THESIS

A STUDY OF THE CLINICAL AND HEMODYNAMIC DERANGEMENTS ASSOCIATED WITH ISOLATED VENTRICULAR SEPTAL DEFECT

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Submitted to the Faculty of Medicine, University of Glasgow, as a thesis for the degree of Doctor of Medicine.

September, 1956

ACKNOWLEDGMENTS

I would like to express my appreciation to Dr. Earl H. Wood and Dr. H. J. C. Swan of the Section of Physiology, and to Dr. Howard B. Burchell of the Section of Cardiology, Mayo Clinic, Rochester, Minnesota, U.S.A., without whose ready advice and help this work could not have been completed.

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A STUDY OF THE CLINICAL AND HEMODYNAMIC DERANGEMENTS ASSOCIATED WITH ISOLATED VENTRICULAR SEPTAL DEFECT.

Introduction and Review of the Literature

The present study was undertaken to examine the hemodynamic derangements and clinical spectrum associated with isolated defects of the interventricular septum. In particular an attempt was made to determine the relative contributions to the abnormal physiology, of age, pulmonary artery systolic pressure, total pulmonary arterial resistance and peripheral arterial resistance and their relationship to the presenting clinical picture.

Defects of the ventricular septum most commonly involve the membranous portion of the septum where they are characteristically single. By the end of the second month of intrauterine life the interventricular foramen is normally sealed over by a plastic mass of connective tissue, derived mostly from the conus ridges and the right tubercles of the atrioventricular canal cushions together with a small contribution from the crest of the muscular portion of the septum. Failure of this union results in a deficient membranous septum.[1]

The first description of the clinical syndrome associated with defective closure of the interventricular septum was published by Roger in 1879, in which he called attention to the loud systolic murmur with its attendant thrill situated in the upper precordium near the midline.[2] It was his opinion that these physical signs were unaccompanied by any symptomatic upset, and this concept was perpetuated to such an extent that as lately as 1950, the accepted viewpoint was expressed by Brown when he stated that it was "the commonest of all congenital abnormalities," and prognostically was "benign and symptomless."[3] This original theory had been thought to be substantiated by reports of cases based on clinical impressions without the benefit of pathologic or physiologic proof, a deficiency for which Roger himself was also criticized.[4, 5] The diagnostic application of cardiac catheterization techniques and careful study of pathologic material has caused a major re-appraisal of these concepts to be made.

In 1897 Eisenmenger described the autopsy findings in a cyanotic adult in whom ventricular septal defect and dextro-position of the aorta were found.[6] Edwards has pointed out that the latter condition shares with the tetralogy of Fallot the characteristics of right ventricular hypertrophy and biventricular origin of the aorta above a defect of the membranous portion of the ventricular septum, but differs from it by the absence of any obstruction in the major pathway to the lungs which may be either normal or wider than normal.[7]

Eisenmenger originally observed that the normally located aorta is in such a position in relation to the ventricular septum that if the membranous portion is deficient the aorta comes into contact with both ventricles, thus producing overriding as a consequence of a large ventricular septal defect in this area, rather than as a developmental dextroposition. Spitzer believes that the same process of maldevelopment which causes transposition of the arterial trunks in its severest form is responsible in its mildest form for isolated membranous ventricular septal defect.[8] Selzer, however, has emphasized the autopsy difficulty in determining whether or not dextroposition of the aorta was present during life, and has advanced the theory that overriding need not be considered a fixed morphologic feature but rather a physiologic one accentuated during life by the existing pressure relationships and topography of the arterial trunks related to gradual dilation of the pulmonary artery and other factors. He considers that there is no clear dividing line between uncomplicated large ventricular septal defect on the one hand and the Eisenmenger complex on the other, the most important distinguishing feature clinically being the presence of anoxemia in the latter.[9]

The use of cardiac catheterization techniques has shed important new light on the functional derangements associated with defects of the ventricular septum. By these methods it has been demonstrated that systemic arterial oxygen desaturation and pulmonary arterial hypertension of a degree equivalent to the pressures existing in the systemic arterial circulation are characteristic features of the Eisenmenger complex of classical type.[10] Isolated ventricular septal defect with pulmonary recirculation of varying magnitude has also been shown to exist both with normal pulmonary artery pressures and with pulmonary hypertension of varying degree. Attempts have been made to explain these widely varied consequences of ventricular septal defect by the presence or absence of pathologic changes in the pulmonary vascular tree as well as on such other factors as the size of the communication between the ventricles. No data at present available, however, would allow a correlation to be made between all the physiologic and morphologic abnormalities which are known to exist.

No matter which diagnostic eponym is attached to the individual patient, the underlying abnormality remains the anatomic one of patency of the interventricular septum. It would be logical to anticipate that the symptoms with which the patient presents himself would be related to a number of factors, the principal of which would include the size of the communication, the volume rate of flow through it, and the nature and magnitude of the resistances offered by the pulmonary and systemic circulations.

The present study was undertaken to assess the possible interrelation of the hemodynamic variables in a series of 38 patients with isolated defects of the ventricular septum studied by the cardiac catheterization technique and their influence on the clinical syndrome. The presence of pulmonary hypertension or desaturation of systemic arterial blood had no bearing on the selection or rejection of cases from this series. The factors examined were those of age, pulmonary artery systolic pressure, systemic and pulmonary blood flow and their related shunts, the presence or absence of peripheral arterial oxygen desaturation, and the vascular resistance of the systemic and pulmonary arterial systems, together with the results of clinical, radiologic and electrocardiographic examinations.

Methods

All the cases included in this study were considered to have an indisputable diagnosis established. This was felt to be confirmed by one or more of the following criteria: (1) A significant increase in blood oxygen saturation value at ventricular level, (2) the presence of a right-to-left shunt at ventricular level as indicated by the dye dilution curves recorded, (3) the passage of the cardiac catheter through the ventricular septal defect, (4) a normal retrograde aortogram in the absence of evidence of a right-to-left shunt between the two circulations beyond the ventricular level. In every patient the catheter entered the pulmonary artery and data permitting the calculation of pulmonary and systemic blood flow values were obtained. In cases #14 and #25, infants of 7 and 12 months respectively, the oxygen consumption could not be measured and flow values were not calculated. These latter cases are included to augment the limited data available in an important age group.

Each patient was subjected to cardiac catheterization by the technique of Cournand and Ranges as developed by Wood and associates. The majority of patients under the age of 10 years were studied under anesthesia as previously described.[11] Pressures within the vascular system were measured by strain gauge manometers. The oxygen saturations of blood samples withdrawn from the heart and great vessels were determined by manometric and photometric techniques.[12, 13, 14]

The oxygen uptake was estimated using the Haldane method following collection of expired air in a conventional gasometer over approximately 5 minutes. During this period blood samples were withdrawn from the pulmonary artery and a systemic artery for analysis in regard to oxygen content (C_{pa}, C_{sa}), and capacity, by the method of Van Slyke.[15]

In addition, blood samples were withdrawn in rapid succession from the pulmonary artery, the outflow and inflow portions of the right ventricle, the right atrium and other locations, through a cuvette oximeter by means of which the oxygen saturation of such samples was instantaneously determined. This instrument permits the recognition of differences between the oxygen saturation of successive blood samples with a precision superior to the usual methods of manometric analysis.[16]

The pulmonary (Q_p) and systemic (Q_s) blood flows were determined by the application of the Fick principle according to the equations:

$$Q_p = \frac{V_{o2}}{C_{pv} - C_{pa}}$$

$$Q_s = \frac{V_{o2}}{C_{sa} - C_{mvb}}$$

where V_{o2} is the oxygen consumption (in ml. per minute), C_{pv}, C_{pa}, C_{sa} and C_{mvb} represent the oxygen content (in ml. per liter) of pulmonary vein, pulmonary artery, systemic artery and mixed venous blood respectively. C_{pv} was assumed to be equal to C_{sa}, except in the presence of a right-to-left shunt, under which circumstance the value for C_{pv} was taken to be 98 per cent of the oxygen content of the patient's blood. The best evidence for the presence of a right-to-left shunt was from the contour of an indicator dilution curve recorded following injection of dye into the right ventricle or at a site upstream to it. Because of the wide range of recorded values (92 - 100 per cent) for normal subjects, oxygen saturation values within the range of normal can be obtained in patients with significant right-to-left shunts.

C_{mvb} was taken as the product of the oxygen capacity, and the oxygen saturation of right atrial blood, when the latter value lay within the estimations of inferior and superior caval blood samples.

Values for Q_s and Q_p were expressed as systemic and pulmonary flow in liters, per min. These values were then related to body surface area and presented as systemic and pulmonary index in liters per min. per square meter.

The total pulmonary resistance (R_p) and total systemic resistance (R_s) were caloulated:

$$R_p = \frac{P_{pam} \times 1332}{Q_p}$$

$$R_s = \frac{P_{sam} \times 1332}{Q_s}$$

where P_{pam} and P_{sam} refer to the mean pulmonary artery and systemic artery pressure respectively and Q_p and Q_s are expressed in ml. per sec. Values for these resistances are expressed as dynes. sec. cm. -5.

To equate the relative influence of total pulmonary resistance and total peripheral resistance in each individual irrespective of body size, the relation between these values is expressed as a dimensionless number: $R = \frac{R_p}{R_s}$

Instantaneous dye dilution curves were recorded in all but 7 cases. Direct recording was made by means of earpiece and cuvette oximeters following the instantaneous injection of Evans blue dye (T - 1824) into central or peripheral injection sites, with the patient at rest and breathing room air.[17] Recording was accomplished by the use of a photokymographic assembly described elsewhere.[12] Eight cases were studied by means of peripheral injection into the brachial vein, but the remainder utilized injection sites in the central veins. In either central or peripheral location single or multiple injections were carried out. Diagnostic interpretations were made as described by Swan and associates.[18, 19]

Clinical history and examination were carefully recorded for each patient and a 12 lead electrocardiogram taken. Radiologic examination comprised a standard 6 foot chest x-ray film in postero-anterior, lateral and both anterior oblique positions together with fluoroscopic screening. Retrograde aortography was carried out on 4 occasions, and during fluoroscopic monitoring of the cardiac catheterization procedure, serial x-ray films were exposed with the catheter tip located in various positions in the heart and great vessels.

The physiologic data to be presented in this thesis were obtained with the patients at rest and spontaneously breathing room air. Other data, including the effect of breathing 100 per cent oxygen, were obtained but are not pertinent to this study.

Results

The relevant hemodynamic data for this group of patients are given in Table 1, in which the cases have been assembled in order of increasing magnitude of pulmonary artery systolic pressure.

The results of clinical, radiologic and electrocardiographic examinations are presented in Table 4 where the cases are similarly arranged. In Table 3 all the physiologic data pertinent to this study are presented. There was a wide range in the ages of the 38 patients studied extending from 7 months to 44 years and the sex distribution was approximately equal. A clear division was possible into two groups depending on the presence or absence of pulmonary hypertension. Patients in whom the pulmonary artery systolic pressure was less than 40 mm. of mercury were considered to have pulmonary artery pressures within the normal range. Systolic and mean pressure values extending from the normal range to values equivalent to systemic pressures were obtained. In this laboratory when the pulmonary artery systolic pressure is within 10 per cent of radial artery systolic pressure, equivalent aortic and pulmonary artery pressures are assumed to be present in the absence of other data due to the peripheral increase in amplitude of the central pressure pulse.[20] The group with equivalent systolic pressures were divided into two groups — those under 12 years of age and those above that age. In the case of the latter, peripheral arterial anoxemia and clinical cyanosis at rest were present in all but one instance while in the younger group, these features were infrequently seen and when present were produced only by exertion.

Greater severity of symptoms was observed as age or pulmonary artery systolic pressure increased. No history suggestive of subacute bacterial endocarditis was obtained in any of the cases studied.

In the absence of pulmonary hypertension the only symptoms of note were those of dyspnoea or ready fatigue on effort occurring in about half the group. There was no episode of failure in any of these patients, and cardiac disability was minimal or totally absent.

In contrast to the paucity of symptoms, physical examination yielded definitely abnormal findings, the most prominent of which was the invariable presence of a loud harsh systolic murmur heard over the whole precordium and frequently in the left infrascapular area and axilla also, but of maximum intensity in the 3rd or 4th intercostal space to the left of the sternal border. This murmur was graded as 2 or 3 on the basis of 4, and in just over half the cases was accompanied by a palpable thrill. The second pulmonary sound was considered to be within normal limits. In 2 cases an accompanying diastolic murmur was heard and in both of these an elevated pulse pressure was found.

When pulmonary hypertension was present the severity of symptoms could be related to its level and to the age of the patient. Dyspnoea, marked fatigue, and syncopal attacks following exertion were increasingly prominent as pulmonary artery pressures became equivalent to those of the systemic circulation, and as the patient became older. Episodes of congestive failure had occurred in more than half of the 26 cases in the group, and recurrent hemoptysis precordial pain following effort, and polycythemia accompanied the higher pressure values rather less frequently.

Clinical cyanosis at rest had its onset in the second decade of life, and was found only in these adults in whom equivalent pressure relationships existed. It was almost invariably accompanied by digital clubbing. In 3 children intermittent cyanosis following stress had appeared within the first 10 days of life but had disappeared completely by the age of 3. In 3 other patients similar transient cyanosis had had its onset at the ages of 5, 7 and 18 years respectively but in the 3 subsequent years of observation had not become permanently present at rest.

In the non-cyanotic patients the systolic murmur did not differ significantly in intensity or location from that heard in the group with normal pulmonary artery pressures. An accompanying thrill was more common, however, and occurred in all but 2 of these 18 cases. In 2 of the 8 permanently cyanotic patients a similar murmur and thrill were present, but in the remainder only a faint localized systolic murmur could be heard in the 3rd or 4th left parasternal interspace. A diastolic murmur was heard in a similar area to the left of the sternum in 7 patients, only 3 of whom were cyanotic. The peripheral pulse was normal in these instances. In 24 instances the second pulmonary sound was accentuated and frequently split. Additional associated clinical findings are presented in Table 6.

The roentgenologic and electrocardiographic findings are summarized in Tables 7 and 8.

Patients # 1 - 12 had pulmonary artery mean pressures within the range of normal, while the average value in the patients with elevated but not equivalent pressures was 53 mm. of mercury (29-70 mm.). Higher average pressures were found in those with equivalent values in the two circulations; those in the younger age group having a value of 70 mm. of mercury (62-79 mm.) and in the older group 83 mm. of mercury (69-100 mm.).

Pulmonary artery wedge pressures were obtained in 16 of the cases studied. In all except one instance (case #28) these values were within normal limits indicating that the resistance to blood flow through the pulmonary vascular tree lay in the vasculature itself rather than at any point beyond it. In the single instance in which an elevated pulmonary artery wedge pressure was found, the cause for it was not evident.

Of particular interest were the values obtained for pulmonary blood flow. Values about two to four times normal were obtained in the patients with normal pulmonary artery pressures, averaging 5.6 $l/m/m^2$ (3.5 - 9.1 $l/m/m^2$). The highest values for all the studied cases occurred in the patients with elevated pulmonary artery pressures but without equivalent aortic and pulmonary artery systolic pressure relationships. These flows were about three to eight times the normal value and presented an average flow of 11.5 $l/m/m^2$ (7.7 - 17.1 $l/m/m^2$). In those with equivalent pressure relationships a markedly contrasting picture was seen, for while the patients in the younger age group still had a high average flow of 8.2 $l/m/m^2$ (4.9 - 13.1 $l/m/m^2$) those in the older and mainly cyanotic group showed a dramatic drop in average value to 2.1 $l/m/m^2$ (1.5 - 3.5 $l/m/m^2$).

As might be expected the total pulmonary resistance tended to increase with the level of pulmonary artery pressure. A normal average value of 184 dynes sec. $cm.^{-5}$ (97 - 432 dynes sec. $cm.^{-5}$) in the group with normal pulmonary artery pressures increased more than tenfold to an average of 1944 dynes sec. $cm.^{-5}$ (1232 - 2960 dynes sec. $cm.^{-5}$) in the adult group with pulmonary hypertension and cyanosis. It is of considerable interest and importance to note that the younger patients with equivalent pulmonary and systemic pressures showed considerable increases in pulmonary blood flow in spite of an elevated resistance in the pulmonary vascular bed. These results are shown in Table 2.

The absolute magnitude of the left-to-right shunt varied considerably, but was greatest in those patients with elevated pulmonary artery pressures which were not equivalent to systemic pressures. Although the vascular resistance in the systemic arterial system showed considerable variation throughout the series, this value in the patients with equivalent arterial pressures and dominant shunting of blood from the right to the left ventricle was usually greater than the values found in the group with entirely normal pulmonary artery pressure levels and those with moderate pulmonary hypertension.

In 22 cases there was evidence of pulmonary recirculation in the recorded dye dilution curves, indicating the presence of an abnormal arteriovenous pathway at some point in the cardiovascular system. The assistance of blood oxygen saturation studies was required to localize the site of the communication to ventricular level. Accurate localization of right-to-left shunts at ventricular level by the dye dilution curve method, was possible in 6 cases. In these, selective injections were made at points downstream from the caval system. A further 3 cases had right-to-left shunts demonstrated but localization was impossible because the injection sites were either peripherally situated or were not selective in the central venous system. Fluctuations in oxygen saturation were prominent in all curves where right-to-left shunting was present. Predominant right-to-left shunts were found only in adult patients with pulmonary hypertension.

Peripheral arterial oxygen desaturation, regarded in this laboratory as less than 92 per cent when recorded by earpiece oximeters, occurred only in adult patients with pulmonary hypertension. Spontaneous variations in oxygen saturation exceeded 2 per cent in each of these, but in the remainder of the 38 patients blood oxygen saturation was within normal limits. Temporary and variable depression of oxygen saturation values occurred in 3 children catheterized under general anesthesia.

Depression of absolute values of blood oxygen saturation in the right heart and great vessels was only observed in those patients with peripheral arterial oxygen desaturation. In every case studied, however, a diagnostic increment in blood oxygen saturation value could be demonstrated between the right atrium and ventricle irrespective of the state of saturation of the peripheral arterial blood. This increment had an average value of 10 per cent with a range of 3 per cent to 26 per cent. Arterialization was most marked in the right ventricular outflow tract in the majority of patients, and the average increase was greatest when left-to-right shunts were largest. These values are presented in Table 3 and summarized in Table 5.

Discussion

The prevalence of isolated defect of the ventricular septum in autopsy material is sufficient evidence that the long-cherished view of its benign nature is no longer tenable.[21] Many children die in the first few months or years of life and those who survive may ultimately develop the stigmata of pulmonary hypertension which then dominates the clinical picture.[22, 23] In the absence of elevated pulmonary artery pressures the clinical history is non-specific and is that of any congenital cardiac anomaly with a communication between the two circulations. Roger's original description of the loud harsh systolic murmur overlapping both heart sounds, with its maximum intensity in the upper precordium near the midline has yet to be bettered.[2] He stressed the frequent presence of a thrill and the absence of symptoms. These characteristics have been infrequently present in the cases studied by physiologic methods, for in most of these reported, varying degrees of pulmonary hypertension have been responsible for the outstanding clinical features and the systolic murmur has been less prominent.[24, 25] Harned and associates have observed in acyanotic patients who developed pulmonary hypertension in the group studied by them changes which they regard as representing a gradual transition to the cyanotic Eisenmenger's complex.[26] Supportive observations that functional overlapping occurs between isolated acyanotic ventricular septal defect on the one hand and the Eisenmenger complex with its classical "cyanose tardive" feature on the other have been forthcoming from the original work of Selzer and associates.[9]

The late onset of clinical cyanosis is no longer regarded as pathognomonic of the Eisenmenger complex of anomalies, however, for a similar picture has been described in cases of patent ductus arteriosus with pulmonary hypertension and reversal of flow,[27] in Ebstein's malformation of the tricuspid valve,[28] and in isolated pulmonary stenosis with valve competent foramen ovale,[29] as well as being theoretically possible in other conditions in which obliterative pulmonary vascular changes produce elevated pulmonary vascular resistance.

The presence of a diastolic murmur to the left of the sternum in company with an elevated pulse pressure has been reported in cases where aortic valvular insufficiency complicates isolated ventricular septal defect,[30] although patent ductus arteriosus or congenital defect of the aortic septum may produce a similar picture.[31] When the pulse pressure is within normal limits, functional mitral stenosis, or incompetence of the pulmonary valve has been suggested depending on whether or not pulmonary hypertension is present.[24]

In the absence of pulmonary hypertension there are frequently no recognizable x-ray features associated with isolated ventricular septal defect. In acyanotic patients in whom pulmonary hypertension is present, however, the common occurrence of biventricular enlargement, a prominent pulmonary artery, pulmonary vascular engorgement and sometimes left atrial enlargement and hilar dance make the roentgenologic diagnosis difficult for a similar picture is seen in any type of aortopulmonary communication with pulmonary hypertension.[32] Retrograde aortograms are most valuable in these circumstances.[33] When cyanosis is present the picture is essentially the same but hilar dance and pulmonary vascular engorgement are diminished or absent.

It has long been recognized that the electrocardiogram in isolated ventricular septal defect does not show diagnostic changes, and in the absence of pulmonary hypertension is frequently normal. When elevated pressures are found in the lesser circulation, combined ventricular hypertrophy is frequently present and is considered to be the most important electrocardiographic abnormality in this anomaly.[34] Dominant right ventricular hypertrophy patterns are regarded as a late stage in the natural course of the disease.[24] Right bundle branch block is much less common than in atrial septal defect and atrioventricular conduction disturbances are no longer thought to be a common feature of isolated defect of the ventricular septum.[35]

A significant increment in blood oxygen saturation value at ventricular level has been described as a diagnostic feature of arteriovenous mixing in the right ventricle. In itself this is not diagnostic of a patent ventricular septum and similar increases may be seen in aortopulmonary communication with pulmonary hypertension and pulmonary valvular insufficiency, or in the presence of a communication between the right sinus of Valsalva and the right ventricle,[37] or in some instances of persistent common atrioventricular canal.[38] The increment in ventricular septal defect has been reported to be most marked in the presence of a large left-to-right shunt,[24] and Wood and associates noted an increase in saturation levels between the body and infundibulum of the right ventricle in 5 of the 40 cases catheterized by them.[25] In these cases the sample from the outflow tract approximated in value to that from the pulmonary artery, while the right atrial sample was approximately the same as that from the low right ventricle. A demonstrable right-to-left shunt beyond atrial level may cause confusion with patent ductus arteriosus with reversal of flow and atypical clinical features. Simultaneous sampling from radial and femoral arteries has been used to obviate this potential error by indicating preferential right-to-left shunting to the lower extremities through a reversing ductus.[39]

The diagnostic application of recorded dye dilution curves in localizing the site of an abnormal communication between the two circulations has proved of considerable value in cyanotic congenital heart disease, and has had further applications in similar defects without cyanosis.[19] A ventricular septal defect with right-to-left shunt can be accurately localized by using multiple injection sites in the heart and great vessels, the pulmonary artery being the only site from which a normal contour will be recorded.[40] Left-to-right shunts in this anomaly are more accurately localized by serial sampling of blood from the right heart and great vessels.

The severity of the clinical and physiologic derangement in isolated defect of the ventricular septum has been variously related to the site or size of the defect, and to the presence or absence of pulmonary hypertension in infancy.[41, 42] In experimental studies, however, it has been clearly shown by Holman and Beck[43] and by Griffin and Essex[44] that the degree of hemodynamic upset on which these changes are based is considerably influenced by the size of the defect, an observation confirmed by the independent pathologic studies of Edwards,[45] Engle[46] and Harned and associates.[26] While the presence or absence of pulmonary hypertension in infancy influences the prognosis, there is no available proof that this factor is necessarily related to the size of the defect.

Bing and associates[10] and Handelsman and associates[47] have suggested that the relatively normal pulmonary blood flow present in the cases of the Eisenmenger complex studied by them must be related to the presence of a high pulmonary vascular resistance possibly accounted for by microscopic lesions demonstrable in the pulmonary vasculature. Such changes have been described by various workers and consist principally of an abnormally thick medial layer of the muscular arteries of the lungs in the presence of normal arterioles.[45, 48, 49] Varnauskas and associates have suggested that cases of isolated ventricular septal defect with increasing pulmonary vascular resistance to blood flow through the lungs will ultimately develop a predominantly right-to-left shunt as the resistance rises, thereby establishing the anoxemia of the Eisenmenger complex.[50] The view that cyanosis in this collection of anomalies was related to a congenital abnormality of the pulmonary epithelium has finally been discarded.[51, 52, 53]

The present study supports the patterns outlined by many investigators and lends weight to the view that from the physiologic standpoint the Eisenmenger complex is only a variant of isolated ventricular septal defect. In this series of 38 cases studied a division into two groups has been made: those with attendant pulmonary arterial hypertension and those without. Those with normal pulmonary artery pressures, taken in this series to be below 40 mm. of mercury pulmonary artery systolic pressure, are attended by physiologic and symptomatic derangements of much less degree than are those with pressures in excess of this value. The selection of this figure is not entirely arbitrary for studies carried out in normal subjects have shown that the upper limit of pulmonary artery systolic pressure lies between 35 and 40 mm. of mercury.[54] There appears to be a definite separation between the two groups referred to in the present series, for only 1 patient has a systolic pulmonary artery pressure between 40 and 60 mm. of mercury.

Isolated Ventricular Septal Defect Without Pulmonary Hypertension

Isolated ventricular septal defect when unaccompanied by arterial hypertension in the pulmonary vascular system was found to be a distinct and separate entity which did not coincide hemodynamically at any point with similar defects complicated by pulmonary hypertension (Fig.1).

<u>Age, pulmonary blood flow and interventricular vascular shunts</u>-Many of the patients with normal pulmonary artery pressures were adults and all the cases studied had interventricular arteriovenous shunting entirely uncomplicated by flow through the defect in the opposite direction. These shunts were of moderate dimensions and usually of less magnitude than those found in the hypertensive group. Within this group the older patients tended to have the smaller pulmonary blood flows.

The hemodynamic alterations consequent upon the interventricular communication and the absence of evidence of progression beyond the age of ten to fifteen years corresponds to the classical picture of meladie de Roger.

<u>Pulmonary artery systolic pressure</u>-No evidence can be advanced from this study that normal pulmonary artery pressure in the first few years of life provides any safeguard against the development of pulmonary hypertension in later years. Conversely it cannot be shown with certainty that any infant with normal pulmonary artery pressure would retain other than normal pressures in adult life.

<u>Blood oxygen saturation and dye dilution curve studies</u>-Peripheral arterial oxygen saturation was not depressed in these patients, and the normal appearance time, shallow primary and absent secondary deflections and prolonged disappearance slope in all dye dilution curves recorded from central or peripheral injection sites indicated the presence of pulmonary recirculation (Fig.2). Multiple sampling

techniques were effective in localizing the shunts to ventricular level where arteriovenous mixing was complete most often in the outflow tract.

Clinical features—A loud harsh systolic murmur with attendant thrill, similar to that originally described by Roger, and unaccompanied by any clinical evidence of pulmonary hypertension was the most outstanding feature of the group. Cardiac reserve was only minimally impaired in about half these patients. A diastolic murmur heard in 2 instances, and accompanied by an elevated pulse pressure in each, was felt to be due to aortic valvular insufficiency in the absence of other evidence of patent ductus arteriosus. The murmurs present were of a to-and-fro character rather than continuous in type. In one of these patients, and in another in whom paroxysmal tachycardia occasionally followed effort, substernal oppression was noted after severe exertion. X-ray changes indicating biventricular enlargement with supportive electrocardiographic evidence of hypertrophy occurred in these 2 patients also, but these investigations were otherwise non-specific or showed variations compatible with a normal interpretation.

Isolated Ventricular Septal Defect With Pulmonary Hypertension

Clinically and hemodynamically the group with elevated pulmonary artery pressures is the more interesting and the more complex, and is associated with the more profound symptomatic and physiologic derangements.

Age-While both children and adults were found in the group with pulmonary hypertension, a notable feature of this series of cases was the absence of significant right-to-left shunting in the children, and frequency of equivalent pressures and cyanosis among the adult patients.

Pulmonary blood flow and pulmonary artery pressure-Within this group there was a steady diminution in pulmonary blood flow with increasing pulmonary artery pressure. This was particularly evident in the adult patients with equivalent pulmonary and systemic arterial pressures. However, large flows were observed in several adult patients in whom the pulmonary and systemic arterial pressures were not equivalent. Such inter-relationships were evident on consideration of the increasing pulmonary resistance, and of the increasing ratio of pulmonary to systemic resistance which exceeded unity only among the adult group. (Fig.3)

Vascular resistance-As the critical ratio of total pulmonary vascular resistance to toal peripheral vascular resistance approached and then exceeded unity, the direction of blood flow from one ventricle to the other proceeded in a predominantly right to left direction. The patients in whom this relationship existed were all in the adult group, and in them, hemodynamic variables were interrelated within relatively narrow limits. (Fig.4)

<u>Blood oxygen saturation and dye dilution curve studies</u>-Peripheral arterial oxygen desaturation occurred only in patients in the adult age group, and was due to right-to-left shunting at ventricular level. This was demonstrated by the characteristically short appearance time and abnormal initial deflection present in all curves recorded from injection sites in or upstream to the right ventricle. (Fig.5) Despite these findings, there was evidence of arterialization of venous blood in the right ventricle indicating bidirectional rather than unidirectional shunting at that level.

In the patients in whom peripheral arterial blood oxygen levels were normal, the dye dilution curves and sampling data were essentially similar to those described for the patients with normal pulmonary artery pressures.

<u>Clinical features</u>-The clinical derangement was more profound than was seen in the presence of normal pulmonary artery pressures. Symptoms were frequently severe and the history often progressive. Established cyanosis at rest occurred only in patients of adult age with equivalent pressures in the two circulations, and was frequently accompanied by digital clubbing and effort syncope. Intermittent cyanosis with effort appeared at birth in 3 instances but had disappeared by the time the child was 3 years old, presumably due to compensatory hemodynamic factors not yet fully understood. All the patients with permanent cyanosis at rest had gradually progressed from a period of intermittent cyanosis following stress commencing

approximately with the second decade. Three other patients had transient effort cyanosis which showed no indication of becoming permanent at the time of examination.

Invariably there was marked fatigue or dyspnoea following exertion and the severity of these symptoms roughly paralleled the degree of pulmonary hypertension present. Physical underdevelopment was a feature in the younger children. Severe cardiac strain manifested itself by episodes of cardiac failure, indicated by repeated bouts of pneumonia or respiratory infection, by persistent basal rales or other signs of congestive failure, and had a tendency to occur at the extremes of the age group in which pulmonary hypertension was found. Hemoptysis and chest pain on effort were accompaniments of elevated pulmonary artery pressures.

Precordial evidence of cardiac distress was striking, and bulging of the left chest, clinical enlargement and overactivity of the heart and a hyperdynamic apical thrust were common. An abnormally loud pulmonary second sound accompanied the pulmonary hypertension but its intensity could not be closely correlated with the level of pulmonary artery systolic pressure. When the pressures in the two circulations approximated and right-to-left shunts were present the characteristic precordial systolic murmur was so diminished in intensity and duration as to be almost inaudible except following exercise. In these cases the typical thrill had disappeared. When a diastolic murmur was heard in the left parasternal area it was believed to be due to pulmonary valve incompetence in about half the cases, while the reason for its presence in the remainder was not clarified.

Enlargement of the right or both ventricles and the pulmonary artery segment were the invariable roentgenologic abnormalities in this group of patients. Pulmonary vascular markings were increased except when pulmonary and systemic arterial pressures were equivalent. In these instances they were either normal or only doubtfully increased. Aortograms were of value in 4 acyanotic patients by excluding patent ductus arteriosus. When difficulty arose in determining which of the major vessels the catheter had entered after passing through the defect, this was resolved by blood oxygen saturation determinations, or by dye dilution curve methods or by advancing the catheter tip. (Fig.6)

Electrocardiographic patterns were compatible with either biventricular hypertrophy (Fig.7) or when pulmonary vascular resistance and pulmonary artery systolic pressure were markedly elevated, with right ventricular hypertrophy. (Fig.8)

It was this disappearance of physiologic lability which constituted the most striking feature of the cyanotic adults in the cases under review. Venoarterial shunts of comparable and moderate dimensions along with normal or diminished pulmonary blood flows reflected the stable dynamic situation present. These values were accompanied by high pulmonary artery pressures, approximately equivalent to systemic arterial pressures. In view of the marked functional alterations in the pulmonary vascular system it is evident from these studies that any concomitant physiologic changes which occurred in the peripheral arterial system were relatively small and of considerably less significance.

This physiologic stability was in marked contrast to the precarious clinical condition in which these patients existed.

In the absence of pulmonary hypertension the clinical picture corresponded to the classical concept of the maladie de Roger with absent or minimal symptoms in the presence of a loud harsh murmur and thrill. Radiologic and electrocardiographic changes were helpful when present but were never diagnostic.

The characteristic picture in the patients studied with ventricular septal defect and pulmonary hypertension was comprised in the first ten years of life, of moderately elevated pulmonary artery systolic pressure, large pulmonary flows in excess of five times the normal value associated with considerable volumes of blood passing entirely or predominantly from the left to the right ventricle across the defect, the absence of demonstrable cyanosis at rest, and a resistance ratio of less than one.

In conformity with the more severe hemodynamic derangements present, there was a greater frequency of physical underdevelopment and precordial deformity and hyperactivity, along with exertional distress and episodic cardiac failure. The classical murmur and thrill remained, but the intensity of the pulmonary second sound was considerably increased. There was evidence of enlargement and hypertrophy of both ventricles on x-ray and electrocardiographic examination, with large hilar vessels, and increased pulmonary vascular markings.

In the second and subsequent decades the hemodynamic alterations were found to be fixed and stable in the majority of cases. This situation was marked by the presence of equivalent systolic pressures in the pulmonary and systemic arterial systems, permanent cyanosis at rest, a normal or low pulmonary blood flow, dominant venoarterial shunting across the defect, and a resistance ratio greater than one.

To the clinical features already described in association with pulmonary hypertension this group added permanent cyanosis at rest, with digital clubbing, effort syncope and hemoptysis, and the poorest exercise tolerance of any group in the series. The typical murmur and thrill associated with isolated defect of the ventricular septum virtually diappeared. Electrocardiographic and x-ray evidence favored right ventricular hypertrophy, and the peripheral lung fields were normal in the presence of a greatly enlarged pulmonary artery segment.

From the study undertaken several facts emerge with clarity. The natural hemodynamic and clinical history of the 38 cases of isolated ventricular septal defect was clearly integrated with the presence or absence of pulmonary arterial hypertension and their stigmata could be related to the level of pulmonary artery systolic pressure, pulmonary blood flow, age of the patient, degree of desaturation of the peripheral arterial blood and the ratio of pulmonary to peripheral vascular resistance. It was not found possible to regard the Eisenmenger complex from a hemodynamic point of view, as other than a logical variant of isolated ventricular septal defect with accompanying pulmonary hypertension.

While it could be speculated that some cases of isolated ventricular septal defect with pulmonary hypertension do in fact progress to the cyanotic Eisenmenger's complex, no substantial body of integrated proof has emerged from the present study to completely verify this assumption.

Insufficient data were available for any conclusions to be drawn about the important group of children under the age of 2 years.

Summary

1. The hemodynamic alterations and clinical features in a series of 38 cases of isolated ventricular septal defect with and without accompanying pulmonary hypertension have been presented.

2. In the absence of elevated pulmonary artery systolic pressures, the anomaly was attended by unidirectional passage of blood across the defect from the left to the right ventricle, by moderate increase in pulmonary blood flow, absence of peripheral arterial oxygen desaturation, and a ratio of pulmonary to peripheral vascular resistance of considerably less than one. This was represented clinically by a loud harsh systolic precordial murmur and thrill with little symptomatic upset and slight or absent deviation from normal on x-ray and electrocardiographic examination.

3. Where pulmonary hypertension was present but the patient was in the first decade of life, pulmonary blood flow was greatly increased, pulmonary artery systolic pressure approached or equalled the values found in the systemic arterial circulation, flow of blood through the defect was entirely or predominantly from left to right, there was no cyanosis at rest, and the resistance ratio approached but was still less than unity. These individuals had symptoms of mild or moderate episodic cardiac embarrassment and failure, a loud systolic murmur and thrill, clinical evidence of pulmonary hypertension and x-ray and electrocardiographic evidence of hypertrophy of the right or both ventricles. Enlarged hilar

vessels and increased pulmonary vascular markings were present.

4. In the presence of pulmonary hypertension beyond the first decade, the pulmonary artery systolic pressure and that in the peripheral arteries were equivalent, there was predominant venoarterial flow of blood between the ventricles with consequent peripheral arterial oxygen desaturation, a normal or low blood flow through the pulmonary arteries, and a resistance ratio which exceeded unity. This hemodynamic situation was fixed and stable. These patients had poor cardiac reserve with episodes of failure, exhibited the onset of permanent cyanosis at rest and digital clubbing in the second decade of life, and suffered from effort syncope and hemoptysis. There was clinical evidence of pulmonary hypertension and a faint or absent systolic murmur and no thrill. Predominantly right ventricular hypertrophy was found in x-ray and electrocardiographic studies, along with enlarged hilar vessels and virtually normal peripheral lung fields.

5. In every case it was possible to demonstrate significant arterialization of the mixed venous blood in the right ventricle, with the greatest increment of blood oxygen saturation occurring most frequently in the right ventricular outflow tract.

6. Indicator dye dilution curve studies either indicated the presence of pulmonary recirculation or accurately localized the level of existing right-to-left shunts.

7. In the cases studied it was impossible to separate

the Eisenmenger complex physiologically from isolated ventricular septal defect with pulmonary hypertension.

8. The hemodynamic and clinical stigmata of isolated ventricular septal defect can be related to the presence or absence of pulmonary arterial hypertension, pulmonary blood flow, age of the patient, degree of desaturation of the peripheral arterial blood, and the resistance ratio.

In the following tables, it has been necessary to divide Tables 3 and 4 into two portions for convenience of binding. In these two tables the patients are identically numbered for convenience of reference.

Table 1

PATIENTS ARRANGED IN ORDER OF INCREASING PULMONARY ARTERY SYSTOLIC PRESSURE. IN THE PULMONARY HYPERTENSIVE CASES WITH EQUIVALENT PRESSURES IN THE TWO CIRCULATIONS, GROUPING IS ALSO RELATED TO AGE.

	Patient	Age	Sex	Peripheral Arterial O_2 Saturation	Pressures (mm. Hg.) Pulmonary Artery S/D	Systemic Artery S/D	Pulmonary Artery Mean	Pulmonary Artery Wedge Mean	Right Ventricular S/D	Cardiac Output Litres/Min/Sq.M. Pulmonary Flow	Systemic Flow	Net Shunt* Litres/Min/Sq.M. L → R	R → L	Total Vascular Resistance Dynes/Sec/Cm.$^{-5}$ Pulmonary P	Systemic p	P/p
	1	14	F	98	18/6	127/66	10	-	22/1	9.1	7.3	1.8	-	57	619	0.09
	2	29	M	98	19/10	131/72	13	-	26/5	4.3	2.3	2.1	-	121	1601	0.08
	3	24	F	98	20/10	122/69	13	7	20/6	3.5	2.9	0.6	-	204	1653	0.12
	4	15	M	97	22/7	141/64	12	8	23/-1	4.0	3.5	0.5	-	125	1074	0.12
	5	43	F	99	22/12	159/91	15	9	24/4	4.0	3.2	0.8	-	153	1448	0.11
	6	4	F	97	23/9	77/40	14	6	20/2	9.0	4.8	4.2	-	200	1357	0.15
1	7	17	M	98	27/8	136/68	14	6	30/3	6.4	5.2	1.1	-	97	764	0.13
	8	34	F	94	27/14	147/75	18	8	34/5	4.2	3.6	0.6	-	175	1129	0.15
	9	18	M	98	34/16	120/59	22	-	38/7	6.0	3.2	2.8	-	194	1288	0.15
	10	40	M	99	37/21	165/79	26	-	33/9	2.4	2.2	0.2	-	432	1966	0.23
	11	14	M	98	38/19	116/67	25	9	42/3	6.5	5.1	1.4	-	195	830	0.23
	12	9	M	96	39/17	90/55	24	-	39/3	7.9	4.4	3.5	-	257	1273	0.20
	13	3	M	92**	43/22	87/54	29	-	46/7	17.1	7.5	9.6	-	241	1235	0.19
	14	1※	F	96**	61/22	93/45	35	-	66/6	-	-	-	-	-	-	-
	15	7	M	96	69/29	123/81	42	-	67/8	11.6	4.2	7.4	-	302	1900	0.16
	16	27	M	98	73/38	96/50	50	-	74/19	11.7	6.2	5.4	-	205	500	0.41
2	17	3	M	93**	78/58	105/60	64	14	77/10	7.8	4.2	3.6	-	1190	2602	0.46
	18	6	M	91**	80/52	100/60	64	9	62/4	11.6	4.8	6.8	-	647	1767	0.37
	19	4	M	95**	82/50	100/53	61	-	78/6	10.0	4.4	5.6	-	668	1725	0.39
	20	5	F	96**	87/46	118/80	60	12	90/5	13.4	5.8	7.7	-	557	2009	0.28
	21	44	F	94	88/38	120/66	55	-	95/6	12.5	6.5	6.0	-	220	647	0.34
	22	8	F	93**	89/60	108/71	70	-	83/4	7.7	3.3	4.4	-	766	2141	0.36
	23	7	M	90**	78/54	69/41	62	-	71/4	13.1	6.6	6.5	-	533	850	0.63
	24	5	F	92**	82/55	76/53	64	12	79/3	8.7	4.6	4.2	-	813	1476	0.55
	25	1	M	93**	86/57	88/48	67	-	105/2✓	-	-	-	-	-	-	-
3a	26	10	M	93	98/58	97/59	71	22	98/13	9.4	6.6	2.7	-	639	914	0.70
	27	12	M	97	100/56	104/72	71	-	104/10	6.5	3.2	3.2	-	692	1618	0.43
	28	8	F	96	102/63	108/62	76	15	98/8	4.9	4.3	0.6	-	1520	1756	0.86
	29	9	M	85**	105/66	111/63	79	-	105/2	6.8	5.6	1.3	-	972	1193	0.81
	30	27	M	91	112/55	123/80	74	-	115/13	2.0	2.3	-	0.3	1643	1833	0.90
	31	19	M	96	112/72	122/76	85	-	112/7	3.5	2.1	1.4	-	1232	2202	0.56
	32	26	F	83	114/67	116/66	83	-	111/0	2.2	3.0	-	0.8	1660	1203	1.38
	33	39	M	84	115/77	125/86	90	-	113/14	1.5	2.1	-	0.5	2565	2079	1.23
3b	34	30	F	76	126/66	132/75	86	13	124/7	1.8	2.6	-	0.8	2546	1880	1.35
	35	17	F	89	128/65	134/81	86	-	132/10	2.3	2.9	-	0.6	1961	1762	1.11
	36	30	F	82	135/83	135/84	100	3	127/6	1.6	2.2	-	0.5	2960	2242	1.32
	37	39	M	80	142/39	140/80	73	-	126/17	2.2	3.1	-	0.9	1358	1310	1.04
	38	36	F	74	151/28	150/81	69	16	153/9	1.7	2.9	-	1.1	2120	1932	1.10

* Difference between flows
** General anesthesia used
※ Age 7 months
✓ No pulmonary stenosis

1 Normal pulmonary artery systolic pressures.
2 Pulmonary hypertension not equivalent to systemic arterial pressures.
3 Pulmonary hypertension equivalent to systemic arterial pressures.
a Under 12 years of age.
b Over 12 years of age.

Table 2

TABLE OF AVERAGE HEMODYNAMIC VALUES

		Age	Pulmonary Artery Mean Pressure (mm. Hg.)	Cardiac Output L/M/M^2 Pulmonary Flow	Cardiac Output L/M/M^2 Systemic Flow	Net Shunt* L/M/M^2 L→R	Net Shunt* L/M/M^2 R→L	Total Vascular Resistance Dynes/Sec/Cm^{-5} Pulmonary P	Total Vascular Resistance Dynes/Sec/Cm^{-5} Systemic p	P/p
1	Average	22	17	5.6	4.0	1.6	-	184	1250	0.15
	Range	4-43	10-26	2.4-9.1	2.2-7.3	0.2-4.2	-	57-432	619-1966	0.08-0.23
	No. Cases	12	12	12	12	12	-	12	12	12
2	Average	11	53	11.5	5.2	6.3	-	533	1614	0.33
	Range	1**-44	29-70	7.8-17.1	3.3-7.5	3.6-9.6	-	205-1190	500-2602	0.16-0.46
	No. Cases	10	10	9	9	9	-	9	9	9
3a	Average	7	70	8.2	5.1	3.1	-	861	1301	0.66
	Range	1-12	62-79	4.9-13.1	3.2-6.6	0.6-6.5	-	533-1520	850-1756	0.43-0.86
	No. Cases	7	7	6	6	6	-	6	6	6
3b	Average	29	83	2.1	2.5	1.4	0.56	1944	1868	1.11
	Range	17-39	69-100	1.5-3.5	2.1-3.1	-	0.3-1.1	1332-2960	1203-2242	0.56-1.38
	No. Cases	9	9	9	9	1	8	9	9	9

* Difference between flows.

** Age 7 months.

1 Normal pulmonary artery pressures.

2 Pulmonary hypertension not equivalent to systemic arterial pressures.

3 Pulmonary hypertension equivalent to systemic arterial pressures.

a Under 12 years of age.

b Over 12 years of age.

Table 3

HEMODYNAMIC AND SATURATION DATA IN 38 CASES OF VENTRICULAR SEPTAL DEFECT WITHOUT PULMONARY STENOSIS

All values obtained with the patient at rest and breathing room air. Cases arranged in order of increasing pulmonary artery systolic pressures

Table 3a Pressure Data

Patient	Age	Sex	Surface Area M^2	Metabolic Rate	Pulmonary Artery			Radial Artery			Right Ventricle		Right Atrium		Mean Pulmonary Artery Wedge Pressure
					S	D	M	S	D	M	S	D	S	D	
1	14	F	1.52	+3	18	6	10	127	66	86	22	1	2	-3	-
2	29	M	1.98	-4	19	10	13	131	72	92	26	5	6	2	-
3	24	F	1.47	-15	20	10	13	122	69	87	20	6	4	0	7
4	15	M	1.91	+1	22	7	12	141	64	90	23	-1	6	-1	8
5	43	F	1.96	-4	22	12	15	159	91	114	24	4	4	2	9
6	4	F	0.62	-8	23	9	14	77	40	51	20	2	4	2	6
7	17	M	1.82	-8	27	8	14	136	68	91	30	3	3	1	6
8	34	F	1.96	+5	27	14	18	147	75	99	34	5	4	-1	8
9	18	M	1.51	+4	34	16	22	120	59	79	38	7	12	7	-
10	40	M	2.02	-3	37	21	26	165	79	108	33	9	19	12	-
11	14	M	1.57	+7	38	19	25	116	67	83	42	3	5	1	9
12	9	M	0.95	-24	39	17	24	90	55	67	39	3	5	2	-
13	3	M	0.56	+2	43	22	29	87	54	65	46	7	12	8	-
14	1	F	-	-	61	22	35	93	45	61	66	6	12	5	-
15	7	M	0.96	+17	69	29	42	123	81	95	67	8	8	2	-
16	27	M	1.67	+28	73	38	50	96	50	65	74	9	9	2	-
17	7	M	0.71	-15	78	54	62	69	41	50	71	4	9	4	-
18	3	M	0.55	+1	78	58	64	105	60	75	77	10	10	-5	14
19	6	M	0.68	-10	80	52	64	100	60	73	62	4	3	-1	9
20	4	M	0.73	-20	82	50	61	100	53	69	78	6	6	-4	-
21	5	F	0.72	-10	82	55	64	76	53	61	79	3	7	4	12
22	1	M	-	-	86	57	67	88	48	61	105	2	8	2	-
23	5	F	0.64	+5	87	46	60	118	80	93	90	5	8	5	12
24	44	F	1.60	+39	88	38	55	120	66	84	95	6	8	4	-
25	8	F	0.95	-20	89	60	70	108	71	83	83	4	5	2	-
26	10	M	0.95	+15	98	58	71	97	59	72	98	13	13	11	22
27	12	M	1.27	+16	100	56	71	104	72	83	104	10	8	1	-
28	8	F	0.82	-10	102	63	70	108	62	77	98	8	9	2	15
29	9	M	0.95	-7	105	66	79	111	63	79	105	2	4	1	-
30	27	M	1.80	0	112	55	74	123	80	94	115	13	6	0	-
31	19	M	1.56	-9	112	72	85	122	76	91	112	7	7	4	-
32	26	F	1.83	+10	114	67	83	116	66	83	111	0	11	7	-
33	39	M	1.83	+2	115	77	90	125	86	99	113	14	14	8	-
34	30	F	1.53	-2	126	66	86	132	75	94	124	7	9	3	13
35	17	F	1.54	+12	128	65	86	134	81	99	132	10	9	2	-
36	30	F	1.66	-8	135	83	100	135	84	101	127	6	-	-	3
37	39	M	1.95	+16	142	39	73	140	80	100	126	17	18	3	-
38	36	F	1.50	+13	151	28	69	150	81	104	153	9	13	5	16

Table 3

HEMODYNAMIC AND SATURATION DATA IN 38 CASES OF VENTRICULAR SEPTAL DEFECT WITHOUT PULMONARY STENOSIS

All values obtained with the patient at rest and breathing room air. Cases arranged in order of increasing pulmonary artery systolic pressure

Table 3b Hemodynamic and Saturation Data

Patient	Pulmonary Index	Systemic Index	Index of Difference Between Pulmonary & Systemic Flows	Index of Difference Between Systemic & Pulmonary Flows	Total Pulmonary Resistance	Total Peripheral Resistance	Total Pulmonary Resistance / Total Peripheral Resistance	Blood Oxygen Saturation (per cent): Pulmonary Artery	Right Ventricular Outflow	Low Right Ventricle	Right Atrium	Oxygen Capacity	Arterial Oxygen Saturation (%)
1	9.1	7.3	1.8	-	57	619	0.09	80	84	77	75	13.5	98
2	4.3	2.3	2.1	-	121	1601	0.08	87	85	79	76	18.9	98
3	3.5	2.9	0.6	-	204	1653	0.12	84	85	71	73	16.7	98
4	4.0	3.5	0.5	-	125	1074	0.12	78	79	-	75	20.4	97
5	4.0	3.2	0.8	-	153	1448	0.11	74	74	69	68	11.1	99
6	9.0	4.8	4.2	-	200	1357	0.15	86	86	85	76	15.3	97*
7	6.4	5.2	1.1	-	97	764	0.13	89	89	85	85	19.9	98
8	4.2	3.6	0.6	-	175	1129	0.15	77	78	-	73	17.1	94
9	6.0	3.2	2.8	-	194	1288	0.15	88	-	86	76	18.4	98
10	2.4	2.2	0.2	-	432	1966	0.23	80	80	77	76	24.7	99
11	6.5	5.1	1.4	-	195	830	0.23	84	84	-	80	18.8	98
12	7.9	4.4	3.5	-	257	1273	0.20	93	93	90	79	16.1	96*
13	17.1	7.5	9.6	-	241	1235	0.19	88	86	76	73	12.9	92*
14	-	-	-	-	-	-	-	88	87	77	62	-	96*
15	11.6	4.2	7.4	-	302	1900	0.16	89	89	86	73	17.3	96
16	11.7	6.2	5.4	-	205	500	0.41	90	89	84	66	18.6	98
17	13.1	6.6	6.5	-	533	850	0.63	82	85	-	76	15.7	90*
18	7.8	4.2	3.6	-	1190	2602	0.46	83	83	82	77	15.5	93*
19	11.6	4.8	6.8	-	647	1767	0.37	79	83	70	59	10.6	91*
20	10.0	4.4	5.6	-	668	1725	0.39	89	89	81	76	15.6	95*
21	8.7	4.6	4.2	-	813	1476	0.55	83	84	74	73	16.1	92*
22	-	-	-	-	-	-	-	76	77	70	71	14.4	93*
23	13.4	5.8	7.7	-	557	2009	0.28	88	88	88	79	15.2	96*
24	12.5	6.5	6.0	-	220	647	0.34	90	90	91	78	17.8	94
25	7.7	3.3	4.4	-	766	2141	0.36	85	84	81	75	16.4	93*
26	9.4	6.6	2.7	-	639	914	0.70	86	86	77	76	16.5	93
27	6.5	3.2	3.2	-	692	1618	0.43	89	90	85	69	17.2	97
28	4.9	4.3	0.6	-	1520	1756	0.86	84	86	79	77	17.2	96
29	6.8	5.6	1.3	-	972	1193	0.81	83	82	71	68	16.5	85*
30	2.0	2.3	-	0.3	1643	1833	0.90	69	71	-	65	23.4	91
31	3.5	2.1	1.4	-	1232	2202	0.56	80	81	-	72	21.7	96
32	2.2	3.0	-	0.8	1660	1203	1.38	72	72	76	69	22.4	83
33	1.5	2.1	-	0.5	2565	2079	1.23	74	75	66	64	30.6	84
34	1.8	2.6	-	0.8	2546	1880	1.35	80	80	64	62	20.4	76
35	2.3	2.9	-	0.6	1961	1762	1.11	69	72	70	70	23.8	89
36	1.6	2.2	-	0.5	2960	2242	1.32	71	71	65	65	29.0	82
37	2.2	3.1	-	0.9	1358	1310	1.04	-	67	-	61	22.8	80
38	1.7	2.9	-	1.1	2120	1932	1.10	74	73	66	57	27.8	74

* Patient under general anesthesia (rectal avertin and intravenous pentothal).

Indices are expressed in litres/min/m^2

Resistances are expressed in dynes/sec./$cm.^{-5}$

Table 4

CLINICAL, RADIOLOGICAL AND ELECTROCARDIOGRAPHIC DATA IN 38 PATIENTS WITH ISOLATED VENTRICULAR SEPTAL DEFECT, CASES ARRANGED IN ORDER OF INCREASING PULMONARY ARTERIAL SYSTOLIC PRESSURE

Table 4a Results of Clinical Examination

				Symptoms on Effort			Clinical Cyanosis					Systolic Murmur and Thrill			Diastolic Murmur		
	Patient	Age	Sex	Dyspnoea or Ready Fatigue	Tachycardia	Syncope	Intensity	Age of Onset	Digital Clubbing	Hemoptysis	Episodes of Failure	Intensity	Site	Thrill	Intensity	Site	Increased Pulmonary Second Sound
Normal Pulmonary Artery Pressures	1	14	F	+	-	-	-	-	-	-	-	+++	3-4 Lis and Back	+	-	-	+
	2	29	M	-	-	-	-	-	-	-	-	++++	4 Lis and Back	+	-	-	-
	3	24	F	-	-	-	-	-	-	-	-	+++	3 Lis	+	-	-	-
	4	15	M	-	-	-	-	-	-	-	-	++	4 Lis	-	-	-	-
	5	43	F	++	-	-	-	-	-	-	-	+++	4 Lis	-	-	-	-
	6	4	F	-	-	-	-	-	-	-	-	+++	3 Lis	+	++	3 Lis	-
	7	17	M	+	+	-	-	-	-	-	-	+++	4 Lis	+	-	-	-
	8	34	F	+	+	-	-	-	-	-	-	++	3-4 Lis	-	-	-	-
	9	18	M	+	-	-	-	-	-	-	-	+++	4 Lis and Back	+	-	-	-
	10	40	M	-	-	-	-	-	-	-	-	++	3 Lis	-	++	3 Lis	++
	11	14	M	+	-	-	-	-	-	-	-	+++	3-4 Lis	-	-	-	-
	12	9	M	-	-	-	-	-	-	-	-	+++	4 Lis	+	-	-	-
Pulmonary Hypertension	13	3	M	+	-	+	±±	10 days	-	-	+	+++	4 Lis	+	-	-	-
	14	1	F	++	-	-	-	-	-	-	+	+++	4 Lis and Back	+	-	-	+
	15	7	M	+	-	-	-	-	-	-	+	++++	3 Lis and Back	+	-	-	+++
	16	27	M	+	+	+	-	-	-	-	+	+++	4 Lis and Back	+	-	-	++
	17	7	M	+	-	-	-	-	-	-	-	+++	3 Lis and Back	+	-	-	+++
	18	3	M	+	-	-	-	-	-	-	+	+++	3 Lis and Back	+	+	2 Lis	+
	19	6	M	+	-	-	-	-	-	-	-	+++	4 Lis	+	-	-	++
	20	4	M	+	-	-	-	-	-	-	-	++	4 Lis and Back	-	-	-	++
	21	5	F	+	+	-	-	-	-	-	-	+++	3 Lis and Back	+	-	-	++
	22	1	M	+	-	-	-	-	-	-	+	+++	3-4 Lis and Back	+	-	-	++
	23	5	F	+	-	-	±±	Birth	-	+	+	+++	4 Lis	+	-	-	++
	24	44	F	+	+	-	-	-	-	-	-	++++	3-4 Lis and Back	+	-	-	-
	25	8	F	-	-	-	-	-	-	-	+	++++	3 Lis and Back	+	+	3 Lis	+++
	26	10	M	++	-	+	±	7	-	-	+	+++	3 Lis	+	+	3 Lis	++
	27	12	M	++	+	-	±	Birth	-	-	-	+++	3 Lis	+	+	4 Lis	++
	28	8	F	++	-	-	±	5	-	-	-	+++	3 Lis	+	-	-	+++
	29	9	M	++	-	-	-	-	-	+	-	+++	3 Lis	+	-	-	+++
	30	27	M	++	-	-	++	14	++	-	-	+	3 Lis	-	-	-	++
	31	19	M	++	+	+	+	18	-	-	-	+	3 Lis	-	++	2 Lis	++++

± Intermittent clinical findings present only following exertion.

Lis. Left intercostal space in the parasternal area.

Table 4 (continued)

				Symptoms on Effort			Clinical Cyanosis					Systolic Murmur and Thrill			Diastolic Murmur		
	Patient	Age	Sex	Dyspnoea or Ready Fatigue	Tachycardia	Syncope	Intensity	Age of Onset	Digital Clubbing	Hemoptysis	Episodes of Failure	Intensity	Site	Thrill	Intensity	Site	Increased Pulmonary Second Sound
Pulmonary Hypertension	32	26	F	+++	-	-	++	15	++	-	+	+	3 Lis	-	-	-	+++
	33	39	M	+++	+	+	++	14	++	+	+	±	2-3 Lis	-	-	-	+
	34	30	F	++	-	+	++	12	++	+	+	++	2-3 Lis	-	++	2-3 Lis	++
	35	17	F	++	-	+	++	10	-	-	-	+	3-4 Lis	-	-	-	++
	36	30	F	+++	-	+	++	14	++	-	+	+	3 Lis	-	-	-	++
	37	39	M	+++	-	-	++	10	++	+	-	+++	3 Lis and Back	+	-	-	++
	38	36	F	+++	+	-	++	12	+++	+	+	++	2-3 Lis	+	++	3 Lis	+++

± Intermittent clinical findings present only following exertion.

Lis Left intercostal space in the parasternal area.

Table 4

CLINICAL, RADIOLOGICAL AND ELECTROCARDIOGRAPHIC DATA IN 38 PATIENTS WITH ISOLATED VENTRICULAR SEPTAL DEFECT, CASES ARRANGED IN ORDER OF INCREASING PULMONARY ARTERIAL SYSTOLIC PRESSURE

Table 4b Results of Radiological Examination and Electrocardiographic Examination

	Patient	Ventricular Enlargement	Enlarged Pulmonary Artery Segment	Increased Pulmonary Vascular Markings	Increased Hilar Pulsation	Retrograde Aortogram	Catheter Through V.S.D.	Electrocardiographic Examination
	1	-	+	-	-	-	-	N
	2	-	-	-	-	-	-	N
	3	-	+	+	-	-	-	BVH
	4	-	+	-	-	-	-	N
	5	-	-	-	-	-	-	RBBB
Normal Pulmonary	6	R&L	+	-	-	-	-	BVH
Artery Pressures	7	-	-	-	-	-	-	N
	8	-	+	-	-	-	-	N
	9	-	-	-	-	-	-	RBBB
	10	R&L	-	-	-	-	+	BVH
	11	-	-	-	-	-	-	N
	12	R&L	-	+	-	-	-	RBBB
	13	R	-	++	-	-	-	RVH
	14	R&L	++	+	-	N	-	BVH
	15	R&L	+	+	-	-	+	RVH
	16	R	++	+	-	-	+	RVH
	17	R	+	+	-	-	-	RVH
	18	R&L	+	++	-	N	+	BVH
Pulmonary	19	R&L	++	+	-	-	-	BVH
Hypertension	20	R&L	+++	++	-	-	-	RVH
	21	R	+++	+	+	-	-	BVH
	22	R	++	++	-	N	+	RVH
	23	R&L	+	++	-	-	+	BVH
	24	R&L	++	+	-	-	-	BVH
	25	R&L	+	++	-	-	-	RVH
	26	R	+++	++	-	-	-	BVH
	27	R&L	++	+	+	-	-	BVH
	28	R&L	++	+	++	-	+	RBBB
	29	R&L	++	+	-	N	-	RVH
	30	R	++	-	-	-	+	RVH
	31	R	++	-	-	-	-	RVH
	32	R	+++	-	-	-	-	RVH
	33	R&L	++	+	-	-	-	RVH
	34	-	+	-	-	-	+	RAD
	35	R	++	-	+	-	+	RVH
	36	R	+++	+	-	-	-	RVH
	37	R&L	+++	+	-	-	-	RBBB
	38	R&L	++	+	-	-	-	RVH

N Within normal limits.

BVH Biventricular hypertrophy **RVH** Right ventriclar hypertrophy **RBBB** Right bundle branch block **RAD** Right axis deviation.

Table 5

AVERAGE ABSOLUTE BLOOD OXYGEN SATURATION VALUES AND SATURATION INCREMENTS THROUGH THE CHAMBERS OF THE RIGHT SIDE OF THE HEART IN 38 PATIENTS WITH ISOLATED VENTRICULAR SEPTAL DEFECT.

Results obtained with the patients at rest and spontaneously breathing room air. Values are expressed as a percentage of oxygen capacity.

			Absolute Blood Oxygen Saturation				Blood Oxygen Saturation Increment		
		Systemic Arterial Oxygen Saturation	Pulmonary Artery	Right Ventricular Outflow Tract	Low Right Ventricle	Right Atrium	Right Atrium → Pulmonary Artery	Right Atrium → Right Ventricular Outflow Tract	Right Atrium → Low Right Ventricle
1	Saturation Value	97	83	83	80	76	+7	+7	+4
	Number of Patients	12	11	9	12	12	12	11	8
2	Saturation Value	94	87	87	82	72	+15	+15	+10
	Number of Patients	10	10	10	10	10	10	10	10
3a	Saturation Value	91*	83	84	76	73	+10	+11	+4
	Number of Patients	7	7	7	6	7	7	7	6
3b	Saturation Value	84	74	73	68	65	+9	+9	+3
	Number of Patients	9	8	9	6	9	8	8	6

* Two patients had desaturation under general anesthesia (rectal avertin and intravenous pentothal) but had normal peripheral aterial oxygen saturation under basal conditions.

1 Normal pulmonary artery pressures.

2 Pulmonary hypertension not equivalent to systemic arterial pressures.

3 Pulmonary hypertension equivalent to systemic arterial pressures.

a Under 12 years of age.

b Over 12 years of age.

Table 6

ADDITIONAL CLINICAL FEATURES IN 38 PATIENTS
WITH ISOLATED VENTRICULAR SEPTAL DEFECT

	Normal Pulmonary Artery Pressures (12 patients)	Pulmonary Hypertension (26 patients)
Physical underdevelopment	1	10
Mental retardation	-	1
Polycythemia	-	4
Marfan's syndrome	-	1
Right sided aorta	-	1
Persistent left superior vena cava	-	2
Aortic insufficiency	2	-
Pulmonary insufficiency	-	4

Table 7

SUMMARY OF RADIOLOGIC FINDINGS IN 38 PATIENTS
WITH ISOLATED VENTRICULAR SEPTAL DEFECT

	Normal Pulmonary Artery Pressures (12 patients)	Pulmonary Hypertension (26 patients)
Ventricular enlargement		
(a) Right ventricle	-	11
(b) Both ventricles	3	14
Enlarged pulmonary artery segment	5	25
Increased pulmonary vascular markings	2	21
Increased hilar pulsations	-	4
Normal retrograde aortogram	-	4
Cardiac catheter through V.S.D.	1	9

Table 8

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS
IN 38 PATIENTS WITH ISOLATED VENTRICULAR SEPTAL DEFECT

	Normal Pulmonary Artery Pressures (12 patients)	Pulmonary Hypertension (26 patients)
Normal electrocardiogram	6	-
Right axis deviation	-	1
Right bundle branch block	3	2
Biventricular hypertrophy	3	8
Right ventricular hypertrophy	-	15

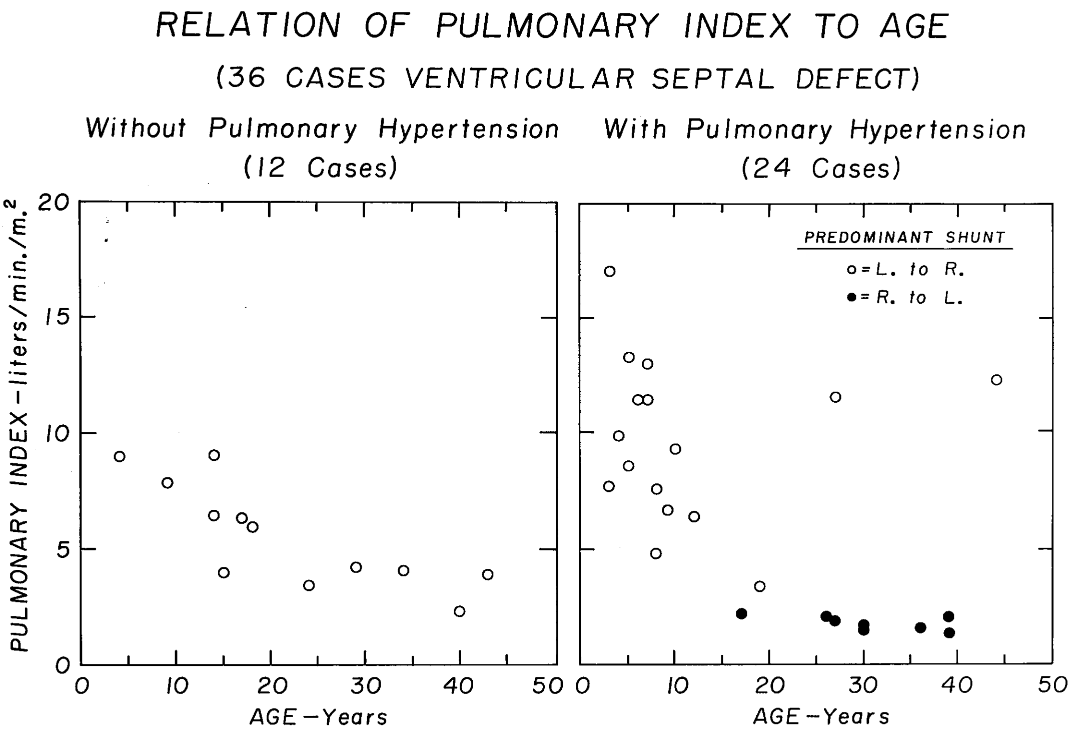

Fig. 1. There is a gradual trend towards a diminishing pulmonary index as age advances in the group with normal pulmonary artery pressures. The trend is more rapid in the presence of pulmonary hypertension and is most rapid in the early years of life. Dominant right-to-left shunts occur only in an older age group with pulmonary hypertension and in these patients the pulmonary index varies little over a considerable range in age.

DEMONSTRATION OF AN EARLY RECIRCULATION PEAK FOLLOWING INJECTION OF DYE INTO PULMONARY ARTERY IN A PATIENT WITH A LEFT TO RIGHT SHUNT

(♀ 24 YEARS-VENTRICULAR SEPTAL DEFECT)

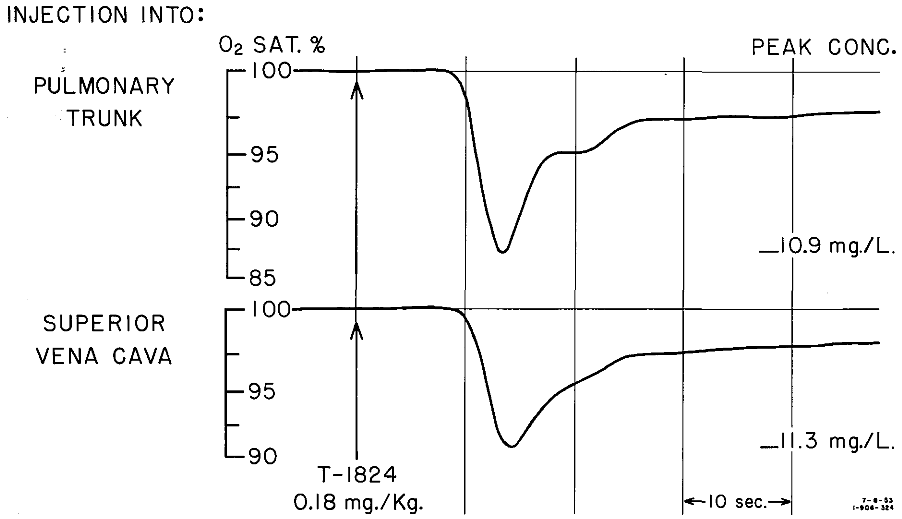

Fig. 2. Demonstration of the abnormal vascular pathway and recorded dye dilution curve following injection of Evans' blue dye (T-1824) into the main pulmonary artery in a patient with isolated ventricular septal defect. The appearance time and buildup time are normal. The magnitude of deflection is reduced, however, and the disappearance slope much prolonged with early appearance of a systemic recirculation peak. This abnormal curve is typical of left-to-right shunts of considerable magnitude and is produced by pulmonary recirculation of a proportion of the dye with a slow clearance of a constant fraction of the recirculating dye into the systemic circulation.

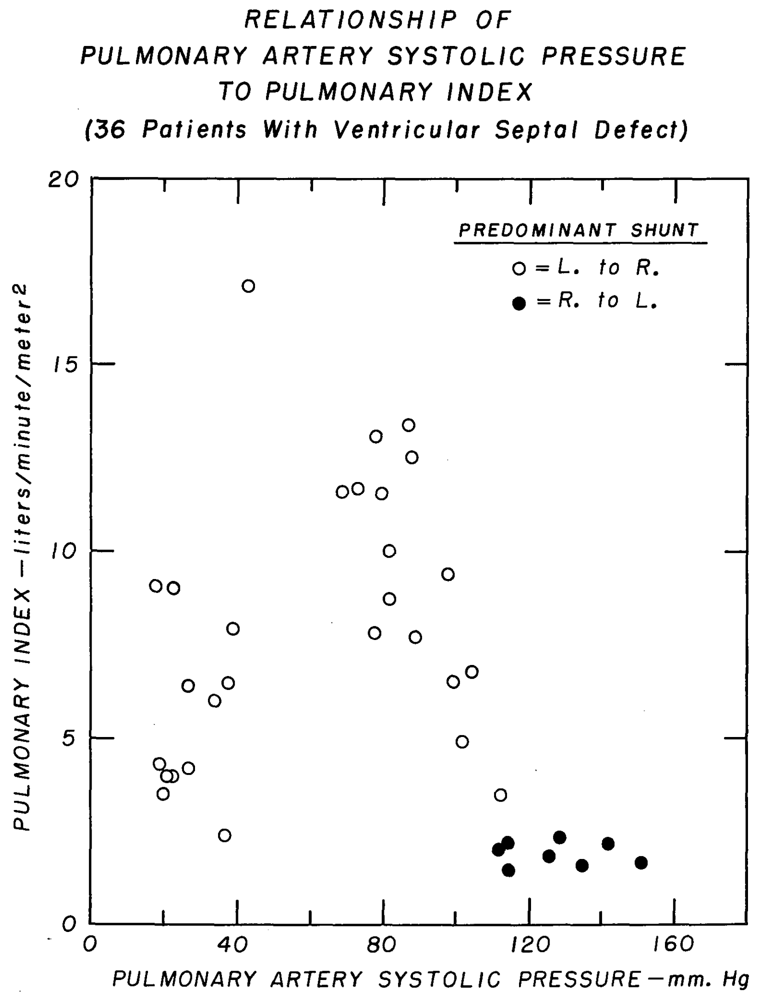

Fig. 3. The extremes of pulmonary blood flow seen in this study in the patients with pulmonary hypertension are not seen in its absence. Dominant right-to-left shunts and diminished pulmonary index are encountered in the presence of the highest pulmonary artery systolic pressures. There is a trend towards progressive diminution of the pulmonary index with increasing pulmonary artery systolic pressure in the hypertensive patients with dominant left-to-right shunts, which is not seen in those with normal pulmonary artery pressures. The clear division between the two groups is apparent.

RELATION OF PULMONARY/SYSTEMIC RESISTANCE RATIO TO DIRECTION AND MAGNITUDE OF SHUNT

(24 Cases With Ventricular Septal Defect, Pulmonary Hypertension)

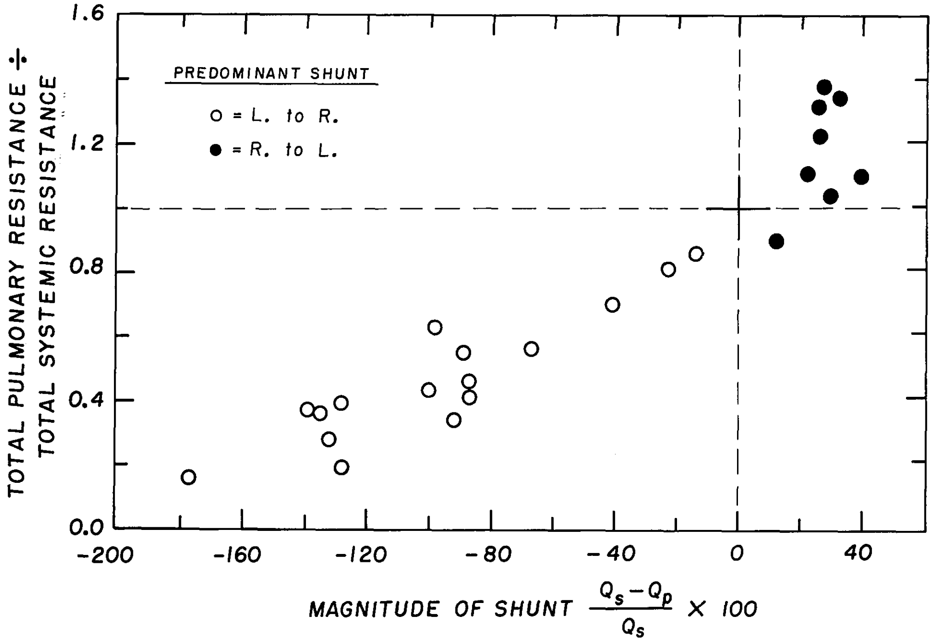

Fig. 4. The relationship of the relative influence of pulmonary vascular resistance and systemic vascular resistance on the direction and magnitude of the intracardiac shunt in those patients with pulmonary hypertension is clearly shown. All calculated shunts are here related to systemic flow. As the ratio of the resistances approaches and exceeds unity the direction of shunt flow becomes revised from left-to-right to right-to-left. Beyond unity the linear relationship of the resistance ratio to the magnitude of shunt becomes altered so that a proportionately smaller increase in shunt accompanies increase in resistance ratio in contrast to this relationship below unity.

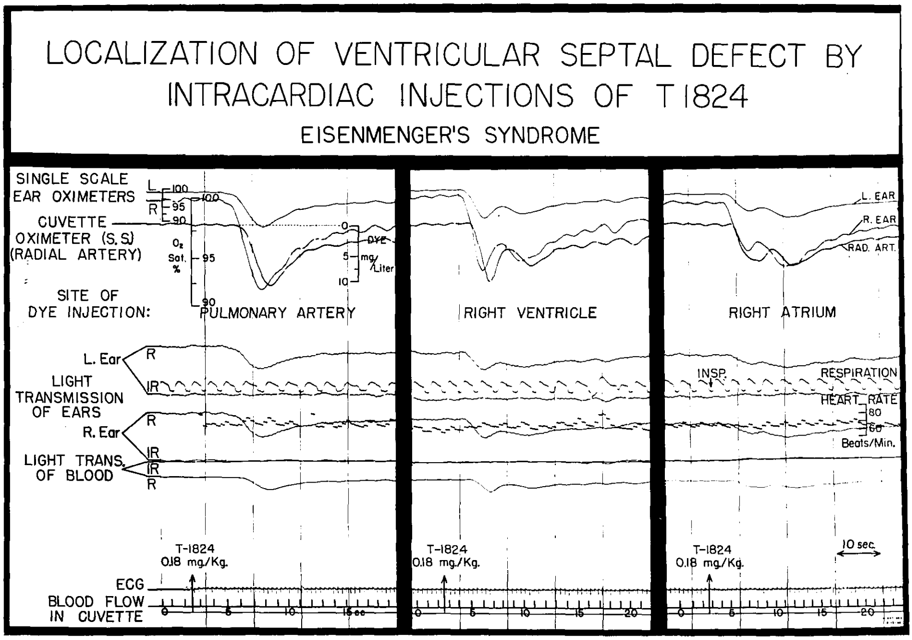

Fig. 5. Following injection of T-1824 into the pulmonary trunk just beyond the pulmonary valve, a dye dilution curve of relatively normal contour has been recorded. The appearance time for this curve is 8 seconds from injection to the first deflection recorded by the earpiece oximeters. After withdrawal of the catheter tip and injection in the right ventricle and right atrium, the appearance times are 4 and 5 seconds respectively, and an abnormal initial hump is present on the main deflection of the curve, due to passage of dye directly into the systemic arterial pathway. This characteristic curve may be recorded after injection of the dye at any point upstream to the defect, and the series illustrated thus localize the defect to ventricular level. Differences in amplitude of simultaneously recorded dye curves are due to variations in the sensitivities of the three oximeters used. Spontaneous variations in systemic arterial oxygen saturation can be seen.

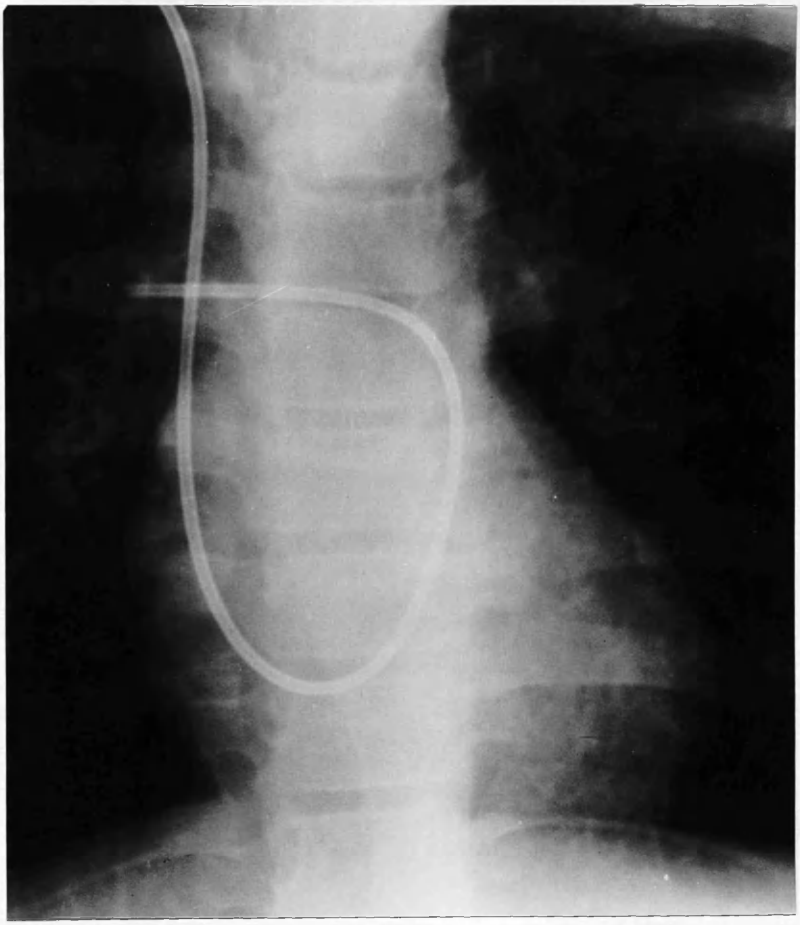

Fig. 6(a). X-ray appearance of the cardiac catheter with the tip advanced to the right main pulmonary artery. The catheter has followed a normal course through the right atrium and ventricle and has been manipulated through the pulmonary valve to the right main pulmonary artery.

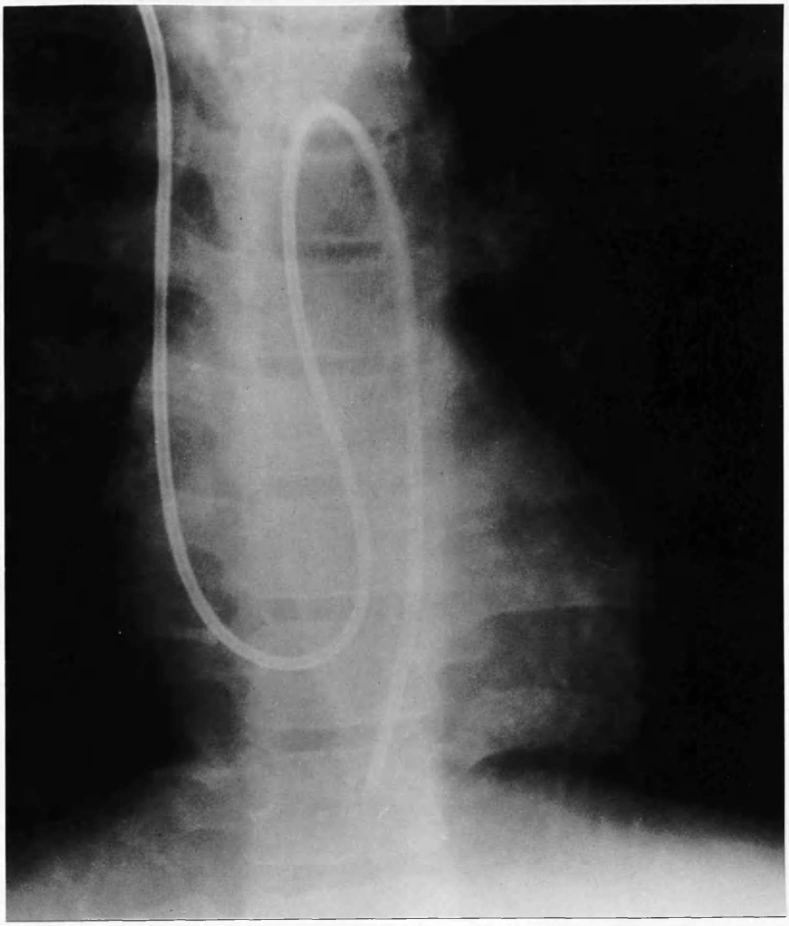

Fig. 6(b). (Same case as Fig. 6a) In this instance the catheter has passed through a ventricular septal defect to enter the left ventricle below the aortic valve, and from there the tip has been advanced to the descending thoracic aorta at the level of the diaphragm. When other anomalies are present difficulty may exist in determining which of the major vessels the catheter has entered. In these circumstances dye dilution curves and saturation studies are of considerable value.

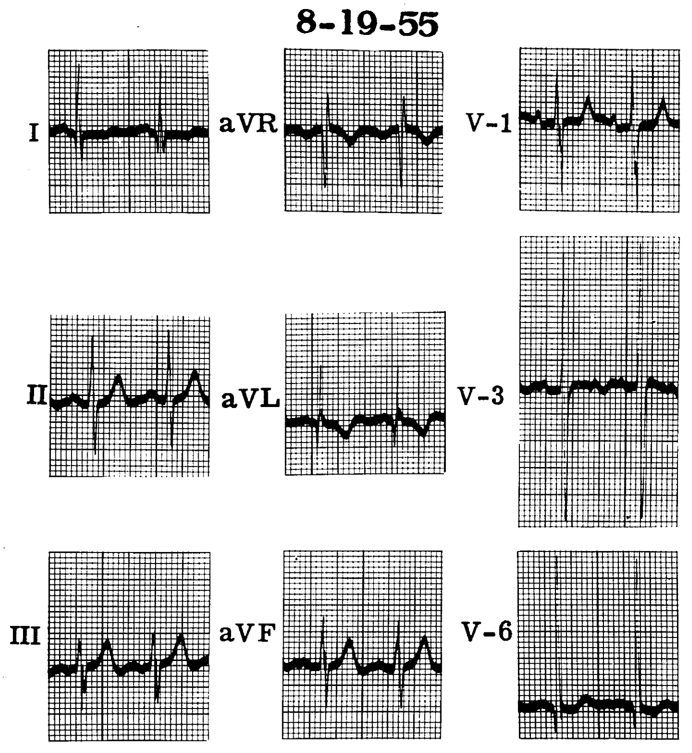

Fig. 7. Electrocardiogram demonstrating biventricular hypertrophy with high amplitude equiphasic QRS complexes in the midprecordial leads (Patient 18). Since the patient is only 3 years old, there is probably left ventricular dominance. Pulmonary artery pressure was 78/58 mm. Hg.

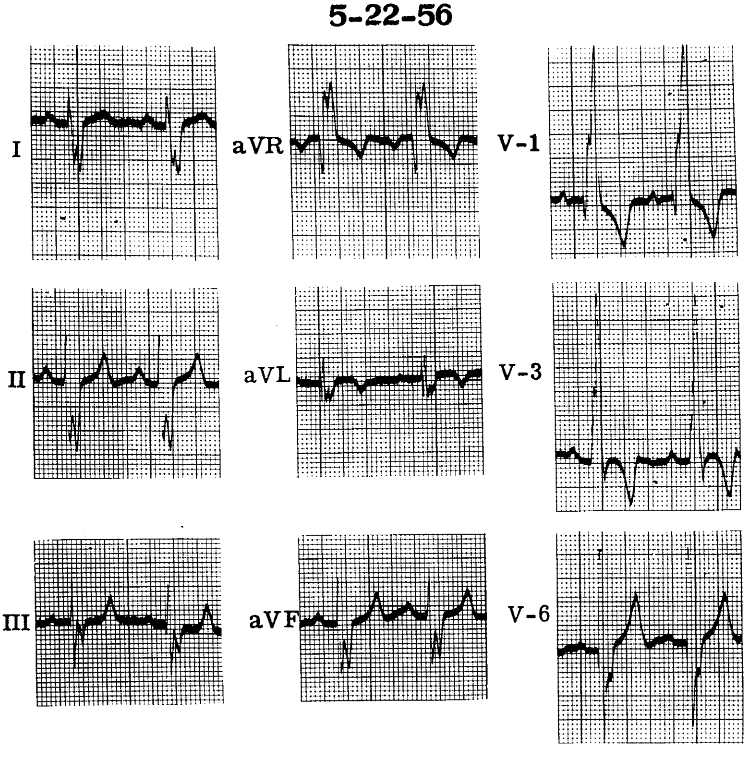

Fig. 8. Electrocardiographic evidence of right ventricular hypertrophy in a 9 year old boy with a pulmonary artery pressure of 105/66 mm. Hg. (Patient 29). The right bundle branch block pattern was seen infrequently in the absence of right ventricular hypertrophy. There is evidence of systolic overloading of the right ventricle.

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