THE GREAT ARTERIES IN NORMAL AND SOME CONGENITALLY MALFORMED HEARTS THEIR INTERNAL CALIBRES AND TUNICA MEDIA IN RELATION TO BLOOD FLOW

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INTRODUCTION

I. Occurrence of congenital malformation of the heart

The road from fertilized egg to newborn baby is a fascinating and complicated one. What happens to eggs that actually come in contact with sperms has been studied by many authors and has been summarized by Witschi in 1969. About 16% of the eggs do not cleave, either because they are not penetrated by sperms or because the mitotic mechanism does not function. Another 15% are lost during the first week, at various preimplantation stages (cleavage and blastocyst stages). The stage of early implantation and development during the second week brings a further loss of 27%. In the third to sixth week there is a loss of 8% and the late abortion loss is about 3%. Live births will then amount to only 31%. It has been shown that 1-12% of all these newborn children carry some major congenital malformation recognizable at or shortly after birth (Yerushalmy, 1969; Lilienfeld, 1969). Reports of congenital malformations show congenital heart malformations in about 0.8% of total births (Kerrebijn, 1964; Hoffman and Christianson, 1978). In the Netherlands with 177.090 newborns in 1976 this will be about 1400 per year of which 123 were surgically corrected and 416 died in the first year of life (Centraal Bureau voor Statistiek, 1976, 1978).

The majority of congenital heart malformations are of unknown etiology and are believed to be the result of the interaction of environmental and genetic influences (Nora, 1968). The risk for recurrence of the same lesion in cases with an affected parent or sibling is small but exceeds the expectation risk for the same lesion in the general population. Vertical transmission of atrial septal defects through four generations has been described (Lynch et al., 1978).

These children born with congenital heart malformations are of special interest to the paediatric cardiologist and cardiovascular surgeon.

II. Trends in the study of congenital malformations of the heart

Circulation of blood through the heart and the great vessels has been studied over many centuries. William Harvey's publication in 1628 of ' De Motu Cordis ', which was translated into Dutch by Nicolaas van Assendelft in 1650, was followed by many discussions (Houtzager and van Leeuwen, 1978). After a certain time textbooks of anatomy were published concentrating on the human bloodvessels. An example of such a textbook is ' Beschrijving der Bloetvaten des Menschen Lichaams ' (Description of bloodvessels in man) published in 1745 by Willem Vink (± 1680 - 1763) (Van Lieburg, 1978). However it took a long time before quantitative studies of the heart and great arteries were carried out. In the late decades of the 19th century the first results of measurements on post mortem material of the heart and its great vessels were published, mostly by pathologists like Beneke (1878; 1879), Roessle, Virchow and others (Gould, 1968). The early measurements added to the understanding of the normal heart and great vessels and of some cardiovascular malformations. Later post mortem material of infants and children aroused a greater interest of the pathologist in congenital cardiovascular malformations and openend a period of investigations on embryologic and foetal development of the heart and vessels.

Interest of the surgeon and the cardiologist in cardiovascular malformations grew following development in the 20th century of techniques allowing operations on the heart (1939, operative closure of the ductus arteriosus by Gross; 1945, aorto-pulmonary anastomosis by Blalock). Simultaneously methods were developed for collecting various morphological and physiological data in the living subject. A major step was the publication of " Congenital malformations of the heart " in 1947 by Hellen B. Taussig and the introduction of cardiac catheterization by André Cournand (1941). However, this technique does not result in accurate measurements of cardiac ostia and of great vessels. Still another technique was introduced recently : M-mode echocardiography. It was established as a diagnostic tool for non-invasive evaluation of cardiovascular malformations not only in the

adult (Somerville and Becu, 1978) but also in infants and children (Solinger et al., 1973; Sahn and Allen, 1978; Bass et al., 1978; Gramiak and Nanda, 1978). However, M-mode echocardiography only provides a one-dimensional view of the heart and great arteries which is the major limitation of the technique. Therefore, another technique of echocardiography, two-dimensional real-time ultrasonic imaging, has been developed (Tajik et al., 1978; Allen et al., 1978; Wing et al., 1978). Interpretation of the sections made by this technique is only possible when the cardiologist has a full understanding of the detailed anatomy and embryology of the heart and great arteries.

III. The anatomical and embryological approach to congenital malformation of the heart

Many investigations have been made of the macroscopical architecture of the different kinds of congenital malformation of the heart and on the development of the heart. Congenital malformations of the heart can be related to embryological development since they are deviations from normal development. The following is a review.

In the human embryo the circulation of blood has almost certainly started by the beginning of the fourth week after conception, that is by the 7 somite stage. The septation of the heart and great vessels takes place mainly in the 10 to 17 mm stage (Hamilton et al., 1964). The anomalies of the heart and associated vessels are often due to arrest in these developmental stages and can be listed as follows, but only the extreme deviations from normal development are mentioned. Anomalies due to incomplete septation or disturbance in septation can develop, that is to say : disturbance in truncus septation including malrotation, disturbance in atrial septation, disturbance in atrio-ventricular cushion fusion and disturbance in ventricular septation. Furthermore, malformations of the aortic arches, pulmonary veins and great veins can develop. Other abnormalities are often due to small disturbances in the balance between development of the left and right part of the heart in the late embryonic and foetal stages. Even when septation of the heart is normal one side of the heart can become

underdeveloped (Los, 1976).

In the embryonic stage the heart will transform from a tubular to a septated one. While the tubular heart functions as a " mono " heart, after septation the two parts of the heart function in parallel to each other, bringing blood from the sinus venosus to the aorta. Even when disturbances in septation of the heart or disturbances in balance between development of the two sides of the heart, functioning in parallel, occur, circulation will be functionally adequate prenatally due to the presence of shunts between the right and left side of the heart. However, problems do occur at or shortly after birth when the two sides of the heart will have to function serially in order to bring about a functionally adequate relationship between the pulmonary and systemic circulation.

Congenital cardiac malformations are very complex and difficult to understand in their development. The majority of occurrences, as has already been mentioned, are of unknown etiology. The normal development of the heart and the great arteries and of the conducting system still leads to many investigations. Macroscopical findings on malformed material may give an indication of the stage of development at which a certain malformation e.g. hypoplasia of the left or right heart has originated. Experimental induction of lesions may allow a more accurate approach (Harh et al., 1973; Pexieder, 1977).

Abnormalities of the heart and great vessels and the different structures of the heart have received their specific names during the centuries. Reviews show that complex cardiac malformations which do not lend themselves to categorization within rigid classifications are being reported with increased frequency. Another problem is that the same structures of the heart have been given different names and also the same name has often been given to totally different structures of the heart. In later reviews an attempt has been made to introduce uniform nomenclature (Shinebourne et al., 1976; Anderson et al., 1977; Van Praagh, 1977; Laane, 1978).

IV. Clinical aspects of congenital malformations of the heart

Clinical signs accompanying congenital cardiac malformations are recognizable at or shortly after birth and are frequently due to shunts between systemic and pulmonary circulation which cause cyanosis or dyspnoea. As has been mentioned, several techniques have been developed to collect various physiological and morphological data on living subjects. The diagnosis of the type of cardiac malformation is often made by combining the findings of murmurs of the heart present in diastole or systole, X-ray data on size and shape of the heart, and axis deviation, conduction and size of left and right ventricle on the electrocardiogram. Further information is given by echocardiography and cardiac catheterization with measurements of blood oxygen saturation and blood pressure as well as by cine-angiocardiography. The prognosis and survival of the patients depends mostly on the size of the systemic-pulmonary shunt, on the amount of arterial desaturation, and on the development of vascular disease of the lungs, which may be a consequence of pulmonary hypertensention which often accompanies such shunts.

V. Background of present work

In spite of the great progress in techniques for in vivo examinations of cardiovascular malformations, there are few detailed quantitative anatomical studies on the heart and great vessels and no generally accepted approaches have developed. Even the sites of measurement of the ostia and arteries differ considerably in the published reports. Data on the aortic and pulmonary ostia and on the great arteries, have mostly been given as external diameter or as external circumferences (Beneke, 1878, 1879; Brenner, 1935; Meyer and Richter, 1956; De la Cruz et al., 1960; Schulz and Giordano, 1962; Wing et al., 1978).

Since cardiovascular malformations are often combined with abnormal calibres of ostia and great arteries it seemed useful to carry out detailed quantitative studies of the heart and great vessels in autopsy material of normal persons and cases of cardiovascular

malformations (publications 1, 2 and 3).

V.-1. Internal calibres of ostia and great vessels

In view of the considerations outlined above, internal calibres were measured with the aid of calibrated probes. By means of such measurements and by calculating the cross-sectional areas a greater insight could possibly be acquired about the degree of functional unbalance of the two sides of the heart and the cause of this unbalance. Furthermore, a suggestion can be given on its time of onset during foetal development and also about the pre- and postnatal development of such and other malformations. Moreover, in this way information could be obtained which is of value to the surgeon in considering the possibilities of surgical reconstruction and postoperative survival.

It seemed useful to find a method allowing comparison of the condition of the heart and great vessels in cases derived from patients of different ages and body size. Accordingly, the sizes of ostia and great vessels were expressed as a percentage of the sum total of the squared diameters of the aortic and pulmonary ostia. Using this approach it could be shown that there is a relation between the internal calibre and the amount of blood passing through a specific part of a vessel or through an ostium both in the normal condition and in one condition of extreme alteration of blood flow i.e. hypoplasia of the left or right heart (publication 1).

Furthermore, measurements of internal calibres of ostia and great arteries of normal hearts showed that there is a correlation between the size of the ostia of the heart and body length of infants and children up to 9 years of age. In view of the functional importance of the aortic isthmus an Isthmus Index was calculated by dividing the cross-sectional area of the aortic isthmus by the cross-sectional area of the descending aorta. This Isthmus Index (I.I.) indicates the presence (and degree) or absence of a narrowing (tubular hypoplasia) of the aortic isthmus (publication 2). Not all congenital malformations are accompanied by abnormal amounts of blood passing through aorta and pulmonary trunk. An example of this are the abnormal ventriculo-arterial

connexions in transposition of the great arteries (TGA). Accordingly, we also measured in cases with this condition the internal calibres, since they are a kind of control material for conditions with abnormal blood flow and abnormal vascular calibres. It was shown that the internal calibres were, in the age group studied, the same as in normal hearts (publication 3).

V.-2. Structure of media of aorta and pulmonary trunk

Since it was shown that there is an adaptation of the internal calibres of the vessels to the amount of blood flow (publication 1), it was of interest to study whether the tunica media of the vessels showed structural changes parallelling occurrence of abnormal calibres. It was already known that during growth and under certain conditions the tunica media undergoes structural changes (Heath et al., 1959; Heath and Edwards, 1960; Saldaña and Arias-Stelle, 1963; Essed et al., 1975). Published quantifications of these changes are rather scarce however. Special attention has been paid during the last decades to the structural changes of the tunica media of the more distal vessels of the pulmonary tree in congenital heart malformations with pulmonary hypertension. Investigations of the tunica media of this vasculature have been made in two different ways. First, the occurrence of six degrees of structural changes of the pulmonary arteries has been investigated in cases with atrial and ventricular septal defects, patent ductus arteriosus and in TGA. The gradations indicate thickening of the media, cellular intimal reaction up to progressive intimal fibrosis, generalized arterial dilatation with formation of complex lesions with, finally, (Grade 6) necrotizing arteritis (Heath and Edwards, 1958). The appearance and degree of these structural changes in lung biopsies of children are an indication of the functional condition and contributes to prediction of postoperative survival.

A second way to investigate the media of the pulmonary tree has been that of measuring the thickness of the media. Studies on the media thickness have been made in different ways. Brenner, in 1935, expressed the media thickness in normal material as a percentage of

the external diameter of the pulmonary arteries. Heath and Best, in 1958, also expressed the thickness of the media as a percentage of the external diameter and calculated the cross-sectional area of the muscle of the media. The calculations were then compared with systolic pulmonary pressure in normotensive cases and in cases with pulmonary arterial hypertension. In the cases of cor pulmonale the pulmonary arteries showed only a slight increase in thickness of the media, but in the cases of congenital cardiac malformations they showed a marked increase of the thickness of the media. Ferguson et al., in 1960, measured in the pulmonary arteries the diameter of the external lamina elastica, of the internal lamina elastica and the lumen diameter. Furthermore, the thickness of the media and the thickness of the intima were measured. The ratios of the diameter of the internal elastica to medial thickness and the ratios of the lumen diameter to wall thickness (media plus intima) were compared with the external diameter of the pulmonary arteries in normal cases and in cases with TGA. By these calculations they showed that in TGA the structure of the pulmonary arteries at birth is retained for about three months, while normal infants show a rapid thinning out of the arterial walls during this period. After three months the transposition group developed further thickening of the arteries, while the opposite trend continued in the normal. In 1978 Haworth and Reid measured the thickness of the media of the pulmonary arteries from external to internal lamina and then calculated twice the media thickness as a percentage of the external diameter. Hereafter this percentage was compared with the external diameters of the pulmonary arteries. These latter calculations are very unusual as are also the measurements of Yamaki and Tezuka in 1976. The latter authors measured the length of the internal and external elastic membrane of the pulmonary arteries and calculated a hypothetical thickness of the media and radius of the pulmonary arteries.

Of these widely differing ways of quantification of structural changes of the tunica media of the pulmonary tree only the use of the six grades of structural changes of the tunica media of the pulmonary arteries and the use of the medial thickness as a percentage of the

external diameter of the pulmonary artery have gained general acceptation by later authors. In our first studies we showed that there is a linear correlation between the internal diameters of the pulmonary and aortic ostia on the one hand and body length as a parameter of bodily development on the other. We therefore compared the thickness of the media of the pulmonary trunk and of the ascending aorta with the internal diameter of these vessels. We also calculated the packing density of the elastic fibres of the media and compared this with the internal diameter of the latter vessels. Attention was paid to the configuration of the elastic fibres in the tunica media of the pulmonary trunk in hypoplasia of the left and right heart and in transposition of the great arteries in relation to the packing density of its elastic fibres. Normal hearts provided a reference material. Adaptations of the tunica media to abnormal conditions were found.

Attention was also paid to the presence or absence of pulmonary vascular disease in cases of transposition of the great arteries with pulmonary hypertension (publication 3).

REVIEW OF FINDINGS

The work reported in this thesis is based on the assumption that quantitative data on internal calibres of ostia and great arteries and quantitative data on the tunica media of the great arteries are of interest, both from the point of view of anatomy and physiology of hearts with congenital malformations as well as clinically. For the cardiologist and cardiac surgeon such data might be helpful in evaluation of cardiac function, of prognosis and of the possibilities of surgical intervention in patients with congenital malformations of the heart.

In this chapter a review of our findings is presented. Observations are presented which the reader may also find in the publications. Some observations not reported in the publications are also included.

I. INTERNAL CALIBRES OF OSTIA AND GREAT ARTERIES

Based upon the assumption that cross-sectional areas of vessels are more directly related to blood flow than other measurements on vessels, measurements of internal diameters of the ostia of the heart and the great vessels were made in this study with the aid of calibrated probes differing 1 mm in diameter (publication 1, Fig. 2 a and b). Since the sizes of the internal diameters differ markedly with the age of infants and children squared values of the internal diameters were expressed as a percentage of the sum total of the squared internal diameters of the aortic and pulmonary ostium in normal hearts and in transposition of the great arteries (TGA) since these ostia are the narrowest sites of the main outflow of blood from the heart. The squared internal diameter of the ostium of the one single functioning vessel was used in cases of left and right hypoplasia. These relative surface areas were represented graphically and these graphs are referred to as aorta and pulmonary curves.

I.-1. Normal hearts and transposition of the great arteries (TGA)

The aorta and pulmonary curves of all 53 normal hearts (Fig. A and B) and of 11 cases of TGA with a normal ventricular septum and open ductus arteriosus (Fig. 1, publication 3) did not differ significantly from each other. The curves for the normal hearts and for the hearts with TGA showed that, in the cases with a closed ductus, the relative cross-sectional areas of the atrio-ventricular orifices tend to be larger than the pulmonary and aortic ostia, i.e. right atrio-ventricular orifices 123% versus 56% for pulmonary ostia, and left atrio-ventricular orifices 78% versus 44% for aortic ostia (aortic plus pulmonary ostium = 100%). The ascending aorta and the pulmonary trunk are possibly slightly larger than the aortic and pulmonary ostia respectively (48% for ascending aorta versus 44% for aortic ostium and 61% for pulmonary trunk versus 56% for pulmonary ostium). In the age range at our disposal : 27 weeks of gestational age up to 9 weeks after birth, the mean relative cross-sectional area of the aortic arch decreases in size after branching, whereas the descending aorta shows a mean size of 25% of the total size of the combined outflow ostia of the ventricles in the cases with a closed ductus. In hearts with an open ductus the left and right pulmonary arteries tend to be smaller than in the hearts with closed ductus, which is probably due to the alteration after birth of blood flow through these pulmonary arteries (Fig. B).

The data summarized in the aorta curve of the normal hearts (Fig. A) show a difference between the cases with and without an open ductus arteriosus in relative cross-sectional areas of the part of the aortic arch between the left subclavian artery and the ductus, called the aortic isthmus (tubular hypoplasia). The size of the aortic isthmus is in cases with an open ductus markedly smaller than in the older cases of normal hearts in which the ductus arteriosus is closed (21% for cases with an open ductus versus 26% for cases with a closed ductus). Special attention was paid to the size of the aortic isthmus since its variable calibre might act as a circulatory bottleneck and might cause clinically demonstrable differences between

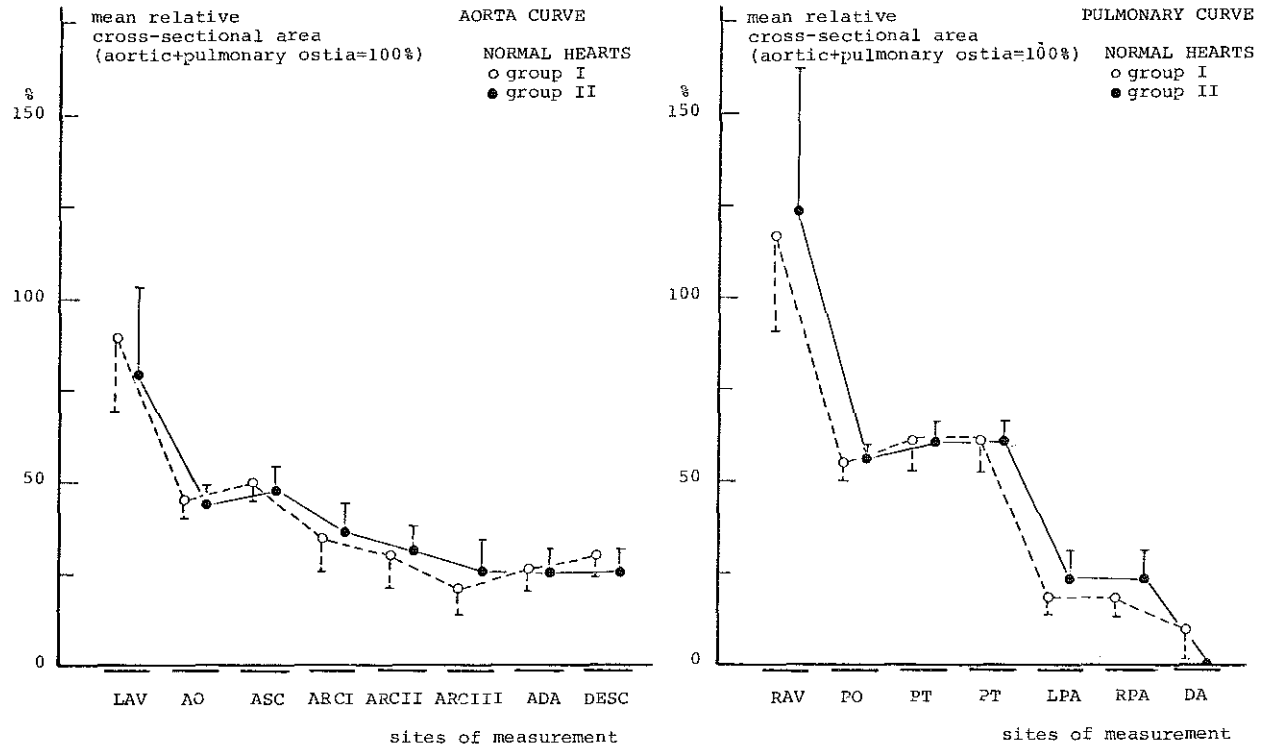

Fig. A and B. Relative cross-sectional areas (mean + or - standard deviation) of cardiac orifices and great vessels of 34 normal hearts with an open ductus (group I) (interrupted line) and 19 normal hearts with a closed ductus (group II) (uninterrupted line). Abbreviations for Fig.A : LAV left atrio-ventricular ostium; AO aortic ostium; ASC ascending aorta; ARC I aortic arch between brachiocephalic and left carotid artery; ARC II aortic arch between left carotid and left subclavian; ARC III aortic arch between left subclavian and ductus arteriosus; ADA aortic arch at connection with ductus arteriosus; DESC descending aorta . Abbreviations for Fig.B : RAV right atrio-ventricular ostium; PO pulmonary ostium; PT pulmonary trunk; LPA left pulmonary artery; RPA right pulmonary artery; DA ductus arteriosus.

systolic pressure of the upper and lower limb (de Swiet et al., 1974) which can mimic a coarctation of the aortic arch at the connexion with the ductus arteriosus or ligamentum arteriosum. The presence and degree of narrowing of the aortic isthmus in the material of the normal hearts was expressed as follows, as already mentioned in Chapter 5-1 of the Introduction. The cross-sectional area of the aortic isthmus at its narrowest site was divided by the cross-sectional area of the descending aorta direct by distal to the ductus arteriosus (= Isthmus Index, I.I.). The cross-sectional area of the aortic isthmus was compared with that of the descending aorta and not, as many investigators did, with that of the ascending aorta (Sinha et al., 1969; Rosenberg et al., 1971; Shinebourne and Elseed, 1974) for reasons as explained in paper 2. A value of the Isthmus Index of 0.81 was arbitrarily chosen as indicative of narrowing. Then, from our observations on normal specimens, the following conclusions about the aortic isthmus could be drawn. 1- under normal conditions narrowing of the aortic isthmus (Isthmus Index $\leq$ 0.81) may or may not exist in babies younger than 10 weeks, both in those born at term and prematurely, whereas in babies older than 10 weeks, born at term, or prematurely, narrowing of the aortic isthmus cannot be expected. 2- in babies younger than 5 weeks pronounced narrowing (I.I. $<$ 0.60) was not exceptional. 3- no dependence of narrowing of the aortic isthmus on developmental stage attained at birth seems to exist. A definition of borderline values between normal and pathological conditions is not yet attempted but can in the future probably be demonstrated by the size of the left and right ventricle of the heart measured by echocardiography (Gutgesell et al., 1977; Graham et al., 1977; Tajik et al., 1978; Wing et al., 1978). The post mortem data for the pulmonary and aortic ostium correspond with those obtained in vivo using echocardiography, when measurements have been made through the centre of the ostium (Solinger et al., 1973; Allen et al., 1978). The ascending aorta dimensions in vivo have often been measured from the outside anterior wall to the outside posterior aortic wall (Epstein et al., 1975; Allen et al., 1978; Wing et al., 1978). In consequence these values are about 3 to 4 mm above our post mortem data and are of limited value clinically.

I-2 Left and right hypoplasia

The aorta and pulmonary curves of the hypoplastic left and right hearts are remarkable different from those of the normal hearts (Publication 1, Figs. 3, 4). The pulmonary curve in left hypoplasia (9 cases) is in accordance with the increased flow through the right part of this type of heart. The cross-sectional area of the pulmonary ostium is 188% of this value in the normal material. The increased size of the pulmonary trunk is not accompanied by an increased size of the pulmonary arteries; they are of the same size as in normal material (left pulmonary arteries 20% versus 18% in normal hearts, right pulmonary arteries 24% versus 18% in normal hearts at birth; aortic plus pulmonary ostium 100%). This will be discussed later on. The aorta curve in left hypoplasia shows a slope quite opposite to that of the normal hearts. The hypoplastic ascending aorta has a blood flow opposite the normal one and supplies blood via the ductus to the arms, neck and head and finally to the coronary arteries. Therefore, it is still a functional vessel and in parallel with the blood flow a decrease of the internal cross-sectional area of the " ascending " aorta is seen.

However, the non-functional vessel in right hypoplasia (7 cases), the pulmonary trunk, shows another pattern which can be related to a difference in haemodynamics. The size of this vessel varies markedly, from far below to above that of the normal hearts at birth (internal diameter 3.5 to 9 mm versus 7 to 8 mm in normal hearts at birth).

The ostium of the one functional vessel in right hypoplasia i.e. the aortic ostium is of a size 222% of that in normal hearts. This could be expected, since it is the only outflow of the heart. The aorta curve shows a decrease in size after branching and no aortic isthmus was found. The aorta is the only functional vessel which supplies not only the greater circulation but also, via the ductus arteriosus, the lungs. As could be expected the descending aorta is smaller in size than the aortic isthmus. The ductus arteriosus which now supplies blood to the lungs is of a normal size (12% of the sum total of pulmonary and aortic ostium versus 11% in normal hearts). The relative calibres of the pulmonary arteries in right hypoplasia are of normal size (20%

versus 18% in normal hearts at birth) as is, as already mentioned, also the case in left hypoplasia. This may be explained by the development without important functional demands of the entire pulmonary vasculature, which is in turn due to the fact that lungfunction is absent prenatally (Dawes et al., 1953; Wagenvoort et al., 1961 c). The ductus arteriosus is of normal size in right hypoplasia. In cases not with absent, but with diminished blood flow through the pulmonary ostium (i.e. tetralogy of Fallot with pulmonary stenosis) a reduced calibre or even absence of the ductus arteriosus can be found (Powell and Hiller, 1957 ; Molz, 1968; Rao et al., 1971; Schenk et al., 1976). Here blood flow through the pulmonary trunk may be just sufficient for the prenatal blood supply of the lungs. In conclusion, it could be shown that a relationship exists between blood flow and the amount of blood passing through the ostia and the various segments of the great vessels.

I-3 Internal calibres of aortic and pulmonary ostia : mutual relation and relation with body length

Internal calibres of the aortic and pulmonary ostia were measured in all normal hearts of different ages and compared with bodily development. As shown in Figs. 2, 3 and 4 (publication 2) a linear correlation was found between body length and the calibres of the aortic and pulmonary ostia and between the calibres of the pulmonary and aortic ostium. These findings are of importance for the cardiologist and surgeon in cases of surgical corrections e.g. in cases of Tetralogy of Fallot, in which the stenosis and the pulmonary ostium is corrected and the size of the ostium to be reconstructed should be estimated.

II TUNICA MEDIA OF GREAT ARTERIES : RELATION TO INTERNAL DIAMETER

Our investigations on normal cardiovascular organs and on abnormal material of hypoplastic left and right heart syndromes and of transposition of the great arteries showed that internal calibres of

ostia of the heart and of the great arteries are related to blood flow. One of the questions that remained to be answered was whether alterations in calibre of the vessel are accompanied by histological changes in the vascular wall. We quantified the structural changes of the tunica media of the ascending aorta and of the pulmonary trunk by measuring the thickness of the media and by calculating the packing density of the elastic fibres of the tunica media (see Material and Methods, publication 3). These data were than related to the internal diameters of the ostia of the vessels. It was shown that in normal hearts, in the period from birth up to 15 years, a fourfold increase of the internal diameter of the ascending aorta was accompanied by a doubling of the thickness of the media and of the packing density of its elastic fibres. In the pulmonary trunk there were no significant changes in the thickness of the media and of the packing density of its elastic fibres accompanying the increase of the internal diameter. The presence or absence of a ductus arteriosus did not seem to influence these parameters.

In left and right hypoplasia the situation is different. The increased functional load on the pulmonary trunk in left hypoplasia is already present during foetal life and is the most plausible explanation of the doubling of the cross-sectional area of the pulmonary ostium and of the pulmonary trunk observed at birth (publication 1). The same situation seems to be present for the aortic ostium and ascending aorta in cases of right hypoplasia. The increase in size of both vessels is accompanied by an increase of the packing density of the elastic fibres of the tunica media only in the case of the pulmonary trunk in left hypoplasia and if compared with the packing density in the pulmonary trunk in normal hearts of the same age. The pulmonary trunk did not show a change in thickness of the media and the markedly enlarged aorta in right hypoplasia remained unchanged in respect to both media parameters. It should be realized, however, that considerable growth of media tissue takes place when the two parameters used remain constant in enlarged vessels. However, comparing the pulmonary trunk in left hypoplasia with the ascending aorta in right hypoplasia there is not only a similarity of the cross-sectional areas of both vessels but there is also a similarity of the thickness and

packing density of its elastic fibres. This means that acting as a sole arterial trunk of the functional single ventricle both vessels, developed from the truncus arteriosus, have the same construction.

The vessels with a reduced or absent function in hypoplastic hearts show dissimilar changes. In left hypoplasia the thickness of the media of the aorta is reduced whereas the packing density of the elastic fibres remains unchanged. In right hypoplasia both parameters remain unchanged in the pulmonary trunk. The difference in adaptation to abnormal or absent blood flow between aorta and pulmonary trunk in hypoplasia can be explained by the fact that the ascending aorta in left hypoplasia is still a functional vessel, whereas the pulmonary trunk in right hypoplasia contains only stagnant blood with undulating pressure.

Earlier we discussed that the calibres of the ascending aorta and of the pulmonary trunk in transposition of the great arteries were, in the age group at our disposal, of the same size as in normal hearts. In accordance with this we found that in cases of TGA dying within 6 months of age after birth the thickness and packing density of the elastic fibres of the tunica media of both ascending aorta and pulmonary trunk have similar values as in normal hearts, independent of the presence or absence of a ventricular septal defect or an open or closed ductus arteriosus. However, the great vessels of the two eldest patients, aged 1 year and 3 months and 2 years and 10 months, differed from the condition in normal hearts which can be explained as follows :

Before birth, in TGA the circulatory condition does not seem to deviate from the normal one (Taussig, 1947). In normal infants, during the first days after birth, when the lungs expand, high pressure which is normally present prenatally in the right ventricle and pulmonary trunk still exists (Dawes et al., 1953; Adams and Lind, 1957; Rudolph et al., 1961; Riggs et al., 1977). After the first 48 hours this pressure falls and is on the third day less than 50% of the systemic pressure (Emmanouilides et al., 1964). Although persistent pulmonary hypertension of unknown cause can exist in otherwise normal infants the pulmonary pressure normally falls to 16 mmHg within 14 days after birth (Berthrong and Cochran, 1955; Haworth and Reid,

1976; Levin et al., 1976, 1978; Peckham and Fox, 1978). In TGA the pulmonary pressure does not fall to normal values and an increase of pulmonary flow is also present (Ferencz, 1966; Tynan, 1972). Graham et al. (1971) showed that in TGA the function of the left ventricle, which now supplies the lungs becomes abnormal after the age of six months : left ventricle end diastolic volume and systolic output exceed the normal values. In cases of TGA with a ventricular septal defect these values are even higher. These physiological data show that adaptation to the abnormal circulatory conditions requires some time to develop. This is in accordance with our morphological data on the two cases which survived longest. In the case of TGA with an age of 1 year and 3 months there was a increase of the thickness of the media of the pulmonary trunk (1050 versus 500 µm in normal hearts with the same internal diameter of the pulmonary trunk) with an increase of the packing density of the elastic fibres : 30% versus 22%, if compared with normal hearts with a pulmonary trunk of the same internal diameter. The pulmonary pressure 1 month before death in this case was 55/18 mmHg. At the age of 3 months a Blalock-Hanlon atrial septectomy was carried out. The child died one year afterwards of congestive heart failure. The other infant with TGA, which survived longer and died at the age of 2 years and 10 months, showed a packing density of the elastic fibres of the tunica media of the pulmonary trunk of about normal value (16% versus 21% in normal pulmonary trunks of the same size) with an abnormal thickness of the media of the pulmonary trunk. The thickness of the media was 824 µm versus 500 µm in normal pulmonary trunks of the same internal diameter. The pulmonary pressure was only measured at the age of 1 month and was 40/5 mmHg and a Blalock-Hanlon atrial septectomy was carried out on the same day. Clinically there were no signs of congestive heart failure, until shortly before death, although mental retardation was present. The patient died suddenly of undetermined cause. Pulmonary pressure probably was almost normal since the configuration of the elastic fibres of the pulmonary trunk showed an adult (pulmonary) type. This line of reasoning will be discussed later on.

III. CONFIGURATION AND PACKING DENSITY OF THE ELASTIC FIBRES OF THE MEDIA OF THE PULMONARY TRUNK

Since in the literature the configuration of the elastic fibre component of the tunica media of the pulmonary trunk is characterized as being of aortic, transitional A, transitional B or pulmonary type according to the classification used by Heath et al.(1959), Saldaña and Arias (1963) and Yamakawa (1966) we tried to find a correlation between these types of configuration and the calculated values of the packing density of the elastic fibres of the media of the pulmonary trunk. The data of Saldaña and Arias (1963) showing that there is a great variability of the elastic fibre configuration of the tunica media of the pulmonary trunk during lifetime was confirmed for the period up to 15 years by our data. No correlation was found between the configuration and the packing density of the elastic fibres of the media of the pulmonary trunk in normal infants and children.

IV. PULMONARY VASCULAR DISEASE IN TRANSPOSITION OF THE GREAT ARTERIES

Special attention was also paid to the presence or absence of pulmonary vascular disease in the cases of TGA with pulmonary hypertension. Although a recent publication describes a new type of grading of pulmonary vascular disease (Rabinovitch et al., 1978) we used the well known and simple six grades following Heath et al. (1958), Heath and Edwards (1959) and Wagenvoort et al. (1964, 1968). Pulmonary vascular disease (of Grade 1 and 2) was found in 5 of the total number of 17 cases of TGA. Systolic blood pressure in the 4 of these 5 cases for which measurements were available ranged from 52 to 72 mmHg. In the other 12 cases systolic blood pressures were measured in 7 cases and ranged from 17 to 75 mmHg. Of the 5 cases with pulmonary vascular disease three died at ages of more than 3 months. The other two died at the ages of 1 and 13 days. We can conclude from these early deaths that pulmonary hypertension, which probably caused the pulmonary vascular disease, was already present during foetal life,

since adaptation to abnormal conditions probably takes some time to develop. Also in the three longer surviving cases only mild pulmonary vascular disease was found as indicated by the occurrence of only Grade 1 and 2 vascular disease as already mentioned. This is fully in accordance with the findings of previous workers (Newfeld et al., 1974; Edwards and Edwards, 1978).

Our findings in 5 cases with TGA, which were accompanied by pulmonary vascular disease, led to the following conclusion. After the age of six months structural changes of the tunica media of the pulmonary trunk and of the wall of the pulmonary arteries of the lungs do develop as an answer to abnormal ventriculo-arterial connexion and to pulmonary hypertension. This gives the surgeon six months to carry out open heart surgery, if necessary, since after that age the quality of the pulmonary arteries deteriorates.

SUMMARY

In this thesis a study is reported on the internal calibres of ostia and great arteries of normal and some types of congenitally malformed hearts. The normal hearts were derived from patients with an age range from 27 weeks of gestational age up to 15 years after birth. The congenitally malformed hearts were of two types: hypoplasia of the right or left ventricle and transposition of the great arteries (TGA). These hearts were all derived from patients who died within 3 years of birth. Based upon the assumption that cross-sectional areas of vessels are more directly related to blood flow than other measurements on vessels the internal diameters of the ostia and of various segments of the great vessels were measured with the aid of calibrated probes, differing 1 mm in diameter. Since in infants and children the internal diameters differ markedly with age squared values of the internal diameters, which indicate cross-sectional areas, were expressed as a percentage of the sum total of the squared internal diameters of the aortic and pulmonary ostium in cases of normal hearts and TGA since these ostia are the narrowest sites of the main outflow of blood from the heart. In the cases of left and right hypoplasia the squared internal diameter of the ostium of the one single functioning vessel was used. These relative cross-sectional areas of the ostia and of the various segments of aorta and pulmonary trunk were represented graphically in so-called aorta and pulmonary curves.

The internal calibres of the aortic and pulmonary ostia were measured in all normal hearts from patients of different ages and compared with bodily development. A linear correlation was found between body length and the internal diameters of the aortic and pulmonary ostia and in consequence between the sizes of aortic and pulmonary ostia.

In the normal hearts the aorta curve shows a difference in relative cross-sectional areas of the aortic isthmus between the cases with and without an open ductus arteriosus. From the sizes of the cross-sectional areas of the aortic isthmus and of the descending

aorta an Isthmus Index was calculated indicating the presence (and degree) or absence of narrowing of the aortic isthmus. Results show that narrowing of the aortic isthmus is inconstantly present in infants younger than 10 weeks, whereas it is absent in infants and children older than 10 weeks. No dependence of narrowing of the aortic isthmus on developmental age obtained at birth is found.

The curves of the hearts with TGA show that the relative cross-sectional areas of the ostia and vessels did not significantly differ from those in normal hearts. The presence of a ventricular septal defect in cases with TGA did not seem to influence these data.

The aorta and pulmonary curves of the hypoplastic left and right hearts differed markedly from those of the normal hearts. The pulmonary curve in left hypoplasia and the aorta curve in right hypoplasia showed cross-sectional areas in accordance with the increased flow through the right or left part of these heart types respectively. A doubling of the normal values for the same age of the cross-sectional areas was found at the ostia of the one single functioning vessel. Furthermore, the aorta curve in left hypoplasia and the pulmonary curve in right hypoplasia showed relative cross-sectional areas in accordance with diminished blood flow.

Attention was also paid to the question of whether the tunica media of the great arteries shows structural changes parallelling occurrence of abnormal calibres due to abnormal blood flow and parallelling occurrence of abnormal ventriculo-arterial connexion. The structural changes of the tunica media of the ascending aorta and pulmonary trunk were quantified by measuring the thickness of the media and calculating the packing density of its elastic fibres. In the cases of TGA up to six months of age the thickness of the tunica media and the packing density of its elastic fibres were the same as in normal hearts, in both the ascending aorta and pulmonary trunk. This corresponds with the clinical findings on the function of the left ventricle in TGA up to six months of age. Changes from the normal condition, indicating adaptations to the abnormal blood flow, were found in the cases of TGA older than one year. In five cases of TGA, three of them older than 3 months, Grade 1 and 2 of pulmonary

vascular disease were found.

In left and right hypoplasia the markedly enlarged functional vessels which, as already mentioned, had a similar doubling of the cross-sectional areas, also showed a similar increase of the thickness and packing density of the elastic fibres of the tunica media. The vessels with a reduced or absent function showed a different structure in left and right hypoplasia. This is discussed and a tentative interpretation is given.

SAMENVATTING

In dit proefschrift wordt een studie beschreven over inwendige diameters van de ostia en grote vaten van normale harten en van enkele typen congenitale hartafwijkingen, met name de onderontwikkelde linker en rechter harten en de transpositie der grote vaten. De normale harten waren afkomstig van patiëntjes met een leeftijd van 27 weken intrauterien leven tot 15 jaar na de geboorte. De harten met de congenitale afwijkingen waren afkomstig van patiëntjes die niet ouder werden dan 3 jaar. Gezien het feit dat oppervlakten van lumendoorsneden van de vaten een meer direkt verband bezitten met de bloeddoorstroming dan b.v. de uitwendige afmetingen van een vat, werden de inwendige diameters van de ostia en van diverse segmenten van de grote vaten gemeten met behulp van gecalibreerde sondes, die 1 mm in diameter verschilden. Daar bij zuigelingen en kinderen de inwendige diameter sterk afhankelijk is van de grootte van de kinderen, werden de kwadraten van de inwendige diameters als maat voor de oppervlakten van de lumendoorsneden gebruikt en uitgedrukt als percentage van de som van de overeenkomstige kwadraten van aorta plus pulmonalis ostium. Dit werd gedaan omdat de beide ostia de totale uitstroomopening van het hart vertegenwoordigen. De relative lumen-groottes van de vaten werden op deze wijze berekend bij de normale harten en in de gevallen van transposities van de grote vaten. In de gevallen van de onderontwikkelde harten werden de relative lumen-groottes berekend als percentage van het kwadraat van de inwendige diameter van het enige funktionele vat. De verkregen relatieve maten van de ostia en de diverse segmenten van de aorta en de truncus pulmonalis werden grafisch weergegeven in de zg. aorta en pulmonalis curve.

De interne diameters van aorta en pulmonalis ostium werden gemeten bij alle normale harten van patiënten van verschillende leeftijden en vergeleken met de lichaamsontwikkeling. Een lineaire correlatie werd gevonden tussen de lichaamslengte en de inwendige diameter van het aorta en pulmonalis ostium en ook tussen het aorta en pulmonalis ostium onderling.

Bij de normale harten vertoont de aorta curve een verschil in

relatieve lumen-groottes van de aorta isthmus tussen de gevallen met en zonder open ductus arteriosus. Uit de afmetingen van de lumina van de aorta isthmus en de aorta descendens werd een Isthmus Index berekend, die de aanwezigheid (en ernst) of afwezigheid van een isthmus vernauwing aangeeft. De gegevens toonden aan dat de vernauwing van de isthmus inconstant aanwezig is bij kinderen jonger dan 10 weken, terwijl er geen vernauwing aanwezig is bij kinderen die ouder zijn dan 10 weken. Er werd geen relatie gevonden tussen de leeftijd bij de geboorte, gerekend van het tijdstip van de conceptie af, en de mate van vernauwing van de aorta isthmus.

De curves van de harten met transposities van de grote vaten toonden geen verschil in relatieve lumen-grootte van de ostia en de vaten ten opzichte van de normale harten. De aanwezigheid van een ventrikel septum defect in de gevallen met transposities van de grote vaten leek niet van invloed te zijn op deze bevindingen.

De aorta en pulmonalis curve van de onderontwikkelde linker en rechter harten verschilden zeer van die van de normale harten. De pulmonalis curve van de onderontwikkelde linker harten en de aorta curve van de onderontwikkelde rechter harten vertoonden lumen-groottes in overeenstemming met de verhoogde bloeddoorstroming door de rechter, respectievelijk linker harthelft. Er bleek een verdubbeling van de lumen-groottes van het enig funktionele vat te zijn opgetreden in vergelijk met normale harten van dezelfde leeftijd. De aorta curve van de onderontwikkelde linker harten en de pulmonalis curve van de onderontwikkelde rechter harten vertoonden relatieve lumen-groottes in overeenstemming met de verminderde bloeddoorstroming.

Er werd ook aandacht besteed aan de vraag of de tunica media van de grote vaten strukturele veranderingen zou vertonen in overeenstemming met de abnormale calibers van de vaten ten gevolge van de abnormale bloeddoorstroming en in overeenstemming met de abnormale ventriculo-arteriële verbinding. De strukturele veranderingen van de tunica media van de aorta ascendens en de truncus pulmonalis werden gequantificeerd door het meten van de dikte van de media en de berekening van de hoeveelheid elastische vezels in de media. In de geval-

len van TGA, die jonger waren dan 6 maanden, waren deze waarden gelijk aan die van de aorta ascendens en truncus pulmonalis van de normale harten van dezelfde leeftijd. Dit komt overeen met de klinische gegevens betreffende de funktie van de linker ventrikel in gevallen van TGA, die jonger waren dan 6 maanden. Veranderingen in de normale samenstelling van de media ten gevolge van de abnormale bloeddoorstroming werd wel gevonden in die gevallen van TGA die ouder werden dan 1 jaar. In vijf gevallen van TGA, waarvan er 3 ouder waren dan 3 maanden, werd graad 1 en 2 van pulmonale vaatafwijkingen gevonden.

In de onderontwikkelde linker en rechter harten vertoonden, zoals reeds eerder werd vermeld, de nog funktionerende vaten een gelijksoortige verdubbeling van de lumen-groottes, en eveneens een gelijksoortige verdikking van de media en een vermeerdering van de hoeveelheid elastische vezels in de media. De vaten met een gereduceerde of afwezige funktie vertoonden een andere opbouw van de tunica media. Dit wordt in discussie gebracht en een mogelijke verklaring ervoor wordt gegeven.

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CURRICULUM VITAE

Te Rotterdam ben ik geboren onder de adem van de Maas ... op 7 december 1940. Na het behalen van het einddiploma 5j-HBS-B in 1959 aan de Van Oldenbarnevelt HBS te Rotterdam, begon ik mijn opleiding tot klinisch-chemisch analiste in het Klinisch-Chemisch laboratorium van het Zuider Ziekenhuis te Rotterdam, hoofd Dr. S.K. Wadman. Mijn belangstelling voor congenitale hartafwijkingen ontstond tijdens deze opleidingsperiode door de intensieve samenwerking tussen het team van de 'open hart'-chirurgie en het laboratorium personeel. In januari 1962 behaalde ik het analiste-diploma. In 1964 trad ik in dienst bij Prof. Dr. B. Leijnse, hoofd van het CKCL van het Dijkzigt Ziekenhuis, na eerst een half jaar werkzaam te zijn geweest in het Tropenlaboratorium van het Havenziekenhuis. Na enige jaren werd ik als hoofdanaliste van het Endrocrinologisch laboratorium aangesteld. Na het veranderen van mijn naam tot de huidige lengte begon ik in 1970 met de studie geneeskunde aan de toenmalige Medische Faculteit te Rotterdam. Het doctoraal examen werd behaald in 1975, het artsexamen werd afgelegd in 1976. In december van dat zelfde jaar begon ik de opleiding tot interniste aan de afdeling Inwendige Geneeskunde I van het Academisch Ziekenhuis Rotterdam, hoofd Prof. Dr J. Gerbrandy.

Van februari 1973 af ben ik werkzaam binnen de vakgroep Anatomie van de Erasmus Universiteit Rotterdam te Rotterdam. In de periode februari tot juli 1973 was ik keuzepracticante, van juli 1973 tot juli 1975 student-assistente en van juli 1975 af wetenschappelijk ambtenaar. Het was in die unieke keuzepracticum periode dat mijn interesse in de congenitale hartafwijkingen zich verdiepte. Binnen de vakgroep Anatomie werd het wetenschappelijk onderzoek, dat de basis vormt van dit proefschrift, verricht. Publicaties volgden in 1974, 1977 en 1979,

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Calibres of Aorta and Pulmonary Artery in Hypoplastic Left and Right Heart Syndromes: Effects of Abnormal Bloodflow?

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Summary. Internal diameters of the cardiac orifices and of the great vessels were determined in 9 hearts with an atresia of the left atrio-ventricular orifice and/or the aortic ostium and in 7 hearts with an atresia of the right atrio-ventricular orifice and/or pulmonary ostium. Hearts which showed a ventricular septal defect in combination with a patent aortic ostium and left hypoplasia or a pulmonary ostium and right hypoplasia were not included in the material. Twenty-four normal hearts served as a control group. The aorta was measured at 6 sites; the pulmonary trunk, the two pulmonary arteries and the ductus arteriosus were all measured at one site. The age range of the material was from birth to 16 months after birth.

Since cross-sectional areas of vessels appear more directly related to bloodflow than diameters and since absolute values of vessel calibres vary markedly with age squared values of internal diameters were expressed in normals as percentage of the sum total of the squared diameters of the pulmonary and the aortic ostium; in the hypoplasia material squared values of internal diameters were expressed as percentage of the squared value of the sole functioning ostium whether aortic or pulmonary. The aortic and pulmonary ostium showed cross-sectional areas of 222% resp. 188% of the normal value, when they functioned as sole outflow orifice. The pulmonary arteries did not evidence any deviation from the normal values neither in left, nor in right hypoplasia. The ductus arteriosus showed a supranormal value in left hypoplasia, but a normal value in right hypoplasia. Subnormal values were obtained for the pulmonary trunk in right hypoplasia, although the reduction in calibre was much more pronounced in the case of the comparable non-functioning first part of the aorta in left hypoplasia. In the latter condition the calibres of the aorta showed a grandual reduction from the descending aorta towards the ascending aorta which coincided with the direction of bloodflow in this cardiac malformation.

These findings demonstrate appropriate functional adaptations of the calibres of the great vessels to conditions of altered bloodflow. The findings also indicate that a time factor should be taken into account in further analysis of such changes in vessel calibre.

Introduction

In the syndromes of hypoplasia of the left or right heart one ventricle has little or no circulatory function and therefore the corresponding vessel whether aorta or pulmonary trunk receives blood mainly or exclusively through the ductus arteriosus. This abnormal circulatory pattern raises the question as to which

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adaptations occur in this type of cardiac malformation. It appears likely that vascular diameters and the corresponding cross-sectional areas would be of crucial interest. Nevertheless a review of the literature revealed mainly genéral statements and only few quantitative data on vascular calibres in these syndromes (Horley, 1955; Gittenberger-de Groot, 1972; Rudolph *et al.*, 1972). Accordingly, internal diameters of the cardiac orifices, of the ascending aorta, the áortic arch and the descending aorta, of the pulmonary trunk and its branches and of the ductus arteriosus have been measured in hearts with atresia of one atrio-ventricular orifice and/or of the aortic respectively pulmonary ostium. It was decided to focus the study on extreme cases of right or left hypoplasia and leave out cases of valvular stenosis.

It was thought that data on vascular calibres might be of value not only from a fundamental point of view, but also from a practical viewpoint in diagnostic problems in congenital cardiac malformations.

Materials and Methods

The control material consisted of 24 normal hearts from patients who died in the perinatal period or up to 16 months after birth. Hearts were considered normal on the basis of absence of cardio-vascular abnormalities during clinical examination or at autopsy. Twenty hearts from children dying within two weeks after birth formed the majority of this material. The abnormal material consisted in part of 9 hearts with an atresia of the left-ventricular orifice and/or the aortic ostium. Age range was 3 days to $6^1/_2$ weeks. The remainder of the non-normal material comprised 7 hearts with an atresia of the right atrio-ventricular orifice and/or pulmonary ostium. Age range was from 1 day to 16 months after birth. Hearts showing mitral atresia in combination with a ventricular septal defect and a patent aortic ostium were not included in the material. Hearts which showed the comparable abnormal condition on the right side were also excluded. Such hearts and those with malformations of types other than those mentioned above were occasionally used as reference material.

The measurements described below were carried out after fixation in a 4% formaldehyde solution over 24 hrs or longer and storage of varying duration in a mixture of 80% ethanol and glycerol (2:1). Seven normal hearts were measured both unfixed and after fixation and storage over at least 5 months. No trend towards recognizable increase or decrease of the measured values could be noticed.

Measurements were carried out as follows. The hearts were opened as shown in Fig. 1. In exceptional cases it was necessary to open also one or both great vessels. Probes differing 1 mm in diameter were introduced in the direction of bloodflow into the atrio-ventricular orifices, the pulmonary and aortic ostium, the aorta, the pulmonary trunk, the pulmonary arteries at their site of branching off and finally the ductus arteriosus. The measurements of the aorta were carried out at various sites. Fig. 2 shows the sites of these measurements. In the case of the ductus arteriosus it was tried to establish as accurately as possible the diameter present at death and to avoid to stretch the vessel. Even so, the measured diameters of the ductus arteriosus are probably less reliable as parameters of the *in vivo* condition than the other measurements. The error of the measurements was ascertained by repeating the measurements in 4 hearts. The standard deviations based on series of 4 measurements for each individual heart and its great vessels ranged from 20% for a diameter of 2 mm to 5% for a diameter of 15 mm.

In order to use the diameters as indicators of bloodflow the squared values of the diameters were used to compare the measurements. These squared values were expressed as a percentage of the sum total of the squared values of the diameters of the aortic and pulmonary ostia in the normal material and as percentage of the squared value of the diameter of the one functioning great vessel in the hypoplastic material. These relative surface areas were represented graphically as shown in Figs. 3 and 4. In the graphic representation of the values for the

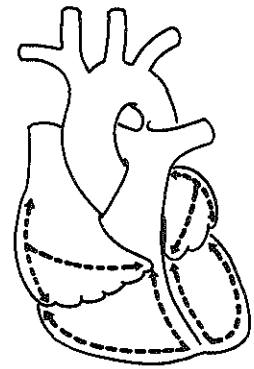

Fig. 1. Routine incisions allowing measurements of cardiac orifices and internal diameters of great vessels including their branches

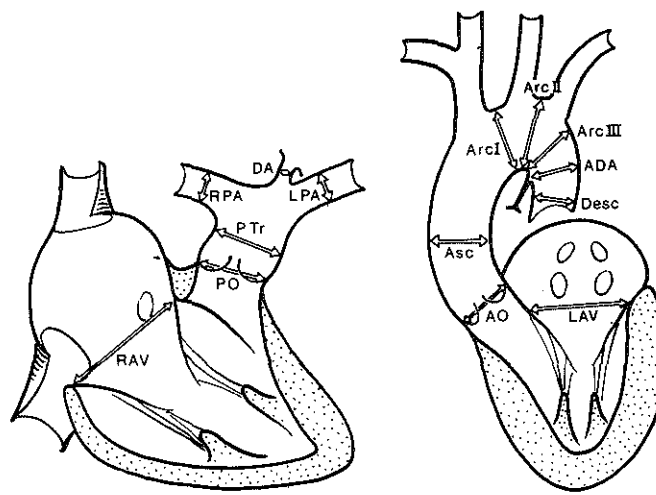

Fig. 2a and b. Sites of measurements. Abbreviations for Fig. 2a: *RAV* right atrio-ventricular ostium; *PO* pulmonary ostium; *PTr* pulmonary trunk; *LPA* left pulmonary artery; *RPA* right pulmonary artery; *DA* ductus arteriosus. Abbreviations for Fig. 2b: *LAV* left atrio-ventricular ostium; *AO* aortic ostium; *Asc* aorta ascendens; *Arc I* aortic arch between brachiocephalic and left carotid artery; *Arc II* aortic arch between left carotid and left subclavian; *Arc III* aortic arch between left subclavian and ductus arteriosus; *ADA* aortic arch at connection with ductus arteriosus; *Desc* descending aorta at indicated site

right side of the heart and its corresponding vasculature the pulmonary trunk was included twice. This made the graph more easily comparable with that for the left side of the heart and its corresponding vessels. These graphic representations of the measurements are referred to as aorta curve and pulmonary curve.

In order to determine the effect of hypoplasia on the diameter of the sole functioning outflow vessel, aorta or pulmonary trunk, the cross-sectional areas of the aortic and pulmonary ostia, expressed per 100 cm body length were calculated in the normal and abnormal material. The absolute values showed so much age dependent variation that they were of little value in comparing the normal and hypoplastic hearts.

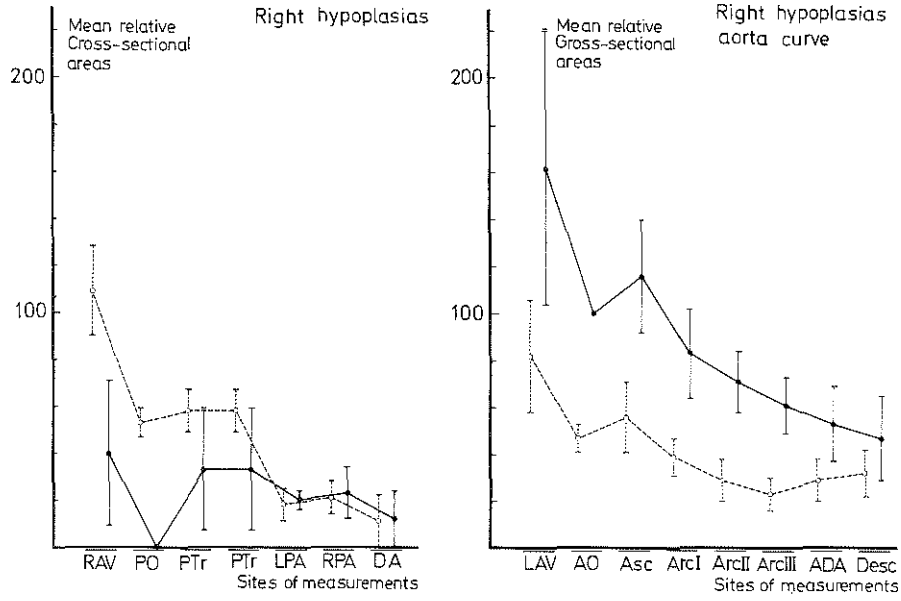

Fig. 3. Relative cross-sectional areas (mean $\pm$ standard deviation) of cardiac orifices and great vessels (see text) of 7 cases of right hypoplasia (uninterrupted line). The normal reference material of 24 normal hearts is included (interrupted line). Abbreviations see Fig. 2

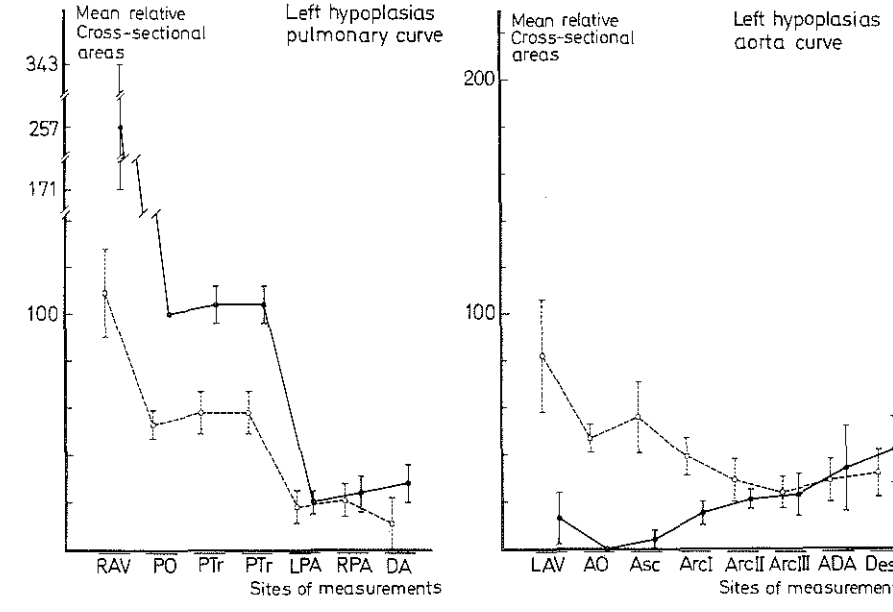

Fig. 4. Relative cross-sectional areas (mean $\pm$ standard deviation) of cardiac orifices and great vessels (see text) of 9 cases of left hypoplasia (uninterrupted line). The normal reference material of 24 normal hearts is included (interrupted line). Abbreviations see Fig. 2

Observations

Normal Hearts. Figs. 3 and 4 include the data from 24 normal hearts. Characteristic features are largely in accordance with the literature (De la Cruz *et al.*, 1960). The atrio-ventricular orifices are much larger than the pulmonary, respectively aortic ostia. Also the right atrio-ventricular orifice tends to be larger than the left one. The combined relative surface areas of the right pulmonary artery, left pulmonary artery and ductus arteriosus closely approach that of the pulmonary trunk. The aorta curve shows the well-known isthmus as a dip at Arc III, i.e. between the left subclavian artery and the connection of the ductus arteriosus with the aorta.

Hypoplastic Right Heart. Fig. 3 depicts graphically the data from 7 hearts. On the pulmonary side the most striking feature is that the functioning vessels, the pulmonary arteries and ductus arteriosus, do not show any deviation from the normal condition in their relative calibres. In the case of the pulmonary trunk a distinct but not very striking trend towards reduction of relative calibre is present. The aorta curve has a pattern which is close to normal, although of course the high values of the various points of the curve reflect the function of the aorta as the sole functioning outflow vessel. The mean cross-sectional area ($\pm$ standard deviation) of the aortic ostium was 143.4 ± 48.8 mm^2/100 cm body length, more than twice the value of 64.5 ± 29.6 mm^2 found in the normal material.

In contrast to the aorta curve of the normal material the aorta curve for the hypoplastic right heart does not show the dip at the site Arc III. This probably reflects prenatal bloodflow via the ductus arteriosus towards the pulmonary arterial system.

Hypoplastic Left Heart. The summarized data on the 9 hearts in this group are shown in Fig. 4. The pulmonary curve reflects in its left-side part the increased flow through the right ventricle and pulmonary trunk. The cross-sectional area of the pulmonary ostium was 153.6 ± 32.5 mm^2 per 100 cm body length versus a value of 81.5 ± 32.5 mm^2 in the control material. Interestingly the relative surface areas of the pulmonary arteries did not show any trend towards abnormal values. In contrast a trend towards a supranormal diameter of the ductus arteriosus was present. In this respect left hypoplasia differs from right hypoplasia. Increased diameter of the ductus arteriosus in this group may reflect that the ductus arteriosus supplies all of the greater circulation in left heart hypoplasia. The aorta curve is clearly abnormal. It shows a slope opposite to that for the normal heart.

Discussion

The condition of left or right sided cardiac hypoplasia causes changes in haemodynamic loads of the great vessels and of specific parts of these vessels. The data presented allow the general conclusion that these changes in functional load are accompanied by appropriate changes in the calibres of the vessels. The most striking example forms the aorta in left hypoplasia. This vessel demonstrates a pattern of cross-sectional areas completely different from the normal condition although it corresponds to the bloodflow which enters the aorta only at the connection with the ductus arteriosus. The calibre of the aorta in right

hypoplasia also supports the conclusion of appropriate functional changes in vessel calibres. Although the various cross-sectional areas are all well above normal the vessel shows the gradual decrease in calibre that is found also under normal conditions. The similarity of this pattern in right hypoplasia to that in the normal condition is most likely due to the unchanged direction of bloodflow in the aorta in this type of hypoplasia. On the other hand, the measurements of the aorta at the entrance of the ductus arteriosus and of the descending aorta seem to contradict the general conclusion reached above. It should be realized however that in the controls from an age group of normals as used here, the values for this section of the aorta will still reflect the prenatal pulmonary-aortic flow in the ductus arteriosus. On the other hand in right hypoplasia the opposite direction of flow is present, both pre- and postnatally.

The size of the pulmonary trunk in right sided hypoplasia does not fit the general picture of cross-sectional areas of the great vessels which corresponds to an abnormal functional load. In contrast to the first part of the aorta in left hypoplasia it shows no clear decrease in calibre which would correspond to the absence of bloodflow. This may be related to a difference in the haemodynamic conditions such as the fact that in left hypoplasia the ascending aorta remains a functioning vessel which carries blood to the coronary arteries. In contrast, the pulmonary trunk contains only stagnant blood. The well-known difference in structure of the wall of the aorta and pulmonary trunk may also play a role.

The relative calibres of the pulmonary arteries show in both groups no abnormality. On one hand this favours the supposition that lung function is maintained at a level approaching the normal one, on the other hand it is remarkable that these calibres are normal particularly since in left hypoplasia the pulmonary arteries may be subjected to an abnormal level of blood pressure. The mechanism responsible for the internal diameter of the pulmonary arteries may well be of an exceptional nature since the entire pulmonary vasculature develops with little functional load (i.e. bloodflow) since lung function is absent prenatally (Dawes *et al.*, 1953; Wagenvoort *et al.*, 1961c).

The pathological cases discussed here have all maintained life postnatally via the shunt provided by the ductus arteriosus. One would expect therefore supranormal calibres of the ductus arteriosus. Surprisingly this seemed to be the case only in left hypoplasia. The antenatal condition may provide an explanation. Since before birth the resistance of the pulmonary arterial tree is high (Dawes *et al.*, 1953; Wagenvoort *et al.*, 1961c) there is little bloodflow through the ductus in right sided hypoplasia which may explain a relatively small calibre. A similarly reduced calibre or even lack of the ductus arteriosus is seen in tetralogy of Fallot with marked pulmonary stenosis as well as in other developmental malformations causing prenatally a diminished bloodflow through the pulmonary trunk (Powell and Hiller, 1957; Molz, 1968; Rao *et al.*, 1971). In contrast, in left hypoplasia nearly all of the bloodflow is by way of the ductus, which supplies indirectly the general circulation. This may be the cause of the relatively large ductus in the left hypoplasia material. As is rather obvious the postnatal condition appears to be the consequence of the antenatal one. Also the size of the aortic isthmus as found in early postnatal life is generally explained along the same line.

Both the fact that the aortic isthmus is still present for some time postnatally, and the difference in calibre of the ductus arteriosus in left vs. right hypoplasia, point to a time factor in the adaptation of calibres of these vessels. Studies on development of collateral circulation and data on the after-effects of cardiac surgery show this time factor (May, 1968; Bonchek *et al.*, 1973; Sunderland *et al.*, 1973).

On the other hand, the data presented allow only a limited appraisal of the degree of "plasticity" of vascular diameters. For one thing: it is unknown exactly when left and right hypoplasia develop during antenatal growth. However, the interventricular septum was usually closed in these cases of atresia of the atrio-ventricular and/or ventricular orifices (similar findings were reported by Bryan and Oppenheimer, 1969; Gittenberger-de Groot, 1972). Further, the aorta and pulmonary trunk showed three-cuspid valves (see Gittenberger-de Groot, 1972). Both findings provide an indication of the stage of development at which right or left hypoplasia may have originated. Experimental production of these syndromes reported by Harh *et al.*, 1973, may eventually allow a more accurate approach here.

A question that remains to be answered is whether alterations in vessel calibre, such as those reported here, are accompanied by histological changes in the vascular wall. In cases with grossly abnormal circulatory conditions like pulmonary hypertension such changes have been observed in the pulmonary vascular tree (Wagenvoort *et al.*, 1969a and b). Abnormalities of the coronary system also occur frequently in conditions similar to those studied by us (Bryan and Oppenheimer, 1969).

In closing, although the clinical value of the data reported here may presently be limited, comparisons of data as presented here and angiographic or echocardiographic measurements of the anatomical conditions in vivo may help in arriving at a correct diagnosis and in the assessment of the chance for surgical correction in individual patients.

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NORMAL INTERNAL CALIBRES OF OSTIA OF GREAT ARTERIES AND OF AORTIC ISTHMUS IN INFANTS AND CHILDREN

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Normal internal calibres of ostia of great arteries and of aortic isthmus in infants and children[1]

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In order to obtain reference data, useful in paediatric cardiology and paediatric cardiovascular surgery, internal diameters of the ostia of the great arteries, of the aortic isthmus, and of the descending aorta were determined with the aid of calibrated probes in 46 necropsy specimens of normal hearts with great vessels. Age range was from 25 weeks of gestational age up to 9 years post partum. *The method used proved to be as accurate as echocardiography* in vivo. *The data revealed linear correlations between body length and calibres of aortic and pulmonary ostia. The correlation between the calibres of the pulmonary and the aortic ostia was also a linear one with the pulmonary ostium being slightly larger than the aortic ostium. From the cross-sectional areas of the aortic isthmus and of the descending aorta an isthmus index was calculated which indicates the presence (and degree) or absence of a narrowing (tubular hypoplasia) of the aortic isthmus. Results show that narrowing of the aortic isthmus is inconstantly present in infants younger than 10 weeks, whereas it is always absent in infants and children older than 10 weeks. No dependence of narrowing of the aortic isthmus on developmental age attained at birth has been found.*

A previous paper (van Meurs-van Woezik and Klein, 1974) confirmed that in congenitally abnormal circulatory conditions, just as in the normal situation, the cross-sectional areas of the ostia of the heart and of the great arteries at different sites correspond to the blood flow through the relevant vessels (Krediet, 1962, 1963, 1965; May, 1968). Clinical methods of quantifying ostial calibres or valve areas (Gorlin and Gorlin, 1951; Yang *et al.*, 1972) have been estimated to be liable to errors as great as 20 to 40 per cent (Rodrigo and Snellen, 1953). Echocardiographic measurements are an exception to this general criticism. Hitherto, however, most of such determinations have been made in older children and adults with evidence of cardiovascular disturbances. When cardiovascular surgery during childhood is considered, one needs reference data on normal infants and children. This paper presents data of such type.

Subjects and method

The material obtained at necropsy consisted of 46

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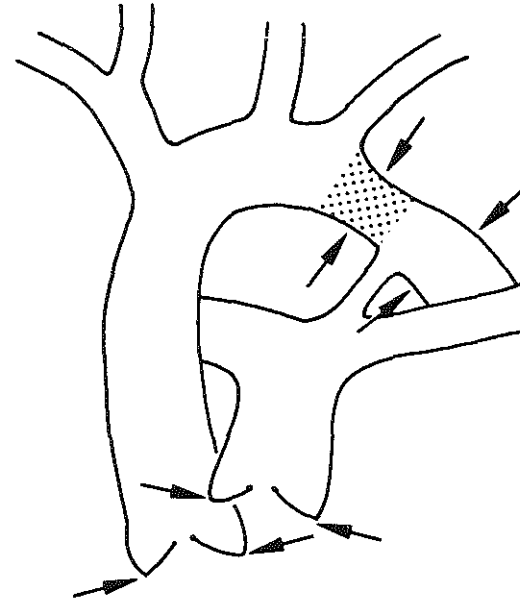

Fig. 1 *Sites of measurements used (arrows); dotted area indicates aortic isthmus (for definition see 'subjects and method').*

hearts with great vessels from babies and children or from 25 weeks of gestational age up to 9 years after birth. The sex distribution was: male 32, female 11, unknown 3 cases. All specimens were considered normal since cardiovascular abnormalities had not been diagnosed, either clinically or at necropsy. Twenty-one specimens were derived from infants and children who had been born at term, 23 from babies born prematurely, and 2 from immature babies (Table; for definition of premature and immature, see Kloosterman, 1973).

Measurements were performed as described previously on fresh material using a range of calibrated probes differing 1 mm in diameter (van Meurs-van Woezik and Klein, 1974). Diameter values of 0·5 mm were ascertained by interpolation; Measurements were carried out at various sites; those used in the present study are shown in Fig. 1. Ostia were measured at the level of the valve annulus.

The aortic isthmus was defined as the part of the aortic arch between the origin of the left subclavian artery and the mouth of the ductus arteriosus or the insertion of the ligamentum arteriosum.

Table *Synopsis of data on internal calibres of ostia and arteries, body length, body weight, isthmus indices, and of grouping (see 'observations')*

Case No.	Body length (cm)	Body weight (g)	Age after birth		Gestational age at birth (w)	Sex	Diameter of ostium (mm)		Diameter (mm)			Isthmus index	Group
			m	d			Aorta	Pulm.	Aortic isthmus	Aorta desc.	Ductus arter.		
1	30	1100	—	0	25	?	4	4·5	2	3	2·5	0·44	I
2	38	1080	—	2½	28	♀	5	6	3	4	2·5	0·56	I
3	41	1300	—	2	30	♂	6	6·5	4·5	4·5	2·5	1·00	II
4	41	1500	—	6	30½	♂	6	8	5	5	4	1·00	II
5	42	1450	—	6	30	?	6	7	4	4·5	2	0·80	I
6	44	1410	—	0	32⅓	♂	6	7·5	3·5	5	5	0·48	I
7	44	1800	—	0	33	♂	7	7	6	6	5	1·00	II
8	44	1490	—	8	31	♀	6·5	6·5	4·5	5·5	2·5	0·67	I
9	44	1790	1	4	27⅓	♀	6	7	3	4·5	0·5	0·45	I
10	45	1950	—	1	31	♂	6·5	6	4	6	4	0·44	I
11	45	1425	—	2	29	♂	5·5	5·5	4	4	3	1·00	II
12	45	2240	—	2	42	♂	6·5	7·5	3·5	4·5	2	0·60	I
13	45	1740	—	11	31	♂	6	6	4	4	1·5	1·00	II
14	45	1950	1	—	Prem.	♂	7	7	4	5	2	0·64	I
15	46	2071	—	0	36⅓	♂	6	7	3·5	6	4·5	0·33	I
16	46	2100	—	1	35⅛	♂	6	6·5	2·5	5	4	0·24	I
17	46	1825	—	6	36	?	5	6·5	3	5	2	0·36	I
18	48	2340	—	7	32–36	♂	6·5	8	4	5	3	0·64	I
19	49	3050	—	0	Mat.	♀	6·5	7·5	4	5·5	3	0·53	I
20	49	2400	—	3	34⅛	♀	7	7	4	5·5	4	0·53	I
21	50	2330	—	¾	34	♂	7	8	6	6	3	1·00	II
22	50	3170	—	20	39	♂	7	6·5	5	6	1	0·70	I
23	50	1990	—	29	35	♂	7	8	5·5	5·5	1	1·00	II
24	50	3700	2	—	36	♂	9	10	6	6·5	2	0·85	II
25	51	2490	—	18	Prem.	♀	8	10	6	7	3	0·73	I
26	51	1900	—	23	34	♀	7	7·5	4·5	6	3	0·56	I
27	52	2900	—	5	40	♂	7·5	8	5	6	6	0·70	I
28	52	2950	4	8	32	♀	7	8·5	5	5	0	1·00	III
29	53	3700	—	1	Mat.	♂	9	10	8	9	7	0·79	I
30	53	3100	—	24	38	♀	7·5	8·5	5·5	6	2·5	0·84	II
31	53	3150	4	1	Mat.	♂	9	11	7	6·5	0	1·17	III
32	57	2470	—	20	37	♂	7	8·5	6	6	0	1·00	III
33	57	3780	3	17	32	♂	8·5	9	6·5	6·5	0	1·00	III
34	58	3300	—	13	40	♂	8	8·5	4	5·5	2	0·53	I
35	63	6290	4	9	Mat.	♂	10	10·5	6·5	6·5	0	1·00	III
36	65	4700	2	8	40	♀	9	10	7	8	2·5	0·77	I
37	70	7500	5	25	Mat.	♂	11	11	9	8·5	0	1·12	III
38	74	8100	9	28	Mat.	♂	10·5	12	8	8	0	1·00	III
39	79	9900	10	6	Mat.	♂	12·5	15	8·5	8	0	1·13	III
			y	m									
40	90	10 100	1	11	Mat.	♂	11	11	?	?	0	?	?
41	116	16 000	3	9	Mat.	♂	15	17	14	14	0	1·00	III
42	117	19 000	6	9	Mat.	♀	15	18	14	13	0	1·16	III
43	122	?	5	11	Mat.	♂	18	19·5	13·5	13·5	0	1·00	III
44	122	21 000	9	11	Mat.	♂	17	22	14	14	0	1·00	III
45	123	38 000	5	8	Mat.	♂	17	20	12	12	0	1·00	III
46	143	36 000	8	—	Mat.	♂	16·5	18	11·5	10·5	0	1·20	III

Abbreviations: Mat., mature; Prem., premature; ? (unknown) indicates incomplete data or incomplete necropsy specimen.

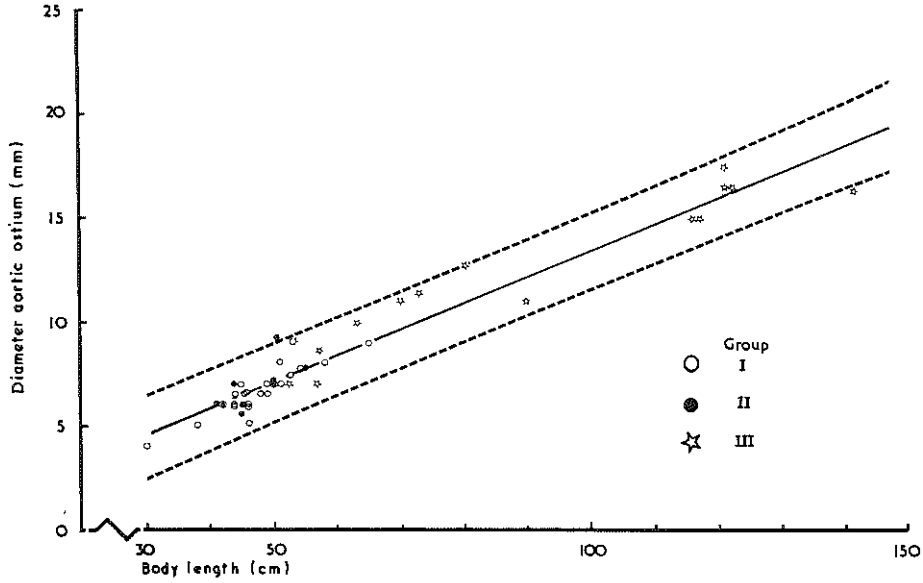

Fig. 2 *Correlation between internal diameters of aortic ostium and body length; interrupted lines indicate prediction interval. For definitions of groups see 'observations' and Table.*

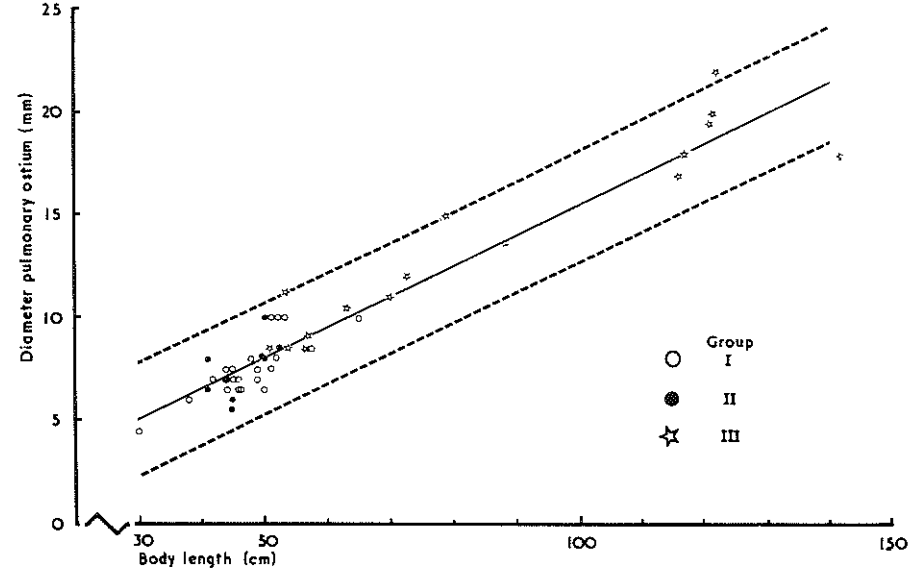

Fig. 3 *Correlation between internal diameters of pulmonary ostium and body length; interrupted lines indicate prediction interval. For definitions of groups see 'observations' and Table.*

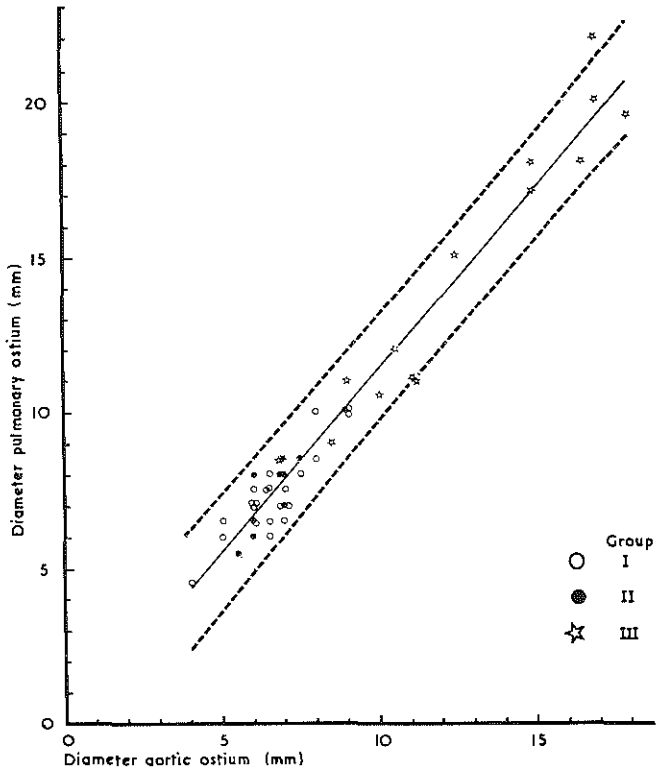

Fig. 4 *Correlation between internal diameters of aortic and pulmonary ostia; interrupted lines indicate prediction interval. For definitions of groups see 'observations' and Table.*

Cross-sectional areas of the ostia of the great arteries, of the aortic isthmus, and of the descending aorta were calculated as an indication of blood flow. Correlations were calculated following Sachs (1973).

Observations

In the Table the data on internal measurements of ostia and arteries, on body length, body weight, and age are summarised. In three graphs the following relations are depicted: diameters of aortic ostia versus body length (Fig. 2), diameters of pulmonary ostia versus body length (Fig. 3), diameters of pulmonary ostia versus diameters of aortic ostia (Fig. 4); prediction intervals are included. Fig. 2 and 3 show that linear correlations exist between body length and calibres of the aortic and pulmonary ostia. As expected, Fig. 4 shows a linear correlation between the diameters of both ostia with the pulmonary ostium being slightly larger than the aortic ostium (1.14:1).

For a judgement of presence or absence of a narrowing of the aortic isthmus we used the index cross-sectional area of the aortic isthmus at its narrowest site divided by cross-sectional area of the descending aorta immediately distal to the ductus arteriosus or to the ligamentum arteriosum. We then defined as follows: isthmus index $< 0{\cdot}81$, presence of narrowing of the aortic isthmus; isthmus index $\geq 0{\cdot}81$, absence of narrowing of the aortic isthmus. The following grouping of the material was then possible.

Group I: Isthmus index $< 0{\cdot}81$ with ductus arteriosus patent, 22 cases (of which 13 were premature, 2 were immature); age after birth from 0 days up to 10 weeks;

Group II: Isthmus index $\geq 0{\cdot}81$ with ductus arteriosus patent, 9 cases (of which 8 were premature, none was immature); age after birth from 0 days up to 2 months;

Group III: Isthmus index $\geq 0{\cdot}81$ with ductus arteriosus closed, 14 cases (of which 2 were premature, none was immature); age after birth from 20 days up to 9 years.

Cases with an isthmus index $< 0{\cdot}81$ together with a closed ductus arteriosus did not occur. Four observations concerning the isthmus should be

mentioned: (1) narrowing of the aortic isthmus was never present in a child older than 10 weeks; (2) of the 23 prematurely born babies, which had died very young (before 11 days after birth), 13 showed a narrowing of the aortic isthmus (Table); (3) narrowing of the aortic isthmus may be severe: out of the 45 cases, 13 had an isthmus index $\leq 0{\cdot}60$, 7 an index $\leq 0{\cdot}50$ but this finding was confined to the infants less than 5 weeks old; (4) a clear correlation between isthmus index and body length was absent.

Discussion

The question dealt with in the present study has received attention over a number of decades and several approaches have been used. The sites of measuring of the ostia and arteries differ considerably in the published reports. Data on the aortic and pulmonary ostia are few, and measurements have often been made 1 to 2 cm beyond their valves (Beneke, 1878, 1879; Sinha *et al.*, 1969; Rudolph *et al.*, 1972; Bruins, 1973).

In normal cases the diameter of the annulus is as a rule smaller than the diameter of the corresponding artery beyond it, that is the ascending aorta, or pulmonary trunk (van Meurs-van Woezik and Klein, 1974). Therefore, we preferred as the sites for measurement these two ostia, the narrowest sites of the main pathways of blood flow through the heart.

In previous studies the measuring techniques have sometimes not been reported or little detail has been given (de la Cruz *et al.*, 1960; Sinha *et al.*, 1969). In addition some measurements have been made using a ruler after slitting and flattening out of the great arteries (Beneke, 1878, 1879). Different pressure on the ruler caused changes in the results of up to 4 mm (Beneke, 1878), which correspond to errors much larger than those observed using our technique, for which relatively small measuring errors have been determined (van Meurs-van Woezik and Klein, 1974). Measurement after histological sectioning has also been used (Odé, 1951), but will be inaccurate because of variable shrinkage and distortion caused by fixation, embedding, and spreading. Measurements from plastic casts (Wright, 1969; Rudolph, 1970; Rudolph *et al.*, 1972) may also not be fully reliable since we have found from personal experience that blood clots and gas bubbles may prevent correct filling by the casting material, especially at the ostia.

Clinically, echocardiography seems to be the most accurate method for measuring ostia and vessels. Our *post mortem* data for the pulmonary ostium correspond exactly with those obtained *in vivo* by Solinger *et al.* (1973) using echocardiography. However, their values for the aortic ostium are constantly 2 mm below ours, probably because measurements have not been made through the centre of this ostium, as indicated by Fig. 5 of the paper by Solinger *et al.* Other methods for clinical determination of calibres of ostia and great vessels seem inaccurate (Rodrigo and Snellen, 1953). Based on personal experience we have found that this also holds for angiographic methods as used by Sinha *et al.* (1969).

Since our study is largely concerned with growing individuals, correlation of our measurements with indices of bodily development is important. Commonly used indices of bodily development are age, body length, body weight, and body surface area. Since age is not closely related with bodily development (Tanner *et al.*, 1966) this measure, used by de la Cruz *et al.* (1960) and Eckner *et al.* (1969), is not a good choice. Furthermore in sick children body weight can change considerably within a short time. Body surface area is usually derived in part from body weight and is, therefore, also a measure of doubtful value. The most useful measure seems to be body length since it is not affected by short term changes caused by ill health. In consequence, we compared our measurements with body length. The echocardiographic data of Solinger *et al.* (1973), recalculated using the table by van Wieringen (1973) for converting body weight to body length, correspond, as mentioned, exactly to our data for the pulmonary ostium.

The data revealed linear correlations between body length and the diameters of aortic and pulmonary ostia. This is plausible because of the linear correlation between body surface, metabolism, and blood flow on the one hand and cross-sectional areas of the great vessels on the other hand.

Since the aortic isthmus with its variable calibre might act as a circulatory bottleneck and might cause clinically demonstrable differences between systolic blood pressure of the upper and lower limbs (De Swiet *et al.*, 1974), special attention has been paid to the presence and degree of narrowing (tubular hypoplasia) of the aortic isthmus in this material of normal hearts and great vessels. Our pertinent observations require some comment. In order to ascertain the presence or absence of narrowing of the aortic isthmus the question arises as to which segment of the aorta should be compared with the aortic isthmus. In our opinion this should be the descending aorta for the following reasons: before birth the total cardiac output, minus the amount of blood given off to head, neck, arms, lungs, and—in part—to the coronary arteries, reassembles in the descending aorta. After birth, when the ductus arteriosus has closed, all blood passing the aorta ostium, minus blood to head, neck, arms and—in part—to the coronary arteries,

will pass via the aortic isthmus also into the descending aorta. Furthermore, since during fetal life calibres of both ascending aorta and aortic isthmus are influenced by the size of the aortic ostium, it seems less appropriate for our purpose to follow Sinha *et al.* (1969) and to compare the aortic isthmus not only with the descending aorta but also with the ascending aorta.

An internal diameter of the aortic isthmus 10 per cent less than that of the descending aorta has been chosen arbitrarily as indicative of narrowing (tubular hypoplasia). Expressed in cross-sectional areas this leads to a borderline value of 0·81 for the isthmus index (see 'subjects and method').

From our observations on normal hearts and great arteries the following conclusions on the aortic isthmus can be drawn.

(1) Under normal conditions narrowing of the aortic isthmus (isthmus index $\leq 0{\cdot}81$) may or may not exist in babies younger than 10 weeks, both in those born at term and pre- or immaturely, whereas in babies older than 10 weeks, born at term, pre-, or immaturely, narrowing of the aortic isthmus cannot be expected.
(2) In the babies younger than 5 weeks pronounced narrowing was not exceptional.
(3) No dependence of narrowing of the aortic isthmus on developmental age attained at birth seems to exist.

In conclusion it should be stressed that these observations, both those on calibres of the aortic and pulmonary ostia and those on the aortic isthmus, characterise quantitative aspects of the normal vasculature. The definition of borderline values between normal and pathological conditions is a desirable next step which we have not yet attempted. However, the data reported provide a necessary starting point for defining such borderline values.

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TUNICA MEDIA OF AORTA AND PULMONARY TRUNK IN RELATION TO INTERNAL CALIBRES IN TRANSPOSITION OF GREAT ARTERIES, IN HYPOPLASTIC AND IN NORMAL HEARTS

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Short title for running heads : tunica media and internal diameters of great arteries in (ab)normal bloodflow.

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SUMMARY

We showed previously that the calibres of the aorta and pulmonary trunk and of the ostia of the heart both in the normal situation and in one condition of extreme alteration of bloodflow are directly related to the functional load on that vessel or ostium.

In spite of the abnormal ventriculo-arterial connexion in transposition of the great arteries (TGA) the calibres of the great arteries and the ostia of the heart proved to be the same as in normal hearts. Up to six months of age the thickness of the tunica media and the packing density of its elastic fibres were in both the ascending aorta and in the pulmonary trunk the same as in normal hearts. This corresponds with the clinical findings on the function of the left ventricle in TGA up to six months. Adaptations to the abnormal bloodflow were found in cases older than one year. In five cases of TGA, three of them older than three months, Grade 1 and 2 of vascular disease of the lungs were found.

In left and right hypoplasia the vessels with reduced or absent function showed a markedly different structure. The internal calibre and thickness of the media of the ascending aorta in left hypoplasia were markedly reduced, whereas the packing density of the elastic fibres of the tunica media remained the same as in normal hearts. The pulmonary trunk in right hypoplasia showed large variations in internal calibre, whereas the thickness and packing density of the elastic fibres of the tunica media remained the same as in normal hearts. However, comparing the markedly enlarged single functional vessel in left hypoplasia with that in right hypoplasia not only the cross-sectional areas were the same but also the thickness and the packing density of the tunica media and both vessels showed in the media adaptations to the changed functional load.

INTRODUCTION

From investigations with normal cardiovascular organs and with abnormal material of the hypoplastic left and right heart syndromes we know fairly well the internal calibres of the ostia and great arteries in normal bloodflow and in these cases with extreme alteration of bloodflow (van Meurs and Klein, 1974; van Meurs et al., 1977). In this study we investigated the calibres of the great arteries and of the ostia of the heart in another condition of abnormal bloodflow i.e. transposition of the great arteries. During normal growth and under certain abnormal conditions the tunica media of the great arteries undergoes structural changes (Heath et al., 1959; Heath and Edwards, 1960; Saldaña and Arias, 1963). Accordingly, we also investigated the relation between the changes of the internal calibres of the great arteries and structural changes of the tunica media of these vessels i.e. thickness and packing density of the elastic fibres, in the following conditions of abnormal bloodflow : left and right hypoplasia and transposition of the great arteries. Normal hearts provided a reference material.

MATERIAL AND METHODS

The postmortem material was put at our disposal by the department of pathology of the Erasmus University Rotterdam. It consisted of specimens of hearts and great arteries, which will be referred to as hearts and lungs.

I. Hearts with transposition of the great arteries (TGA). This group consisted of 17 hearts from patients with an age range from 14 hours after birth to 2 years and 10 months and was subdivided as follows : 1- Two cases of TGA with ventricular septal defect and patent ductus arteriosus, age : in both cases 4 weeks; 2- One case of TGA with ventricular septal defect and closed ductus arteriosus, age : 1 year and 3 months; 3- Eleven cases of TGA without septal defect and with an open ductus, age range : 4 hours to $5\frac{1}{2}$ months; 4- Three cases of TGA without septal defect and with a closed ductus, age range : 13 days to 2 years and 10 months.

II. Hypoplastic left hearts. Nine hearts with atresia of the left ventricular orifice and/or aortic ostium, derived from patients with an age range from 2 days to 5 weeks.

III. Hypoplastic right hearts. Seven hearts with atresia of the right ventricular orifice and/or pulmonary ostium, derived from patients with an age range from 1 day to 1 year.

IV. Normal hearts. This control material consisted of 53 specimens derived from infants and children with an age range from 27 weeks of gestation up to 15 years after birth. It was devided into two groups : 1 - 34 hearts with an open ductus, age range : from 27 weeks of gestation to 2 months and 8 days after birth; 2 - 19 hearts with a closed ductus, age range : from $2\frac{1}{2}$ days post partem to 15 years.

In this material the internal diameters of the aortic and pulmonary ostium, ascending aorta, aortic arch, pulmonary trunk and pulmonary arteries were measured with the aid of calibrated probes. This method and part of the material have been

described previously (van Meurs and Klein, 1974; van Meurs et al., 1977). The internal diameters of aortic and pulmonary ostium, ascending aorta and pulmonary trunk were compared with body length as parameter of development. The squared values of the various diameters measured were expressed as a percentage of the sum total of the squared values of the diameter of the aortic and pulmonary ostium in both the normal material and the cases with transposition of the great arteries, and in the hypoplasia material as a percentage of the squared diameter of the one functioning outflow ostium. The changes of these relative cross-sectional areas along the course of the great arteries will be represented graphically and will be called aortic and pulmonary curves (van Meurs and Klein, 1974 and this paper).

In addition to these measurements the thickness of the media of the ascending aorta and the pulmonary trunk and the condition of their elastic fibre component were determined. Transverse rings, located 1 to 2 cm above the ostia, were taken out of the formalin fixed arteries, 7 µm transverse sections were stained with haematoxylin and eosin or with the Van Gieson's method. The mean thickness of the media was calculated from 20 determinations equally distributed over the circumference of the vessel. The packing density of the elastic fibres, i.e. the percentage of the cross-sectional area of the media occupied by elastic fibres, was calculated from 20 determinations by the method of point counting as described by Weibel and Elias (1967).

In order to determine the regional distribution of the elastic fibres the media of the ascending aorta and pulmonary trunk was divided, in ten normal and four pathologic cases, into an internal, intermediate and external layer and subdivided into four sectors of 90^{o}. In each of these four sectors the mean percentage of the area occupied by elastic fibres was calculated separately for each of the three layers mentioned from five measurements. Since no significant regional differences

were found between these four sectors nor between the three layers, these data will be omitted in the description of our results.

The configuration of the elastic component of the media of the pulmonary trunk will be characterized as being of aortic, transitional A, transitional B or pulmonary type, according to the classification used by Heath et al. (1959), by Saldaña and Arias (1963) and by Yamakawa et al. (1966).

Formalin fixed material from the lungs of the TGA cases, sectioned at 7 μm and stained with haematoxylin and eosin and with Van Gieson's method, was examined for the presence of pulmonary vascular disease accompanying pulmonary hypertension, as described by Heath et al. (1958), Heath and Edwards (1959) and by Wagenvoort et al. (1964, 1968).

The statistical analysis of the results was carried out using Student's t-test. A difference was considered as significant if the two tailed probability was < 0.05.

OBSERVATIONS

I. Internal diameters of aorta and pulmonary trunk.

a. Transposition of the great arteries. In TGA correlations calculated between body length and internal diameters of the aortic and pulmonary ostium, and of the ascending aorta and pulmonary trunk did not differ significantly from those previously calculated for normal hearts (van Meurs et al., 1977). Accordingly, the graphic representation of the cross-sectional areas of the great arteries yielded the same results as for the normal hearts (Fig. 1). The aortic and pulmonary curves of the other groups of TGA obtained were all fully similar to those illustrated in Fig. 1.

b. Hypoplastic and normal hearts. In this paper we will use the diameters and cross-sectional areas as described previously (van Meurs and Klein, 1974; van Meurs et al., 1977).

II. Tunica media of the ascending aorta and pulmonary trunk : thickness and packing density of its elastic fibres : relation to the internal diameters of these arteries.

a. Normal hearts. In the normal hearts the age related differences in internal diameters of the ascending aorta of 4 to 22 mm were accompanied by parallel differences in thickness of the media from 270 to 930 µm and by parallel differences in the packing density of the elastic fibres from 16 to 46% (Fig. 2 A,B). Similarly, the differences in internal diameters of the pulmonary trunk from 3.5 to 23 mm were accompanied by parallel differences in the thickness of the media from 290 to 780 µm, while the packing density of the elastic fibres varied from 15 to 35% (Fig. 2 C,D).

b. Transposition of the great arteries. In the cases from patients dying within six months after birth, the thickness and packing density of the elastic fibres of the media of the ascending aorta and pulmonary trunk showed similar values as in normal hearts (ascending aorta : thickness 360 - 800 versus 270 - 930 µm, packing density 18 - 33 versus 16 - 46%; pulmonary trunk : thickness 350 - 730 versus 290 - 780 µm, packing density 16 - 31 versus 15 - 35%) (Fig. 3 A,B,C and D), independent of the presence or absence of a ventricular septal defect and of an open or closed ductus arteriosus. The values were within the prediction interval of 95%. However, the hearts from the two eldest patients, age resp. 1 year 3 months and 2 years 10 months, yielded contrasting data.

c. Hypoplastic left hearts. In the nine hypoplastic left hearts, all derived from patients dying within 5 weeks, the thickness of the media (160 - 600 µm) of the very small ascending aorta, internal diameter of 1 to 3 mm, was significantly smaller than the value in normal hearts at birth (270 - 700 µm) which had a mean internal diameter of the aorta of 6 mm. However, the packing density of the elastic fibres

showed the same variation (16 - 25%) as in normal hearts at birth (19 - 27%).

The thickness of the media of the exceptionally large pulmonary trunk, internal diameter of 8 to 12 mm, was between 380 and 910 μm, a value consistent with a normal pulmonary trunk of the same calibre (320 - 780 μm) and with the pulmonary trunk of normal hearts at birth (350 - 650 μm), mean internal diameter of 7 mm. The packing density of the elastic fibres (23 - 34%), was significantly higher than in normal cases with a similar internal diameter (16 - 31%) and also higher than in pulmonary trunks of normal hearts at birth (20 - 28%) (Fig. 4 A,B,C and D).

d. Hypoplastic right hearts. In the seven hypoplastic right hearts, all derived from patients dying within 1 year, the thickness of the media of the ascending aorta was significantly below that in normal hearts with a similar internal diameter of the ascending aorta of 9 to 14 mm (400 - 690 versus 550 - 900 um), but had the same thickness as in normal hearts at birth (400 - 690 versus 270 - 700 um). The packing density of the elastic fibres of the ascending aorta was the same as in normal hearts with a similar internal diameter (22 - 26% versus 23 - 30%) and also the same as in normal hearts at birth (22 - 26 versus 20 - 28%).

The thickness of the media of the pulmonary trunk was normal if compared with vessels with a similar internal diameter of 3 to 9.5 mm (300 - 500 versus 350 - 800 μm and also was the same as in normal hearts at birth (300 - 500 versus 350 - 650 μm). The packing density of the elastic fibres of the pulmonary trunk was the same as in normal hearts with a similar internal diameter of 3 to 9.5 mm (15 - 26 versus 15 - 33%) and the same as in normal hearts at birth (15 - 26 versus 20 - 28%) (Fig. 4 A, B, C and D).

Comparing the pulmonary trunk in left hypoplasia with the ascending aorta in right hypoplasia it has been shown previously that the internal calibres of these vessels were of the same size (van Meurs and Klein, 1974). The present data on the tunica

media of these vessels show that the thickness of the media as well as the packing density of its elastic fibres in these enlarged vessels had the same values (media thickness : 400 - 900 versus 400 - 690 μm, packing density : 23 - 34 versus 22 - 26%) (Figs. 4 C, D and 4 A, B).

III. Media of the pulmonary trunk : configuration of the elastic fibres in relation to their packing density.

In normal hearts a marked variability of the configuration of elastic fibres in the pulmonary trunk was found. The same variability was found in our material of transpositions of the great arteries. Some of the eldest cases were an exception to this rule (Table). No correlation was found between the configuration and the packing density of the elastic fibres of the pulmonary trunk, neither in normal cases nor in transposition of the great arteries. In the hypoplastic hearts, at ages up to 5 weeks, the pulmonary trunk showed an aortic type elastic fibre configuration. In the eldest cases a transitional type was found (age $7\frac{1}{2}$ months resp. 1 year).

IV. Transposition of the great arteries and pulmonary vascular disease.

Pulmonary vascular disease was found in 5 of the total number of 17 cases of TGA (Table). Three of these five patients were older than 3 months. The blood pressure in the left ventricle was in the 11 TGA cases for which such measurements were available between 17 and 75 mmHg, but ranged from 52 to 72 mmHg in the 4 out of the 5 cases with pulmonary vascular disease for which measurements were available. These data were given for reasons of completeness.

DISCUSSION

In this study we investigated the internal calibres and two characteristics of the media of the aorta and pulmonary trunk in TGA and hypoplastic hearts. Normal hearts

	Body length (cm)	Age after birth y	m	d	Gestational age at birth (w)	Internal diameter (mm) Aorta ostium	Asc. aorta	Media asc.aorta Thick.	Pack.dens. el.fibres	Internal diameter (mm) Pulm. ostium	Pulm. Trunk	Media Pulm.Trunk Thick.	Pack.dens. el.fibres	Diameter (mm) DAB	VSD	ASD	Config. el.fibres Pulmonary Trunk	Pulm.vasc. disease Grade
1	36	-	-	0	27	4	4	516	16	3.5	3.5	403	16	3.5	-	-	A	-
2	36	-	-	7	prem.	5.5	5.5	581	22	6	6	511	22	1	-	-	A	-
3	38	-	-	2	28	5	5.5	531	23	6	6.5	485	20	2.5	-	-	A	-
4	41	-	-	6	30½	6	6	269	27	8	8	347	27	4	-	-	A	-
5	41	-	-	2	30	6	6.5	366	22	6.5	7	294	22	2.5	-	-	A	-
6	42	-	-	6	30	6	6.5	398	21	7	7	356	28	2	-	-	A	-
7	43	-	-	9	32	6	6.5	546	25	4	6.5	505	22	2.5	-	-	A	-
8	44	-	-	0	32½	6	6	549	19	7.5	8	398	17	5	-	-	Tr A	-
9	44	-	-	1	33	7	8	421	20	7	8	372	22	5	-	-	A	-
10	44	-	-	1	31	6.5	7	555	16	6.5	7	513	22	2.5	-	-	A	-
11	44	-	1	7	27½	6	6.5	561	24	7	7	356	20	0.5	-	-	Tr A	-
12	45	-	-	1	31	6.5	6	510	23	6	6	401	20	4	-	-	A	-
13	45	-	-	1	prem.	5	5	634	29	5.5	6	536	33	2	-	-	A	-
14	45	-	-	2	29	5.5	6	506	26	5.5	6	404	26	3	-	-	A	-
15	45	-	-	2	42	6.5	6	658	26	7.5	8	593	25	2	-	-	A	-
16	45	-	-	11	31	6	6	552	27	6	6	473	27	1.5	-	-	A	-
17	45	-	-	17	35½	4.5	5	477	22	6	6	361	26	1.5	-	-	A	-
18	45	-	1	-	prem.	7	7	597	21	7	7	377	26	2	-	-	A	-
19	46	-	-	1	35½	6	6	479	20	6.5	7	422	20	4	-	-	Tr A	-
20	46	-	-	6	36	5	5	629	21	6.5	7	641	28	2	-	-	Tr B	-
21	46	-	-	0	36½	6	6.5	458	17	7	7.5	495	18	4.5	-	-	Tr B	-
22	48	-	-	7	32-36	6.5	7	570	23	8	8	503	22	3	-	-	A	-
23	49	-	-	3	mat.	7	7	516	28	7	7	369	24	4	-	-	A	-
24	50	-	-	29	35	7	7.5	783	25	8	8.5	419	31	1	-	-	A	-
25	50	-	-	¾	34	7	8	636	22	8	8.5	520	19	3	-	-	Tr B	-
26	50	-	-	20	39	7	7	798	28	6.5	6.5	378	31	1	-	-	Tr A	-
27	50	-	2	-	36	9	10	661	23	10	11	557	21	3	-	-	Tr A	-
28	51	-	-	23	34	7	7.5	413	22	7.5	8	467	22	3	-	-	A	-
29	52	-	-	1	mat.	6	6	722	23	5	5	768	22	4	-	-	A	-
30	52	-	-	2½	mat.	8	7.5	577	19	8	8	647	14	0	-	-	Tr A	-
31	52	-	4	8	32	7	7.5	930	27	8.5	9	488	16	0	-	-	Tr A	-
32	53	-	-	1	mat.	9	10	566	24	10	11	445	26	7	-	-	A	-
33	53	-	-	24	38	7.5	8	611	28	8.5	9	709	26	2.5	-	-	Tr A	-
34	53	-	4	1	mat.	9	9	698	23	11	11.5	393	23	0	-	-	Tr A	-
35	57	-	1	15	37	7	8	780	25	8.5	9	614	20	0	-	-	Tr B	-
36	57	-	3	17	32	8.5	9.5	787	26	9	9.5	457	22	0	-	-	Tr B	-
37	58	-	-	13	40	8	8	910	26	8.5	9	672	27	2	-	-	Tr B	-
38	?			?	?	8	8	785	18	9	9	522	26	3	-	-	Tr B	-
39	63	-	4	9	mat.	10	10	910	30	10.5	11	782	22	0	-	-	Tr A	-
40	65	-	2	8	40	9	9	690	29	10	11	740	28	2.5	-	-	A	-
41	70	-	5	25	mat.	11	12	573	30	11	12	328	27	0	-	-	A	-
42	73	2	9	-	mat.	12	12	742	39	13	13	340	17	0	-	-	Tr A	-
43	74	-	9	28	mat.	10.5	11	868	25	12	12	706	25	0	-	-	Tr B	-
44	79	-	10	6	mat.	12.5	13	508	18	15	15	403	24	0	-	-	Tr B	-
45	90	1	11	-	mat.	11	11	761	44	11	11	580	20	0	-	-	Tr A	-
46	?	-	4	15	mat.	11	11	898	28	13	13	733	26	0	-	-	Tr B	-
47	116	3	9	-	mat.	15	15	893	24	17	17	494	15	0	-	-	Tr A	-
48	117	6	9	-	mat.	15	16	920	27	18	19	679	35	0	-	-	A	-
49	122	5	11	-	mat.	18	19	760	46	19.5	20	493	19	0	-	-	Tr A	-

50	122	9	11	–	mat.	17	18	886	38	22	23	612	25	0	–	–	Tr A	–
51	143	8	–	–	mat.	16.5	17	858	32	18	19	580	17	0	–	–	Tr A	–
52	?	5	–	–	mat.	20	20	845	42	20	22	494	22	0	–	–	A	–
53	170	15	–	–	mat.	22	22	797	38	23	23	652	15	0	–	–	P	–
	TRANSPOSITION OF THE GREAT ARTERIES																	
	GROUP I (VSD and open ductus arteriosus)																	
1	46	–	–	28	?	6.5	7	403	32	7	8.5	426	28	4.5	4	11	A	–
2	57	–	–	28	40	7.5	8	684	25	7	7	449	25	2	2	12	A	–
	GROUP II (VSD and closed DAB)																	
3	74	1	3	–		9	9.5	734	30	12	13	1053	30	0	9	12	A	1
	GROUP III (without SD and open DAB)																	
4	64	–	5	15	mat.	8.5	9	712	26	8.5	10	601	20	1	0	12	Tr B	1
5	47	–	–	1	?	7	7.5	621	22	7.5	8	426	28	1	0	6	A	–
6	58	–	–	1	mat.	7.5	8	356	29	7.5	8	508	22	4	0	7	A	–
7	52	–	–	11	mat.	6	6	519	33	7	7	441	31	2	0	5	Tr B	–
8	52	–	–	8	40	6	6.5	528	25	6	6.5	546	26	2	0	10	Tr A	–
9	49	–	–	1	mat.	6.	6.5	514	18	6	7	594	19	2	0	6	A	–
10	52	–	–	1	mat.	6	6	575	20	6	6	561	22	2	0	4	Tr A	–
11	56	–	1	21	40	8.5	9	527	24	9	10	524	24	3	0	7	A	–
12	49	–	–	13	41	7	7	583	22	7	7	718	23	2	0	8	A	–
13	?	–	–	1	?	6.5	7	596	18	7	7	481	18	4	0	6	Tr B	1
14	56	–	1	15	41	9	9	558	19	12	12	389	19	2	0	11	Tr B	–
	GROUP IV (without SD and closed DAB)																	
15	54	–		13	39	7	7.5	501	33	7	7	354	31	0	0	9	Tr B	2
16	59	–	3	–	mat.	9.5	10	808	21	11.5	12	613	20	0	0	8	Tr B	2
17	105	2	10	–	mat.	11	12	566	31	14	15	824	16	0	0	16	P	–
	HYPOPLASTIC LEFT HEARTS																	
1	51	–	–	3	41	0	2	335	24	10	10	578	28	4	–	–	A	
2	54	–	–	3	40	0	2	374	22	10	11	413	28	7	–	–	A	
3	50	–	–	7	41	0	1	292	16	11	11	494	23	5.5	–	–	A	
4	52	–	–	10	40	0	1	235	17	12	12	514	24	5	–	–	A	
5	52	–	1	7	41	0	3	390	24	10	10	523	27	7	–	–	A	
6	52	–	–	2	mat.	0	2	386	25	9	9	377	23	4	–	–	A	
7	50	–	–	4	mat	0	2	358	21	8	8	467	23	4	–	–	A	
8	51	–	–	3	mat.	0	1.5	600	17	11	11	913	34	5	–	–	A	
9	50	–	–	3	40	0	1	168	23	8	8	404	30	4	–	–	A	
	HYPOPLASTIC RIGHT HEARTS																	
1	54	–	–	13	44	10	10	689	21	0	9.5	605	20	4	–	–	A	
2	52	–	–	1	44	10	11	440	28	0	6	347	24	3	–	–	A	
3	47	–	–	13	40	8	9	686	19	0	5	500	19	2	–	–	A	
4	?	–	–	1	mat.	10	11	550	28	0	3	513	26	4	–	–	A	
5	60	–	7	15	34	12	14	550	21	0	8	285	15	3	–	–	Tr B	
6	61	1	–	–	40	12	12	642	26	0	7	278	16	2	–	–	Tr B	
7	51	–	–	16	mat.	11	11	630	22	0	4	322	19	3	–	–	A	

Table: Synopsis of data on internal diameters of aortic and pulmonary ostia,ascending aorta and pulmonary trunk, thickness of tunica media and packing density of its elastic fibres, configuration type of elastic fibres of tunica media of pulmonary trunk and on pulmonary vascular disease (see 'observations'). Abbreviations : mat., mature; prem., premature; ?, incomplete data; elastic fibre configuration of pulmonary trunk: A, aortic type; Tr A, transitional type A; Tr B, transitional type B; P, pulmonary adult type.

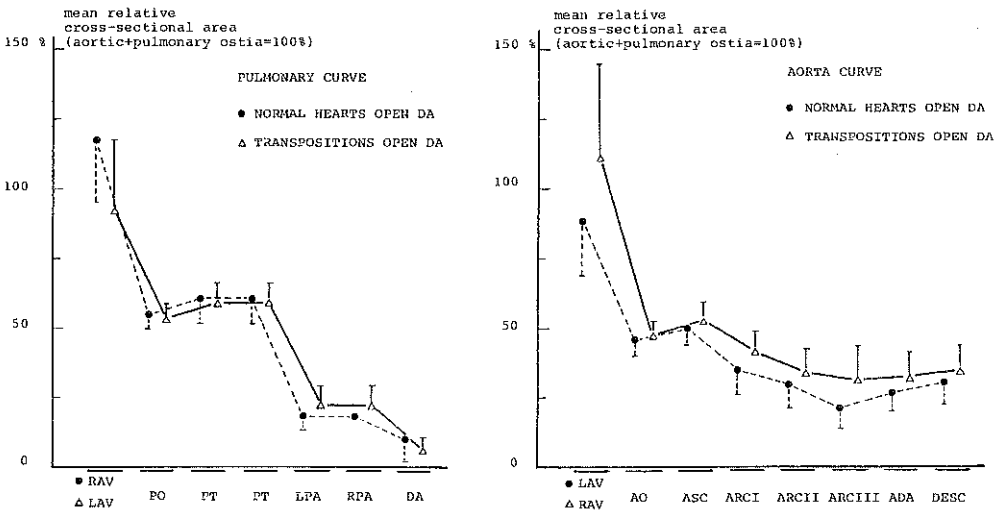

Fig.1: Relative cross-sectional areas (mean ± standard deviation) of cardiac orifices and great vessels of 11 cases of transposition of great arteries without septal defect and with open ductus arteriosus, GROUP III, (uninterrupted line). The reference material of 34 normal hearts with open ductus, GROUP I, is included (interrupted line). Abbreviations : RAV, right atrioventricular ostium; PO, pulmonary ostium; PT, pulmonary trunk; LPA, left pulmonary artery; RPA, right pulmonary artery; DA, ductus arteriosus; LAV, left atrioventricular ostium; AO, aortic ostium; ASC, ascending aorta; ARC I, aortic arch between brachiocephalic and left carotid artery; ARC II, aortic arch between left carotid and left subclavian; ARC III, aortic isthmus between left subclavian and ductus arteriosus; ADA, Aorta at connection with ductus arteriosus; DESC, descending aorta.

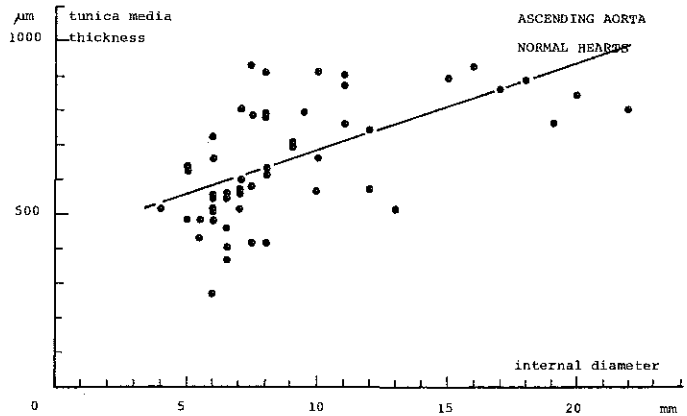

Fig.2A:Correlation between thickness of tunica media and internal diameter of ascending aorta in all 53 cases of normal hearts.

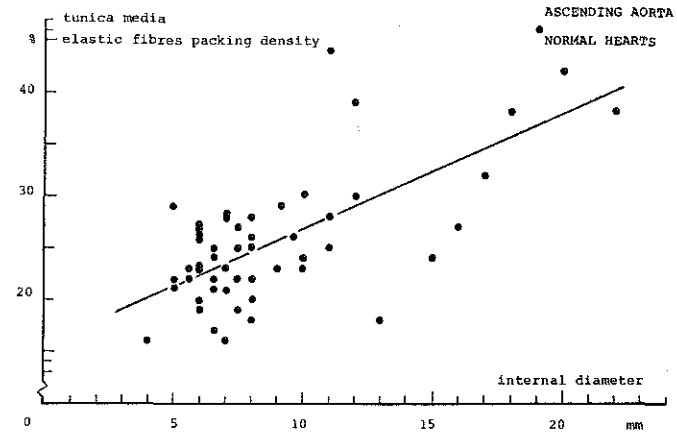

Fig.2B: Correlation between packing density of elastic fibres of tunica media and internal diameter of ascending aorta in all 53 cases of normal hearts.

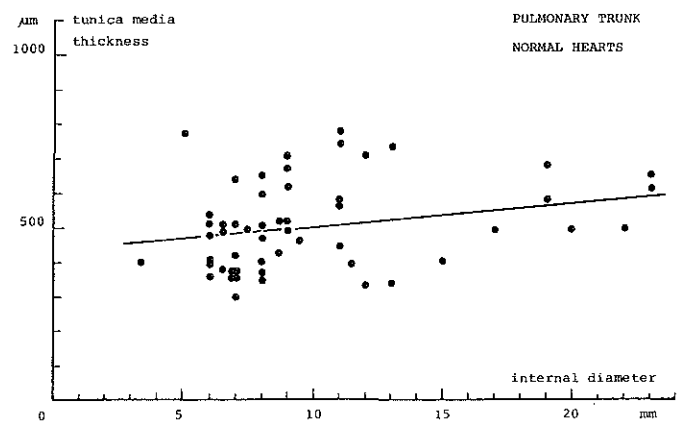

Fig.2C: Correlation between thickness of tunica media and internal diameter of pulmonary trunk in all 53 cases of normal hearts.

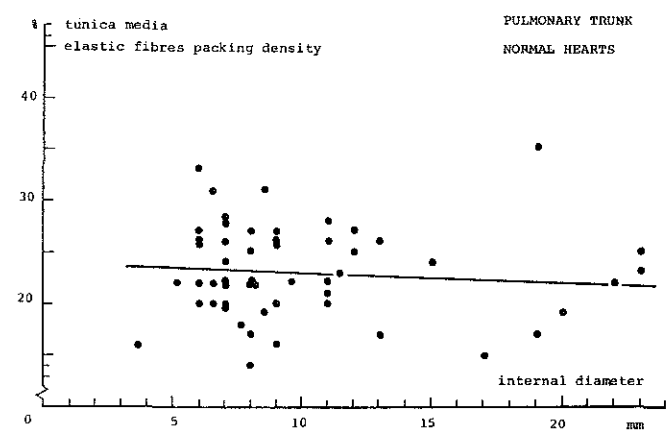

Fig.2D: Correlation between packing density of elastic fibres of tunica media and internal diameter of the pulmonary trunk in all 53 cases of normal hearts.

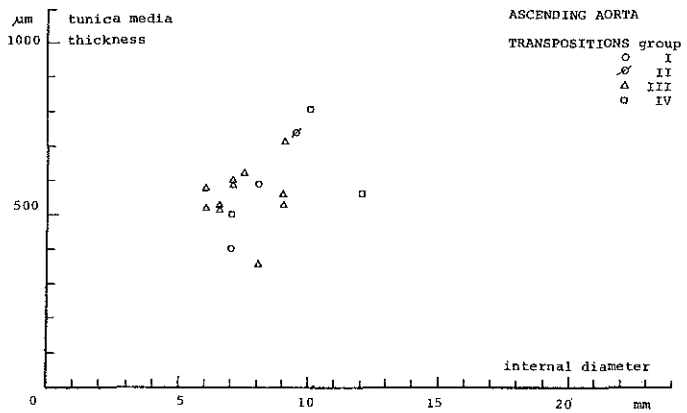

Fig.3A: Correlation between thickness of tunica media and internal diameter of ascending aorta in 17 cases of transposition of the great arteries. *

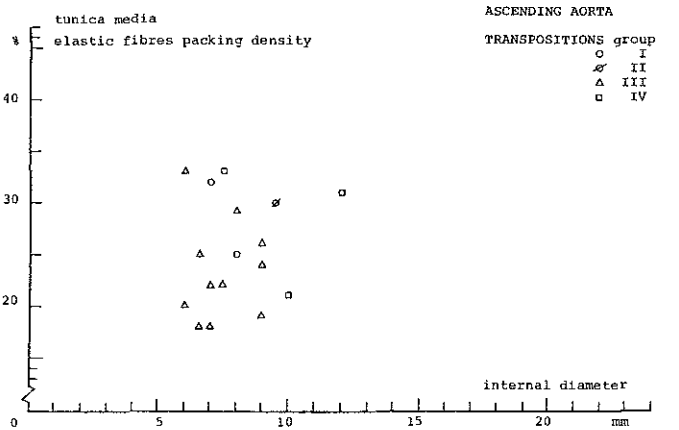

Fig.3B: Correlation between packing density of elastic fibres of tunica media and internal diameter of ascending aorta in 17 cases of transposition of the great arteries. *

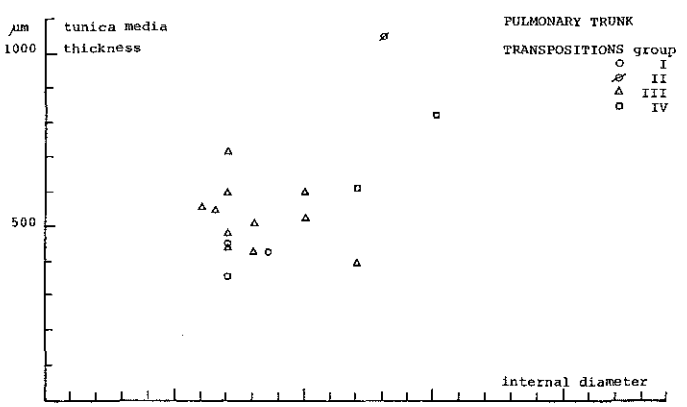

Fig.3C: Correlation between thickness of tunica media and internal diameter of pulmonary trunk in 17 cases of transposition of the great arteries. *

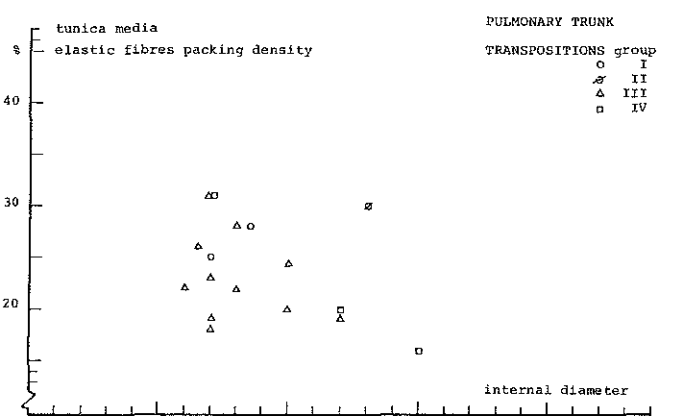

Fig.3D: Correlation between packing density of elastic fibres of tunica media and internal diameter of pulmonary trunk in 17 cases of transposition of the great arteries.

*, for definition of groups see 'observations' and Table.

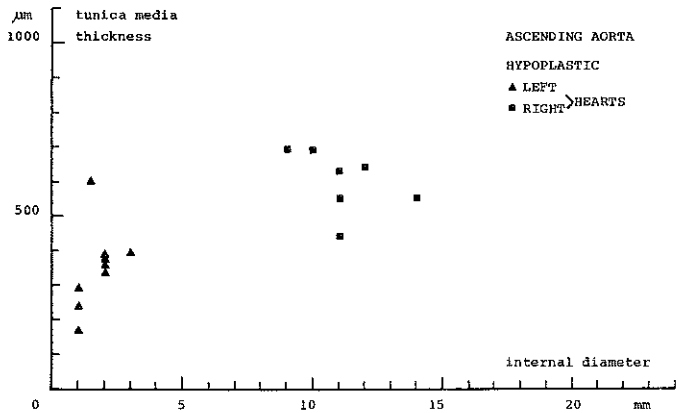

Fig.4A: Correlation between thickness of tunica media and internal diameter of ascending aorta in 9 cases of hypoplasia of the left heart and in 7 cases of hypoplasia of the right heart.

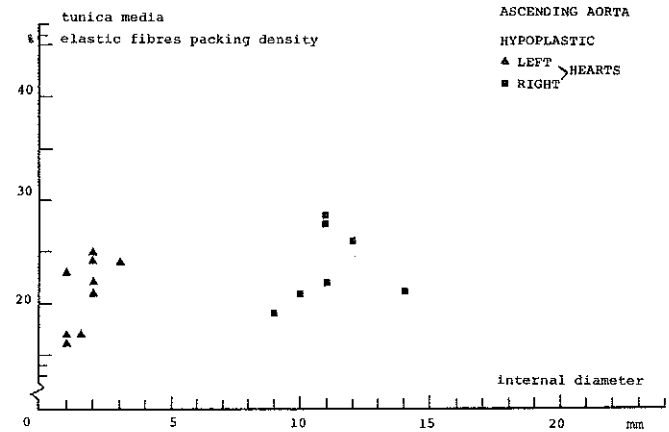

Fig.4B: Correlation between packing density of elastic fibres of tunica media and internal diameter of ascending aorta in 9 cases of hypoplasia of the left heart and in 7 cases of hypoplasia of the right heart.

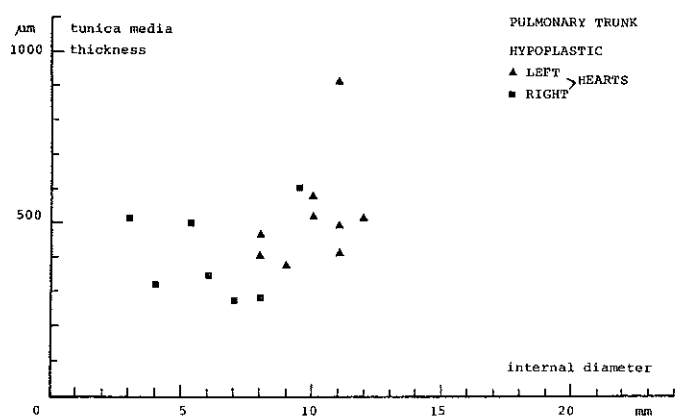

Fig.4C: Correlation between thickness of tunica media and internal diameter of pulmonary trunk in 9 cases of hypoplasia of the left heart and in 7 cases of hypoplasia of the right heart.

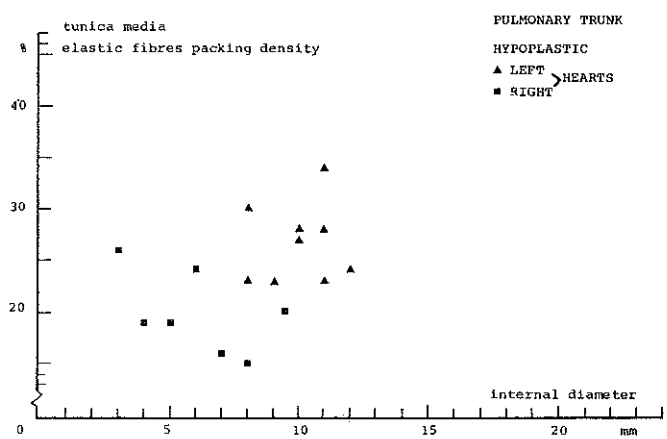

Fig.4D: Correlation between packing density of elastic fibres of tunica media of pulmonary trunk in 9 cases of hypoplasia of the left heart and in 7 cases of hypoplasia of the right heart.

provided a reference material. The possibility of abnormalities of the tunica media of the great vessels accompanying abnormal circulation was studied in two ways : the thickness of the media and the packing density of its elastic fibres were investigated.

Normal hearts. In normal hearts we noticed, in the period from birth to 15 years, in the ascending aorta a doubling of the thickness of the media and of the packing density of the elastic fibres parallelling a fourfold increase of the internal diameter. The presence of an open or closed ductus arteriosus did not seem to influence these changes. In the pulmonary trunk there were no significant changes in thickness and packing density of the elastic fibres of the media accompanying the increase of the internal diameter from 3.5 to 22 mm which occurred from birth to 15 years. This may be related to the smaller functional load on the pulmonary trunk than on the aorta under normal circulatory conditions.

Transposition of the great arteries. Before birth, in transposition of the great arteries, the circulatory condition does not seem to deviate from the normal one. After birth, however, such deviations do develop (Rudolp et al., 1961; Adams and Lind, 1957; Riggs et al., 1977; Emmanouilides et al., 1964; Rowe and James, 1957; Haworth and Reid, 1976; Berthrong et al., 1955; Ferencz, 1966 and Tynan, 1972). Pulmonary pressure does not fall to normal values and after the age of six months the function of the left ventricle which now supplies the lungs becomes abnormal : Left Ventricle End Diastolic Volume and Systolic Output exceed the normal values (Graham et al., 1971). In the cases of TGA with a ventricular septal defect these values are even higher. In the assumption that morphological adaptations to abnormal functional conditions require some time to develop, our morphological findings are in accordance with the physiological data. In the hearts from children not older than six months no abnormalities were found : the cross-sectional areas of the aorta and pulmonary trunk as well as the thickness of the media and the packing density of its

elastic fibres were also the same as in normal children of the same age. Fully in line with the assumption of a delay between the development of morphological changes and the onset of the causative functional deviations from the normal condition are the data on our two eldest cases, aged 1 year and 3 months and 2 years and 10 months respectively. Here, in the pulmonary trunk the thickness of the media, in both cases, and the packing density of its elastic fibres, in one case, were greater than in normal children of the same age.

Hypoplastic hearts. The increased functional load on the pulmonary trunk in left hypoplasia which is already present during foetal life, is accompanied by doubling of the cross-sectional area of the pulmonary ostium in combination with a comparable increase in size of the pulmonary trunk (van Meurs and Klein, 1974). The present study indicates that the increase in size of this vessel is accompanied by a marked increase of the volume of the media, since it maintains in the enlarged vessel its normal thickness in combination with a higher packing density of its elastic fibres. The comparable adaptation of the aorta in right hypoplasia appeared to be less pronounced. The doubling in size of the aorta was accompanied by changes in the media which did not give it a thickness equal to that of the aorta of the same size and the packing density of its elastic fibres does not exceed that normally present, as was observed in the enlarged pulmonary trunks.

The similar increase in size of the pulmonary trunk in left hypoplasia and the aorta in right hypoplasia were, as mentioned above, not accompanied by fully comparable changes in the media of these vessels if compared with these in normal hearts. However, comparing the pulmonary trunk in left hypoplasia with the aorta in right hypoplasia there is not only a similarity of the cross-sectional areas of both vessels but there is also similarity of the thickness of the media and of the packing density of its elastic fibres. This means, that acting as the sole arterial trunk of the functional single ventricle, both vessels are of the same construction.

The vessels with reduced or absent function, the aorta in left hypoplasia, still supplying the coronary arteries and the complete afunctional pulmonary trunk in right hypoplasia, showed dissimilar changes. In the left hypoplasia the thickness of the media of the aorta was reduced, whereas the packing density of the elastic fibres remained unchanged. In right hypoplasia both parameters remained unchanges in the pulmonary trunk. Therefore, the adaptation of aorta and pulmonary trunk to abnormally low and to absent bloodflow seems to differ markedly. This may be explained as follows. The hypoplastic ascending aorta acts as a normal artery of small size, it has pressure waves passing through it. The hypoplastic pulmonary trunk contains stagnant blood. A pressure wave out of the ductus arteriosus is followed by an immediate rise of the static pressure on the whole wall of the cul-de-sac trunk. Pressure on each part of this wall lasts longer than in a vessel with a dynamic pulsating flow. This may be the explanation of the difference between the " non " functioning aorta and pulmonary trunk in hypoplastic left resp. right heart syndromes.

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