)	5/16 (31%) 0/10
3. Positive urinary protein	2/5 0/0

Table IV. Group 2 (After Blalock operation)

1. Hb 18 Gm/100 ml	over 6/16 below 10/16
2. Blood Pressure >140 mmHg (syst.) and/or >90 mmHg (diast.)	0/5
3. Positive urinary protein	2/5

Table V. Group 1: 85 cases

1. Hb	> 18 Gm/100 ml 30/85				< 18 Gm/100 ml 55/85			
2. Hypertension >140 mmHg (syst.) and/or >90 mmHg (diast.)	(+) 8/30		(-) 22/30		(+) 4/55		(-) 51/55	
3. Urinary protein	(+) 2/8	(-) 6/8	(+) 0	(-) 22/22	(+) 0	(-) 4/4	(+) 2/51	(-) 49/51
4. Operative death	2	2	(1)	(5)	0	0	0	(1)

Table VI. Group 2: 26 cases (Before Blalock operation)

1. Hb	> 18 Gm/100 ml 16/26				< 18 Gm/100 ml 10/26			
2. Hypertension >140 mmHg (syst.) and/or >90 mmHg (diast.)	(+) 5/16		(-) 11/16		(+) 0		(-) 10/10	
3. Urinary protein	(+) 2/5	(-) 3/5	(+) 1/11	(-) 10/11	(+) 0	(-) 0	(+) 0	(-) 0
4. Operative death	0	0	0	0	0	0	0	0

Effects of respective Blalock operation, corrective surgery following Blalock operation and primary corrective operation on cases with systemic hypertension have been evaluated including autopsy findings of 1 case.

Case: 1 26-year-old female.

Her delivery was normal, however, she was found to have heart disease at the medical examination for an unweaned child, at which time her growth was markedly retarded. Thereafter, her exercise tolerance gradually improved through the days of an elementary and a junior high school and at the age of 17, she was diagnosed

Table VII. Case 1: 26-year-old female

	First admission (Left Blalock op.)	Second admission (Corrective surg.)	At discharge
Blood pressure (mmHg)	190-128	134-92	105-83
Hematologic study			
RBC ($\times 10^4$)	749	607	443
Hb (Gm/100 ml)	17.1	17.6	14
Hct (%)	60	59.5	49
WBC	3,700	7,400	6,800
Urinalysis			
Alubstix for albumin	(+)	(-)	(-)
Sediment	Normal	Normal	Normal
Other tests			
Urinary VMA	(-)		
Regitin test	(-)

Fig. 1

to be tetralogy of Fallot and advised to have Blalock operation. At the 1st admission to the University Hospital, the patient was cyanotic and revealed clubbed fingers.

On auscultation, grade 4 systolic murmur was detected in the 3rd intercostal space along the left sternal border and also grade 4 systolic murmur was audible in the 2nd intercostal space along the right sternal border with thrill over the same area. ECG revealed electric axis of 105° and RVH. In the chest X-ray film, bilateral old tuberculous lesions and normal peripheral pulmonary vascularities were noted. Results of various tests including blood pressure, hematologic study, urinalysis etc were summarized in the Table VII. In May, 1970, with an expectation to improve blood pressure, Blalock operation was performed on the left. The postoperative course of blood pressure and Hb-content is shown in Fig. 1. Blood pressure started to drop 6 months postoperatively and its value just before corrective surgery was 134–92 mmHg. On the other hand, Hb-content gradually increased up to 17.6 Gm/100 ml until corrective surgery following a temporary postoperative amelioration.

At the 2nd admission in November, 1970, corrective surgery was done and her postoperative course was uneventful in spite of minimal wound infection. Blood pressure 2 months after surgery was 120–70 mmHg.

Comment:

In this series, 5 cases including this one, blood pressure was improved following Blalock operation. However, no definite trend for high Hb-content and positive urinary protein was obtained with surgery, and more ameliorations on these findings seemed to be achieved through corrective surgery.

Case 2: 12-year-old male.

The patient was noticed to be cyanotic shortly after birth, and pointed out to have congenital heart disease. At the age of 3, he had Blalock operation on the left, resulting in marked improvement of cyanosis and clubbed fingers. However, he was noticed to have hypertension at about the age of 6, and has been followed up at the outpatient clinic of Pediatrics of this University. His family history showed a hypertensive tendency on the father's side and his 2 younger siblings have been hypertensive for their ages.

At the 1st admission to the hospital, he was acyanotic, and on auscultation, grade 5 systolic murmur was audible in the 3rd intercostal space along the left sternal border with thrill. Shunt murmur of Blalock anastomosis was also noticeable in the 2nd intercostal space on the left. Second sound was accentuated. ECG showed $+105^\circ$ of electric axis, and hypertrophy of the right atrium and ventricle. Cardiac shadow was characteristic to tetralogy of Fallot and peripheral pulmonary vascularities were also within normal limit on the chest film. Results of various tests are disclosed in the Table VIII.

Changes of blood pressure are disclosed in the lower part of Fig. 1. Because of a decrease of blood pressure following the previous Blalock operation performed in 1961, which would be suspicious of the further desirable effect on blood pressure by Blalock operation on the opposite side, Blalock operation was carried out on the right in July of 1968.

At the 2nd admission in October, 1969, corrective surgery was performed despite continuous hypertension following the 2nd Blalock operation, because of no evidence of abnormal renal functions, and he was discharged on the 45th postopera-

Table VIII. Case 2: 12-year-old male

	First admission (Right Blalock op.)	Second admission (Corrective surg.)	At discharge
Blood pressure (mmHg)	180-138	190-80	168-85
Hematologic study			
RBC ($\times 10^4$)	746	448	379
Hb (Gm/100 ml)	21	16.1	12.5
Hct (%)	67	48.5	36
WBC	4,700	7,800	
Urinalysis			
Alubstix for albumin	(+ - ++)	(-)	(-)
Sediment	Normal	Normal	Normal
Other tests			
BUN (mg/100 ml)	17.6		
PSP (15 min)	30.5%		
CRP	(-)		
ASL-O (Todd)	125		
Urinary VMA	(-)		
Regitin test	(-)		
Histamin test	(-)		
Renogram	Normal		
Pneumoretroperitoneum	Normal		
Renal angiogram	Normal		

tive day uneventfully.

Comment:

In this case, family history might be important for this peculiar course of hypertension following Blalock operation. This experience is also impressive to give a clue in considering the patient with hypertension to operate upon for a few hours under extracorporeal bypass (controlled shock).

Case 3: 30-year-old female.

She was found to have congenital heart disease soon after her birth because of cyanosis and suffered from squatting after a short distance walk even in her junior high school days. During these periods she was diagnosed to be tetralogy of Fallot in the outpatient clinic of the other University hospital. At the age of 23, in addition to palpitation and edema, she was found to have hypertension with systolic pressure of over 200 mmHg and treated temporarily by antihypertensive drugs without desirable effect.

In the same year, she had Blalock operation. Since then her condition improved except for occasional bouts of palpitation. At the age of 28, during dancing, she suddenly experienced dizziness, nausea and vomiting which was ameliorated gradually, but headache aggravated reversely. She visited the outpatient clinic with complaints of palpitation and a sensation of compression over the anterior chest wall.

At the 1st admission, the patient was cyanotic and accompanied by clubbed fingers.

Fig. 2. Chest X-ray film of Case 3, indicating the presence of calcification in the aortic knob, concaved pulmonary artery segment, and fairly developed hilar and pulmonary vascular markings.

Table IX. Case 3: 30-year-old female

	First and second admission (Exam. for op. indication)	Third admission (Corrective surg.)
Blood pressure (mmHg)	205-132	178-116
Hematologic study		
RBC ($\times 10^4$)	710	642
Hb (Gm/100 ml)	18.7	17.5
Hct (%)	64	65.5
WBC	4,900	3,800
Urinalysis		
Alubstix for albumin	(+)	(+)
Sediment	Normal	brief RBC and WBC
Other tests		
NPN (mg/100 ml)	32.8	24.4
PSP (15 min)	15.5%	32.5%

On auscultation, grade 3-4 systolic murmur in the 4th intercostal space along the left sternal border and shunt murmur of Blalock operation in the 2nd intercostal space on the left were audible. ECG showed electric axis of $+135^\circ$ and biventricular hypertrophy with more prevalence of that of the right ventricle. Chest X-ray film revealed cardiac shadow compatible with tetralogy of Fallot and almost normal peripheral pulmonary vascularities. Calcification of the aorta also was demonstrable (Fig. 2). Results of tests are shown in the Table IX. The cause of dizziness and headache was attributed to vascular disorders of brain stem.

Shunt murmur of the previous Blalock operation disappeared during visits to the outpatient clinic after the 1st admission. It was 7 years after the operation. With the purpose to investigate the cause of hypertension and the possibility of radical operation, the patient was re-admitted. Results of chemical tests are in the Table VIII. After discharge from the 2nd admission, she suffered from severe nasal bleeding and resultant hypotension which she was able to tolerate well. Blood pressure of systolic 120 mmHg continued for a while, but no damage to the brain, heart and kidney was recognized. Because of well-tolerated episode of hypotension, corrective surgery was attempted and performed at the 3rd admission. During operation, marked tortuosity and calcification of the right coronary artery were found. The patient expired on the 2nd postoperative day. Gross anatomic findings of the postmortem examination revealed 550 Gm of the heart with marked hypertrophy of both ventricles, especially of the right ventricle, and the aorta and coronary arteries showed advanced atheromatous changes with calcification. Besides, hemorrhagic tendency was observed over the pericardial sac, pleural cavity etc. As microscopic findings including various kinds of staining, the wall of the aorta revealed deposits of cholesterol crystals and fats (Figs. 3 and 4), and in the kidney

Fig. 3. Histologic section of the aortic wall in Case 3 shows deposit of cholesterol crystals and calcium inside the intima. (Hematoxylin and eosin: orig. mag. $\times 40$)

simultaneous enlargement, congestion, cellular proliferation and hyalinization of the glomeruli were marked and indicated the presence of their sclerosis (Fig. 5).

Fig. 4. Microphotograph revealing massive deposit of fat in the intima of the aorta in Case 3. (Suddan III: orig. mag. $\times 12$)

Fig. 5. Enlarged glomeruli with hypercellularity and hyaline degeneration in the kidney. (Hematoxylin and eosin: orig. mag. $\times 100$)

Table X. Case 4: 10-year-old male

	First admission	At discharge
Blood pressure (mmHg)	144-100	100-70
Hematologic study		
RBC ($\times 10^4$)	847	562
Hb (Gm/100 ml)	25	
Hct (%)	77	56
WBC	5,800	8,600
Urinalysis		
Alubstix for albumin	(+++)	(-)
Sediment	Multiple RBC	Normal
Other tests		
NPN (mg/100 ml)	14.5	
PSP (15 min)	32.5%

Fig. 6. Histologic section of renal biopsy of a 10-year-old boy, demonstrating enlarged glomeruli for his age with capillary dilatations and slight hypercellularity, and red blood cells and eosinophilic substances inside the enlarged capsules. (Hematoxylin and eosin: orig. mag. $\times 100$)

Comment:

This case is in advanced age for tetralogy of Fallot, and concomitant high Hb-content, hypertension and positive urinary protein revealed many problems to decide operative indication, although relationship between macro- and microscopic findings in autopsy and the cause of death was difficult to estimate. These findings were the most advanced stage to consider the pathophysiology of tetralogy of Fallot.

Case 4: 10-year-old male.

The patient was found to have cyanosis soon after birth. At the age of 8, he was diagnosed to be tetralogy of Fallot. During these periods, cyanosis increased gradually and squatting was resulted following short distance walk. At the admission to the University Hospital, he was cyanotic with clubbed fingers. On auscultation, grade 4 systolic murmur was audible in the 3rd to 4th intercostal space along the left sternal border. Thrill was also palpable over the same area. Second sound accentuated, ECG revealed right electric axis deviation ($+120^\circ$), P-pulmonale and RVH. Chest X-ray film showed concaved pulmonary segment of cardiac shadow and usual pulmonary vascular markings. Results of various examination are summarized in the Table X.

From the previous experiences as to this situation, primary corrective surgery was attempted and carried out in February of 1971. Postoperative course was uneventful and the patient was discharged on the 32nd postoperative day.

Comment:

This is a case which was operated upon after this investigation, and also valuable to decide primary corrective surgery even under the situation accompanied by high Hb-content, hypertension and urinary protein at this range of the age.

Further pre- and postoperative morphological comparisons of the kidney by renal biopsy will be presented in other paper (Fig. 6).

DISCUSSION

The progression of surgical treatment for tetralogy of Fallot has been striking, however, to improve its operative results, various conditions accompanied by the disease should be understood. Pathophysiology of the disease is dependent on chronic metabolic disturbance of the tissue due to chronic oxygen deficit and on an effect of blood stasis secondary to an increase of circulating blood volume and polycythemia, basing on primary consequence of a decreased pulmonary blood flow with arteriovenous blood mixture at the level of the ventricles. Accordingly, to consider hypertension under this condition, a level of polycythemia or Hb-content, its duration and pathologic changes of the kidney, as the mostly related organ to blood pressure, should be minded.

In this paper, we used 18 Gm/100 ml of Hb-content as an indicator of polycythemia because of its adequate value as a standard in discussing operative mortality of the disease and in expressing its severity of the disease from surgical point of view.¹⁾ As to hypertension, although various factors such as age, sex etc should be considered, we chose value over 140 and/or 90 mmHg as respective systolic and diastolic pressure.

An increase of the erythrocyte count in association with hypertension has been recognized since Gaisboeck's description on polycythemia hypertonica in 1922.²⁾ However, the cause of hypertension was not clarified and viscosity of the blood was not also attributable to its cause because of no definite relation of a level of hypertension to an increased Ht. On the other hand, Lawren and

Berlin³⁾ pointed out the presence of polycythemia secondary to dehydration to any causes and psychosomatic stresses, and it was called "stress polycythemia", "benign polycythemia", and "relative" or "pseudo-polycythemia".⁴⁾⁻⁶⁾ Accompanied hypertension in this condition was also unable to clarify its nature.

Tarazi et al⁴⁾ suggested a possible etiologic relation between renal vascular hypertension and polycythemia due to renal vascular lesions basing on the renal origin of both erythropoietin and renin. McKee et al⁸⁾ on one hand, showed that hypertension was not a precursor to the development of erythrocytosis, either as a result of renal vascular damage or plasma volume depletion, but blood Hb-content appeared to be a significant contributor to the development of hypertension. Replogle and Merrill,⁹⁾ through experimentally induced normovolemic polycythemia raising the value of Ht from 38% to 60.5%, was unable to produce hypertension, however, revealed the effects of polycythemia upon metabolism of cells and hemodynamics physiologically. As being supposed from descriptions above, no exact cause-and-effect relationship between polycythemia and hypertension can be clarified and more complicated mechanism to produce hypertension may be acting on cases of tetralogy of Fallot. From the point of renal structures in cyanotic congenital heart diseases, Imai,^{10), 11)} stressing its relation to age distributions at death, classified glomerular alteration into 3 stages; 1) ectasis of the glomerular capillaries below the age of 5 years, 2) glomerular enlargement, degenerative changes of capillary walls, and proliferation and swelling of the mesangium at the age of 5 to 10 years, and 3) glomerular sclerosis over the age of 20 years. Case 3 of our experiences was a 30-year-old female and revealed glomerular sclerosis, calcification and atheromatous changes of the aorta and coronary arteries. Case 4 of a 10-year-old boy also exhibited proliferation of the mesangium nuclei in concomitant with fibrin thrombus in the glomerular capillaries by renal biopsy.

In our series of 111 cases of tetralogy of Fallot, 30 cases with over 18 Gm/100 ml of Hb-content in group 1 included 8 hypertensive patients (28%), but only 4 of the remaining 55 cases with below 18 Gm/100 ml of Hb-content were hypertensive (7.3%). However, 5 out of 16 cases with high Hb-content were hypertensive in group 2, and in the remaining 10 cases without high Hb-content, no hypertension in cases with high Hb-content was clinically apparent.

It has been reported that slight urinary protein was occasionally recognized in patients with cyanotic congenital heart disease and pathologic changes were always associated with positive urinary protein. In this series, 3 conditions—high Hb-content, hypertension and positive urinary protein—

will be estimated to occur in a patient at about the age of 10 years with tetralogy of Fallot.

Through this investigation, final results obtained in the group 1 and 2 clearly indicated that Blalock operation was preferable to improve high Hb-content and hypertension, however, present clinical observation alone could not give an active clue to perform Blalock operation because of continuous progression in open-heart surgery. That is, for example, a 10-year-old boy with renal biopsy underwent corrective surgery primarily, and was normotensive of 100–70 mmHg with negative urinary protein and normal sediment 2 weeks postoperatively. The fact showed possibly that at this age, anatomic abnormalities over the outflow tract of the right ventricle will be more important to the prognosis of tetralogy of Fallot than pathophysiology expressed as hypertension in this series.

Accordingly, from point of operative indication for tetralogy of Fallot, hypertension itself will not be decisive, however, its various effects including an especial relation to the kidney and age upon the disease should be considered as discussed in this paper.

In addition, renal biopsy will be a powerful mean to understand the effects of palliative or corrective surgery for tetralogy of Fallot on the kidney of the cyanotic patients and also should be utilized to investigate the reversibility of the renal structures following operations.

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