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SEVERE VALVULAR PULMONARY STENOSIS WITH NORMAL AORTIC ROOT*

IMMEDIATE RESULTS OF TRANSARTERIAL VALVOTOMY, WITH NOTES ON THE CLINICAL ASSESSMENT OF PATIENTS BEFORE AND AFTER OPERATION

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INTRODUCTION

SINCE THE FIRST valvotomies were performed for severe congenital pulmonary stenosis with normal aortic root,[1, 2] large numbers of patients with this malformation have undergone surgical treatment.

Initially the valve was attacked indirectly through the right ventricular wall. With incision and fracture of the dome stenosis, a severe valvular obstruction was converted to a moderate one with corresponding reduction in right ventricular pressure postoperatively. Mortality was low and results were consistently good in Brock's hands.[3] Other surgeons obtained less uniform success.[4] In some cases an inadequate reduction in right ventricular pressure postoperatively was found to be due to the presence of an unsuspected associated infundibular obstruction,[5] but in many cases it became obvious that the reason the right ventricular pressure was not reduced enough was inadequate division of valve tissue.

In younger children and infants the ease with which the rubbery dome of the severely stenosed pulmonary valve admitted knives and large dilators without influencing the degree of stenosis was demonstrated by Keith.[6] This type of result led Swan[4] to attempt excision of the valve stenosis by an approach through the pulmonary artery utilizing hypothermic techniques. The first report of five cases was encouraging, since normal right ventricular pressures and abolition of the pressure gradient across the valve resulted, but concern was expressed at the production of pulmonary valve incompetence.[7]

Poor results in younger patients at the Hospital for Sick Children, Toronto, led us to abandon the transventricular approach in favour of a modified Swan technique in January 1956. This paper presents the immediate results of the newer method of treatment in 21 cases of severe valvular pulmonary stenosis with normal aortic root operated on between January 1956 and August 1957. In this period 24 patients underwent operation with one death. Twenty-one of the 23 surviving patients have been studied by preoperative and postoperative cardiac catheterization.

MATERIAL AND METHODS

1. *The Patients*

The average age of the 21 patients is 6½ years and the range, 8 months to 16 years. Four are under 2 years of age, 7 are between 2 and 5 years of age, 5 are between 6 and 10 years of age and 5 are more than 10 years old. There are 11 males and 10 females in the series.

The diagnosis was made on clinical grounds in all cases. Electrocardiography was performed with standard techniques using direct writing equipment. The severity of pulmonary stenosis was confirmed preoperatively by cardiac catheterization. In 15 cases this study was done two days before operation while in 6 others the catheterization was performed at varying intervals up to two years previously. Cardiac catheterization was repeated on the 9th postoperative day on the average (range, 7th to 15th day).

Three of the 21 patients had had previous Brock operations without relief as judged by cardiac catheterization. These were Cases 5, 8 and 18, operated upon at 2 years, 4 years, and 4 years respectively.

2. *Surgical Technique*

The preoperative sedation is by meperidine (Demerol) and atropine in routine doses. Thiopentone (Pentothal) induction is followed by a relaxant (usually succinylcholine), endotracheal nitrous oxide with controlled respiration being employed throughout the remainder of the procedure. Infants are placed in a water bath at 40° C. and the temperature is lowered to 34° C. by addition of

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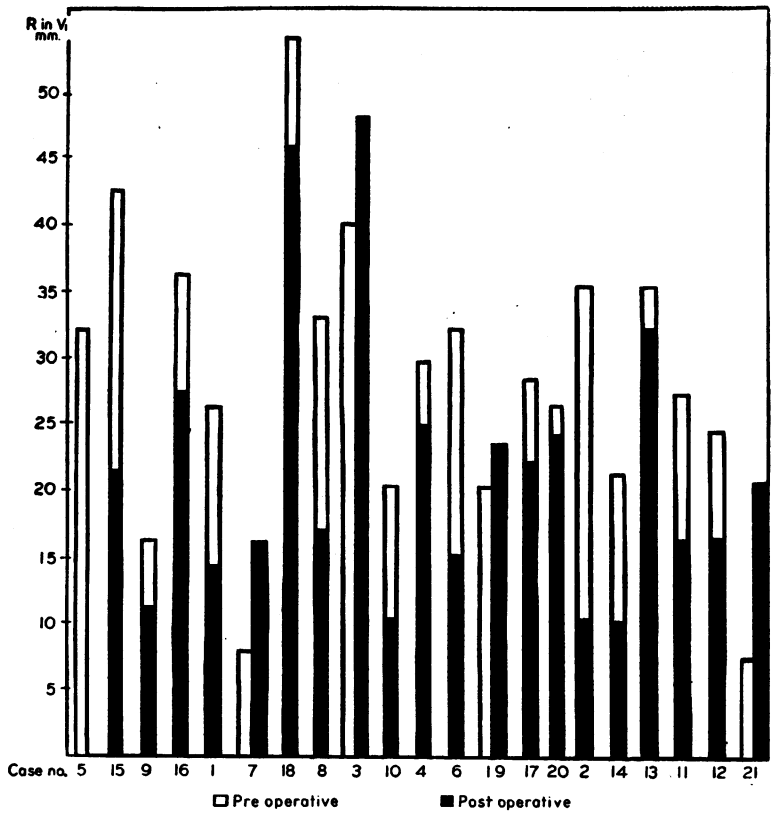

Fig. 1.—The electrocardiogram in 20 patients with severe valvular pulmonic stenosis with normal aortic root. The height in mm. of R in V_1 before and after operation.

ice. The infant is then placed on a refrigerating blanket and after a drift to about 31° C. rewarming is commenced. With older children blanket cooling is used with ice cubes covered in cellophane bags placed under the blanket till the temperature reaches 33° C. Drift to 31° is then permitted, at which level rewarming is started. Infants cool and drift much faster than the older children and have required close watching. Cardiac irregularities are very rare above the level of 30° C. and we feel this to be a perfectly safe level of hypothermia.

A midline sternal splitting incision is employed, care being taken to reflect the pleura from the under surface of the sternum and not enter either pleural cavity. The thymus gland is dissected back, the pericardial sac is opened and the dilated pulmonary artery palpated for the presence of a jet and the cone of the pulmonary valve. The infundibulum is examined for the possibility of infundibular stenosis. Tapes are placed around both superior and inferior vena cava within the pericardium and these tapes are passed through rubber tourniquets. No attempt is made to dissect the pulmonary artery free of the aorta. The pericardium is simply cleared down some distance to allow the placing of a curved Potts' clamp across the pulmonary artery from the left side, avoiding the tip of the atrial appendage. Two stay sutures are inserted a distance of about 3 cm. apart in the pulmonary artery about 1 cm. from the valve ring. These stay sutures are then picked up and a curved Potts' clamp is placed beneath them to include a portion of the pulmonary artery which is divided with the clamp on. A suture is then put in the end of this incision, tied and left on the needle driver for closure later; two other stay sutures are used to retract.

The superior and inferior vena cava are then occluded in turn, the heart is allowed to empty, the clamp is placed across the pulmonary artery and the clamp removed from the incised area in the artery. The valve is readily visualized and grasped with forceps and delivered into the incised portion of the pulmonary artery. The central orifice is usually of a size allowing the tip of the scissors to be inserted. If it is not, the cone is snipped off to make the opening large enough. Whether to make two or three cuts is a decision that varies with the individual surgeon. Our preference is for two cuts only because of the danger of regurgitation. These cuts are made right through the valve to the ring. At this time the heart is almost completely empty and the tape on the superior vena cava is loosened to allow blood to flow in and flood the right atrium, closing off the foramen ovale and preventing any possibility of air embolism. Just before the clamp is replaced on the incisional area of the pulmonary artery, the tape on the superior vena cava is completely released and the blood is allowed to well up and fill the right ventricle and the pulmonary artery down to the clamp and then the clamp is applied over the incised area. The pulmonary artery clamp is removed and the inferior vena cava tape is removed. The usual length of circulatory occlusion varies between 1½ and 3 minutes. The patient is then re-warmed with the warming blanket to 34° C. before returning to the recovery room.

RESULTS

1. *Physical Signs*

(a) *Cyanosis.*—Six of the 21 patients were cyanosed preoperatively (Cases 2, 7, 8, 10, 14 and 18). This ranged from gross cyanosis with clubbing to slight cyanosis on exercise. In all cases cyanosis was abolished postoperatively.

(b) *The second heart sound in the pulmonary area.*—At preoperative auscultation that part of the second heart sound due to aortic valve closure was obscured by the systolic murmur in 20 patients; in these, pulmonary valve closure was either absent (8 cases) or extremely faint (12 cases). In one case (Case 12) a widely split sound was audible preoperatively. Postoperatively, detailed analysis of the second sound was available in only 10 patients.

In these aortic valve closure was audible in all except one case (Case 5). Pulmonary valve closure was audible and thus a distinct split was heard in 5 patients (Cases 8, 11, 12, 18 and 21) while in the other 5 (Cases 1, 4, 5, 9 and 20) there was no change in the pulmonary valve component of the sound. Only 2 of those patients whose second heart sound in the pulmonary area was unchanged had right ventricular pressures of 60 mm. Hg or below in systole, whereas all of those who developed a split sound had right ventricular systolic pressures of 60 mm. Hg or less postoperatively. Recent phonocardiographic studies have related more precisely the width of splitting to right ventricular systolic pressures,[12] and there is no doubt that routine use of high-frequency phonocardiography will provide more uniform and objective information in the assessment of these cases before and after operation.

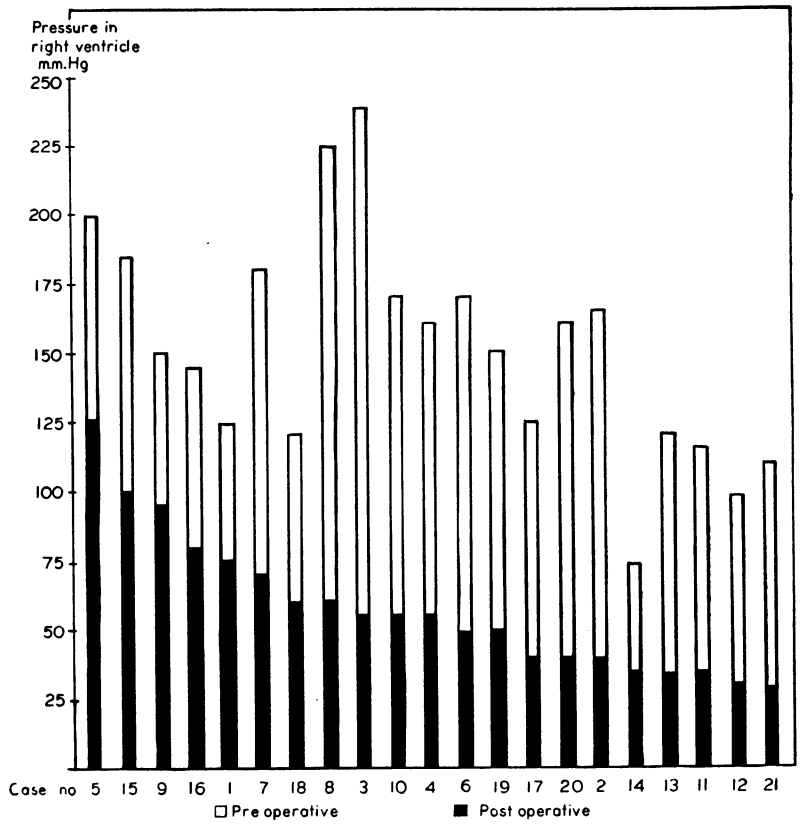

Fig. 2.—Cardiac catheterization in severe pulmonic valvular stenosis with normal aortic root. The systolic right ventricular pressure in mm. Hg before and after operation.

(c) *Murmurs.*—A very harsh, stenotic, systolic murmur of Grade V (Levine) intensity with thrill was audible in 19 of the cases. In 2 cases the murmur was of Grade II-III intensity (Case 7 with gross obesity and Case 19 with a minute orifice in the pulmonary valve at operation). Postoperatively the systolic murmur was usually reduced by two intensity grades and a thrill disappeared. In one case there was no change in murmur or thrill (Case 15).

No patient had a diastolic murmur of pulmonary incompetence preoperatively. Immediately postoperatively only one case (Case 8) had this type of murmur and it was of Grade III intensity. At eight-month follow-up, two further patients (Cases 3 and 6) had a pulmonary diastolic murmur, while two (Cases 8 and 1), seen 3 and 9 months postoperatively respectively, did not have pulmonary incompetence. The remainder have not yet been examined.

2. *Radiological Signs*

In 17 of the 21 chest roentgenograms taken preoperatively, the cardiothoracic ratio exceeded 0.50 in 12 cases and 0.55 in 5 cases (Cases 1, 3, 8, 13 and 18). Postoperatively there was no immediate change in heart size.

3. *Electrocardiography*

Severe right ventricular hypertrophy, frequently with right atrial hypertrophy preoperatively, was converted to a more moderate degree of right ventricular hypertrophy by the operation. Particular attention was paid to a decrease in voltage of R in lead V_1 as a measure of this electrocardiographic improvement. The voltage of R in V_1 was reduced immediately postoperatively in about two-thirds of the patients. In the remaining one-third there was no change (Fig. 1).

4. *Cardiac Catheterization*

In right atrial pressure tracings of the 21 patients the "a" wave exceeded "v" by more than 3 mm. in 12 cases preoperatively (Cases 1, 2, 5, 6, 7, 8, 9, 10, 16, 18, 19 and 20) and four postoperatively (Cases 2, 5, 10 and 18).

The right ventricular systolic pressure level preoperatively exceeded 70 mm. Hg in all cases and 109 mm. Hg in 19 patients. The highest value was 240 mm. Hg (Case 3). Postoperatively a reduction occurred in all patients, the systolic level being below 75 mm. in 17 patients (Fig. 2).

Preoperatively the right ventricular pressure pulse was classically that of valvular obstruction, having a symmetrical and rounded form in 17 patients (Table I). In the remaining four the pulse was of a similar type but a deflection of the upstroke suggested the presence of an associated infundibular obstruction. Postoperatively the appearance of the right ventricular pressure pulse was characteristic of valvular obstruction in five patients and of infundibular obstruction in three. In the other 13 the pressure pulse was of normal appearance in that there was a short isometric contraction, an ejection plateau and a short period of isometric relaxation.

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TABLE I.—DATA FROM CARDIAC CATHETERIZATION IN 21 PATIENTS REGARDING THE SITE OF OBSTRUCTION TO PULMONARY BLOOD FLOW.

Site of obstruction	*Preoperative*		*Postoperative*	
	Withdrawal from pulmonary artery	*Character of pressure pulse*	*Withdrawal from pulmonary artery*	*Character of pressure pulse*
Valvular	11 (Cases 2, 4, 5, 7, 8, 9, 11, 12, 13, 14, 15)	17 (Cases 1, 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 19, 20, 21)	7 (Cases 2, 3, 8, 9, 11, 12, 20)	5 (Cases 7, 9, 12, 14, 19)
Infundibular	0	4 (Cases 4, 7, 17, 18)	4 (Cases 5, 16, 18, 21)	3 (Cases 5, 15, 18)
Pulmonary artery not entered	10 (Cases 1, 3, 6, 10, 16, 17, 18, 19, 20, 21)		10 (Cases 1, 4, 6, 7, 10, 13, 14, 15, 17, 19)	
Normal form of right ventricular pressure pulse	0		13 (Cases 1, 2, 3, 4, 6, 8, 10, 11, 13, 16, 20, 21)	

These appearances, coupled with information obtained from pressure records during withdrawal of the catheter from pulmonary artery to right ventricle, led us to conclude that only two of 21 patients (9.5%) had even suggestive evidence of an associated infundibular stenosis preoperatively. In contrast, after valvotomy, infundibular obstruction became evident in five of 15 patients (33%), being of severe degree in three of this number.

5. *Operative Mortality and Postoperative Course*

In the 24 operations there was one death. This was in a four-year-old girl with a systolic right ventricular pressure of 260 mm. Hg who died from coronary air embolism. There was one case of wound infection and one of respiratory infection, but the postoperative course was usually smooth. One patient (Case 10) had dramatic and immediate postoperative relief from preoperative gross congestive heart failure, and another (Case 19) with extreme hypoxia (arterial oxygen saturation at rest, 31%) improved her arterial oxygen saturation to 91% at rest postoperatively.

DISCUSSION

Examination of this small series of 24 cases of valvular pulmonary stenosis with normal aortic root treated by open operation indicates that the technique is effective and the mortality risk low. Comparison with a similar group of 38 cases treated by the Brock method prior to January 1956 shows that the results are considerably better with the newer technique (Table II). The mortality and percentage of cases not helped have been reduced by at least one-half, while the proportion with moderate improvement or a good result has been almost doubled. A similar trend has been observed by others.[8, 9] It should be pointed out that neither the over-all immediate reduction in right ventricular pressure nor the mortality rate is significantly different in our group operated on by the direct method from those treated by the indirect method by Brock himself. Nevertheless, the results of the indirect operation as performed by most surgeons would suggest that the direct procedure is a more satisfactory method of treatment.

Though all of our recent group of cases have had a significant fall in right ventricular pressure, measured immediately postoperatively, the degree of fall was not uniform. If one accepts an immediate lowering of right ventricular systolic pressure to 40 mm. Hg or less as a good result, then in our cases a good result was achieved in only 43%. Relating the results to age at operation, it will be seen that three-quarters of those operated on up to the age of five years had good results, whereas only 10% of those over five years had a good result (Fig. 3). A poor result was defined as any case in which right ventricular pressure exceeded 75 mm. Hg immediately after operation. This occurred in 19% of our group. Correlation of these results with age at operation shows that there were no poor results up to five years of age but 40% of those over five had this type of result (Fig. 4). Further analysis of these four cases revealed a known incomplete division of the valve in one (Case 9) and postoperative catheterization evidence of infundibular obstruction in three (Cases 5, 15 and 16).

TABLE II.—COMPARISON OF RESULTS OF INDIRECT VERSUS DIRECT VALVOTOMY FOR SEVERE PULMONIC VALVULAR STENOSIS WITH NORMAL AORTIC ROOT.

	Trans-ventricular valvotomy		*Trans-arterial valvotomy*	
Number of patients	32		24	
Age range	6 mos. to 16 years		8 mos. to 16 years	
Results:		%		%
Operative death	4	12.5	1	4.0
Unrelieved or slight relief	10	32.0	4	17.0
Moderate improvement	6	18.5	8	33.0
Good result	7	21.5	9	38.0
No follow-up	5	15.5	2	8.0
		100.0		100.0

Slight = Right ventricular systolic pressure > 75 mm. Hg
Moderate = Right ventricular systolic pressure above 50 mm. Hg
Good = Right ventricular systolic pressure < 51 mm. Hg

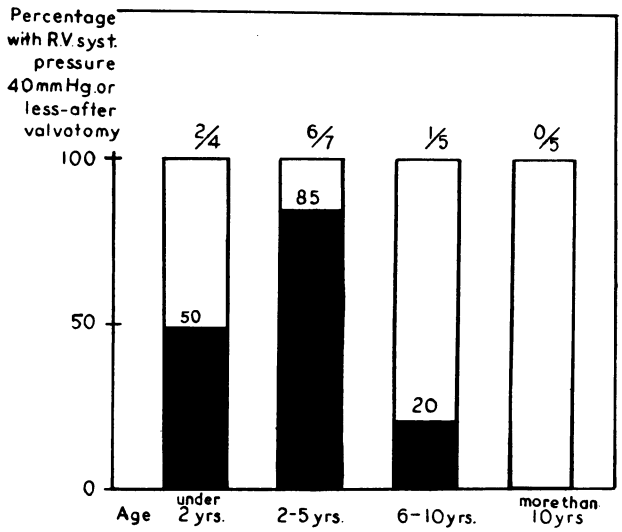

Fig. 3.—The relationship between good result from open valvotomy and age. The percentage of patients with a good result, i.e. a right ventricular systolic pressure of 40 mm. Hg or less, is represented by the shaded area in each age period.

There is some basis for the concept that after adequate valvotomy any residual infundibular stenosis is due to a hypertrophy of the boundary of the outflow tract and particularly of the crista supraventricularis secondary to long-standing obstruction of the valve. This is seen in the anatomical examination of the outflow tract at autopsies of older cases, a feature which has not been noted in infants. Further, three of our five patients with residual infundibular stenosis were over 12 years and all were more than five years old. Finally, after relief of the valve obstruction the right ventricular pressure level, though occasionally high immediately postoperatively, can fall to normal values by the end of one year.[10]

These observations would therefore suggest that early and adequate division of the valve can avoid postoperative elevation of right ventricular pressure due to secondary infundibular stenosis. In older children the chances appear good that after adequate valvotomy any residual elevation of right ventricular pressure may be expected to subside over a period of months or years. Whether a degree of infundibular stenosis constituting a permanent obstruction may be reached in older patients is at present uncertain.

The immediate result of direct operation provides little useful information on the important question of the production of pulmonary valve incompetence by the newer operation. Only time will settle this question definitely. We suspect that valve incompetence may prove to be more common with the newer technique while the surgeon is developing a nice balance in regard to the extent of valve division. But, provided the incompetence is not gross, there need be no cause for concern. It is certainly not a valid argument against open technique.

The physical signs allowing a diagnosis of pulmonary stenosis with normal aortic root are now well known, having been emphasized by numerous authors since the classical paper of Abrahams and Wood.[11] The physician is interested in two key points about any individual with this malformation. The first is the degree and the other is the site of pulmonary stenosis.

Physical signs each pointing to a severe obstruction are cyanosis, giant *a* waves in the jugular venous pulse, a long harsh ejection systolic murmur, inaudible aortic valve closure and inaudible or reduced and markedly delayed pulmonary valve closure on auscultation in the pulmonary area. Radiographic signs of cardiac enlargement are always serious but by no means an invariable accompaniment of severe stenosis. The electrocardiogram is undoubtedly very helpful; signs of marked right ventricular hypertrophy are the rule. Data from the present cases suggest that if R in V_1 exceeds 25 mm. in amplitude, the pressure in the right ventricle will exceed 100 mm. Hg and that the converse of this is usually true. One case (Case 9) of the present group was a true exception to this rule in that the R in V_1 was 16 mm. and the systolic right ventricular pressure was 150 mm. Hg. Three other cases with a voltage of R in V_1 of less than 25 mm. but high systolic right ventricular pressures were explained respectively by the presence of congestive failure with œdema and effusion (Case 10), extreme hypoxia (Case 19) and extreme obesity (Case 7). Thus a fairly accurate prediction of the systolic level of right ventricular pressure which will be found at cardiac catheterization is possible.

The site of obstruction is less easily determined. At the outset one may conclude that isolated infundibular stenosis or stenosis of the pulmonary artery distal to its valve of severe degree is uncommon; probably they together represent less than 10% of the total cases. A low position of the site of maximal intensity of the murmur is unfortun-

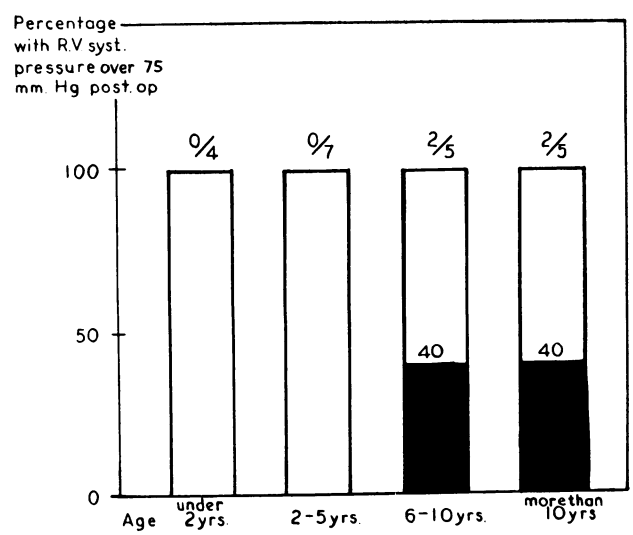

Fig. 4.—The relationship between poor result from open valvotomy and age. The percentage of patients with a poor result, i.e. a right ventricular systolic pressure of 75 mm. Hg or more, is represented by the shaded area in each age period.

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ately not a reliable guide to the site of stenosis. The second sound in the pulmonary area has the same characteristics in either severe infundibular or severe valvular stenosis.[11] A loud, normal or closely split second heart sound in the pulmonary area occurs in supravalvular stenosis. Clinically the only helpful sign differentiating infundibular from valvular stenosis is radiographic; an infundibular chamber is visible and marked post-stenotic dilatation of the main pulmonary artery is usually absent in the former type. Catheterization and selective angiocardiography are essential confirmatory procedures in doubtful cases.

The more common valve obstruction is suggested by both the systolic murmur and the character of the second heart sound in the pulmonary area. Radiologically post-stenotic dilatation of the pulmonary artery is invariable. The site of obstruction may be confirmed by cardiac catheterization or selective angiocardiography.

The most difficult problem is to decide preoperatively, when valvular stenosis exists, whether there is a significant associated infundibular obstruction. Clinically it is not possible to separate this group from the cases of isolated valvular stenosis. At cardiac catheterization it is seldom possible to do so. A rounded, symmetrical right ventricular pressure pulse characteristic of valvular stenosis is frequently present in combined stenosis preoperatively.

If the right ventricular pressure is lowered by surgical treatment and the symmetrical pressure pulse remains, valvular stenosis alone may be assumed. A slope on the pressure pulse preoperatively may mean infundibular obstruction but just as often does not, though this sign usually has significance postoperatively. An abrupt pressure change on entering the right ventricle from the pulmonary trunk preoperatively may be obtained in either valvular or combined stenosis. A normal right ventricular pressure pulse contour is never seen in either type of obstruction with high right ventricular pressures preoperatively, but after valvotomy may be encountered in both valvular or infundibular stenosis. In other words, cardiac catheterization is most helpful in pointing to valvular stenosis preoperatively and completely unhelpful in relation to any associated infundibular obstruction, whereas postoperatively it is often possible to assess the situation more accurately.

Selective angiocardiography using ciné-techniques may provide the answer to this preoperative problem. In Case 21, a preoperative ciné-angiocardiogram demonstrated very convincingly the presence of a dome valve stenosis with jet, but examination of the outflow tract also indicated severe systolic constriction. Postoperative angiocardiography revealed a normal degree of outflow tract systolic contraction, but withdrawal pressures from the pulmonary artery to right ventricular indicated a definite though mild gradient at the infundibular level.

Immediate postoperative assessment of the cases of pulmonary valvular stenosis with normal aortic root after either operative approach has shown that certain clinical features allow prediction of an adequate fall in right ventricular pressure. These are a very soft residual systolic murmur, absence of thrill, audible aortic valve closure and normal or near normal splitting of the second heart sound in the pulmonary area. Usually there is, in addition, a marked reduction in the height of R in V_1 in the electrocardiogram or a change to right bundle branch block. In our cases, if R in V_1 is decreased in voltage, the right ventricular pressure has been significantly lowered. The converse is not always true, for, despite a good pressure drop, the R voltage in V_1 on occasion may remain high. By contrast an unchanged systolic murmur and thrill, inaudible aortic valve with faint or absent pulmonary valve closure, or an unchanged electrocardiogram indicated inadequate relief of the stenosis. Three of our 24 cases treated by direct operation had the latter clinical signs associated with unchanged right ventricular pressure after a previous Brock operation.

SUMMARY

Direct vision transarterial valvotomy for severe pulmonary valvular stenosis with normal aortic root has been employed in 24 children with one operative death. In 21 of the 23 survivors full assessment in the postoperative period was performed. All were improved as judged by the immediate decrease in right ventricular pressure, the result being classified as good in nine cases, fair in eight and poor in four cases. Reasons are advanced indicating that some patients at present in the "poor" category have secondary infundibular stenosis and may enter the "good" category during the first or second postoperative year.

The best results obtain in patients operated upon before the sixth year of life.

A comparison of results obtained in a similar group of children treated by indirect valvotomy shows that in our hands the mortality is lower and the relief greater with the newer technique.

Correlation of the preoperative and postoperative clinical examination with the level of right ventricular pressure obtained at cardiac catheterization has allowed the use of clinical signs to assess the postoperative improvement of individual cases.

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RÉSUMÉ

On a eu recours à la valvulotomie transartérielle sous vision directe pour sténose grave de la valvule pulmonaire chez 24 enfants, avec une mort opératoire. Chez 21 des 23 survivants on dressa un bilan hémodynamique complet dans la période post-opératoire. Tous accusèrent une amélioration comme le témoigne un abaissement de la pression intransventriculaire droite. Les résultats furent jugés bons dans 9 cas, passables dans 8 et médiocres dans 4. On a raison de croire que certains malades aux résultats passables présentent une sténose secondaire du cône artériel, et atteindront peut-être le niveau des bons résultats au cours de la première ou de la deuxième année après l'opération. Les meilleurs résultats sont obtenus chez les enfants opérés avant l'âge de six ans. Une comparaison dressée entre nos résultats et ceux qui suivent la valvulotomie indirecte indique que la nouvelle technique entre nos mains donne une moindre mortalité et une meilleure correction de l'anomalie. La corrélation entre les faits cliniques pré- et post-opératoires d'une part, et d'autre part les niveaux de pression ventriculaire droite fournis par le cathétérisme cardiaque, nous a permis de suivre l'évolution post-opératoire de nos malades d'après les signes cliniques.

EXPERIENCE WITH OUTPATIENT ANTICOAGULANT THERAPY*

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THE OCCURRENCE of thrombotic episodes is one of the major problems in clinical medicine. The problem is intensified when thrombosis recurs. There is insufficient knowledge at present to predict when a patient may suffer from thrombo-embolism although these complications are more common under certain conditions, e.g. in the postoperative state, in congestive heart failure and in mitral stenosis with atrial fibrillation. Most of these do not warrant any special therapy, but continued anticoagulant therapy must be considered when thrombotic lesions are recurrent. With this end in view a trial of anticoagulant therapy has been conducted for several years on patients with recurrent venous thrombosis. Recently the series has been extended to include patients with recurrent coronary thrombosis and patients with peripheral embolism complicating heart disease. Anticoagulant therapy has also been tried in patients who had had repeated attacks of carotid and cerebral artery insufficiency and who were likely to develop complete obstruction of these arteries by thrombosis.

PERSONAL SERIES

Fifty-nine patients have received an anticoagulant drug while attending the Cardiovascular Unit of the Toronto General Hospital as outpatients. The duration of treatment ranged from three months to five years, with an average time of 11 months on anticoagulants. In Table I the patients are listed according to diagnosis.

TABLE I.—59 OUTPATIENTS ON ANTICOAGULANT THERAPY

	Number
Recurring venous thrombosis	14
Carotid and cerebral arterial stenosis	6
Repeated myocardial infarction	28
Rheumatic heart disease and embolism	5
Peripheral arterial disease	6
	59

Fourteen patients had recurring episodes of venous thrombosis. There were 12 men and two women, all between the ages of 30 and 45. In the men the original attack did not follow an injury or operation and no other associated disease could be demonstrated. The two women had their first attack of venous thrombosis in the postpartum period. Six patients with carotid and cerebral artery stenosis had transient attacks, e.g. weakness and numbness of one side of the body, disturbances of vision, facial weakness, or difficulty in swallowing. The recovery from the attacks before anticoagulant therapy was started was either complete or nearly complete. If cerebral softening was suspected the drug was withheld. Twenty-eight patients had two or more episodes of myocardial infarction within the space of two years. These patients were under the age of 60 years and it appeared that their outlook was poor. Five patients had embolism complicating chronic rheumatic heart disease, and six patients had occlusive arterial disease of the lower extremities; other methods of therapy including vasodilator drugs had been tried before dicoumarol administration was begun.[1]

Dicoumarol, the drug employed, reduces the prothrombin level less rapidly than some of the newer agents, for example coumadin[2] and phenylindanedione.[3] The depression of prothrombin, however, is not as long and delayed as it is with cyclocumarol.[3] Thus it provides a happy medium between too rapid an effect on the one hand and too slow an effect on the other. This is a desirable property for an anticoagulant which is to be used on outpatients, where prothrombin times can be determined less frequently than with patients treated in hospital. Most fluctuation in prothrombin times occurred during the first month. After this it was usually possible to regulate the dose by determining prothrombin times once every two weeks. An attempt was made to keep the prothrombin time between 20 and 28 seconds (normal one-stage prothrombin time 14-15 seconds). The usual dose of dicoumarol necessary for this was 50 mg. a day. This was increased or decreased slightly according to the prothrombin time. For example, if the prothrombin time was less than 20 seconds, the dose could be increased by giving 75 mg. every second or third day. If the prothrombin time was higher than 28 seconds, the dose could be

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