Series Editor J.P. Shillingford

CONGENITAL HEART DISEASE

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Preface

After the allies landed on the Normandy beaches in 1944, the immediate sense of celebration was followed by an acrimonious dispute as to the overall strategy. Eisenhower favoured the advance of all the armies on a broad front. Montgomery wanted to concentrate the bulk of the allied front on a narrow front, a rapier thrust to the heart of Germany. The broad front was bound to be slow. The rapier thrust was likely to be risky, because of the attentuation of supply lines and the danger of an exposed flank.

These strategic issues were, as ever, complicated by personal ones. Montgomery's sense of his own destiny made the idea of a rapier thrust led by him particularly attractive: the idea of Patton's army advancing on a narrow front would almost certainly have seemed to him less appealing. Eisenhower, in his role as supreme allied commander, undoubtedly wanted to be seen to be fair to each of the ambitious generals under his command. If so, advance on a broad front was inevitable.

The parallels with scientific advance are striking. Inside each researcher battling to push back the frontiers in this own particular small patch is a Montgomery. Lurking within anyone involved in the distribution of rewards for scientific research is an Eisenhower, be he responsible for acceptance of papers, granting of research applications or nomination for prizes.

Where does editing a book come into this scheme of things? I suspect mainly at the Eisenhower end, though most doctors I know regard being asked to write a chapter as a penalty rather than a prize, and I certainly do not see myself as some kind of benevolent sponsor handing out laurel wreaths. In no way have I felt constrained to present the whole of a broad front; there are many exciting new areas of development, such as in non-invasive imaging, measurement and biochemical analysis, which do not appear here. My guiding principle has been to cover widely divergent *approaches* to research in paediatric cardiology, be they philosophical, as in questions of nomenclature, statistical, as in survival analysis, technological, as in interventional catheterization,

descriptive, as in fetal echocardiography, physiological, as in analysis of ventricular function and the Fontan circulation, or pharmacological, as in medical manipulation of the arterial duct. This book really belongs to the contributors, whom I can hardly thank enough for their diligence and promptness. I trust that every paediatric cardiologist will find at least one chapter which is of immediate importance and relevance.

Fergus J. Macartney

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Series Editor's Note

The last few decades have seen an explosion in our knowledge of cardiovascular disease as a result of research in many disciplines. The tempo of research is ever increasing, so that it is becoming more and more difficult for one person to encompass the whole spectrum of the advances taking place on many fronts.

Even more difficult is to include the advances as they affect clinical practice in one textbook of cardiovascular disease. Fifty years ago all that was known about cardiology could be included in one textbook of moderate size and at that time there was little research so that a textbook remained up to date for several years. Today all this has changed, and books have to be updated at frequent intervals to keep up with the results of research and changing fashions.

The present series has been designed to cover the field of cardiovascular medicine in a series of, initially, eight volumes which can be updated at regular intervals and at the same time give a sound basis of practice for doctors looking after patients.

The volumes include the following subjects: heart muscle disease; congenital heart disease, invasive and non-invasive diagnosis; ischaemic heart disease; immunology and molecular biology of the heart in health and disease; irregularities of the heart beat; and each is edited by a distinguished British author with an international reputation, together with an international panel of contributors.

The series will be mainly designed for the consultant cardiologist as reference books to assist him in his day-to-day practice and keep him up to date in the various fields of cardiovascular medicine at the same time as being of manageable size.

J.P. Shillingford
British Heart Foundation

1
The diagnosis and naming of congenitally malformed hearts

R. H. ANDERSON AND SIEW YEN HO

INTRODUCTION

Some people become very irritated with the amount of time and journal space taken up by the gurus of cardiac morphology in polemics concerning the semantics of congenitally malformed hearts. At the same time, other people, perhaps even those who object to unseemly disputations, find certain aspects of congenital heart disease difficult to understand. This is particularly so in those so-called 'complex' cases where the arrangements and relationships of the cardiac segments are not as anticipated in the normal heart. These 'complex' cases are, in reality, no harder to understand than is the morphology of the normal heart.

A combination of circumstances conspires against the universal understanding of both normal and abnormal morphology at present. The basis for analysis in the past has often been presumed knowledge of cardiac morphogenesis which, for the most part, remains speculative. A plethora of Latin terms, often compounded by alphanumeric subcategorizations, has then all too regularly been used for descriptions and classification. Definitive terms have frequently been interposed between originator and receiver when a simple descriptive phrase would have been preferable. In short, there has been an unhealthy desire to create brief and cryptic nosologies suited for 'corridor talk'. It is true that brevity is the soul of wit. In most circumstances, understanding is much more important.

It is our belief that the morphology of congenitally malformed hearts is a simple topic. It can and should be understood by all concerned with diagnosis and treatment. This is as true for the intensive care nurse or the echocardiographic technician as for the paediatric cardiologist or surgeon. Indeed, it is possibly easier for the former presently to achieve this understanding. They are less likely to be constrained by the preconceived notions and received wisdom that

prevent, in some cases, the acquisition of new ideas by the latter. In this chapter we set out concepts, derived from studies with many collaborators, which might provide the required simplicity. We discuss at the same time a number of features which may in future ease the exchange of information. Any system for diagnosis can only be as good as the words used to describe it. We start, therefore, with a plea for the abandonment of Latin terms. Instead, we recommend the substitution (at the appropriate time and place) of the vernacular equivalents. We then discuss the role of knowledge and of normal anatomy in the understanding of the abnormal. In doing so, we show how certain basic features of anatomy are retained in all hearts no matter how malformed, yet other prominent features of malformed hearts have no counterpart in the normal. Finally, we summarize a system of sequential segmental analysis which permits any heart, no matter how severely malformed, to be described logically and succinctly, even if it has never been encountered before.

USE OF LATIN TERMS

In bygone years it could reasonably be argued that Latin provided a common language for scientific discourse. Nowadays there is little doubt that English has become the universal language. More and more journals of national societies are being published in English. It makes sense, therefore, to discontinue the use of Latin terms such as abound in the vocabulary used for congenital heart malformations. The rewards of this enterprise in terms of style and syntax can be great. How many know that the plural of 'ductus' is 'ductus' (a fourth declension Latin noun)? The plural of 'duct' is self-evidently 'ducts'! How many know the correct plural of 'vena cava'? When this term is used as an adjective, does the user stop to think whether flow (for example) is venous or hollow (cava = hollow)? In other words, are we more correct in describing 'caval venous' or 'vena caval' flow? Over and above this, there are good scientific reasons for discontinuing the use of Latin. The 'atrioventricularis communis' defect is more readily understood on the basis of the defective atrioventricular septation underscoring this group of lesions. Is not 'common arterial trunk' more readily understood than 'truncus arteriosus'? The conservative may find this approach unpalatable and argue that many Latin words have already become assimilated into the English language. True. But mostly they have been adopted in anglicized form. The beauty of the English language is its electicism. We can continue this process by substituting good Anglo-Saxon synonyms and translations in paediatric cardiology.

NORMAL VERSUS ABNORMAL CARDIAC ANATOMY

Study of malformations of the heart requires a thorough understanding of normal cardiac anatomy. At the same time, overzealous application

of principles derived from study of the normal can in some circumstances produce difficulties in the description of abnormality. As an example, take the group of lesions variously described as 'endocardial cushion defects' or 'atrioventricular canal malformations'. These hearts are unified because of a deficiency of atrioventricular septation[1]. To understand this, it is necessary to have precise knowledge of the extent of the normal atrioventricular septum. This points to the need for knowledge of the normal. Thereafter it is also necessary to consider the effects of abnormal septation on the rest of the heart. The usual anatomy of the atrioventricular septal defect itself must then be taken as the norm. Thus, the left valve in these hearts bears scant resemblance to a normal mitral valve beyond its residence in the morphologically left ventricle. Yet the substrate for regurgitation across this valve has almost universally been described in terms of a 'cleft mitral valve'. Only when it is appreciated that morphologically the structure is *not* a mitral valve can its function be understood and the valve be appropriately repaired[2]. The principle to be adduced from this example is that analysis should start with a thorough knowledge of normal anatomy. Thereafter, features of normality are used in descriptions of abnormal hearts as far as they can be applied with accuracy. Whenever this proves impossible, the abnormal hearts should be described in terms of their own intrinsic features rather than instituting Procrustean remedies.

The morphological method

The cornerstone of analysis of any malformed heart is the establishment of the nature, connections and relationships of the different chambers and structures within each of the cardiac segments[3]. This we describe in our section devoted to sequential analysis (see below). Fundamental to this approach is the principle introduced by Lev[4] and dubbed by Van Praagh[5] the 'morphological method'. In simple terms, structures must be analysed in terms of their own intrinsic morphology. This means that parts of a given chamber or artery which are inconstant cannot be used as criteria for identification. Inherent in the morphological method, therefore, is also the need to identify the segments or 'building blocks' of the heart.

The pioneering studies of Van Praagh and his colleagues[6] identified the three basic cardiac components, namely the atrial chambers, the ventricular mass and the arterial trunks (Figure 1.1). We follow this division precisely, but find it desirable to give a secure definition to the middle segment, the ventricular mass, which is lacking in the approach of Van Praagh *et al.*[6] We define this part of the heart as extending from the atrioventricular to the ventriculo-arterial junctions. The myocardial mass thus delimited is an anatomical whole and functions electrically as a single unit. It is separated from the atrial muscle mass by the fibro-fatty atrioventricular tissue planes at all points around the

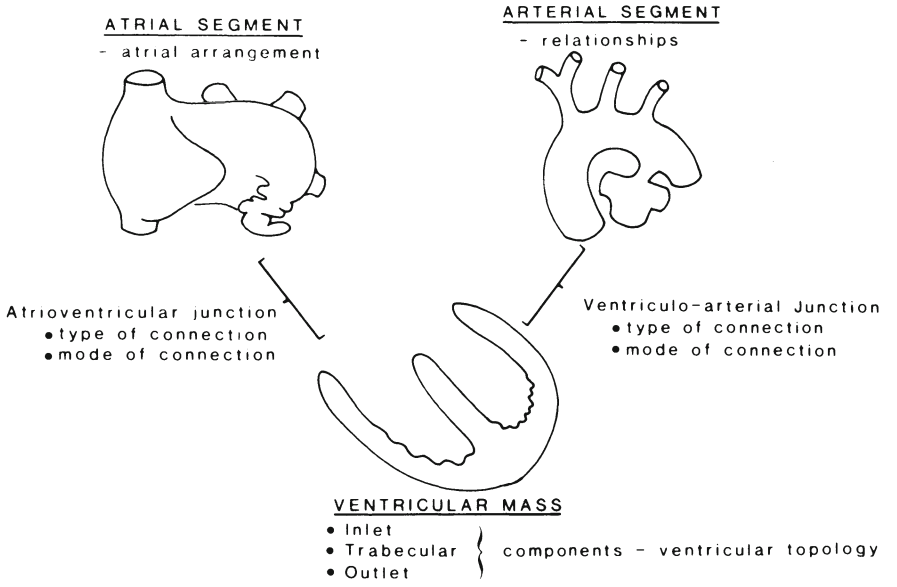

Figure 1.1 Diagram of the three basic cardiac segments

junction except at the site of penetration of the atrioventricular conduction axis. Its distal extent is limited by the semilunar attachments of the sinuses of the arterial valves (in part to ventricular muscle and in part to the fibrous cardiac skeleton). By defining the ventricular mass in this fashion we avoid the need to introduce further segments (the atrioventricular canal and conus) as suggested more recently by Van Praagh[7]. These additional parts are an integral part of the ventricular mass as here defined and can readily be described as such.

In most hearts the ventricular mass possesses two cavities, which conventionally are described as 'ventricles'. These ventricles do not always possess all the parts found in the normal heart. The ventricular mass may rarely be composed of a solitary chamber. More frequently one or other of the ventricles is variously rudimentary or supernormal. A system of ventricular subdivision must therefore be devised which accounts for all known varieties of ventricles irrespective of whether they are or are not connected to the atrial chambers and the arterial trunks, respectively. Here the 'morphological method' comes into its own. The connections or non-connections of the ventricles to the adjacent segments cannot be taken into account when naming the ventricles, since they themselves are the most significant variables. Indeed, the time-honoured convention of dividing a ventricle into inflow and outflow is disqualified by the morphological method. An inflow tract, or 'sinus', is conventionally defined as the part of the ventricle containing the atrioventricular valve. The outflow tract is usually de-

scribed as the 'conus'[6]. Such a system founders irretrievably when applied to one particular variety of heart with two ventricles. This is the case with one ventricle connected to both atria and both arterial trunks and the other ventricle connected to neither an atrial chamber nor an arterial trunk (Figure 1.2). To cater for this and other abnormal arrangements, it is preferable to consider ventricles as having three

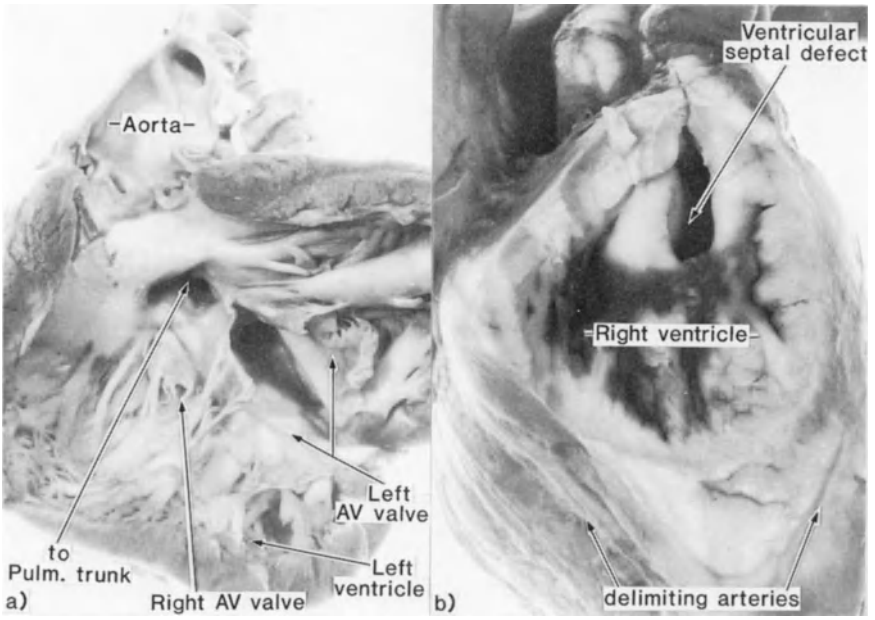

Figure 1.2 A specimen with both arterial trunks arising from a morphologically left ventricle which has a double inlet atrioventricular connection: (a) is a left ventricular view and (b) shows the rudimentary right ventricle which is a trabecular pouch

basic components. These are the inlet, apical trabecular and outlet portions (Figure 1.3). In the normal heart with two normal ventricles it is not possible to draw with precision the boundaries between these parts. In rough terms, nonetheless, it is possible to recognize that the inlet component extends from the atrioventricular junction to the distal attachments of the tension apparatus of the atrioventricular valve. Similarly, the outlet component can be recognized in broad terms as the region supporting the semilunar attachments of the arterial valve. The apical trabecular component is then recognized as the third part by exclusion of the other two.

When considered in this fashion, the apical trabecular component (unrecognized when ventricles are divided into 'sinus' and 'conus') is the most constant part of a ventricle irrespective of how abnormal it may be. Furthermore, it is the nature of this apical component which

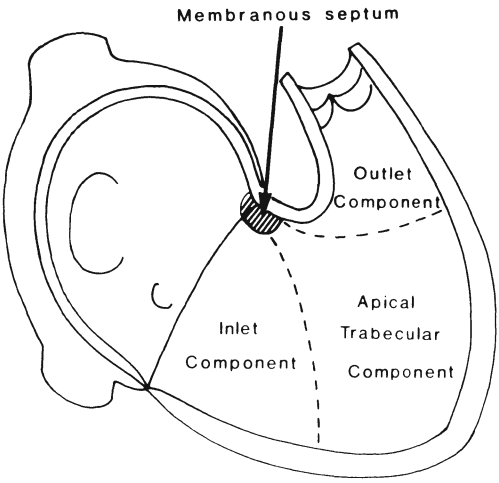

Figure 1.3 Diagram of the tripartite ventricular septum

most readily differentiates a morphologically right from a left ventricle, being coarsely trabeculated in one and fine in the other (Figure 1.4). All varieties of biventricular hearts (hearts with two chambers in their ventricular mass) are then readily described according to the way in which the inlet and outlet components are shared between the apical trabecular parts. In doing this, note should be taken that one or other inlet or outlet portion may be totally lacking in some hearts with so-called atrioventricular or arterial valve atresia (Figure 1.5). When considered in this light, it can readily be seen that the 'ventricle proper' of Van Praagh is not the 'sinus' but is the apical trabecular component. The 'atrioventricular canal' and 'conus' defined by Van Praagh[7] are directly comparable with the ventricular inlet and outlet components respectively. In short, by recognizing the extent of the ventricular mass anatomically and by dividing it according to the morphological method, it is possible to construct a simple tripartite template within the three segmental model of the heart[6] which accounts for all known types of abnormal ventricle.

Fully to describe such abnormal ventricles it is then necessary to account for their morphology according to the pattern of the apical trabecular component; for their component make-up; for their relationships and finally for their size. All of these are mutually independent features. In the context of morphology, it should be noted that almost always ventricles in congenitally malformed hearts are of right or left ventricular type and almost always they coexist. Very rarely, however, hearts are encountered having a solitary ventricle. Sometimes these hearts are of right or left ventricular morphology, the complementary ventricle being so tiny as to be unrecognizable. More fre-

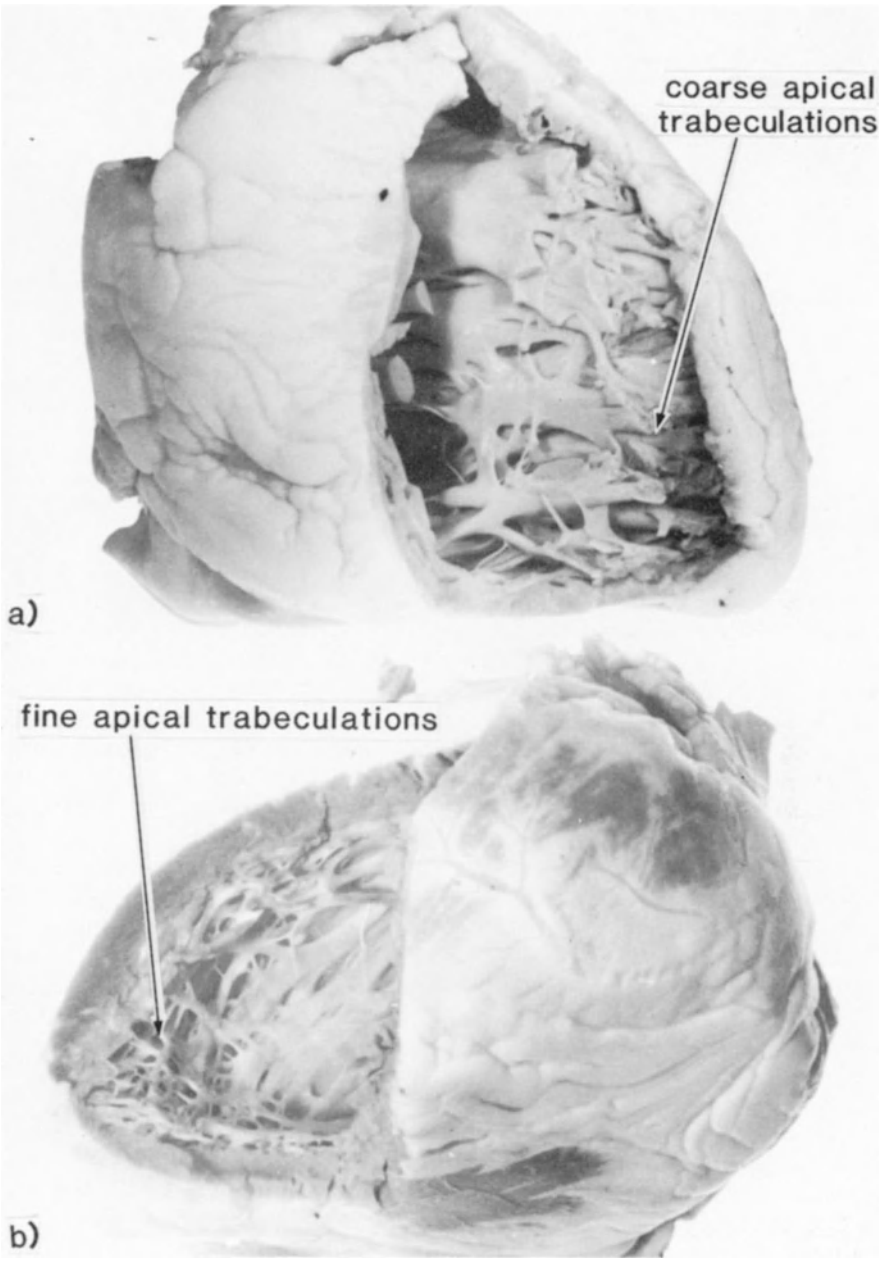

Figure 1.4 Dissections of the ventricular apices: (a) shows the coarse apical trabeculations of the right ventricle in contrast to the fine trabeculations of the left ventricle (b)

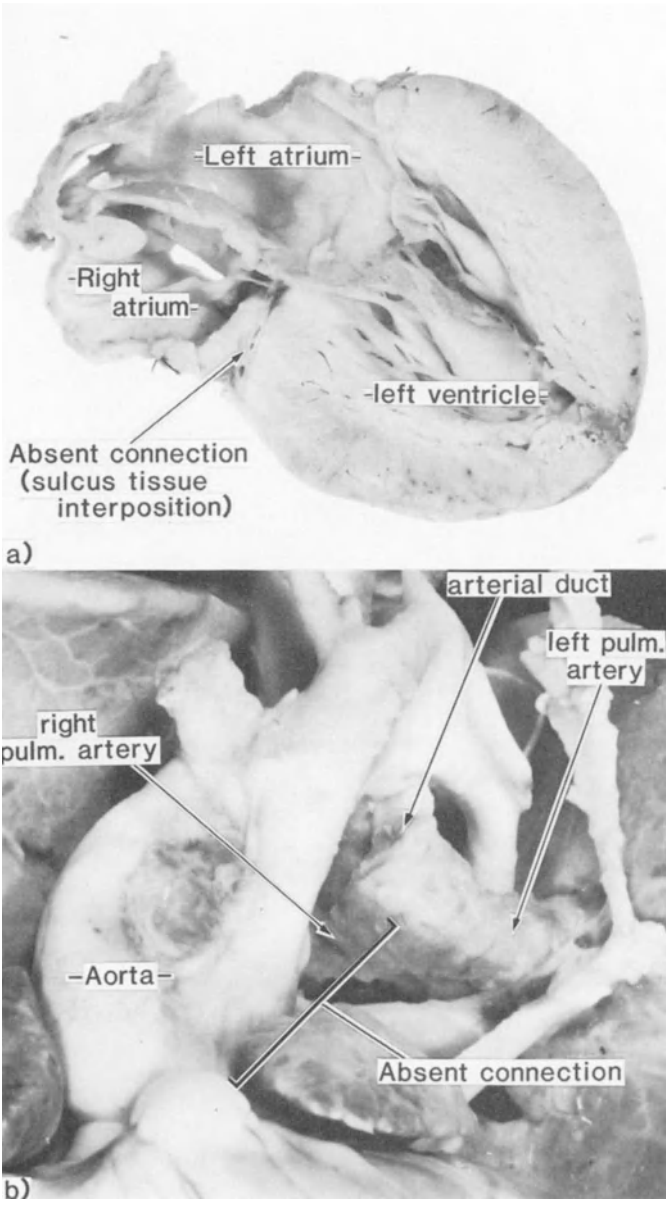

Figure 1.5 A heart with 'tricuspid atresia' and another with 'pulmonary atresia' showing the absent connection in each: (a) is a long axis section illustrating the muscular floor of the right atrium: (b) shows the pulmonary arteries supplied via a duct from the aorta and absence of the intrapericardial pulmonary trunk

quently the solitary ventricle is of neither right nor left ventricular morphology and possesses no apical septum. The apical trabecular component of these ventricles is most distinct, being coarser than a morphologically right ventricle and being criss-crossed by one or more large trabeculations. Such solitary ventricles are of indeterminate morphology (Figure 1.6).

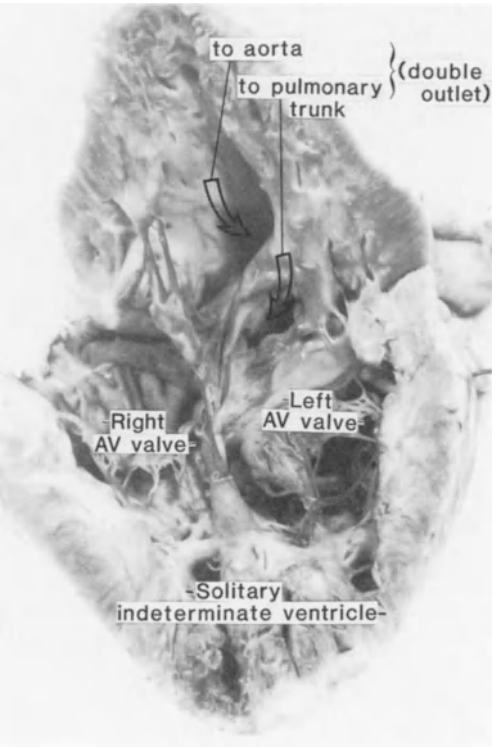

Figure 1.6 A specimen with double inlet solitary and indeterminate ventricle opened like a clam

When the atrial segment of the heart is considered in a fashion analogous to that described above for the ventricles, it is immediately evident that variable components are themselves ruled out as hallmarks for identification. In this way we exclude the great veins (frequently anomalously connected) and the atrial septum (frequently absent) as markers of morphological rightness or leftness. All that remains are the atrial appendages. These are the most constant parts of the atria. Their morphology readily permits atrial differentiation (Figure 1.7). The morphologically right atrium has a characteristic triangular shape with a broad junction with the venous component. The junction is

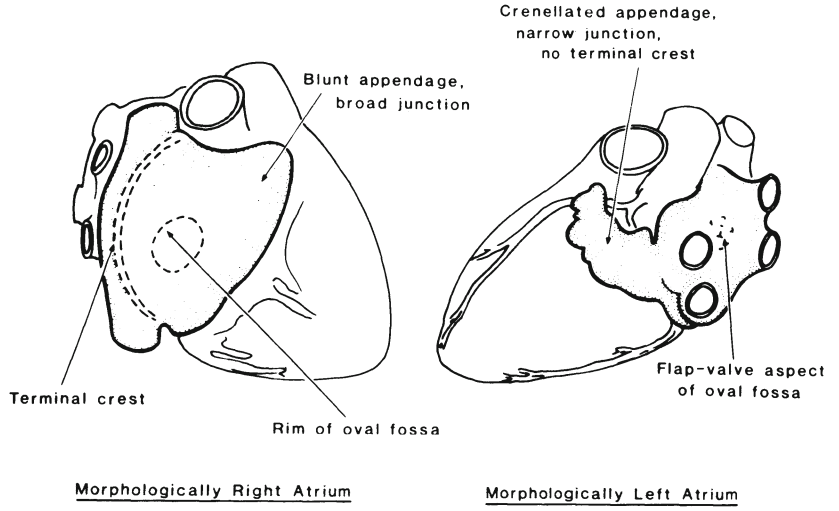

Figure 1.7 Diagrams showing the different morphological features between right atrium and left atrium

marked internally by the terminal crest and externally by the terminal groove. The morphologically left atrium has a narrow and convoluted shape with a constricted junction with the venous component which is not marked by a terminal crest or groove.

When we turn our attention to the third cardiac segment, the arterial trunks, the morphological method is found to be of less help in distinguishing the types of trunk (Figure 1.8). This is because the great arteries have no constant intrinsic differentiating feature. Rather they are recognized according to their branching pattern which is more-or-less variable. Fortunately the varieties of branching are rarely (if ever) severe enough to prevent distinction of an aorta from a pulmonary trunk from a common arterial trunk. In simple terms, the aorta gives off the coronary arteries followed by the systemic arteries. The pulmonary trunk does not normally give rise to coronary arteries and usually branches into its two major components. A common arterial trunk exits from the heart through a single arterial valve and branches immediately into coronary, pulmonary and systemic arteries. There are certain lesions which conspire to defeat these criteria, such as anomalous origin of the coronary arteries from the pulmonary trunk or origin of one pulmonary artery from the aorta. These are hardly, if ever, found in combinations such as to make differentiation impossible. One arrangement does rule out positive identification of an arterial trunk. This is when a solitary great artery supplies the coronary and systemic arteries in absence of any intrapericardial pulmonary arteries (pulmonary blood supply then almost always being supplied through major systemic–pulmonary collateral arteries but rarely through bi-

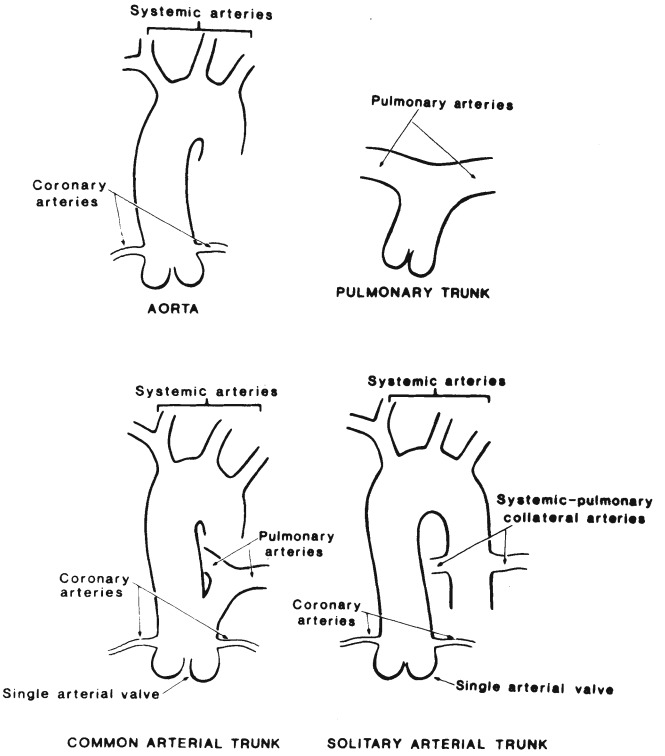

Figure 1.8 A diagram showing the four types of arterial trunk

lateral ducts). In this circumstance the only solution which is both simple and accurate is to label the trunk as a solitary arterial trunk.

Cardiac septation

Most of the simple cardiac malformations, which themselves account for the majority of congenital cardiac lesions, are either communications between the cardiac segments ('septal defects') or else stenoses along the systemic or pulmonary flow pathways. A sound knowledge of the normal septal structures is a prerequisite for complete understanding and accurate naming of septal defects. Surprisingly few textbooks of either anatomy or paediatric cardiology give the necessary information.

The atrial and ventricular chambers are separated by three rather than two septal structures. As may be anticipated, there is an atrial and a ventricular septum. The third septal structure is the atrioventricular septum. This has two components in the normal heart, the muscular and membranous portions. They exist because of two important

features of normal anatomy. These are the off-setting of the proximal septal attachments of the atrioventricular valves (Figure 1.9) and the deeply-wedged position of the subaortic outflow tract (Figure 1.10). Because of the valvar off-setting, the distal portion of the right atrial myocardium is separated from the left ventricular inlet to give the muscular atrioventricular septum. Because of the wedged position of the subaortic outflow tract, the supratricuspid component of the membranous part of the septum is separated from the left ventricular outlet component by the atrioventricular membranous septum. Deficiencies of these parts of the normal septum give rise to a particular group of lesions variously termed 'atrioventricular canal malformations' or 'endocardial cushion defects'. It makes more sense to label them for what they are – atrioventricular septal defects[1].

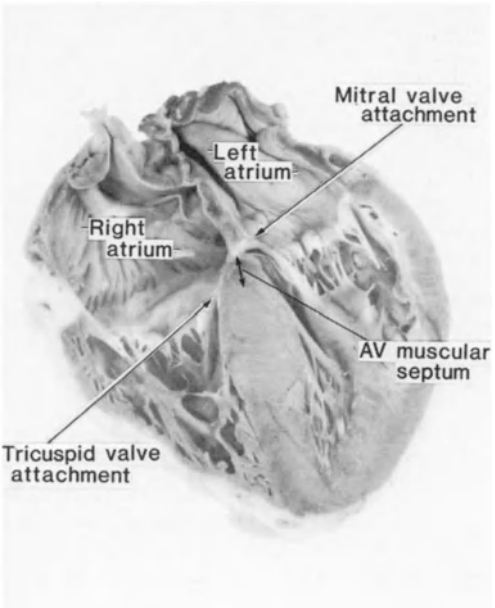

Figure 1.9 A long axis four chamber section showing the off-setting of the septal attachments of the tricuspid and mitral valves

When the adjacent parts of the atrial chambers are dissected, it is found that the interatrial septum is much less extensive than it seems at first sight (Figure 1.11). The area of true septum is confined to the oval fossa and its immediate environs. True atrial septal defects can exist only within this area, and are best termed oval fossa defects. Various other lesions can produce the facility for interatrial shunting of blood even though they are not defects within the atrial septum

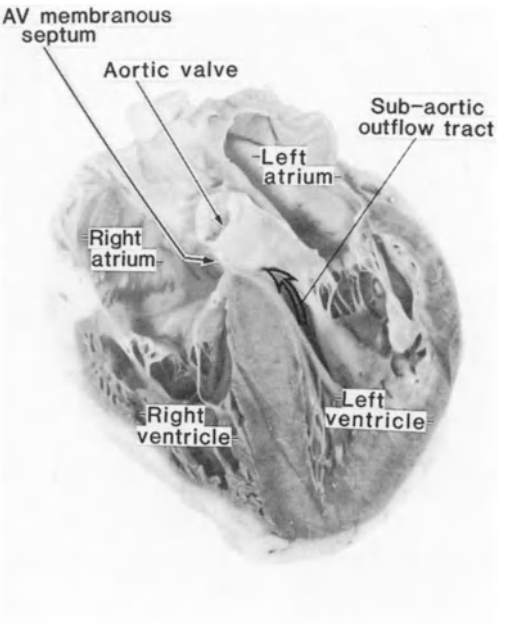

Figure 1.10 A long axis section taken anterior to Figure 1.9 showing the subaortic outflow tract in wedged position

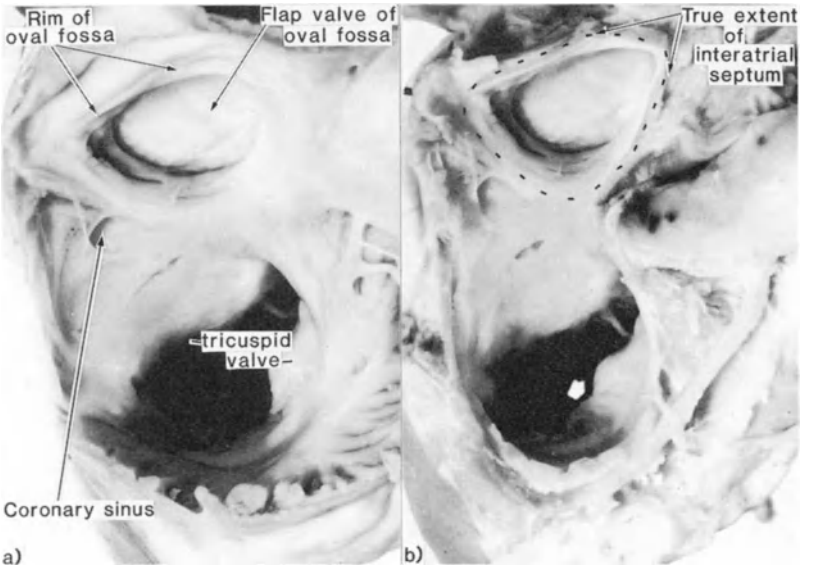

Figure 1.11 Dissections into the right atrium showing the true extent of the interatrial septum. The apparently extensive septum is displayed in (a). The true interatrial component is the flap valve of the oval fossa and its immediate rim as shown in (b).

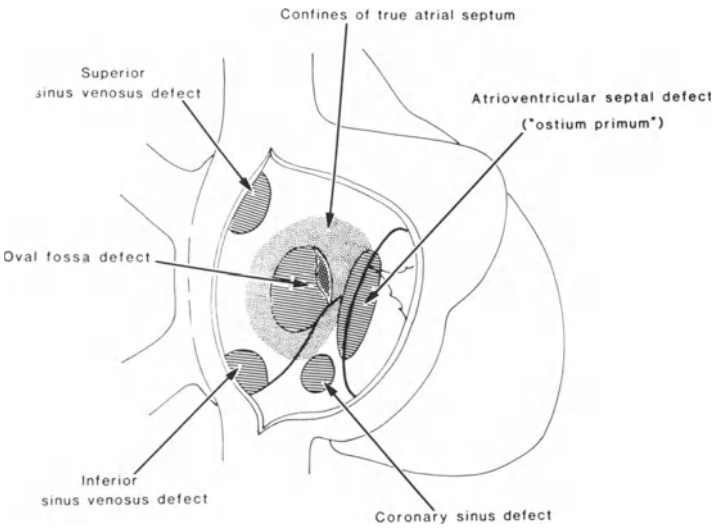

Figure 1.12 A diagram showing the types of interatrial communications. Only the oval fossa defect is within the true atrial septum

(Figure 1.12). Although more accurately termed 'interatrial communications', these lesions will almost certainly continue to be called 'atrial septal defects'. It is important to understand their true nature, however, so as accurately to identify them with cross-sectional echocardiography. The so-called 'ostium primum defect' unequivocally provides an interatrial communication. It does so through an atrioventricular septal defect by virtue of the atrioventricular valve leaflets being depressed into the ventricular mass and attached to the crest of the ventricular septum. The sinus venosus defect provides the potential for interatrial shunting either because a caval vein or else the right pulmonary veins are connected to both right and left atrial chambers, thus producing an 'extracardiac' interatrial conduit (Figure 1.13). The final defect permitting interatrial communication outside the confines of the atrial septum is at the orifice of the coronary sinus. This is possible when the 'party wall' between the left atrium and the sinus is eroded – the so-called unroofing of the coronary sinus.

The morphology of the interventricular septum is also different from what would be expected from a casual examination of its right ventricular surface (Figure 1.14). The extent of the atrioventricular septum has already been described. It is at the outlet, however, where the deception is greatest. At first sight the subpulmonary outflow tract would seem to have an extensive septal component. We have previously described it in this fashion. In reality, the pulmonary valve is supported on a sleeve of exclusively right ventricular myocardium. In the normal heart at least, the outlet septum is an insignificant structure

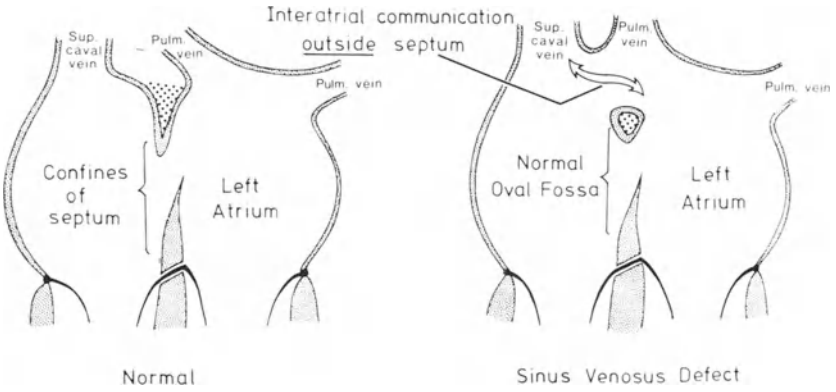

Figure 1.13 Diagrams showing the position of the sinus venosus defect which is outside the interatrial septum

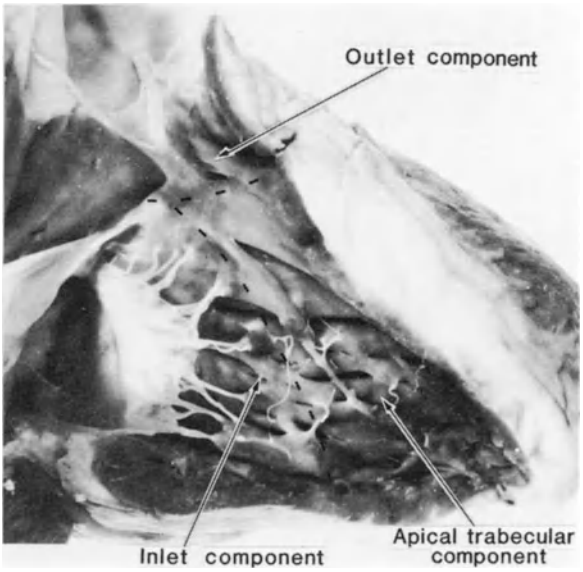

Figure 1.14 The normal right ventricle opened to show the apparent extent of the interventricular septum

(Figure 1.15). Furthermore, when viewed from its right side, the inlet component of the septum seems considerable, extending from the proximal attachment of the septal leaflet of the tricuspid valve to its distal chordal attachments (Figure 1.14). But, because of the wedge position of the subaortic outflow, the septum in part separates the right ventricular inlet from the left ventricular outlet. It is an inlet–outlet septum (Figure 1.16). These peculiarities of configuration must

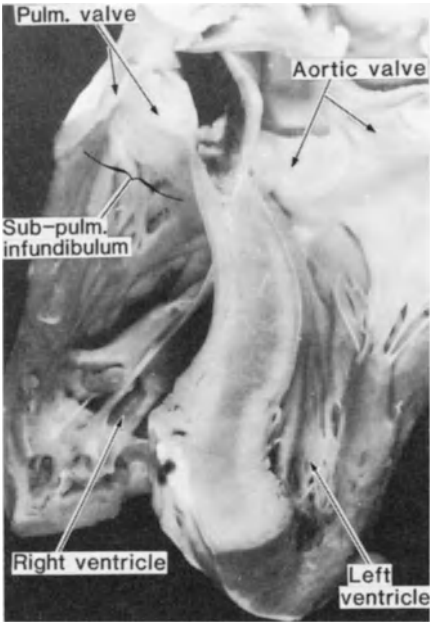

Figure 1.15 A dissection of the subarterial outflow tracts in the normal heart showing the pulmonary valve supported on a small sleeve of ventricular myocardium

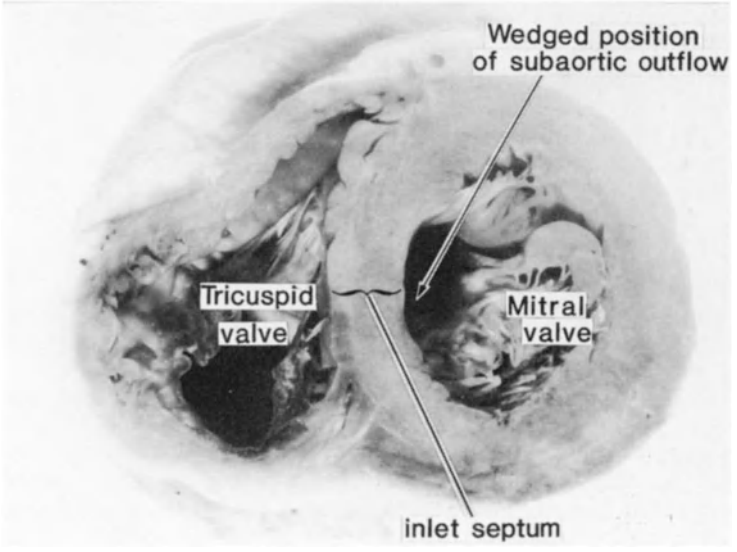

Figure 1.16 A short axis section through the ventricular mass showing the inlet valves and the wedged position of the left ventricular outflow tract

be kept in mind when describing interventricular communications. In this respect, 'interventricular communication' is strictly a more accurate term than 'ventricular septal defect'. It is highly unlikely, however, that the latter term will pass from the vocabulary! Communications between the ventricles can be divided into two basic types: those which abut on the area of the central fibrous body and those which have completely muscular borders. The latter are universally termed muscular defects and can be subdivided according to whether they are located within the inlet, apical trabecular or outlet parts of the muscular septum or whether they are central. Muscular defects can also be multiple and, when occupying the apical septum, these are termed Swiss cheese defects. The defects which abut directly on the central fibrous body are more difficult to name. Traditionally they have been called 'membranous defects', but the membranous part of the septum (notably the atrioventricular component) is intact in their presence. They exist because of a deficiency of the muscular septum *around* the area of the membranous septum. For this reason, we prefer to call them perimembranous defects. They can be subdivided according to the major area of the muscular septum which is deficient. Often the deficiency is considerable all round the radiating point of the membranous septum. This gives a confluent defect. Alternatively, the septum may be eroded postero-inferiorly to permit shunting primarily between the inlet components, or in the antero-cephalad direction to produce a communication mostly between the outlets. Very rarely the deficiency may be slit-like and extend towards the apex giving a perimembranous communication between the trabecular components.

There is then a third specific type of ventricular septal defect produced when there is deficiency of the outlet septum immediately beneath the arterial valves. These structures are then in fibrous continuity in the roof of the defect. This particular type of outlet defect is doubly committed and subarterial. It can extend to become perimembranous. Alternatively, it can have a muscular postero-inferior rim if the septomarginal trabeculation of the right ventricle fuses with the ventriculo-infundibular fold so as to separate the tricuspid and aortic valves. Combining these features gives a relatively simple categorization of 'isolated' ventricular septal defects (Table 1.1). If the feature of malalignment of septal structures is added, the categorization then caters for many other contingencies, notably tetralogy of Fallot. In this respect it should be noted that the extensive outlet septum which is manifest in lesions such as tetralogy and double outlet right ventricle (Figure 1.17) has no counterpart in the normal heart. Furthermore, in double outlet right ventricle both outlets are committed to the right ventricle. In this setting it makes no sense to speak of an outlet defect in the sense of a defect between the outlets. Rather the defect itself is the outlet from the left ventricle. In terms of its relationship to the right ventricular outlets, it may be subaortic, subpulmonary, doubly committed or non-committed[8]. When viewed from the right ventricle,

Table 1.1 Categorization of 'isolated' ventricular septal defects

Type of defect	*Communication between*	*Other features*
Perimembranous	Inlet components	Malalignment of septal components
	Trabecular components	
Muscular	Outlet components (or Confluent)	
Doubly committed and subarterial		Muscular postero-inferior rim Extends to become perimembranous

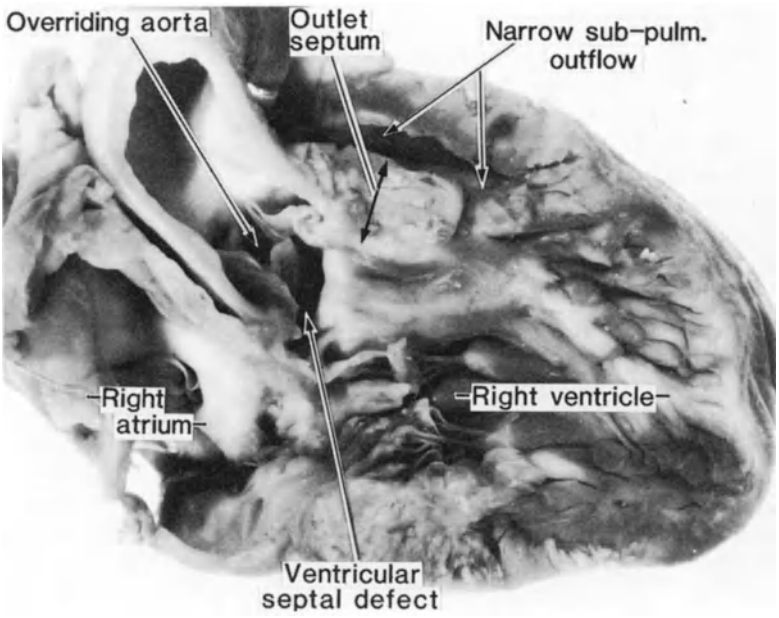

Figure 1.17 The subpulmonary outflow tract of tetralogy of Fallot showing the well-defined outlet septum

however, it may have completely muscular rims or be perimembranous.

It is pertinent at this point to consider the naming of the prominent muscular structures within the outflow tract of the right ventricle. The normal right ventricular outflow tract differs markedly from that of the left ventricle since it is a complete muscular structure. Part of this muscular cone separates the tricuspid valve from the pulmonary valve in the roof of the ventricle. It has traditionally been termed the supraventricular crest (crista supraventricularis). Indiscriminate description of other structures using the term 'crista' has markedly devalued this

usage in the cardiological literature. Furthermore, the arrangement seen in the normal right ventricle rarely exists in hearts with abnormal ventriculo-arterial connections. For these reasons, we have preferred to distinguish separately the various components making up the normal outflow tract. Almost all the supraventricular crest is made up of the inner heart wall between tricuspid and pulmonary valves. We name this tissue the ventriculo-infundibular fold. It, or its analogue, can be found in the roof of ventricles of any morphology. Previously we thought the outlet (infundibular) septum made up a significant part of the normal supraventricular crest. Now we appreciate that the normal outlet septum is a relatively insignificant and indistinct structure. Nonetheless, a much better formed outlet septum can exist in hearts with abnormal ventriculo-arterial connections or in the presence of a ventricular septal defect. In all these situations (and irrespective of its size) we define the outlet septum as the muscular structure separating the subarterial outflow tracts. There is then a further muscular structure which requires attention. This is the extensive trabeculation of the morphologically right ventricle which branches at the base of the normal heart to embrace the supraventricular crest. It also extends apically, crossing the cavity of the right ventricle as the moderator band. We name this structure the septomarginal trabeculation (Figure 1.18). In both normal and abnormal hearts a series of smaller trabeculations spring from the anterior surface of this marginal trabeculation and extend to the parietal wall of the right ventricle. These are the septoparietal trabeculations[9].

The atrioventricular valves

Adequate description and diagnosis of congenitally malformed hearts requires a knowledge of the morphology of both normally structured and abnormal atrioventricular valves. The atrioventricular valves are complex structures with several components. They are made up of (or incorporate) part of the atrial myocardium, the fibro-fatty atrioventricular tissue plane, the leaflets, the tendinous chords, the papillary muscles and part of the ventricular myocardium[10]. It is conventional to describe the valves of the morphologically right and left ventricle as the tricuspid and mitral valves respectively. It is often less easy to distinguish them as having three and two leaflets. Indeed, it has been suggested that the mitral valve has four leaflets[11]. Distinction depends upon the definition of a leaflet. Following the precedent of the Toronto investigators[12], most would define a leaflet as the segment of valve skirt between two commissures. A commissure is then defined as the division in the skirt supported by a prominent fan-shaped chord found atop a more-or-less constantly positioned papillary muscle. In this way, the paired left ventricular papillary muscles dictate two commissures and two leaflets in the mitral valve. The leaflets are of markedly dissimilar size and shape (Figure 1.19). The 'anterior' leaflet

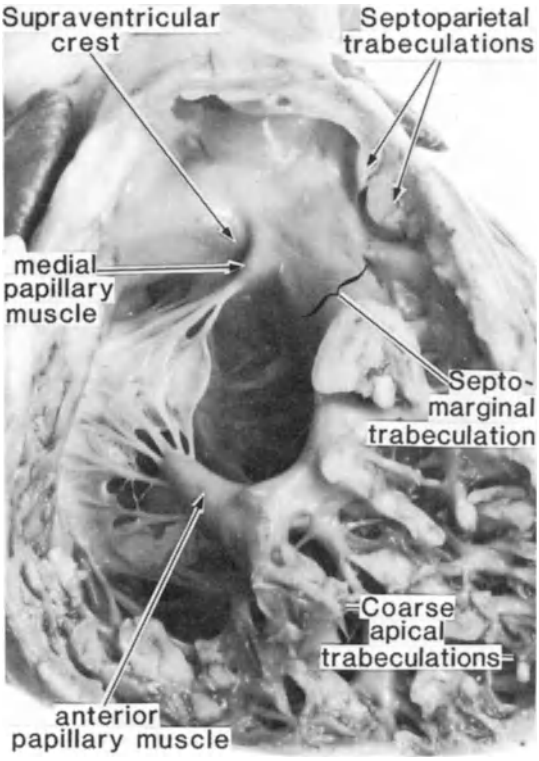

Figure 1.18 A dissection of the right ventricle in a normal heart showing the septo-marginal trabeculation which clasps the supraventricular crest

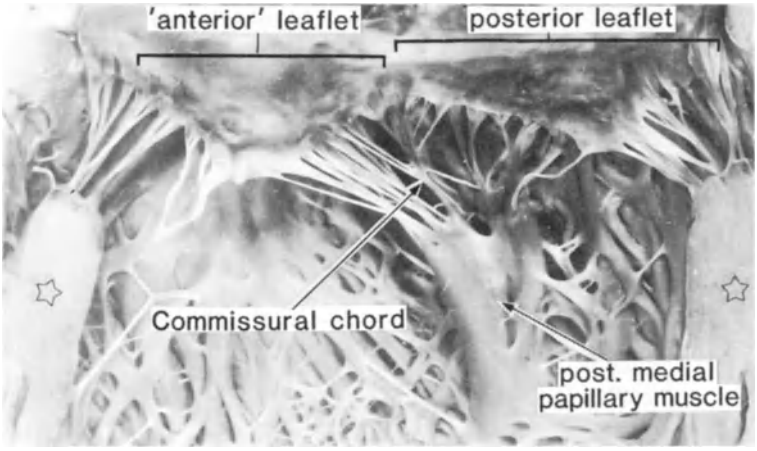

Figure 1.19 The mitral valve displayed following longitudinal dissection of the antero-lateral papillary muscle (*) and separation of the two halves

is square and occupies one third of the annular circumference. It is better referred to as the aortic leaflet. This is because it is always in fibrous continuity with the aortic valve in the normal heart but is rarely a directly anterior structure. The other leaflet has less depth but occupies two thirds of the annular circumference. It is accurately described as the mural leaflet. The three leaflets of the tricuspid valve, extending between commissures supported by medial, anterior and inferior papillary muscles, are well described as the septal, antero-superior and inferior or mural leaflets respectively (Figure 1.20).

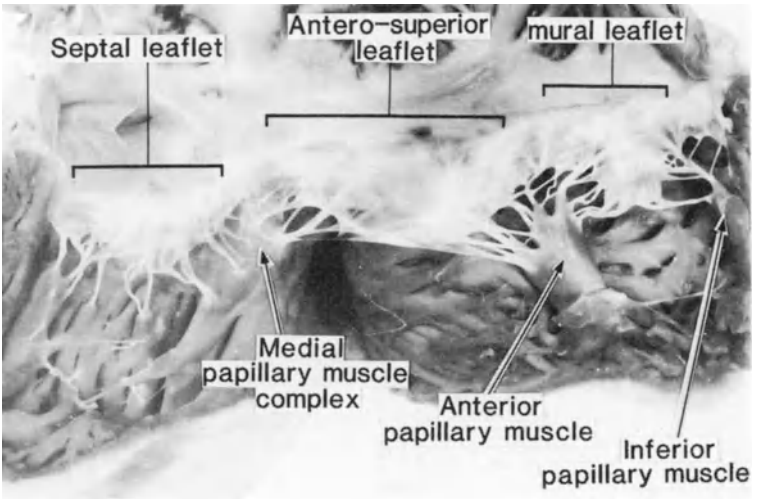

Figure 1.20 The three leaflets of the tricuspid valve

The number of leaflets, however, is neither an easy nor an accurate feature to determine so as to distinguish the mitral and tricuspid valves. A better feature in the normal heart is the more apical attachment of the tricuspid valve to the atrioventricular septum than that of the mitral valve. This feature loses its value in several malformed hearts, such as those possessing perimembranous ventricular septal defects[13]. In our experience the feature which most reliably distinguishes a mitral from a tricuspid valve is the presence or absence of chordal attachments to the ventricular inlet septum. The morphologically tricuspid valve always possesses such attachments; the morphologically mitral valve hardly if ever (Figure 1.9). The presence or absence of such septal attachments serves to distinguish morphologically mitral from morphologically tricuspid valves in the majority, but not all, of cases with double inlet atrioventricular connection. They also serve to distinguish the morphologically right from the morphologically left components of many common atrioventricular valves. In most other respects the morphologically left component of a common valve bears

scant resemblance to a mitral valve, particularly when found in the setting of an atrioventricular septal defect[14, 15]. For this reason, we prefer to distinguish right and left valves (or right and left components of a common valve) in an atrioventricular septal defect rather than tricuspid and mitral valves. On balance it is also probably more accurate to describe right and left valves in hearts with univentricular atrioventricular connection, although the morphologist at least can distinguish tricuspid or mitral morphology of most of these valves when he examines a heart.

The arterial valves

The concept of the atrioventricular valve 'complex' is well established[10]. It is less well established that the arterial valves also have a complex arrangement, albeit less marked than in the atrioventricular valves. The major components are unequivocally the leaflets which meet in semilunar fashion[16]. Rarely are the three normal leaflets of equal size[16, 17]. Equally significant in normal function of the valve are the aortic sinuses and the subvalvar outflow tract. The interleaflet subvalvar triangles are particularly complex in the left ventricle (Figure 1.21). In both ventricles, the commissures of the valves extend well above the extent of the ventricular septum, this being significant in the setting of infectious endocarditis or aneurysm of the aortic sinuses[18].

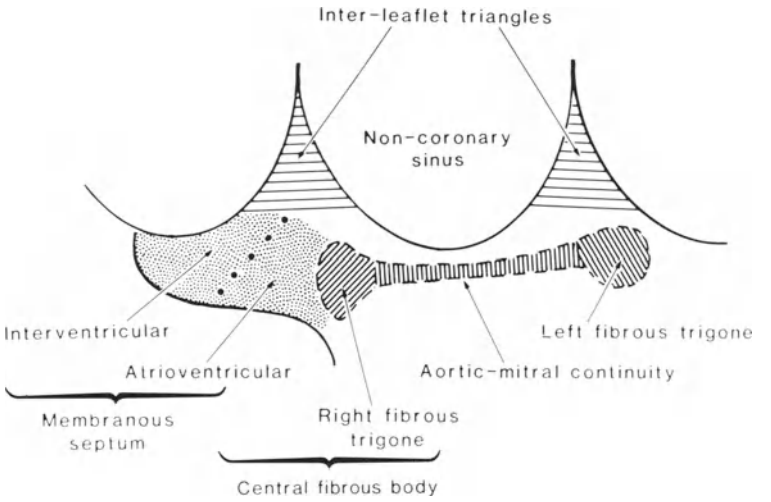

Figure 1.21 Diagrammatic representation of the subaortic region showing the interleaflet triangles and their relationship to the non-coronary leaflet and the fibrous trigones of the mitral ring

SEQUENTIAL SEGMENTAL ANALYSIS

The philosophy and morphology described and discussed in the previous sections set the scene for the most important process in the diagnosis of congenitally malformed hearts. This is to determine the arrangement, connections and relationships of the three cardiac segments. Although the majority of congenitally malformed hearts have the usual arrangement and connections of the cardiac structures, these features cannot be presumed. They must be proved. Thus, the process of sequential segmental analysis adds rigour to the diagnosis of all cases, be they complex or simple. The approach is first to determine the arrangement of the atrial chambers. Then an analysis is made of the atrioventricular and ventriculo-arterial junctions. Finally, all associated malformations are catalogued, including an anomalous position of the heart itself.

Atrial arrangement

All hearts possess two atrial chambers, even when the atrial septum is lacking so that there is a common atrium. It is always possible to recognize two atrial appendages (except in the exceedingly rare circumstances when one is absent). As described above, it is the appendage anatomy which determines the morphological rightness or leftness of a given atrium. Thus, there are only four possible arrangements of the atria: usual (solitus); mirror-image (inversus); right isomerism and left isomerism (Figure 1.22). Ideally, these arrangements should be determined directly from examination of the atrial appendages. This is possible for the morphologist and the surgeon but rarely feasible for the physician. The physician must turn to other techniques and hence infer the atrial arrangement. The most accurate means of achieving this are either examination of bronchial morphology (Figure 1.23) or determination of the arrangement of the abdominal great vessels relative to the spine in short axis sections (Figure 1.24). Inference according to the arrangement of the abdominal organs is much less accurate. Nonetheless, generally speaking, right atrial isomerism accompanies asplenia while left atrial isomerism usually goes with polysplenia. The two isomeric arrangements are usually part of the syndrome of visceral heterotaxy. From the standpoint of the heart, however, it is important to commence sequential segmental analysis by determining the precise atrial arrangement rather than splenic status.

The atrioventricular junction

Fully to analyse this junction it is necessary to know the atrial arrangement and the morphology and topology of the ventricular mass. Knowing this, it is then possible to determine the type and mode of atrioventricular connection. By the types of connection, we mean the fashion

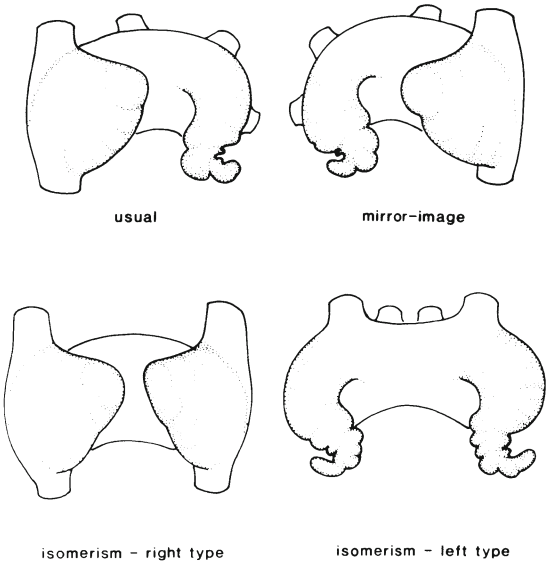

Figure 1.22 Diagrammatic representations of the four types of atrial arrangement

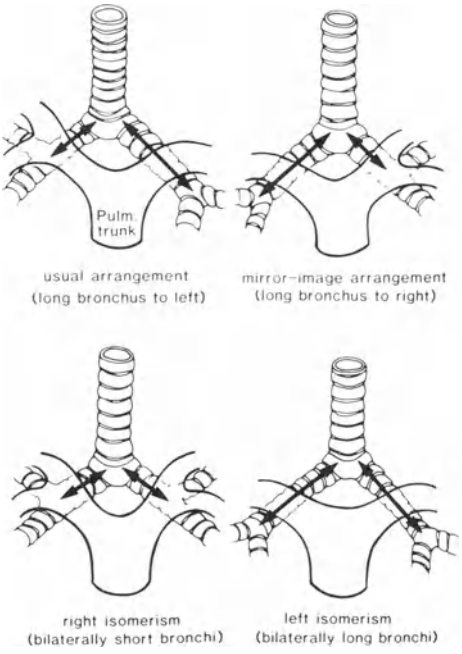

Figure 1.23 The bronchial morphology which allows inference of the different patterns of atrial arrangement

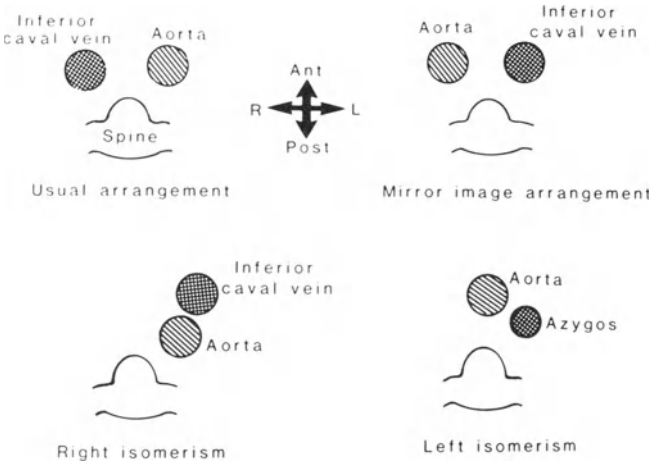

Figure 1.24 Diagrammatic representations of the different arrangements of the abdominal vessels relative to the spine as detected by cross-sectional echocardiography

to which the atrial myocardium is, or is not, connected to the ventricular myocardium at the atrioventricular junction. By mode of connection, we mean the morphological arrangement of the valves which guard the atrioventricular junction. Also important is the relationship of the ventricles to one another within the ventricular mass.

The type of atrioventricular connection is conditioned by the arrangement of the atrial chambers and the morphology of the ventricular mass. Although there are four atrial arrangements, these can be grouped into lateralized (usual and mirror-image) and isomeric forms. In terms of the connection of the atrial to the ventricular myocardium, two further groups can be distinguished. The first exists when both atrial chambers are connected to their own ventricle (biventricular atrioventricular connections). The second is found when the atrial chambers connect to only one ventricle (univentricular atrioventricular connection). Each of these groups encompasses three specific types of connection. The first two connections in the biventricular group can exist only in hearts with lateralized atria. These are the concordant and discordant ones (Figure 1.25). A concordant atrioventricular connection exists when lateralized atrial chambers (usual or mirror-image) connect with mutually appropriate ventricles. When the atria each connect with mutually inappropriate ventricles, then the type of connection is discordant. In this respect it should be noted that when Van Praagh and his colleagues used the adjectives 'concordant' and 'discordant'[19], they applied them to the presence of harmony or discord between the atrial and ventricular segments of the heart. Thus, if both the atrial and ventricular segments were usually arranged, or both had a mirror-image arrangement, atrioventricular concordance was said to

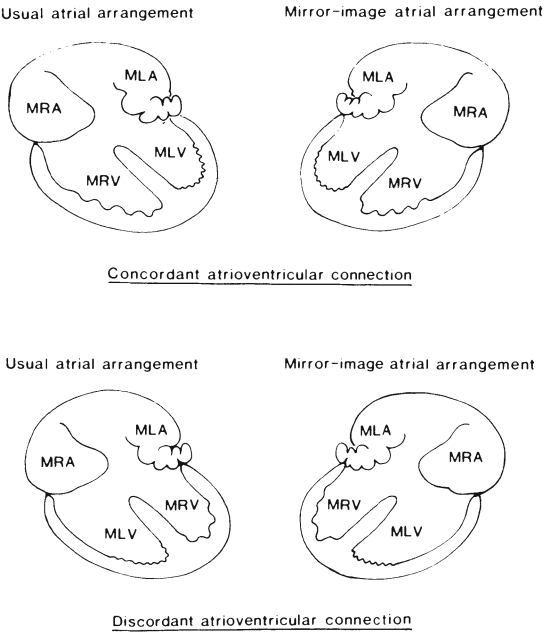

Figure 1.25 Diagrams showing concordant and discordant atrioventricular connections in association with usual or mirror-image atrial arrangement

be present. This was so irrespective of the type of atrioventricular connection. It was Kirklin and his colleagues[20] who refined this system by applying the adjectives to the connections themselves rather than to the congruency of the segments. Congruency of the segments goes along with the given connection in most instances. Thus, almost without exception, cases with a concordant atrioventricular connection have a congruent topology of the atrial and ventricular segments. In contrast, cases with a discordant atrioventricular connection have unlike arrangements of the atrial and ventricular segments. Van Praagh and his colleagues[21] initially described ventricular topology in terms of 'looping'. They subsequently expanded this concept[22] to show how the topological arrangement of the ventricular mass could be likened to the way the palmar surface of the observer's hand could be placed on the septal surface of the morphologically right ventricle. This procedure was performed with the thumb in the inlet, the wrist in the apical trabecular component and the fingers in the outlet (Figure 1.26). We prefer this latter approach. We therefore describe ventricular topology in terms of right-hand and left-hand patterns. The patterns of topology are particularly important in hearts with isomeric atrial arrangement and a biventricular atrioventricular connection (Figure 1.27). Such a connection of necessity can be neither concordant nor discordant. It is

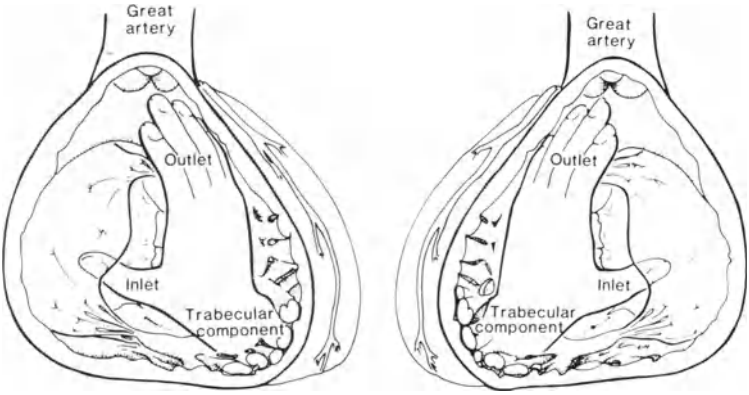

Figure 1.26 The concept of topological arrangement of the ventricular mass

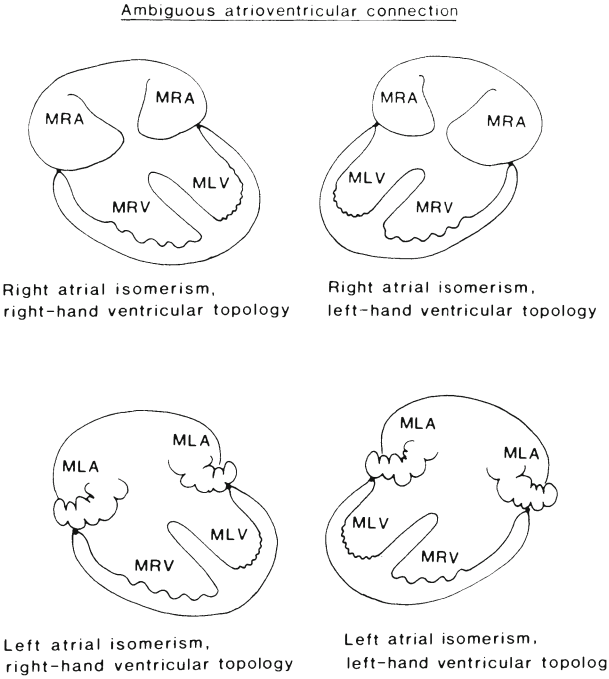

Figure 1.27 In hearts with isomeric atrial arrangement and a biventricular atrioventricular connection the ventricular topology can be described as either left-hand or right-hand pattern

ambiguous. But ambiguous atrioventricular connections, as thus defined, can be found with right or left atrial isomerism and with right-hand or left-hand ventricular topology. Hence, fully to describe the atrioventricular junction in these instances, it is necessary to specify atrial arrangement, type of atrioventricular connection and ventricular topology. In the case of concordant or discordant atrioventricular connections, the ventricular topology can be presumed to be congruent with the atrial arrangement unless specifically stated to be otherwise. Cases with discongruency are exceedingly rare. One example would be usual atrial arrangement with a concordant atrioventricular connection and left-hand-pattern ventricular morphology.

The second group is made up of those hearts with a univentricular atrioventricular connection. These are less frequent than those with a biventricular atrioventricular connection, but, like the former group, can be produced by one of three specific types of atrioventricular connection. These are double inlet, absent right or absent left atrioventricular connection. All three can be found with any atrial arrangement and can be found with the atrial chambers connected to a morphologically right, a morphologically left or a solitary and indeterminate ventricle (Figure 1.28). Hearts with double inlet left ventricle have conventionally been considered to be the exemplar of 'single ventricle'. This is despite the fact that almost all examples of this lesion possess two ventricles. This convention of defining 'single ven-

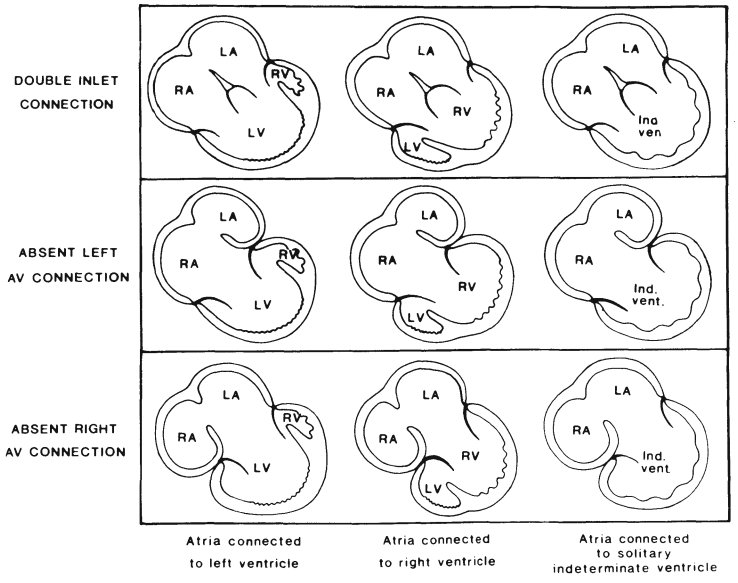

Figure 1.28 A diagram showing the combinations of atrioventricular connection and ventricular morphology which make up the univentricular atrioventricular connection

tricle' in terms of double inlet has led to much confusion[21, 23–25]. The solution to the 'single ventricle trap'[26] is simply to avoid using 'single ventricle' or 'univentricular heart' for description of hearts possessing two ventricles. Double inlet left or right ventricle can be described as such, and so on. There is no need to produce confusion by introducing an illogical convention concerning singularity of the ventricular mass.

Further confusion surrounds the categorization of mitral and tricuspid atresia in terms of a univentricular heart or a univentricular atrioventricular connection. Very few examples of atrioventricular valve atresia have solitary ventricles. In contrast, most do possess a univentricular atrioventricular connection. This is because the usual substrate for atrioventricular valve atresia is total absence of the atrioventricular connection. This should be distinguished from the rare variant produced by an imperforate valve membrane (Figure 1.29). The latter may or may not be an example of a univentricular atrioventricular connection. It can coexist with concordant, discordant, ambiguous or double inlet connections. The double inlet variant with imperforate valve gives a univentricular connection.

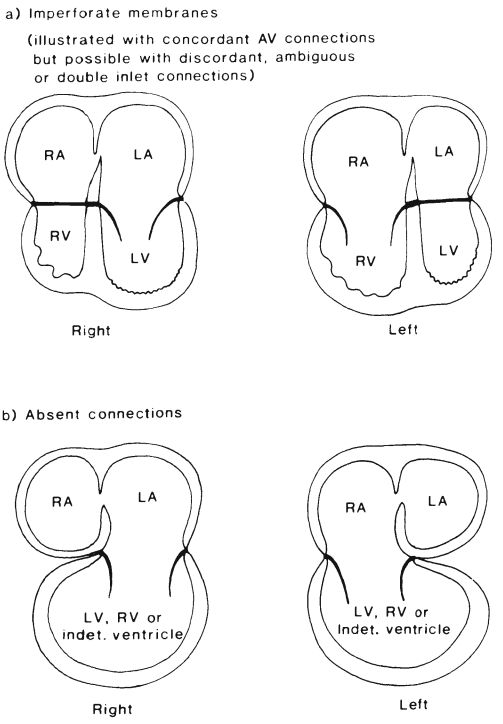

Figure 1.29 Diagram showing the morphological differences between an imperforate valve membrane and absent connection in atrioventricular valve atresias.

In all these settings, the arguments that have concerned the singularity of the ventricular mass in hearts with univentricular atrioventricular connection[5, 23–26] should not obscure the significance of the relationship of a rudimentary ventricle (if present) in determining the morphology of the dominant ventricle. Ideally, the ventricular morphology should be determined according to the pattern of the apical trabecular components. Sometimes this is not possible in a clinical setting. Advantage can then be taken of the fact that, almost without exception, rudimentary right ventricles are found in antero-superior position while rudimentary left ventricles are located postero-inferiorly. Rudimentary ventricles of either type can be to the right or the left of the dominant ventricle. Fully to describe the atrioventricular junction, therefore, it is necessary to specify the atrial arrangement, the type of atrioventricular connection, the morphology of the ventricular mass and the relationship of the dominant and rudimentary ventricles (if present).

Mode of atrioventricular connection

This feature accounts for the morphology of the valves which guard the atrioventricular junction. For example, a concordant atrioventricular connection can coexist with the junction guarded by two atrioventricular valves or a common valve. The common valve, if present, is a mode of connection. Different modes of connection can also exist in the presence of two valves. Thus, one of the valves may be imperforate, as may the right or left component of a common valve. Equally, the chords of one or both valves may straddle through a ventricular septal defect, as may the chords of part of a common valve. Straddling and imperforateness, therefore, are further modes of connection. The final mode is perhaps more significant, since it may condition the type of connection. This is the presence of overriding of an atrioventricular annulus. The valve overrides when its leaflets are attached to the ventricles on both sides of the ventricular septum. The precise degree of override determines the type of connection present. This is because we assign overriding valves, in terms of the connection, to the ventricle connected to the greater part of the overriding annulus – the 50% law[20]. In the presence of an overriding valve, therefore, there is either univentricular (double inlet) or biventricular (concordant, discordant or ambiguous) atrioventricular connection: the precise type of connection varying according to the morphology of the chambers connected together. The type of connection really does change according to the degree of override of the valve: the ventricular morphology does not.

Ventricular relationships

It has been explained how ventricular topology is an independent variable from the atrioventricular connection, although almost always

there is congruency between the two. The relationship between two ventricles is a further variable, and has many more degrees of freedom. Nonetheless, in general terms, the morphologically right ventricle is right-sided and anterior when there is right-hand ventricular topology, whilst it is left-sided and anterior (or side-by-side) with left-hand topology. Variations in ventricular relationships for a ventricular topology underscore the malformations described as 'criss-cross' hearts or supero-inferior ventricles[27]. In the criss-cross lesion, there is rotation of the ventricular mass along its long axis so that the morphologically right ventricle is no longer in its anticipated position for the given topology and connection present. Supero-inferior ventricles exist when the ventricular mass is tilted along its long axis. The terms indicate no more than the presence of an unexpected ventricular relationship. They give no information concerning the type and mode of atrioventricular connection, although overriding valves frequently coexist with supero-inferior ventricles.

Ventricular relationships are more variable when there is a univentricular atrioventricular connection. Thus, rudimentary ventricles can be right-sided or left-sided be they of morphologically right or left type. As discussed, however, the antero-superior and postero-inferior relationships are much more constant and help markedly in determining the morphology of the dominant ventricle. Rudimentary left ventricles in our experience have always occupied a postero-inferior position (in the hip pocket of the ventricular mass). In contrast, rudimentary right ventricles are always carried antero-superiorly on the shoulder of the dominant left ventricle, even though on occasions the apical trabecular component may 'point' posteriorly.

The ventriculo-arterial junction

Analysis of this junction proceeds in the same way as for the atrioventricular junction. Thus, we account separately (using mutually exclusive terms) for the type and mode of ventriculo-arterial connection, for the morphology of the ventricular outlet components and for the relationship of the arterial trunks.

There are four possible types of ventriculo-arterial connection. Concordant and discordant connections exist when the great arteries are connected to their morphologically appropriate or inappropriate ventricles, respectively. Double outlet ventricle exists when more than half of both great arterial valves are connected to the same ventricle, which may be of right, left or solitary and indeterminate morphology. Single outlet of the heart is diagnosed when only one arterial trunk can be traced to make contact with the ventricular mass. The solitary trunk may also be a common trunk, supplying directly the systemic, coronary and pulmonary arteries through a common arterial valve. Alternatively, it may be a solitary aorta or pulmonary trunk when the other arterial trunk is atretic and cannot be traced to make contact with a

ventricle. When there is complete absence of the intrapericardial pulmonary arteries, it may not be possible to distinguish a common trunk from a solitary aorta. In this situation, therefore, we simply describe the presence of a solitary arterial trunk. With the first three types of connection (concordant, discordant and double outlet) the ventricular origins of the arterial trunks are, of necessity, fixed. This is not the case with single outlet. Whatever the morphological nature of the solitary trunk, it may override the septum and have a balanced connection or may be predominantly or exclusively connected to a right, left or indeterminate ventricle. In the presence of a single outlet, therefore, it is always necessary additionally to code the precise ventricular connection of the trunk.

The modes of ventriculo-arterial connection are strictly limited in comparison to those found at the atrioventricular junction. Since a common valve exists only with a common trunk, this is not a mode of connection. Since an arterial valve has no tension apparatus, it cannot straddle. Thus, the only options are for one of two valves to be imperforate or for one or both valves to override. The degree of override of a solitary valve will be accounted for when describing the connection of the solitary trunk. An imperforate valve results in pulmonary or aortic atresia in the setting of concordant, discordant or double outlet connections. It is to be distinguished from arterial valve atresia in the setting of single outlet of the heart. Overriding arterial valves form a spectrum between double outlet and either concordant or discordant ventriculo-arterial connections in a manner which is directly comparable to overriding atrioventricular valves. The 50% rule is used to determine the connection present just as at the atrioventricular junction.

Considerable emphasis has traditionally been placed on the ventricular outlet components (the 'conus') as a marker of ventriculo-arterial connections. This is generally overvalued. Any outlet morphology can exist with any ventriculo-arterial connection. Furthermore, the presence or absence of a completely muscular subarterial infundibulum is a bagatelle in comparison to the significance of precise description and diagnosis of the connection. Nonetheless, for completeness it is often necessary to describe infundibular morphologies. The options are a complete subpulmonary infundibulum, a complete subaortic infundibulum, a bilaterally complete infundibulum or bilaterally deficient infundibular structures.

Similar emphasis has been placed on the relationships of the great arteries as the marker of the ventriculo-arterial connection (the 'loop rule'). It is now generally accepted that the significance of this relatively inaccurate marker has been greatly overemphasized. But arterial relationships do remain a significant feature. We take note of the interrelationships of the aortic and pulmonary valves in terms of right–left and anterior–posterior co-ordinates. We also describe (when appropriate) the pattern of the arterial trunks, which may be spiral or parallel.

Almost without exception, the aortic arch curves over the bifurcation of the pulmonary trunk. We have now seen, however, three well-documented examples of a pulmonary trunk running superiorly to the aortic arch.

Associated malformations

Analysis of the atrial chambers and the cardiac junctions builds the 'flow template' of the heart. In the majority of patients seen clinically this flow template will be normal. In the cases coming to autopsy, however, a significant proportion will have abnormal chamber arrangements and connections[28]. It is always important, therefore, to carry out full sequential segmental analysis in order to prove normality. This cannot be assumed. Thereafter, it is equally important to document all the associated malformations. In this respect we again find it helpful to examine the heart sequentially, and we have constructed an extensive code to account for the myriad possibilities at each level of the heart[29]. Only by conducting analysis in this fashion is it possible to account for the almost infinite combinations of lesions which might exist in a given patient with a congenitally malformed heart.

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2
Atrial and ventricular dependent circulations

CATHERINE BULL

INTRODUCTION

It is now more than ten years since Fontan first connected the right atrium to the pulmonary artery, diverting the whole caval return directly to the lungs in a patient with tricuspid atresia[1]. The atriopulmonary connection now constitutes the 'definitive repair' for a variety of complex congenital heart defects in which only one ventricular chamber is present or where anomalies of the tricuspid valve (straddling, Ebstein's anomaly) sometimes preclude repair as a biventricular heart. The operation is still finding its place in conditions where a right ventricle, though present, is hypoplastic.

The many survivors of these atriopulmonary connections testify to the dispensability of the right ventricle. However, the 'cost' of right ventricular bypass is measured in terms of a decreased flexibility of the circulation. This chapter aims to examine the properties of circulations without subpulmonary ventricles and perhaps to delineate the circumstances in which they can work.

Cardiac function is usually quantitated using the increasingly sophisticated derivatives of muscle mechanics (e.g. ejection fraction, velocity of fibre shortening) which modern technology allows us to measure. The alternative treatment of the heart as a pump, examining the relationship of the pressures at the inlet and outlet of the heart – as Starling did for the normal heart – is less fashionable, but remains a legitimate alternative approach.

THE NORMAL CIRCULATION

Left ventricular work is sufficient to open the aortic valve, overcome the systemic vascular resistance, drive blood across the tricuspid valve in early diastole and provide most of the work done in filling the right ventricle, which occurs mainly before atrial systole. Similarly, right

ventricular work is sufficient to overcome any resistance in the right ventricular outflow tract, perfuse the pulmonary vascular bed and drive blood across the mitral valve to fill the left ventricle during the most rapid phase of ventricular filling. The advantage of thinking in terms of resistances relates to their property that, provided the whole cardiac output crosses each element in the pathway, the resistances summate.

Resistance to RV emptying	=	Resistance across RVOT	+	Pulmonary vascular resistance	+	Resistance across mitral valve	+	Resistance to LV filling in early diastole
Resistance to LV emptying	=	Resistance across LVOT	+	Systemic vascular resistance	+	Resistance to TV in early diastole	+	Resistance to RV filling

Where RV, LV = right and left ventricles; RVOT, LVOT = right and left ventricular outflow tracts; TV = tricuspid valve.

An objection to this simplified view of the sources of circulatory work is its neglect of the 'auxiliary pumps' which contribute to the circulation; these are atrial contraction, respiratory movements and the muscle pump. However, none of these 'pumps' is essential to the function of the normal circulation, as the occurrence of atrial fibrillation, apnoea and rest shows. The part played by atrial contraction will be considered later.

The flexibility of the normal circulation and other circulations incorporating a right (or subpulmonary) ventricle is substantial. Right ventricular power (rate of working) is sufficient to tolerate acute (e.g. pulmonary embolism) and even greater chronic (e.g. pulmonary vascular obstructive disease) elevations in pulmonary vascular resistance, gradients across the mitral valve and decreases in left ventricular compliance with disease. Since the resistances across the normal aortic,

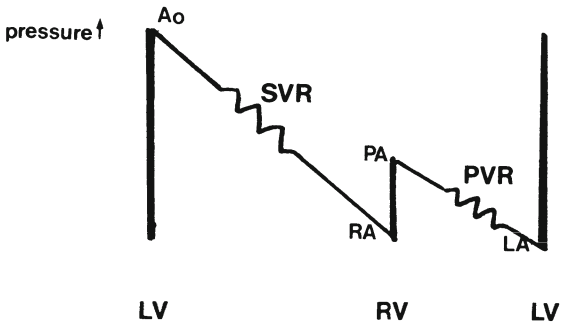

Figure 2.1a Normal: Right ventricle dependent pulmonary circulation
Ao = aortic pressure, LA = left atrial pressure, LV = left ventricle, PA = pulmonary artery pressure, PVR = pulmonary vascular resistance, RA = right atrial pressure, RV = right ventricle, SVR = systemic vascular resistance

pulmonary, mitral and tricuspid valves are trivial, the normal circulation, simplified even further could be depicted as in Figure 2.1a. Normally right and left atrial pressures are comparable, the left slightly exceeding the right due to the greater stiffness of the corresponding ventricle. By comparison with circulations with atriopulmonary connections, this could be called a 'right ventricle dependent pulmonary circulation'.

THE ATRIUM DEPENDENT PULMONARY CIRCULATION

If there is no ventricle interposed between right atrium and pulmonary artery, the 'atrium dependent pulmonary circulation' could be considered in the same way.

Resistance to RA outflow	=	Resistance across atrio pulmonary connection	+	Resistance PA−LA	+	Resistance across MV	+	Resistance to LV filling

Where RA, LA = right and left atria; PA = pulmonary artery; MV = mitral valve; and the resistance PA − LA is the pulmonary vascular resistance (PVR).

Provided the resistance across the atriopulmonary connection (which sometimes incorporates a valve) is trivial, this circulation can be depicted as in Figure 2.1b. The amount of work contributed and pressure generated by the right atrium will depend on its rhythm, efficiency (valve related) and the degree of atrial hypertrophy. In practice there is no increment in pressure between right atrium and pulmonary artery in these circuits (at least in the absence of valves at the caval orifices). In contrast to the right ventricular dependent pulmonary circulation, this circulation requires an obligatory relationship between right and left atrial pressures such that the former is higher by an amount which is related to the resistance to right atrial outflow.

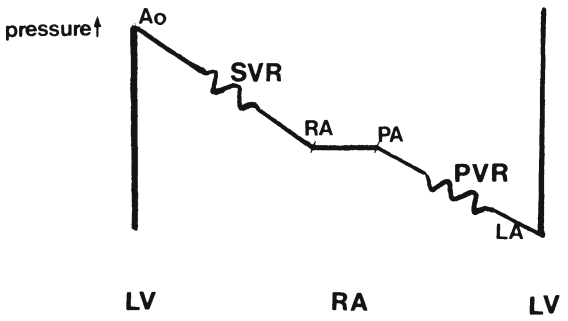

Figure 2.1b 'Atrial dependent' pulmonary circulation

Bypass of the entire right heart, with connection of the whole systemic venous return directly to the pulmonary artery has been achieved in at least two patients[2], leaving the left ventricle as the only possible pump for the central circulation (Figure 2.1c).

Resistance to LV outflow	=	Resistance across Ao valve	+	SVR + PVR	+	Resistance across MV	+	Resistance to LV filling

Where Ao = aorta; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

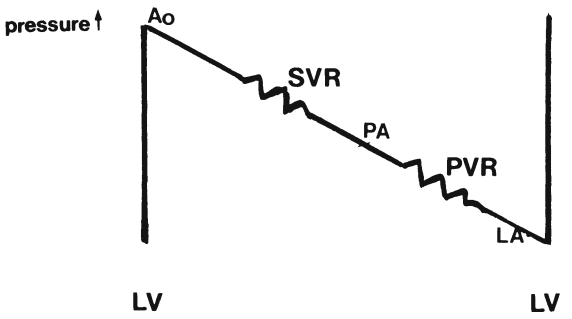

Figure 2.1c Total bypass of the right heart

It is interesting to note that the addition of a normal pulmonary vascular resistance (e.g. 2 U.m^2) in series with a normal systemic vascular resistance (e.g. 20 U.m^2) constitutes only a small extra demand on left ventricular systolic performance - comparable to very modest systemic hypertension.

LIMITATIONS FUNDAMENTAL TO ANY CIRCULATION

There are some limitations within which any circulation must work even when stressed. These are suggested in Table 2.1.

Table 2.1 Circulation limitations

Parameter	*Limit*
Minimum cardiac output	1.5 l min^{-1} m^{-2}
Minimum aortic pressure	50 mmHg
Maximum atrial pressure	22 mmHg
Minimum heart rate	30.min
Maximum heart rate	200.min
Maximum power of heart	

The figures are approximate as these 'rules' can undoubtedly be transgressed for brief periods. However, a resting cardiac output chronically below about $1.5\,l\,min^{-1}\,m^{-2}$ is precarious, a mean aortic pressure below about 50 mmHg would soon impair coronary perfusion or upright posture and atrial pressure above about 22 mmHg will result in pulmonary or systemic oedema (oedema is generated at an even lower atrial pressure when the serum albumin is low). There will also be a limit to the ability of both ventricles to sustain pressure and volume loads, though chronically overloaded ventricles are able to maintain a rate of working many times greater than normal.

LIMITATIONS ON THE RIGHT VENTRICLE DEPENDENT CIRCULATION

Without transgressing the rules suggested in Table 2.1 the right ventricle dependent circulation can tolerate a variety of haemodynamic loads imposed by organic valvular disease, systemic or pulmonary hypertension or ventricular dysfunction. This flexibility is limited only by the critical values suggested, e.g. increasing mitral stenosis causes a progressive rise in left atrial pressure which can approach the critical level. Further stenosis is then only accommodated by a fall in cardiac output which reduces the gradient across the mitral valve, maintaining the left atrial pressure within the tolerable range.

LIMITATIONS ON THE ATRIAL DEPENDENT CIRCULATION

Besides conforming to the 'rules' of Table 2.1, this circulation works under the additional constraint that the right atrial pressure must exceed the left atrial pressure by an amount related to the resistance to right atrial outflow. In these circumstances the 'rule' requiring the right atrial pressure to be maintained below about 22 mmHg is likely to be the first to become limiting. In clinical experience also, the height of the right atrial pressure is the single most important determinant of a successful outcome of an atriopulmonary connection; cardiac output or aortic pressure are rarely inadequate unless the right atrial pressure is also excessive. The height of the right atrial pressure depends on the resistances to right atrial outflow (which are additive) and the flow through the circuit (cardiac output). Unfortunately, relatively small differences in right atrial pressure correspond to wide differences in outcome; the early postoperative course and later quality of life are likely to be very different in three patients whose right atrial pressures are 12, 18 and 22 mmHg after an atriopulmonary connection. This small margin highlights the difficulties of patient selection.

Unfortunately, assessment of an individual patient's compatibility with the haemodynamic changes imposed by an atriopulmonary connection must be made when the child's circulation is 'built' in a completely different way. Preoperatively the patients have intra- and extra-

cardiac shunts with a volume loaded single ventricle. Misjudgements about patient selection probably account for most perioperative deaths associated with this procedure.

FONTAN'S RULES FOR PATIENT SELECTION

From their extensive and early experience with the atriopulmonary connection, Fontan's group suggested a set of rules, the 'Ten Commandments'[3], within which the operation could be expected to be successful (Table 2.2). These rules form the basis of most discussions of selection criteria and were essential to the early development of the operation. More recently it has been realized that some defects or combination of defects outside Fontan's criteria are compatible with

Table 2.2 Fontan's 'Ten Commandments'

Rule	*Parameter*	*Limit*
1.	Age	4–15 years
2.	Sinus rhythm	Stable
3.	Drainage of vena cava	Normal
4.	Volume of right atrium	Normal
5.	Mean PA pressure	<15 mmHg
6.	PVR	<4 U.m^2
7.	Pa–Ao diameter ratio	>0.75
8.	Ventricular function	Normal
	With ejection fraction	>0.6
9.	Mitral valve competence	No incompetence
10.	Previous shunt	No impairing effects

a reasonable operative result, though deviations from several criteria in a single patient are associated with increased operative risk. However, even if this incremental risk is quantifiable, as the Mayo Clinic group imply[4] (no mortality for tricuspid atresia when all criteria are met, 10% if one criterion is not fulfilled, 37% if two or more are not fulfilled), this cannot help the assessment of the individual preoperative patient whose particular combination of lesions either is or is not compatible with survival after surgery.

Any lesion or combination of lesions with potential to increase the resistance of right atrial outflow may push the right atrial pressure beyond the proscribed limit, beyond which the circulation fails.

Left ventricular or mitral valve dysfunction

It is unlikely that a ventricle would fail to support the additional systolic work necessary to maintain even the circulation in Figure 2.1c, provided the pulmonary vascular resistance is normal. However, in the presence of left ventricular dysfunction this systolic work may only be generated at the expense of an increased left ventricular end diastolic pressure (LVEDP) (Figure 2.2).

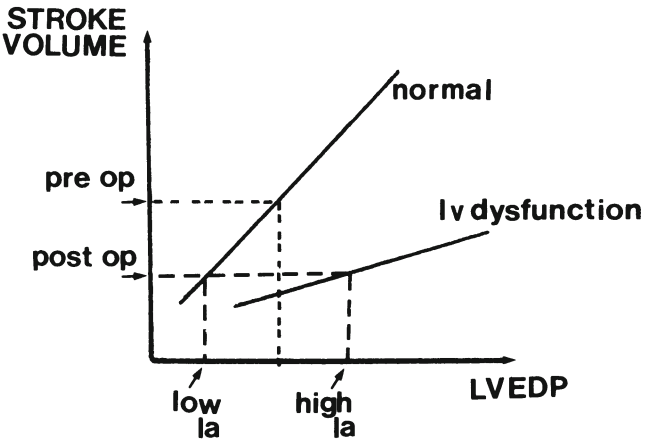

Figure 2.2 Effect of left ventricular dysfunction. Preoperatively patients have a large stroke volume due to intra- and intact extracardiac shunts. Postoperatively, if the ventricular function is normal the left atrial pressure is low; in the presence of left ventricular dysfunction, adequate stroke volume is generated only when the left ventricular end diastolic pressure (LVEDP) – and thus the left atrial pressure – is high

If, for example, the postoperative LVEDP is 16 mmHg, and there is no measurable gradient across the mitral valve, the mean left atrial pressure will be around 16 mmHg. Assuming a low pulmonary vascular resistance, e.g. 2 U.m^2, and a cardiac index of 3 l min^{-1} m^{-2} the expected right atrial pressure would be about $16 + (2 \times 3) = 22$ mmHg, a level barely compatible with a successful outcome. Exercise tolerance would be very limited for, even if the LVEDP rises no further, to double the cardiac index would require a right atrial pressure of $16 + (2 \times 6) = 28$ mmHg. Thus, the atrial dependent circulation becomes limited by right atrial hypertension at a level of left ventricular dysfunction which would be readily tolerated if a subpulmonary ventricle were present. In a right ventricular dependent pulmonary circulation a rise in the mean pulmonary artery pressure to 28 mmHg would be readily accommodated by a modest rise in right ventricular work and reflected in a trivial rise in right atrial pressure. Unfortunately, unless cardiac output is measured and work curves similar to those in Figure 2.2 are generated, a raised LVEDP at preoperative cardiac catheterization may be interpreted as only reflecting the volume overloading of the ventricle (high left ventricular stroke work) generally present at this stage (e.g. tricuspid atresia). Ejection fraction at substantially elevated left ventricular end diastolic volumes in the absence of valvular incompetence can give a needlessly pessimistic impression of ventricular performance.

Stenosis or incompetence of the left atrioventricular valve will also be associated with an elevated left and thus right atrial pressure. Though presently available prosthetic valves are all somewhat obstructive even at normal flow rates, mitral valve replacement may be neces-

sary in the presence of dysfunction of the left atrioventricular valve and may still be compatible with tolerable left and thus right atrial pressure, if other variables are favourable. For example:

LVEDP	+	Gradient across prosthetic MV	+	PVR × Cardiac index	+	Gradient across conduit valve	=	Expected RA pressure
6	+	6	+	(2 × 3)	+	0	=	18 mmHg

Pulmonary artery size, pulmonary vascular resistance, pulmonary artery pressure

These three variables are related:

Pulmonary artery size

Pulmonary artery size is likely to be a critical determinant of the success of some atriopulmonary conduit operations as most patients like those with tetralogy of Fallot, have had a low pulmonary blood flow most of their lives and may have hypoplastic pulmonary arteries but no pulmonary vascular obstructive disease. But how small is too small? Three different criteria of adequacy have been suggested, each using a different method of preoperative assessment.

PA size using the PVR – Sade *et al.*[5] point out that pulmonary artery size is one determinant of the PVR as conventionally calculated (Table 2.3) and argue that provided this is within tolerable limits no separate criterion of size need apply. However, PVR estimation preoperatively requires measurement of pulmonary artery pressures (which are usually low), shunts (with their wide margin for error in calculation) and flows (which are often assumed). The eventual figure has therefore a large percentage error and provides only a very crude index of pulmonary artery size (Table 2.4).

Table 2.3 Determinants of PVR

PA size
Pulmonary vascular obstructive disease
Pulmonary bed (e.g. one lung)

Table 2.4 PVR as a crude determinant of PA size: some examples

PA pressure (mmHg)	*LA pressure* (mmHg)	*Estimated pulmonary blood flow* ($l\,min^{-1}\,m^{-2}$)	*PVR* ($U.m^2$)
12	8	1	4
12	8	2	2
15	8	1	7
15	8	2	2.5

Fontan's rule - Fontan chooses to measure the size of the main pulmonary artery angiographically and relates this to the diameter of the descending aorta, suggesting a lower limit of 0.75 for the ratio PA/Ao. For conditions with pulmonary atresia and diminutive main but larger left and right pulmonary arteries, a size criterion for the latter is required.

Tetralogy of Fallot material - It is tempting to make use of the extensive material (relating to pulmonary artery size, residual right ventricular hypertension and postoperative survival in the tetralogy of Fallot) published from the University of Birmingham, Alabama[6]. Of course, without a ventricle to contribute to the work required to drive blood through restrictive pulmonary arteries, one would expect the minimum pulmonary artery size compatible with a good repair to be larger for an atriopulmonary conduit than for tetralogy. From the nomogram generated by Alfieri *et al.*[6] (Figure 2.3) the expected ratio of right and left ventricular pressures after tetralogy repair can be derived from preoperative angiographic measurements of right and left pulmonary arteries and the descending aorta.

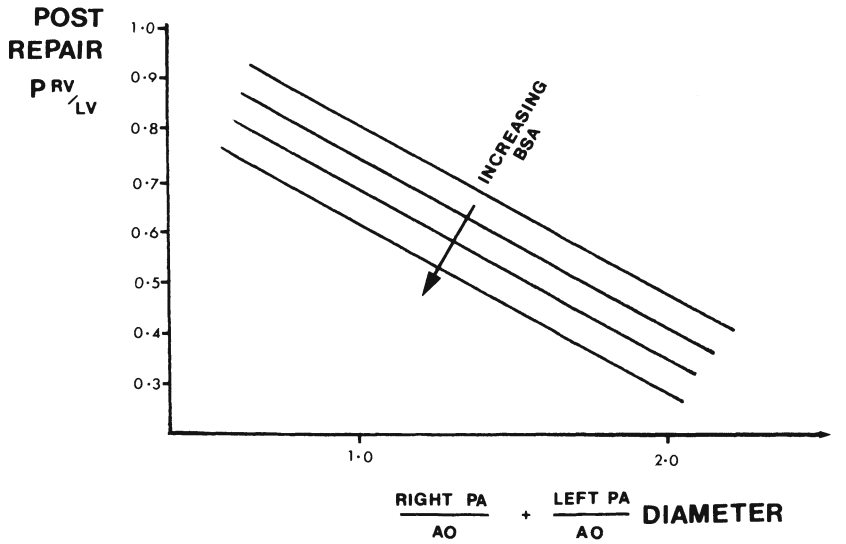

Figure 2.3 Relationship of post-repair RV/LV pressure ratio to right and left pulmonary artery diameter measured angiographically for tetralogy of Fallot. (From Alfieri *et al.*[6])

If it were argued that the right atrium functioned as the ventricle in the atrium dependent circulation and the maximum RA/Ao ratio tolerable was 20 mmHg/100 mmHg = 0.2, the minimum compatible pulmonary artery size demanded is very large - both right and left pulmonary arteries would have to be larger than the descending aorta.

The assumption that right ventricular hypertension remaining after a tetralogy repair is entirely due to inadequate pulmonary artery size, disregarding any residual gradient across the right ventricular outflow tract, accounts for the rather conservative recommendations which follow from this rule. If after any of these considerations, pulmonary artery size in an individual seems borderline, the patient might be better served by a systemic to pulmonary shunt which might stimulate pulmonary artery growth.

Pulmonary vascular resistance

Fontan's criteria require a PVR of less than $4\,U.m^2$. Thus, with no gradient across the atriopulmonary connection, a postoperative left atrial pressure of, e.g., 8 mmHg and a cardiac index of $3\,l\,min^{-1}m^{-2}$ would give an $RA = 8 + (4 \times 3) = 20$ mmHg. Besides small pulmonary artery size, an elevated PVR may be encountered in the presence of pulmonary vascular obstructive disease or a limited pulmonary bed. Longstanding excessive pulmonary blood flow associated with a large systemic–pulmonary shunt or an inadequate pulmonary artery band, may engender a degree of pulmonary vascular obstructive disease which would be readily tolerated by a right ventricle dependent pulmonary circulation (e.g. after ventricular septal defect closure) but be incompatible with an atrial dependent circulation.

The calculated PVR when the whole systemic venous return is to be directed to a single pulmonary artery may be within Fontan's limits, provided the artery is large enough. Sade *et al.*[5] have reported a successful repair onto a single pulmonary artery.

PA pressure

By setting an upper limit to both pulmonary artery pressure and pulmonary vascular resistance, Fontan *et al.* have effectively excluded patients with a very high pulmonary blood flow and low pulmonary vascular resistance from consideration for surgery. In an attempt to offer definitive repair to a child with complex intracardiac anatomy and an excessive pulmonary blood flow (mean PA pressure = 28 mmHg; $PVR = 2\,U.m^2$) we have performed an unsuccessful atriopulmonary conduit operation. The Mayo Clinic report one similar case of a patient who died postoperatively despite the use of Tolazoline[4]. It is not clear why such patients should be unsuitable for this operation unless they have more muscular pulmonary arteries which produce an exaggerated reaction to the insults of cardiopulmonary bypass and postoperative ventilation known to produce exacerbations of pulmonary hypertension in patients with more advanced pulmonary vascular obstructive disease[7].

Age

Fontan sets age limits of 4–15 years as optimal for this operation. Most younger patients would be well served by an alternative procedure, usually a systemic to pulmonary shunt or pulmonary artery banding, depending on their pulmonary blood flow. However, an occasional younger child may present with suitable anatomy and haemodynamics to benefit from an atriopulmonary connection. This operation is more appealing in a young child if no conduit is used, a direct anastomosis being fashioned between the roof of the right atrium and the pulmonary artery. Survival of Fontan operations has been reported in infants[8], but success would not be anticipated in the neonatal period before the regression of fetal pulmonary muscularity.

Sinus rhythm

Preoperative stable sinus rhythm is often demanded. A paroxysm of atrial fibrillation after an atriopulmonary connection results in acute loss of function of the subpulmonary 'pump' while the systemic ventricle contracts coordinately, though irregularly. It was thought that this would necessarily result in acute circulatory failure. The fact that atrial fibrillation after an atriopulmonary connection is in fact compatible with tolerable haemodynamics is interesting in itself, challenging the conception of the atrium as a useful pump. The onset of atrial fibrillation involves the loss of atrial kick both on the right side (the subpulmonary pump) and on the left side of the heart. We have already seen that the 'atrium dependent circulation' is much more sensitive to left ventricular dysfunction than a right ventricular dependent circulation. If the circulation after an atriopulmonary connection is already precarious in sinus rhythm (i.e. with a very high right atrial pressure), it may seriously decompensate with the onset of atrial fibrillation. Any rise in left atrial pressure related to atrial dysrhythmia must increase the right atrial pressure; if this is already excessive the cardiac output will fall. Conversely a child with more favourable haemodynamics and a lower right atrial pressure can accommodate fluctuations in left atrial pressure related to atrial arrhythmias with relative ease.

THE ATRIUM AS A PUMP

It is often said that the atrium is acting as the ventricle for the pulmonary circulation in the atriopulmonary conduit circuit. The manifestations of systemic venous hypertension are much the most striking sequelae of this operation; does this correspond to 'atrial failure'?

A normal ventricle does not function efficiently without both inflow and outlet valves; the inflow valve protects the proximal chamber (atrium) from exposure to ventricular pressures while the outlet valve protects the pumping chamber from volume overload. Thus both

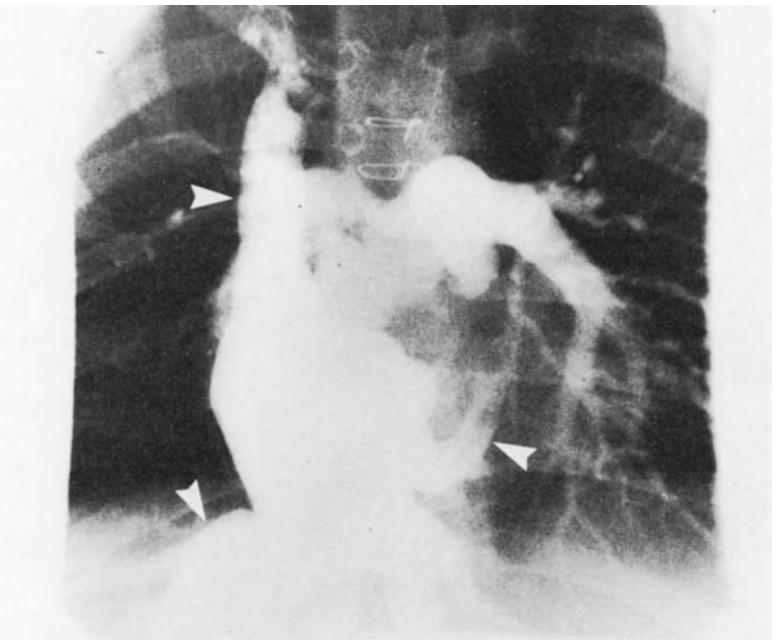

Figure 2.4 Right atrial injection after atriopulmonary connection. Atrial systole fills superior and inferior venae cavae and the coronary sinus (arrows)

valves contribute to ventricular efficiency. After an atriopulmonary connection without a caval valve, atrial systole drives some blood back into the compliant venous system, some forward into the pulmonary arterial bed (Figure 2.4).

In recognition of this, many of the first atriopulmonary conduit repairs incorporated valves (usually heterografts or homografts) at the orifice of the inferior vena cava and even of the superior vena cava[1]. In time it became clear that these were dispensable (though not necessarily useless); worse, they sometimes stenosed, becoming fixed in a semi-open position and introducing a gradient impeding venous return[4]. This potentially disastrous situation may have arisen because presently available heterograft valves inevitably deteriorate in children. Alternatively the atria may not have been capable of 'serving as a ventricle'. If atrial systole ejects less than the left ventricular stroke volume forward into the pulmonary artery, then, in order to maintain cardiac output, both caval and conduit valves would have to be open during much of atrial diastole to allow systemic venous blood to reach the pulmonary bed. Failing ever to close, these caval valves would eventually stiffen and stenose. At Great Ormond Street we have no experience with caval valves but pressure withdrawals across the right heart after a Fontan procedure have all had the pattern of Figure 2.5,

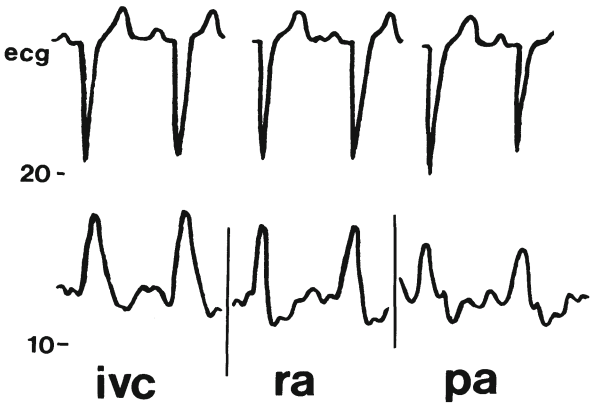

Figure 2.5 Pressure withdrawal from pulmonary artery to inferior vena cava after an atriopulmonary connection. The pulmonary artery pressure is no higher than the caval pressure

with no increment in pressure between cavae and pulmonary artery attributable to right atrial work (see Figure 2.1b).

The usefulness of a conduit valve is also controversial. To be useful a valve must close, otherwise a valveless conduit would be more appropriate. Without a caval valve, a valve in an atriopulmonary conduit is less likely to close because the efficiency of atrial contraction is impaired. The atriopulmonary conduit valve will 'float' more or less open as blood flows along the conduit throughout the cardiac cycle (Figure 2.6).

USEFULNESS OF AN OUTLET CHAMBER

Incorporation of a small subpulmonary outlet chamber in the repair (e.g. an atrium–outlet chamber conduit for tricuspid atresia with normally related great arteries) does not affect the status of the circulation which remains 'atrium dependent'. This is because, though the outlet chamber beats with the left ventricle, its stroke volume is less than the stroke volume of the left ventricle. Thus in order to maintain cardiac output, blood must reach the pulmonary artery at a time other than ventricular systole. The right atrial pressure must be high, comparable to the diastolic pressure in the pulmonary artery, so that atrial systole kicks open the pulmonary valve to produce forward flow into the pulmonary artery. This is illustrated in Figure 2.7 which shows the pressures in right atrium, outlet chamber and the pulmonary artery early after such an operation. Right and left atrial pressures have the same relationship in any atrial dependent circulation, i.e. that the right atrial pressure exceeds the left by an amount related to the resistance to right atrial outflow.

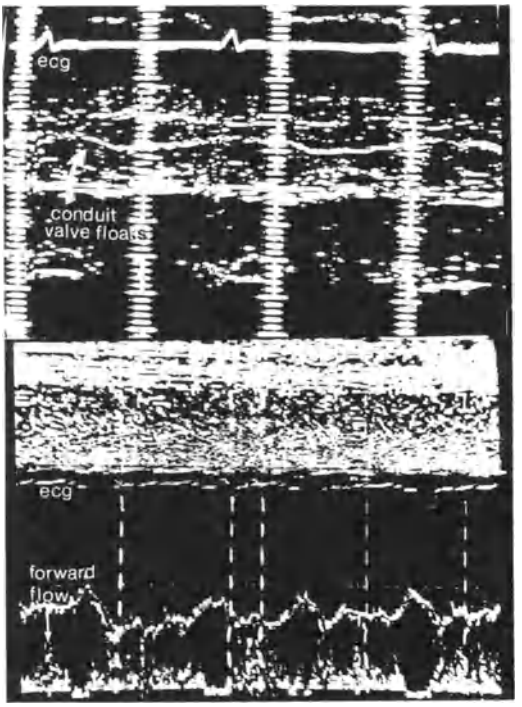

Figure 2.6 M-mode echo of conduit valve motion (above) and Doppler recording of flow pattern in the pulmonary artery after an atriopulmonary connection. The conduit valve floats more or less open and there is forward flow into the pulmonary artery throughout the cardiac cycle

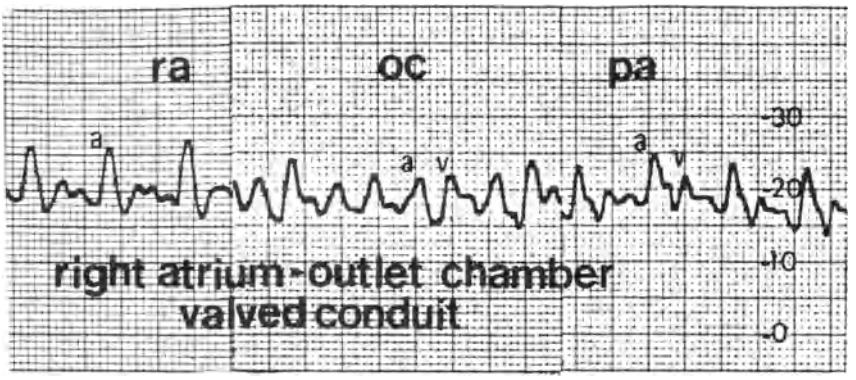

Figure 2.7 Pressure tracings after a right atrium to outlet chamber valved connection in a patient with tricuspid atresia. Note that the right atrial pressure is high and the pulmonary artery tracing shows peaks corresponding both to ventricular and atrial systole

Despite this there are potential advantages in including a small ventricle or outlet chamber in a repair. Particularly in the presence of an atrioventricular conduit valve, the chamber can contribute useful work to the circulation. However, the chamber can sometimes grow to the extent that it is able to maintain a stroke output equal to the left ventricular output, rendering the circulation 'right ventricle dependent' with all the advantages of flexibility and low venous pressure.

The presence of an 'a' wave in the pulmonary pressure trace could be regarded as the hallmark of an 'atrial dependent' circulation. It is worth pointing out that 'atrium dependency' can be seen in other contexts, where the right ventricle is small or its function profoundly impaired. Figure 2.8 illustrates two examples.

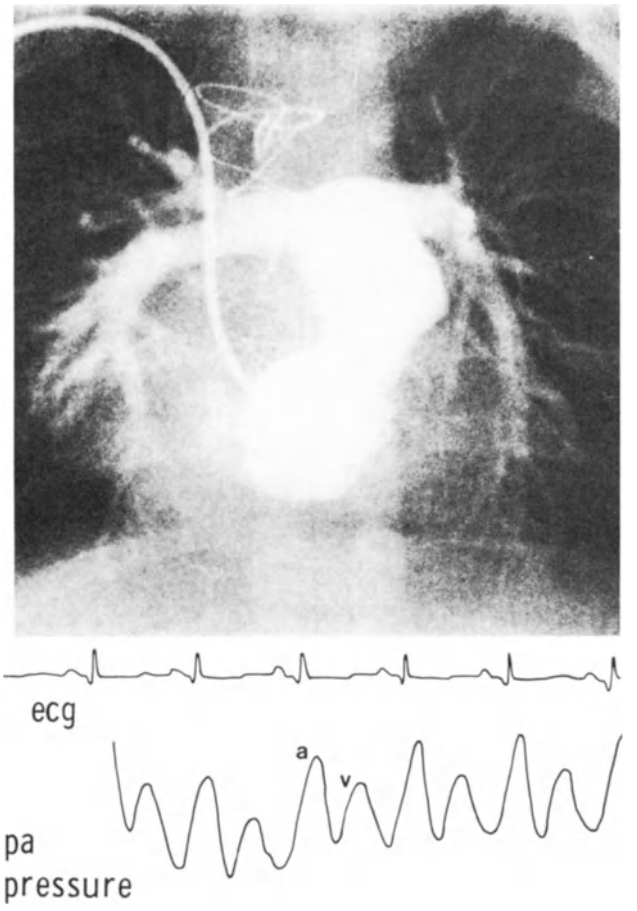

Figure 2.8a Pulmonary atresia with intact ventricular septum with a hypoplastic right ventricular cavity after right ventricular outflow tract reconstruction. Below is the pulmonary artery pressure trace which shows pressure peaks corresponding to atrial as well as ventricular systole

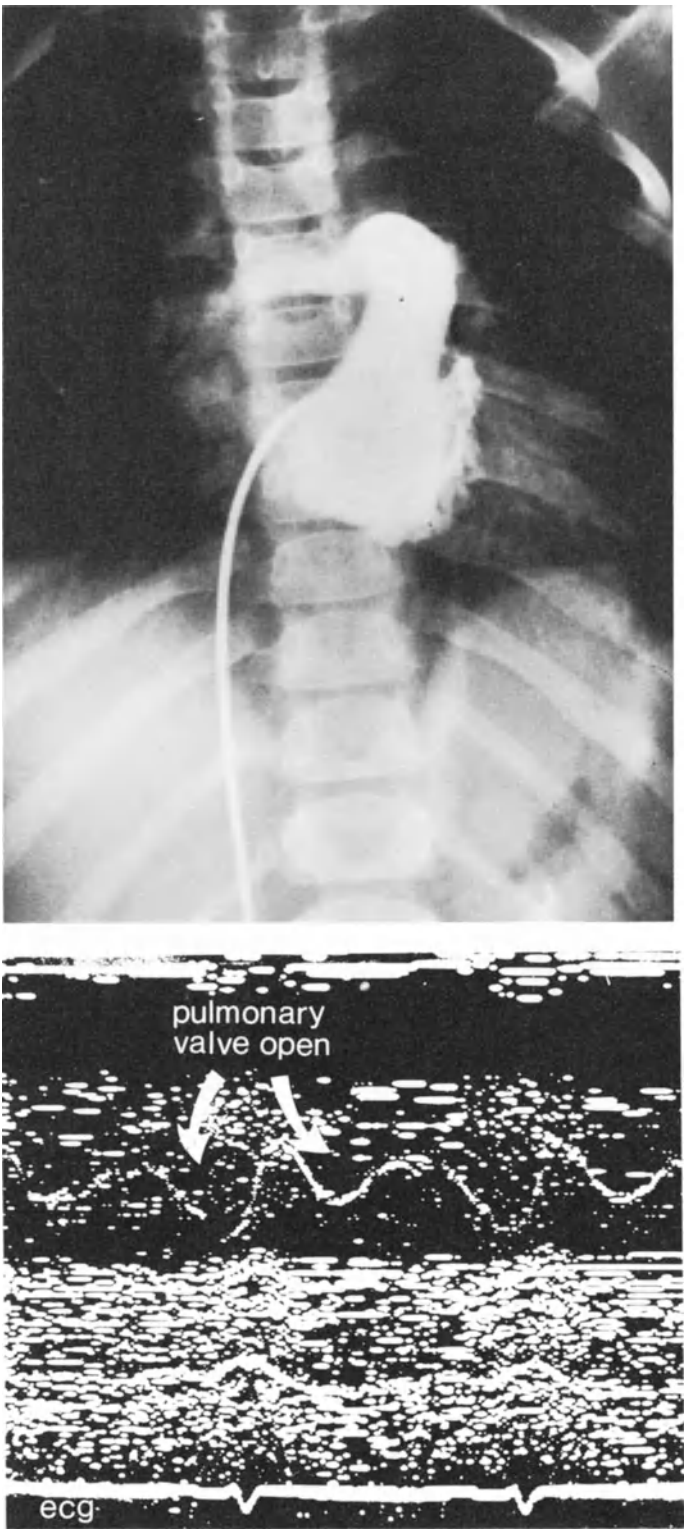

Figure 2.8b 'Isolated right ventricular hypoplasia.' Below is an M-mode echo recording of pulmonary valve movement after closure of an atrial septal defect. The valve opens for atrial as well as ventricular systole

(a) Shows the small right ventricle of a patient with pulmonary atresia and intact ventricular septum who had a right ventricular outflow patch with closure of the inter-atrial communication.
(b) Shows the right ventricle of a patient with 'isolated right ventricular hypoplasia' who underwent closure of the atrial septal defect.

Because right atrial systole must produce forward flow into the pulmonary artery, the repairs illustrated in (a) and (b) require the same obligatory relationship between right and left atrial pressures as is required for the atriopulmonary conduit (RA higher than LA pressure by an amount related to the resistance to right atrial outflow). Thus, consideration of closure of the atrial septal defect in patient (b) demands the same careful consideration of the determinants of the resistance to right atrial outflow, including tricuspid stenosis or left ventricular or mitral valve dysfunction, as would be required if the patient were undergoing a Fontan procedure.

THE GOOD RESULT

The best combination of circumstances - a good left ventricle, normal mitral valve and low pulmonary vascular resistance - gives a final right atrial pressure around 12 mmHg. For example:

LVEDP	+	Mitral valve gradient	+	PVR × Cardiac index	+	Conduit valve gradient	=	Expected RA pressure
8		0	+	(1 × 3)	+	0	=	11 mmHg

Such a right atrial pressure is comparable to that seen in many other conditions with right ventricular hypertrophy, even after repair. It is well tolerated without conspicuous systemic venous congestion. Such patients should have the capacity significantly to increase their cardiac output on exercise without exceeding the maximum tolerable right atrial pressure. They should require no drugs. For example:

LVEDP	+	PVR × Cardiac index	=	Expected RA pressure
8	+	(1 × 9)	=	17 mmHg

THE POOR RESULT

In contrast, a less satisfactory outcome is that in a patient with a right atrial pressure around 20 mmHg who has chronic oedema, ascites and pleural effusions and paroxysmal atrial arrhythmias associated with right atrial distension. Cardiac output may also be low if a normal output cannot be sustained in the face of a raised resistance to right atrial outflow. The patient will have a very poor exercise tolerance

and will require digoxin and diuretics. However, over-diuresis sufficient to lower right atrial pressure rather than simply to control ascites and effusion will cause a further lowering of cardiac output.

THE LONG TERM

On the positive side, the left ventricle is usually relieved of a volume load and the embolic risks of massive right to left shunting are abolished after an atriopulmonary conduit repair. To speculate on the long term limitations of a new operation may be depressing but potential problems include:

(a) *Atrial arrhythmias which occur late* in the natural history of other conditions with chronic atrial pressure and volume overload (e.g. atrial septal defect);
(b) *Chronic elevation of right atrial pressure* (e.g. in constrictive pericarditis) eventually brings hepatic, renal and gastrointestinal dysfunction (protein losing enteropathy has already been documented after a modified Fontan procedure[9]);
(c) *The effect of minimally pulsatile pulmonary artery flow* in terms of ventilation/perfusion mismatch has been demonstrated after the Glenn procedure[10] and may also apply to the atriopulmonary conduit. Pulmonary venous desaturation due to arteriovenous shunting particularly in the lower lobes may be an increasing problem.

Patients with a wide variety of underlying lesions are now being considered for an atriopulmonary conduit operation and a further group in which a small right ventricular chamber is included in the repair require similar careful preoperative assessment. An understanding of the properties of atrial dependent circulations may be more helpful than a set of rules some of which seem more, some less, absolute for purposes of selection. For all these patients this selection remains the key to surgical success. When the operation works well the patient is offered an excellent quality of life at least in the medium term while, if an excessive right atrial pressure is required to sustain the circulation, the operation becomes an elaborate palliation rather than an attractive repair.

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3
Analysis of death (survival analysis) and other time-related events

E. H. BLACKSTONE

CONCEPTS

Information about death (or its opposite, survival) and other time-related events in patients with congenital heart disease or other conditions can be presented simply as raw data. Such presentations consist of lengthy tabulations, and serve only as records of natural history or of achievements of one sort of management or another. The raw tabulations are of very limited value as a basis for inferences as to the survival that might be expected in a future similar group of patients, the times of greatest risk to survival, and the variables possibly associated with long or short survival. Also, the tabulations allow only limited comparisons of the survival in various subsets of the patient population observed, limited valid comparisons with other groups of patients treated in different ways, and almost no explorations of the laboratory and clinical studies needed to improve results.

The alternative to presentation of the raw survival data as a simple record of fact or achievement is the use of special methods of data organization and analysis that allow inferences and insights into the reasons for the occurrence and distribution of death or other events, comparisons with other experiences and other methods of management, and the development of laboratory and clinical investigations for the generation of new knowledge that will affect the future incidence of the events under study. The analyses must be based on the fewest possible assumptions, be mathematically tractable and robust, and display data concerning survival and other time-related events in a way that is useful. Usually this means that the method must be parametric and allow the generation of graphical or numerical nomograms that provide an appreciation of the nature of the relations between variables and events.

Essentially all methods of derived data presentation and analysis, in contrast to simple tabular presentations, assume the continuity of

nature and the transferability of inferences from current experience to future experience. As an example of the assumption as to the continuity of nature it is believed that observation of the amount of damage to the brain after profoundly hypothermic total circulatory arrest of 15, 30, 45, 60, 75 and 90 min provides some information, with appropriate estimates as to variability and degree of uncertainty, about the amount of damage that would occur after 35 or 50 or 100 min of arrest, even though no observations were made after these arrest times[1]. It is this assumption of nature's continuity that suggests that, rather than subcategorizing a congenital anomaly into its most detailed 'homogeneous' subgroups, the widest possible spectrum of cases with the anomaly be included in a single analysis. Morphological details and their interrelations are then accounted for along with other variables as risk factors in a multivariate analysis. Fundamental trends running through the entire spectrum of the anomaly may thereby be identified. These are possibly hidden by subgrouping, since the number of patients in the subgroups becomes small.

Many of the methods in use for data organization and analysis of time-related events are not completely satisfactory to the serious investigator. Simple contingency tables of hospital or 30 day survival after balloon septostomy or repair of tetralogy of Fallot, for example, ignore the possibility that deaths occurring in the early weeks after either of these artificial time barriers represent the same phenomena as those occurring earlier. Logistic regression analysis applies only to events occurring within some specified interval of time and is unable to analyse the time relatedness of those events. Actuarial analysis is useful in analysing the time relatedness of an event such as death; and when each death is shown across time on top of an actuarial plot, some of the raw data as well as the derived actuarial estimates are portrayed. Actuarial analysis has the disadvantage of not being parametric, and therefore not amenable to multivariate risk factor analysis with subsequent generation of time varying risk estimates for specific subsets within the group. Stratification of actuarial curves as a substitute for the latter is useful, but has the same limitations as simple contingency tables. Multivariate analysis by the Cox method has augmented actuarial analysis and provided important insights, but the kinds of inferences that can be drawn are limited by the method's limited ability to identify the time course of the risks or to generate nomograms. A completely parametric method overcomes many of the disadvantages of these earlier methods and therefore will be emphasized in this chapter.

The usefulness of the analysis of death across time (survival analyses) and of other time-varying events extends far beyond an understanding of the incidence and time distribution of that event. A major use of survival analysis is in drawing inferences from comparisons. These may be comparisons of the survival of treated patients having a congenital cardiac condition with that of the untreated ones, and

from such comparisons may come inferences concerning indications and timing of operation[2–6]. Comparisons may be made within the context of a multivariate analysis of risk factors to determine the independent effect of a specified variable, such as time of repair, with all others held constant[7, 8]. Comparisons may be made between teated patients and a matched general population, which yields information concerning *premature* late death and cure versus palliation of a particular condition[9, 10]. Comparisons may also be made of the time-related relative efficacy of various treatment modalities, preferably taking into account other possible risk factors which may affect the comparison. Identification of incremental risk factors can direct attention to fruitful avenues of research for discovering the causes of death and other time-related events, while providing effective interim information for improving results by empirical application of the inferences drawn from the observed associations[2].

HISTORICAL NOTE

A rudimentary life table was developed from the Bills of Mortality for the City of London and expressed for the first time in terms of survival by John Graunt in 1662, during the years of the bubonic plague[11, 12]. While some 30 years were to pass before Edmund Halley derived the correct mathematics for life table calculations[13], three elements of the early work of Graunt remain important motivations for survival analysis today: identification of incremental risk factors; comparisons among life tables; and calculation, display, and use of the hazard function[11]. In regard to incremental risk factors, Graunt introduced 'classification' into the analysis of survival data, the process of grouping like with like[11]. From Graunt's 'risk factor analysis', practical recommendations were made to Londoners, which were: (1) to flee the foul air brought in by ships from overseas; (2) to avoid animals; and (3) to erect houses of quarantine[13]. The viewing of these seventeenth century inferences today underscores the idea that risk factors are associations, and a causative relation is not necessarily implied[7]. Nevertheless, they did provide effective management until the cause could be found, and they did suggest a direction of research to discover those causes.

Graunt also introduced the idea of comparisons between life tables for the purpose of identifying significant 'differentials', as he called them. These included comparisons with life table data of historically earlier populations to detect trends across time[11]. These comparisons helped Graunt to draw inferences about the natural history of the plague, to exclude certain hypotheses about its causes, and to reinforce other hypotheses offered at the time.

Finally, John Graunt introduced the hazard function. He borrowed the term from dicing[13]. He defined the hazard function as the peril or danger of the occurrence of various calamities over a specified interval

of time, which he expressed as the proportion of individuals exposed to risk at the beginning of the interval. In his work he considered only calculations (incorrect at that) based on a constant hazard; that is, the risk to living persons was considered to be the same during all time intervals. His colleague William Petty, however, insisted that the value of the hazard function was time-related, increasing as the age of the population increased. Throughout the history of actuarial sciences the hazard function has provided complementary information to that derived from the survivorship function[14]. However, because of the relatively small numbers of patients involved in clinical studies, the instantaneous risk of an event among patients having not as yet experienced it (the hazard function), when estimated by non-parametric life table methods, is an unstable and poorly reproducible quantity[15, 16]. However, the advantages of hazard function analysis are currently available if there is willingness to use the techniques developed initially by Graunt, but by now greatly expanded to express the hazard function in terms of parametric models of the distribution of events[17, 18].

Meanwhile, the modern application of already well-established actuarial sciences methods to the analysis of clinical experiences began with Berkson at the Mayo Clinic in the 1940s[19]. Subsequently, based on early twentieth century work, refinements of these methods for small sample sizes were made by Kaplan (at Bell Telephone Laboratories investigating the life history of vacuum tubes in the repeaters in telephone cables buried in the ocean) and Meier (involved at that time in biostatistical analyses at Johns Hopkins University)[20]. The formal and informal testing of life tables was developed by a number of workers, based on various assumptions (see review in reference 21). These comparisons were crude compared to a formal analysis of risk factors since they were based entirely on univariate, stratified actuarial curves.

In the analysis of data from the Framingham Study during the mid-1960s, Walker and Duncan probably first applied logistic multivariate regression (earlier developed in the 1920s by Berkson) to estimate the probability of an event within a specified time period[22]. This refined the concept of risk factor analyses[23] and introduced a highly fruitful method for analysing events which were not time-related[16, 24, 25]. At this same time Feigel and Zelen applied multivariate risk factor analysis to time-related death from acute myelogenous leukaemia under the assumption of a constant hazard across time[26]. Being completely parametric, their method permitted them to display graphically the effects upon survival of varying levels of risk factors (such as the white blood cell count and the presence or absence of Auer rods). In 1972 Cox introduced a scheme for multivariate analysis of time-related events which incorporated a parametric, log-linear model of risk factors which were assumed to affect an underlying, unestimated, hazard function[27, 28]. His method used as its fundamental basis the actual time to each event. Thus, although the method did not take into account

time-related structure which might be present in the data (and thus it is called a semi-parametric method), it for the first time placed a robust, well-conceived, well-documented, tested, general methodology for multivariate analysis of time-related events into the hands of investigators. Perhaps of as much importance, it has stimulated research and development of many methods for analysis of censored time-failure data[29]. The development and use of these methods has become one of the most active and, thus, changing fields in biostatistics today.

THE MECHANICS OF STUDIES OF DEATH AND OTHER TIME-RELATED EVENTS

The process of establishing definitions

The event

Defining the event for an analysis may be straightforward, such as death from any cause. Other events may be of interest, such as death in a number of different modes, all of which require clear definition. In the case of a palliative procedure such as a shunting operation, interim death before repair may be a specific event of interest. Other non-fatal events, such as brain abscess, reoperations, reoperations for a specific event, degeneration of a heterograft valve, development of angina, and so forth may also be analysed. A clear and strict definition of the event of interest is necessary, in order to define clearly an uncensored patient who experiences the event, and a censored one who at some point in time becomes untraced as regards the event.

Caution must be exercised in considering the time-relatedness of some events. For example, degeneration of a porcine heterograft or the development of angina are themselves time-related processes. The timing of a reoperation, therefore, in part depends upon the rate of the process, upon the patient's response to that process, and perhaps upon certain physician- and surgeon-related factors.

Censoring

Patients who have not experienced the event of interest and become untraced for the event are censored, and are dropped from further consideration at the time they are no longer so traced. There are two general categories of censoring. First, censoring may result simply from the fact that the patient has not experienced the event by the end of the study period. This occurrence represents incomplete data concerning the event since the patient remains at risk for the event. This same category of censoring applies to the patient who becomes lost to follow-up during the course of the study. Actuarial methods were developed specifically to provide a way to estimate survival and freedom from various events in the face of such incomplete data[19].

For an event such as death from all causes and under any circumstance, the definition of a censored patient is, obviously, one alive at the time of last follow-up. For almost any other situation a second category of censoring pertains when the patient is actually removed from being at risk of the event. For example, if the event is interim death between balloon septostomy and definitive repair for transposition of the great arteries, an individual is no longer at risk of an interim death when his definitive operation is performed. Thus, he is censored on the date of repair. Similarly, if a patient has removal of a heterograft-containing valved extracardiac conduit, he is no longer at risk of degeneration of the valved conduit removed, and is to be censored at that time. This second category of censoring does not represent incomplete data, but dictates that a certain proportion of the original group of patients will never experience the event of interest. Chiang describes modifications to standard actuarial methods to distinguish between these two types of censoring[30]. The underlying assumptions of various completely parametric methods determine the specific effect of the two categories of censoring.

The assumption is made in the actuarial method that censoring is the result of a process independent of the event of interest (so-called 'non-informative' censoring)[31]. This assumption may be violated in the analysis of some events. For example, in the case of the event 'death between a palliative and a reparative operation' for congenital heart disease, an elective repair probably does not violate the independent censoring assumption, but repair performed because of a deteriorating clinical condition almost certainly violates the assumption, since censoring in this instance is probably correlated with the deterioration that would probably lead to the event death. The possible influence of such censoring patterns on the resulting actuarial curve has been investigated recently[31].

Follow-up interval

Calculation of the follow-up interval requires precise definition of the time of the patient's entry into a study and either the time of the event or the time of censoring. The time of study entry is easily defined when analysing the results of a surgical intervention, since the date of surgery is a clear entry point. The date of birth is also a clear entry point. However, some studies of congenital heart disease take as the point of entry the date of diagnosis, the date of first clinic visit, or some other quite arbitrary date, and this must be taken into account when interpreting the results.

The actual calculation of the interval between study entry and the event or censoring is best accomplished using algorithms which generate intervals between Julian dates[32]. These are available on many calculators, microcomputer programs, and in all the major statistical packages. In some instances when the interval between study entry and

event is extremely short, rather precise interval information, in terms of hours or even minutes, is required. In general, the precision with which the timing of an event must be measured depends upon the time-related pattern of the hazard function. The steeper it is, the greater the precision required.

Situations will arise when the precise timing of an event is not possible, and the data available indicate only a time at which the patient was surely free of the event and a later time when he was surely known to have experienced the event. These are known as interval censored data. All non-parametric and parametric methods for analysing time-related events can be adapted to accept such data[6].

Methods of follow-up

Anniversary method

In the anniversary method the patient is either contacted yearly on the anniversary of his entry into the study, or is given a set of forms to send to the investigators on the anniversary of his entry. This method is perhaps best for sampling the time-varying condition of the patient, such as his functional status, freedom from angina, and growth and developmental patterns. However, few time-series analyses of clinical experiences have been performed using data obtained in this manner. The anniversary method has the added advantage of keeping at least yearly contact with the patient, an important consideration in a mobile society.

The anniversary method has certain disadvantages when standard actuarial methods are employed to analyse the events[33]. Since anniversary data are analysed actuarially at a specific point in time, living patients will of necessity have a varying date of censoring within the year prior to data analysis. Thus, unless a separate follow-up study is performed for them, any patient entering into the study in the preceding year will be untraced. The staggering of the follow-up information over the preceding year also introduces a bias into actuarial methods which employ intervals of time, such as that proposed by Berkson and Gage[19]. Drolette has suggested some ways of avoiding this bias, but her method requires that some of the information deliberately be lost[33]. The product-limit method described by Kaplan and Meier[20] should, in theory, not be biased by this method of follow-up.

Common closing date method

In the common closing date method, a specific follow-up inquiry of all patients known to be alive is initiated, whose purpose is to obtain the cross-sectional status of all patients at a specific instant in time. In practice, however, a finite period of time is necessary to conduct the

follow-up study. For example, the follow-up portion of the study reported by McGrath *et al.* on patients with atrioventricular discordant connection was initiated by telephone and by mail on 1 December 1983[34]. Answers to inquiries were received through the period up to 18 January 1984, although there was contact with only three patients between 7 January and 18 January. Using the common closing date method, and the above example, some date between 1 December 1983, and 18 January 1984, is selected as the date of inquiry or common closing date. Proponents of the method generally select the date of receipt of the first reply as the common closing date, 1 December 1983, in the above example. Any events reported to have occurred between 1 December and 18 January are, therefore, ignored, and all patients known to be alive on or after 1 December would be censored on that date. This method best fulfils the theoretical assumptions of all actuarial methods, and should introduce the least bias. If the duration of the follow-up inquiry is short, little information is lost.

Date of last report method

The method employing the date of last report was commonly practised by Berkson at the Mayo Clinic[35]. All information available from the time of initiating the follow-up inquiry until the date of 'last report' is included in the sample information. This method maximizes the available information. If, following receipt of a follow-up report, but before the close of the study or date of analysis, additional information comes to light, it is included in the analysis. This has the disadvantage that information is usually not random, but concerns the event of interest. It tends, thus, to bias the analysis unfavourably.

The University of Alabama at Birmingham (UAB) method falls between that of the common closing date method and the method of date of last report. For any given inquiry (in large studies the patients are grouped according to year and 'waves' of inquiry are made), a specific date of *study closure* is determined. For example in the study by McGrath *et al.*, the date of 6 January was chosen[34]. Information received concerning events occurring subsequent to that date is ignored, and the patient censored as of the study closure date. Further, only the first information received from the patient before or during the inquiry period is used in the analysis. It is not uncommon in a large study to receive a letter or telephone call from a patient's family shortly after the questionnaire is returned telling of the patient's demise shortly after the inquiry was made. Clearly such information biases the analysis, since living patients are not similarly recontacted. The UAB method is close to the unbiassed method using the common closing date, but uses nearly as much of the information potentially available, as does the method of last report.

Goodness of follow-up

It has been shown repeatedly that untraced patients have a very much higher probability of having died than the traced patients[36]. A large number of untraced patients will, therefore, introduce bias into any analysis and inference derived from the data. Therefore, any presentation of studies of time-related events should include information about the completeness of follow-up.

At UAB, the number of patients traced beyond hospital discharge is explicitly stated, generally accompanied by a statement concerning the median and range of follow-up intervals among the surviving patients (the 'average' follow-up time is often a biassed statistic, which is the reason for using the median). It is important that only the follow-up intervals for censored living patients be used in this determination, since dying patients bias the duration inappropriately downward.

Grunkemeier[37] has described a patient-year method for estimating goodness of follow-up based on observed and maximum possible follow-up duration. For each patient the duration of follow-up actually possible is computed (this is the interval until death for an uncensored observation and the interval from study entry to the common closing or study date, anniversary date, or analysis date in censored patients, depending upon the type of follow-up study performed). The ratio of total observed follow-up duration compared to total maximum possible follow-up duration is used as a measure of goodness of follow-up. For example, in McGrath *et al.*'s study of 99 reparative operations in patients with atrioventricular discordant connection, all patients were traced beyond hospital discharge[34]. However, one patient was 'lost to follow-up' after 58 months when potentially he could have been traced for another 67 months. Three additional patients with follow-up information for 87, 100, and 112 months had been seen at UAB within a year of the follow-up inquiry and were not recontacted, resulting in a loss of 5, 12 and 5 months of follow-up, respectively. In aggregate, the follow-up was, thus, 'incomplete' by 89 patient-months. Of the 'potential' 5361 patient-months of follow-up, only 5272 were actually achieved, a goodness of follow-up of 98.3% for all patient-months.

Neither of these two methods adequately indicates the degree of information lost by incomplete follow-up. The UAB method may be overly optimistic, and the Grunkemeier method has the same drawback as all patient-year methods in that it reflects loss of information accurately only when the hazard function for the event is reasonably constant. For example, if a patient has been traced for 10 years, but has been lost for the past 5 years, the contribution to the goodness of follow-up statistic proposed by Grunkemeier would be the same as that of five individuals who were lost just after study entry (for example, after hospital discharge) 1 year ago. If the hazard function is steeply falling in the first year, as it often is, and is then very low after

10 to 15 years, the information lost by failure to trace the five recent patients is far greater than the information lost by the failure to trace further the patient with a follow-up duration of 10 years already.

It may be possible to devise a better expression of goodness of follow-up. For example, if a parametric estimate of the cumulative hazard function is made, then the difference in potential versus actual cumulative hazard experienced (expressed as a percentage) by the patients may better account for the time-related loss of information. However, the important thing is to expend a great effort to obtain complete follow-up information[38]. Failure to trace a substantial number of patients, however expressed, makes the analysis, no matter how sophisticated, suspect.

ANALYSIS OF TIME-RELATED EVENTS

Non-parametric analysis

Crude life table method

The most direct method for estimating survival (or freedom from any other time-related event) at a specific point in time is by constructing a crude life table. Each estimate consists simply of the proportion of patients alive who have been followed from study entry to at least the specified time point. This proportion is, thus, the probability of surviving until the time point of interest.

The drawbacks to the method become apparent, however, when one considers the details of making these simple calculations for a group of patients. Consider the 310 patients who underwent repair of A-V septal (canal) defects at UAB between 1967 and 1982, and who were followed up in 1983. To obtain an estimate of 10 year survival, one first excludes from consideration all operations performed more recently than 1973 (10 years ago). This group of patients operated upon between 1967 and 1973 forms the denominator for the proportion, and the number of these patients still living the numerator. Then, to estimate 5 year survival, all cases are excluded who underwent operation more recently than 5 years ago, and the process of calculations is repeated.

If some patients are for any reason lost to follow-up during the interval of interest, these untraced individuals must be handled in one of several possible ways in the calculations. Berkson says one may as well exclude these patients[19]; of course, he also states that he has generally been able to trace 99% of the patients in his studies for the requisite number of years.

Since the group of patients making up the denominator is different for each calculation, it is quite possible to obtain 'unaesthetic' results, such as a 5 year survival that is lower than the 10 year survival. Of course, such estimates only represent the variability present in small samples. This phenomenon is common in cross-sectional data[39].

One serious drawback of the crude life table is that it does not make full use of the available information. The fact that a number of recent cases have survived at least a year is not considered at all when estimating survival beyond a year. Thus, despite its great simplicity, it has been abandoned by most investigators in favour of the actuarial methods which do attempt to use all the available information (and which are 'aesthetic' as well).

Actuarial methods

The above two deficiencies in the crude life table method are eliminated by the actuarial method. Each estimate is dependent upon preceding estimates so that the survival curve strictly decreases as additional events occur as time progresses, and all the information on all study patients is used in the calculations. The price one pays for this is a slight increase in complexity of the calculations and the introduction of specific assumptions relating to censored patients.

The essence of the actuarial method is to make crude estimates of survival within successive time intervals, and then to relate these interval estimates to one another as a sequential product across time. The mechanics are as follows. To determine the probability of survival within the i'th interval, $p(t_i)$, the number of patients alive at the end of the interval is divided by the number alive and at risk at the beginning of the interval. The probability of surviving from time 0 until the end of the i'th interval, $P(t_i)$, is simply the product of surviving to the end of the previous interval, $P(t_{i-1})$, and surviving within the interval:

$$P(t_i) = P(t_{i-1})p(t_i) \tag{1}$$

Since the probability of surviving within the interval is 1.0 or less, $P(t_i)$ is guaranteed to be less than or equal to $P(t_{i-1})$. Thus the estimates are monotonically decreasing and aesthetic. More importantly, all patients traced at least to the beginning of the interval being considered are included in the analysis. For example, for the first time interval all patients are included who have entered the study. Progressively fewer are available for later intervals, but the information from the entire group is propagated by the continuing product of current interval survival and that of all preceding intervals. Thus, actuarial methods employ the same computations as for the crude life table method, but they do so for each interval, rather than starting at time zero each time. The only real added complexity is the connecting of all the interval estimates by means of a continuing product, starting at time zero.

Differing actuarial methods use differing ways for selecting the time intervals to be considered and differing ways (assumptions) for handling patients who become censored within the interval. The actuarial method described by Berkson and Gage[19] employs equal time intervals, and assumes censored patients are lost halfway through the interval.

Thus, if 100 patients are at risk at the beginning of the interval, and 20 of these become untraced during the interval (censored), the denominator used in determining $P(t_i)$ is $100-20/2$ or 90. The product-limit method described by Kaplan and Meier uses unequal intervals, namely the interval between consecutive events[20]. Patients who are censored within the interval are simply not counted as at risk within the interval.

Because events, particularly after surgery for congenital heart disease, are not distributed uniformly over time, but are prone to occur with a greater frequency early after operation, an actuarial method which best reflects such a distribution is to be recommended. Thus, the product-limit method devised by Kaplan and Meier[20] is preferred to the use of the interval actuarial method of Berkson and Gage[19]. These estimates should be accompanied by an expression of the degree of uncertainty of the estimate (see Appendix 1).

From an inferential point of view, actuarial methods retain the properties of even the crudest estimates of survival, namely, simple contingency tables. (The difference is that the actuarial method describes the events across time.) An actuarial analysis may be descriptive of an event in an overall sense, or the analysis may be made according to subsets (stratified), with tests of the possibility that one actuarial curve is different from another[29], just as in the comparisons within a contingency table. The tests generally made are for 'indepedence' (one or more estimates differing from the average by more than is attributable to chance). Just as in similar comparisons for contingency tables, the ordering within a categorical variable such as New York Heart Association functional class is not tested. For such variables a test of trend within the table, and, by analogy, across actuarial strata, is more appropriate for drawing an inference. The Cox proportional hazards model provides for just such a comparison among actuarial curves, and is analogous to a logistic test for trend within a contingency table[27].

Controversy exists as to the connection of the actuarial estimates, the display and estimate of an apparently 0% survival, and the display of living patients after the last event. All are probably matters of style.

(a) Perhaps the correct form for connecting actuarial estimates in a graphical display, if one is willing to connect them at all, is by use of a step function. However, as originally pointed out by Berkson, the fundamental purpose of the method is to obtain a survival *curve*[19]. Since the important assumption of continuity in nature is essential in drawing inferences from clinical experiences, a smoother interpolation between these estimates is justifiable. The simplest and recommended method of interpolation simply is to draw a straight line (so-called 'first order interpolation') between estimates, as did Berkson.

(b) A 0% survival is calculated when the patient traced for the longest interval experiences an event (see Appendix 1). This is likely,

however, to be a spurious estimate, and is the extreme example for the known tendency of the product-limit method to underestimate survival probability at the 'tail end' of the curve[28]. If it is reasonable to assume that other currently living patients will eventually live longer than the present longest interval, then the calculation given in Appendix 1 may be used, or this estimate simply not displayed.

(c) An indication on the actuarial plot of traced patients beyond the last event by a broken line is reasonable. An extremely protracted interval without events, particularly when the number of living traced patients remains large, connotes a low hazard function beyond that point.

All these features of graphical display of actuarial analysis are evident in Figure 3.1. Such an analysis and display should be the first section of the presentation of results of an intervention for the treatment of a cardiac anomaly or of the life history of such an anomaly.

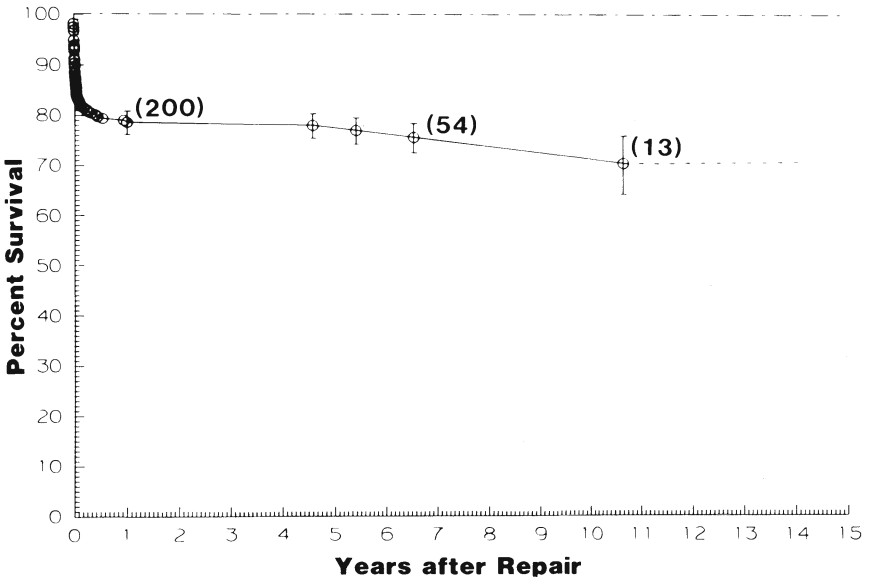


Figure 3.1 Non-parametric product-limit actuarial estimates of survival following repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n=310$; 70 deaths). Time 0 is the end of the operation. Each circle represents a death. The vertical bars enclose the 70% confidence limits (equivalent to ± 1 standard deviation) of the actuarial estimates. The numbers in parentheses indicate the number of patients traced beyond that event. The horizontal dashed line extending beyond the last event shown indicates the inability to estimate actuarial survival beyond this point, despite the presence of traced, living patients. The dash-dot-dash line is survival in an age–sex–race matched general population, shown for informal comparison. One of the 310 patients is untraced since hospital dismissal

Hazard function estimates

Some of the most interesting and useful aspects of survival analysis are concerned with the changing distribution across time of the events under study. The possibly changing rate of mortality, or of other time-related events, across time is expressed by the hazard function. It is the instantaneous rate of dying at any moment in time. Its relationship to other functions of survival are expressed as follows:

$$\text{Hazard function: } \lambda(t) \tag{2}$$
$$\text{Cumulative hazard function: } \Lambda(t) = \int_0^t \lambda(u)\mathrm{d}u \tag{3}$$
$$\text{Survival function: } S(t) = \exp[-\Lambda(t)] \tag{4}$$

where exp is e, the base of the natural logarithms, and t is time. Fluctuations of risk, expressed by the hazard function, may be masked by the actuarial estimate of the survival function since these become integrated across time (equation 3) and only their cumulative effects are portrayed.

The hazard function can be estimated empirically by non-parametric methods over the course of an interval of time, Δt_i. Recall that for each time interval i, the actuarial method requires a calculation of the probability of surviving within the interval, which was called $p(t_i)$. The probability of dying within the interval is $1-p(t_i)$. An estimate of hazard to the *centre* of the interval, $\lambda(t_{mi})$, is:

$$\hat{\lambda}(t_{mi}) = \frac{1-p(t_i)}{1+p(t_i)} \cdot \frac{2}{\Delta t_i} \tag{5}$$

The approximate standard deviation for this quantity is developed in Gross and Clark[15]. Alternatively, the difference between successive cumulative hazard estimates, divided by Δt_i, may be used (see below).

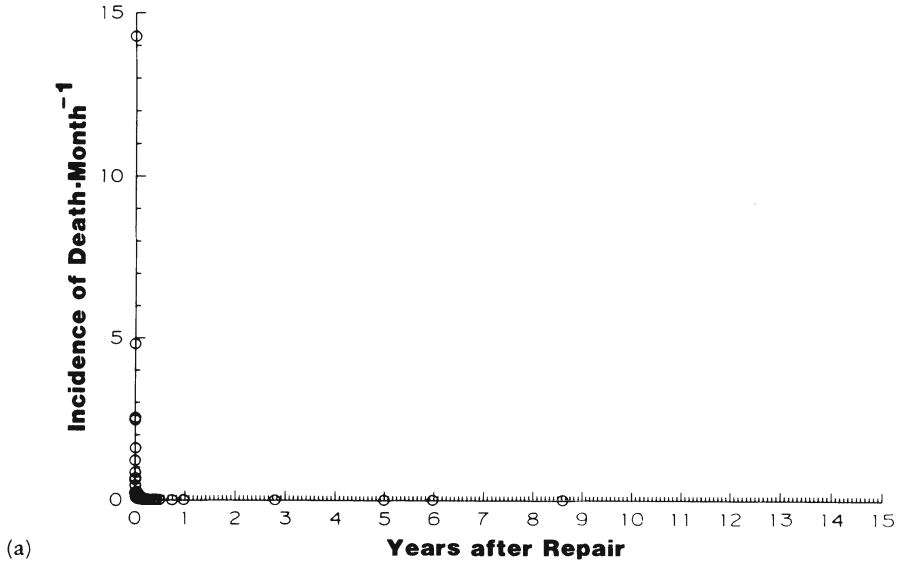
As Gross and Clark demonstrate, and as is evident in Figure 3.2, these empirical estimates of the hazard function are often unstable (unsmooth), but it is our experience that they can be a valuable check on the reasonableness of parametric estimates of the hazard function (which do display a smooth curve).

Cumulative hazard function estimates

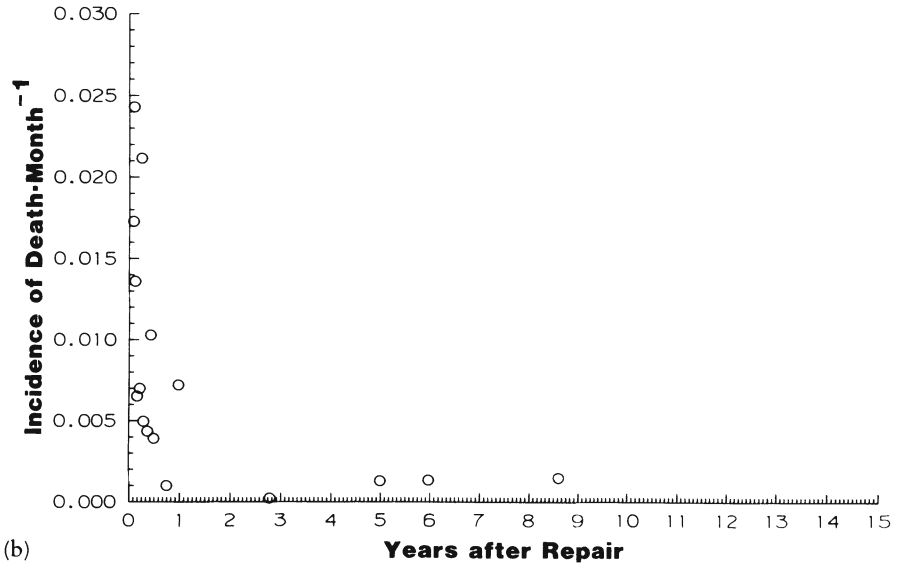
The cumulative hazard function is the time integral of the hazard function (equation 3). It is also related to the survival function as shown in equation 4, which can be rearranged as follows:

$$\text{Cumulative hazard function: } \Lambda(t) = -\ln[S(t)]. \tag{6}$$

That is, it is minus the natural logarithm (ln) of the survival function, and, of course, the hazard function is simply the slope (time-derivative) of the cumulative hazard function. The cumulative hazard function is expressed in terms of prevalence of the event.



(a)



(b)

Figure 3.2 Non-parametric hazard function estimates for death after repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n = 310$; 70 deaths), expressed as incidence of death per month.
(a) Display of all data points.
(b) Display along the vertical axis is truncated at 0.03

Nelson at the General Electric Corporation has suggested that since the display of cumulative hazard is naturally smoother than the empirical hazard function, it is more amenable to the formulation of notions concerning the true shape of the hazard function than the empirical hazard function itself[40–42]. The non-parametric estimate of cumulative hazard is derived directly from the actuarial analysis using equation 6 (Figure 3.3). At time 0, cumulative hazard is always zero. As time increases, cumulative hazard also increases such that it reaches infinity, in the case of the event death, when the last subject is dead.

The cumulative hazard function is useful in several contexts. First, it is useful in verifying the assumption that two hazard rates are proportional one to the other, an underlying assumption of the important Cox proportional hazards model. Calculation and display of stratified actuarial analysis to determine, at least visually, the reasonableness of the proportionality assumption are detailed in Appendix 2. Secondly, the cumulative hazard function is useful in the process of developing a parametric expression for the distribution of time-related events. From it the number of phases of hazard and their probable shape can be deduced. For example, if the cumulative hazard function is entirely, or even in part, rising in a straight line, the hazard function must be constant, either entirely or within that portion, as shown in Figure 3.3. If the cumulative hazard function is curving upward, then the hazard

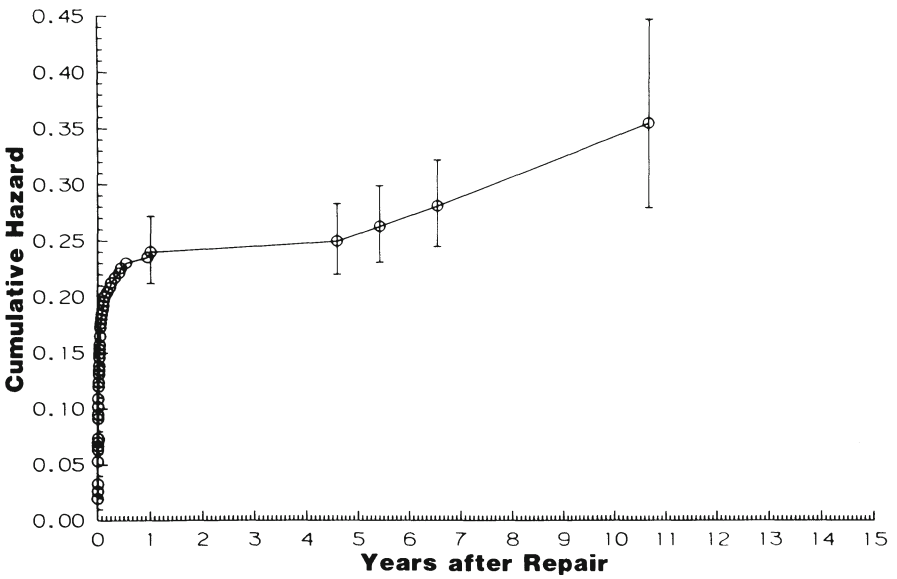


Figure 3.3 Non-parametric product-limit estimates of the cumulative hazard function after repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n=310$; 70 deaths). The depiction is that of Figure 3.1, except that the negative logarithm has been taken of all estimates, including those of the confidence limits

function must be increasing. If the slope of the cumulative hazard appears to be decreasing, then the hazard function is decreasing. The cumulative hazard function is also useful in the many situations in which a comparison is to be made between observed and expected number of events, as will be described in later sections of this chapter.

Parametric analysis

Analysis of constant hazard

When the risk of an event among surviving patients is not related to time, then the cumulative hazard function increases linearly with time, survival is exponentially decreasing, and the hazard function is constant according to the following relations:

$$\text{Hazard function: } \lambda(t) = \beta \tag{7}$$
$$\text{Cumulative hazard: } \Lambda(t) = \beta t \tag{8}$$
$$\text{Survival: } S(t) = \exp(-\beta t) \tag{9}$$

where β is a parameter expressing the constant hazard, and exp is the base of the natural logarithms. The parameter β can be estimated quite simply as the number of events divided by the sum total duration of follow-up. The parameter is often expressed, therefore, as events per patient year. It also has the straightforward interpretation that it is inversely related to the time at which half the patients are expected to be dead:

$$\tfrac{1}{2} = \exp(-\beta t_{\frac{1}{2}}) \tag{10}$$
$$t_{\frac{1}{2}} = \ln(2)/\beta \tag{11}$$

Determination of a straight-line cumulative hazard, equivalent to a constant hazard, may be made by visual inspection of a semilogarithmic plot of the actuarial estimates. A somewhat more formal approach is to fit empirical cumulative hazard estimates by ordinary linear regression and examine a plot of residuals (observed minus predicted values) for absence of a systematic pattern (alternatively a time and time squared regression can be performed; the coefficient for the quadratic regression term should be not significantly different from zero). If a multiple-phase model is used, then a specific likelihood ratio test is made to indicate whether a constant hazard phase is adequate to explain the distribution of events. This latter method is the appropriate formal test. Grunkemeier[43] and Gross and Clark[15] illustrate techniques for determining if the constant hazard assumption is appropriate.

Certain misuses and misconceptions have arisen in the expression and calculation of constant hazard rates, in part because of their ease of computation. First, if the hazard function is actually changing with time, as it almost surely does either after an operation or even early

after the diagnosis of a congenital heart defect, then the calculated quantity is completely without meaning. Secondly, the effect of the constant hazard rate is often misinterpreted as the proportion of patients dying each year. But from equation (9), note that if $\beta = 0.1$ (10% per patient-year), this does *not* mean that after 1 year 90% of patients will be alive, after 2 years 80%, and 5 years 50%. Instead, at the end of 1 year $\exp(-0.1) = 0.905$, or 90.5%, will be alive, at 2 years $\exp(-0.1.2) = 0.819$ or 81.9%, and at 5 years $\exp(-0.1.5) = 0.607$ or 60.7%.

Analysis of time-varying hazard

Rarely has the distribution of events after some invasive form of treatment of congenital heart disease taken the form of a constant hazard. Thus the time-varying hazard function must be described. When the hazard varies with time, parameters relating to the distribution of the event are estimated in a way that is completely analogous to the expression of the distribution of a variable such as cardiac index by two parameters, the mean and the standard deviation[18]. For describing

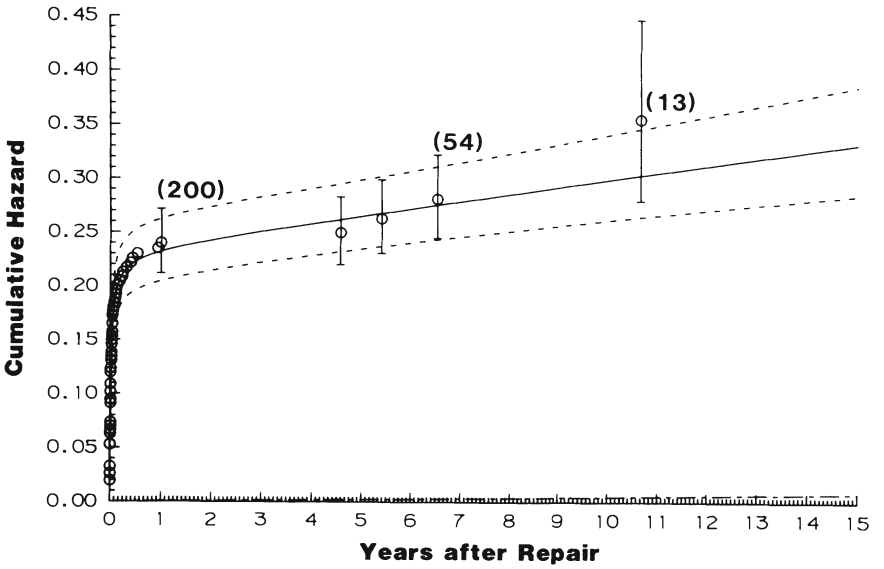


Figure 3.4 Parametric estimate of the cumulative hazard function after repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n = 310$; 70 deaths). The non-parametric product limit estimates (Figure 3.3) are shown superimposed on the parametric estimate and its 70% confidence limits. The cumulative hazard function for the matched general population is depicted by the dash-dot-dash line. The apparent divergence of the completely independent parametric and non-parametric estimates of cumulative hazard at 11 years is assumed to be due to the recognized overestimation of hazard by the non-parametric method at the extreme end of the curve when few subjects remain at risk

time-related hazard, however, two parameters rarely suffice, so flexible parametric functions have been developed by many investigators which can quite faithfully portray a wide range of shapes in the distribution of events[15, 21, 29].

One such parametric survival analysis system has been developed at UAB[18]. It is conceptualized in terms of the cumulative hazard function since (a) the empirical cumulative hazard can be used as a comparison to judge the reasonableness of the parametric estimate (Figure 3.4); (b) the cumulative hazard function is easily exponentiated into a survivorship function (Figure 3.5) and differentiated into the hazard function (Figure 3.6), both of which provide complementary and useful information; and (c) initial starting guesses for the shaping parameters may be obtained from the empirical cumulative hazard function.

The system is made both robust and mathematically tractable by considering that a possibly quite complex distribution of events over time is structured so as to be amenable to decomposition into a mixture of a small number of simpler, medically meaningful, time-related phases which are overlapping and additive. Thus, immediately after repair of a congenital heart anomaly, there generally is a phase of high risk which rapidly diminishes (the equations also permit the early hazard phase to rise to a peak before it diminishes in influence). This

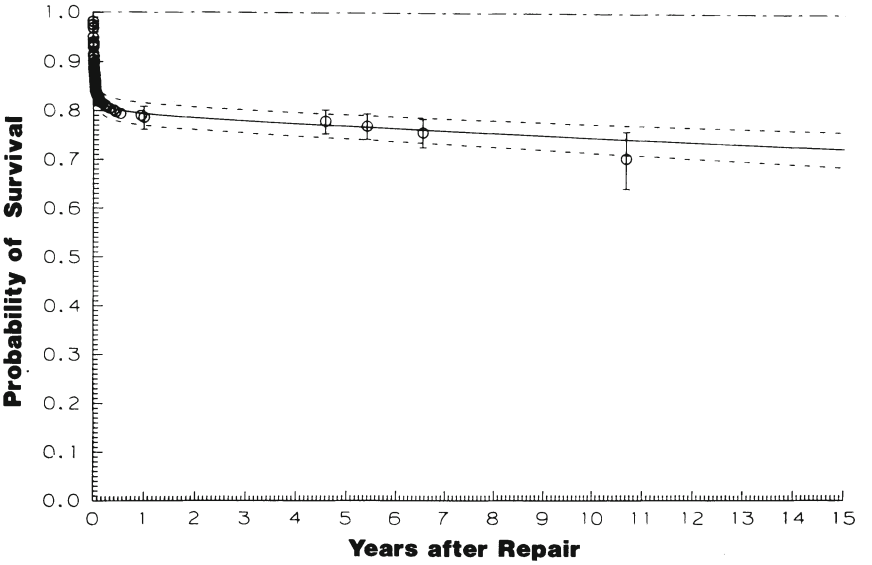


Figure 3.5 Parametric estimate of the probability of survival after repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n=310$; 70 deaths). The non-parametric product-limit estimates (Figure 3.1) are shown superimposed on the parametric estimate and its 70% confidence limits. They demonstrate informally the general agreement between the two independent methods for estimating time-related survival. The depiction is otherwise as in Figure 3.1

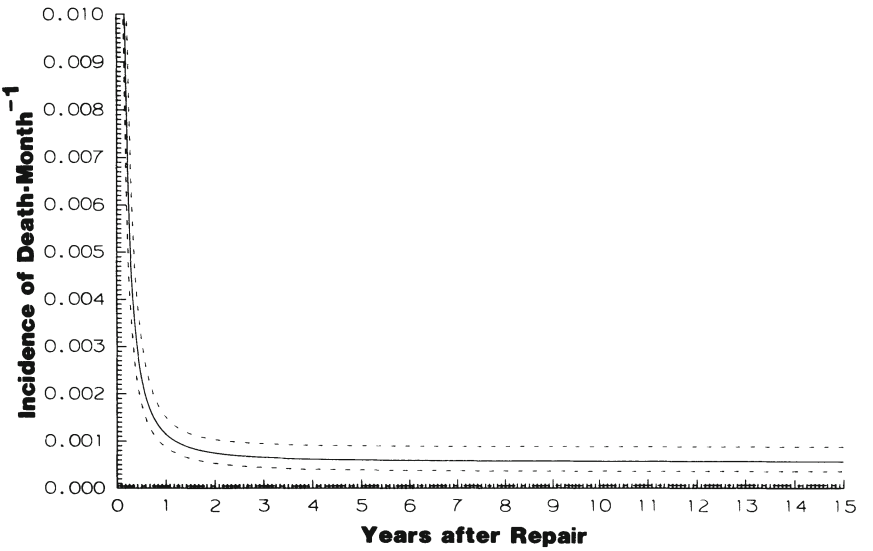


Figure 3.6 Parametric estimate of the hazard function for death after repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n = 310$; 70 deaths). The two phases of hazard identified are evident: a constant phase which affects survival throughout the period of follow-up and an early decreasing phase immediately after operation, extending for about 2 years thereafter, which is added to the constant hazard phase. The dashed lines enclose the 70% confidence limits of the hazard function. The barely perceptible dash-dot-dash line at the bottom of the figure is the hazard function for an age–race–sex matched general population. At 0, 5 and 15 years after operation its value is 0.000037, 0.000042, and 0.000071 per month, respectively, compared with the constant hazard in the surgical experience of 0.00054

phase is of variable duration, but in our experience has often extended some months beyond hospital dismissal. This early phase of high risk often merges in time with a lower phase of constant hazard. We have expressed this lower phase as one of constant influence throughout the period of follow-up. It in part reflects the expected naturally occurring modes of death (such as death from trauma in children), but it also may represent some deaths from the residual effects of the congenital heart disease and its treatment. Eventually, perhaps after many years, a phase of increasing hazard is expected to become influential, if from nothing else than natural events. However, late events of the original disease and its treatment may have effects in this phase as well.

The mathematical equation describing the parametric system can be stated in reasonably simple form:

$$\Lambda(t,\boldsymbol{x}) = \sum_{j=1}^{k} \mu j(\boldsymbol{x}j,\boldsymbol{\beta}j) \cdot Gj(t,\boldsymbol{\Theta}j) \qquad (12)$$

where $\Lambda(t)$ is the time-related cumulative hazard function, Σ indicates that there are 1 to k additive phases, μj is a scaling parameter related to the strength of influence of each phase, and $Gj(t,\boldsymbol{\Theta}j)$ stands for a

time-related shaping equation whose shaping parameters are indicated by $\boldsymbol{\Theta}$. The number of phases, their scaling parameters, and the number and magnitude of their shaping parameters are estimated statistically from the data using the method of maximum likelihood. The data consist simply of the follow-up interval for each patient and an indicator variable as to whether the patient is censored at that time or has experienced an event.

For the constant hazard phase, $G(t,\boldsymbol{\Theta}) = t$; that is, it is simply a linear increase in cumulative hazard with time. Its scaling parameter is the slop of this line and the constant value of the hazard function across time.

For the early phase a very flexible three-parameter model is used:

$$G_1(t,\boldsymbol{\Theta}) = \left[1 + \frac{m}{|m|}\left(\frac{|m|+m}{2|m|} + \alpha|m|vt\right)^{-1/v}\right]^{-1/m} \tag{13}$$

Although this model appears formidable, the sign and magnitude of the parameters m and v, when fitted to data, permit a large family of much simpler equations to be derived. For example, if m is greater than zero, and if the substitution $\rho = 1/(\alpha|m|v)$ is made, then:

$$G_1(t,\boldsymbol{\Theta}) = \left[1 + (t/\rho)^{-1/v}\right]^{-1/m} \tag{14}$$

Further, m is often close to 1, which simplifies the equation even further to $t^{1/v}/(t^{1/v} + \rho^{1/v})$, and so forth. The parameter ρ relates to the duration of the influence of the early hazard phase (in fact, to the half-time of cumulative hazard from time = 0). The exponent v relates to the shape of the hazard function as time approaches zero. It permits the hazard function to rise to a peak from the baseline, or to start at infinity and fall, or to fall from any intermediate value. In the analysis, as many simplifications of the equation are made as are suggested by the data so that the final model is in simplest form with the fewest number of parameters (Law of Parsimony). The most important fact about the form of the shaping function for the early phase is that its influence approaches zero as time increases. Thus its scaling parameter actually represents the total area beneath the early phase component of the hazard function.

For the late phase of increasing risk we have employed an exponential function of normalized time, also having up to 3 parameters:

$$G_3(t,\Theta) = \left[\exp(t/\delta)^{\gamma-1}\right]^{\eta} \tag{15}$$

The most important is δ, a parameter which indicates the point in time when risk is decidedly accelerated. The other two accommodate what is in essence a longer or shorter delay before the risk accelerates (γ), and a parameter (η) whose magnitude is indicative of a simplification of the equation, just as in the early phase equation. Under most circumstances, we have found that a simplification to the single parameter δ is adequate to fit the data:

$$G_3(t,\boldsymbol{\Theta}) = \exp(t/\delta)^2 - 1 \tag{16}$$

It is difficult to imagine a situation which would demand that all phases and all shaping and scaling parameters be used. Rather, they permit great flexibility in identifying structure in diverse distributions of events using really quite simple equations that are most appropriate to the data. This makes the system quite robust. Nevertheless, the system is desirably constrained so as to be little influenced by small deviations apparent in the non-parametric estimates (that is, the system generates a smooth curve) and by 'tail-end' effects which plague all non-parametric methods. For example, not shown on the actuarial graph in Figure 3.1 is the fact that the patient with the longest follow-up died; depicting an estimate of zero at 15 years would surely be spurious. This data point was retained in the parametric analyses, which are not sensitive to this end-effect.

Note that no attempt is made *a priori* to associate an individual death (or other event) with any particular phase. Rather, the distribution of all events generates the appropriate structure of the hazard function components. However, after the parameters are estimated a particular death may be said with a specific probability to be associated with each phase. This probability is based on the relative strength of the hazard function for each phase in relation to the overall hazard function, at the time of the death. Nevertheless, the method does estimate the number of deaths attributed to each hazard phase. The number is found by calculating the cumulative hazard experienced by each person to the time of follow-up (or death), and summing all such values. (The total number of observed deaths is guaranteed to be the sum of the deaths calculated in this way for each phase.)

Once the parameters in either the UAB system of equations or any other completely parametric system of equations have been determined, a graphic portrayal of the hazard function and the survivorship function and their confidence intervals is made (see Figures 3.5 and 3.6).

MULTIVARIATE RISK FACTOR ANALYSIS FOR TIME-RELATED EVENTS

Definitions

Factors or variables which can be shown to increase the probability of an untoward event are termed *incremental risk factors*[7, 44]. These can be considered as correlations or associations with such events. In the surgical setting, they can also be considered as variables which affect the degree of difficulty of preventing surgical failures. Because an untoward event, such as surgical failure, is dependent upon multiple factors which interact one with another to increment the risk, they have been called *incremental* risk factors.

Risk factors are not the causes of the events being analysed, but their identification does aid in designing clinical and laboratory re-

search to identify causes. Knowledge of risk factors may also lead to altered patient management programmes to reduce the risk of certain events.

Either because the size of the group of patients is small, or the patients extremely heterogeneous, a risk factor analysis using multivariate techniques may be inappropriate. Risk factor analysis is also less likely to be satisfactory when there are very few events or a very high incidence of events within a very short time-frame. Traditional methods of insight and intuition are the most useful ones for drawing inferences from such data in some of these situations.

The process

The process of performing a multivariate analysis of incremental risk factors is a challenging one involving medical and statistical investigators who have quite intimate knowledge of the study's purpose, its variables, and its data[44, 45]. The process is aided by modern high-speed computers which make the actual calculations and assist in selection and rejection of variables.

The process of identifying risk factors and of estimating the likelihood of their association with the event being due to chance involves the empirical use of a simple linear model of demographic, clinical, morphological, and surgical variables (x) in relationship to an expression of outcome (z):

$$z = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta x_k. \qquad (17)$$

in this equation β_0 is an intercept term, and the βs are regression coefficients which quantify the strength and direction, positive or negative, of the association of the risk factor to the event. For a change of one unit within x_i, z will change by β_i. In the statistical estimating process not only are βs estimated (as adjusted for all other variables which simultaneously appear in the model) but their standard deviations as well (s_i). The relationship between $\hat{\beta}_i$ and its variability as measured by $\hat{s}_i$ is one way to determine the statistical significance of the association. It is assumed that at least for when the n is large, the ratio $\hat{\beta}_i/\hat{s}_i$ is asymptotically normally distributed. Therefore, a p-value for the null hypothesis that $\beta_i = 0$ can be determined. It is this p-value which estimates the likelihood of the association being due to chance. (Alternatively the likelihood ratio test may be used with the variable included, then excluded from the model.)

As a matter of style, and in keeping with the notion of incrementing the risk, variables are entered into the analysis in such a way that, insofar as possible, the coefficient representing the strength of association for a unit change in the risk factor has a positive sign.

Risk factor analysis according to the structure of events across time

An important component of the multivariate analysis of risk factors is the form of z to which the incremental risk factors are related. In survival analysis, this function may be an equation such as a logistic equation[22]. More generally, the risk factors are related in some way to the time-related structure of the distribution of events. All such analyses require iterative procedures for determining the βs, and perhaps shaping parameters as well. That is, based on the data and specific criteria, the computer must make a series of successively refined 'guesses' at the parameter estimates. Such processes require a great deal of computer time and resources, but are essential to the medical inferential process. Below, we consider three forms for the structure of the distribution of time-related events.

Risk factors for a constant hazard

The first parametric analysis of survival using modern methods was by Fiegel and Zelen in 1965[26], and was extended to censored observations by Zippin and Armitage in 1966[46]. They related risk factors to the inverse of the constant hazard rate:

$$1/\lambda = \beta_0 + \beta_1 x_1 \ldots \tag{18}$$

Since $1/\lambda$ is directly proportional to length of survival (a small hazard means a larger lifetime), the 'risk' factors actually were related to longer, rather than shorter, survival. Procedures for estimating the coefficients are given by these authors and also by Gross and Clark[15].

Since the hazard function is a strictly positive quantity, the constant hazard analysis might better be performed using the function:

$$\lambda = \exp(\beta_0 + \beta_1 x_1 \ldots). \tag{19}$$

At least some portion of the survival curve for patients undergoing repair of congenital heart disease is reasonably approximated by a constant hazard.

Risk factors for a structurally unspecified hazard (Cox Proportional Hazards Model)

In 1972 D.R. Cox proposed what has become the most widely employed regression scheme for estimating risk factors for survival data[25]. He proposed that:

$$\lambda(t) = \lambda_0(t)\, f(\boldsymbol{x}, \boldsymbol{\beta}). \tag{20}$$

That is, some underlying, structurally unspecified hazard function $\lambda_0(t)$ is shifted up and down by some function (f) of risk factors (x), and

their coefficients ($\boldsymbol{\beta}$). The form of $f(\boldsymbol{x}, \boldsymbol{\beta})$ is most tractable when it is made to be exponential:

$$f(\boldsymbol{x}, \boldsymbol{\beta}) = \exp(\beta_1 x_1 + \beta_2 x_2 + \ \ldots \ + \beta_k x_k) \qquad (21)$$

No intercept is needed, since $\lambda_0(t)$ can be thought of as that intercept. This form of the regression equation implies that a risk factor causes a proportionate (not an additive) change in survival (see Appendix 2).

Cox showed that the regression coefficients could be estimated in the absence of any knowledge about structure in the underlying hazard function $\lambda_0(t)$. The method is thus parametric with respect to incremental risk factors, but non-parametric with respect to the hazard function. Assuming that proportionality of hazards holds (Appendix 2) and that risk factors retain their strength throughout the period of follow-up, a semblance of graphical portrayal of the influence of variables is possible by appropriately scaling non-parametric survival estimates for a given set of risk factors[47].

Because the early hazard phase after surgical intervention could dominate the analysis, it is prudent in practice to perform Cox regression analysis on late events only. Elimination of at least hospital deaths is appropriate; however the early hazard phase often extends beyond this, and it may be necessary to eliminate all patients with follow-up intervals (with or without events) less than some appropriate time (e.g. 3, 6, or 12 months). Such arbitrary decisions are unnecessary if a method for analysing multiple phases of time-varying hazard is employed.

Risk factors for time-varying hazard

When the distribution of events varies in a time-related pattern, we advocate estimating parameters which describe the structure of this hazard function, and relating incremental risk factors to each of the phases identified in this hazard function. While, theoretically at least, each of the shaping parameters in the UAB parametric system could be made a function of risk factors, it has been our observation that the parameters most sensitive to changes in risk factors are the scaling parameters.

In keeping with the Cox model, constant hazard and increasing hazard phases have been scaled by an exponential function of the risk factors. However, in keeping with the fact that the scaling parameter for the early hazard phase represents the total early risk (that is, the area beneath the early phase of hazard), and that logistic regression has been used to analyse the probability of early events, we have embedded the logistic regression equation into the early phase scaling function:

$$\mu = \ln[1 + \exp(\beta_0 + \beta_1 x_1 + \ \ldots \ \beta_k x_k)] \qquad (22)$$

By appropriate rearrangement of this equation, and using the relation between $S(t)$ and $\Lambda(t)$ given by equation (4):

$$\ln\{[1-S(\infty)]/S(\infty)\}=\beta_0+\beta_1 x_1+\ldots+\beta_k x_k \qquad (23)$$

where $1-S(\infty)$ is simply the total probability of an early phase event, and the entire left side of the equation is the logistic relationship.

Estimating the regression coefficients for each phase is done simultaneously, so that more than one stream of risk factors is being considered during the analysis. While such analyses are, therefore, complex, the final result fits well with medical knowledge. That is, the influence of some risk factors disappears in time, while others are always present, and yet others gain in importance.

An example of this process is the analysis of events after the repair of A-V canal defects. Table 3.1 lists the incremental risk factors for death following repair[7, 10]. To illustrate its use, this table and the resulting nomograms from solving the equation it represents, can be used to yield the best available estimate of the difference in risk imposed by the presence of an interventricular communication. The actuarial analysis can be stratified (Figure 3.7) to depict the overall difference in survival of the patients with and without an interventricular communication. However, it is likely that the prevalence of other risk factors is different in the two groups of patients, and these affect the

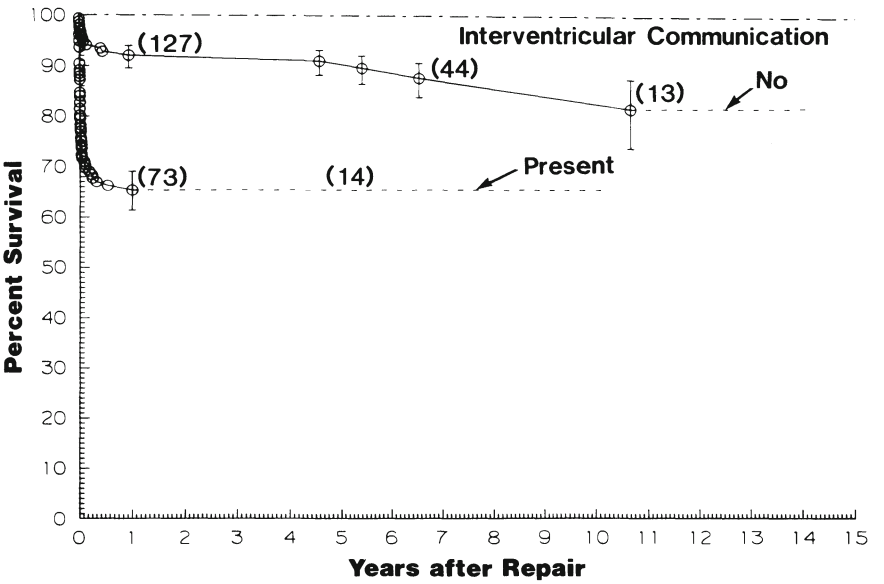


Figure 3.7 Actuarial analysis of survival following repair of atrioventricular septal (canal) defects stratified according to the presence or absence of an interventricular communication (UAB; 1967–1982; $n=310$, 70 deaths). Depiction is as in Figure 3.1

Table 3.1 Incremental risk factors for mortality during the entire follow-up period after repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n=310$; 70 deaths)

Incremental risk factor	*Time of influence (phase)*[a]			
	Throughout and constant		*Early and decreasing*	
	Coefficient $\pm$ *SD*	p-*value*	*Coefficient* $\pm$ *SD*	p-*value*
Demographic variables				
(Younger) age in months, at repair	—		-0.043 ± 0.0131	0.001
(Earlier) date of operation, in months from 1 January 1967	—		-0.024 ± 0.0062	<0.0001
Interaction of age with date of operation	—		0.00028 ± 0.000083	0.0009
Clinical variable				
(Increasing) level of disability (NYHA Class I–V)	1.0 ± 0.78	0.18	0.7 ± 0.21	0.0008
Morphological variables				
Interventricular communication	—		1.5 ± 0.48	0.001
(Increasing) severity of preoperative left A–V valve incompetence (Grade 0–5)	1.4 ± 0.49	0.005	—	
Accessory valve orifice	3.1 ± 0.86	0.0003	—	
Major associated cardiac anomaly	—		0.9 ± 0.36	0.02
Intercepts	-14.7		-0.77	

Abbreviations: AV = atrioventricular; NYHA = New York Heart Association; SD = standard deviation

[a] Two phases were identified in the hazard function (Figure 3.6), a phase of constant influence throughout the study period and an early phase of decreasing influence immediately after operation. Shaping parameters for equation (14) in the text are: $m=-1$, $\rho=0.1512$, and $v=0.6951$. The words in parentheses express verbally the direction of the risk.

stratified actuarial representation of survival. The best estimate of the true effect of an interventricular communication is, thus, obtained from the multivariate analysis by holding the value for all other risk factors constant, and then comparing two equations, in one of which interventricular communication is entered 'no' and in the other 'yes' (Figure 3.8).

This type of portrayal uses the time-related survival data and their analysis to the maximum extent for drawing inferences. It does make several assumptions, however. The most important assumption is that

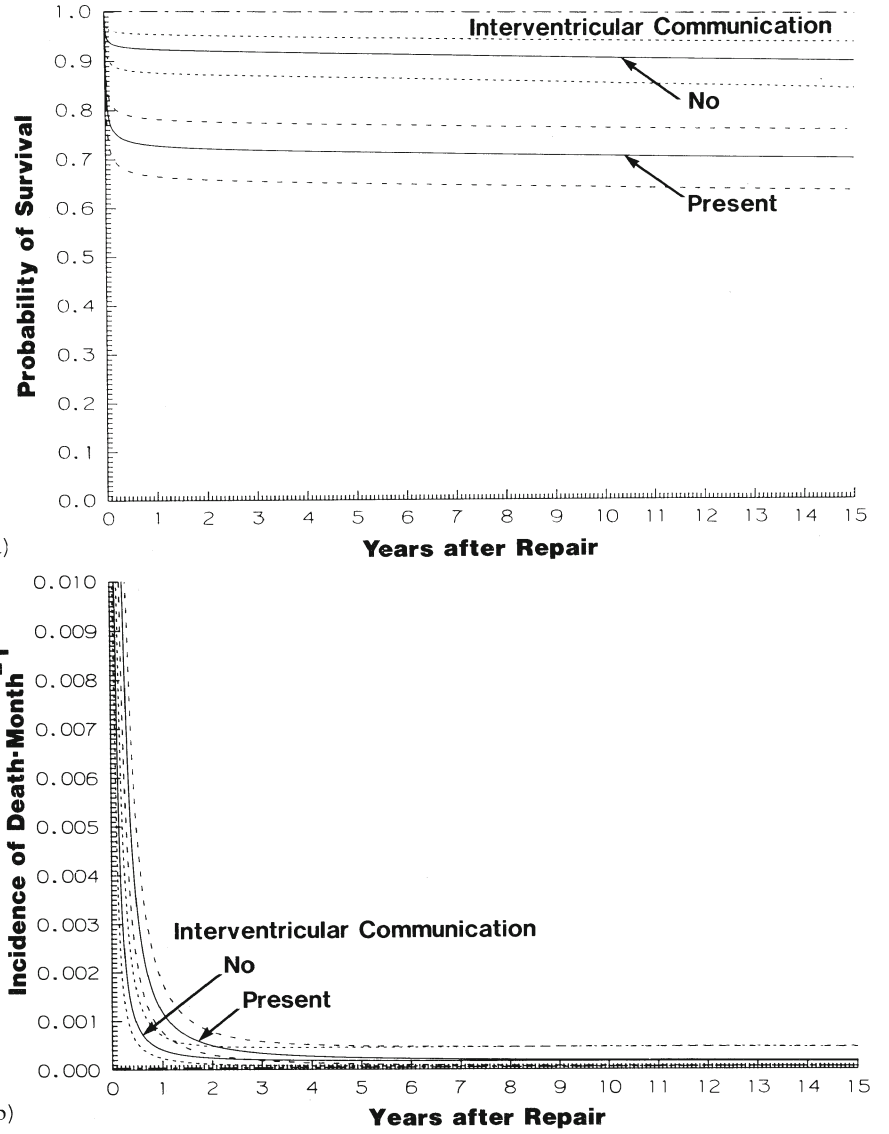


Figure 3.8 Parametric representation of the independent effect of an interventricular communication on survival after repair of atrioventricular septal (canal) defects (UAB; 1967–1982; $n = 310$; 70 deaths). To construct this figure, the coefficients in both phases of hazard listed in Table 3.1 were utilized as follows. Date of operation was set to the recent era (1980) after which the influence of young age was no longer present, the functional status was set to III, the grade of left atrioventricular valve incompetence preoperatively was set at mild-to-moderate (grade 2), accessory atrioventricular valve orifice was set to 'no' (0), and the presence of major associated cardiac anomalies was set to 'no' (0). Thus, the only factor which was changed in constructing the figure was the presence (1) or absence (0) of an interventricular communication

(a) Parametric representation of the probability of survival. Presentation is as in Figure 3.5

(b) Hazard function. Notice that the presence of an interventricular communication affects only the early, decreasing phase of hazard. Also notice that for the conditions specified the hazard function more closely approaches that of the matched general population, with its lower confidence limits just touching the estimate of survival in the matched population ($p = 0.15$) by 10 years after operation

the hypothesis of continuity in nature is valid (see earlier discussion). This hypothesis permits the display of predicted results for a hypothetical patient (or a real new patient), even if a patient with precisely the characteristics portrayed has not been seen previously, although they do fall between values previously observed (so-called interpolation). However, care must be exercised not to extrapolate beyond the data analysed in the experience without explicit indication as to where this has been done (for example, by use of a dotted line).

COMPARISONS INVOLVING TIME-RELATED EVENTS

Comparisons with natural history

Many congenital cardiac anomalies are associated with premature death. In part because of the development of cardiac surgery before the advent of widespread population studies and detailed diagnostic techniques, the survival curve of untreated patients with cardiac anomalies is described only for the anomaly in general, with little information on the subsets within the anomaly. Nevertheless, some useful comparisons of surgical results to those expected in untreated patients can be made[4, 6, 48].

The major limitation of these studies is that the natural history is undoubtedly influenced by risk factors such as morphological variants of the anomaly, associated cardiovascular and somatic anomalies, type and aggressiveness of medical treatment, the era, the geographical location of the patient, and the time-relatedness of the clinical status of such individuals. It is, thus, sometimes difficult to generate a reliable estimate of the natural history for an infant of a specific age, with a specific cardiac condition, and in a specific functional condition.

When data are available, age-related survival and hazard functions can be constructed accompanied by a measure of uncertainty. Parametric methods are particularly suited to combining longitudinal data from autopsy series and cross-sectional data from population studies[4, 6]. The process, then, of comparing the time-related results of surgical treatment with the age-related natural history involves the estimation of age-specific survival functions for both. If the surgical risk is not age-related, then the average curve is used throughout. The relative overlap of confidence limits of these curves may be then examined. In addition, a specific one- or two-tailed test of the difference may be estimated. Construction of a test statistic for the latter may not be straightforward. If a parametric model has been used, we advocate making the comparison after applying to both curves the same transform used to construct their individual confidence limits (e.g. the logistic transform). Then:

$$Z = \frac{f(P_1) - f(P_2)}{\sqrt{\text{Var}\,[f(P_1)] + \text{Var}\,[f(P_2)]}} \qquad (24)$$

The test statistic Z is then used to find a p-value whch quantitates the probability that the difference in the functions of these probabilities, $f(P_1)$ and $f(P_2)$, given their variances (var), is due to chance. Note that such a comparison may be made at any point on the curves (in fact, a time-related curve of p-values may be generated).

In specific circumstances, not just survival, but freedom from symptoms as well may be used in the comparisons. Often this involves the amalgamation of diverse sets of data, a possibly complex process[5, 48]. Calculation of a test statistic with approximately normally distributed properties may then require use of such transformations as the arcsine-square root transformation[49].

Comparisons with a general population

Treatment of patients with congenital heart disease has as its goal the cure of the patient, that is, the restoration of a usual life expectancy and full functional capacity[44]. If with current techniques cure is not attainable, then treatment has the more limited goal of palliation, that is, improvement in the life expectancy and functional capacity over that imposed by the disease. Comparison of the survival of treated patients with that expected in a general population matched with the patient population for age, sex, and race is one step in determining if the goal of treatment has been achieved.

Several methods for comparing the survival of a group of patients with that of a general population have been proposed, each with specific usefulness in drawing inferences about the possibility of premature death[21]. A comparison can be made between the number of deaths observed in the study group over the interval of follow-up with that expected in a matched general population[50] (see Appendix 3 for a description of a method for constructing a general population life table matched for patients' age, race, and gender, and Appendix 4 for details of the method and controversies associated with the calculation of the expected number of deaths). In a study of post-hospital deaths after repair of tetralogy of Fallot, Katz *et al.* used such a method to determine that three deaths were expected during the follow-up period[9]. Nine deaths were, however, observed. This number of excess (premature) deaths was unlikely to be due to chance ($p = 0.0005$). Interestingly enough, prior to this calculation, three of the deaths were determined to be in modes unrelated to the cardiac anomaly or its correction. In Studer *et al.*'s study of post-hospital deaths after repair of atrioventricular canal defects, an excess number of deaths over the 2.1 expected was also found[10]. Again, two patients died in modes considered to be non-cardiac. While these findings are reassuring, it is sobering to note that in both studies most post-hospital deaths must be considered premature.

In both studies cited, subgroups of individuals could be identified whose life expectancy approached that of a matched general popula-

tion, and who can be considered, therefore, to have avoided premature death. An appropriate way informally to compare either the actuarial or parametrically determined estimate of survival of a study group with that of a matched general population is to superimpose both on the same graphical display (see Figure 3.1). The population survival curve is generally that for a weighted average of individuals of each sex and race having the median age observed for each sex–race subgroup (see Appendix 3). Comparison can be made by examining the degree of overlap of 70% or 90% actuarial confidence limits (p approximately 0.15 and 0.05, respectively, for a difference). A direct comparison, either at the time of an event using the actuarial method or at any specified time using the parametric survival method, may be made using a normal or t-distribution statistic of the difference between observed and population survival divided by the standard deviation of the observed estimates.

Both of these methods evaluate relative survival over the entire time interval of follow-up. It is possible, however, that the instantaneous risk (hazard function) for death in the study group may be changing with time. Patients initially at a high risk of premature death may eventually approach a risk more closely approximating that in the general population. Thus, any inferences from comparisons of survival after either medical or surgical intervention to that in the general population are incomplete, unless they take into consideration the separate pattern across time of the distribution of deaths after such interventions. Breslow has suggested that a 'local' (that is, at every instant in time) estimate of 'cure', or lack of risk of premature death, be made by comparing the hazard function for death in the study group to that of the matched general population[51]. The availability of the hazard function from a parametric survival analysis of clinical data for such comparisons is one of the important features of using a parametric method. The hazard function for death in the general population is calculated either empirically at mid-year intervals or parametrically as described and illustrated in Appendix 3.

Several methods of comparison of the hazard functions may be employed. The informal observation of the degree of overlap of the confidence limits around the estimated hazard function for the clinical experience is always informative (see Figure 3.6). The ratio of observed and expected hazard functions can be calculated and tested also against the expected value of 1 at each time instant (this ratio can be displayed graphically)[21, 51]. Comparisons in the hazard function domain may reveal that the risk over the follow-up period never approaches that of the general population, or that it has reached it. It is also possible to observe a later departure from the risk in the general population (see Kirklin, Blackstone and Roger's analysis of survival after coronary artery bypass grafting in adult patients for an example of this phenomenon[8]). The comparison using the survival function is complementary to the comparison of local behaviour using the hazard function,

since it is possible for the observed hazard function to have confidence limits completely overlapping the hazard function for the general population, and yet for the accumulative effect of that hazard function (as assessed by the survival curve) to demonstrate an excess number of observed deaths.

If age, race, or sex have been demonstrated to affect survival after a corrective operation for a congenital heart defect, comparisons of parametrically derived survival and hazard functions should employ the appropriate age–race–sex matched life table specifically calculated for conditions identical to those portrayed in the analysis presented, rather than the overall matched life table. Tables of age-adjusted life expectancy after treatment of some congenital heart lesions have been compiled by Singer and Levinson[3], and various strategies for their comparison with the general population reviewed by Gail and Ware[52], Hakulinen[53], Lilienfeld and Pyne[54], and Elandt-Johnson and Johnson[21]. Oleinick and Mantel have suggested that a further refinement for such comparisons may be possible by using life tables specific for the cohort of patients being studied (that is, not only is the life table matched for age, sex, and race but also for year of birth)[55].

Two arguments are raised against using any such comparisons, formal or informal, with survival of a general population. The first is that the assumption is made that the survival of the general population is unaffected by deaths related to the disease being studied. This argument may be cogent with respect to ischaemic heart disease; however, because of its relative rarity congenital heart disease affects the population life table negligibly[56]. Thus, use of the so-called decrement life tables with congenital heart disease eliminated is probably not necessary. The second argument is that the patient population may not be matched socio-economically and determination of avoidance of premature death may be underestimated using the general population life table. Again, this may be less of a problem for congenital heart disease today than it is for patients with acquired heart disease. Some advocate, however, use of insured population life tables, rather than governmental life tables, in an attempt to match patients socio-economically with those in the general population who have life insurance. It is important to understand, however, that the use of a population comparison for drawing inferences concerning premature death lies not so much in the absolute numerical comparison as in its service as a useful reference point.

Comparisons between varying treatment modalities

Inferences from comparisons of time-related events, such as death, after different treatment modalities of a condition (such as the subclavian flap repair versus end-to-end anastomosis for the repair of coarctation in neonates and infants) are important for optimizing current treatment protocols and developing new information and techniques

to improve results. The most reliable inferences from such comparisons are afforded by randomized clinical trials. Their advantage is that the treatments are assessed concurrently and that unmeasured factors possibly influencing the comparison may be neutralized by the randomization process. In congenital heart disease, the number of patients available for randomization may be undesirably small, one reason for the paucity of such studies. A small number (n) of available patients protracts the entry of patients into the study and thus may not offer truly concurrent comparisons; also in this setting there may not be a homogeneous sample of patients. The small n also reduces the power of any comparison.

Observational studies of patients in predetermined treatment protocols provide another mechanism for making comparisons. Often these are not concurrent studies, but with care reasonable inferences can be drawn from such comparisons. Comparisons of the results of different treatment protocols in different institutions are more difficult, and inferences from these are drawn with caution.

If the endpoints for such studies are time-related events, then the several different methods described in this chapter may be applied to the comparison. The most reliable method is to make the comparison part of a multivariate analysis of incremental risk factors with a specific test of the effect of treatment modality. In this way, measured differences between the patients treated by each protocol are taken into account, and the specific effect of the different treatments evaluated. The treatment-specific differences can be demonstrated mathematically by solving two equations for hazard function and survivorship in which all the risk factors except the specific treatments being compared are given the same values. In one equation the specific treatment is entered as 'no', in the other 'yes'. This is the system of using two multivariate equations to compare results of treatment. Of course if neither treatment is a risk factor, the multivariate analysis has already indicated that neither treatment is superior with regard to the time-related event being studied. This technique is particularly powerful in observational studies with relatively large numbers of patients, and in many situations may offer the only practical technique for treatment-specific comparisons.

The planning of an analysis of an observational study often requires careful thought. For example, in the comparison of treatment protocols that are sequential, the possibly confounding effect of date of operation must be considered. In the study of a one-stage versus multistage treatment protocol, the selection of time zero for the time-related analyses poses a challenge. Ideally, the entire curve of the time-related event under study is assessed starting at the initiation of treatment. It is possible that the resulting hazard function of a staged repair is of very different structure from that after a one-stage procedure. The comparison will often then need to be made by the use of two multivariate equations, entering one-stage repair yes in one, no in the other.

The assessment of a staged treatment protocol introduces time-varying covariates, yet another area of intense research interest in survival analysis. A time-varying covariate is a risk factor which changes in value across time, and that change is to be either assessed or taken into account. For example, the variable 'complete repair' may be set to 'no' initially in the analysis of events after the first stage of palliation, and is set to 'yes' on the date of definitive repair. The appropriate incorporation of such risk factors into an analysis was suggested by Cox in his original description of his regression scheme[27]. Various approaches to the appropriate modelling and incorporation of such factors into completely parametric methods for analysis of time-related events are being investigated, but the Cox regression setting is currently the only readily available model for performing such assessments.

Interinstitutional comparisons, although difficult, are of value because assessment of treatment superiority within one institution is open to the criticism that inferences made from it are applicable only to that local setting. When complete data from the different institutions are available, a risk factor analysis is made, entering the institutions themselves in the variables tested in the multivariate analysis.

Although such analyses of time-related events would seem to provide the most secure and clinically relevant comparisons of varying treatment modalities, in practice there are limitations. If the event used in the comparison is relatively rare under any of the treatment modalities, the identification of a clinically important and statistically significant difference requires a large number of patients, perhaps followed for many years. In such situations it may be possible to use another end point for the comparison, such as a relevant, but more frequently occurring, event, or a more-or-less continuous variable which has a higher information content and requires a smaller sample size. The second limitation is the protracted period of follow-up itself. Over that period, newer treatment modalities may be introduced making the study and its findings obsolete. Finally, the impact of differing surgical modalities might affect only one phase of time-varying hazard, such as the early phase. If this is the case, prolonged follow-up will be unrewarding, and only the relative immediate short-term benefits of the treatments should be compared.

REFINEMENTS IN THE ANALYSIS OF SURVIVAL

Modes of death (analysis of competing risks)

In order to refine the risk factors associated with death and better to understand the prevention of death, it is helpful to categorize deaths after cardiac surgery by the modes of death[44]. The mode of death is defined as the syndrome or pattern which appears to be primarily associated with the death. Generally the mode describes a subsystem

failure. The modes of death typically include death with cardiac failure (which may be acute, within hours of the operation; subacute, characterized by a low cardiac output persisting for some period of time after a procedure and often associated with secondary failure of multiple subsystems; or chronic heart failure), death with respiratory failure, sudden death (unexpected death within 1 hour of the onset of distress, in an otherwise well patient[57]), death with haemorrhage, death with infection, and death with arrhythmia. The unique distribution across time is determined for each mode of death, and a risk factor analysis in the hazard function domain is made for each mode[58]. Categorizing each death according to mode avoids premature assignment of the cause of death. It is also not dependent upon autopsy findings, which are frequently missing, and is generally not controversial compared with the cause of death. While the number of events for analysis is decreased, the potential for added information of a useful nature which can be so derived makes a mode-specific analysis a worthwhile endeavour.

Certain limitations, both practical and theoretical, must be recognized in performing such analyses. In an analysis of all deaths there is no equivocation about the event. However, the lack of specificity, in the event death, limits the inferences which can be drawn. The assignment of a mode of death is, on the other hand, open to the possibility of a different interpretation of the medical information surrounding the death; so while an analysis of the modes of death may be highly informative it is more subject to uncertainty. Also, the variable autopsy findings within one mode of death indicate the caution that must be used in interpreting the results.

From a theoretical point of view, in time-related studies of a mode of death a form of non-independent censoring is introduced for the remaining modes of death. Since the censoring is now no longer independent (non-informative), certain biases are expected to occur in such analyses of modes of death. These have unknown effects. A substantial body of knowledge is being developed in analyses of this type, which are termed analyses of competing risks[59], and this may clarify these issues and encourage use of this potentially informative area of analysis.

Causes of death

While the specific mechanism of premature death after a surgical procedure is rarely known or agreed upon, there is a useful approach to assignment of a cause of premature death or any other event which represents a surgical failure. It is to consider that death (in the case of survival analysis) is caused either by human error, or by lack of scientific progress[44]. To reduce the risk of premature death, at least self and group education and discipline are required to minimize deaths from human error. Wigglesworth[60], Haddon[61], and Lawrence[62] have shown

in a wide spectrum of riskful situations that a creative approach to non-culpable human errors, to which all living human beings are susceptible, can result in lowering of their incidence and of the seriousness of their effects. Research and development are required to minimize future deaths that might occur from lack of scientific progress[2].

Thus a careful, unemotional, analytical consideration of the cause of premature death in each non-surviving patient may in and of itself be the most valuable part of a serious, contemplative survival analysis.

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APPENDIXES

Appendix 1: Product-limit actuarial estimates and their confidence limits

The product-limit[20] actuarial estimate $S(t_i)$ at the time interval t_i of the i'th event is calculated as follows.

Let:

N = the original number of individuals at risk for the event.
N_{ui} = the accumulated number of individuals censored by t_i.
N_{pi} = the total number of individuals known to have experienced the event by t_{i-1} (that is, the number of events occurring prior to time t_i).
N_{di} = the number of individuals experiencing the event at time = t_i.

By convention, if a patient is censored at exactly the same time as an observed event, the event is assumed to have occurred slightly preceding the censoring. At time t_i the number of patients at risk of the event is:

$$n_i = N - N_{ui} - N_{pi} \quad (1)$$

and the number of patients free of the event following the event(s) at t_i is:

$$r_i = n_i - N_{di} \tag{2}$$

The proportion of patients free of the event at t_i is thus r_i/n_i. The product-limit estimate $\hat{S}(t_i)$ of freedom from an event from time zero through t_i is the product (Π) of all such proportions:

$$\hat{S}(t_i) = \prod_{k=1}^{i} r_k/n_k \tag{3}$$

In practice, then, $\hat{S}(t_i) = \hat{S}(t_{t-1}) r_i/n_i$; that is, it is the product of the probability of surviving through the preceding event and the current event.

An obvious difficulty arises when the last event(s) occurs in the patient(s) with the longest duration of follow-up. Instead of allowing $r = 0$, we let

$$r_{\text{final}} = \frac{n_{\text{final}}}{(N+1)\hat{S}(t_{i-1})} \tag{4}$$

where n_{final} is the number of patients at the final calculation and $S(t_{i-1})$ is the survival probability up to the time of calculating the final estimate.

The variance $s(t_i)^2$ of $\hat{S}(t_i)$ is given by the equation[30]:

$$s(t_i)^2 = \hat{S}(t_i)^2 \left[\left(\prod_{k=1}^{i} \left\{ \frac{1}{r_k} - \frac{1}{n_k} + 1 \right\} \right) - 1 \right] \tag{5}$$

The standard deviation of $S(t_i)$ is the square root of $s(t_i)^2$.

Dr Malcolm Turner, Jr, Professor of Biostatistics and Biomathematics at The University of Alabama at Birmingham, has derived the formula for calculating the asymmetric confidence limits for the product-limit estimates based on a logistic transformation:

$$\text{CL}[S(t_i)] = \frac{\hat{S}(t_i)}{\hat{S}(t_i) + [1 - \hat{S}(t_i)] \cdot \exp\left[K \cdot \text{sign}/n_e(t_i)\right]} \tag{6}$$

where K is the test statistic from the normal distribution corresponding to the confidence coefficient; sign $= -1$ for the upper confidence limit and sign $= +1$ for the lower confidence limit; and $n_e(t_i)$ is:

$$n_e(t_i) = \hat{S}(t_i) \cdot [1 - \hat{S}(t_i)]/\text{s}(t_i) \tag{7}$$

Since at UAB we customarily use ± 1 standard deviation to express uncertainty, we recommend use of the equivalent 70% (or actually 68.3%) confidence limits, with the confidence coefficient $K = 1$. The confidence limits calculated by equations (6) and (7) are guaranteed to be contained within the interval 0–1, unlike the simple use of symmetrical standard deviations. The use of the logistic transformation[63]

is appealing to us rather than the use of the binomial approach suggested by Rothman[64], in part because the upper and lower limits converge to 1 as time approaches 0 and to 0 as time approaches infinity.

Appendix 2: Exploring the proportionality assumption in a Cox model

The Cox proportional hazards model for a single dichotomous (yes–no) variable is expressed as follows:

$$\lambda(t) = \lambda_0(t)\exp(\beta x) \tag{1}$$

where x can take on the value of 0 or 1 (for no, yes), β is an estimated regression coefficient, exp is the base of the natural logarithms, $\lambda_0(t)$ is the hazard function[27]. Transforming to survival functions:

$$S(t,x=0) = \exp[-\textstyle\int_0^t \lambda_0(u)\mathrm{d}u] \tag{2}$$

and

$$S(t,x=1) = \exp[-\exp(\beta)\textstyle\int_0^t \lambda_0(u)\mathrm{d}u] \tag{3}$$

thus,

$$S(t,x=1) = S(t,x=0)^{\alpha} \tag{4}$$

where

$$\alpha = \exp(\beta) \tag{5}$$

Since the integral of the hazard function is estimated by the cumulative hazard function as $\Lambda(t) = -\ln[S(t)]$, then each stratified actuarial curve is first transformed to cumulative hazard. Since equation (4) above becomes:

$$\Lambda(t,x=1) = \Lambda(t,x=0)\alpha \tag{6}$$

the logarithms of the cumulative hazard functions should display a constant separation one from another of $\ln(\alpha) = \beta$:

$$\ln[\Lambda(t,x=1)] = \ln[\Lambda(t,x=0)] + \beta \tag{7}$$

If the logarithm of the stratified empirical estimates of the cumulative hazard functions does not demonstrate such a relationship, it may be possible to transform the variable x or to include an interaction of x with time (x multiplied by time) as a covariate in the regression model. The latter interaction with time is permissible only if the implementation of the regression model permits such terms.

Appendix 3: Matched population life tables

A life table for the general population can be constructed which matches at least the age characteristics (and generally also the sex and race characteristics, if desired) of the patient group under study. The general population life table for the United States for 1976 is shown in Figure 3.9[65], as is its empirically estimated cumulative hazard and hazard function (calculated according to the method given by Gross and Clark[15]).

To construct an age-normalized life table for a group of patients, the median age T at entry into the study is determined, as is the survival to that median age in the general population $S(T)$. Survival $S_T(t)$ of the age-matched population for any time t after study entry is:

$$S_T(t) = S(t+T)/S(T) \tag{1}$$

To construct a life table matched not only for age but also for sex and race, the patients must be sorted according to sex and race. Then weighting coefficients are formed, based upon the number of cases in each sex–race category:

$$\alpha_{wm} = n_{wm}/N \tag{2}$$
$$\alpha_{wf} = n_{wf}/N \tag{3}$$
$$\alpha_{om} = n_{om}/N \tag{4}$$
$$\alpha_{of} = n_{of}/N \tag{5}$$

where wm = white male, wf = white female, om = other (race) male, of = other (race) female; n is the number of patients in each category, and N is the total number of cases:

$$N = n_{wm} + n_{om} + n_{wf} + n_{of} \tag{6}$$

and,

$$\alpha_{wm} + {}_{wf} + \alpha_{om} + \alpha_{of} = 1 \tag{7}$$

Within each of these four subgroups of patients, the median age at study entry is determined: T_{wm}, T_{wf}, T_{om}, and T_{of}. From the individual life tables, or a parametric equation (see below), for each sex–race group, the survival at that median age is determined: $S_{wm}(T)$, $S_{wf}(T)$, $S_{om}(T)$, and $S_{of}(T)$. Then the composite survival curve $S_c(t)$ is calculated, starting from the date of study entry ($t=0$) through as many years as desired:

$$\begin{aligned} S_c(t) = {} & \alpha_{wm} \cdot S_{wm}(t+T_{wm})/S_{wm}(T_{wm}) \\ & + \alpha_{wf} \cdot S_{wf}(t+T_{wf})/S_{wf}(T_{wf}) \\ & + \alpha_{om} \cdot S_{om}(t+T_{om})/S_{om}(T_{om}) \\ & + \alpha_{of} \cdot S_{of}(t+T_{of})/S_{of}(T_{of}) \end{aligned} \tag{8}$$

These population survival curves can be determined using empirical parametric fits to the US life table[17]. A series of equations for such use is shown in Table 3.2. They consist of three phases, an early decreasing hazard phase, a constant-hazard phase, and a late increasing-hazard phase. Each phase is scaled by a parametric function of E0, C0, and L0 respectively, and two shaping parameters are used in the early (E1, E2) and late (L1, L3) phases. Coefficients for the overall life table and for each sex–race subgroup are given in Table 3.3. Since the scaling coefficients are the ones that change most among the subcategories, a multivariate analysis was done to determine the 'incremental risk' of

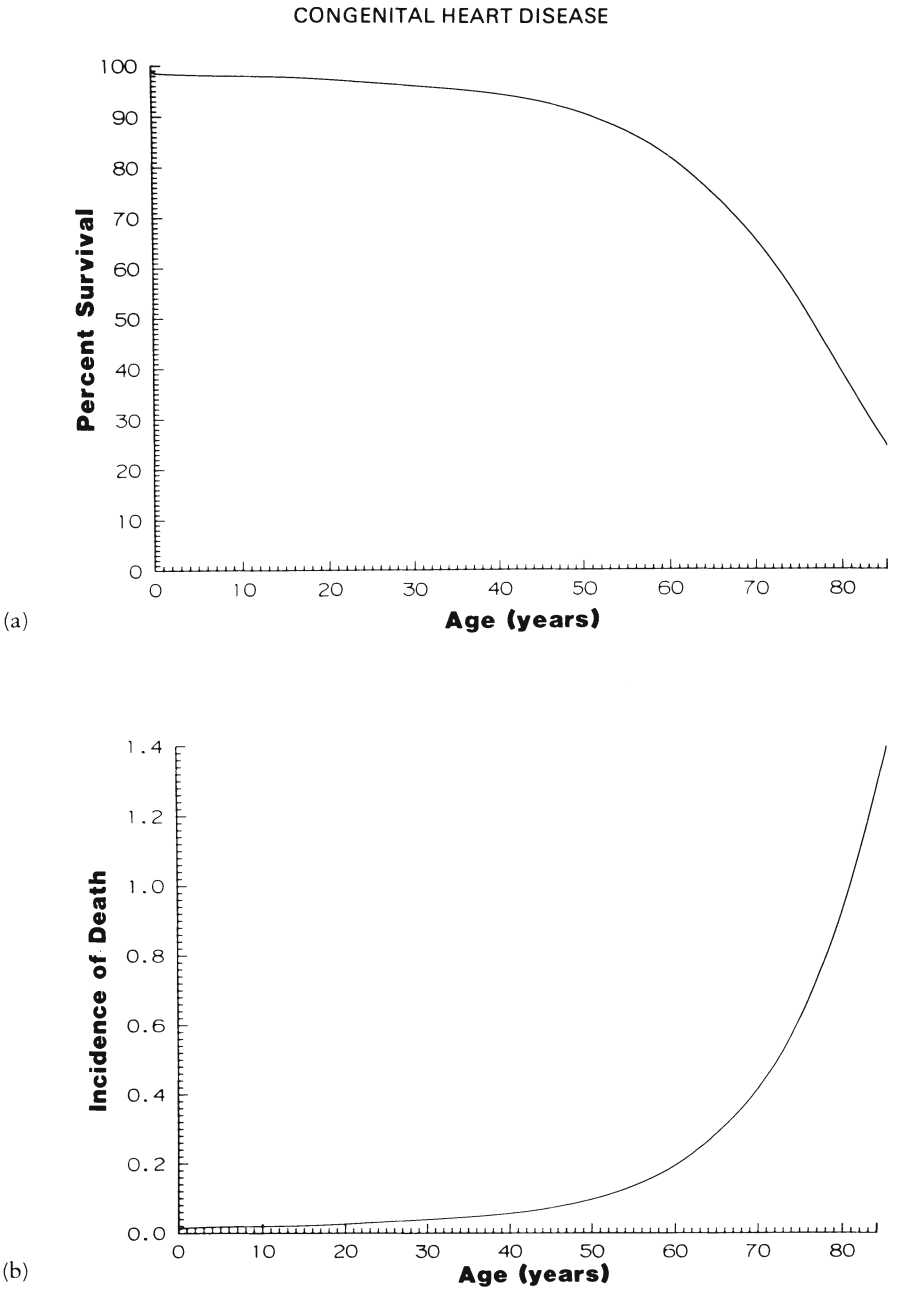
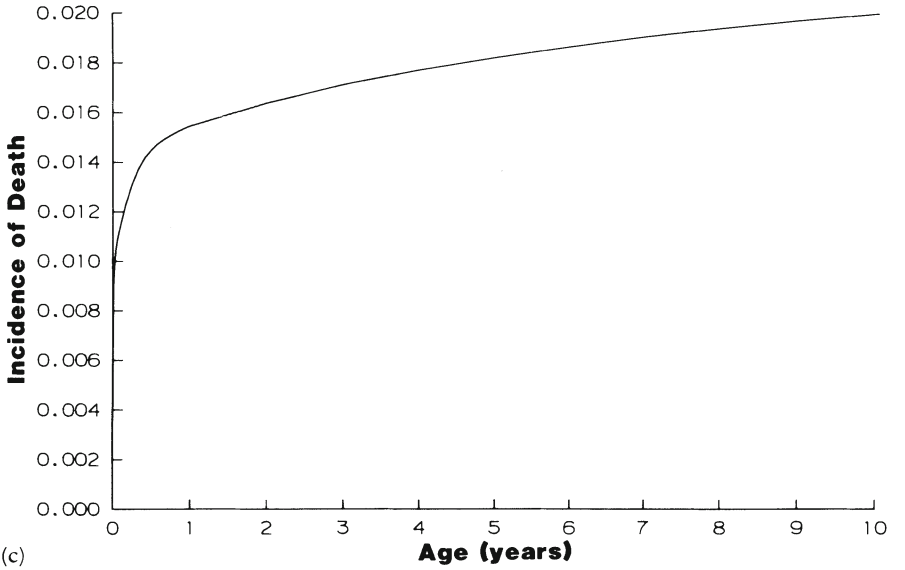
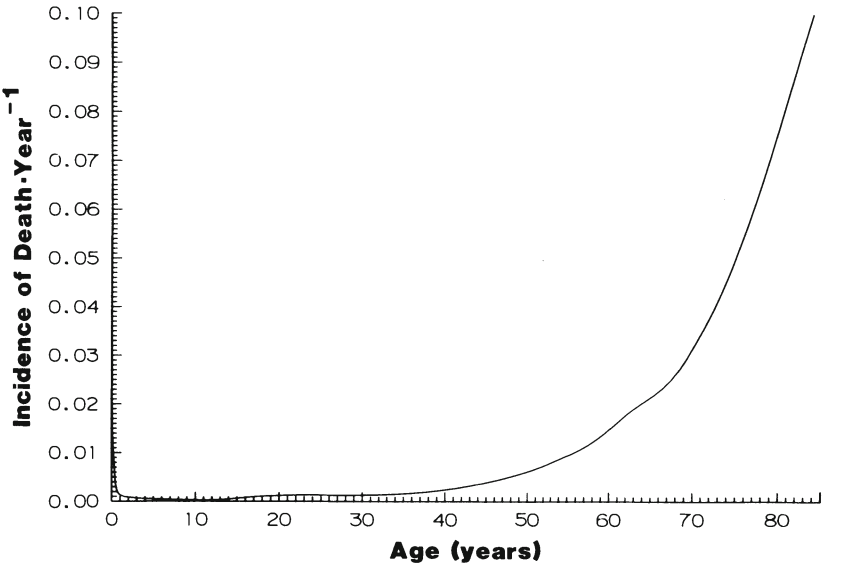


Figure 3.9 Non-parametric representation of the US Life Table for the year 1976, for all persons age 0–85 years showing: in (a) (top figure) survival from birth to 85 years; and in (b) (lower figure) cumulative hazard function derived by calculating the negative logarithm of the survival curve shown in (a)



(c)



(d)

Figure 3.9 (cont.) (c) (top figure) the cumulative hazard function as in (b) for the first 10 years of life. This illustrates the early decreasing hazard phase and constant phase marked by a linear rise in cumulative hazard; and in (d) (lower figure) hazard function, calculated as in Gross and Clark[15]. Notice the early decreasing phase, the constant hazard phase and the phase of accelerating risk. Although the numbers beyond age 85 years depicted in this figure are small, the rate of acceleration probably slows somewhat beyond this age[21]

Table 3.2 Parametric equations used to determine survival $S(t)$, cumulative hazard $\Lambda(t)$, and the hazard function $\lambda(t)$ for a matched general population

Model parameters
$\mu_1 = \ln[1 + \exp(E0)]$
$\mu_2 = \exp(C0)$
$\mu_3 = \exp(L0)$
$\rho = \exp(E1)$
$\nu = \exp(E2)$
$\delta = \exp(L1)$
$\eta = \exp(L3)$
Cumulative hazard phases:
$\Lambda_1(t) = \mu_1[1 + (\rho/t)^{\nu}]^{-1}$
$\Lambda_2(t) = \mu_2 t$
$\Lambda_3(t) = \mu_3[(\delta/t)^2 - 1]^{-\eta}$
$\Lambda(t) = \Lambda_1(t) + \Lambda_2(t) + \Lambda_3(t)$
Hazard phases:
$\lambda_1(t) = \Lambda_1(t) \cdot [1 + (\rho/t)^{\nu}/t$
$\lambda_2(t) = \mu_2$
$\lambda_3(t) = \Lambda_3[\eta\delta/(t[t-\delta])]$
$\lambda(t) = \lambda_1(t) + \lambda_2 + \lambda_3(t)$
Survivorship function:
$S(t) = \exp[-\Lambda(t)]$

Time t was expressed in *years* in determining the coefficients E0, E1, E2, C0, L0, L1, and L3 used in the above equations. If a time scale of months is desired, then multiply ρ and δ by 12 and divide μ_2 by 12. This is necessary since there is no simple scaler transformation between hazard rates expressed in differing time scales.

Table 3.3 Coefficients for generating population life tables, used in conjunction with the equations shown in Table 3.2

Category	*E0*	*C0*	*L0*	*E1*	*E2*	*L1*	*L3*
All	−4.16426	−7.5599	−1.07633	−4.94928	−0.622882	4.93375	1.11629
White males	−4.23245	−7.32122	−1.14847	−5.17720	−0.565571	4.88417	1.10556
White females	−4.38749	−8.00834	−1.05640	−4.80422	−0.698583	5.00042	1.25910
Other males	−3.57348	−7.87705	−0.247593	−4.52834	−0.66944	4.95107	0.861658
Other females	−3.75637	−7.83325	0.420104	−4.50560	−0.654352	5.15951	1.10412

male gender and other race, while estimating the overall shaping parameters. This was accomplished by allowing E0, C0, and L0 to become a linear, additive function of the two variables MALE (0 if female, 1 if male) and OTHER (0 if white race, 1 if other race); e.g. E0 = constant + coefficient·MALE + coefficient·OTHER. The constant and coefficients for each phase are shown in Table 3.4.

Table 3.4 Coefficients from multivariate equation more simply expressing both the shape of the population survival curve and the incremental risk of male gender and other race in each hazard phase

Variable	*Time of influence (phase)*		
	Throughout and constant (C0)	*Early and decreasing (E0)*	*Late and increasing (L0)*
Constant	−8.47581	−4.34513	−1.55561
Male	0.892782	0.171010	**0.625395**
Other race	0.698005	0.537807	0.481880

E1 = −4.766920; E2 = −0.645618; L1 = 4.91773; L3 = 1.04214

Appendix 4: Expected versus observed deaths

The 'subject-years' method for calculating the expected number of deaths is based upon a determination of each individual's probability of dying within the period of observation according to the population life table[50]. The expected probability P_i for the i'th individual of age T to survive the interval τ is:

$$P_i = S_i(T) - [S_i(T+\tau)]/S_i(T) \qquad (1)$$

where $S_i(T)$ is the expected sex-race survival of a patient age T at entry into the study, τ is the duration of follow-up (the interval between study entry and the last date known alive), and $S_i(T+\tau)$ is the expected survival for a patient of age $T+\tau$. $S_i(T)$ may be determined directly from a population life table; however, it is generally necessary to interpolate linearly between the yearly entries. For example, if a male, white patient is 8.3 years old, then the entries at 8 and 9 years are found (0.98078 and 0.98048 respectively in the 1976 US Life Tables[65]), and 0.3 of the difference is added to the 8 year entry (0.98078 + 0.3·0.000030 = 0.98087).

Similarly, the survival at age $T+\tau$ is found (or, again, interpolation between entries is used). Alternatively, both $S_i(T)$ and $S_i(T+\tau)$ are calculated directly from the parametric equations presented in Appendix 3 (which can be thought of as smoothly interpolating between enries).

The sum of all the individual P_i is then found and this is the *expected number of deaths*. A comparison of observed and expected number of deaths is now possible using the chi-square test:

$$\chi^2 = (\text{dead}_{obs} - \text{dead}_{exp})^2/\text{dead}_{exp} + (\text{alive}_{obs} - \text{alive}_{exp})^2/\text{alive}_{exp}, \qquad (2)$$

where dead_{obs} = number of observed deaths, dead_{exp} = number of expected deaths, alive_{obs} = number of observed alive, and alive_{exp} = number of expected alive. The p-value for drawing inferences as to whether the difference in observed versus expected deaths might

be due to chance is based on a chi-square table or formula with 1 degree of freedom (see also Gail and Ware[52]).

Alternatively, the expected number of deaths may be found using the cumulative hazard function, since the units for cumulative hazard are prevalence of death':

$$\Lambda_i(T) = -\ln S_i(T), \tag{3}$$

$$\Lambda_i(T+\tau) = -\ln S_i(T+\tau), \tag{4}$$

$$\Lambda_i(\tau) = \Lambda_i(T+\tau) - \Lambda_i(T), \tag{5}$$

where ln is the natural logarithm. The sum of all the individual $\Lambda_i(\tau)$ is the *expected number of deaths*. The comparison of expected and observed number of deaths is made exactly as above.

The number of expected deaths predicted using equation (5) is slightly higher than that predicted by equation (1). We recommend use of equation (5).

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4
Fetal echocardiography

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Recent developments in ultrasonic imaging techniques allow the visualization of fetal anatomy in extraordinarily fine detail. Cross-sectional imaging can display the connections of the fetal heart from as early as 14–16 weeks' gestation. M-mode echocardiography and Doppler interrogation can give additional information about the measurement and function of the fetal heart. Thus structural and functional anomalies of the heart can be explored in prenatal life.

Examination of the heart in intrauterine life is of interest for several reasons. Firstly, the normal anatomy and growth of the heart can be studied[1–6]. Study of the normal physiological function of the heart *in utero* has hitherto been confined to animal experiments but can now be directly evaluated in the human fetus by Doppler ultrasound. This can provide blood flow measurements of reasonable accuracy.[7] Secondly, when disordered cardiac anatomy is demonstrated in early pregnancy the parents have the option of termination where a major defect is present. Alternatively, preparation for the abnormality and delivery in a centre equipped for immediate paediatric cardiological care will optimize the infant's chance of survival. Delay in diagnosis and inter-hospital transfer of a sick neonate are significant factors contributing to the morbidity and mortality of congenital heart disease in infancy. If prenatal diagnosis can eliminate these factors, this should be reflected in improved infant survival. However, it should be noted that the nature of the technique and the pattern of referral will produce a predominance of major structural heart disease particularly associated with extracardiac anomalies, for whom the prognosis is unavoidably extremely poor. Doppler evaluation will increase the precision of the diagnosis of structural abnormalities. Lastly, once the normal cardiovascular physiology is thoroughly understood, the extension of flow investigation into disordered obstetric states promises interesting results[8,9]. Such measurements should give greater insight into some of the mechanisms controlling the fetal circulation.

TECHNIQUE OF CROSS-SECTIONAL SCANNING

Once experience in fetal heart scanning has been gained, no matter how the heart is approached at the start of the examination, structures can be readily recognized. However, when beginning fetal heart scanning, the fetal position should first of all be ascertained, so that the orientation of the heart within the fetal thorax can be understood. A four-chamber view of the fetal heart can then be seen by visualizing a transverse cross-section of the fetal thorax. Angling the transducer from this section can allow complete identification of all the venous, intracardiac and arterial connections ideally in a continuous sweep. Figure 4.1 illustrates the directions of the transducer beam, relative to

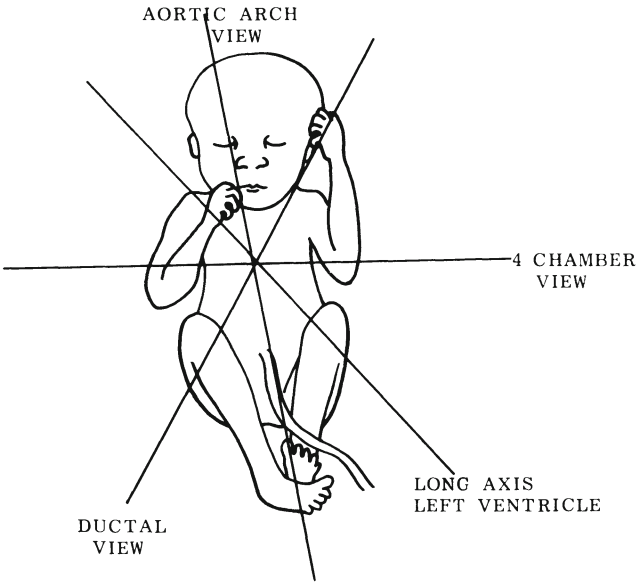

Figure 4.1 The transducer orientation, relative to the whole fetus, necessary to produce the described cardiac sections

the whole fetus, which are necessary to visualize the cardiac connections. Figure 4.2a and b shows the transducer orientation relative to the intracardiac structures to achieve each required section.

Figure 4.3 shows a four-chamber view of the normal fetal heart. Many important features should be noted in examining this projection. The descending aorta is seen as a circle in cross-section, lying between spine and left atrium. The two ventricles are of approximately equal size with the right ventricle lying beneath the sternum. The thicknesses of the posterior left ventricular wall, right ventricular wall and interventricular septum are approximately the same. The two atria are of

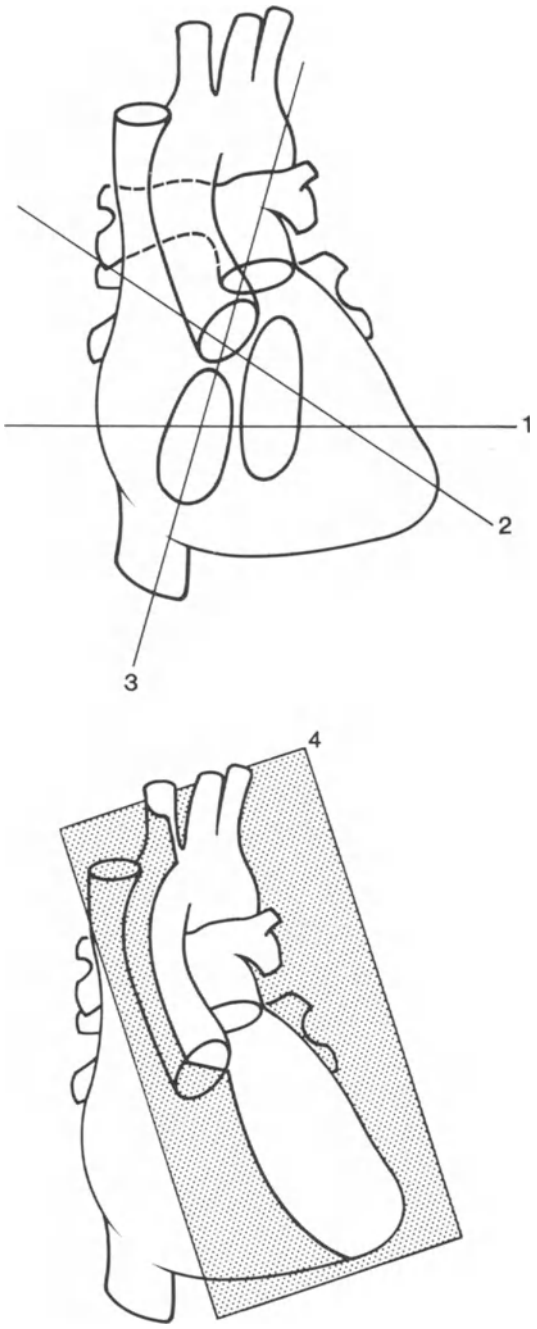

Figure 4.2a The transducer beam orientation as it cuts the heart in each of three in the sections: the four chamber (1); long axis left ventricle (2); right heart connections (3). The beam slices straight into the heart in these sections unlike the angled direction necessary to visualize the aortic arch which is illustrated in Figure 4.2b

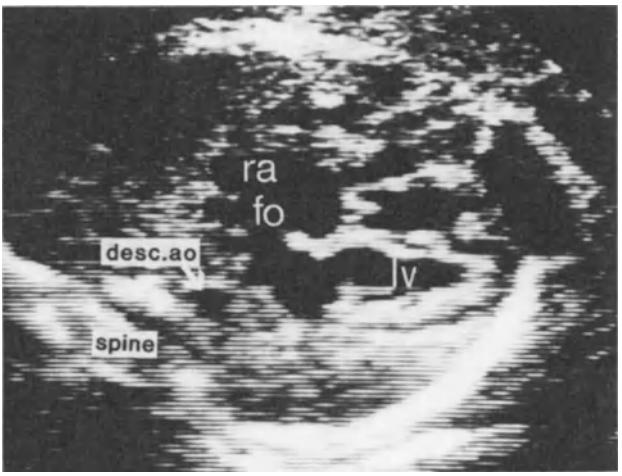

Figure 4.3 A transverse section of the fetal thorax allows the four chambers of the heart to be visualized. The spine is posterior, the sternum anterior. fo = foramen ovale; ra = right atrium; lv = left ventricle; desc.ao = descending aorta

similar size and there is a defect in the atrial septum which is the foramen ovale. The foramen ovale flap valve is a prominent moving structure which lies within the body of the left atrium. The two atrioventricular valves open normally. The typical 'offset' appearance at the crux of the heart representing insertion of the septal leaflets of the atrioventricular valves at different levels can be noted. The increased trabeculation of the right ventricle can often be appreciated. The differences in papillary muscle attachment of the two atrioventricular valves can sometimes be identified. Angling the transducer from this projection to visualize the left ventricle in long axis will display the features seen in Figure 4.4. The infundibulum of the right ventricle is seen anteriorly. The following connections of the left heart can be seen: one right pulmonary vein draining to left atrium; the connection of left atrium through mitral valve to left ventricle and the connection of left ventricle to ascending aorta. Continuity of the posterior aortic wall to mitral valve and anterior aortic wall to septum can also be seen. Figure 4.5 illustrates the connections of the right heart. The inferior vena cava drains to right atrium, which in turn connects to right ventricle via a patent tricuspid valve. The muscular infundibulum can be seen 'wrapping around' the central aorta and supporting the pulmonary valve. The main pulmonary artery can be seen in this projection to connect through the ductus arteriosus to the descending aorta. The arch of the aorta can be seen in the long axis of the fetus, giving rise to head and neck vessels. The right pulmonary artery is visible in cross-section in the centre of the hook-shaped aortic arch in Figure 4.6.

Examination of each of these sections to identify venous intracardiac

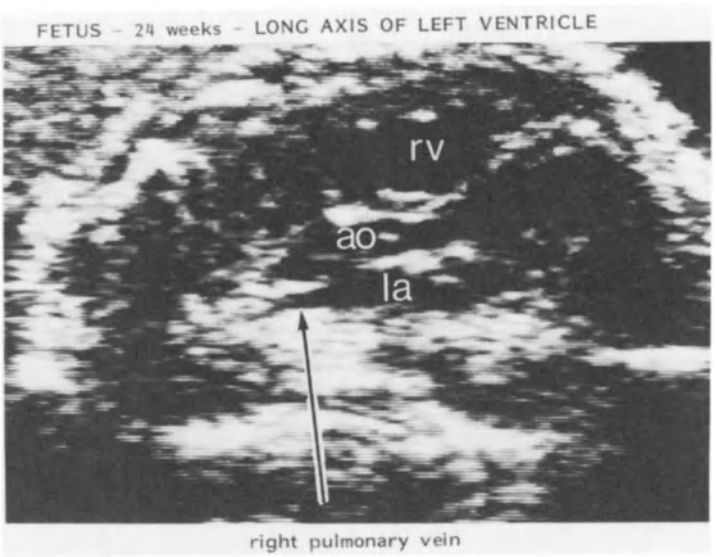

Figure 4.4 The left ventricle seen in long axis. The aorta arises from the left ventricle

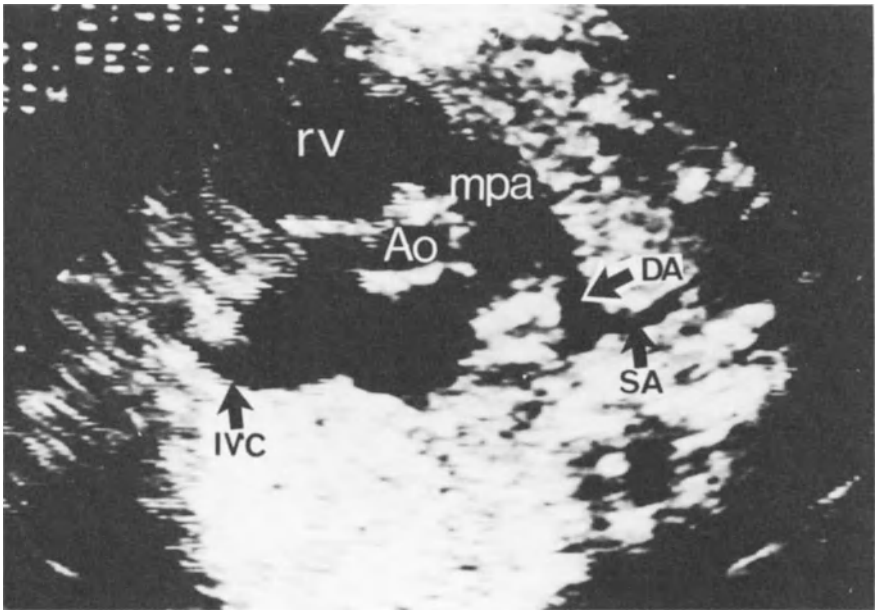

Figure 4.5 The inferior vena cava (IVC) can be seen to drain to right atrium. The right ventricular (rv) outflow 'wraps' around the central aorta (Ao). The main pulmonary artery (mpa) connects to the descending aorta via the ductus arteriosus (DA) at the site of entry of the subclavian artery (SA)

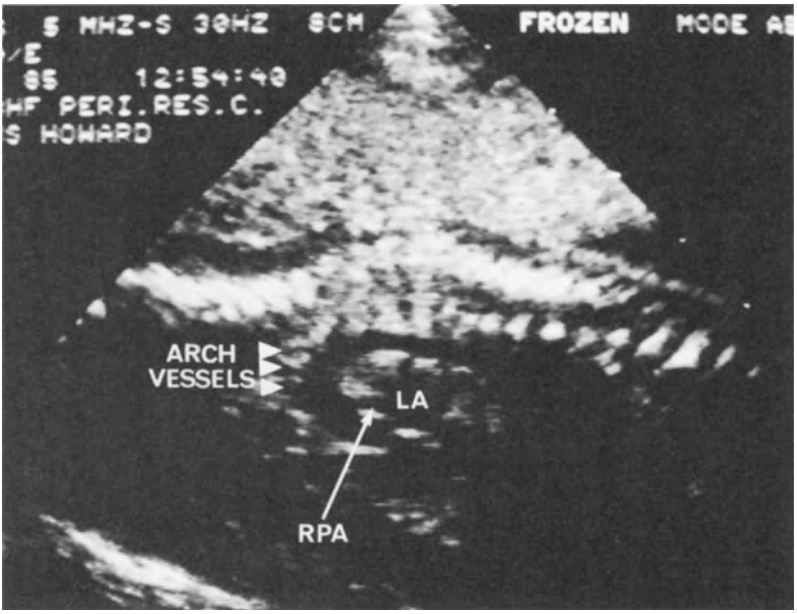

Figure 4.6 The arch of the aorta with the head and neck vessels arising from it. The right pulmonary artery (RPA) lies within the 'hook' of the arch

and arterial connections will exclude the vast majority of major congenital heart disease.

By 12 weeks of gestation it is possible to recognize four cardiac chambers and two great arteries. Figure 4.7 is a short axis view of the great arteries in a 10 week fetus. By 20 weeks all the connections

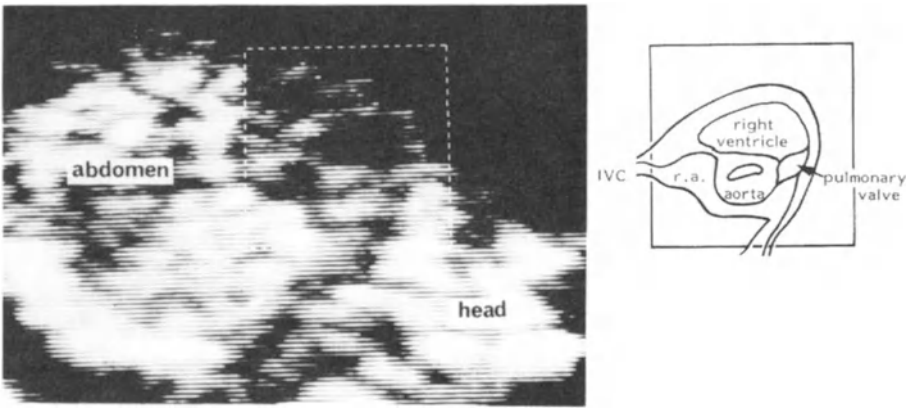

Figure 4.7 Two normally related great arteries in a section of a 10 week fetus

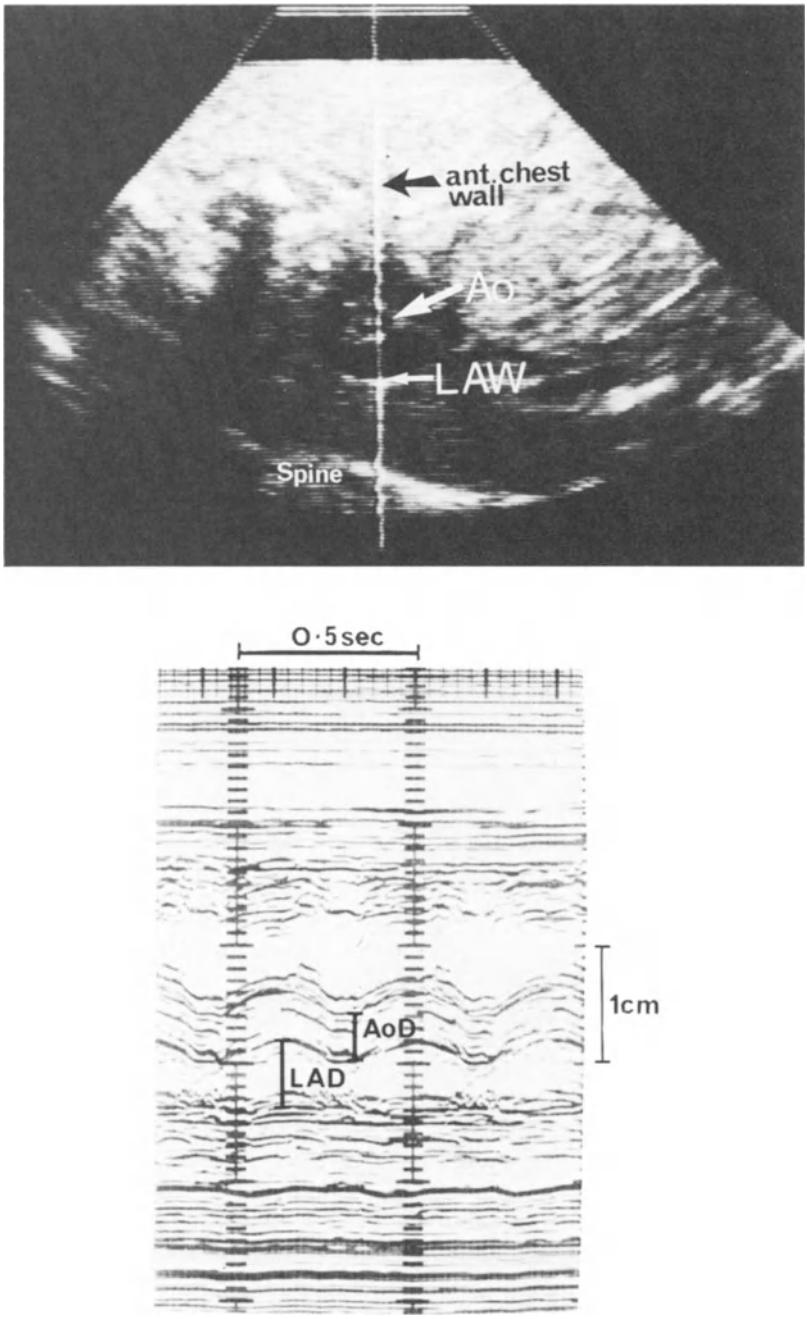

Figure 4.8 The M-line passing through the anterior chest wall to the aorta (Ao) and left atrium behind. The tracing achieved in this position is seen below

described above can be recognized. In the last few weeks of pregnancy, penetration of the ultrasound beam is reduced by rib shadowing and the increased distance between the transducer and the fetal heart, making complete evaluation of cardiac connections more difficult although still possible. Oligohydramnios or maternal obesity will also limit image quality, rendering the study more difficult.

THE M-MODE ECHOCARDIOGRAM

M-mode echocardiography can provide accurate measurements of intracardiac structures. This method is preferred to the measuring of a frozen frame cross-sectional image as endocardial surfaces can be more precisely identified, and measurements can be timed within the cardiac cycles. Once the anatomy of the heart has been identified, the M-line can be directed in a standard and repeatable way. The aortic root and left atrium are identified in the projection seen in Figure 4.8a and the M-line directed across them: the tracing seen in Figure 4.8b will result. The aortic root is about two thirds of the size of the left atrium throughout pregnancy. Figures 4.9 and 4.10 chart the growth of these structures throughout pregnancy. The section shown in Figure 4.11 is sought in order to record left and right ventricular internal dimensions in systole and diastole, together with septal and posterior left ventricular wall thickness. A suitable tracing from which to make these measurements is seen in Figure 4.12. The growth of these measurements

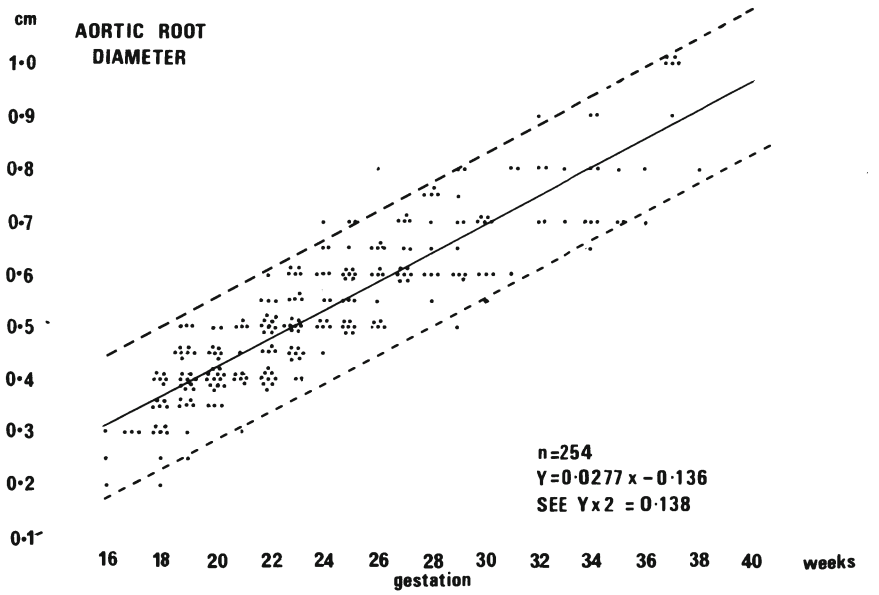

Figure 4.9 Aortic root growth with gestational age from 16 weeks to term

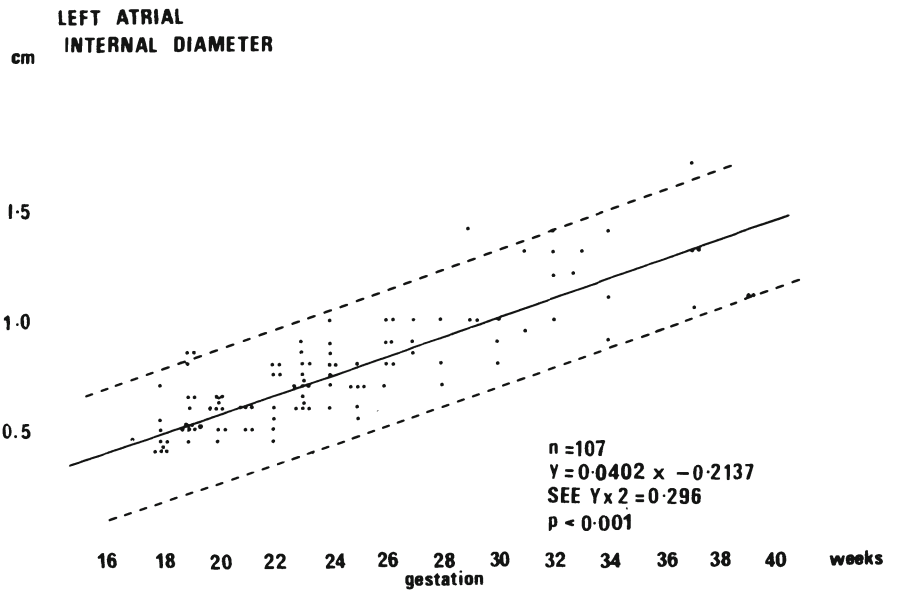

Figure 4.10 Left atrial dimensions between 16 weeks and term

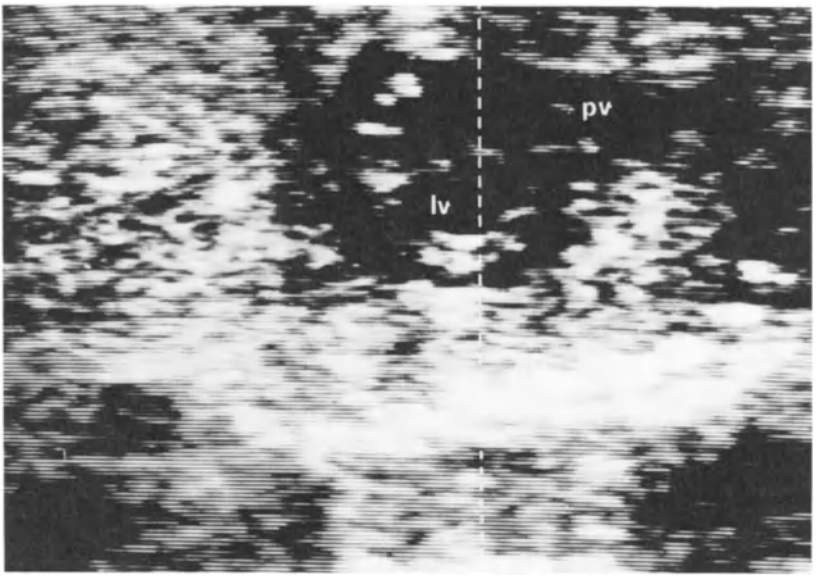

Figure 4.11 The heart sectioned to display the left ventricle in short axis. If the M-line is positioned through this plane the dimensions of two ventricles can be recorded

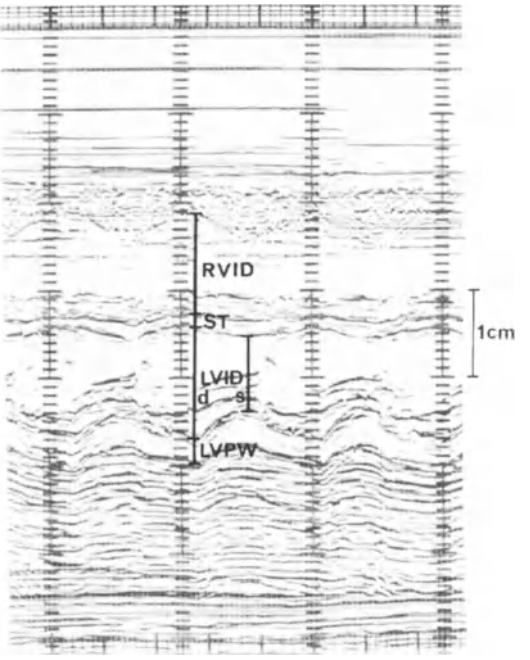

Figure 4.12 The M-mode and echocardiogram of the two ventricular chambers. The measurements which can be made from it are indicated

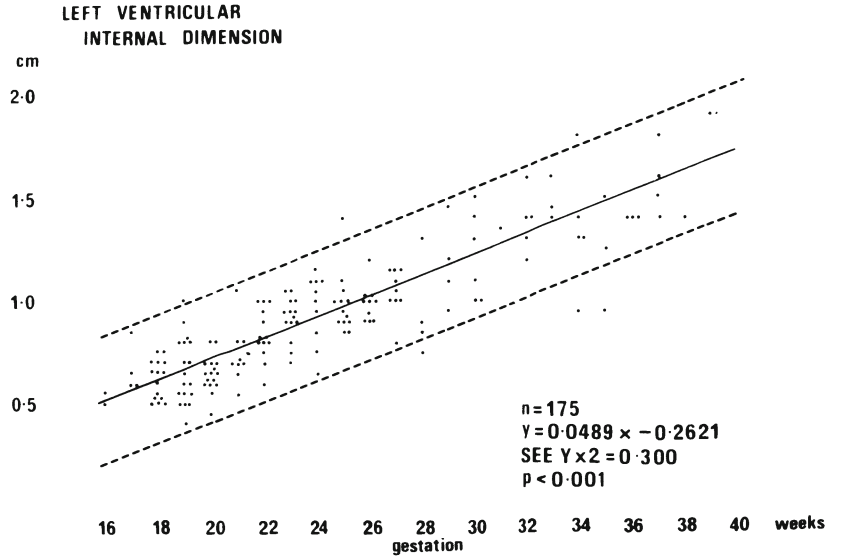

Figure 4.13 The growth of the left ventricular internal dimension in diastole throughout the second and third trimesters of pregnancy

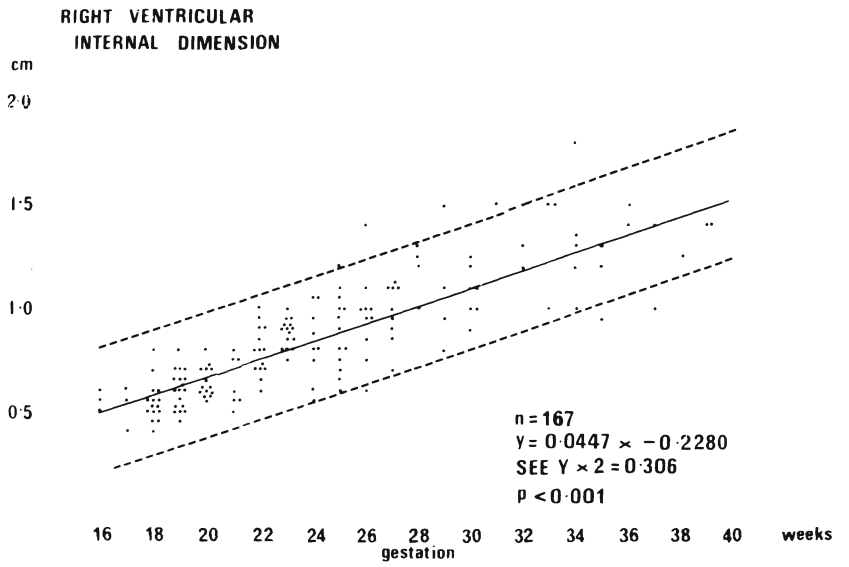

Figure 4.14 The growth of the right ventricular cavity

during pregnancy is seen in Figures 4.13, 4.14, 4.15 and 4.16. The growth charts are of particular value in the evaluation of structural cardiac anomalies. For example, if the ventricular chambers are of disparate sizes, it is not always obvious whether one is larger than appropriate for the gestational age or the other is too small. Reference to the growth charts will help clarify this. Doppler interrogation of all four cardiac valve orifices can be achieved in intrauterine life and blood flow characteristics observed. The traces achieved with spectral analysis are displayed in Figure 4.17. From these traces blood flow estimations can be made but results are still preliminary. It appears, however, that right heart flow is greater than left, becoming more equal to it towards term[10].

STRUCTURAL CARDIAC ANOMALIES

The majority of structural cardiac malformations have now been identified in intrauterine life[11–14]. The exception to this is anomalous venous connection but it appears potentially possible to visualize such defects (Figure 4.4). At the atrioventricular junction, absent connection, partial and complete atrioventricular defects and double inlet connection have all been identified. The criteria for recognition of these anomalies are similar to those in postnatal life. The insertion of the two atrioventricular valves at the same level is seen in Figure 4.18; this

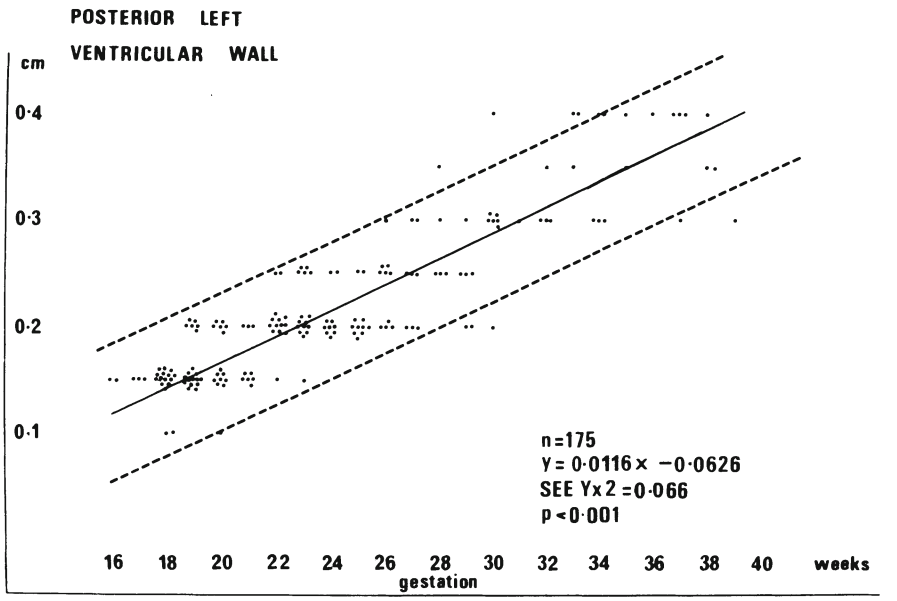

Figure 4.15 Left ventricular posterior wall thickness related to gestational age

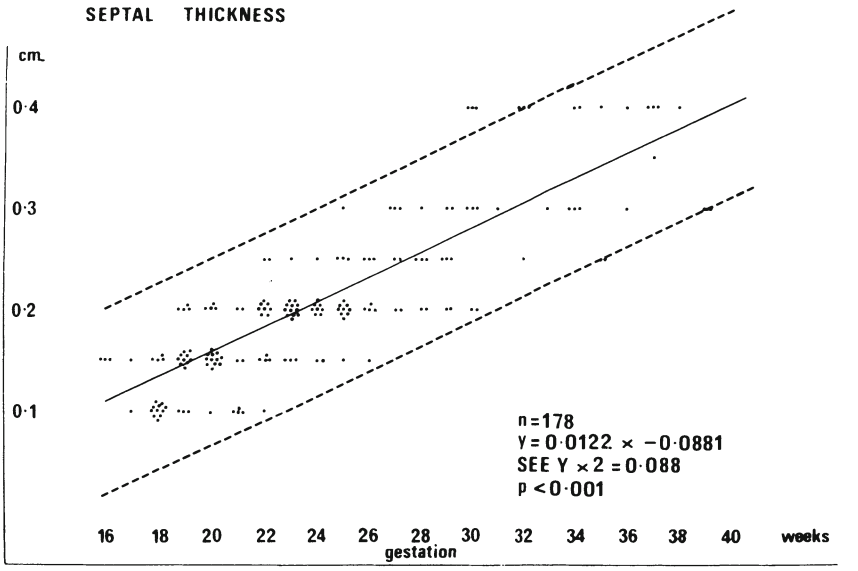

Figure 4.16 Septal thickness related to gestational age

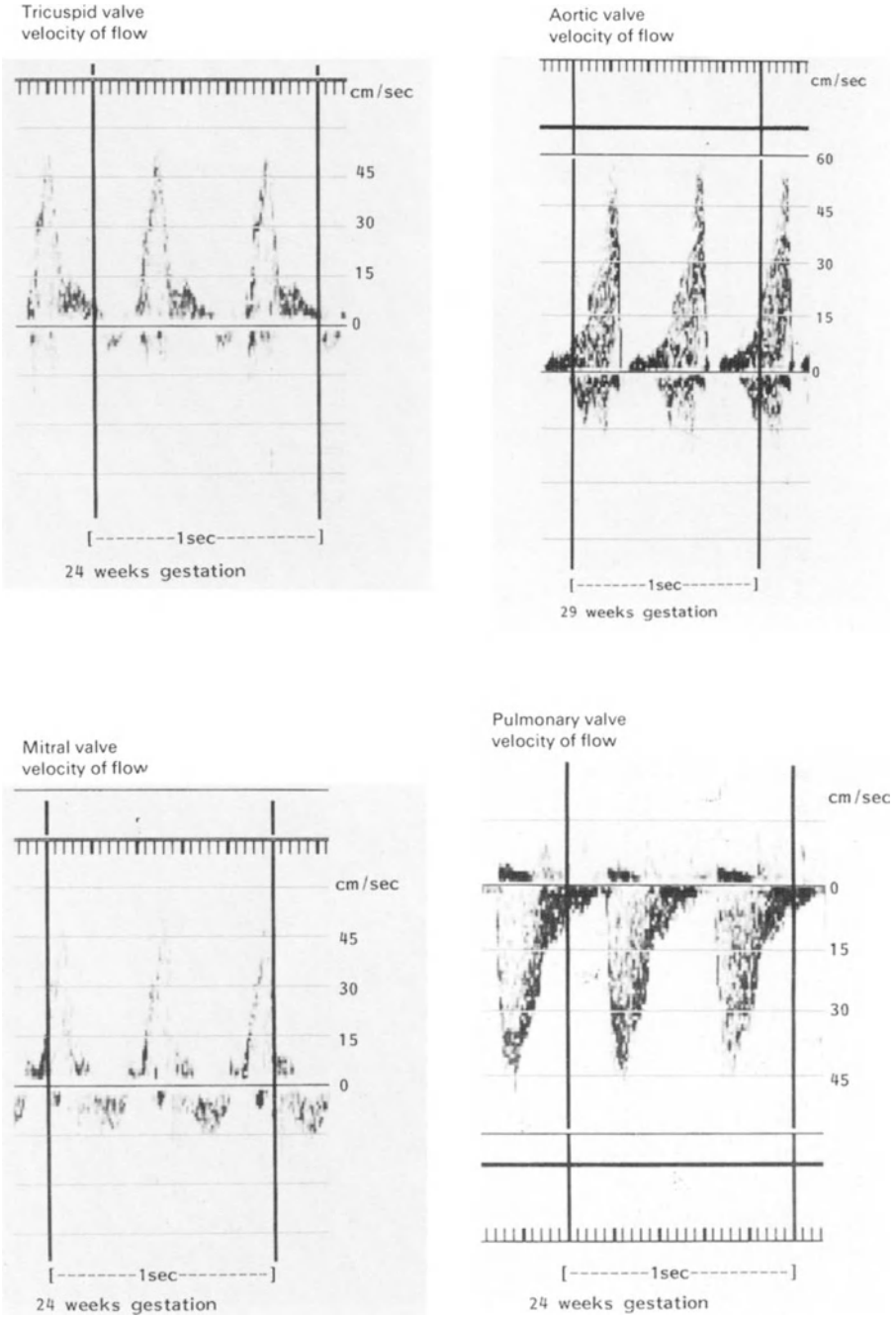

Figure 4.17 The Doppler tracings achieved across each cardiac valve

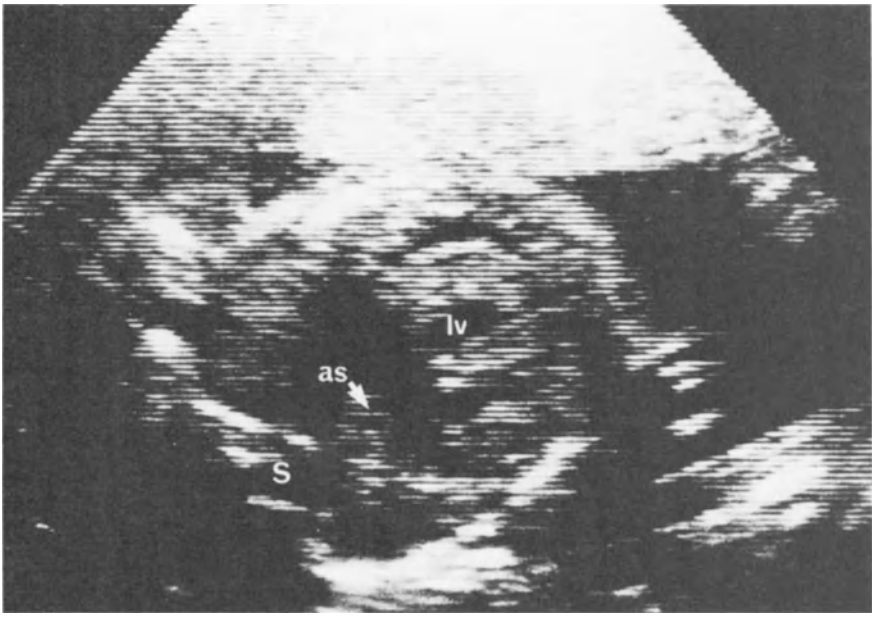

Figure 4.18 The heart in a four-chamber view. Only a small portion of atrial septum (as) can be seen

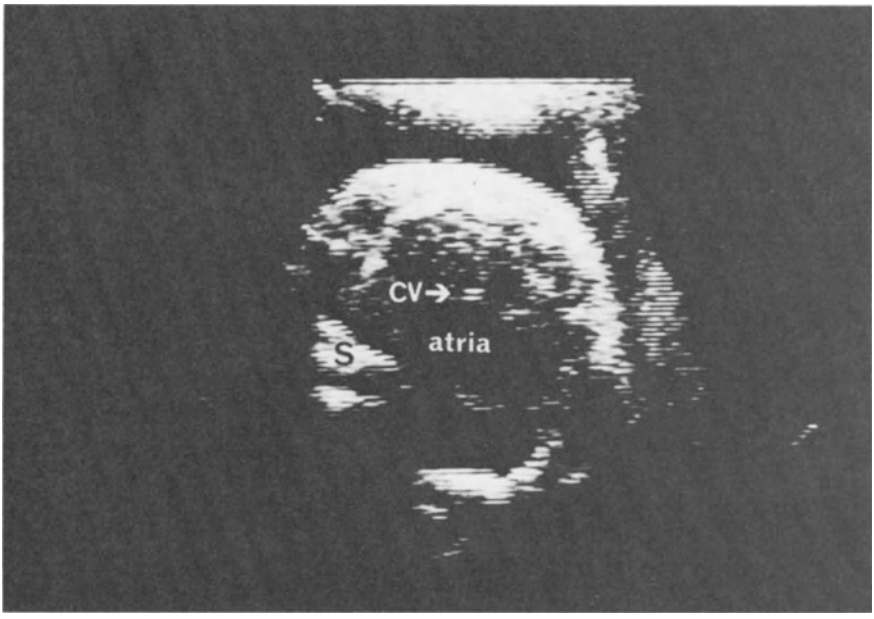

Figure 4.19 A common atrium with a common valve (cv) opening across the ventricular septum

is typical of an ostium primum atrial septal defect. A common atrioventricular valve is seen in Figure 4.19, in systole and diastole, in a complete atrioventricular septal defect. In an atrioventricular defect where the ventricular component is not large, the M-mode echocardiogram of the common valve is often helpful in confirming the diagnosis. Figure 4.20 illustrates such an instance. Absent left connection is seen in Figure 4.21, no communication being seen between the floor of the left atrium and a ventricular cavity. There was absent right connection in the case illustrated in Figure 4.22. This was an unusual case with ectopia cordis and the heart lying freely in the amniotic fluid. The left atrial appendage was clearly outlined and the aorta was seen to arise astride the rudimentary right ventricle and the main chamber. A further abnormality seen at the atrioventricular junction is illustrated in Figure 4.23 where the septal attachment of the tricuspid valve is displaced into the body of the right ventricle as a result of Ebstein's anomaly.

Anomalies of the ventriculoarterial junction can also be identified. Pulmonary and aortic atresia, complete transposition, double outlet right ventricle, tetralogy of Fallot and truncus arteriosus have all been correctly recognized. Figure 4.24 shows a heart with a good sized right atrium and right ventricle. The membrane across the main pulmonary artery moved with each cardiac cycle but did not open. There was, therefore, pulmonary atresia, but free tricuspid incompetence produced a right ventricular cavity of good size. A tiny aortic root is seen in cross-section in Figure 4.25, indicating aortic atresia. Figure 4.26 illustrates the parallel great artery orientation seen in complete transposition. This is a difficult diagnosis to make as the pulmonary artery–ductal

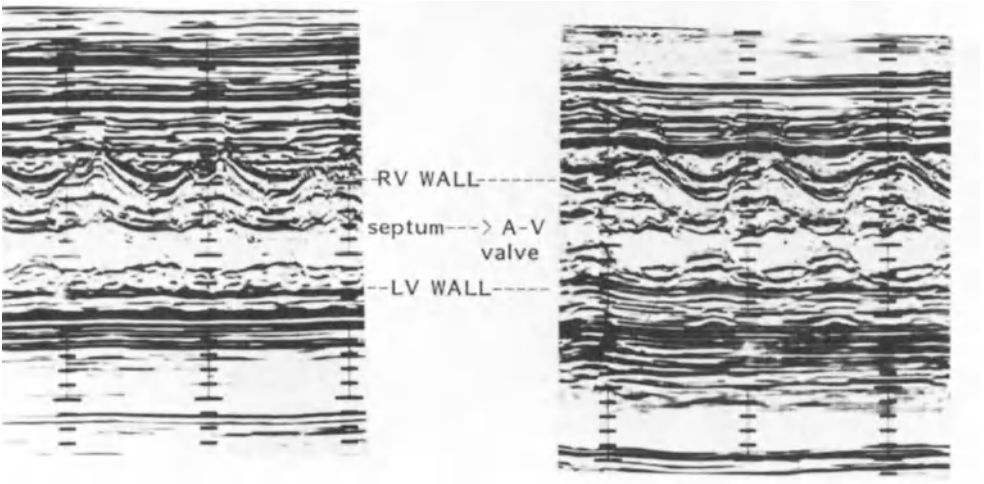

Figure 4.20 M-mode echocardiogram confirming the diagnosis of a common atrioventricular valve. Sweep from body of ventricles to A–V junction

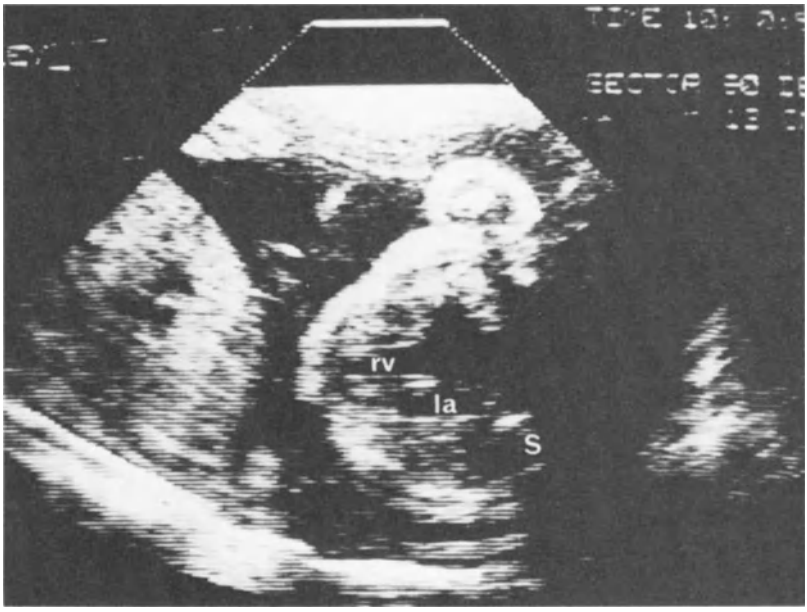

Figure 4.21 The heart seen in a cross-section of the thorax. There is only one ventricular chamber (rv) visible. There is no communication between left atrium (la) and a ventricular cavity

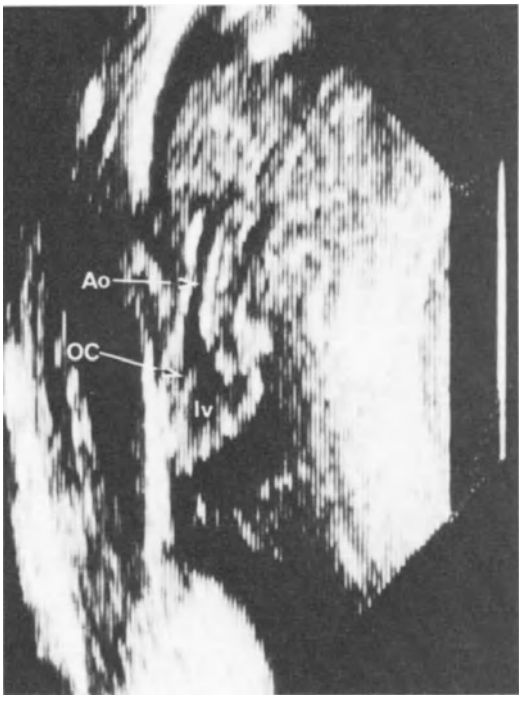

Figure 4.22 The aorta (Ao) arising astride an outlet chamber (oc) and the main chamber. There is no patent right atrioventricular valve

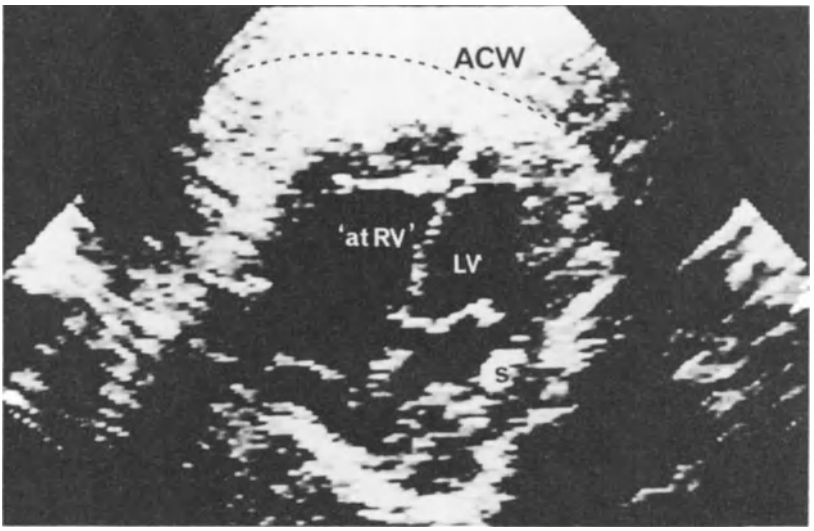

Figure 4.23 The heart filling most of the thorax. The triscuspid valve is displaced far down into the ventricular cavity producing a large 'atrialized' portion of right ventricle ('at RV'). ACW = anterior chest wall

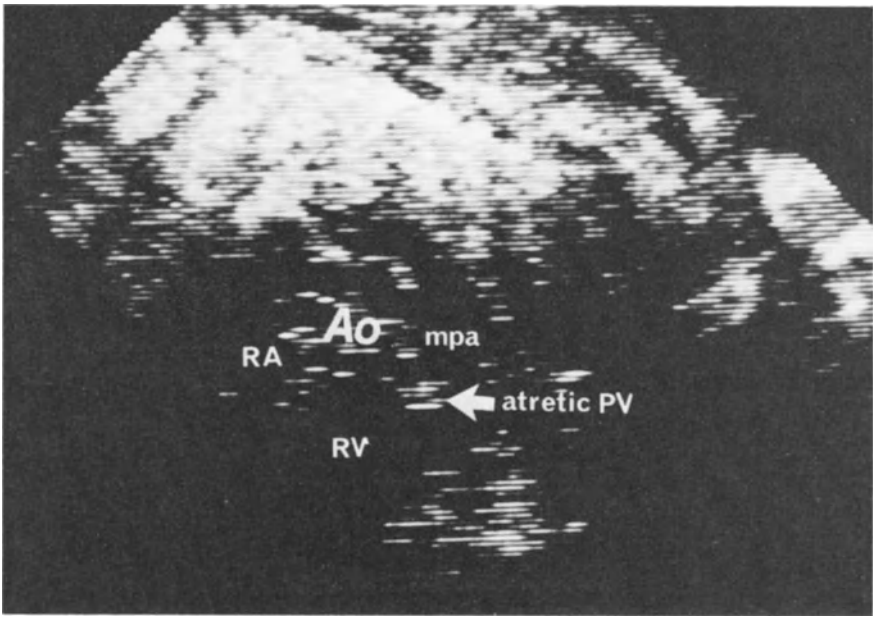

Figure 4.24 The heart sectioned to visualize right heart connections. The pulmonary valve (PV) did not open with ventricular systole

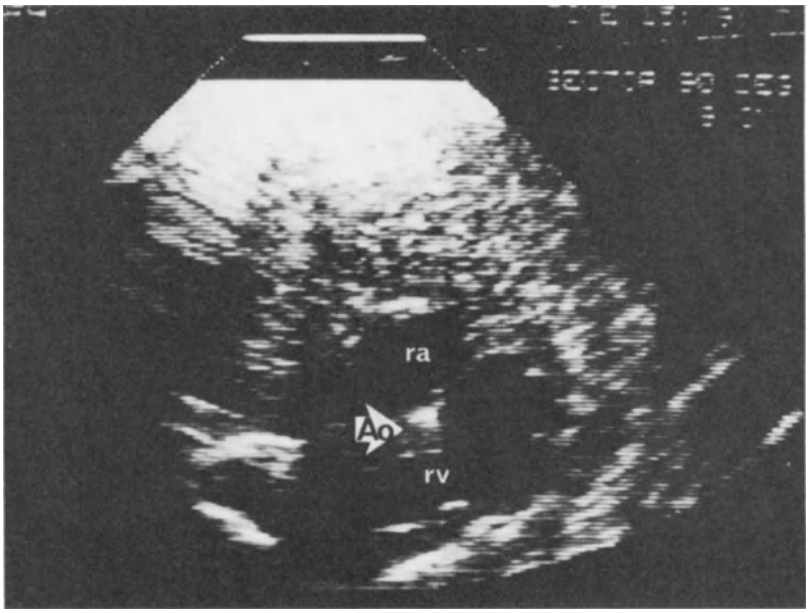

Figure 4.25 The heart cut to show right heart connections. The central aorta (Ao) is small and there was no discernible valve opening within it

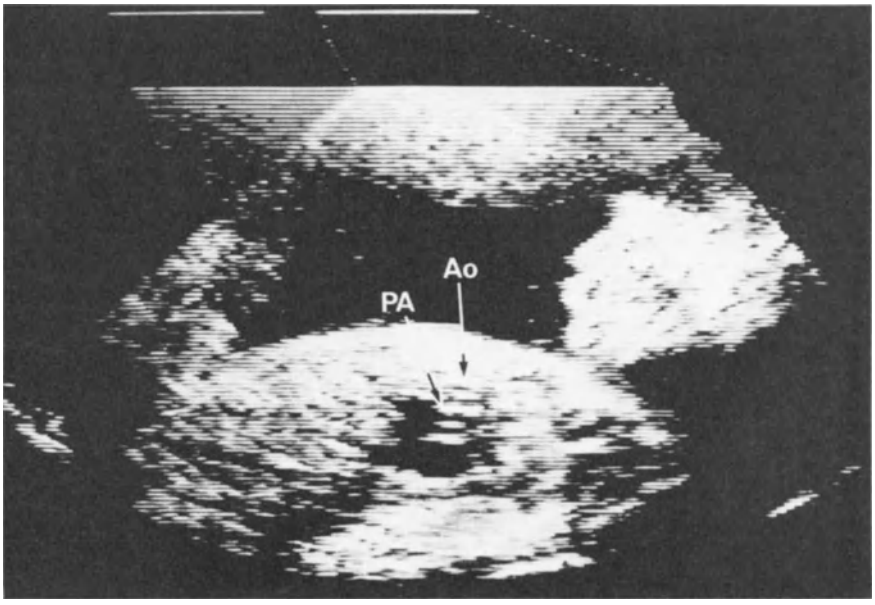

Figure 4.26a The heart sectioned (top) to show right heart connections but two circular great arteries (PA and Ao) are seen in parallel orientation. In the long axis of the left ventricle (below) two parallel great arteries are seen arising from each ventricle

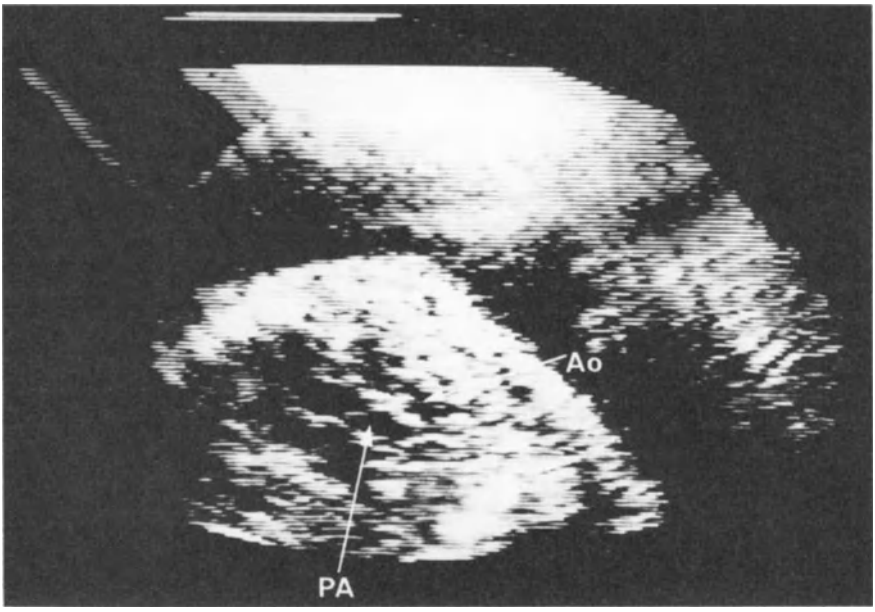

Figure 4.26b

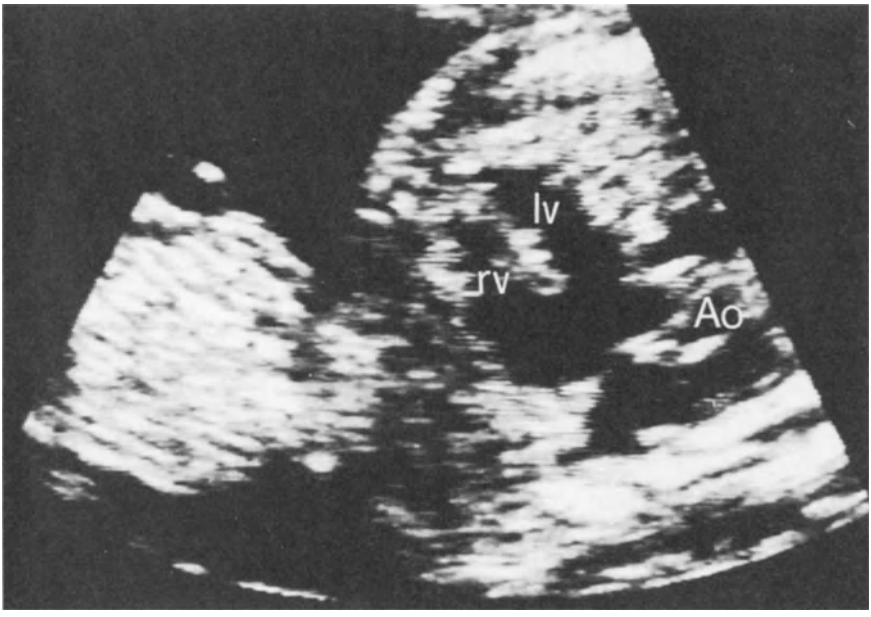

Figure 4.27 The aorta (Ao) arising astride a large ventricular septal defect

communication can mimic the appearance of the arch of the aorta. However, if head and neck vessels arising from the arch are always sought, mistakes should be avoided. Furthermore, the typical 'wrap around' appearance of the right ventricular outflow tract anterior to the aorta is not found in transposition. In the normal fetal heart this is always readily obtained. Figure 4.27 shows aortic override in a heart where the pulmonary valve was found, denoting tetralogy of Fallot. In contrast, Figure 4.28a shows aortic override but in this patient no pulmonary outflow tract or pulmonary valve was found. The main pulmonary artery was seen instead to arise from the back of the single outlet of the heart (Figure 4.28b). This, therefore, was truncus arteriosus.

Additional intracardiac defects which have been detected include ventricular septal defects, cardiac tumours and critical aortic stenosis. A trabecular ventricular septal defect was seen at 22 weeks' gestation (Figure 4.29). It was nearly the same size as the aortic root and maintained this proportionate size until term. The left to right shunt was 3.1 to 1 through this defect in postnatal life and the infant required surgery. A cardiac tumour is illustrated in Figure 4.30. Histologically this was a rhabdomyoma. Critical aortic stenosis, seen in Figure 4.31, was associated with endocardial fibroelastosis affecting the left atrium and left ventricle. This produced a dilated poorly contracting left ventricle on echocardiography with a densely echogenic endocardial surface. The aortic root could be seen to be very small, only a pinhole orifice to the aortic valve being found at autopsy.

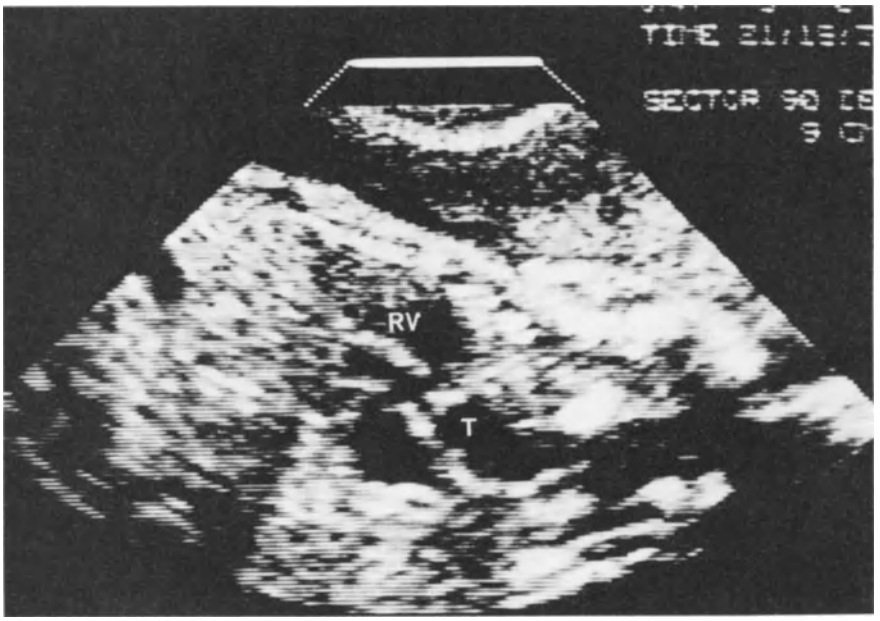

Figure 4.28a A single outlet of the heart seen to override the ventricular septum

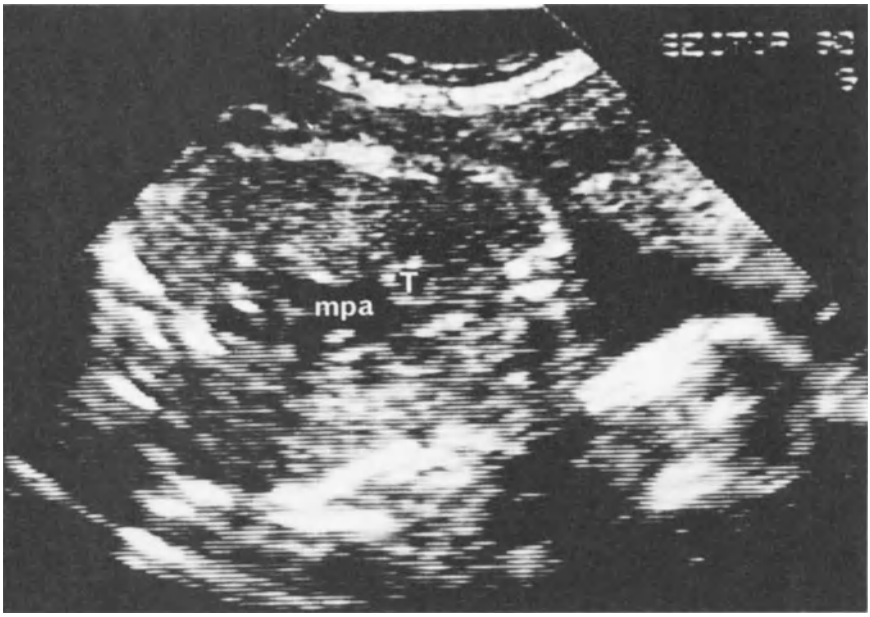

Figure 4.28b The main pulmonary artery seen to arise from the back of the artery shown in Figure 4.28a

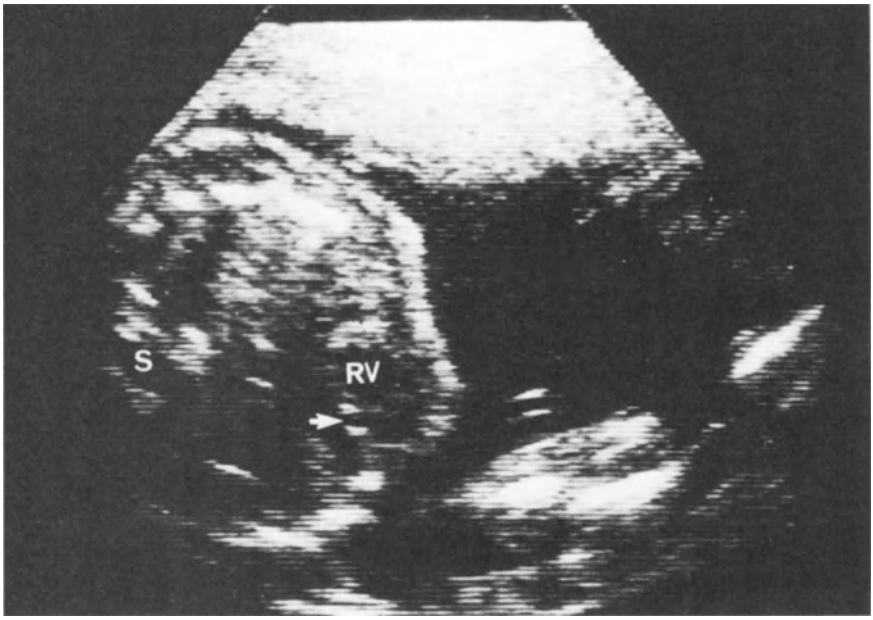

Figure 4.29 A well-defined trabecular ventricular septal defect (arrowed) seen in a four-chamber view of the heart

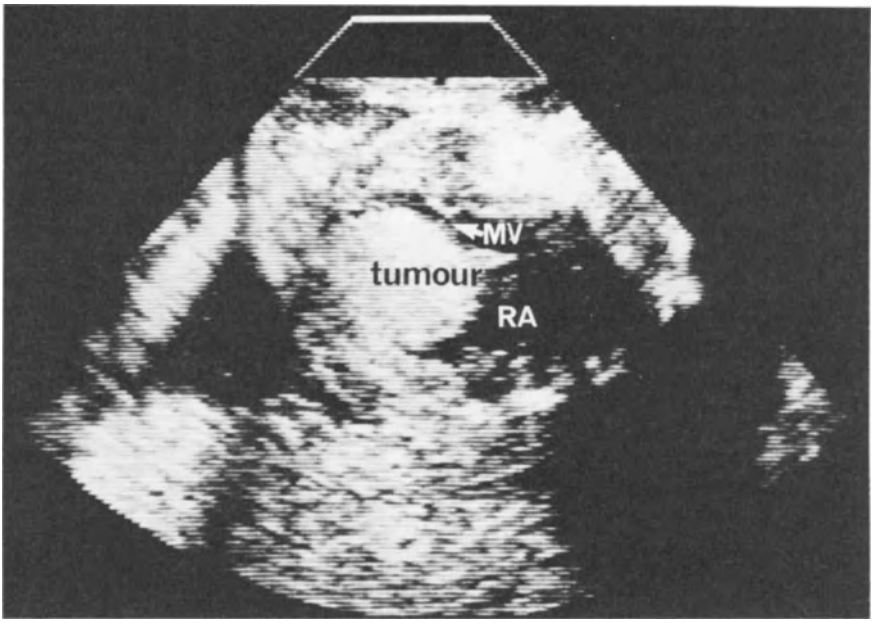

Figure 4.30 A large tumour seen in the ventricular septum causing obstruction to left and right ventricular inflow and outflow

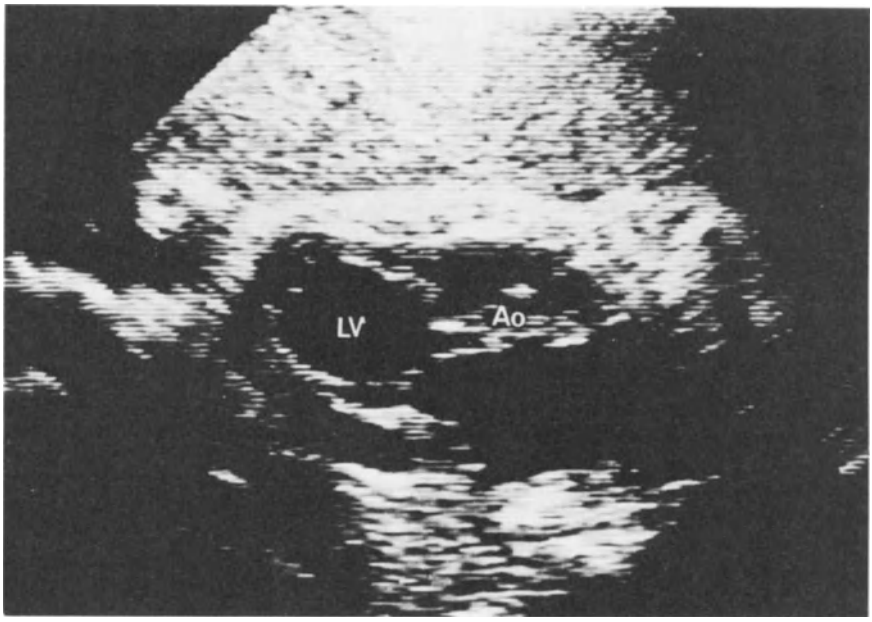

Figure 4.31 The aortic root, small for the gestational age. The left atrium and left ventricle were dilated and poorly contracting

Aortic arch anomalies can also be seen. Figure 4.32 illustrates a very small aortic root which was found to stop and branch instead of forming an arch. This fetal heart was of only 18 weeks' gestation. Thus enlarging the echocardiogram does not give a good result. The anatomical specimen, in the same case, however, is cut in the same projection. In our experience direct examination of the aortic arch cannot exclude coarctation. Where the diagnosis of coarctation of the aorta has been made in intrauterine life, the clues have been from intracardiac findings, namely right ventricular dilatation and hypertrophy. The reasons for such findings are purely speculative[15], but probably relate to altered haemodynamics such that right ventricular output is increased in this situation.

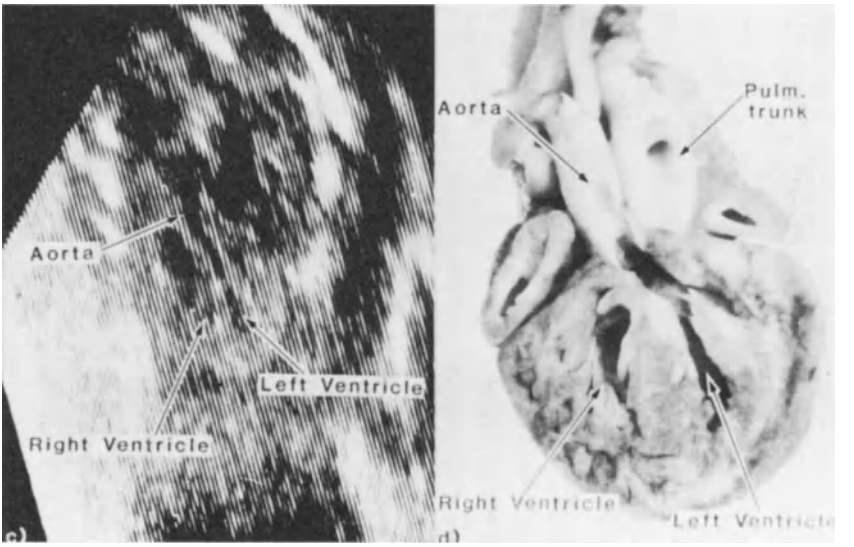

Figure 4.32 A small aorta which stopped and branched but did not form an arch

SELECTION OF HIGH RISK PREGNANCIES

The incidence of major structural heart disease of the kind readily detectable in intrauterine life is low, probably 4 per 1000 if unselected pregnancies are examined. However, population screening in the future is not beyond the realms of possibility as imaging equipment improves and an increasing number of centres include cardiac scanning as part of a routine obstetric scan. The ability to distinguish normal from abnormal cardiac structure is not difficult in general and an increasing source of our high yield referrals are pregnancies where the ultrasonographer is suspicious of cardiac abnormality. At present, however, high risk pregnancies are selected for examination. They are scanned electively at 18 weeks' gestation and again at 24–26 weeks. These

pregnancies are those with a family history of congenital heart disease, maternal diabetes or exposure to a cardiac teratogen in early pregnancy. Alternatively, identification of a high risk factor appearing in an individual fetus, such as extracardiac fetal anomaly, cardiac arrhythmia or hydrops fetalis, is an indication for specialized scanning. The recurrence rate of congenital heart disease where there has been an affected child in the family is approximately 1:50 in subsequent pregnancies[16], but where a parent has been affected the recurrence in offspring may be as high as 10–15%[17, 18]. Maternal diabetes is said to double the risk of congenital heart disease[19]. Known cardiac teratogens, if the mother is exposed in early pregnancy, include lithium, phenytoin, steroids and rubella infection. Where an extracardiac anomaly is detected in fetal life, it is important also to scan the heart. Abnormality in more than one system may suggest a chromosomal anomaly or syndrome defect. Alternatively, the combination of two structural defects may influence the prognosis for surgery. Figure 4.33 illustrates a case of exomphalos with a large inlet ventricular septal defect. Exomphalos is associated with congenital heart disease in about one third of cases[20] but renal and intracranial defects also have a high incidence of associated cardiac anomaly.

Cardiac arrhythmias may be associated with structural heart disease. In our experience of twelve cases of tachyarrhythmia, this was not associated with cardiac malformation but some authors suggest an

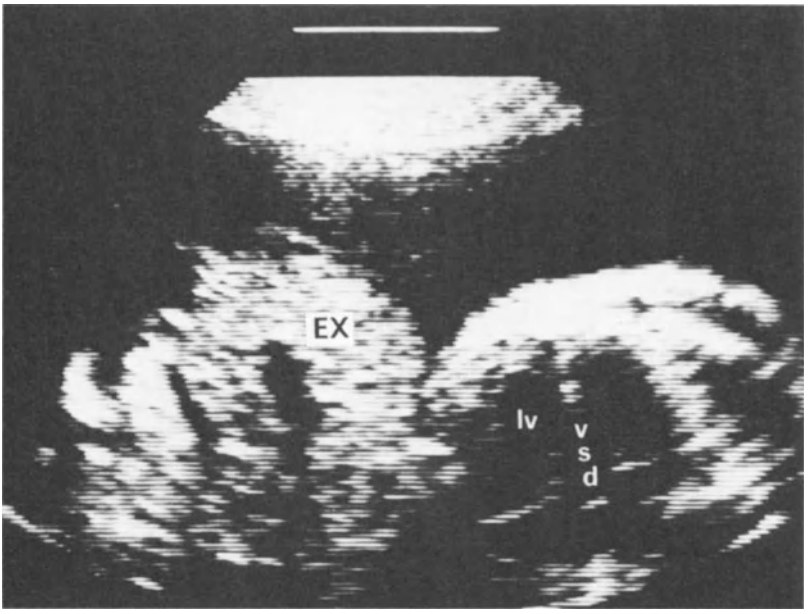

Figure 4.33 A large inlet ventricular septal defect (vsd). The exomphalos (Ex) is seen to the left of the thorax

association as high as 11%[21]. However, complete heart block has a high incidence of associated heart disease. The incidence recorded in postnatal life is of the order of 25% but this is probably an underestimate[22].

The method of identification of arrhythmias involves the M-mode echocardiographic recording of atrial and ventricular contraction simultaneously. Normally atrial contraction precedes every ventricular contraction with a fixed time interval. Figure 4.34 illustrates this. Figure 4.35 illustrates atrial contraction occurring at approximately twice the rate of ventricular contraction and dissociated from it. This, therefore, is complete heart block. Figure 4.36 illustrates atrial contraction occurring at 480/min with a ventricular response to every second atrial contraction. This is atrial flutter with 2:1 conduction. We have not yet seen a ventricular tachycardia *in utero* but feel that it should be identifiable as such, unless it is very fast and there is retrograde conduction of every beat.

In our experience of thirteen cases of complete heart block, over 50% had structural heart disease[23]. Complete heart block with structural heart disease implies a very poor prognosis, and is commonly associated with atrial isomerism[24]. All our cases had atrial isomerism. On the other hand, isolated complete heart block usually has a good prognosis. Our one loss out of seven cases occurred for obstetric reasons. All our cases of isolated complete heart block had evidence of connec-

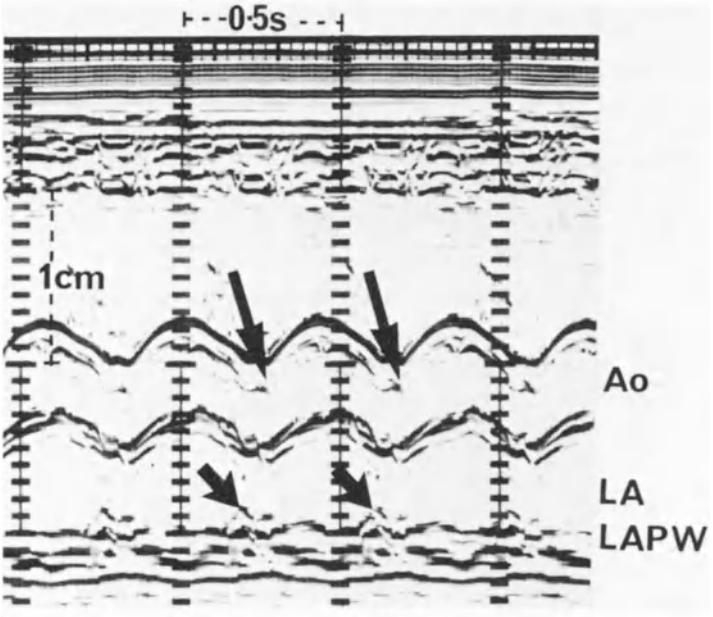

Figure 4.34 The normal sequence of atrioventricular contraction, atrial contraction occurring less than 80 ms prior to each ventricular contraction

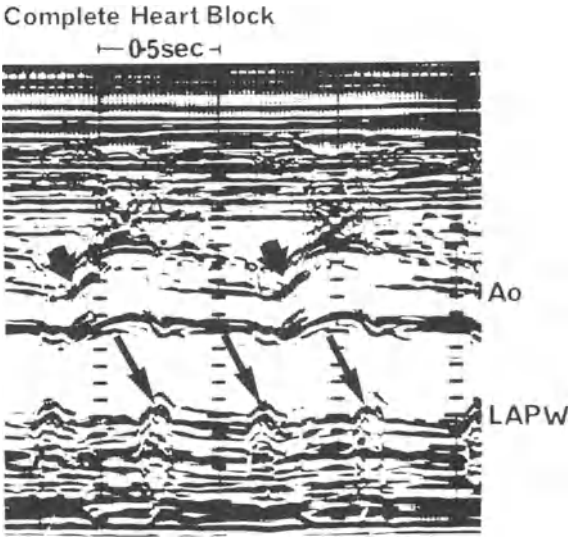

Figure 4.35 Atrial contraction occurring at approximately twice the rate of ventricular contraction (smaller arrows) and dissociated from it

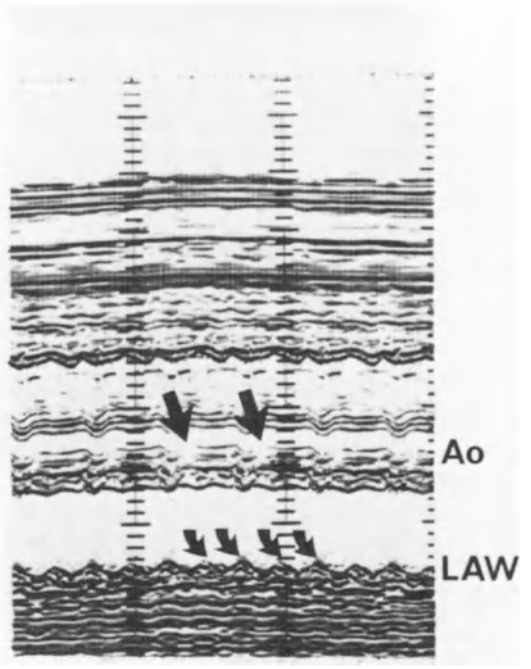

Figure 4.36 The posterior atrial wall is seen to flutter. Ventricular response is to every second contraction

tive tissue disease in maternal serum[25]. This is an important association to seek, as the recurrence of complete heart block in such mothers is of the order of 30%[26].

Our current policy with supraventricular tachycardias is to treat the mother with digoxin, verapamil or often a combination of the two. If there is intrauterine cardiac failure, it is important to achieve adequate blood levels of verapamil and digoxin both in the mother and the fetus. Placental transfer is less good if there is fetal hydrops. One should obtain therapeutic levels in maternal serum for at least a week to be sure that adequate quantities of the drugs are reaching the fetus. If there is no cardiac failure it is safe to start treatment with digoxin only and to add verapamil if control is not achieved with well-tolerated doses of digoxin.

Non-immune hydrops fetalis can be due to intrauterine cardiac failure as a result of structural heart disease. This therefore is an important high risk group of pregnancies to study. In our series of 40 referrals with non-immune hydrops, 11 had cardiac malformations and in a further seven cases the aetiology was a tachyarrhythmia.

CONFIDENCE LIMITS OF THE FETAL ECHOCARDIOGRAPHIC TECHNIQUE

To date we have not made a major false positive diagnosis in a series of 2000 pregnancies. Extensive experience of the fetal echocardiographic technique must be gained before a diagnosis of normality or abnormality can be considered reliable. This is particularly true if intervention in a pregnancy is contemplated.

Eight cardiac malformations have been overlooked in intrauterine life. Three were major abnormalities of connection but were overlooked early in our experience. The scanning technique has been modified since then so that such errors should not be made in the future. Five more minor abnormalities have been overlooked: atrial septal defect; two ventricular septal defects; and two cases of coarctation of the aorta. In order to avoid overlooking ventricular septal defects of functional significance our current policy is to ensure cardiac connections at the initial visit at 18 weeks' gestation and to schedule the second visit for 24–26 weeks. The resolution capacity of current equipment will display a defect of greater than 2 mm in size. Such a defect is approaching half aortic root size at 24–26 weeks. If this proportion is maintained the defect will be of functional significance at birth[27]. Conversely, defects of less than 2 mm at this gestation will not be functionally important. It will remain, however, impossible to exclude all small defects, just as in postnatal life. Coarctation of the aorta may continue to be a weak spot of the fetal echocardiographic technique. Three cases have been recognized *in utero*, and two overlooked. The cases recognized were diagnosed from associated intracardiac features rather than directly from the appearance of the aortic arch, namely

right ventricular dilatation and hypertrophy. A change in policy to re-scan patients with a history of coarctation at 32 weeks' gestation and the addition of a Doppler evaluation may improve our accuracy in this condition.

OUTCOME AND RESULTS

Largely as a result of the referral policy, the cases of congenital heart disease that have been detected in prenatal life have had a poor outcome. Over half of the abnormalities seen had extracardiac anomalies occurring in association. The major distortions of cardiac structure recognizable by routine obstetric screening or causing intrauterine cardiac failure are also likely to have a poor prognosis. This is reflected in Figure 4.37 which tabulates the outcome of the first fifty cases of congenital heart disease recognized *in utero*. The three survivors had relatively minor heart disease and the outcome was not influenced by prenatal detection. However, in the future it is to be hoped that less complex lesions will be detected; anticipation of the defect prenatally will then improve the outcome. Delay in diagnosis and transfer of a sick infant also influences morbidity and mortality in congenital heart disease. The transferring of antenatal care so that delivery takes place in a centre which also provides paediatric cardiological care should optimize the chance of infant survival.

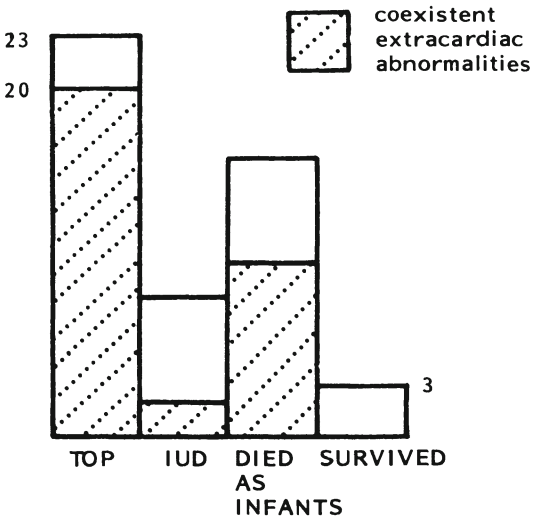

Figure 4.37 The outcome in the first 50 cases in which congenital heart disease (CHD) was predicted. Over half the cases had coexistent extracardiac anomalies

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5
Medical manipulation of the ductus arteriosus

E. D. SILOVE

PHYSIOLOGICAL CONSIDERATIONS

The postnatal rise in blood oxygen tension is widely recognized as the trigger to ductus arteriosus closure[1]. Various other factors have been invoked, the most important of which are probably the prostaglandins[2]. It is beyond the scope of this chapter to discuss the biosynthetic pathways involved in the production and inactivation of prostaglandins[3,4]. However, awareness of some of the experimental evidence will help in the understanding of certain therapeutic principles.

Some years ago it was suggested that increased oxygen tension may promote the conversion of arachidonic acid to prostaglandin $F_{2\alpha}$ which is known to be present in ductus arteriosus tissue and is a ductus constrictor[5]. An alternative proposal was that patency of the fetal ductus arteriosus may be actively sustained by intramural prostaglandin E_2 (PGE_2) and that postnatal exposure to oxygen reduces the responsiveness to PGE_2 of the ductus[2]. Whatever the mechanism, there are certain clinical conditions in which the oxygen trigger does not appear to operate fully. For example, in congenital right heart obstructive lesions, despite severe hypoxaemia, the ductus arteriosus often closes though usually more slowly than normal. On the other hand, ductus patency often persists in premature infants despite normal blood oxygen tensions. These are the specific abnormalities that have stimulated the major research and clinical interest in the prostaglandins in relation to the ductus arteriosus. Therapy has been directed on the one hand towards the use of the E-type prostaglandins to maintain ductus arteriosus patency and, on the other, towards the drug inhibition of prostaglandin synthesis to encourage ductus constriction. Indomethacin has been the drug most widely used as a prostaglandin synthetase inhibitor.

MANAGEMENT OF PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS

Delayed closure of the ductus arteriosus (PDA) in premature infants with the respiratory distress syndrome and the consequent left to right shunting, is associated with prolonged respiratory complications[6]. The problem was initially tackled by surgical closure of the PDA[7]. The demonstration that indomethacin administration could achieve PDA closure in such infants[8,9] led to a major collaborative randomized trial in the United States[10].

Evidence for the value of indomethacin: the United States trial

Infants were considered eligible for the trial if they weighed 1750 g or less and had no congenital or chromosomal abnormalities. They entered the trial if the PDA was considered to be 'haemodynamically significant', i.e., large enough to compromise cardiorespiratory function. Approximately 20% of 3559 infants met the criteria for having a 'haemodynamically significant' PDA. These included the need for ventilatory support together with a murmur and the other clinical signs of a PDA, with or without the presence of cardiac failure. Considerable importance was attached to the echocardiographic evidence of left atrial enlargement (left atrium : aorta $\geqslant 1.15$)[11]. The trial also laid down certain contraindications to entry. The chief exclusions were evidence of poor renal function, a bleeding tendency or evidence of necrotizing enterocolitis. Approximately 9% of the whole group of infants consequently entered the trial.

All infants were given conventional medical treatment aimed at reducing the effect of volume overload on the cardiovascular system. This included fluid restriction and administration of diuretics. Indomethacin was either given at the commencement of 'usual medical therapy' or after 36–48 h of such therapy or not at all, the groups having been randomized and the physicians 'blinded'.

At 48 h after treatment with indomethacin and usual medical treatment, 79% of infants no longer had a 'haemodynamically significant' PDA compared with 28% of infants who received placebo and usual medical treatment. Although the PDA reopened in 26% of those who received indomethacin, it subsequently closed again in most of them and surgery was required in very few. Overall, permanent closure of the ductus arteriosus occurred without the need for surgery in 79% of the infants who received indomethacin and in 35% of those who received placebo. In infants whose birth weight was less than 1000 g, the closure rate associated with indomethacin treatment was three times the spontaneous closure rate. However, the incidence of indomethacin failures was slightly (but not significantly) higher in this group than in infants weighing more than 1000 g.

The overall mortality did not differ significantly whether infants were given usual medical therapy with initial or later indomethacin or whether they proceeded to surgical ligation of the ductus arteriosus having been in the placebo or the indomethacin group. However, the surgical group had a higher complication rate, especially pneumothorax and retrolental fibroplasia, and the infants who were given indomethacin as part of the initial therapy had a higher incidence of bleeding than those to whom it was given only when usual medical therapy had failed. It is perhaps noteworthy that bronchopulmonary dysplasia and necrotizing enterocolitis had a similar incidence in each of these groups.

The trial also consisted of a follow-up evaluation of the groups of infants at the age of 1 year[11]. At that time there were no significant differences between the groups in terms of the prevalence of various conditions or in terms of the proportion of infants with poor outcome.

Conclusions

The results of the multicentre trial of indomethacin suggest that there may be some merit in using intravenous indomethacin in those infants with a significant PDA who do not respond to a 36–48 h period of fluid restriction and diuretics and in whom there is no contraindication to its use. It might then be anticipated that approximately two-thirds of the infants would require indomethacin. Approximately one-quarter of all infants with a significant PDA would probably require surgical closure compared with two-thirds if indomethacin were not used. The multicentre study did not report whether the results varied from one centre to another. It is probable that the timing of surgical closure of the ductus would have been based on the individual clinical assessment of each infant and might conceivably have influenced the outcome in the various centres. It is therefore difficult to advise a firm policy on the basis of the collaborative study. Perhaps it might be argued that a policy of surgical closure may have better results in one centre while indomethacin after usual medical therapy, and later surgery if that fails, may be preferable in another.

Principles of management

Both before and during indomethacin administration and prior to resorting to surgery, fluid control is an essential part of the management of these infants[12]. Restriction of fluid intake to 80–120 ml/kg per day may alone be effective in reducing volume overload and promoting closure of the PDA. It may become necessary to add a diuretic, the most popular and effective being frusemide. A dose of 1–2 mg/kg body weight may be given two or three times daily. The serum electrolytes must be monitored and maintained at physiological levels. Frusemide has a theoretical disadvantage in that it stimulates the renal synthesis

of PGE_2 which, in turn, may increase the incidence of ductus patency. A study of two groups of infants, one given frusemide and the other given chlorthiazide, showed that the incidence of PDA was higher in the frusemide group but the survival rate was similar in both[13].

In the collaborative study indomethacin was administered intravenously. It is conceivable that oral administration may result in unreliable absorption and may irritate the gastrointestinal tract. The recommended initial intravenous dose is 0.2 mg/kg body weight. This is repeated at 12-hourly intervals for a total of three doses. The second or third dose should not be given if contraindications develop or if there is evidence that complete closure of the ductus arteriosus has already occurred. In those infants who are 8 days or older, the second and third doses may be increased to 0.25 mg/kg body weight because there is evidence that indomethacin is metabolized more rapidly by the premature infant as postnatal age advances[14].

A small randomized study has been reported in which infants weighing 1000 g or less were given indomethacin as a prophylactic measure when they presented with the early signs of a patent ductus arteriosus and before the left-to-right shunt became significant[15]. Although a lower incidence of subsequent significant shunting was shown, the overall benefits of this strategy must remain speculative until a more extensive study has been undertaken.

DUCTUS-DEPENDENT CONGENITAL HEART DISEASE

The E-type prostanglandins: pathophysiological considerations

Experiments both *in vitro*[16] and *in vivo*[17] have shown that the E-type prostaglandins (PGE) cause relaxation of ductus arteriosus muscle. In early clinical studies infusions of either PGE_1 or PGE_2 were consistently effective in improving the oxygenation of neonates whose pulmonary blood flow depended on patency of the ductus arteriosus[18–23]. PGE_1 infusions were also helpful in neonates with interrupted aortic arch, juxtaductal coarctation of the aorta and hypoplastic left heart syndrome[24–26]. It was clearly shown that by maintaining ductus patency in this way, the descending aortic pressure rose and consequently the pressure gradient between the pulmonary artery (or ascending aorta) and the descending aorta was reduced[26]. It is probable that the improvement in descending aortic flow also improves perfusion of the kidneys, thus helping to eliminate fluid and correct the acidosis. PGE_1 has more recently been applied to the treatment of neonates with critical aortic stenosis[27,28]. Artman *et al.*[27] demonstrated that right to left ductal shunting in this situation improved the abdominal aortic blood pressure, increased the urinary output and decreased the acidaemia. Leoni *et al.*[28] observed improvement in their treated patients with critical aortic stenosis but suggested that the mechanism was uncertain.

The other important application of PGE therapy is the presence of complete transposition of the great arteries when inter-atrial mixing is poor. It may be used either before or after balloon atrial septostomy[23,29,30]. The increased flow through the ductus arteriosus from the aorta to the pulmonary artery results in an increase in pulmonary blood flow and an increased pulmonary venous return to the left atrium. The left atrial pressure rises, encouraging the flow of oxygenated blood across the inter-atrial communication into the right heart and the systemic circulation.

Clinical evaluation of prostaglandin therapy

An extensive assessment of the use of PGE_1 infusion in treating infants with ductus dependent congenital heart disease was undertaken in a collaborative clinical trial in the United States involving a total of 492 infants[31,32]. Initially it had been recommended that PGE_1 should be infused continuously into the aorta, near the origin of the ductus arteriosus in a dose of 0.05 to 0.1 $\mu g\,kg^{-1}\,min^{-1}$. Later it was shown that PGE_1 was also effective if infused intravenously and if the dose was decreased. In almost all the cases in the study the infusion was continued for no more than several hours, the objective being to stabilize the infant in preparation for emergency palliative surgery. In the group with cyanotic congenital heart disease, the mean PaO_2 increased from 3.6 kPa to 5.1 kPa during infusion. Those with an initial PaO_2 less than 2.7 kPa had the greatest improvement while those with an initial PaO_2 greater than 5.3 kPa had virtually no response. In the infants with interrupted aortic arch or coarctation of the aorta the descending aortic blood pressure increased and there was general clinical improvement.

It is probable that PGE_1 (rather than PGE_2) was chosen for the trial and for later marketing because it had featured more extensively in the earlier experiments and trials. It was regarded as a more powerful pulmonary vasodilator than PGE_2 and might therefore have been expected to promote a greater increase in pulmonary blood flow. However, no clinical evidence had been presented to show that PGE_2 was any less effective than PGE_1 in maintaining ductus arteriosus patency in critical congenital heart disease.

The earlier reports and the collaborative study have emphasized the use of PGE_1 or PGE_2 infusion for a period of a few hours prior to emergency surgery. Longer term infusion was initially reported in pre-term infants[24] and several more reports have emerged of longer term treatment with PGE_1 infusions[33–35].

Enthusiasm for long term infusion has probably been limited partly by practical considerations as well as a significant incidence of side effects[20,24,29,34,35]. In this institution we had considered it desirable to avoid intravenous infusions, if possible, and therefore elected to evaluate an oral preparation of PGE_2 that had been commercially available

in the United Kingdom for obstetric purposes[36]. The initial evaluation was conducted in infants with a ductus dependent pulmonary circulation[37,38] and subsequently in two patients with interrupted aortic arch[39].

In the initial study we tested whether oral PGE_2 would consistently maintain ductus patency and whether it could easily be substituted for intravenous therapy. We evaluated the requirements in terms of dosage and frequency of administration and in some cases tested the ductus responsiveness on several occasions over a period of months. The chief clinical objective was to postpone operative intervention beyond the early neonatal period and to encourage growth of the infants and of the major blood vessels in order to decrease the surgical risk.

The effectiveness of oral PGE_2 was confirmed both by clinical improvement and by an increas in arterial oxygen content in those infants with a ductus dependent pulmonary circulation in whom measurements were made. The improved arterial oxygenation after a single oral dose of PGE_2 was similar to that reported in the United States collaborative study when PGE_1 intravenous infusion was used. Blood oxygen values were similar whether PGE_2 was given orally or by intravenous infusion and the plasma PGE_2 concentration reached similar values whichever route of administration was used.

In most cases the arterial oxygen tension and saturation and the plasma PGE_2 concentration increased rapidly within 15 to 30 min after an oral dose. These observations implied rapid absorption from the alimentary tract. When the oral dose was increased, there was a proportionate increase in plasma PGE_2 concentration, confirming that absorption was efficient. However, higher plasma PGE_2 concentrations were not usually associated with better blood oxygenation, probably because the ductus had been fully dilated by the lower dose. These observations helped to rationalize both the route of administration and the appropriate dosage.

It was found that hourly administration of oral PGE_2 was necessary in order to maintain arterial oxygenation at satisfactory levels for the first week or two. Subsequently the requirement usually diminished and the dosage or its frequency could be reduced. The ductus arteriosus did not retain its patency if PGE_2 therapy was discontinued, even after many months of treatment, but it was possible in some cases to lengthen the periods between doses to as much as every 4 to 6 h.

Of 42 infants who were treated for more than 14 days, 29 gained weight satisfactorily, nine more slowly than expected and four failed to gain at all. Two of the four with no weight gain had aortic arch interruption. Growth of the pulmonary artery was demonstrated in most of the infants with diminished pulmonary blood flow who had had repeat angiograms after a period of PGE_2 therapy.

Complications of E-type prostaglandins

The side effects of PGE_1 infusion were detailed in the report of the United States collaborative study[31]. Cardiovascular reactions were the most common, particularly hypotension, cutaneous vasodilatation (especially during intra-aortic infusion) and rhythm disturbances. Central nervous complications included pyrexia, jitteriness and muscle twitching. Respiratory depression was the third most common complication, having occurred in 12% of all the infants treated. Gastrointestinal complications occurred in only 2%, diarrhoea being the most common while necrotizing enterocolitis occurred only occasionally. Long term PGE_1 infusions have been associated with complications such as cortical hyperostosis[34,35], friability of the ductus arteriosus[40] and damage to the pulmonary arterial vessel walls[41].

The complications associated with PGE_2 have been less widely reported probably because it has been less widely used. We have recently examined the incidence of complications in the first 62 patients treated in our institution and found that 44% had complications thought to be caused by PGE_2 therapy. This is virtually identical to the incidence reported in the United States collaborative study using PGE_1. However, most of the complications in our patients occurred several days or weeks after the institution of treatment while those in the collaborative study were usually within hours.

Apnoea occurred in relation to PGE_2 therapy in only three patients (5%), a much lower incidence than in the collaborative study, and none required ventilatory support. We have not seen cases of apnoea associated with prolonged ductus patency or with acidosis[42,43] and suggest that the reported cases might have been dose-related or associated with an abnormally high pulmonary blood flow and cardiac failure.

No infant in our series had a cardiovascular complication. Fever occurred in 23% of our patients, often during the first few days of treatment but it usually settled and did not influence management. This compared with an incidence of 5% of those treated short term in the collaborative study. Jitteriness or seizure occurred in 5% of our patients but always associated with an alternative explanation such as severe hypoxia and acidosis or birth asphyxia. This compared with an incidence of 7% of those in the collaborative study.

Diarrhoea was one of the commonest complications occurring in infants treated with PGE_2 and almost always in those treated long term with the oral preparation. It settled rapidly when low-dosage i.v. therapy was substituted and usually did not recur when oral therapy was reinstituted. It occurred in 21% of infants compared with about 2% in the collaborative study.

Necrotizing enterocolitis occurred in 8% of the neonates in our series and has been well documented in infants following cardiac catheterization. Dickinson *et al.*[44] found an incidence of 14 out of 111 catheterizations. All the infants who developed this complication had

undergone cardiac catheterization. In this series necrotizing enterocolitis was therefore not considered to have been related to PGE_2 therapy.

None of the longer term complications such as cortical hyperostosis, friability of the ductus arteriosus or damage to pulmonary vascular smooth muscle[45] were seen in infants treated with long term PGE_2. We suggest that the occurrence of cortical hyperostosis reported by others during long term PGE_1 infusion was probably dose-related[34,35]. If PGE_2 influences bone resorption in the same way as PGE_1, it would appear that our patients might have been protected from this complication by the low dosage that they received. It is likely that the other reported complications of long term therapy were also dose-related.

Rationale of therapy with PGE

The efficacy of intravenous PGE_1 and PGE_2 and of oral PGE_2 therapy in maintaining ductus arteriosus patency has been well documented as outlined above. There are distinct advantages in using the oral preparation in preference to the intravenous. It is easier to administer and its absorption and beneficial effects are rapid. It is particularly suitable for long term use and it has enabled the majority of infants so treated to grow satisfactorily. During the course of treatment it is usually possible to increase the interval between doses and such infants may be discharged from hospital to be treated at home.

There is probably little to choose between PGE_1 and PGE_2 for intravenous infusion. The beneficial effects are similar and the available evidence suggests that they have similar side effects. PGE_2 occurs naturally in ductus arteriosus tissue, in the lungs and in the circulating plasma in higher concentrations than PGE_1; its pharmacological use might therefore be more appropriate. PGE_1 has been more widely tested but in doses that are at least ten-fold the doses of PGE_2 that we have shown to be effective[38,39]. There is evidence that PGE_1 is effective when used in the low dosages which we have recommended for PGE_2. It also seems that the side effects are largely dose-related[46], again confirming our own experience of using PGE_2. There may be a strong economic argument in favour of PGE_2: the cost of the intravenous preparation is one-fifth the cost of PGE_1 and the daily cost of treatment with the oral preparation is only 14% the cost of an ampoule of PGE_1.

It is difficult to assess whether the long term outlook for infants treated with long term PGE is likely to be improved by delaying surgery, but the surgeons in this institution prefer to operate on infants weighing 3.5 kg or more. There is probably no significant long term advantage in the long term treatment of patients with interrupted aortic arch; although the metabolic state of our patients improved, they remained in congestive cardiac failure and did not thrive.

It is our practice to commence therapy with PGE_2 as soon as the diagnosis has been established by cross-sectional echocardiography. If a subsequent diagnostic cardiac catheterization is to be performed, it

is better done when the neonate's oxygenation and metabolic state have been improved by treatment. A diagnosis of right heart obstruction or of the coarctation syndrome is the prime indication for the use of PGE. In cases of complete transposition of the great arteries the decision to use PGE will depend on the clinical state of the infant and on the anticipated delay before balloon atrial septostomy. It is not our practice to attempt to maintain ductus patency in cases of hypoplastic left heart syndrome. An argument has been advanced in favour of commencing treatment in the neonatal unit before transferring the infant to the cardiac referral centre[46]. Such a decision should preferably be reached in consultation with the cardiologist because there are potential risks if infants with total anomalous pulmonary venous return or persistent fetal circulation are inadvertently given PGE.

We recommend that the initial oral administration of PGE_2 should be in doses of 20–25 μg/kg hourly, decreasing the frequency of the doses after the first week. The tablet is divided into the appropriate size doses, each of which is suspended in 4–5 ml water and given either into the mouth or through a nasogastric tube. When gastrointestinal absorption is expected to be poor, when oral therapy is ineffective or if diarrhoea becomes troublesome, an intravenous infusion should be commenced in a dose of 0.003 $\mu g\ kg^{-1}.\ min^{-1}$. Occasionally it is necessary to increase the infusion dose for a few hours and we have found it exceptional to have to use doses as high as 0.01 $\mu g\ kg^{-1}\ min^{-1}$. There appears to be little justification for the continued advocacy of doses as high as 0.05–0.10 $\mu g\ kg^{-1}\ min^{-1}$ even if PGE_1 is used. Our current practice is to treat this group of patients with oral PGE_2 for between 1 and 4 weeks initially and then to decide on an individual basis whether to proceed with surgery or to plan a longer course of treatment to encourage further growth.

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6
Ventricular function

T. P. GRAHAM

The subject of ventricular function continues both to fascinate and to plague the clinical cardiologist who attempts to correlate patients' symptoms with laboratory measurements of cardiac performance. The frequent discrepancies between symptoms and measured ventricular function indicate the need for improved methods for both measurement and description of cardiac performance. Loading conditions of the heart, contractile state, distensibility of the ventricles, ventricular interaction, and the concepts of cardiac reserve all can enter into a patient's clinical symptoms and should be assessed separately whenever possible. In this review I shall try to outline a comprehensive conceptual framework of ventricular function, indicate how currently available methods can be used to assess ventricular function, and then indicate examples of how these concepts and methods can be applied to patients with congenital heart disease.

BASIC CONCEPTS OF VENTRICULAR FUNCTION

In the most basic terms, the purpose of the heart is to pump sufficient blood for the body's demands both at rest and with any type of stress. Cardiac output (C.O.) then is the simplest measurement of cardiovascular performance and is the product of end-diastolic volume (EDV), ejection fraction (EF), and heart rate. Thus the control of cardiac output is directly related to factors which alter these variables.

Figure 6.1 illustrates the multiple factors which can alter EDV and thus C.O. These determinants vary greatly in the role they play in altering preload. For example, intrathoracic pressure changes and ventricular interaction are probably minor influences on EDV in the normal resting individual, but in the patient with pulmonary hypertension who is on a positive pressure ventilator these variables assume major importance. Diastolic filling time is seldom limiting in terms of ventricular volume at rest but supraventricular tachydardia may severely reduce EDV.

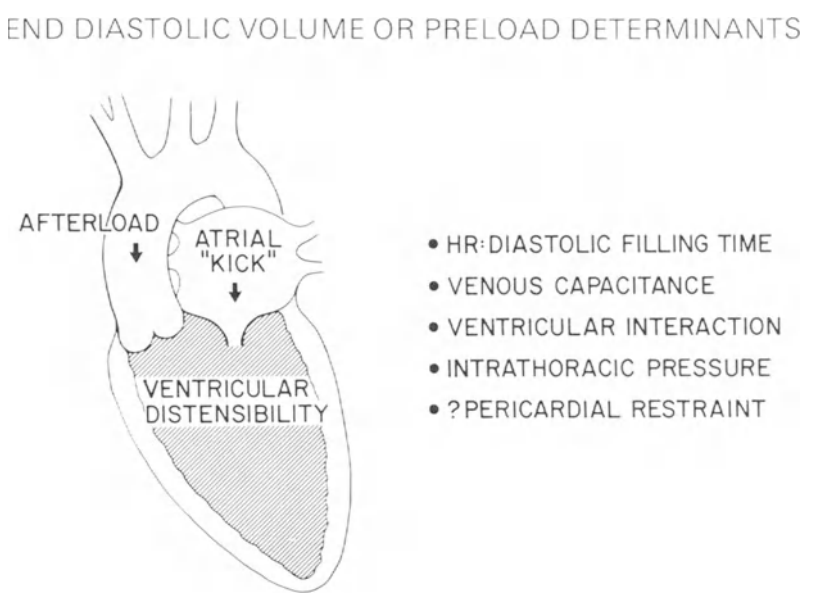

Figure 6.1 Schematic diagram of the multiple determinants of end diastolic volume

Figure 6.2 shows the multiple determinants of EF. This variable has been used to assess ventricular function but is highly dependent on afterload and to a lesser extent on preload. In addition, ventricular hypertrophy can increase EF without an alteration in cardiac muscle contractile state. The use of EF to estimate ventricular function must therefore be tempered with some estimation of preload, afterload, and hypertrophy.

Acute preload and afterload reserve

In Figure 6.3 schematic pressure–volume loops are shown to illustrate normal ventricular performance and the concepts of preload and afterload reserve. Under normal resting conditions a 10-year-old child would be expected to have the pressure–volume loop shown with an EDV of 71 ml/m^2, an EF of 0.63, and cardiac index (C.I.) of 3.5 l.min^{-1}.m^{-2}. With an acute increase in volume loading such as might occur with overhydration to a patient in intensive care, EDV theoretically could increase approximately 50% with end-diastolic pressure (EDP) increasing from 8 to 25 mmHg. By the use of the Frank-Starling mechanism, the heart pumps out whatever increase in venous return is presented to it (the 'ascending limb' of the Starling curve) over a fairly broad range. Thus end-systolic volume (ESV) remains unchanged under these conditions, EF is increased to 0.75, and C.I. to 6.3. Further increases in volume loading could increase

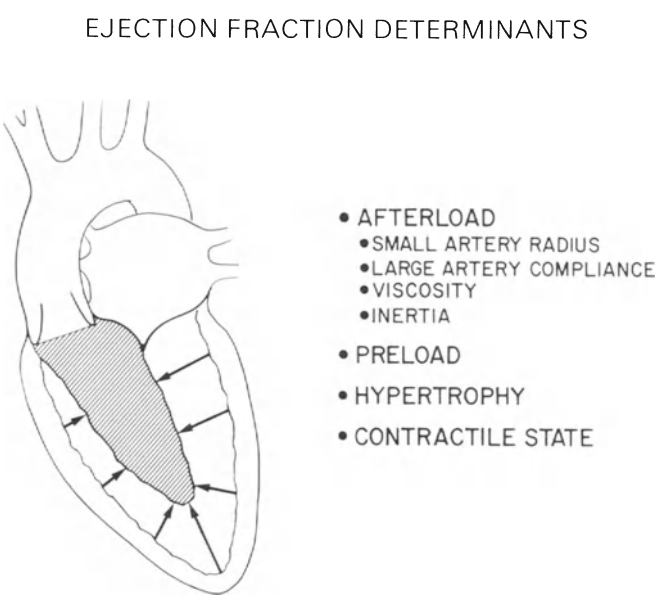

Figure 6.2 Schematic diagram of important determinants of ejection fraction

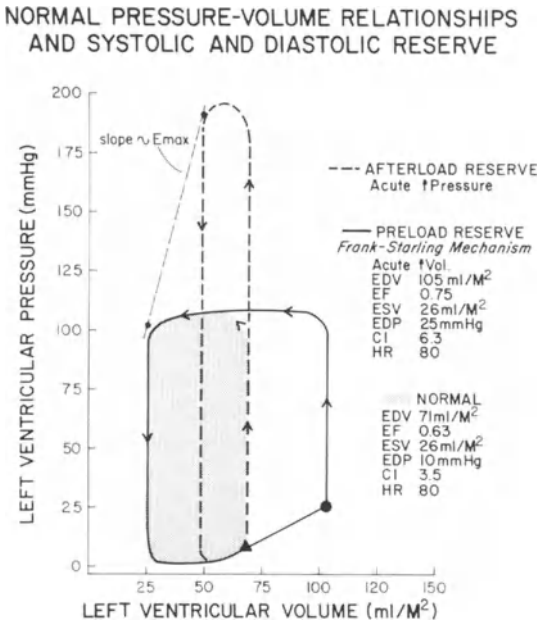

Figure 6.3 Schematic pressure–volume loops for a normal 10-year-old child illustrating concepts of acute preload and afterload reserve

EDP to unacceptable levels whereby pulmonary congestion would occur and thereby exceed the normal preload reserve.

In addition to acute preload reserve, the heart also has an acute afterload reserve whereby with a sudden increase in afterload (or resistance to aortic ejection), the heart can continue to eject blood although at a reduced rate and amount. The actual increase in aortic pressure tolerated is not known precisely but probably approximates an increase of 100%, that is from 100 to 200 mmHg. With such an acute increase, EF on the first beat following the pressure rise will fall abruptly. The slope of the line obtained by connecting the end-systolic pressure–volume points on the normal and post afterload increase loops (Figure 6.3) will be an approximation of Emax – a theoretical load independent measurement of ventricular function to be discussed later in this chapter.

It should be noted that the actual numbers employed to illustrate the concepts of preload (diastolic) reserve and afterload (systolic) reserve are only estimates. In real life there are no 'pure' acute preload or afterload changes. Acute increases in afterload also affect preload. For example, following the first beat with an altered afterload, EDV will increase as EF falls. Similarly preload changes can cause an increase in afterload as systolic pressure, ventricular dimensions, and wall stress increase.

Chronic preload and afterload changes

Chronic changes in preload or afterload can produce marked alterations in diastolic pressure–volume relationships. Figure 6.4 illustrates chronic changes with isolated volume or pressure overload seen in compensated children with ventricular septal defect (VSD) or aortic stenosis (AS). These figures were derived from actual data previously published in 11 children with VSD (average age of 4.8 years)[1], 14 children with AS (average age 7.8 years)[2], and 25 children with normal left ventricles (average 7.9 years)[1].

With the large volume overload secondary to a VSD, left ventricle (LV) end-diastolic volume is almost twice normal but LV end-diastolic pressure and EF are virtually unchanged. Thus a major change in the diastolic pressure–volume relationship has occurred with a marked increase in operative volume distensibility[3] such that the left ventricle can pump over twice as much blood as normally without severe elevation of end-diastolic or pulmonary venous pressure. Ventricular pump function as assessed by EF is 'normal'. With an increased preload and a lowered afterload or resistance to ejection through a large VSD, however, one would predict an increased EF in the presence of normal ventricular function. Thus a normal EF in this instance suggests that ventricular function actually may be depressed. This example also indicates the difficulty in assessing ventricular function in situations with altered loading conditions.

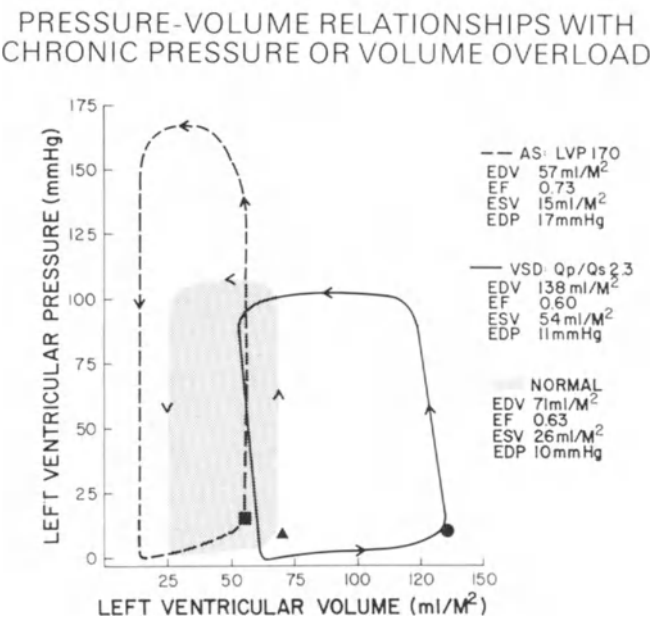

Figure 6.4 Illustrative pressure–volume loops with chronic pressure or volume overload in childhood

Isolated pressure overload is depicted in Figure 6.4 by aortic stenosis with peak LVP averaging 170 mmHg (versus 99 mmHg in the normal group). These patients demonstrate a decreased EDV (>20% below normal), an increased EF (16% above normal), and a normal cardiac index. End-diastolic pressure is significantly increased (55% above normal) indicating a marked decrease in operative volume distensibility[3]. LV wall mass in these patients averaged 126 g/m² versus a normal value of 82 g/m². Thus with isolated pressure overload in children, compensation is achieved by marked concentric hypertrophy which alters filling characteristics but increases ejection fraction and maintains cardiac output. The position of the end-systolic pressure–volume points in Figure 6.4 suggest that ventricular function ('Emax') is increased with AS and depressed with VSD.

Afterload mismatch

The concept of afterload mismatch popularized by Ross and associates[4] is directly applicable to congenital heart disease. Figure 6.5 illustrates data from infants with symptomatic coarctation studied at an average age of 9 days[5]. This clinical situation is characterized by a sudden increase in afterload at the time of ductal constriction. The infant's myocardium is poorly equipped to handle such a stress due to

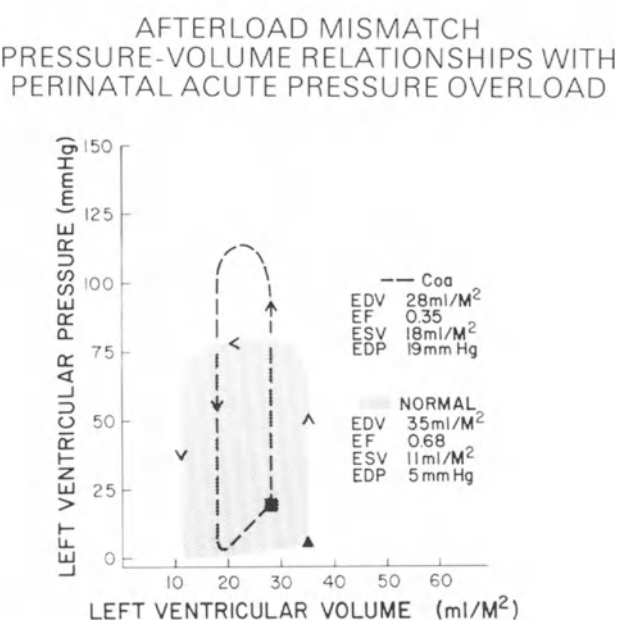

Figure 6.5 Pressure–volume loops for a normal neonate compared with a neonate with symptomatic coarctation and severe afterload mismatch[5]

its decreased contractile tissue per gram of myocardium, decreased distensibility, and probable decrease in cardiac sympathetic innervation[6–8]. This results in a marked decrease in left ventricular ejection fraction, an increase in end-diastolic pressure, and a fall in cardiac output to only 39% of normal. Left ventricular wall mass is normal since there is no time for hypertrophy to occur. These changes usually are all secondary to afterload mismatch and not abnormal myocardial contractility since patients studied after coarctation repair showed normal or increased LV pump function by echocardiography[5].

Figure 6.6 shows similar data from infants aged 3 months whose coarctation probably occurred more gradually with resultant time for myocardial hypertrophy to occur and a reasonable degree of compensation achieved with cardiac index being 93% of normal. These patients had a marked increase in LV mass averaging 222% of normal. With this degree of hypertrophy, compensation was possible with a near normal EF and a cardiac index of $4.1\,l.min^{-1}\ m^{-2}$ or 93% of normal[5].

With this background concerning the effects of loading conditions on pump function as well as acute and chronic adaptation to heart defects, I will attempt to indicate how currently available methods to assess ventricular function have been used in patients with congenital heart disease.

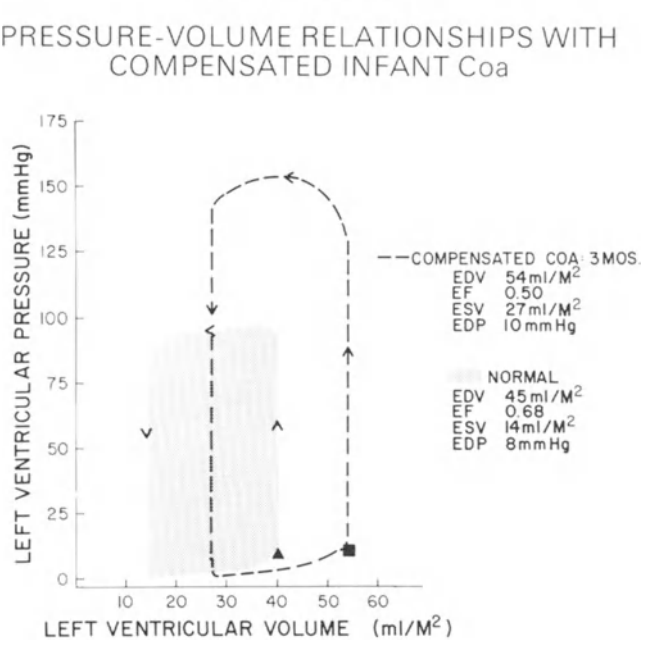

Figure 6.6 Pressure–volume loops for a normal 3-month-old infant compared with an infant with compensated coarctation[5]

EVALUATION OF RESTING VENTRICULAR FUNCTION

Quantitative angiography

Quantitative angiography has been the 'gold standard' for assessment of resting right and left ventricular function in patients with congenital heart disease[9–19]. With this methodology end-diastolic volume, ejection fraction, systolic output, and left ventricular wall mass can be calculated. Details of methodology can be found in the references cited above. Normal values for pertinent variables are shown in Table 6.1. These values have been derived from nine different studies for the right ventricle and six different studies for the left ventricle[9–19]. There is reasonably close agreement between all of the studies cited. In most studies, RVEDV has been found slightly larger than LVEDV along with a slightly lower RVEF. These data yield average stroke volumes of approximately 45 ml/m² and end-systolic volume of 25 ml/m² for both ventricles.

Particular caution is required when assessing volume data in infants and young children. The relationship between RVEDV or LVEDV and body surface area (BSA) or any other body size variable (height, weight) is an exponential one as described by three separate groups[11, 13, 14]. This relationship, however, closely approximates a linear one in patients

with BSA above 0.50 m^2 and thus Table 6.1 shows values for EDV in ml/m^2 which can be used for older patients. For younger patients the regression equations shown in Table 6.1 should be used to calculate a predicted EDV for a given BSA and derive EDV for each patient as a % of the predicted value. The normal range is 75–125% of predicted. Table 6.1 gives a normal range of EDVs in ml for two ample BSAs; the values for 0.20 m^2 relate closely to a normal newborn's size.

Table 6.1 Normal angiographic data for cardiac volumes of (A) infants and young children, and (B) older children, adolescents and adults with BSA > 0.5 m^2 (taken from references 9–19)

Group	*Body surface area* (m^2)	*Volume* (units)	*Normal value*	*Range*
A	0.2	[a]LVEDV(ml)	6.8	5.1–8.5
	0.2	[a]RVEDV(ml)	7.5	5.6–9.4
	0.5	[a]LVEDV(ml)	26.5	19.9–33.1
	0.5	RVEDV(ml)	26.1	19.6–32.6
	—	LVEF	0.68 ± 0.05	0.58–0.78
	—	RVEF	0.66 ± 0.07	0.52–0.80
B	>0.5	LVEDV(ml/m^2)	70 ± 11	48–92
	>0.5	LVESV(ml/m^2)	23	
	>0.5	RVEDV(ml/m^2)	72 ± 13	46–92
	>0.5	RVESV(ml/m^2)	27	
	>0.5	LVEF	0.67 ± 0.06	0.55–0.79
	>0.5	RVEF	0.62 ± 0.06	0.50–0.74

[a] Predicted EDV for younger patients are calculated from the equations

$$LVEDV(ml) = 74.3\ (BSA)^{1.43}$$
$$RVEDV(ml) = 67.0\ (BSA)^{1.32}$$

Echocardiography

Echocardiographic data are also useful for evaluating resting LV wall thickness, axis dimension, and shortening fractions for patients with circular or near circular LV cavities[20]. LV volumes have also been derived from cross-sectional echoes; these generally yield smaller volumes than angiographic data with a higher variability[21,22]. Ejection fraction or % change in LV short axis cross-sectional area can be useful for estimating pump function and regional wall motion in patients whose left ventricle is abnormally shaped and/or dyskinetic[23]. Right ventricular volumes and ejection fractions have also been derived from echo images but are more difficult to obtain and are associated with considerable variability[24,25]. These usually require a regression equation using angio data to 'correct' the echo values. A summary of normal echo values is shown in Table 6.2.

Table 6.2 Normal values for echocardiographic data

Parameter	*Normal value*
M-mode	
A. LV dimensions (must be related to wt or BSA)	Non-linear functions so mm/m² not adequate for infants and children
B. LV minor axis shortening factor	28–44% (mean 36%)
C. LV posterior wall thickening	30–100% (mean 60%)
D. Maximal velocity of posterior wall lengthening	77 ± 14 mm/s (newborns) 145 ± 34 mm/s (adults)
E. VcF (heart rate dependent)	VcF = 1.075 + 0.005(HR) − 0.02 (Age)
F. Peak VcF	3.8 ± 1.0 s^{-1} (newborns) 2.7 ± 0.4 s^{-1} (adults)
G. LVPEP/ET	< 0.40
H. RVPEP/ET	< 0.33
Cross-sectional echo	
I. LV area (% change)	43–67%
J. LVEF (similar to angiographic values)	55–70% (approx.)

Radionuclide data

Radionuclide angiography (RNA) studies can also be used to assess ventricular size and function. Both first pass and equilibrium studies have been used for this purpose and normal values are shown in Table 6.3[26–28]. Volume data are similar to the values found with angiography although variability with RNA is greater[29]. It should be noted that the lower limit for LVEF for both RNA and angiographic studies is approximately 55%. For the RVEF, the lower limit is approximately 50% for angio studies but only 35–40% for RNA evaluations.

Table 6.3 Normal radionuclide angiographic values

	Mean ± S.D.	*range*
First Pass Studies (rest)	LVEF 0.68 ± 0.09 RVEF 0.53 ± 0.06	0.50–0.86 0.41–0.65
Equilibrium Studies (rest)	LVEF 0.63 ± 0.06 RVEF 0.50 ± 0.07	0.55–0.75 0.35–0.65
Equilibrium Studies (exercise)	LVEF 0.70 ± 0.07 RVEF 0.63 ± 0.06	0.55–0.85 0.50–0.75

EXERCISE EVALUATION OF VENTRICULAR FUNCTION

Measurement of pump function with exercise can be used to assess ventricular function and this technique provides a more sensitive estimate of ventricular function than resting studies alone. Figure 6.7 shows LVSF measured by echocardiography performed while at rest

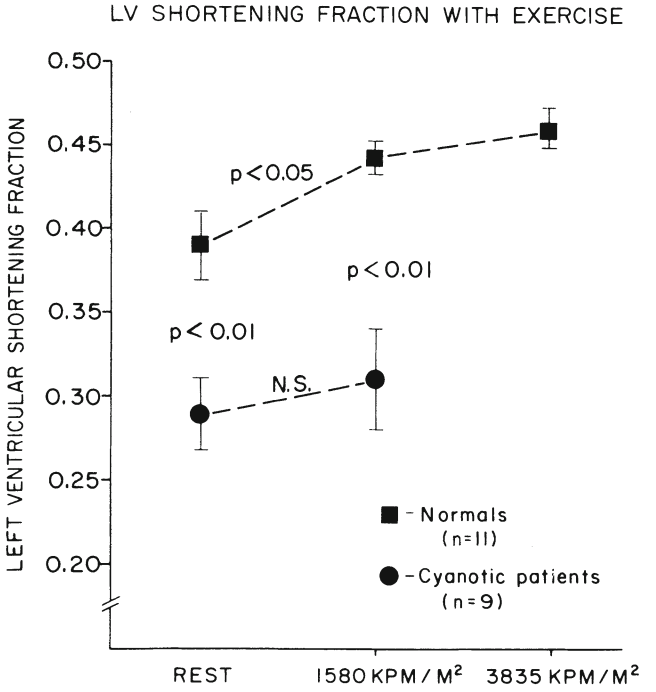

Figure 6.7 Echocardiographic left ventricular shortening fraction as a function of workload during supine bicycle exercise in normal children and cyanotic patients with univentricular hearts and decreased pulmonary blood flow

and with progressive supine bicycle exercise in nine cyanotic patients compared with eleven normals of similar age. The patients had univentricular hearts with pulmonary stenosis or atresia. Normal children showed a progressive increase in SF with exercise whereas cyanotic patients showed no significant change. These measurements are useful in those patients with whom echocardiography is relatively easy to use, but chest movement and respiratory changes make it a difficult method in many patients.

Radionuclide measurements of both RV and LVEF response is a more generally applicable method for assessing ventricular function. A normal response is an increase in EF by $\geqslant 5$ EF units unless resting EF is high in which case no change may occur. Figure 6.8 demonstrates mean RVEF (systemic ventricle) response to exercise in 11 patients who had prior repair of TGA using Mustard's technique as well as five patients with congenitally corrected TGA (CCTGA). Neither the postoperative TGA nor the CCTGA patients had a normal response. Similar data have now been published from four different institutions and show remarkably similar results, that is, a failure to increase RVEF during bicycle exercise, Figure 6.9. In these studies, 24/78 patients

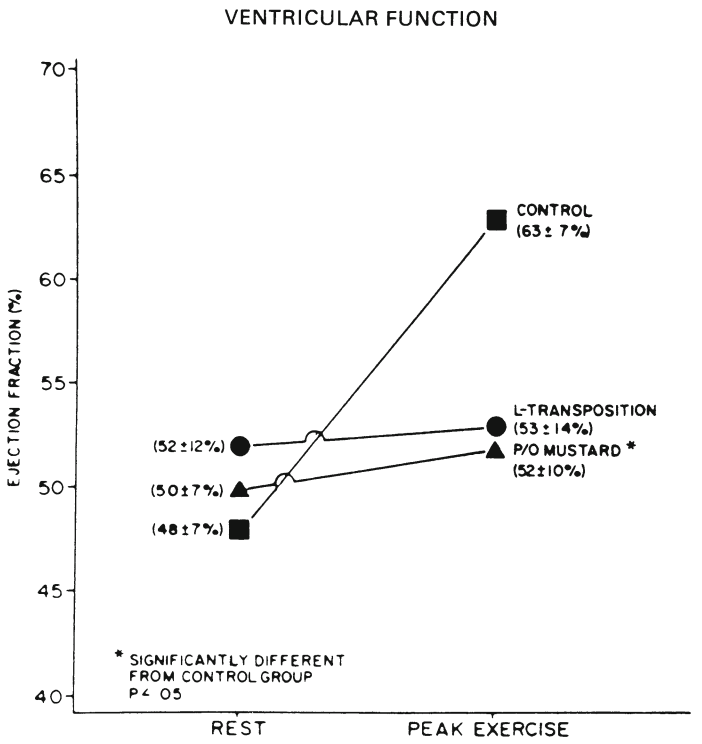

Figure 6.8 Mean systemic ventricular ejection fraction obtained with radionuclide angiography at rest and at peak supine bicycle exercise for normal children, patients studied following Mustard's repair of transposition, and patients with congenitally corrected transposition (by permission)[27]

(31%) showed a fall and 26/78 (33%) showed no change in RVEF at peak exercise. These data are markedly abnormal in that nearly all normal subjects will show an increase in EF with this type of stress.

VENTRICULAR FUNCTION EVALUATION WITH AFTERLOAD STRESS

Assessment of function during acute pharmacologically-induced afterload stress is another useful method to assess ventricular function. Borow and associates[30] have used such a technique whereby systemic blood pressure is increased by methoxamine infusion to 45–70% above control. Cardiac index, systemic mean pressure during systole, and end-diastolic pressure are measured before and during this type of afterload stress while heart rate is kept constant, or nearly so, by atropine. The change in systemic ventricular minute work index (MWI) is then plotted versus change in end-diastolic pressure (EDP) to assess response. MWI = CI (MSP − EDP) × 0.0136, where MSP = mean systolic pressure for the systemic ventricle obtained by averaging the area

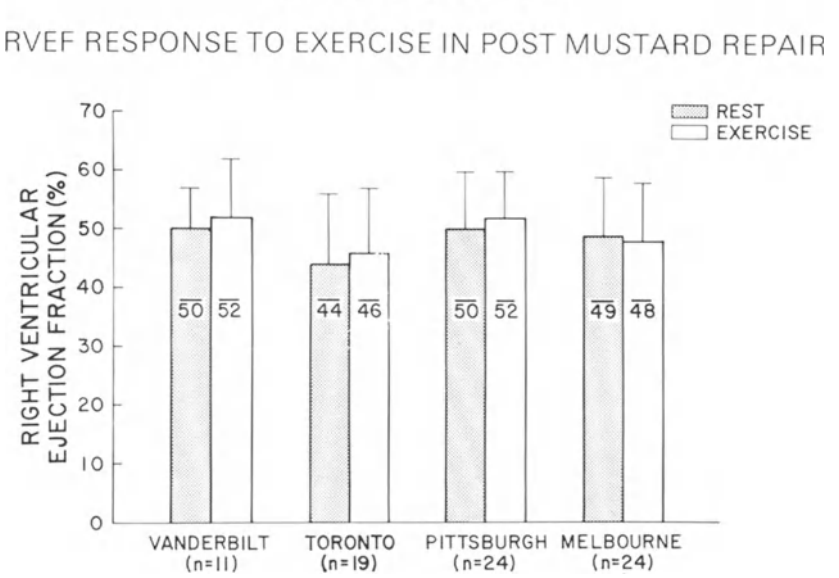

Figure 6.9 Rest and exercise right ventricular ejection fraction data from four different institutions in patients studied following Mustard's repair of transposition

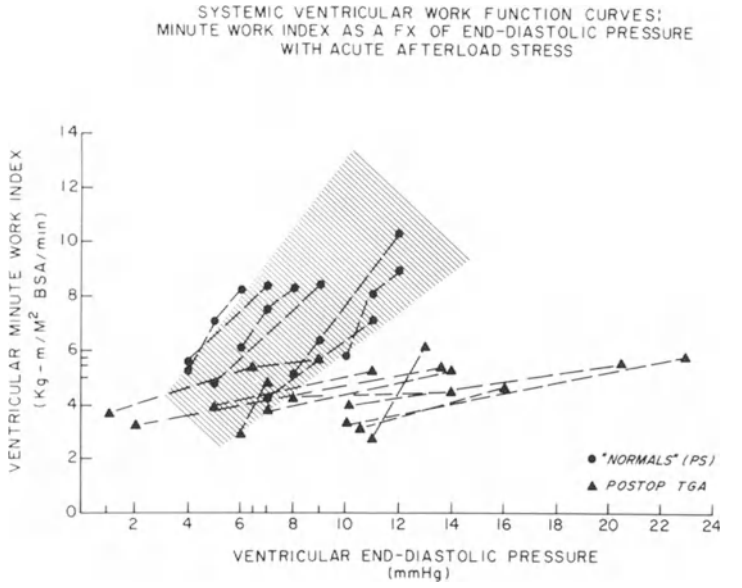

Figure 6.10 Systemic ventricular minute work index as a function of end-diastolic pressure during acute afterload stress. Normal data from Borow *et al.*[30]. Postoperative patients had Senning repair of TGA at least 1 year prior to study; only 2/10 have a normal response

under the systolic phase of the aortic pressure curve, and 0.0136 is the conversion factor for changing mmHg-cm^3 to kg-m. The normal response found in six patients with mild to moderate pulmonary stenosis and one patient with no significant heart disease in terms of MWI/EDP was 1.13 ± 0.12[30]. Figure 6.10 shows data for ten postoperative TGA patients studied with this method in our laboratory. Eight of the ten had an abnormal response when compared with normal data, as previously shown by Borow and associates[31]. The two patients with a normal response had repair of TGA in the first 2 weeks of life whereas all other patients were repaired at a later date.

Non-invasive estimates of ventricular function

With the relatively recent improvements in non-invasive imaging, there has been increasing emphasis on use of this method for assessing ventricular function under conditions which are independent of preload and afterload. Such a method has been developed by Borow and associates[32] to determine LV function using echocardiography and non-invasive blood pressure measurements. In this method, LV end-systolic meridional wall stress (LVESS) is calculated using end-systolic pressure, LV posterior wall thickness, and minor axis dimension. A linear inverse relationship between LVESS and LVSF or circumferential fibre shortening velocity (VcF) has been found with afterload stress. Normal values have been obtained for this relationship and Figure 6.11

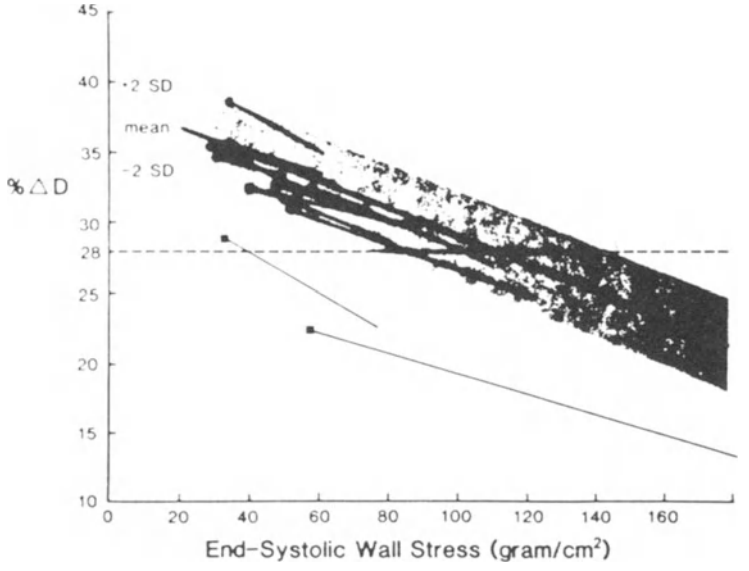

Figure 6.11 Percentage change in left ventricular minor axis shortening as a function of end-systolic wall stress during rest and afterload stress for normal (shaded area) and 12 patients studied after arterial repair of TGA (by permission)

shows these data along with patient data from 12 children studied from 0.4 to 4.8 years following arterial repair of TGA[32]. By this method 10/12 patients had normal LV function.

Subsequently Colan and associates[33] have determined that the LVESS–SF relationship may be dependent on preload and thus not as useful a measure of LV function as previously believed. These authors did, however, demonstrate that VcF normalized for heart rate was inversely related to ESS in a linear manner, was independent of preload, and incorporates afterload. Figure 6.12 shows the relationship between rate corrected VcF and LVESS for normal subjects aged 3 to 70 years in the shaded area[33]. Two patients from our laboratory are plotted against this background. The patient indicated with the triangle was an 11-month-old patient with a small ventricular septal defect and mild pulmonary stenosis. Cardiac catheterization revealed normal LV pressure (105/8), slightly elevated RV pressure (42/8), and normal angiographic LVEDV (47 ml/m^2) and EF 0.77. Her VcF value is well within the normal range as expected and indicates that this range of normal values may well be appropriate for infants as well as older children.

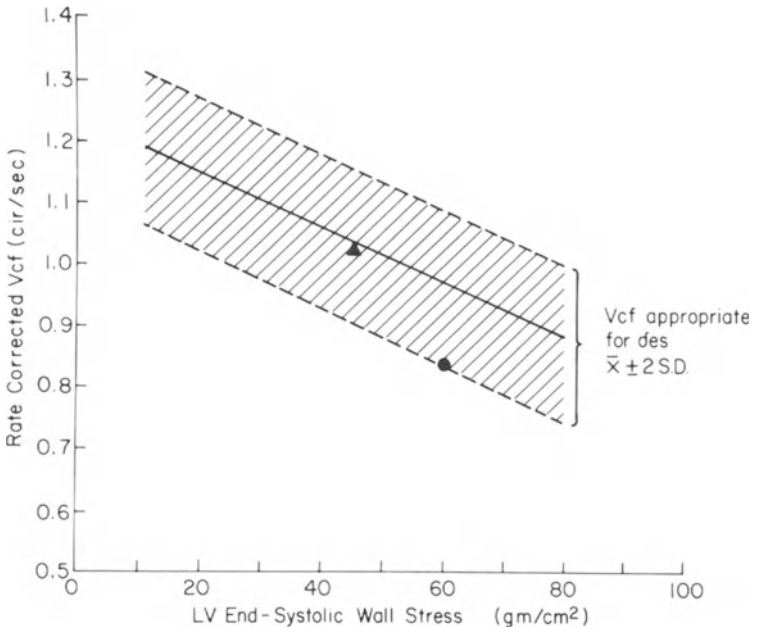

Figure 6.12 Rate corrected VcF as a function of LV and end-systolic wall stress. Normal values from Colan *et al.*[33] Triangle indicates 11-month-old with normal VcF and stress. Circle indicates 11-month-old with severe LV pressure overload from coarctation who has a depressed VcF value which nevertheless is appropriate for the degree of elevation of wall stress

The patient indicated by the circle was also an 11-month-old who had had a previous repair of an interrupted aortic arch in infancy. She subsequently developed a severe coarctation with catheterization data showing an LV pressure of 175/15, with a thickened LV wall and depressed value for VcF. When her VcF value was plotted as a function of LVESS, however, it falls within the appropriate range. Thus for this degree of elevated wall stress, ventricular function is still within the lower limits of normal. This index should prove quite useful for assessing LV function in patients whose echo images are good and whose ventricle is cylindrical and contracts symmetrically.

FUTURE DIRECTIONS

There remain many difficulties in the accurate assessment of ventricular function in man. There are no current methods for RV systolic function assessment which are independent of preload and afterload. Non-invasive measurements of diastolic function of both RV and LV are neither very sensitive nor specific and are probably at least partially dependent on preload, afterload, contractile state, and heart rate. Much progress has been made in the last 20 years in both invasive and non-invasive measurements of cardiac function, but the challenge to improve these methods and solve the problems listed above is clear.

Acknowledgement

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7
Interventional cardiac catheterization

J. E. LOCK, J. F. KEANE and K. E. FELLOWS

During the past 30 years, cardiac catheterization has been primarily a diagnostic exercise. Although the first attempts to correct congenital cardiac defects are as old as catheterization itself[1], such procedures attracted little attention until the work of Rashkind and Miller describing balloon atrial septostomy[2]. A wide variety of therapeutic tools are now available to the catheterizing cardiologist, and they are gaining rapid acceptance. Though the precise indications for and risks of these procedures are still being established, enough experience has been accumulated in several centres to provide an initial assessment. This chapter will review the experimental and clinical experiences with balloon and blade atrial septostomies, percutaneous pericardial drainage, balloon angioplasty and valvuloplasty, the embolization of abnormal vessels, and occlusion of the patent ductus arteriosus.

BALLOON AND BLADE ATRIAL SEPTOSTOMY

Balloon atrial septostomy remains the standard initial therapy for infants with transposition of the great arteries (TGA). Although the principles governing the use of this procedure have changed little in the past 15 years, several modifications have been made in the catheters and their usage. These changes made the procedure easier and more effective. The use of a percutaneous femoral or umbilical 6F or 7F sheath has eliminated the need to repair the femoral vein after cutdown access[3]. However, care must be taken to avoid air embolus when using a sheath to introduce the septostomy catheter particularly if the umbilical vein is used. The Edwards-Miller balloons are larger, and will accommodate 4 cm^3 of fluid, resulting in an increased effective balloon diameter ranging from 14 to 17 mm[4]. The Rashkind USCI 6F septostomy catheter, with a recessed balloon, will pass through a 6F sheath, but will fully inflate with only 1.5 cm^3. We have found that these balloons will produce an atrial septal tear whose size can be easily seen on echocardiography, although a 4 cm^3 balloon in a congenitally small left

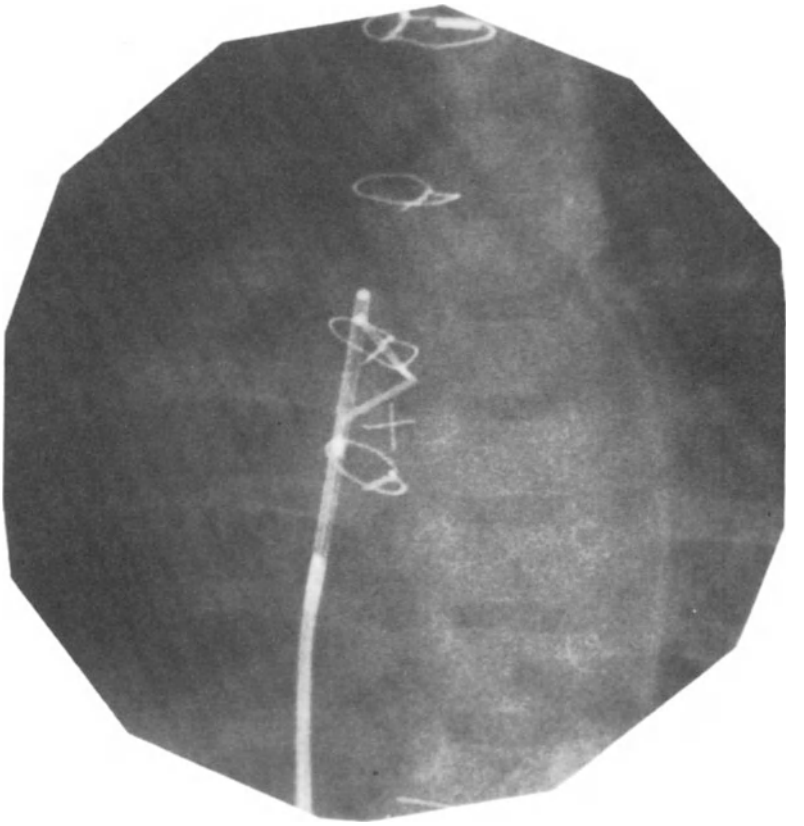

Figure 7.1 PA and lateral roentgenogram of a septostomy blade opened in the left atrium of a patient with mitral atresia. Prior to pulling across the atrial septum, the blade is positioned leftward and about 30° anterior

atrium (i.e. mitral atresia) may injure the back wall of the left atrium during septostomy.

It soon became clear that successful balloon atrial septostomy was a procedure limited to the first few weeks of life. Park *et al.*, after a series of animal experiments, developed a blade atrial septostomy catheter[5]. The utility and relative safety of the procedure was demonstrated in a recent collaborative study[6].

Blade atrial septostomy has been used primarily in the treatment of poor mixing in infants with TGA outside the first month of life. In such patients, the left atrial size and anatomy is normal, making the procedure quite safe. The blade catheter is advanced into the left atrium, the curve of the catheter is pointed toward the left shoulder, and the blade is slowly extruded by advancing the activating guidewire. The blade should be extruded only if it opens easily; resistance to

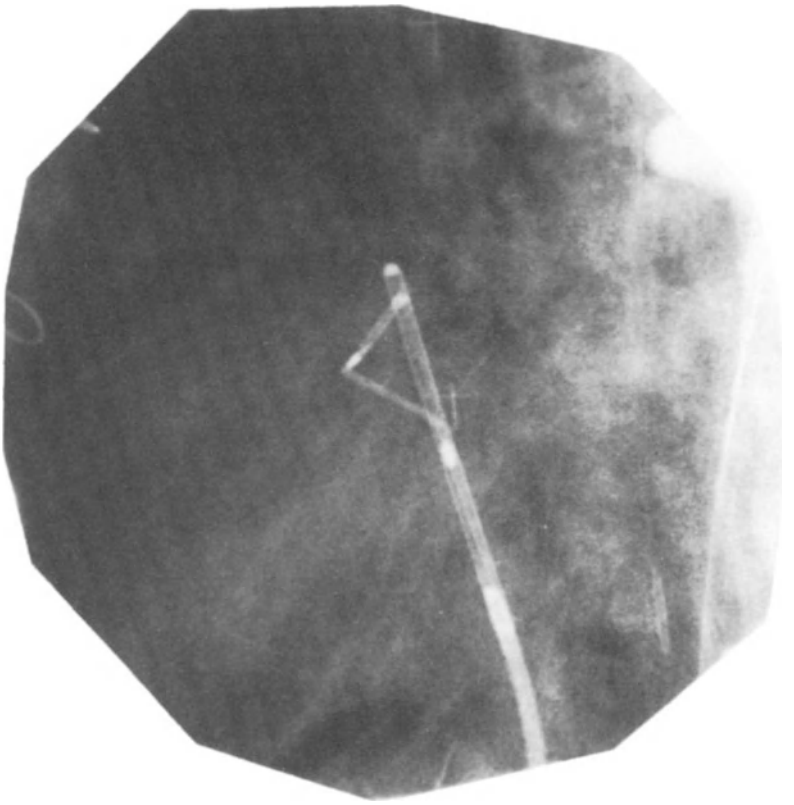

Figure 7.1—*continued*

opening could indicate that the blade tip is being buried in the atrial wall or in a pulmonary vein. The safest blade position in infants with TGA is with its open end towards the left diaphragm on the PA view and with the blade slightly anterior on the lateral camera (Figure 7.1). To open the septum, one fixes the blade in the open position, and withdraws it slowly through the atrial septum with gentle but firm pressure. Resistance can be quite formidable, so bracing one's hands against the fluoroscopy table during withdrawal will prevent sudden retraction of the open blade down the inferior vena cava after it passes through the septum. After a successful pass, Park *et al.* recommended attempting to enlarge the tear with balloon atrial septostomy.

Since the advent of reparative surgery for TGA in the neonatal period at our centre[7] and others, there has been little need for repeat atrial septostomy in infants with TGA. However, in complex cardiac abnormalities associated with mitral stenosis or atresia, progressive narrowing of the atrial septal opening frequently occurs resulting in pulmonary odema. Blade atrial septostomy has been quite helpful in delaying or avoiding open atrial septostomy in these infants. Left atrial

anatomy may be highly variable in such infants and complications have been reported from blade septostomy in such cases[6]. When performing blade atrial septostomy in these infants we carefully assess left atrial size and position by echocardiography and angiography, noting the relationship of the atrial opening to the two ends of the septum. If the left atrium has a diameter of less than 1.5 cm in the axis parallel to the septum, it may be too small for safe blade septostomy. In addition, if the opening is low in the atrial septum, the blade might damage the tricuspid valve or conduction system. The blade is advanced to the left atrium through a previously positioned Mullins long sheath (USCI), and opened as noted above. The blade is positioned as noted in Figure 7.1. Frequently we try to make several cuts, 15 to 30° anterior and posterior to the position noted in Figure 7.1. To try and enlarge the hole further, blade septostomy is followed by balloon septostomy. Using these precautions, we have successfully reduced the transatrial gradient in seven consecutive children with left ventricular inflow obstruction, without morbidity (Figure 7.2).

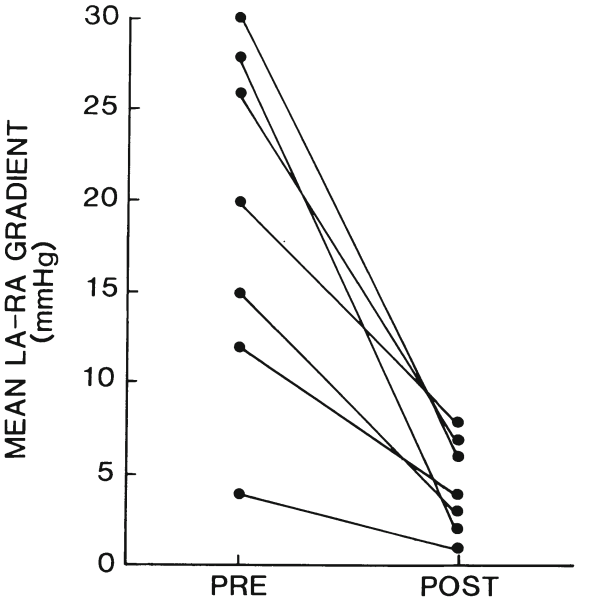

Figure 7.2 Pressure differences between mean left atrial and right atrial pressures before and after combined blade and balloon atrial septostomy. All children had mitral atresia or severe stenosis and were older than 3 months

PERCUTANEOUS PERICARDIAL DRAINAGE

Standard textbooks of pediatric cardiology recommend the percutaneous approach to the pericardium for diagnostic purposes only, with

drainage an operative procedure[8, 9]. Several case reports have documented the feasibility of pericardial drainage with catheters in selected cases[10, 11], and we have modified the standard 8 French angiographic catheter to successfully drain pericardial fluid of various causes, including purulent pericarditis[12].

The procedure is relatively simple; the nature and distribution of the fluid is carefully assessed by echocardiography. Some children will have pericardial collections that are largely posterior (e.g. after Fontan's operation) but the effusions can still be reached from a left anterior thoracic approach. Once the optimum needle course is identified and local anaesthesia is injected, a 6 cm 18 gauge thin-walled needle is advanced toward the pericardial space using gentle syringe aspiration. When pericardial fluid is obtained, a 0.038″ J-tipped curved guidewire is advanced into the pericardial space. Once the wire is placed, its intrapericardial position must be confirmed with either fluoroscopy or echocardiography. A stab wound is made, and an 8 French short pigtail catheter with specially modified side holes (0.060″ diameter, Cook Inc.) is advanced over the wire and positioned in the posterior pericardium (Figure 3). Fluid may then be aspirated for as long as 7 to 10 days. In purulent pericarditis, catheter drainage and antibiotics are usually sufficient to effect a cure. If, however, fever and leukocytosis persist for more than 3 days, operative evacuation with pericardial resection should be considered.

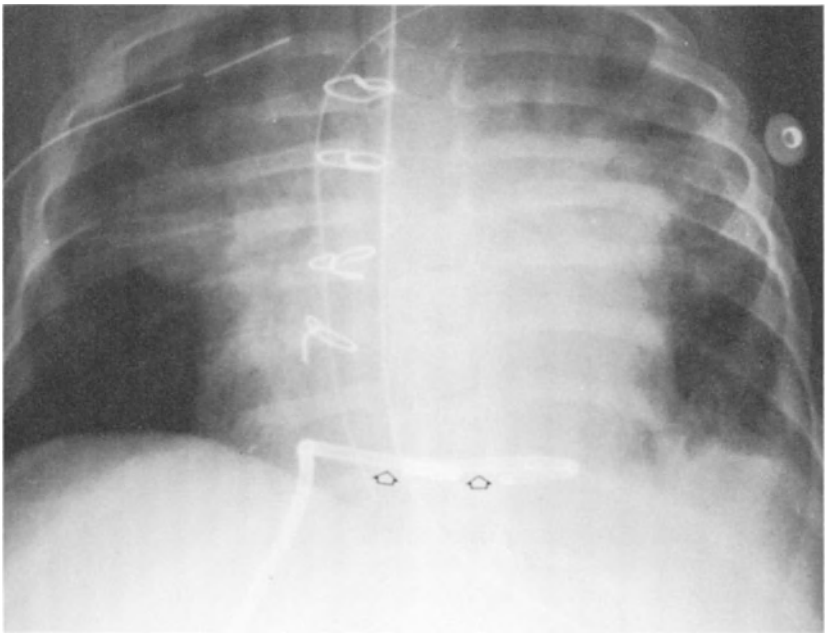

Figure 7.3 PA and lateral roentgenogram of a pericardial pigtail catheter. The catheter was directed inferiorly and posteriorly at the time of placement

BALLOON ANGIOPLASTY AND VALVULOPLASTY

Balloon angioplasty for atherosclerotic heart disease is now a decade old. Since early workers theorized that angioplasty succeeded in atherosclerosis by squeezing a soft plaque[13], and since there is no soft plaque in congenital cardiac disease, attempts to dilate vessels or valves in children were delayed until postmortem[14] and experimental[15, 16] studies indicated that the procedure might be feasible. An informal survey has indicated that over 600 angioplasty procedures had been performed in children by the end of 1984, with a relatively small number of deaths or serious complications. Before discussing the use of angioplasty in valvar pulmonary stenosis, branch pulmonary arterial narrowings, coarctation of the aorta, valvar aortic stenosis, postoperative baffle obstructions, and pulmonary venous obstructions, it would be wiser to consider some general principles.

Angioplasty succeeds in children by tearing the intima and part or all of the media. The annulus (in the case of valves) and the vascular adventitia (in the case of vessels) maintain vascular integrity during the procedure and prevent vascular rupture. Healing of the intima and media occur over the course of 2 to 6 weeks[15, 16] with reconstitution of normal appearing intima and replacement of the media with vascular scar tissue[15, 16]. In valves, the tear can occur through the leaflets or along the commissures[17], and even leaflet avulsion can occur.

Late follow-up is not yet available for angioplasty of any cardiac defects in children. Thus far, there has been little evidence that recurrent stenosis is a problem. However, since angioplasty tears the vessel and injures the wall, considerable potential exists for accelerated atherosclerosis and progressive aneurysm formation. Although these complications have not yet been observed with follow-ups of a few years, much longer observation is required before the late effects of this procedure are understood.

In general, angioplasty may be safer if one avoids balloon rupture[18]. A ruptured balloon may conceivably promote vascular rupture from a jet effect. Furthermore, the balloon itself can tear circumferentially rather than along its long axis. Balloons torn in such a fashion can be difficult to remove from a femoral vessel, and may necessitate operative removal. Rupture pressures vary from balloon to balloon and from manufacturer to manufacturer; in general, polyethylene balloons less than 10 mm in diameter will withstand 7 atmospheres or more, whereas balloons 20 mm or more in diameter will rupture at 4 or 5 atmospheres.

The guidelines for angioplasty catheter selection and manipulation are similar for all lesions. The severity of the lesion to be dilated is documented angiographically and haemodynamically. Using an end hole catheter capable of accepting a large bore (0.038″) guidewire, the lesion is crossed and the tip of the catheter is positioned as far distally as possible. A long Teflon coated guidewire is advanced through the

catheter and stabilized. Both catheter and introducing sheath are removed, and the angioplasty catheter is advanced over the wire. In traversing the skin the wire should be held taut, the balloon should be aspirated, and the catheter must be rotated (counterclockwise if the balloon is folded clockwise) to avoid excess vascular trauma. The catheter should always be positioned so that the obstruction is very close to the centre of the balloon: if the balloon is inflated with the obstruction off centre, the balloon will tend to migrate during inflation. Finally, since angioplasty works by causing an intimal and medial tear, it is vital never to cross a recently dilated vessel with a catheter or wire. In order to avoid extension of the vascular tear through the media, the original guidewire should be left in place (straddling the dilated stenosis) until all attempts at dilation and catheter passage are completed.

Pulmonary valve stenosis

Since the original case report by Kan *et al.*[19] several clinical studies have confirmed that balloon valvuloplasty for stenotic pulmonary valves is safe and relatively effective[20, 21]. The average gradient reduction has been 65%, which approaches the gradient reduction achieved by surgical management[22]. In these earlier reports, the balloons used were

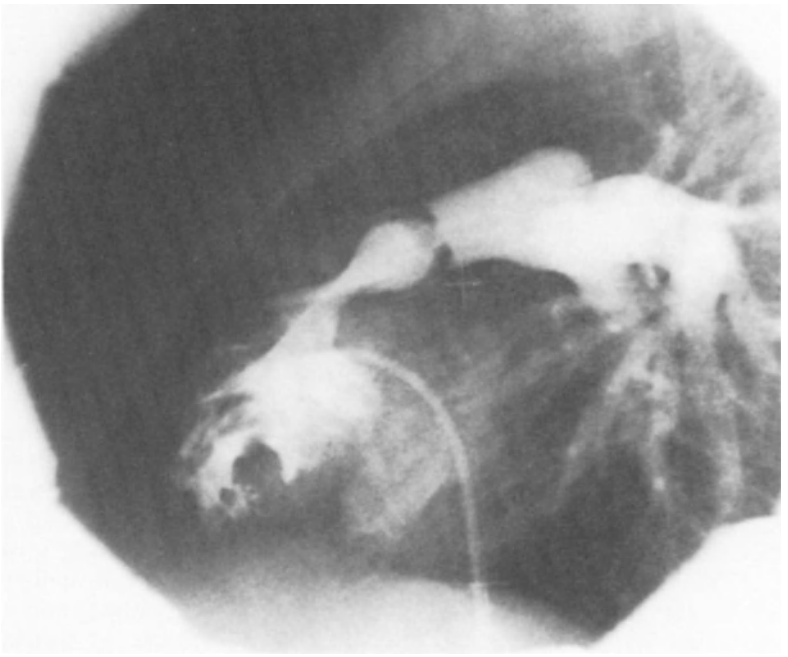

Figure 7.4 Lateral roentgenogram of a dysplastic pulmonary valve before balloon dilation valvuloplasty. Despite marked leaflet thickening and poor mobility, the gradient fell from 80 mmHg to 40 mmHg

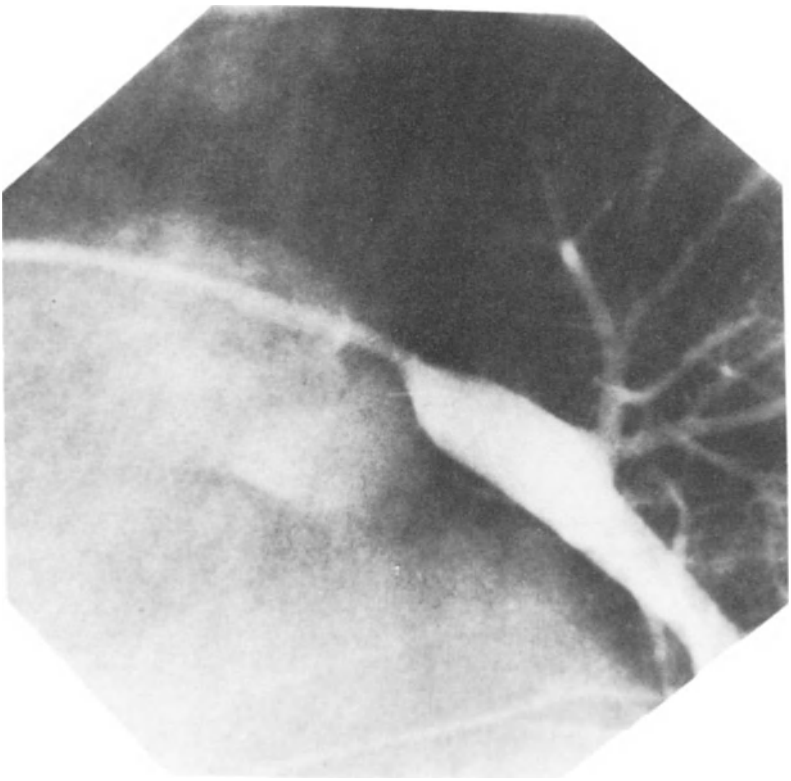

Figure 7.5 Lateral pulmonary arteriogram of child with hypoplastic main left pulmonary artery (associated with tetralogy of Fallot) before and immediately after balloon angioplasty. The 7F catheter almost occludes the vessel predilation. Note vascular irregularity post-dilation, presumably representing tears in the intima and media

the size of the annulus or smaller. However, recent experimental work has indicated that balloons 20 to 40% larger than the annulus will cause little intracardiac injury, and may improve overall gradient results[23].

Proper case selection is still a bit uncertain. Although younger infants have been successfully dilated they may be somewhat unstable during dilation, as the uninflated catheter itself can obstruct a severely narrowed pulmonary valve. It seems likely that dysplastic pulmonary valves will be more difficult to dilate[24], although we have been able acutely to diminish the gradient across the dysplastic pulmonary valve of a child with Noonan's syndrome (Figure 7.4). Late follow-up has indicated that pulmonary regurgitation is a minor problem, and that recurrent stenoses are, thus far, uncommon. If the use of overlarge balloons can produce gradient reductions approaching 75%, it seems likely that balloon valvuloplasty will become the treatment of choice in the management of valvar pulmonary stenosis.

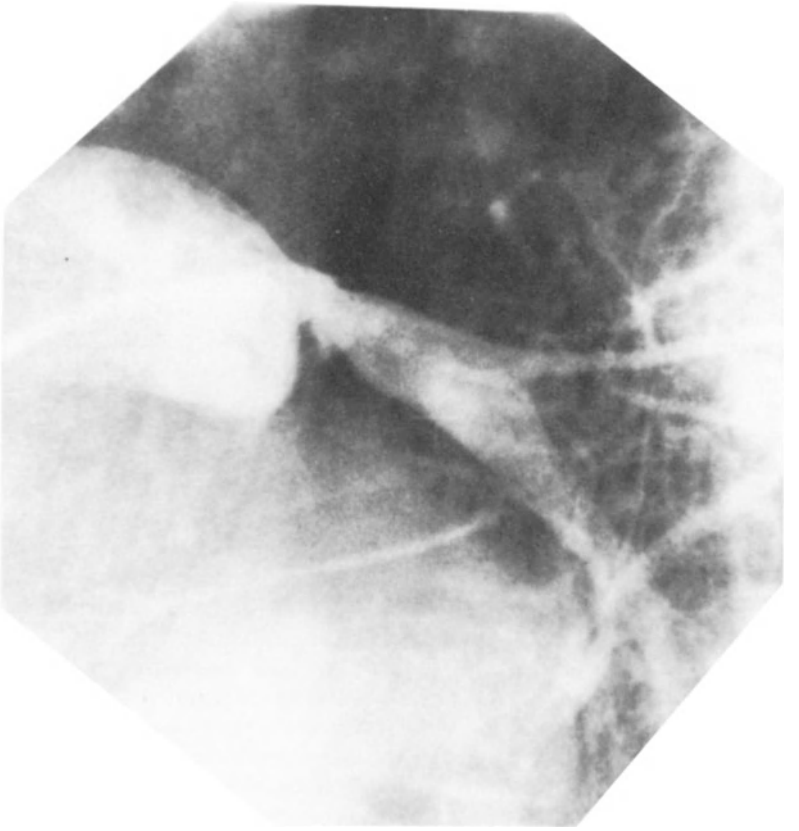

Figure 7.5—*continued*

Pulmonary artery stenosis or hypoplasia

Since operative management of these lesions has been largely unsuccessful[25], the advent of angioplasty for these lesions has been of particular clinical significance[26]. Experimental studies have demonstrated that the branch pulmonary artery is a particularly compliant lesion, stretching but not tearing with rather large balloons. In children, angioplasty can be a technically difficult procedure: since the lesions tend to be very distal it can be difficult to pass a stiff dilating catheter across these lesions. Nonetheless, recent data indicate that 50% or more of branch pulmonary artery narrowings can be successfully dilated[20, 27, 28], although balloons roughly four times larger than the narrowed vessel are required. These studies[28] further suggest that the younger the child, the more likely the procedure will be successful. The procedure seems most successful with long hypoplastic narrowings (Figure 7.5). Late follow-up has indicated that improvement persists in most patients.

Coarctation of the aorta

Experimental and excised specimen studies have indicated that the native coarctation can be dilated by tearing the intima and media of the aorta, although relatively high dilating pressures are required[16, 29]. Dilation of the native infant coarctation can be successful initially, although restenosis within days or months is quite common[30, 31]. Dilation of the native coarctation in older (2 years or more) children has been quite successful on early follow-up[32]. Since dilation angioplasty is known to tear the aortic wall in these children, produces areas of medial thinning in experimental animals[16] and does not remove the apparent nidus for aneurysms, dissections, or bacterial aortitis, considerable concern about the late follow-up of these children exists[33].

In addition to native coarctation, the recurrent coarctation has been successfully managed (Figure 7.6) in most children with balloon dilation angioplasty[30, 34]. Considering the additional morbidity and mortality associated with operative management of these children the use of balloon angioplasty in recurrent coarctation now appears to be a reasonable approach.

The methodology for dilation of aortic coarctation is straightforward. Access to the femoral artery is obtained percutaneously, and the coarctation anatomy is precisely outlined by angiography. A guidewire is positioned in the aortic root and an angioplasty balloon is chosen to be either three times the diameter of the narrowest segment[30] or about equal to the diameter of the normal aorta above the coarctation[34]. The balloon catheter is inserted without a sheath over the guidewire, and positioned to straddle the coarctation site. Although occlusion of the coarctation is well tolerated haemodynamically for many minutes, care must be taken not to occlude a carotid artery for over a minute. Heparinization (100 u/kg) appears safe, and may reduce the risk of femoral arterial compromise. After dilation, the balloon catheter is replaced (over the guidewire) with a Gensini catheter, and successful dilation is confirmed angiographically before the catheter is withdrawn across the dilated site.

Aortic valvar stenosis

We have limited experience with dilation of left ventricular outflow obstructions (valvar or subvalvar) and our success has been similarly limited. However, Lababidi *et al.* have reported excellent results in a series of children with severe aortic valvar stenosis, using balloons about the same size as the aortic root and very high dilating pressures[35]. Despite the fact that valvuloplasty is known to produce commissural tears in the pulmonary valve[17], less than one third of the patients had (at most mild) postdilation regurgitation. Additionally, the fact that closed valvotomies performed in the operating room have been found to cause relatively little aortic regurgitation and still

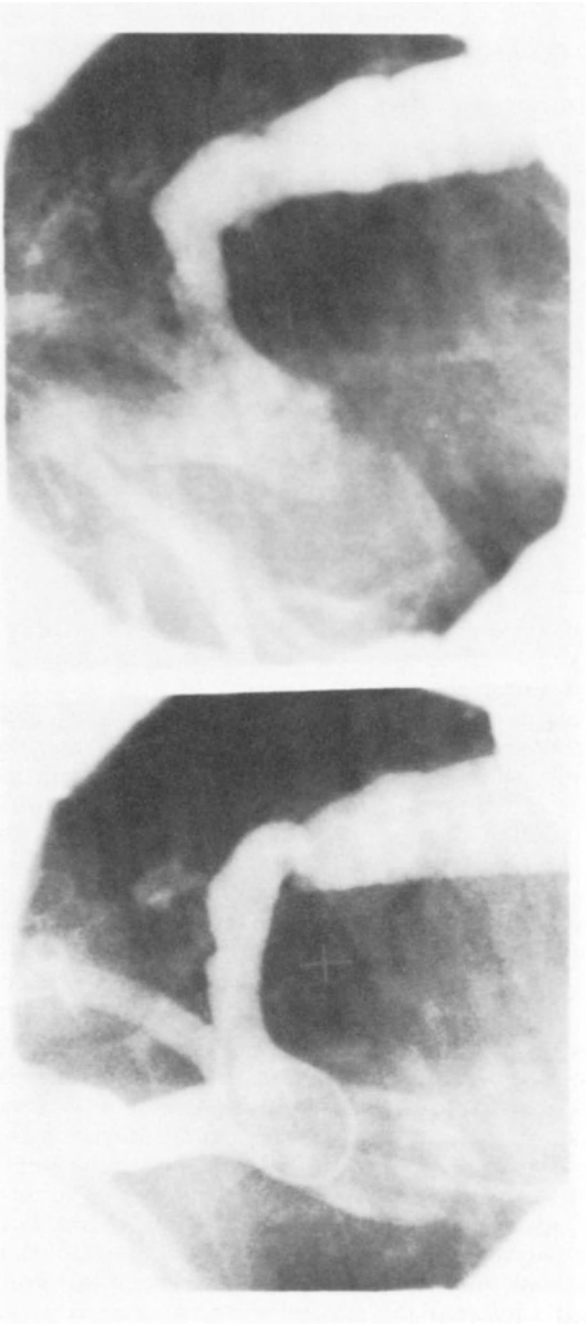

Figure 7.6 Lateral aortogram of recurrent coarctation before and after balloon angioplasty. Although the anatomy is not restored to normal, the diameter is doubled

achieve significant gradient reduction allows one to hope that balloon valvuloplasty, perhaps even repeatedly, will prove of long term benefit in the management of some forms of aortic valvar stenosis.

Venous baffle obstructions

Residual or recurrent pressure gradients are known complications of both the Senning and Mustard repairs for transposition of the great arteries[36]. Although the first published attempt to dilate an operative venous obstruction (in total anomalous pulmonary venous connection) with a small balloon was inconclusive[37] the use of very large balloons (six to ten times larger than the diameter of the venous obstruction) has proved quite successful[38] (see Figure 7.7).

At times, two balloons are required successfully to dilate these very compliant lesions. Late follow-up in these patients has lasted only a few years, so that the procedure can only be considered palliative at present. Although pathological specimens of successfully dilated baffles have not been published, it appears angiographically that the structure being dilated is the ridge of atrial septal tissue where either limb of the baffle crosses the old atrial septum.

Stenosis of individual pulmonary veins

The first congenitally narrowed lesion to undergo an attempt at balloon angioplasty was apparently the narrowed pulmonary vein[39]. In that early report the procedure was unsuccessful in several children and adults, although relatively small balloons were used. Since then, a series of five children have undergone angioplasty of their narrowed pulmonary veins[38]. Although large balloons have been used the results were the same: the lesions are undilatable. Surprisingly, pulmonary veins cannot be dilated because their structure is too rigid, the waist in the balloon which can be seen easily at low pressure cannot be eliminated even at very high dilating pressures. The histological and mechanical properties of stenosed pulmonary veins which make them undilatable have not been identified.

Other lesions

With the success noted above, angioplasty has now been considered as a therapeutic option for every known stenosis in children with abnormal circulations. Perhaps the most promising use of this procedure in childhood and in young adults is in the management of rheumatic mitral stenosis. Closed or open blunt valvotomy of the mitral valve remains the mainstay of surgical therapy in a number of countries[40, 41]. The shortage of adequate surgical facilities has limited the availability of this procedure in a number of countries, and therefore a catheter directed approach to this lesion has considerable appeal. Preliminary work has already indicated the feasibility of this procedure in some patients[42], although large balloons are required.

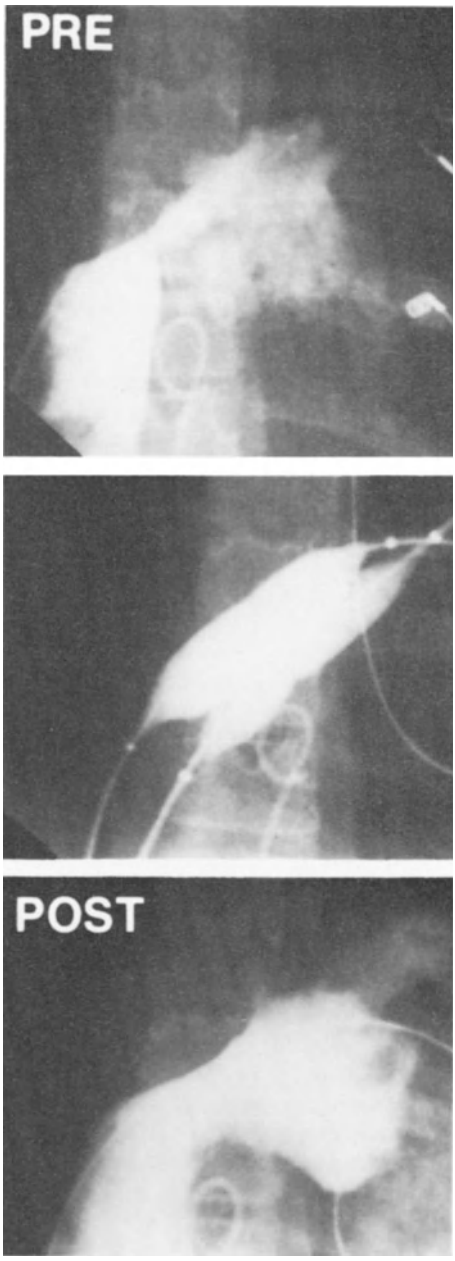

Figure 7.7 Dilation angioplasty of obstruction of the inferior limb of a Mustard baffle. These lesions are very compliant, requiring very large balloons (see text) for successful dilation. (Reprinted with permission from *Circulation*, **70**, 285, 1984.)

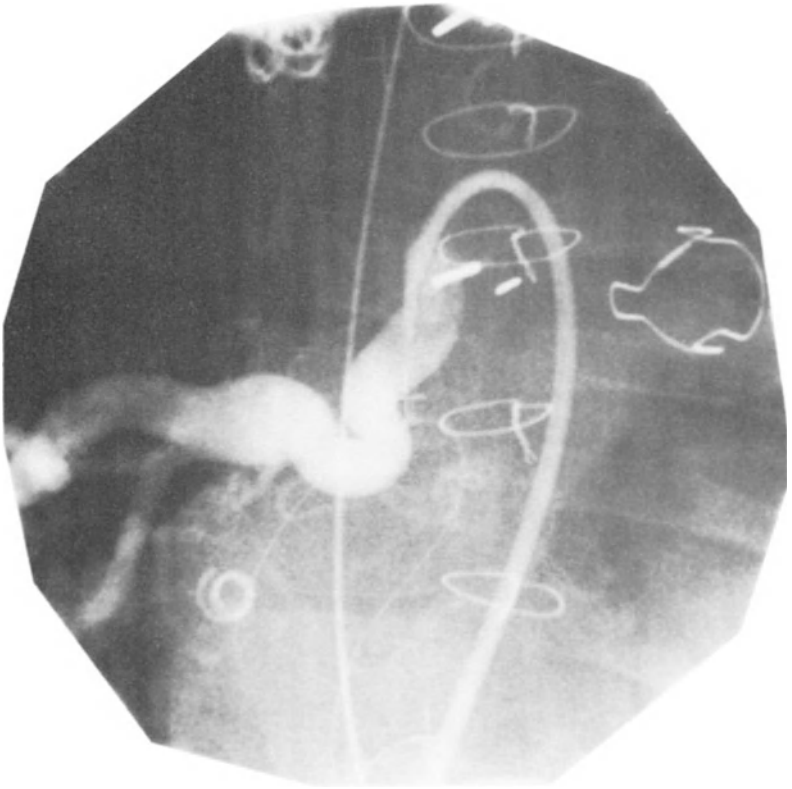

Figure 7.8 Selective arteriograms into a right lung systemic pulmonary collateral in a child with tetralogy of Fallot. After placement of several coils, antegrade flow is abolished

EMBOLIZATION OF ABNORMAL VESSELS

There is a wide variety of abnormal vessels which may require closure in childhood, including pulmonary arteriovenous malformations, systemic arteriovenous malformations, systemic pulmonary collateral vessels associated with cyanotic congenital cardiac disease, and several surgically created anastomoses. Most of these lesions are quite accessible to a catheter, and a variety of agents and debris have been used to effect transcatheter closure. Gelfoam pieces (1 to 3 mm square) can be injected into a bleeding vessel to close it[43], although the chance of systemic embolization is high if the vascular communications are not quite small. Terry *et al.* have used detachable silastic balloons to close numerous arteriovenous malformations successfully[44], although this has been done primarily in adults with systemic arteriovenous malformations. The detachable balloons are delivered through a large bore catheter, inflated in the proper position, and then released with a sharp

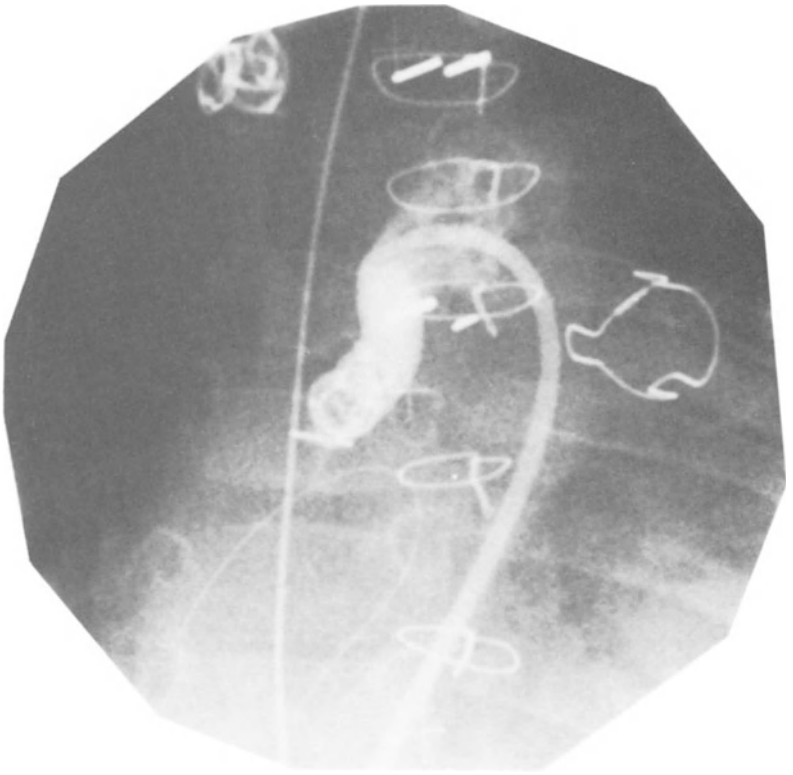

Figure 7.8—*continued*

tug. This procedure, although not suited to small infants because of the catheter sizes required, has been highly successful in a large number of patients.

We have found Gianturco steel coils to be a relatively safe and effective method for closing large abnormal vessels even in small infants[45]. These coils can be packed to a diameter of 0.038″, but when they are extruded from the tip of a catheter they will assume a spiral shape that is 3, 5 or 8 mm in diameter. Dacron strands attached to the coils help promote clot formation, and they can be delivered with catheters as small as 5F. We have used these coils to close pulmonary of arteriovenous malformations, systemic pulmonary collaterals, and other abnormal vessels in children (see Figure 7.8) with a high (80%) success rate and no significant morbidity. Late follow-up in these patients, when available, has not provided evidence of recanalization of coil occluded vessels. The procedure appears to be especially safe when a standard 7F balloon-tipped wedge catheter is used to deliver the coil: the balloon is inflated in the abnormal vessel, thus fixing the position of the tip and preventing tip dislodgement while the coil is being extruded.

TRANSCATHETER CLOSURE OF THE PATENT DUCTUS ARTERIOSUS

The non-operative closure of patent ductus arteriosus (PDA) in children was reported over 15 years ago by Porstmann *et al.*[46] who described a double wire and plug method: a wire is passed into the pulmonary artery across the ductus from the arterial side, and a second wire is manipulated to snare the first wire and deliver it to the femoral vein and out of the body. A preformed plug is then inserted into the femoral artery by the cutdown method, passed over the wire, and advanced to the patent ductus. The plug is securely positioned with a second transaortic catheter, and the long guidewire is removed. This method has been successfully employed both in Berlin[46] and Japan[47], although it requires a large femoral artery and thus is apparently unsuitable for infants and small children.

More recently, Rashkind[48] has developed a double-disc spring-loaded device which can be passed across the patent ductus in either a retrograde or antegrade direction. The prosthesis is partially extruded to allow the distal arm to open, the device is then pulled snugly into the PDA, and then the proximal arms are allowed to open. Bash and Mullins[49] recently modified the technique by using a long sheath to position the catheter across the PDA (see Figure 7.9). Although a number of potential hazards have been identified, including injury to right heart valves if one attempts to retrieve a misplaced device[50], further experience and modifications have improved the success rate of this device and reduced the number of misplaced prostheses. It seems likely that this procedure will become more widespread with further experience, although cardiologists will have a difficult time significantly improving on the success and safety of operative ductal ligation.

OTHER CATHETER INTERVENTIONS

In addition to the above procedures, several other methods for correcting congenitally malformed hearts are under further investigation. King *et al.* reported the use of a transcatheter device to close the atrial septum a decade ago[51] although the very large size of the required catheter (23 French) has sharply limited its use. Rashkind is currently investigating a spring-loaded device with six arms that can be passed across the atrial septum, opened in the left atrium, and secured against the left side of the septum[48]. To date, clinical experience with this device is limited to a few cases.

The possibility that laser energy could be used therapeutically in children has been explored by Riemenschneider *et al.*[52] They have demonstrated in preliminary studies that part of the atrial wall could be vaporized in an experimental animal, and have begun to investigate the structural effects of catheter directed laser energy on the immature myocardium. Since it appears that the amount of laser energy delivered

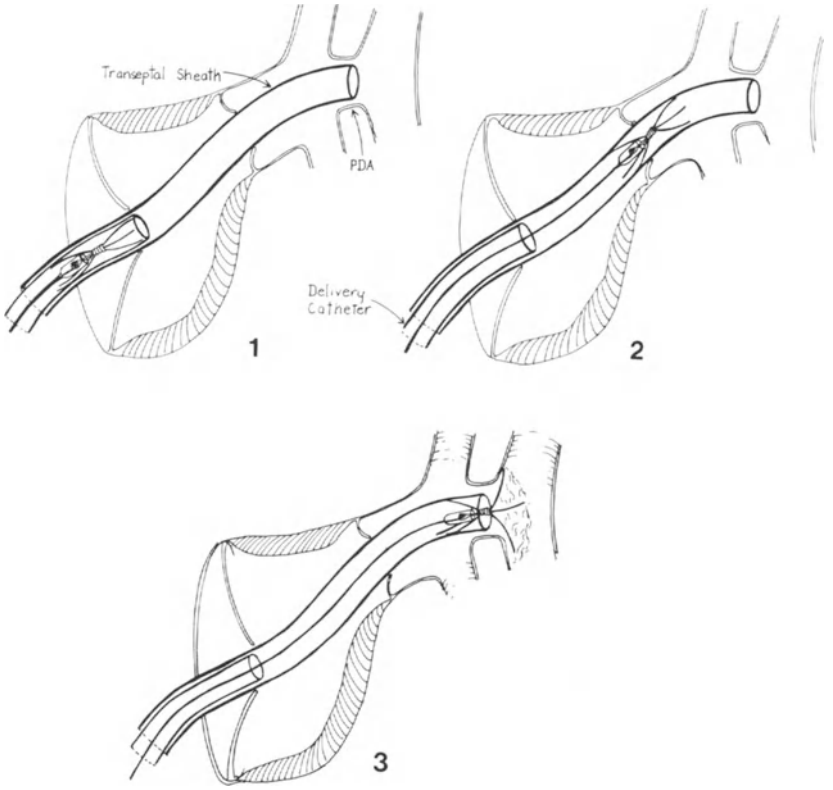

Figure 7.9 Schematic drawing of method used to close experimental patent ductus arteriosus. The long sheath is used as an extension of the delivery catheter (see text)

must be precisely controlled to be used safely, direct visualization of the structure being vaporized appears to be necessary.

Finally, Gallagher *et al.* have demonstrated that arrhythmogenic foci and His bundles can be obliterated using the transcatheter methodology, either electrically or with cryotherapy[53]. Thus far these techniques have not been reported in children, but it may nonetheless prove possible to treat certain arrhythmias in children in this fashion.

SUMMARY

Transcatheter therapy is gaining wide acceptance in a number of centres for the treatment of cardiovascular disorders in children. This acceptance is understandable for a number of reasons: transcatheter therapy has the potential to reduce morbidity, medical costs and trauma to a child and his family. At the same time the introduction of any new procedure is likely to create new and unforeseen problems.

The history of pediatric cardiology is replete with examples of new therapies whose most serious complications were not observed for years or even decades. The proper role of transcatheter therapy in children must remain subject to careful investigation for many years to come.

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